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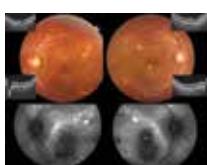
Quiz question

Young male presenting with recent onset diminution of vision in both eyes. Please give two differential diagnosis.

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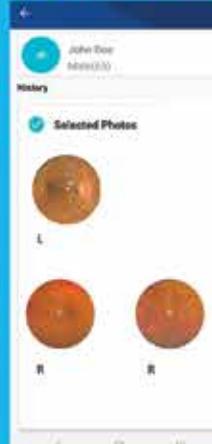
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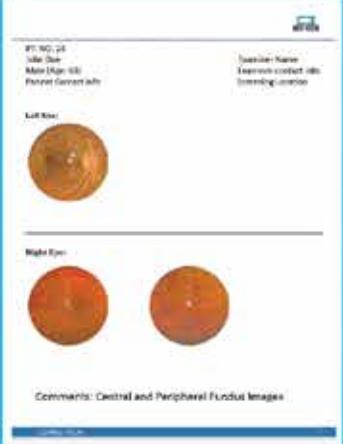
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How do we deal with keratoconic corneas lesser than 400 microns thickness?

Hypo-osmolar riboflavin is indicated for use in collagen cross-linking (CxL) for cases of progressive keratoconus with a post-epithelial debridement central corneal thickness less than 400 μm to artificially thicken thin corneas prior to CxL to decrease safety concerns to the corneal endothelium.^[1] The long-term safety and efficacy at 3 years follow-up were analyzed. CxL with hypo-osmolar riboflavin solution in thin corneas has been shown to be equivocal as that of standard CxL in progressive keratoconic eyes with the visual, refractive, keratometric, tomographic, and aberrometric outcomes being comparable.^[2] Confocal microscopic evaluation of the structural changes of keratoconic corneas less than 400 μm that underwent CxL with hypo-osmolar riboflavin noted posterior corneal structural changes along with a decreased endothelial cell count.^[3] Though accelerated CxL (9 mW/cm² for 10 minutes) with hypo-osmolar riboflavin in thin keratoconic corneas with less than 400 μm epioff was noted to be effective, a significant decrease in endothelial cell counts post treatment remains a concern.^[4]

Contact lens-assisted corneal cross-linking (CACxL) for CxL in thin keratoconic corneas using a riboflavin-soaked soft contact lens mandates ensuring the thinnest pachymetry to be greater than 400 μm before application of UV-A and to take care to avoid sub-contact lens riboflavin film and an excessively thick supra-contact lens riboflavin film and frequent reapplications.^[5] CACxL in thin keratoconus corneas was observed to halt progression in 80% and induce flattening in 45%, with significant improvement in visual and topographic outcomes and no associated damage to the corneal endothelium and the depth of demarcation line being shallower than that of conventional CxL.^[6-10] Accelerated CACxL has also been reported as an alternative for keratoconus with thin corneas.^[11]

Epi-off-lenticule-on corneal collagen cross-linking in thin keratoconic corneas is a recently described technique effective in progressive keratoconus with a minimum corneal thickness less than 400 μm . This consists of overlaying a femtosecond laser-cut lenticule of human corneal stroma (8.5 mm diameter and 100 μm thickness) with both host cornea and donor lenticules being subjected to epithelial debridement before collagen cross-linking.^[12] The reduced keratocyte density and stromal edema observed in the first treatment month along with mild subepithelial haze was seen to resolve by 6 months in these cases.

The Sub400 protocol which was then described comprised epi-off CxL with ultraviolet irradiation of 3 mW/cm² with irradiation times being custom-adapted to stromal thickness.^[13] Exploring the application of the sub400 protocol of CxL with custom fluence application to halt progression in a retrospective case series of keratoconus cases with ultrathin corneas (range of corneal thickness of 214 to 398 μm) over 12-month follow-up noted a success rate of 90% with no endothelial cell count decrease. The demarcation line depth in this series was

concluded not to be predictive of the treatment outcome but to the extent of stromal microstructural changes following CxL.

Another modified technique of CxL employing SMILE refractive lenticule (lenticule-assisted CxL) in eyes with progressive keratoconus thin corneas lesser than 400 μm thickness in a small case series reported corneal flattening and stabilization over a 5-year period.^[14] A combination of SMILE lenticule-assisted CxL with intracorneal ring segment implantation in ultrathin corneas is also explored as an alternative for stabilization and visual rehabilitation in thin keratoconic eyes.^[15] Customized peripheral corneal cross-linking (P-CxL) in stage 3 and 4 keratoconus ultrathin corneas with the thinnest pachymetry below 400 μm is another approach module for thin corneas. Tomography-guided customized epithelial debridement, with 9.0 mW/cm² UV-A irradiation for 10 min, observed a success rate of 85.7% in a small series.^[16]

As our understanding evolves, with more evidence-based support from studies across the world, the concerns on the safety to the endothelium, corneal microstructural changes, and the need for repeat treatment still remain.

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Mission possible: No waiting for corneal transplants

Eye banking in India has undergone various levels of transformation. From voluntary eye donation, we shifted to the hospital cornea retrieval program (HCRP). We require path-breaking strategies now, which will prevent the needless blindness due to corneal pathologies and also treat them through corneal transplants. The recent rapid assessment of avoidable blindness (RAAB) survey (2015–2019) by the National Program for Control of Blindness and Visual Impairment (NPCBVI), Government of India, reveals that corneal blindness is the second most common cause of blindness (8.2%) in the population aged 50 years or above, and at the same time, it is the leading cause of blindness (37.5%) in those between 0 and 49 years of age.^[1] As per the recent survey from North India, this figure may be much higher (unpublished data).

Conventionally, we require 100,000 transplants per year to reduce the burden of corneal blindness. We add 50,000 cases of corneal blindness each year. We collect almost 50% of this and transplant approximately 48,000 corneas as per the latest Eye Bank Association of India (EBAI) statistics. Hence, to meet the needs of corneal transplantation, nearly 200,000 corneas need to be harvested.

Eye banking must be tackled in a professional manner at all levels. We may not be able to enforce "presumed consent law" in our country, wherein it is assumed that the donation of the corneas is permitted, unless specifically denied by the donor when alive. Hence, "mandatory death notification" should be essential for all hospitals in the country so that all families get a chance to take the decision to donate. All hospitals in the country should be under the "HCRP" network.^[2] This network should also include mortuaries which may or may not be part of the hospitals. Furthermore, delay in dealing with the medicolegal cases should be avoided, which would be required with the cooperation of the police and the forensic medicine departments in the hospitals and the mortuaries. Many of the states in the country have the information about the donor on the "driving license"; this could also be linked to the unique identification cards of the country such as "Aadhar card" in India to expand the pool of the potential donors. Furthermore, the eye banking should be part of the curriculum in paramedical courses, nursing courses, and even schools and colleges.^[3]

Currently, there are approximately 730 eye banks/collection centers in India, out of which approximately 150 are active. It is important to realize the potential of the eye banks/collection centers, and wherever possible, these should be revived. In the same spirit, the inactive eye banks/collection centers should be weaned off to optimize the resources.

Capacity building is an important task in both the existing eye banks and the inactive eye banks to realize and maximize the potential of cornea retrievals and transplants. A professional network of eye donation counsellors who counsel the families of the deceased, technicians who

retrieve the eyes, eye bank managers, and transplant coordinators are required in all regions so that the entire country is covered. Furthermore, regular training courses and refresher courses should be organized in the country to update the knowledge of the paramedical staff. Currently in our country, health is a state subject which may prevent movement of donor corneas difficult from one state, where there is excess of eyes, to another state, where there may be a deficit. For the purpose of 'eye banking', this should be exempted. The transportation of the donor corneas should be facilitated through railways and airlines so that the corneas are distributed optimally throughout the country.

Capacity building is also required at the level of the corneal transplant surgeons whose numbers need to be augmented, and it must be ensured that they are available uniformly across the country. This can be done at the level of both the government medical colleges and the private sector. Ensuring the presence of trained corneal surgeons in rural areas will not only enhance access to keratoplasty facilities but also facilitate improved adherence to postoperative follow-up and care, which are essential components of the corneal transplant journey. General ophthalmologists should be trained in the postoperative follow-up of the corneal transplants so that they may follow up patients even in the remote areas after the corneal transplant is done and appropriately referred as and when required, in the event of an emergency. Training corneal surgeons in recent lamellar keratoplasties and other emerging surgical modalities will result in improved outcomes and enable utilization of multiple grafts from a single donor tissue, maximizing the potential benefits of the eye donation.

The role of eye donation awareness and voluntary eye donation cannot be undermined, which has stood by us for a long time, and the above measures will only work cumulatively, if the community at large is involved.

In conclusion, it requires a concerted effort by the policy makers, government and nongovernment organizations, ophthalmologists, paramedical workers, and the community at large to make the "mission possible for no waiting list for corneal transplants" in the country.

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She is the first Indian to be inducted as "Director at large" International member in the Cornea Society International of USA. She has recently being inducted as the Council member of the Asia Cornea Society (ACS) from India in the year 2024 and also the Section Editor, Cornea & External eye diseases, British Journal of Ophthalmology (BJO). She was awarded as one of the Top 100 Most Influential Ophthalmologists 2022 by the APJO and APAO Senior Achievement Award 2023. She has been awarded Distinguished Service Award, Leadership Award and Senior Achievement Award by APAO. She has over 600 publications in international peer reviewed journals, authored 19 books and has 120 book chapters. Her total citations: 15301, H Index: 62 and i10 Index is 333. She has 2 patents and 50 awards to her credit. She has conducted many Instruction courses and has been invited faculty at various national and international conferences like AAO, ASCRS, ESCRS, EuCornea, APAO for the last 20 years and is Brand ambassador for Tear Film and Ocular Surface Society (TFOS-DEWS II) in India.

The great masquerader!

A 10-year-old girl presented with diminution of vision in both eyes and headaches for the last 1 month. The patient had no known systemic illness and was not on any systemic medication. Her best corrected visual acuity in both eyes was 20/800, and intraocular pressure in both eyes was 16 mmHg. The fundus of both eyes revealed optic disc edema, extensive hard exudates, and subretinal fluid around the posterior pole along with arteriolar attenuation [Fig. 1a and b]. Her blood pressure was 240/160 mmHg.

What Would be Your Next Step?

- A. Emergency referral for hypertension followed by systemic workup
- B. OCT
- C. Fundus autofluorescence
- D. Fluorescein angiography.

Findings

Fig. 1 (a, right eye) and (b, left eye) reveals optic disc edema, marked arteriolar attenuation, tortuous vessels, multiple dense hard exudates and cotton wool spots, flame-shaped hemorrhages, and subretinal fluid around the posterior pole. Wide-field images [Fig. 1c and d] in addition revealed multiple Elschnig spots (blue arrowhead) in mid-periphery.

Diagnosis

Malignant hypertensive retinopathy.

Correct Answer

(A) Emergency referral for hypertension followed by systemic workup. Fundus picture of severe hypertensive retinopathy with papillopathy and choroidopathy with a blood pressure of 240/160 mmHg in a 10-year-old patient warranted a thorough systemic workup by a pediatrician after systemic stabilization. The

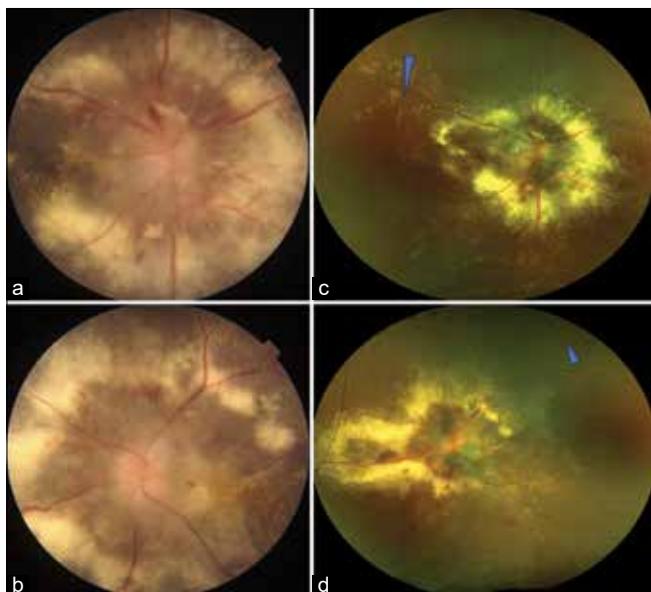


Figure 1: (a, right eye) and (b, left eye) reveals optic disc edema, marked arteriolar attenuation, tortuous vessels, multiple dense hard exudates and cotton wool spots, flame shaped hemorrhages, and subretinal fluid around posterior pole (c, right eye) and (d, left eye) shows widefield images in addition to previous findings revealing multiple Elschnig spots (blue arrowhead) in mid-periphery

patient was diagnosed with phaeochromocytoma. When diagnosed in its early stages, phaeochromocytoma can result in reversible damage and lead to a good visual recovery. This case also highlights the occurrence of all hypertensive changes in the posterior segment due to a severe and persistent rise in blood pressure.

Discussion

Hypertensive retinopathy is a condition characterized by vascular changes in the retina in the event of increased blood pressure. Although mostly the changes are seen in the retina, there can be involvement of the choroid and optic nerve as well.^[1] There can be primary and secondary hypertension. Pheochromocytoma is a cause of secondary hypertension and is a rare tumor arising in chromaffin cells of the adrenal medulla or paraganglia. Clinical features are mainly due to the constriction of vessels by the circulating catecholamines and the obstruction of arterioles, leading to the disruption of the blood-retina barrier.^[2] Visual prognosis is generally good, especially in milder cases. Vision loss may result from prolonged papilledema or retinal pigment changes due to serous retinal detachment.^[3]

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/ their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Role of optical coherence tomography angiography in retinal tumors: A narrative review

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Intraocular tumors constitute a small subset of cases in ophthalmologic practice. Proper diagnosis of intraocular tumors is crucial because some pose threat to vision and life, while others may indicate underlying systemic disorders. Intraocular tumors comprise benign and malignant lesions affecting the retina, choroid, optic disc, iris, and ciliary body. Retinal tumors can be classified as vascular, neural, glial, and retinal pigment epithelial tumors. Optical coherence tomography angiography (OCTA) is a noninvasive imaging modality employed in diagnosis and management of retinal and choroidal vascular diseases, and has enhanced our knowledge in better understanding of the vascular physiology and pathology. Multiple case reports and small series evaluating the role of OCTA in retinal tumors are published in literature. OCTA helps in better understanding of the vascularity of intraocular tumors. In addition to this, OCTA has its role in clinical practice. It helps in identification of small retinal capillary hemangioblastoma (RCH), assessment of treatment response, and identification of tumor recurrence in RCH. It aids in identification of retinal astrocytic hamartoma missed on clinical examination and differentiating retinal astrocytic hamartoma and presumed solitary circumscribed retinal astrocytic proliferation. It helps in assessment of risk of tumor recurrence in retinoblastoma. It helps in differentiating tumors of retinal pigment epithelium (RPE) origin from pigmented tumors of the choroid. It also helps in detection of choroidal neovascular membrane in combined hamartoma of the retina and RPE.

Key words: Intraocular tumors, optical coherence tomography angiography, retinal capillary hemangioblastoma, retinoblastoma

Intraocular tumors constitute a small subset of cases in ophthalmologic practice. Proper diagnosis of intraocular tumors is crucial because some pose threat to vision and life, while others may indicate underlying systemic disorders. Intraocular tumors comprise benign and malignant lesions affecting the retina, choroid, optic disc, iris, and the ciliary body. Retinal tumors include vascular tumors [retinal capillary hemangioblastoma (RCH), cavernous hemangioma of the retina, vasoproliferative retinal tumor (VPRT)], glial tumors [retinal astrocytic hamartoma (RAH), acquired retinal astrocytoma (ARA), focal nodular gliosis, presumed solitary circumscribed retinal astrocytic proliferation (PSCRAP)], tumors of neural origin (retinoblastoma, retinocytoma), and tumors of retinal pigment epithelium (RPE) [congenital hypertrophy of RPE (CHRPE), congenital simple hamartoma of RPE (CSHRPE), RPE adenoma]. Combined hamartoma of retina and RPE (CHRRPE) is composed of multiple components: glial, vascular, and RPE.^[1-3]

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Optical coherence tomography angiography (OCTA) is a noninvasive imaging modality used in the diagnosis and management of retinal and choroidal vascular diseases. OCTA has significantly contributed toward better understanding of vascular physiology and pathology.^[4] It serves as both a research and clinical tool. Most commercially available OCTA platforms operate based on the split-spectrum amplitude decorrelation angiography principle, detecting blood vessels by analyzing changes in reflectance signals caused by blood flow. This algorithm divides the optical coherence tomography (OCT) spectrum into narrower bands, and the intensity decorrelation in each band is detected.^[4] Numerous studies have elaborated on the clinical utility of OCTA in diabetic retinopathy, vein occlusions, choroidal neovascularization, and other vascular disorders of the retina and choroid. Multiple case reports and small series evaluating the role of OCTA in retinal tumors are published in the literature. In this article, we would review the OCTA characteristics of retinal tumors and their clinical utility.

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Methods

This is a narrative review of peer-reviewed articles evaluating the role of OCTA in retinal tumors, which are available in the PubMed database. Thirteen keywords were used to search the articles: "optical coherence tomography angiography retinal capillary hemangioblastoma," "optical coherence tomography angiography cavernous hemangioma of retina," "optical coherence tomography angiography vasoproliferative retinal tumor," "optical coherence tomography angiography retinal astrocytic hamartoma," optical coherence tomography angiography acquired retinal astrocytoma," "optical coherence tomography angiography focal nodular gliosis," "optical coherence tomography angiography presumed solitary circumscribed retinal astrocytic proliferation," "optical coherence tomography angiography congenital hypertrophy of retinal pigment epithelium," "optical coherence tomography angiography congenital simple hamartoma of retinal pigment epithelium," "optical coherence tomography angiography retinal pigment epithelial adenoma," "optical coherence tomography angiography retinoblastoma," "optical coherence tomography angiography retinocytoma," and "optical coherence tomography angiography combined hamartoma of retina and retinal pigment epithelium." The search extended from April 1, 2016 to October 15, 2023. The search resulted in a total of 301 articles. Abstract of each article was screened to assess whether OCTA was part of the methodology. Articles unrelated to OCTA and those in languages other than English were excluded after scanning. Finally, 64 articles were reviewed (RCH: 16 articles, cavernous hemangioma of the retina: nine, VPTR: one, RAH: seven, PSCRAP: four, retinoblastoma: 12, CHRPE: four, CSHRPE: three, and CHRRPE: eight). All the articles were reviewed thoroughly with emphasis on the vascular characteristics of tumor detected on OCTA and the clinical utility of OCTA in diagnosis, follow-up, and treatment of retinal tumor.

Vascular tumors of the retina

Retina capillary hemangioblastoma

RCH is a vascular hamartoma that can occur as an isolated lesion or as a part of von Hippel–Lindau (VHL) disease. Two types of tumors are described based on the location: juxtapapillary RCH (JRCH) and peripheral RCH. Early detection of RCH and frequent monitoring of the tumor are important as large tumors are difficult to treat.

OCTA characteristics

In a cross-sectional study of 84 RCHs (48 patients), swept-source OCTA (SS-OCTA) images of 48 tumors and spectral-domain OCTA (SD-OCTA) images of 39 tumors were suitable for analysis. A high proportion of tumors could not be imaged well due to motion artifacts and peripheral location of the tumor. Though the tumor size measured by OCTA and clinically estimated tumor size had a strong correlation, 14.5% of tumors were estimated larger and 4.2% of tumors were estimated smaller clinically compared to OCTA. In case of small tumors, the tumor area measured by both the devices (SS-OCTA and SD-OCTA) matched. But with increasing tumor size, SS-OCTA measured larger area compared to SD-OCTA. Reich *et al.*^[5] postulated that, the area measured by SS OCTA represents the actual tumor size as it has better tissue penetration even in larger tumors and is not affected by shadow artifacts.

RCH is seen as a well-defined lesion with compact vascularity with flow signal on OCTA irrespective of the presence or absence of exudation^[6–8] [Fig. 1]. In contrast to this, Schoen *et al.*^[9] described a tumor detected on fundus fluorescein angiography (FFA) as a "no flow" lesion on OCTA and considered it to be an inactive tumor. Custo Greig and Duker^[10] noted that the center of JRCH is robustly vascular with dense capillary meshwork and the periphery of the lesion has a branching network with terminal budding. Similarly, terminal "aneurysm-like bulbs" were reported in JRCH by Russell *et al.*^[11] Feeder and draining vessels are seen in the superficial slab in peripheral RCH.^[7] Feeder and draining vessels are typically absent in JRCH. But Russell *et al.*^[11] and Sagar *et al.*^[7] described the presence of dilated vein coursing from the deeper part of JRCH into the inner retina and communicating with a retinal vein, possibly indicating a draining vessel on OCTA [Fig. 2].

Few articles have described the posttreatment characteristics of RCH. Immediately after laser photocoagulation, the tumor displays absence of vascular signals.^[6,12] This can be either due to decrease in vascular perfusion or the reflection of light from the photocoagulated retina, thereby obscuring the underlying tumor.

Takahashi *et al.*^[13] described a novel retinal vascular proliferation in VHL eyes using OCTA. They classified RCH into "nodular RCH" and "flat RCH" types. Nodular RCH represents the typical RCH with dilated feeder and draining vessels described above, whereas flat RCH appears clinically as retinal hemorrhage or faint retinal vessels within the macula or peripapillary area without definite feeder or draining vessels. Flat RCH had abundant flow signal detectable on OCTA and was located between the retinal nerve fiber layer (RNFL) and the ganglion cell layer. In a series of seven eyes with flat RCH, none of the lesions showed progression in size, exudation, or traction over a mean follow-up of 20.4 ± 15.0 months.

Pilotto *et al.*^[14] evaluated the radial peripapillary capillary (RPC) plexus in 28 healthy individuals and 61 patients with VHL. The peripapillary retinal nerve fiber layer (pRNFL) was thinner in VHL eyes without RCH compared to those with RCH and controls. Vessel area density, vessel diameter index, and vessel length fraction were reduced in VHL eyes compared to healthy eyes. However, these vascular parameters were

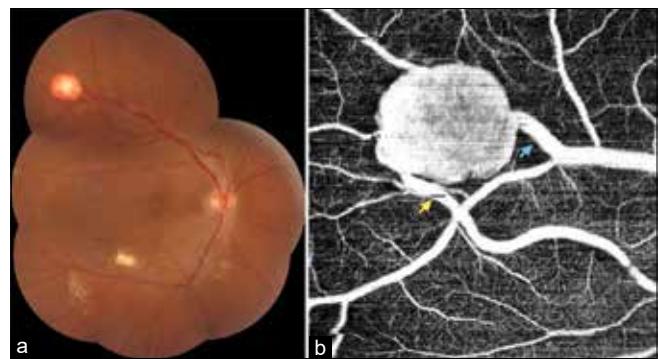


Figure 1: (a) Color fundus photograph of the right eye showing midperipheral retinal capillary hemangioblastoma in superotemporal quadrant with dilated tortuous feeder and draining vessels. (b) En face OCTA showing tortuous feeder vessel (yellow arrow), dilated draining vessel (blue arrow), and tumor with compact flow signal (image credits: Dr. Rama Kumar GVM). OCTA = optical coherence tomography angiography



Figure 2: (a) Color fundus photograph of the right eye showing peripapillary RCH. (b) En face OCTA showing compact vascularity of the tumor. (c) Cross-sectional OCTA showing flow signal within the tumor. OCTA = optical coherence tomography angiography, RCH = retinal capillary hemangioblastoma

similar between VHL eyes with RCH and without RCH. The authors postulated that VHL eyes show reduction in RPC plexus density irrespective of the presence or absence of RCH. This would correspond to the reduction in pRNFL thickness, which is seen in VHL eyes without RCH. However, in VHL eyes with RCH, pRNFL is thicker due to proliferation of retinal astrocytes in the peripapillary area, as documented in histologic studies.

Clinical utility

OCTA can help to identify small posterior tumors^[7,15,16] [Fig. 3] and JRCH^[9] missed on clinical examination, but this is limited by the smaller field of view.^[17] Chun *et al.*^[15] demonstrated that OCTA could rule out the possibility of a vascular tumor in suspicious lesions. OCTA aids in the identification of the structure and size of RCH in the posterior pole more precisely.^[17] OCTA can identify individual tumors distinctly along with feeder and draining vessels compared to FFA.^[7] Combined en face OCTA and OCTA B-scan helps classify JRCH as endophytic, sessile, or exophytic.^[18] The exophytic and sessile juxtapapillary tumors can mimic papilledema, peripapillary choroidal neovascularization (CNV), or papillitis as they lack the characteristic orange red color. OCTA can identify the compact vascular signal within the lesion and would help in confirming the diagnosis of such cases.^[7,12,19] OCTA helps in the assessment of response to treatment, incomplete treatment, and recurrence. In large tumors, a decrease in vascular density identified on OCTA correlates with resolution of exudation.^[17,20] In small tumors, OCTA can identify vascular network within the scar after treatment in cases with incomplete treatment, which would be difficult to identify on color photograph.^[12,20] Lang *et al.*^[12] evaluated RCH lesions previously treated with laser photocoagulation and demonstrated that OCTA can identify recurrence of lesion in areas with retinal alterations like hyperpigmentation, which would be difficult to identify on ophthalmoscopy. Russell *et al.*^[11] noted a transient decrease in vascular congestion on OCTA following 1–2 weeks of intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy. The reduction in vascular congestion, which cannot be picked

up by other imaging modalities, can be picked up by OCTA. Progressive growth of JRCH over 37 weeks was noted on OCTA by Smid *et al.*^[18] despite multiple intravitreal anti-VEGF therapy.

Cavernous hemangioma of the retina

Cavernous hemangioma of the retina is a rare vascular hamartoma. It is mostly unilateral with few reports of bilateral occurrences. It is recognized as a phakomatosis with the involvement of the retina, skin, and the central nervous system. It is usually asymptomatic, but the development of epiretinal membrane and vitreous hemorrhage can lead to visual symptoms. The description of OCTA characteristics in cavernous hemangioma is limited to nine case reports. In one report, the tumor does not exhibit the classical features of cavernous hemangioma on multimodal imaging. In another report, the segmentation is improper. So, in this article, we would not discuss these two reports.

OCTA characteristics

“Spider-like” projection of blood vessels extending from the tumor was consistently reported in five articles^[21–25] [Fig. 4]. This feature is also described as a root-like projection^[23] and coral seaman.^[24] In all the cases, these projections were seen to be communicating with a large venule. Alternating areas of saccular dilatation and narrowing of these projecting blood vessels were seen in two cases.^[21,24] Signal void areas were seen adjacent to these projecting blood vessels in both the cases. Nodular, grape-like saccular structures could be identified in four reports.^[22,23,25,26] Few saccular structures were completely hyporeflective (signal void) and few were heterogenous. The authors attribute this to the slow flow within these saccules. Fluid level (signal void area inferiorly and bright signal superiorly) within the saccular structures corresponding to the fluorescein cap on FFA was evident in a few saccules in one case.^[26] “Reverse fluorescein cap,” described as signal void area superiorly and bright signal inferiorly, is reported in one case of cavernous hemangioma of the optic disc.^[27]

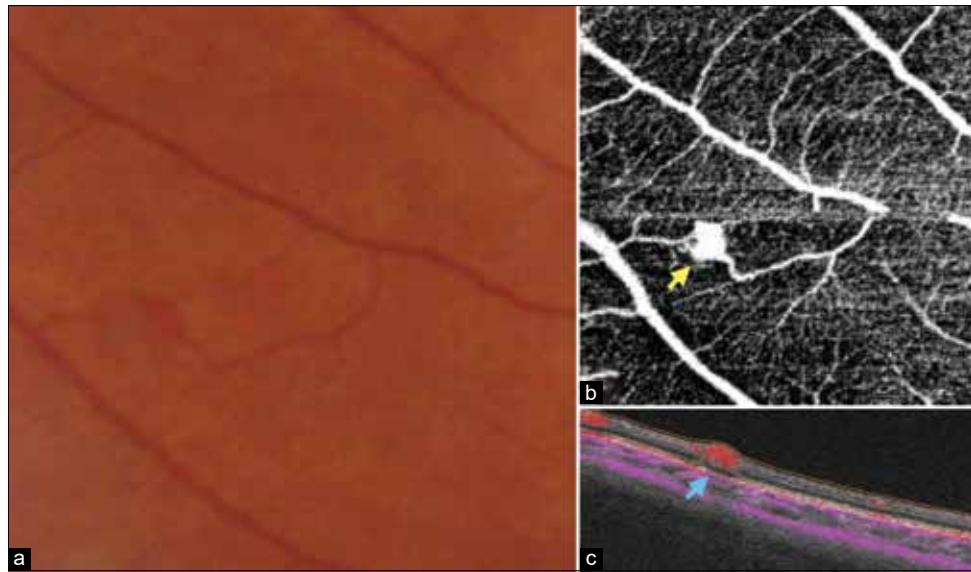


Figure 3: (a) Color fundus photograph showing small RCH. (b) En face OCTA showing compact vascularity of the tumor with feeder and draining vessels. (c) Cross-sectional OCTA showing compact flow signal within the tumor in the inner retina. OCTA = optical coherence tomography angiography, RCH = retinal capillary hemangioblastoma

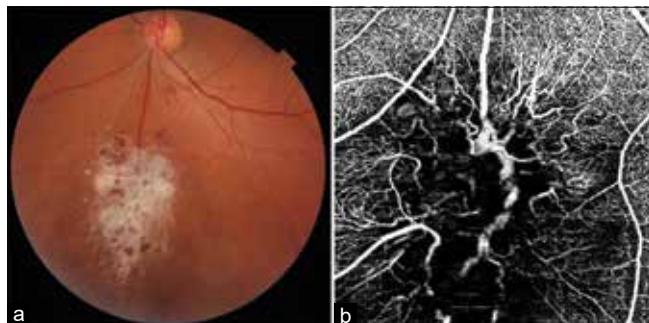


Figure 4: (a) Color fundus photograph showing cavernous hemangioma of the retina in inferior midperiphery. (b) En face OCTA showing root-like projection of blood vessels communicating with a venule. OCTA = optical coherence tomography angiography

Vasoproliferative retinal tumor

VPRT is a rare vascular tumor of the retina which is usually located in the retinal periphery. It can lead to subretinal exudation, cystoid macular edema, exudative retinal detachment, and epiretinal membrane.

OCTA characteristics

Considering it to be a peripheral tumor, the description of OCTA characteristics is limited to one case report. Tanimukai *et al.*^[28] used widefield SS-OCTA to acquire image of a peripheral VPRT. The image depicted distinct vascularity corresponding to the vascularity detected on indocyanine green angiography (ICGA). The authors demonstrated regression of flow signal on OCTA following triple freeze thaw cryotherapy.

Glial tumors of the retina

Retinal astrocytic hamartoma

RAH is a benign intraocular tumor arising from the superficial retinal layers. It is usually associated with tuberous sclerosis complex or neurofibromatosis type 1, but may occur as

isolated cases. Pichi *et al.*^[29] classified the tumor into four types based on the SD-OCT features: flat and within the nerve fiber layer (type 1), slight elevation with retinal traction (type 2), associated "moth-eaten" areas due to calcification (type 3), and associated optically empty intralesional cavities (type 4). OCTA characteristics of RAH are less known.

OCTA characteristics

OCTA precisely analyzes the retinal capillary system, and hence clearly delineates the tumor vasculature.^[30] Yung *et al.*^[31] first reported the OCTA features of a type 1 RAH, showing a central feeder vessel (not seen clinically) with associated abnormal tumor vascular plexus. However, Ramtohul *et al.*^[32] noted a draining vessel arising from the dense intralesional honeycomb-like vascular network. Amoroso *et al.*^[33] also observed the presence of intratumoral vascular plexus in a type 1 RAH, but the feeder/draining vessels were not identifiable. No abnormalities were found at the level of deep capillary plexus (DCP), outer retina, and choriocapillaris (CC). They also documented the nonprogressive nature of the tumor by analyzing the tumor area and vascular density over a period of 2 years [Fig. 5]. Type 2 RAH showed diffuse vascular network in both superficial capillary plexus (SCP) and DCP with the presence of overlying vitreous abnormalities.^[34] Gündüz *et al.*^[35] described the occurrence of hyporeflective changes secondary to shadowing due to the presence of calcium and projection artifacts of the moth-eaten cavities in the choriocapillaries slab, in addition to the vasculature in a type 3 RAH. OCT-A of type 4 RAH was reported to have central hyporeflectivity (due to the cavity) with peripheral hyperreflectivity due to thin-caliber vasculature arranged in a honeycomb pattern along the cavity walls within the tumor.^[36]

Clinical utility

OCTA has the ability to detect subtle lesions not identifiable on clinical examination. It can also help to differentiate RAH from other common superficial retinal lesions such

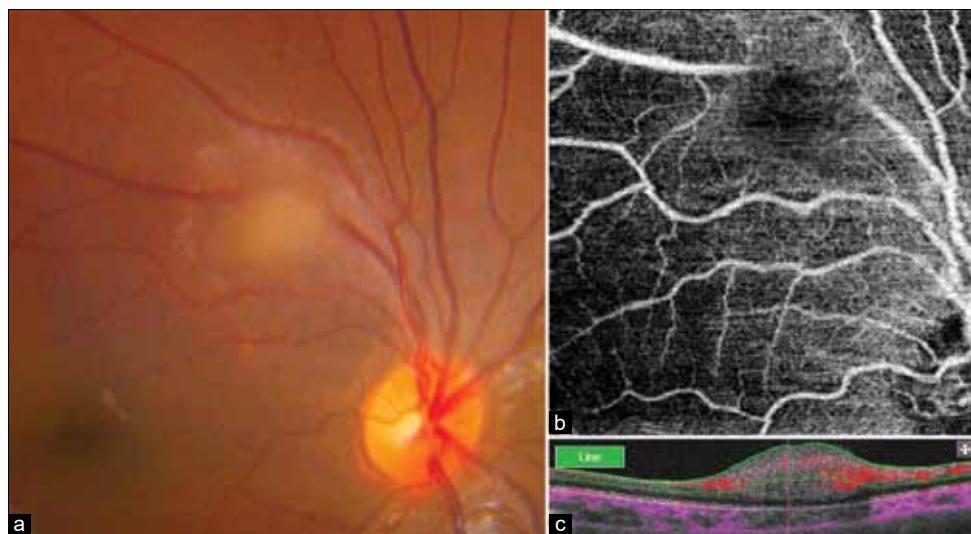


Figure 5: (a) Color fundus photograph showing type 1 astrocytic hamartoma obscuring the blood vessel. (b) En face OCTA showing minimal intrinsic vascularity within the tumor. (c) Cross-sectional OCTA showing few flow signals within the tumor in the inner retina. OCTA = optical coherence tomography angiography

as myelinated nerve fiber (MNF) and PSCRAP (described later). The vascular density at the level of RNFL has been found to be significantly lower in MNF in comparison to the surrounding retina, in contrast to RAH which shows intrinsic vascularity.^[37]

Presumed solitary circumscribed retinal astrocytic proliferation
PSCRAP is a solitary, superficial, well-circumscribed, white lesion in eyes with clear media and no prior ocular insult. It is an isolated lesion not known to be associated with any genetic disorder. PSCRAP is typically located deeper in the neurosensory retina with intact RNFL.^[38] Description of the OCTA characteristics of PSCRAP is limited to four case reports.

OCTA characteristics

Goldberg and Raja^[39] first reported the OCTA findings. They found that the tumor lacked any intrinsic vascularity and the blood vessels in SCP were normal. Vasculature surrounding the lesion did not show any flow signal entering the tumor. Dubey *et al.*^[40] also reported lack of intrinsic intratumoral vascularity, with superficial retinal vessels of normal caliber traversing through or around the tumor (without supplying it), along with obscuration of underlying vasculature. Lack of intrinsic vasculature was confirmed by Goldberg and Raja^[39] and Ansary *et al.*^[41]

Clinical utility

OCTA helps to differentiate PSCRAP from RAH in which intratumoral vascularity is present, unlike PSCRAP.^[42]

Acquired retinal astrocytoma

ARA is a benign intraocular glial tumor, not associated with any genetic disorder. Unlike RAH, it lacks calcification and exhibits progressive growth and exudation.^[43,44]

OCTA features of ARA have not been reported in the literature yet. On OCTA, ARA showed the presence of distinct intrinsic tumor vascularity along with the presence of a feeder

vessel. Posttreatment reduction in tumor vascularity was also appreciated (unpublished data from our center) [Fig. 6].

Tumors of neural origin

Retinoblastoma

Retinoblastoma is the most common primary intraocular malignancy in children.^[45] As a standard procedure, patients are monitored by fundus photography, ultrasonography, and magnetic resonance imaging. OCT and OCTA are recent additions in the evaluation of tumors.^[46,47] In this article, we have reviewed 12 published articles which studied a total of 84 human eyes and 77 rabbit eyes.^[48-50]

OCTA characteristics

House *et al.*^[45] described the OCTA findings of an active retinoblastoma lesion using an investigational portable OCTA system (Spectralis with FLEX and OCTA module, Heidelberg Engineering, Heidelberg, Germany, 2.8 × 2.8 mm scan) for the first time. They demonstrated the presence of superficial medium-sized vessels arising from the retinal vasculature circumscribing the tumor and feeding the dense intrinsic network of vessels. Later, similar findings were reported by Thomas *et al.*^[51] in a study, in which they evaluated tumor vasculature in various tumor regression patterns.

Clinical utility

In studies conducted by Nadiarnykh *et al.*,^[52] Thomas *et al.*,^[51] and Fernandez *et al.*,^[53] it was noted that the vascular features of the tumor correspond to the pattern of tumor regression and clinical activity. Posttreatment, the feeder/draining vessels appear diminutive in the areas of tumor regression, while at the sites of tumor reactivation, dilated draining vessel can be seen.^[51]

Nadiarnykh *et al.*^[52] evaluated the tumor vasculature in type 2, 3, and 4 regression patterns posttreatment using phase-based OCTA. In type 2 regression pattern, the tumor appears avascular or shows minimal vasculature due to strong attenuation

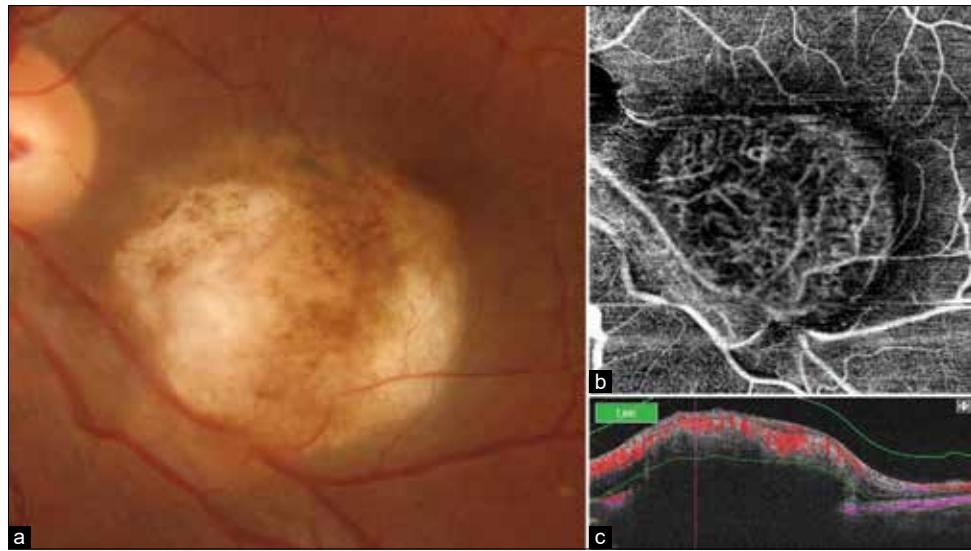


Figure 6: (a) Color fundus photograph showing acquired retinal astrocytoma. (b) En face OCTA showing intrinsic vascularity with branching network. (c) Cross-sectional OCTA showing flow signal within the tumor. OCTA = optical coherence tomography angiography

properties of the tumor; in type 3 regression, abnormally dense vasculature is seen, which is tortuous and lacks normal branching directionality; while in type 4 regression, flow void areas are seen in the retinal slab and CC. They postulated that the presence of vascularity is a reason for highest risk for recurrence of malignancy in type 3 regression pattern. Thomas *et al.*^[51] evaluated the tumor vasculature in type 1–4 regression patterns posttreatment using OCTA (Spectralis with Flex and OCTA module; Heidelberg Engineering, Heidelberg, Germany, 20° × 20° scan). In type 1 regression, significant vascularity is noted in the retina superficial to calcification with dilated and tortuous, less-densely packed vessels in the deeper retina. In type 2 regression, prominent vascularity is noted in both superficial and deeper slab with somewhat prominent feeder vessels. Lesions with type 3 regression have calcific and noncalcific areas; the calcific areas behave similar to type 1 regression and the noncalcific areas show complex network of vessels in the superficial aspect of the tumor with prominent feeder vessels, while deeper to the tumor, fine network of vessels can be seen along with projection artifacts. In type 4 regression, there is diffuse flow void at the level of the retina and CC. Sioufi *et al.*^[54] evaluated the effect of intravenous chemotherapy for retinoblastoma on foveal microvasculature using OCTA. They demonstrated microvascular ischemia at the level of the DCP without any visual impairment after intravenous chemotherapy.

Daniels *et al.*^[48] evaluated the toxicity of intra-arterial chemotherapy (IAC) in New Zealand white rabbits using custom-built ophthalmic scanner and noted that there was no microvascular loss compared to the pretreatment levels or contralateral eye with occasional vascular pruning and microvascular loss. In a study conducted later, Daniels *et al.*^[49] compared the retinal toxicity of IAC and intravenous chemotherapy in New Zealand white rabbits and noted that there was no microvascular loss on OCTA imaging in either group. Bogan *et al.*^[50] compared the safety and efficacy of intravitreal melphalan hydrochloride and propylene glycol-free melphalan using a custom-built, 780-nm spectral-domain engine and noted similar loss of retinal microvasculature in both groups, with much severe pruning seen on the side nearer to the injection site.

Kaczmarek *et al.*^[55] utilized OCTA to assess the retinal toxicity of intravitreal belinostat and noted that in contrast to vascular pruning noted in the melphalan group, all belinostat-treated eyes showed normal and full retinal microvasculature.

Riazi-Esfahani *et al.*^[56] compared the microvascular toxicity of IAC versus systemic chemotherapy using OCTA and noted that superficial capillary density was markedly reduced in the IAC group compared to the systemic chemotherapy and control group, while deep capillary density and CC density decreased in both intervention groups compared to controls.

Ashkenazy *et al.*^[57] demonstrated the role of OCTA in detecting atypical tumor recurrence in a case of 4-month-old boy who underwent IAC and local therapy by showing vascularity in the roof of the cystic lesion.

Tumors of RPE

Congenital hypertrophy of retinal pigment epithelium

CHRPE is a benign, pigmented, flat lesion arising from RPE.^[58] Various retinal vascular anomalies associated with CHRPE have been described. Conventional imaging tools like FFA and ICGA fail to image the choroidal vasculature in CHRPE due to masking by the hypertrophied RPE.^[59,60] This can be overcome by imaging with OCTA, in which the retinal and choroidal vasculature of CHRPE can be visualized. The description of OCTA characteristics of CHRPE is limited to three case reports which studied four eyes.

OCTA characteristics

Shanmugam *et al.*^[61] noted that the retinal vasculature over the solitary CHRPE was normal. Masking artifacts due to hyperpigmented RPE resulted in signal void areas at the level of CC layer. In the region underlying the lacunae, flow signals could be noted due to unmasking. Raval *et al.*^[62] noted vascular attenuation over solitary CHRPE and normal retinal and choroidal vasculature over grouped CHRPE. Elahi *et al.*^[63] described four zones in a case of peripapillary CHRPE based on OCT. Zone 1 corresponds to lacunae and is characterized by complete RPE and outer retinal atrophy. Zone 2 corresponds

to hyperpigmented areas and is characterized by incomplete RPE and outer retinal atrophy. Zone 3 corresponds to the halo surrounding the lesion and is characterized by outer retinal atrophy. Zone 4 corresponds to normal retina adjacent to the lesion. On OCTA, increase in flow deficit area was noted in zones 2 and 3. In Zone 4, the CC is normal.

Congenital simple hamartoma of retinal pigment epithelium (CSHRPE) is a focal, pigmented, nodular, benign tumor. The description of OCTA characteristics of CSHRPE is limited to three articles.^[64-66]

OCTA characteristics

Zola *et al.*^[65] reported the presence of intrinsic vascularity at the level of SCP. In the superficial scans, the retinal vessels were noted to be oriented radial to the tumor and were continuous with the intrinsic vasculature. Arjmand *et al.*^[66] reported haphazard intrinsic vascular network, and the full thickness of tumor was occupied by vessels of 100–200 µm caliber. The vascular details were appreciated well on OCTA compared to fluorescein angiography.

Combined hamartoma of the retina and retinal pigment epithelium

CHRRPE was first described by Gass^[67] in 1973. It is a rare benign hamartoma composed of glial cells, vascular tissue, and pigment epithelial cells. It is usually unilateral and results in retinal dragging and disorganization of retinal architecture.^[68] The introduction of OCTA in clinical practice has significantly improved the detailed understanding of the micro-architectural changes in CHRRPE. Due to the rarity of this tumor, the existing knowledge regarding the OCTA findings and clinical application is still in its infancy. The largest multicenter series published till date includes data from 20 patients.

OCTA characteristics

The OCTA features of CHRRPE include increased tortuosity of superficial retinal vasculature, rarefaction of vascular density in

SCP, DCP, and CC, along with loss of foveal avascular zone.^[69] An associated CNV can be identified.^[70-73]

Gupta *et al.*^[74] described the filigree vascular pattern of flow on OCTA, based on previously published histopathologic data. Based on the average number of flow signals in DCP in volume scans, they graded the flow signal as high (>20), intermediate (10–20), and low (<10). They observed high density of filigree vascular pattern in the lesions with peripapillary location, minimal pre-retinal fibrosis, and full-thickness retinal disorganization. They hypothesized that the presence of these hyperflow signals in CHRRPE instead of well-defined vascular patterns is attributable to the lack of structural organization within the dysplastic tissue. Scupola *et al.*^[75] noted increase in vascular caliber, tortuosity, vessel stretching within the tumor [Fig. 7].

Clinical utility

OCTA might have a role in the follow-up of patients undergoing surgery for CHRRPE. Arrigo *et al.*^[70] observed a near-complete recovery of the architectural distortion and restoration of vascular density on OCTA in a patient who underwent surgery for CHRRPE at 1-year follow-up.

CNV associated with CHRRPE was picked up on an OCTA in a series of three patients, while two of them showed leakage from CNV on FFA. The third patient had no leakage on FFA, but a hot spot corresponding to the lesion was observed on ICGA.^[72]

OCTA also helps to differentiate CHRRPE from other clinically similar tumors like choroidal nevus and small choroidal melanoma, where the superficial retinal architecture is relatively preserved with the presence of signal void areas only at the level of CC.^[76]

Limitations of OCTA

Peripheral tumors cannot be imaged well on OCTA due to smaller field of view.^[7] Poor fixation result in motion artifacts and poor image quality. Automated segmentation may be

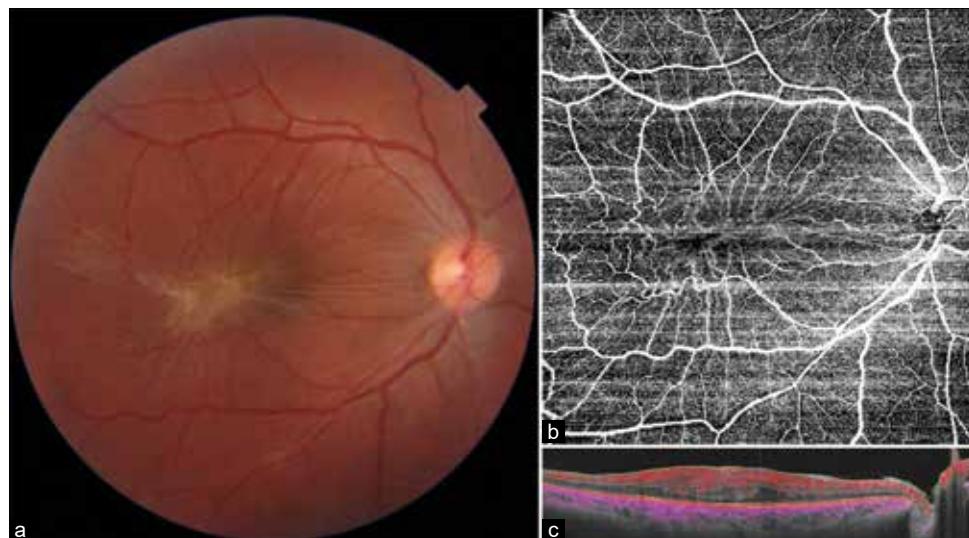


Figure 7: (a) Color fundus photograph showing CHRRPE. (b) En face OCTA showing increased tortuosity of superficial retinal vasculature. (c) Cross-sectional OCTA showing flow signal within the inner retina. CHRRPE = Combined hamartoma of retina and retinal pigment epithelium, OCTA = optical coherence tomography angiography

improper in tumors, and manual segmentation may reduce segmentation artifacts. If the flow velocity in the tissue scanned is beyond the range of detectable flow velocity, it may appear as a signal void area, even if it is vascular.^[77]

Conclusion

As OCTA is a relatively newer imaging modality, our understanding of OCTA characteristics of intraocular tumors is still in infancy. OCTA has a role in understanding the tumor vascularity. OCTA helps in identification of subtle tumors such as small RCH and small retinoblastoma, which can be missed on clinical examination. OCTA helps in differentiating retinal tumors from non-neoplastic "mimicker" lesions: JRCH from papilledema or peripapillary CNV. OCTA helps in differentiating similar appearing retinal tumors: ARA versus PSCRAP. OCTA has a role in identification of secondary complications such as CNV: CHRRPE. OCTA plays an important role in assessment of response to therapy and need for retreatment: RCH, retinoblastoma. However, our knowledge about the role of OCTA in retina tumors is limited to case reports and small case series. Multicentric studies with larger sample size would be required to validate these findings.

Advances in the field of OCTA have enabled us to capture widefield OCTA up to 130°. Availability of widefield OCTA would help in imaging the peripheral tumors.

Motion and blink artifacts compromise the image quality and limit the utility of OCTA. Development of standardized protocols for patient fixation during OCTA imaging sessions would minimize motion artifacts. Though eye tracking technology is incorporated in OCTA platforms, the development of image stabilization algorithms to compensate for involuntary eye movements would further improve the image quality.

Segmentation error is common in larger tumors and to overcome this, manual segmentation becomes necessary, which is usually cumbersome. Artificial intelligence and deep learning integration with imaging software have the potential to refine automated segmentation algorithms specifically tailored to the characteristics of intraocular tumors.

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Gene therapy for retinal diseases: From genetics to treatment

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The gene therapy approach for retinal disorders has been considered largely over the last decade owing to the favorable outcomes of the US Food and Drug Administration-approved commercial gene therapy, Luxturna. Technological advances in recent years, such as next-generation sequencing, research in molecular pathogenesis of retinal disorders, and precise correlations with their clinical phenotypes, have contributed to the progress of gene therapies for various diseases worldwide, and more recently in India as well. Thus, considerable research is being conducted for the right choice of vectors, transgene engineering, and accessible and cost-effective large-scale vector production. Many retinal disease-specific clinical trials are presently being conducted, thereby necessitating the collation of such information as a ready reference for the scientific and clinical community. In this article, we present an overview of existing gene therapy research, which is derived from an extensive search across PubMed, Google Scholar, and clinicaltrials.gov sources. This contributes to prime the understanding of basic aspects of this cutting-edge technology and information regarding current clinical trials across many different conditions. This information will provide a comprehensive evaluation of therapies in existing use/research for personalized treatment approaches in retinal disorders.

Key words: Clinical trials, inherited retinal disorders, retinal gene therapy, viral vectors

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The retina is an intricate structure that converts light into electrical signals that enable the perception of vision. Several genes playing roles in mechanisms such as retinal architecture, development, function, maintenance, and survival are implicated in retinal disorders.^[1] Various retinal diseases and their subtypes [Fig. 1] compromise vision, often leading to partial or complete blindness.^[2] Recent developments in personalized health care are being discussed as new avenues for a patient-prioritized treatment strategy. Gene therapy (GT) is used to treat genetic disorders of high severity and less prevalence.^[3] It aims to treat genetic disorders by modifying faulty genes or replacing them with a healthy gene to mitigate pathologic effects with long-lasting, persistent benefits and does not require repeated interventions.^[4] It can treat a broad range of genetic and acquired diseases,^[5] including certain types of inherited retinal disorders (IRDs),^[6] as well as age-related degenerative diseases.^[7] Our review collates the status of the emerging trials in retinal GT.

Method of Literature Review

We conducted an extensive literature search for this article using PubMed, Google Scholar, and <https://clinicaltrials.gov>. We utilized keywords such as "retina," "gene therapy," "non-viral vectors," "viral vectors," and "retinal disorders" for finding relevant review articles, original research, book chapters, and web reports. We also considered references within these sources

and did not restrict the search by publication year. Fig. 2 depicts the increasing trajectory of clinical trials dedicated to retinal gene therapy throughout the years.

IRDs encompass rare genetic conditions that primarily affect the neurosensory retina, retinal pigment epithelium (RPE), and sometimes the choroid. Gene mutations affecting the retinal structure, function, and/or maintenance cause these conditions.^[8] Mutations may be inherited via autosomal dominant or autosomal recessive or X-linked or mitochondrial mode.^[9] These conditions can be stationary or progressive, and the latter are typically characterized by progressive retinal degeneration, leading to vision impairment or social blindness.^[10] These are further classified into non-syndromic IRDs having exclusive ocular presentation and syndromic IRDs with ocular and extraocular manifestations. Non-inherited retinal disorders (NIRDS) include age-related macular degeneration (AMD), diabetic retinopathy (DR), etc. The following sections report and describe IRDs that have been considered for GT as per <https://clinicaltrials.gov>.

Non-syndromic IRDs

Retinitis pigmentosa

Retinitis pigmentosa (RP) causes photoreceptor (PR) degeneration starting in the mid-peripheral retina. It typically starts with night/dark vision problems with progressive narrowing of the field of vision. Common genes implicated are CERKL, EYS, and PROM1. GT trials for RP often target

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specific gene mutations that cause the disease. Promising clinical trials involving the *RPE65* gene have shown improvements in patient vision. Thirty-three US Food and Drug Administration (FDA)-approved trials have been listed [Table S1], and multiple ongoing trials aim to expand the purview of gene therapies for RP.^[11]

Leber congenital amaurosis

Leber congenital amaurosis (LCA) is a severe IRD that affects infants and young children, resulting in blindness from birth. *CEP290*, *RPE65*, and *GUCY2D* gene mutations, among others, cause LCA.^[12] Ground-breaking GT trials have demonstrated remarkable success in treating some LCA subtypes.^[13] Among these Luxturna (Spark Therapeutics, Philadelphia, PA, United States) is an FDA-approved GT that targets the *RPE65* gene and has shown considerable improvement offering hope for those affected by this debilitating condition.^[12] Despite its excellent potential, Luxturna faces significant hurdles including its exorbitant price tag, approximately US\$ 850,000 per eye, which raises concerns about affordability and accessibility.^[6] Twenty-one approved LCA clinical trials are listed at <https://clinicaltrials.gov> [Table S1].

Stargardt disease

Stargardt disease (STGD) is an IRD that mostly affects children and young adults. It leads to central vision loss caused by PR degeneration starting at the macula. The most commonly implicated genes are *ABCA4* followed by *PROM1* and *ELOVL4*.^[14] Only one GT trial reported for STGD (<https://clinicaltrials.gov>) [Table S1] aims to halt or reverse this degeneration. Several ongoing strategies investigate different gene editing techniques and vectors for the delivery of therapeutic genes.^[15]

Achromatopsia

Achromatopsia (ACHM) is an IRD characterized by stationary cone dysfunction with severe loss of color vision. Common genes implicated are *CNGB3*, *CNGA3*, *GNAT2*, *PDE6C*, and *PDE6H*.^[16] Six GT trials for ACHM have been listed so far [Table S1].

Gyrate atrophy

Gyrate atrophy (GA) is an autosomal recessive condition wherein

increase in ornithine levels in the plasma due to ornithine aminotransferase enzyme deficiency is caused by mutations in its gene (*OAT*).^[17] GA occurs within the first two decades of life and involves chorioretinal atrophic patches starting from the mid-peripheral retina, spreading to the central retina, and presenting with nyctalopia, visual field constriction, and central vision diminution due to macular edema in most cases. The earliest clinical trial for GT for any retinal dystrophy was a phase-1 safety and efficacy study on *ex-vivo* transfer of keratinocytes to treat gyrate atrophy, listed in 1998 [Table S1]. This approach involved taking a skin biopsy, gene transfer into the biopsy, and these cells with increased OAT protein are grafted back.

Bietti's crystalline dystrophy

Bietti's crystalline dystrophy (BCD) is an autosomal recessive IRD causing predominant retinal, sometimes corneal, degeneration, with classic crystalline deposits and sometimes sclerosis of choroidal vessels. The genetic cause for this disorder is mutations in *CYP4V2* gene, This gene gives instructions to make the steroid and fatty acid metabolism-associated family of enzymes cytochrome P450.^[18] Four GT clinical trials are listed for BCD [Table S1].

Choroideremia

Choroideremia (CHM) is an X-linked rare IRD characterized by progressive chorioretinal degeneration causing symptoms like nyctalopia and loss of peripheral vision, with preservation of central vision up to late adulthood.^[19] The gene *CHM* that codes Rab Escort Protein-1 (REP-1) causes CHM. Nine GT clinical trials have been listed for CHM.^[20] Adeno-associated virus (AAV)-mediated GT for CHM is a feasible venture due to the gene's small size (~1.9 kb) and macular region preservation in the advanced disease stages.

Leber hereditary optic neuropathy

Leber hereditary optic neuropathy (LHON) is a rare mitochondrially inherited ganglion cell and optic nerve disorder. It is caused by NADH dehydrogenase *MT-ND1*, *MT-ND4*, and *MT-ND6* gene mutations. These genes play a major role in mitochondrial respiratory chain. The disorder

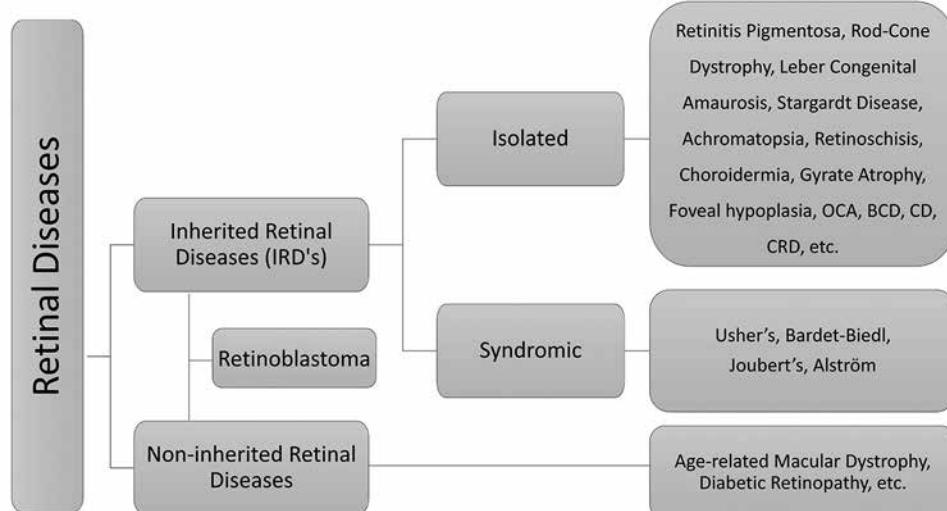


Figure 1: Categories of retinal diseases with examples. BCD = Bietti's crystalline dystrophy, CD = cone dystrophy, CRD = cone–rod dystrophy, OCA = oculocutaneous albinism

primarily affects the retinal ganglion cells (RGCs) that are selectively vulnerable to mitochondrial dysfunction.^[21] Two MT-ND4 clinical trials are listed so far [Table S1].

Juvenile X-linked retinoschisis

Juvenile X-linked retinoschisis is typically an X-linked IRD affecting male children. In this condition, retinoschisin 1 (*RS1*) gene mutation causes unusual splitting of retinal layers, predominantly in the macula and sometimes in the peripheral retina.^[22] *RS1* provides lateral adhesion of cells. Three clinical trials are listed for retinoschisis so far.^[22]

Syndromic IRDs

Usher syndrome

Usher syndrome (US) is characterized by auditory loss and retinal degeneration. It has several subtypes based on the genes involved and clinical presentation. Common genes implicated are *USH2A* and *MYO7A*. Clinical trials of GT explore strategies to restore both hearing and vision in affected individuals. Six GT trials are listed [Table S1]. These trials often involve simultaneous targeting of associated genes.^[23]

Bardet-Biedl syndrome

Bardet-Biedl syndrome, an autosomal recessively inherited IRD impacting multiple body systems, including the genitalia, brain, kidneys, and eye, is caused by mutations in genes involved in primary cilia function. Frequently implicated genes are *BBS1*, *BBS10*, and *BBS2*. The common feature in patients is a severe rod-cone dystrophy phenotype. Other associated systemic features include cognitive impairment, renal abnormalities, hypogonadism/genitourinary anomalies, truncal obesity, postaxial polydactyly, etc.^[24] AXV101, the lead program developed by Axovia Therapeutics, is an AAV (AAV9)-based GT specifically targeting *BBS1* gene mutation-carrying patients.^[25]

Non-inherited retinal disorders

The following sections report and describe multifactorial retinal disorders that have been considered for GT as per <https://clinicaltrials.gov>.

Age-related macular degeneration

AMD causes vision loss in older adults. While treatment for wet AMD involves anti-vascular endothelial growth factor (anti-VEGF) drugs, dry AMD currently has no cure. GT clinical trials for AMD explore approaches to slow disease progression.^[26] Twenty wet AMD and four dry AMD clinical trials listed [Table S1] involve therapeutic gene delivery to retinal cells.^[27] ADVM-022 is a GT trial that utilizes AAV2.7m8 equipped with a potent, widespread expression system containing a codon-optimized cDNA of the afibbercept protein. This offers the promise of addressing neovascularization, which occurs before vision impairment in individuals with wet AMD, making it a potential consideration for therapy.^[28] Reid *et al.*^[29] described a wet AMD GT approach involving recombinant AAV-based anti-VEGF treatment. This therapy aims to prevent choroidal neovascularization by inducing Eylea (afibbercept) overexpression. In another study, a breakthrough approach involved delivering an optimized NADH-ubiquinone oxidoreductase (*ND1*) gene using AAV vector. This GT was orchestrated by a specific promoter *VMD2*, which is specific to the RPE cells. The results significantly

enhanced mitochondrial function, with notable functional improvements *in vivo*. This stands as the first example of GT directly targeting mitochondrial function.^[30]

Diabetic retinopathy

Diabetic retinopathy is a chronic and progressive condition characterized by the onset of microvascular alterations within retinal tissues, primarily induced by prolonged hyperglycemia.^[31] In its advanced stages, DR can lead to severe impairment of vision or blindness. Early detection through regular ophthalmic examinations is imperative as timely interventions involving laser photocoagulation, intravitreal anti-VEGF therapy, or surgical procedures can effectively curtail disease progression.^[32]

Diabetic macular edema (DME) is a pathologic condition stemming from diabetes-induced vascular damage.^[33] Timely identification and intervention via therapies such as laser photocoagulation, anti-VEGF agent intravitreal injections, or surgical procedures are imperative to mitigate progressive vision impairment. Currently, eight clinical trials are listed for DR and 13 trials are reported for DME [Table S1].

Retinoblastoma

Retinoblastoma is considered the most frequent childhood ocular malignancy. It is caused by *RB1* gene mutations, causing inactivation of both its alleles, leading to an RB that is defective, further causing uncontrolled cell proliferation and impairment of the cell cycle.^[34] An oncolytic adenovirus, VCN-01, was designed to selectively replicate in tumor cells. This is suggestive of a tumor-specific, chemotherapy-independent treatment.^[35] A reported RB clinical trial began in 2017 and was completed in 2022.

Gene Transfer Modalities in Use for Retinal Diseases

Retinal GT is delivered in multiple ways using various vehicles as discussed below and illustrated in Fig. 3.^[36,37] It must be noted that the genetic element of the treatment itself has three categories: gene augmentation, gene editing, and gene silencing.^[38] The most common modality is gene augmentation, which is used for autosomal recessive conditions, X-linked conditions, and polygenic/multifactorial diseases. Here, the normal gene copy produces a protein that makes up for the functional loss. Gene editing and silencing are suitable for dominant conditions or gene mutations, where supplying a normal gene copy would not be useful since the dominant mutant protein's effect needs to be nullified. Gene editing (including base and prime editing) is done by Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas enzyme systems, which target a specific site on the DNA to make modifications/corrections/deletions, thereby removing the disease cause. Gene silencing and exon skipping methods can alter the expression status of mutant alleles or dominant causative molecular pathways to bring about the therapeutic effect. To deliver the genetic element, an effective vector is required. Finally, selecting the appropriate route of delivery of a GT vector and patient selection are the critical components of therapeutic success. These include subretinal, intravitreal, and suprachoroidal routes [Fig. 3]. Of these, the subretinal delivery route has been the choice for most of the IRD treatments.

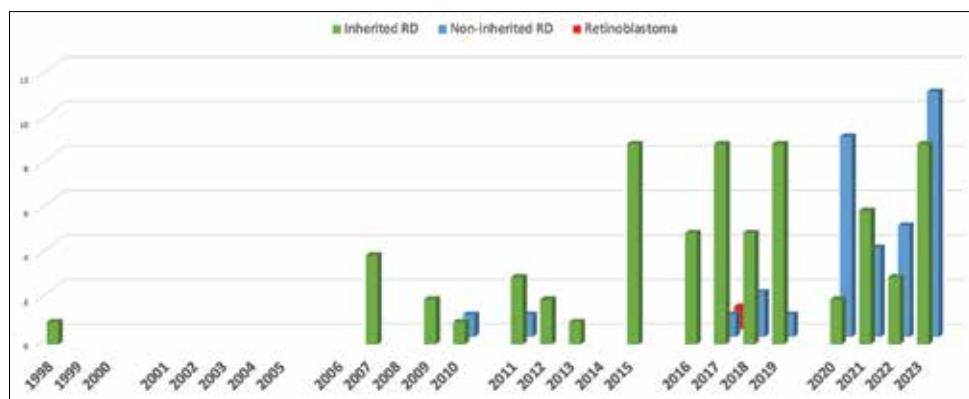


Figure 2: Bar graph representing increase in clinical trial numbers in retinal gene therapy over the years as listed in clinicaltrials.gov until September 2023

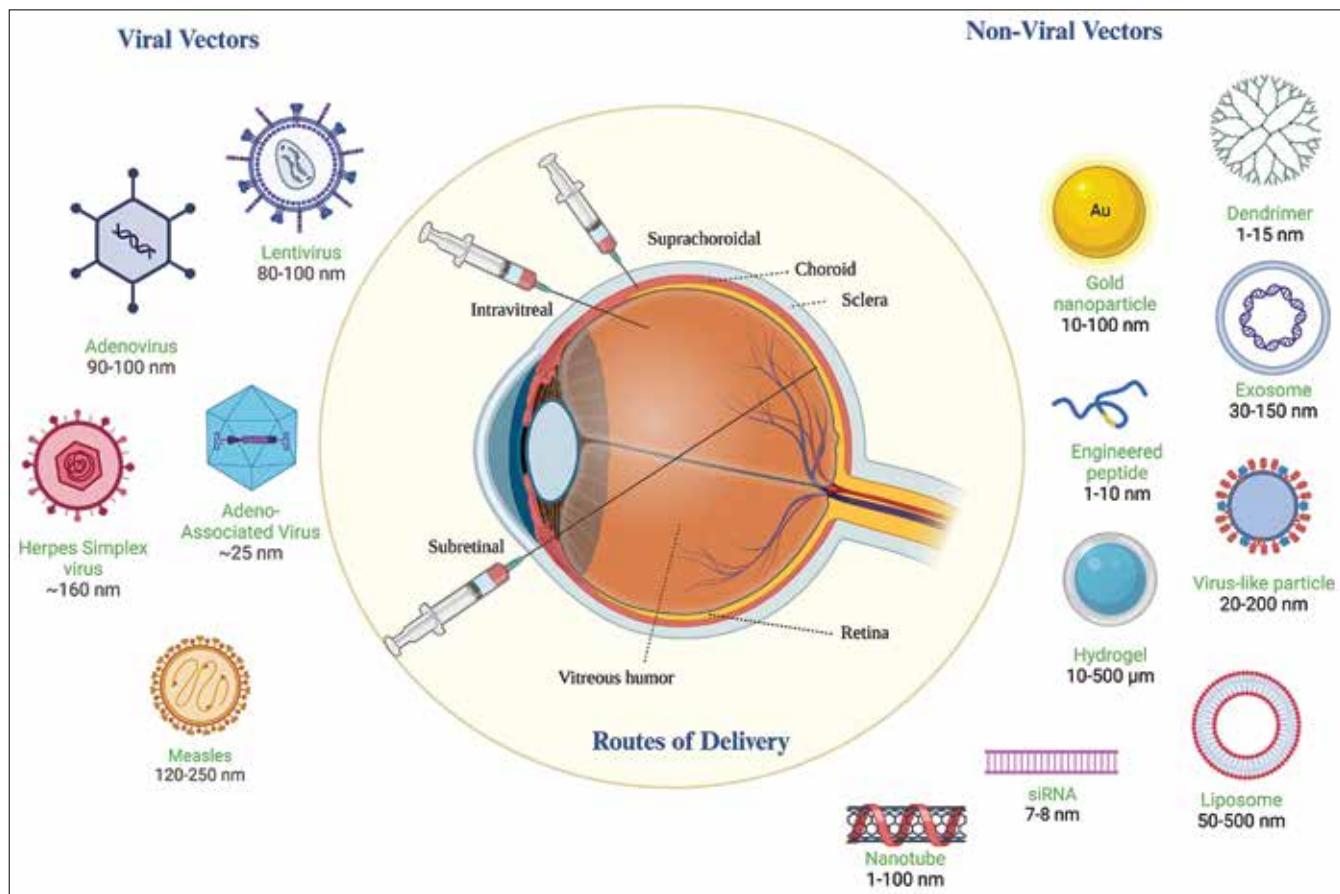


Figure 3: Classification of gene therapy vectors and different delivery routes; illustration created by Biorender.com

A suitable vector serves as a carrier to transport the genetic material safely and effectively without side effects.^[39,40] The vector must also be nontoxic and should enable long-term gene expression in target tissues/cells. In the following sections, we describe different categories of vectors [Tables 1 and 2] currently used for therapeutic gene delivery:

1. Viral vectors
2. Nonviral vectors.

Viral vectors

a. Adenovirus vectors:

Adenovirus vectors are promising tools in GT, offering unique advantages and challenges.^[41] These nonenveloped, double-stranded DNA viruses with good transduction ability accommodate large DNA payloads (~40 kb) and can be administered in retinal cells.^[42] In a study, recombinant adenovirus (rAd) carrying the *MERTK* gene to treat RPE defects showed increased PR count in the regions injected and enhanced PR function lasting for 1 month posttreatment. Adenoviruses can effectively infect dividing and nondividing cells, which is a crucial feature in the postmitotic retina. Another study showed that adenovirus

vectors (Ad-*ABCA1*) were utilized for developing a targeted approach to treat glaucoma. Full-length human *ABCA1* gene was delivered, following which the upregulation of *ABCA1* resulted in a notable decline in the nuclear translocation of *ANXA1* experimentally *in vivo* and *in vitro*. This reduction in *ANXA1* nuclear localization was concomitant with a significant amelioration of retinal degeneration and RGCs' preservation following ischemia–reperfusion injury.^[43]

b. Retrovirus vectors:

These are the first viral vectors listed for *in vivo* GT. These RNA-carrying vectors perform reverse transcription of their genetic material to form double-stranded DNA, leading to host genome integration,^[44] ensuring that the therapeutic gene becomes constitutive of the target cell's genome.^[45] In addition, retrovirus vectors show promise in targeting specific cells, such as PR or RPE cells, which is critical for addressing various retinal diseases. However, the integration process that makes retroviruses attractive for long-term expression also poses potential risks. Random integration could cause insertional mutagenesis, where insertion of the therapeutic gene disrupts the function of existing genes, potentially causing adverse effects.^[46]

c. Lentivirus vectors:

Lentiviruses belong to the retrovirus group and are commonly applied for long-term GT. Lentivirus vectors are used in retinal GT because they target specific retinal cell types.^[44] With advancements in vector design, these can be tailored to deliver genes to specific retinal cells^[47] and achieve stable and long-term gene expression. A lentivirus enables the integration of the therapeutic gene into the host genome. This feature is useful for inherited diseases that require lifelong gene expression, such as RP. They can also deliver large and complex genetic payloads, which is significant for retinal GT as many retinal genetic disorders involve multiple genes or require the delivery of large therapeutic constructs.^[47]

d. AAV vectors:

These are nonpathogenic viruses providing stable, long-term gene expression without integration into the host genome.^[40] They are often used in clinical trials owing to their safety and efficacy. AAVs are a versatile and highly effective tool in GT.^[48] These are ~25-nm, nonenveloped viruses of the parvovirus family and have garnered significant attention for their safety, efficiency, and targeted gene delivery capabilities. Phylogenetic analysis has classified AAV into 12 serotypes with >108 isolates known as serovars.^[49,50] Serotypes 1, 3, 4, 7, 8, 10, and 11 were initially found in non-human primates, while serotypes 2, 5, 6, and 9 originated in humans. This classification aids in understanding the evolutionary relationships and is significant for applications like GT.^[50] AAV capsids can also be engineered to selectively transduce specific cell types^[51] such as PR or RPE cells.^[52] This precision-focused strategy minimizes off-target effects, reduces immunogenic responses, and maximizes therapeutic efficacy.^[53] However, some challenges are associated with AAV vectors in retinal GT. One of them is their limited packaging capacity (~4.7 kb) restricting the deliverable genetic payload size,^[54] which may be a limitation in treating disorders caused by large genes or requiring complex genetic constructs.^[55] Dual AAV or split gene vectors such as hybrid dual AAVs are well suited for delivering large therapeutic genes,^[49] including

genome-editing tools like CRISPR-Cas9.^[56] Although toxic immune responses to AAVs are rare, cross-reactive resistance in individuals reduces the efficacy of these vectors.

Nonviral vectors

These are synthetic carriers of therapeutic nucleic acids into host cells. These vectors are designed to efficiently deliver genes, minimizing immunogenicity and viral vector-associated safety concerns.^[57] They encompass lipids, polymeric nanoparticles (NPs) like poly (lactic) acid, and poly (lactide-co-glycolide) (PLGA) NPs gene transfer.^[58] Similarly, in ARPE-19 cells, PLGA NPs improved the intracellular delivery of a VEGF antisense oligonucleotide, leading to a reduction in both VEGF secretion and mRNA expression.^[59] Physical methods like electroporation, etc., are all aimed at improving controlled gene transfer for therapeutic purposes.^[60]

Plasmid DNA: Circular DNA (plasmids) with the therapeutic transgene can directly be introduced into target cells through physical or chemical methods. In a previous paper, pure plasmid DNA (pDNA:pCMV-lacZ) expression was better than adenovirus (avMena-lacZ) and retrovirus (rvMoMULV-lacZ) injections in mature tibialis anterior muscles of mice, while the differences (>10%) were not significant in regenerative muscle.^[61] Likewise, few more studies suggest the use of pDNA as a vector system for GT.^[62]

RNA-based gene modulation

The types of gene modulation therapies explored based on RNA are single-stranded antisense oligonucleotides (AONs), double-stranded small interfering RNAs, mRNAs and aptamers.^[63] AONs are therapeutic approaches for treatment of certain IRD subtypes. An advantage is that they act at the RNA level and do not alter the genome.^[64] NCT05176717 is a clinical trial listed as an RNA-based therapy, QR-421 for treating Usher's Syndrome has been considered a promising option for the future of clinical development.

Gene Editing Vectors

- CRISPR-Cas9 Vectors:** CRISPR and CRISPR-associated proteins (Cas) are used to perform precise gene editing by introducing, modifying, or deleting specific genomic sequences.^[65] Studies show the achievement of efficient gene modification by delivering a CRISPR/SpCas9 construct in the retina through AAV7m8-mediated delivery.^[66] CRISPR-Cas9 technology was used to rescue endoplasmic reticulum stress associated with mutant myocilin gene (*MYOC*), causing decreased intraocular pressure and prevention of glaucomatous damage in mice and *in vitro* trabecular meshwork cell and skin fibroblast models.^[67]
- Zinc finger nuclease (ZFN) vectors:** ZFNs are engineered proteins that are applied to specifically target and edit DNA sequences.^[68] In a previous study, designed ZFNs could drive site-specific incorporation of long stretches of DNA into a predetermined genomic locus. Segments of DNA between 12 base pairs and ~8 kilo bases of length were shown to integrate with high frequency.^[69]
- Transcription activator-like effector nuclease (TALEN) vectors:** TALENs are custom-designed proteins that can be applied in targeted gene editing. They feature a central

Table 1: Viral vectors used in retinal gene therapy clinical trials

Viral vectors	Target disease	Gene	Ongoing clinical trials
Adenovirus	Retinoblastoma	<i>RB1</i>	NCT03284268 ^[104]
Lentivirus	Diseases of the retina, choroidal neovascularization (nAMD, DME, RVO-ME)	Cas9 mRNA and expression cassettes for a guide RNA targeting VEGF-A	NCT05099094 ^[35,105]
AAV	wAMD, nAMD, DMR/DR, RP, X-linked retinoschisis, non-syndromic retinitis pigmentosa, X-linked retinitis pigmentosa	Anti-VEGF, afibercept, <i>RS1, PDE6B, RPGR</i>	NCT05984927, NCT05536973, NCT05930561, NCT05748873, NCT05657301, NCT06066008, NCT05672121, NCT05197270, NCT03326336, NCT03328130, NCT03316560 ^[28,106,107]
Retrovirus	GA	<i>OAT</i>	NCT00001735 ^[108,109]
Herpes simplex virus	NA	NA	NA
Measles virus	NA	NA	NA
Vaccinia virus	NA	NA	NA

AAV=Adeno-associated virus, DME=Diabetic macular edema, DR=Diabetic retinopathy, GA=Gyrate atrophy, RP=Retinitis pigmentosa, RVO-ME=Retinal vein occlusion – Macular edema, nAMD=Neovascular Age related macular degeneration

Table 2: List of nonviral vectors used in retinal gene therapy

Nonviral vectors	Target disease	Gene	Ongoing clinical trials
Liposomes	NA	NA	
Dendrimer	nAMD, DME	Aflibercept	NCT05387837, NCT05105607
Exosomes	NA	NA	
CRISPR-Cas9 ribonucleoproteins	LCA	<i>CEP290</i>	NCT03872479 ^[110]
Hydrogels	NA	NA	
Nanotubes	NA	NA	

LCA=Leber congenital amaurosis

DNA-binding region with tandem repeats, typically consisting of 34 amino acids. The sequence within these repeats is close to identical, except in the case of variable amino acid residues at 12 and 13 positions. These are called repeat variable di-residues that dictate the sequential specificity of base recognition.^[70]

Exosome-based vectors

These tiny vesicles, naturally secreted by cells, can carry specific genes or therapeutic molecules, allowing targeted delivery to cells or tissues.^[71] In an exosome-based study (Exo-AAV2), the green fluorescent protein (GFP) gene showed deep penetration in the retina, primarily extending into the inner nuclear layer (INL) and the outer plexiform layer, with limited presence in the outer nuclear layer, establishing Exo-AAV2 as a reliable tool in the mouse retina.^[72]

Dendrimers

Dendrimers are highly branched macromolecules that offer precise targeting by attaching ligands to target specific types of retinal cells, reducing off-target effects.^[73] Previous reports suggest systemic delivery of hydroxyl-terminated polyamidoamine dendrimer-triamcinolone acetonide conjugate in rats, with selective uptake by injured microglia/macrophage and RPE.^[74] Both intravitreal and systemic administration effectively target activated retinal microglia, demonstrating excellent biodistribution.^[75] The potential use of dendrimer-based drug formulations for treating retinal diseases associated with microglial activation, such as AMD, DR, and retinal degenerations.^[76] Recently, Ashvattha Therapeutics (Redwood City, CA, USA) has announced

enrollment of the first patient in clinical trial (Phase 1/2). Its release highlights ^{[18]F} OP-801 as an imaging agent based on hydroxyl dendrimers, which have the unique capability of specifically targeting reactive macrophages and microglia.^[75]

Lipid-based vectors

Liposomes have an internal aqueous compartment encapsulated by a phospholipid bilayer membrane, typically ranging from 10 to 100 nm in diameter. These spherical vesicles can deliver therapeutic genes, small molecules, proteins, etc.^[77] Liposomes have been effectively delivered to the rabbit retina and validated in patients experiencing treatment-resistant macular edema.^[78] In a previous study, liposomes of hydrogenated soybean phosphatidylcholine and cholesterol were surface modified by coating with Agm6-M-oleate, a synthetic cell penetration enhancer, and 5% mPEG_{2kDa}-DSPE to cargo dexamethasone hemisuccinate into the posterior eye segment of rat retina.^[78]

Hydrogels

These are biodegradable three-dimensional polymeric particles made by conjugating one or more synthetic and nonsynthetic monomers, having a higher water content due to numerous hydrophilic functional groups, facilitating the entrapment of therapeutic agents.^[79] Injectable or implantable hydrogels can be loaded with GT constructs and put in the subretinal space or vitreous humor to provide sustained release and controlled delivery of therapeutic genetic material.^[80]

Nanotubes

Nanotubes have emerged as promising GT vectors due to

their small size, which enables cellular penetration, and their customizable surface chemistry for targeted transportation of genetic material.^[81] Carbon nanotubes (CNTs) offer unique physical properties that can aid in gene delivery.^[82] Toxicity and action mechanisms of multi-walled CNTs were confirmed in human corneal epithelial cells by assessing differentially expressed genes. Furthermore, Quantitative polymerase chain reaction, colorimetric analysis, enzyme-linked immunosorbent assay, and western blotting were employed to validate the mRNA and protein expression of key genes involved in this process.^[82]

Virus-Like Particles

Virus-like particles (VLPs) are self-assembling structures mimicking viral shape, lacking genetic material, and enhancing safety.^[83] These offer promising prospects in GT as they do not replicate, minimizing the viral vector-associated infection risks, and can be modified for precise cell-type targeting, enhancing treatment accuracy.^[84] In a previous report, co-transfection of a recombinant ABCA4 with a plasmid that expresses murine leukemia virus proteins gag and pol in HEK293T cells, formed virus-like particles (VLPs lacking viral RNA) enriched with the recombinant ABCA4.^[85]

Peptide-Based Vectors

Cell-penetrating peptides facilitate cellular uptake of genetic material. These peptides can be modified to target retinal cells.^[86] In one such research endeavor, Peptide for Ocular Delivery (POD)-GFP fusion protein showed successful expression in epithelial lung and kidney cells, and when injected in the subretinal region, POD-GFP delivery remained localized to the RPE and PR cells.^[87] While vitreous injection targeted ganglion cells, INL, and the lens capsule, ocular surface topical application led to corneal epithelium uptake and even transduction of nonocular tissues like the skin's epidermis.^[88]

Additional delivery systems

Some other innovative techniques employed in gene delivery are electroporation, hydrodynamic delivery, and ultrasound-mediated delivery, each offering distinct advantages.^[89] Electroporation applies electric pulses creating transient pores in cells' membranes, facilitating the entry of genetic material.^[90] Hydrodynamic delivery utilizes controlled large-volume solution injection to achieve efficient gene transfer through mechanical forces.^[91,92] Ultrasound-mediated delivery employs focused ultrasound waves to improve cell membrane permeability, aiding in the uptake of genetic cargo.^[93-95] These methods play a pivotal role in overcoming size constraints associated with traditional gene delivery systems, allowing efficient gene transfer. Importantly, these techniques mitigate potential insertional mutagenesis hazards, a concern linked to some viral vectors, by providing a safer and more controlled means of gene delivery.^[96,97] In addition, they exhibit low immunogenicity, reducing the likelihood of an immune trigger, which is important for successful integration of therapeutic genes into target cells.

Clinical trials in retinal GT

A total of 110 retinal GT trials are listed on clinicaltrials.gov. The earliest GT clinical trial was reported in 1998 for GA. The next trial started in the year 2007. Across 2007–2013, one to

four cases had been listed yearly; from 2015 to 2020, a drastic increase in cases (5–10 cases per year) was observed. The last 3 years have shown a considerable hike in the trial numbers (up to 21). While the trials listed for IRDs are shown across the years, NIRD trials appeared only in 2010 and 2011. The number of NIRD trials increased only after 2017 [Fig. 4].

On examining the pie chart [Fig. 4], it becomes evident that a considerable percentage of trials, amounting to 32%, have reached the completion stage. Approximately 31% of trials are actively recruiting participants, with an additional 6% enrolling participants via invitation. Furthermore, 19% of trials are currently in an active state. For a more granular insight into the trial status according to specific diseases, refer to Fig. 5.

When we categorize trials based on disease types, we observe that the highest number of trials focus on RP, followed by AMD and LCA. This pattern could be owing to high prevalence of RP, the significant disease burden associated with AMD, and the popularity of successful GT treatments for LCA.^[98]

In contrast, diseases like CHM, DME, ACHM, BCD, dry AMD, DME with DR, US with RP, RP with LCA, retinoschisis, DR, and LHON have fewer trials listed.

The diseases with the lowest number of trials include RB, GA, retinal degeneration, US, and STGD. For a comprehensive description of genes associated with these diseases, refer to Fig. 6.

Limitations associated with GT

The approval and success of Luxturna in treating patients with *RPE65* mutation-associated IRD have overlaid the way to develop other GT agents, with an aim to restore vision or halt PR degeneration in retinal diseases.^[99] This progress holds the potential to expedite the production of therapeutics for previously untreatable conditions.^[100] Beneficial effects persisted for up to 4–10 years, with ongoing follow-up extending to 15 years. Control recipients, eligible for Luxturna after 1 year, exhibited improvements during subsequent follow-ups (up to 3 years postinjection), mirroring those who received Luxturna at baseline. The therapeutic impact endured for at least 10 years

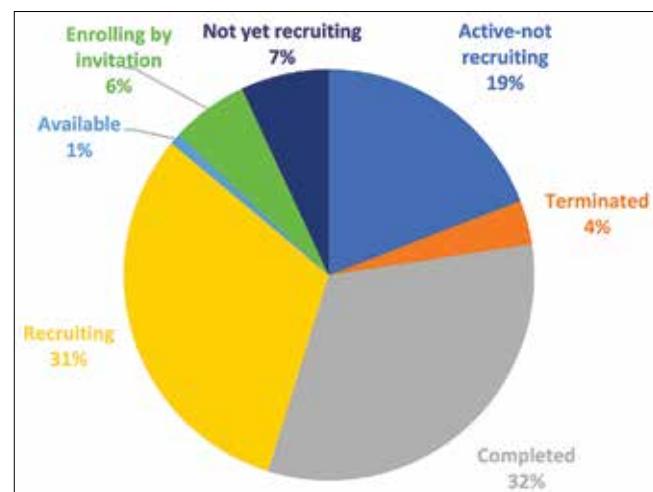


Figure 4: Distribution of the status of retinal gene therapy clinical trials as listed in clinicaltrials.gov until September 2023

in animal models, yet in the crucial Phase III trial, considerable improvements could be observed till 7.5 years.^[101] Despite a safety concern with retinal detachment occurring in a patient in the fourth year, adverse reactions were asymptomatic, transient, and nonserious, resolving without sequelae.

While GT is promising in its potential, it has struggled with wide acceptance and accessibility mainly due to its high costs; Luxturna costs ~US\$ 85,000 for both eyes. The high cost associated with raw materials and manufacturing is an additional bottleneck for GT vector production.^[101] This has led to successful gene therapies being presented for approval only in Western world markets with higher gross domestic product and universal insurance coverage. This excludes developing nations such as India from the therapy being available, since it is not economically feasible for the biotech industry to market such therapies in our country; understandably, therapies worth multiple crores are difficult to afford for the general Indian population. Furthermore, the affected patient pool for any given gene mutated in eye diseases is relatively small; thus, developing a treatment modality, testing it in various models, regulatory processes, and trial costs, all drive the final cost of the therapy high, thereby limiting interest in its continued development. This limitation becomes evident in complexities such as RP, which involves more than 150 different gene mutations (www.sph.uth.edu/RetNet). In addition, in case of complex or multifactorial diseases, translation of GT results from animals to humans is occasionally unsuccessful owing to physiologic distinctions between animal and human eyes. Therefore, a lot of development in terms of cost-effective platform techniques and vector technologies is required to make GT acceptable and accessible to the larger patient population.

GT status in India

Currently, no treatment options are available in India for ocular genetic disorders. The incidence of RP in rural India

was estimated at 1:750, which is a considerably greater ratio than in USA and other countries, primarily attributed to the higher number of consanguineous marriages in several communities.^[102] GT for various diseases is being developed at several institutes around the country, such as Christian Medical College (CMC) and Vellore Institute of Technology (VIT), Vellore, Indian Institute of Technology (IIT), Mumbai, Kanpur, etc., Institute of Genomics and Integrative Biology (IGIB) New Delhi, Narayana Netralaya Foundation (NNF), Bangalore, L V Prasad Eye Institute (LVPEI), Hyderabad. Among these, scientists of the GROW research laboratory at NNF in Bengaluru are currently developing cost-effective, clinical-grade AAV GT vectors. These vectors are being designed to target a broad range of ocular disorders, including keratoconus as outlined in,^[103] LCA, AMD, STGD, and others. To develop indigenous GT platforms that can be cost-effective, it is of value to establish proprietary AAV vectors for which IP rights are held in the country. Such vectors have been indigenously developed at GROW research laboratory to target several genetic diseases, including novel dual AAV vector systems,^[37] representing a novel approach to accommodate larger therapeutic genes within AAV capsids. Furthermore, GROW research laboratory has taken significant steps by establishing a Good Manufacturing Practice (GMP)-grade AAV vector production facility equipped to produce entirely indigenous, high-quality cGMP-grade vectors for both ocular and systemic disorders. This progress in GT is driven not only by cutting-edge scientific developments, but also by the support of various government agencies and regulatory bodies.

Future perspectives: To ensure sustained growth in this field, it is imperative that the government plays a pivotal role by increasing financial support and ensuring stability in funding. Furthermore, involving patients and caregiver groups at specific regulatory

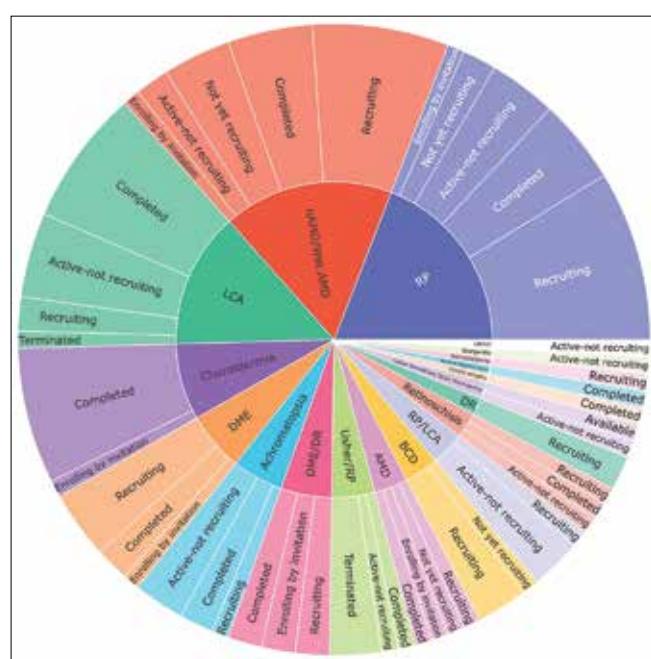
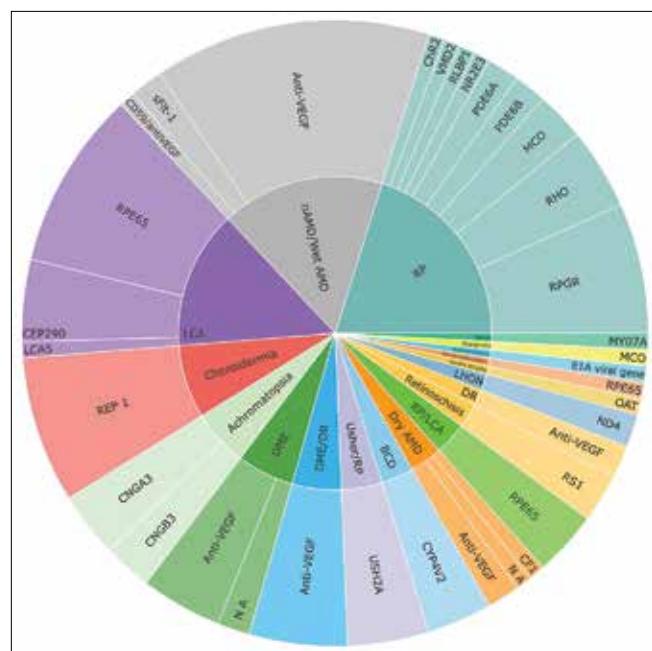


Figure 5: Sunburst chart representation of the disease-wise status of retinal gene therapy clinical trials as listed in clinicaltrials.gov until September 2023



checkpoints is crucial. This engagement can raise awareness about disorders of genetic origin and underscore the significance of early diagnosis. In addition, there is room for improvement in streamlining regulatory processes to promote both scientists and industry players to launch more trials while maintaining scientific rigor. Simultaneously, the Indian GT community must prioritize innovation in GT products, economical raw material production, and comprehensive clinical trial design development. Overall, by fostering greater awareness and collaboration among patient communities, clinicians, scientists, and government-sponsored organizations, we can bridge the information gap and expedite the deployment of GT and cell therapy, ultimately benefiting a multitude of patients with genetic disorders.

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Author's contribution

AK, GPM, and AG drafted the manuscript, and PB, TMB, RS, and AG edited the final manuscript.

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Table S1: Clinical trials categorized based on specific retinal diseases as reported in clinicaltrials.gov

	NCT Number	Study Title	Acronym	Study Status	Conditions	Interventions	Phases	Start Date	Completion Date
1	NCT02065011	A Study to Determine the Long-Term Safety, Tolerability and Biological Activity of SAR421869 in Patients With Usher Syndrome Type 1B	Usher Syndrome	ACTIVE NOT RECRUITING	Usher's Syndrome	DRUG: Blood draw for the laboratory assessment	PHASE1 PHASE2	12-09-2013	13-06-2031
2	NCT05176717	Study to Evaluate the Efficacy Safety and Tolerability of QR-421a in Subjects With RP Due to Mutations in Exon 13 of the USH2A Gene With Early to Moderate Vision Loss (Celeste)	Usher Syndrome and RP	TERMINATED	Retinitis Pigmentosa Usher Syndrome Type 2 Deaf Blind Retinal Disease Eye Diseases Eye Diseases, Hereditary Eye Disorders Congenital Vision Disorders	DRUG: QR-421a OTHER: Sham-procedure	PHASE2 PHASE3	15-12-2021	02-08-2022
3	NCT05085964	An Open-Label Extension Study to Evaluate Safety & Tolerability of QR-421a in Subjects With Retinitis Pigmentosa	HELIJA	TERMINATED	Retinitis Pigmentosa Usher Syndrome Type 2	DRUG: RNA antisense oligonucleotide for intravitreal injection	PHASE2	16-09-2021	18-10-2022
4	NCT03780257	Study to Evaluate Safety and Tolerability of QR-421a in Subjects With RP Due to Mutations in Exon 13 of the USH2A Gene	Stellar	COMPLETED	Retinitis Pigmentosa Usher Syndrome Type 2 Deaf Blind Retinal Disease Eye Diseases Eye Diseases, Hereditary Eye Disorders Congenital Vision Disorders	DRUG: QR-421a OTHER: Sham procedure (dose cohort 1&2 only)	PHASE1 PHASE2	06-03-2019	14-10-2021
5	NCT05158296	Study to Evaluate the Efficacy Safety and Tolerability of Ultrevisen in Subjects With RP Due to Mutations in Exon 13 of the USH2A Gene (Sirius)	RP	ACTIVE NOT RECRUITING	Retinitis Pigmentosa Usher Syndrome Type 2 Deaf Blind Retinal Disease Eye Diseases Eye Diseases, Hereditary Eye Disorders Congenital Vision Disorders	DRUG: Ultrevisen OTHER: Sham-procedure	PHASE2 PHASE3	08-12-2021	2024-12
6	NCT01505062	Study of SAR421869 in Participants With Retinitis Pigmentosa Associated With Usher Syndrome Type 1B	RESTORE	TERMINATED	Usher Syndrome Retinitis Pigmentosa	DRUG: SAR421869	PHASE1 PHASE2	26-03-2012	16-08-2019
1	NCT04945772	Efficacy and Safety of MICO-010 Optogenetic Therapy in Adults With Retinitis Pigmentosa [RESTORE]	RP	ACTIVE NOT RECRUITING	Retinitis Pigmentosa Retinitis Diseases Eye Diseases Eye Diseases, Hereditary Retinal Dystrophies Retinal Degeneration	BIOLOGICAL: Gene Therapy Product-MICO-010 PROCEDURE: Sham injection	PHASE2	13-07-2021	01-03-2024
2	NCT04611503	PDE6A Gene Therapy for Retinitis Pigmentosa	Pigment	ACTIVE NOT RECRUITING	Retinitis Pigmentosa	DRUG: subretinal injection of rAAV:hpPDE6A	PHASE1 PHASE2	24-09-2019	2027-07

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3	NCT05203939	Study to Assess the Safety and Efficacy of OCU400 for Retinitis Pigmentosa and Leber Congenital Amurosis	RECRUITING	Retinitis Pigmentosa Leber Congenital Amurosis	DRUG: OCU400 Low Dose DRUG: OCU400 Med Dose DRUG: OCU400 High Dose	PHASE1 PHASE2	24-01-2022	2024-02
4	NCT05805007	Safety and Tolerability Study of Gene Editing Drug ZVS203e in Participants With Retinitis Pigmentosa	NOT_YET_RECRRUITING	Retinitis Pigmentosa	DRUG: ZVS203e	EARLY_PHASE1	2023-06	2026-04
5	NCT0322847	Gene Therapy for X-linked Retinitis Pigmentosa (XLRP) - Retinitis Pigmentosa GTPase Regulator (RPGR)	COMPLETED	X-Linked Retinitis Pigmentosa	GENETIC: AAvg2/5-RPGR	PHASE1 PHASE2	14-07-2017	18-11-2024
6	NCT02416622	Safety and Efficacy of rAAV-hRS1 in Patients With X-linked Retinoschisis (XRS)	COMPLETED	X-linked Retinoschisis	BIOLOGICAL: rAAV2/2tYF-CB-hRS1	PHASE1 PHASE2	2015-05	09-05-2023
7	NCT03328130	Safety and Efficacy Study in Patients With Retinitis Pigmentosa Due to Mutations in PDE6B Gene	RECRUITING	Retinitis Pigmentosa	BIOLOGICAL: AAvg2/5-hPDE6B	PHASE1 PHASE2	06-11-2017	2029-12
8	NCT04278131	BS01 in Patients With Retinitis Pigmentosa	RECRUITING	Retinitis Pigmentosa	DRUG: BS01	PHASE1 PHASE2	06-02-2020	30-12-2029
9	NCT05921162	A Long-Term Follow-Up Study in Subjects Who Received vMCO-1 Administered Via Intravitreal Injection	EXTEND	ENROLLING_BY_INVITATION	Retinitis Pigmentosa Retinal Disease Retinal Degeneration	BIOLOGICAL: Gene Therapy product:vMCO-1	14-07-2023	2024-12
10	NCT05748873	Promising Rod-cone Dystrophy PRODGY Gene therapy	RECRUITING	Retinitis Pigmentosa	DRUG: SPVN06	PHASE1 PHASE2	12-04-2023	2029-03
11	NCT04312672	Long Term Follow-Up Gene Therapy Study for XLRP RPGR	RECRUITING	X-Linked Retinitis Pigmentosa	BIOLOGICAL: AAvg-RPGR		18-02-2019	2023-06
12	NCT03316560	Safety and Efficacy of rAAV2/2tYF-GRK1-RPGR in Subjects With X-linked Retinitis Pigmentosa Caused by RPGR Mutations	RECRUITING	X-Linked Retinitis Pigmentosa	BIOLOGICAL: rAAV2/2tYF-GRK1-RPGR	PHASE1 PHASE2	16-04-2018	2026-08
13	NCT05874310	Gene Therapy for Subjects With RPGR Mutation-associated X-linked Retinitis Pigmentosa	RECRUITING	X-Linked Retinitis Pigmentosa	GENETIC: FT-002	EARLY_PHASE1	01-02-2023	01-11-2027
14	NCT04919473	Dose-Escalation Study to Evaluate the Safety and Tolerability of Intravitreal vMCO-1 in Patients With Advanced Retinitis Pigmentosa	COMPLETED	Retinitis Pigmentosa Retinal Diseases Retinal Degeneration	BIOLOGICAL: Gene Therapy product:vMCO-1	PHASE1 PHASE2	23-10-2019	31-10-2020
15	NCT04830118	A Clinical Trial Evaluating the Safety and Efficacy of a Single Subretinal Injection of AGTC-501 in Participants With X-linked Retinitis Pigmentosa Caused by RPGR Mutations	NOT_YET_RECRRUITING	X-Linked Retinitis Pigmentosa	BIOLOGICAL: rAAV2/2tYF-GRK1-hRPGRco	PHASE2 PHASE3	2021-08	2029-03

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			PIONEER	RECRUITING	Non-syndromic Retinitis Pigmentosa	COMBINATION_PRODUCT: Gene therapy: GS030-DP AND Medical device: GS030-MD	PHASE1 PHASE2	26-09-2018	2025-12
16	NCT03326336	Dose-escalation Study to Evaluate the Safety and Tolerability of GS030 in Subjects With Retinitis Pigmentosa	XIRIUS	COMPLETED	X-Linked Retinitis Pigmentosa	BIOLOGICAL: BIB112	PHASE1 PHASE2	16-03-2017	18-11-2020
17	NCT03116113	A Clinical Trial of Retinal Gene Therapy for X-linked Retinitis Pigmentosa Using BIB112	RST-001 Phase I/II Trial for Advanced Retinitis Pigmentosa	ACTIVE_NOT_R_ECRUITING	Advanced Retinitis Pigmentosa	DRUG: RST-001	PHASE1 PHASE2	14-12-2015	02-09-2024
18	NCT02556736	Follow-up Gene Therapy Trial for the Treatment of X-linked Retinitis Pigmentosa Associated With Variants in the RPGR Gene	RST-001 Phase I/II Trial for Advanced Retinitis Pigmentosa	RECRUITING	X-Linked Retinitis Pigmentosa	BIOLOGICAL: Genetic: AAV5-RPGR 4e11 BIOLOGICAL: Genetic: AAV5-RPGR 2e11	PHASE3	16-03-2021	2029-05
19	NCT04794101	A First-in-Human, Proof of Concept Study of CPK850 in Patients With RLBP1 Retinitis Pigmentosa	ACTIVE_NOT_R_ECRUITING	Retinitis Pigmentosa	BIOLGICAL: CPP850	PHASE1 PHASE2	22-08-2018	11-05-2026	
20	NCT03374657	Trial of Subretinal Injection of (rAAV2-VMID2-hMERTK)	COMPLETED	Retinal Disease Retinitis Pigmentosa	BIOLOGICAL: Subretinal administration of rAAV2-VMID2-hMERTK recombinant Adeno-Associated Virus	PHASE1	2011-08	2019-08	
21	NCT01482195	A Study of AAV5-hRKp.RPGR for the Treatment of Japanese Participants With X-linked Retinitis Pigmentosa	RECRUITING	X-Linked Retinitis Pigmentosa	GENETIC: AAV5-hRKp.RPGR GENETIC: AAV5-hRKp.RPGR	PHASE3	21-08-2023	10-05-2029	
22	NCT05926583	RP/LCA	RECRUITING	Biallelic RP65 Mutation-associated Retinal Dystrophy	GENETIC: FT-001 Low Dose GENETIC: FT-001 Mid Dose GENETIC: FT-001 High Dose	PHASE2	30-11-2022	30-11-2029	
23	NCT05858983	Gene Therapy in Subjects With Biallelic RP65 Mutation-associated Retinal Dystrophy	ACTIVE_NOT_R_ECRUITING	Inherited Retinal Dystrophy Due to RP65 Mutations	BIOLOGICAL: AAV2-hRP65v2		2015-06	2030-06	
24	NCT03602820	Long-term Follow-up Study in Subjects Who Received Voretigene Neparvovec-rzyl (AAV2-hRP65v2)	ACTIVE_NOT_R_ECRUITING	Biallelic RP65 Mutation-associated Retinal Dystrophy	GENETIC: voretigene neparvovec	PHASE3	24-11-2020	31-05-2026	
25	NCT04516369	Study of Efficacy and Safety of Voretigene Neparvovec in Japanese Patients With Biallelic RP65 Mutation-associated Retinal Dystrophy	ACTIVE_NOT_R_ECRUITING	Confirmed Biallelic RP65 Mutation-associated Retinal Dystrophy	BIOLOGICAL: AAV2-hRP65v2; voretigene neparvovec-rzyl		10-01-2019	2025-06	
26	NCT03597399	A Patient Registry Study for Patients Treated With Voretigene Neparvovec in US	LCA						

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27	NCT03913130	Extension Study to Study PQ-110-001 (NCT03140969)	INSIGHT	TERMINATED	Leber Congenital Amaurosis 10 Blindness Leber Congenital Amaurosis Vision Disorders Sensation Disorders Neurologic Manifestations Eye Diseases Eye Diseases, Hereditary Eye Disorders, Congenital Retinal Disease	DRUG: QR-110	PHASE1 PHASE2	13-05-2019
28	NCT02946879	Long-Term Follow-Up Gene Therapy Study for Leber Congenital Amaurosis OPTIRPE65 (Retinal Dystrophy Associated With Defects in RPE65)		COMPLETED	Leber Congenital Amaurosis (LCA) Eye Diseases Eye Diseases, Hereditary Retinal Diseases	BIOLOGICAL: AAV OPTIRPE65		2016-11
29	NCT03872479	Single Ascending Dose Study in Participants With LCA10		ACTIVE_NOT_ECRUITING	Leber Congenital Amaurosis 10 Inherited Retinal Dystrophies Eye Diseases, Hereditary Retinal Disease Retinal Degeneration Vision Disorders Eye Disorders Congenital	DRUG: EDIT-101	PHASE1 PHASE2	26-09-2019
30	NCT03913143	A Study to Evaluate Efficacy, Safety, Tolerability and Exposure After a Repeat-dose of Sepofarsen (QR-110) in LCA10 (ILLUMINATE)	ILLUMINATE	ACTIVE_NOT_R_ECRUITING	Leber Congenital Amaurosis 10 Blindness Leber Congenital Amaurosis Vision Disorders Sensation Disorders Neurologic Manifestations Eye Diseases Eye Diseases, Hereditary Eye Disorders, Congenital Retinal Disease	DRUG: sepofarsen OTHER: Sham	PHASE2 PHASE3	04-04-2019
31	NCT00643747	Safety Study of RPE65 Gene Therapy to Treat Leber Congenital Amaurosis		COMPLETED	Retinal Degeneration	BIOLOGICAL: tgAAG76 (rAAV 2/2-hRPE65p-hRPE65)	PHASE1 PHASE2	2007-01
32	NCT01208389	Phase 1 Follow-on Study of AAV2-hRPE65v2 Vector in Subjects With Leber Congenital Amaurosis (LCA) 2		ACTIVE_NOT_R_ECRUITING	Leber Congenital Amaurosis	BIOLOGICAL: voretigene nepanavovec-rzyl	PHASE1 PHASE2	2010-11
33	NCT00481546	Phase I Trial of Gene Vector to Patients With Retinal Disease Due to RPE65 Mutations	LCA	ACTIVE_NOT_R_ECRUITING	Amaurosis of Leber Retinal Diseases	GENETIC: rAAV2-CBSB-hRPE65	PHASE1	2007-07
34	NCT05906953	A Safety and Efficacy Study of HG004 in Subjects With Leber Congenital Amaurosis		NOT_YET_RECRUITING	Leber Congenital Amaurosis	DRUG: HG004	PHASE1 PHASE2	2023-09
35	NCT0099609	Safety and Efficacy Study in Subjects With Leber Congenital Amaurosis		ACTIVE_NOT_R_ECRUITING	Inherited Retinal Dystrophy Due to RPE65 Mutations Leber Congenital Amaurosis	BIOLOGICAL: AAV2-hRPE65v2,voretigene nepanavovec-rzyl	PHASE3	2012-10
								2029-07

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			RECRUITING	LCAS	BIOLOGICAL: AAV8-hCas9	PHASE1 PHASE2	15-06-2023	30-09-2027
36	NCT05616793	Safety and Tolerability Subretinal OFGx-001 for LCAS-Associated Inherited Retinal Degeneration (LCAS-IRD)						
37	NCT04855045	An Open-label, Dose Escalation and Double-masked, Randomized, Controlled Trial Evaluating Safety and Tolerability of Sepofarsen in Children (<8 Years of Age) With LCA10 Caused by Mutations in the CEP290 Gene.	BRIGHTEN	RECRUITING	Leber Congenital Amaurosis 10 Blindness Leber Congenital Amaurosis Vision Disorders Sensation Disorders Neurologic Manifestations Eye Diseases Eye Disorders Congenital Retinal Disease Retinal Degeneration Retinal Dystrophies	DRUG: sepofarsen	PHASE2 PHASE3	23-03-2021 2023-12
38	NCT00821340	Clinical Trial of Gene Therapy for Leber Congenital Amaurosis Caused by RPE65 Mutations		COMPLETED	Leber Congenital Amaurosis	GENETIC: rAAV2-hRPE65	PHASE1	01-02-2009 01-01-2017
39	NCT00749957	Phase 1/2 Safety and Efficacy Study of AAV-RPE65 Vector to Treat Leber Congenital Amaurosis		COMPLETED	Leber Congenital Amaurosis	BIOLOGICAL: rAAV2-CB-RPE65	PHASE1 PHASE2	17-06-2009 22-09-2017
40	NCT03140969	Study to Evaluate QR-110 in Leber's Congenital Amaurosis (LCA) Due to the c.2991+1655A>G Mutation (p.Cys98X) in the CEP290 Gene		COMPLETED	Leber's Congenital Amaurosis	DRUG: QR-110	PHASE1 PHASE2	16-10-2017 02-10-2019
41	NCT00516477	Safety Study in Subjects With Leber Congenital Amaurosis		COMPLETED	Leber Congenital Amaurosis	BIOLOGICAL: vorotigene nepanvec-zyl	PHASE1	2007-09 20-03-2018
42	NCT02781480	Clinical Trial of Gene Therapy for the Treatment of Leber Congenital Amaurosis (LCA)		OPTIRPE65	COMPLETED	Leber Congenital Amaurosis	BIOLOGICAL: AAV RPE65	PHASE1 PHASE2 2016-04 2018-12
43	NCT01496040	Clinical Gene Therapy Protocol for the Treatment of Retinal Dystrophy Caused by Defects in RPE65		RPE65	COMPLETED	Leber Congenital Amaurosis	DRUG: rAAV2/4-hRPE65	PHASE1 PHASE2 2011-09 2014-08
nAMD/Wet AMD				NOT_YET_RECruITING	Neovascular Age-related Macular Degeneration	GENETIC: SKG0106	PHASE1 PHASE2	30-10-2023 30-09-2029
44	NCT05986864	Phase I/II Study to Evaluate the Safety, Preliminary Efficacy, Immunogenicity, and Pharmacokinetics of SKG0106 Intracocular Solution in Patients With Neovascular Age-related Macular Degeneration (nAMD)						
45	NCT03555556	AAVCA6GCD59 for the Treatment of Wet AMD		COMPLETED	Wet Age-related Macular Degeneration	DRUG: Intravitreal anti-VEGF BIOLOGICAL: Intravitreal AAVCA6GCD59 DRUG: Oral prednisolone	PHASE1	13-09-2018 18-01-2022

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46	NCT04704921	Pivotal 1 Study of RGX-314 Gene Therapy in Participants With nAMD	ATMOSPHERE	RECRUITING	AMD nAMD Wet Age-related Macular Degeneration wAMD Wet AMD CNV	GENETIC: RGX-314 GENETIC: RGX-314 BIOLOGICAL: Ranibizumab (LUCENTIS®)	PHASE2 PHASE3	29-12-2020	2026-05
47	NCT04645212	Long-term Study of ADV/M-022 in Neovascular (Wet) AMD [OPTIC-EXT]		ACTIVE_NOT_ECRUITING	Wet Age-related Macular Degeneration Neovascular Age-related Macular Degeneration	BIOLOGICAL: ADVM-022		14-12-2020	2025-06
48	NCT05536973	Safety and Efficacy of ADVM-022 in Treatment-Experienced Patients With Neovascular Age-related Macular Degeneration [LUNA]		RECRUITING	Neovascular Age-related Macular Degeneration	GENETIC: ADVM-022 GENETIC: ADVM-022	PHASE2	23-08-2022	2024-02
49	NCT04514653	RGX-314 Gene Therapy Administered in the Suprachoroidal Space for Participants With Neovascular Age-Related Macular Degeneration (nAMD)	AAV/AIE	RECRUITING	Neovascular Age-Related Macular Degeneration (nAMD)	GENETIC: RGX-314 Dose 1 GENETIC: RGX-314 Dose 2 BIOLOGICAL: Ranibizumab GENETIC: RGX-314 Dose 3 DRUG: Local steroid DRUG: Topical steroid	PHASE2	25-08-2020	2024-01
50	NCT05059094	VEGFA-targeting Gene Therapy to Treat Retinal and Choroidal Neovascularization Diseases		RECRUITING	Neovascular Age-related Macular Degeneration Diabetic Macular Edema Retinal Vein Occlusion	GENETIC: BD311	EARLY_PHASE1	25-11-2021	2023-09
51	NCT06031727	CRISPR/Cas13-mediated RNA Targeting Therapy for the Treatment of nAMD Investigator-initiated Trial (SIGHT-I)		NOT_YET_RECRUITING	Neovascular Age-related Macular Degeneration(nAMD)	GENETIC: HG202	EARLY_PHASE1	30-09-2023	27-06-2025
52	NCT01494805	Safety and Efficacy Study of rAAV.SFlt-1 in Patients With Exudative Age-Related Macular Degeneration	AMD	COMPLETED	Macular Degeneration Age-related Maculopathies Age-related Maculopathy Maculopathies,Age-related Maculopathy/Age-related Retinal Degeneration Retinal Neovascularization Eye Diseases	BIOLOGICAL: rAAV.SFlt-1 BIOLOGICAL: rAAV.SFlt-1 OTHER: Control (ranibizumab alone)	PHASE1 PHASE2	2011-12	2017-08
53	NCT05903794	A Study of EXG102-031 in Patients With wAMD (Everest)		RECRUITING	Neovascular (Wet) Age-related Macular Degeneration (nAMD)	BIOLOGICAL: EXG102-031	PHASE1	24-07-2023	31-12-2025
54	NCT05407636	Pivotal 2 Study of RGX-314 Gene Therapy in Participants With nAMD	ASCENT	RECRUITING	AMD nAMD Wet Age-related Macular Degeneration wAMD Wet AMD CNV	GENETIC: RGX-314 Dose 1 GENETIC: RGX-314 Dose 2 BIOLOGICAL: Afibercept (EYLEA®)	PHASE3	28-12-2021	2025-12

55	NCT01024998	Safety and Tolerability Study of AAV2-sFLT01 in Patients With Neovascular Age-Related Macular Degeneration (AMD)		COMPLETED	Macular Degeneration Age-Related Maculopathies Age-Related Maculopathy (Maculopathies, Age-Related Retinal Degeneration Retinal Neovascularization Gene Therapy Gene Eye Diseases	BIOLOGICAL: AAV2-sFLT01 BIOLOGICAL: AAV2-sFLT01 BIOLOGICAL: AAV2-sFLT01 BIOLOGICAL: AAV2-sFLT01	PHASE1	11-01-2010	2018-07
56	NCT05611424	Gene Therapy for Wet AMD		NOT_YET_RECruiting	Neovascular Age-related Macular Degeneration	GENETIC: FT-003	PHASE1	01-05-2023	30-12-2027
57	NCT05197270	4D-150 in Patients With Neovascular (Wet) Age-Related Macular Degeneration		RECRUITING	Neovascular (Wet) Age-Related Macular Degeneration	BIOLOGICAL: 4D-150 IVT BIOLOGICAL: Afiblerecept IVT	PHASE1 PHASE2	09-12-2021	2025-11
58	NCT03999801	Long-term Follow-up Study of RGX-314 and SRLTFU	RGX-314 SRLTFU	ENROLLING_BY_INVITATION	Neovascular Age-related Macular Degeneration Wet Macular Degeneration	GENETIC: RGX-314	PHASE2	31-05-2019	2028-12
59	NCT03748784	ADV/M-022 Intravitreal Gene Therapy for Wet AMD	OPTIC	COMPLETED	Wet Age-related Macular Degeneration Neovascular Age-related Macular Degeneration	BIOLOGICAL: ADV/M-022	PHASE1	14-11-2018	22-06-2022
60	NCT03066258	Safety and Tolerability of RGX-314 (Investigational Product) Gene Therapy for Neovascular AMD Trial		COMPLETED	Neovascular Age-related Macular Degeneration Wet Age-related Macular Degeneration	GENETIC: RGX-314	PHASE1 PHASE2	29-03-2017	17-06-2024
61	NCT05657301	Safety and Tolerability of KH631 Gene Therapy in Participants With Neovascular Age-related Macular Degeneration		RECRUITING	Age-Related Macular Degeneration	DRUG: KH631	PHASE1	2023-08	2027-09
62	NCT04832724	RGX-314 Gene Therapy Pharmacodynamic Study for Neovascular Age-related Macular Degeneration (nAMD)		ACTIVE_NOT_ECRUITING	Neovascular Age-related Macular Degeneration Wet Macular Degeneration Wet Age-related Macular Degeneration	GENETIC: RGX-314	PHASE2	22-02-2021	18-03-2024
63	NCT06022744	An Exploratory Clinical Trial Evaluating LX109 Gene Therapy in Patients With nAMD		NOT_YET_RECruiting	To Evaluate the Safety and Tolerability of Intravitreal Injection of LX109 in Patients With nAMD	DRUG: LX109	NA	01-09-2023	30-09-2027
Choroideremia				COMPLETED	Choroideremia	GENETIC: rAAV2.REP1	PHASE2	2016-01	2018-02
64	NCT02671539	THOR - Tubingen Choroideremia Gene Therapy Trial	THOR	COMPLETED	Choroideremia	GENETIC: rAAV2.REP1	PHASE2	2016-01	2018-02
65	NCT03507686	A Safety Study of Retinal Gene Therapy for Choroideremia With Administration of BIIB111	GEMINI	COMPLETED	Choroideremia	DRUG: BIIB111	PHASE2	29-11-2017	29-06-2022

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66	NCT02341807	Safety and Dose Escalation Study of AAV2-hCHM in Subjects With CHM (Choroideremia) Gene Mutations		COMPLETED	Choroideremia CHM (Choroideremia) Gene Mutations	BIOLOGICAL: AAV2-hCHM	PHASE1 PHASE2	2015-01	12-10-2022
67	NCT03496012	Efficacy and Safety of BIIb111 for the Treatment of Choroideremia	STAR	COMPLETED	Choroideremia	GENETIC: BIIb111	PHASE3	11-12-2017	01-12-2020
68	NCT03584165	Long-term Safety and Efficacy Follow-up of BIIb111 for the Treatment of Choroideremia and BIIb112 for the Treatment of X-Linked Retinitis Pigmentosa	SOLSTICE	ENROLLING_BY_INVITATION	Choroideremia X-Linked Retinitis Pigmentosa	GENETIC: BIIb111 GENETIC: BIIb112	PHASE3	04-06-2018	04-06-2026
69	NCT02077361	An Open Label Clinical Trial of Retinal Gene Therapy for Choroideremia		COMPLETED	Choroideremia	GENETIC: rAAV2-REP1 vector	PHASE1 PHASE2	2015-04	16-05-2022
70	NCT02407678	REP1 Gene Replacement Therapy for Choroideremia	REGENERATE	COMPLETED	Choroideremia	GENETIC: AAV-mediated REP1 gene replacement	PHASE2	16-08-2016	23-07-2021
71	NCT01461213	Gene Therapy for Blindness Caused by Choroideremia		COMPLETED	Choroideremia	DRUG: rAAV2-REP1	PHASE1 PHASE2	2011-10	2017-10
72	NCT02553135	Choroideremia Gene Therapy Clinical Trial		COMPLETED	Choroideremia	BIOLOGICAL: Injection of AAV2-REP1 (10e11 vg)	PHASE2	2015-09	2018-02
Stargardts									
73	NCT05417126	Safety and Effects of a Single Intravitreal Injection of vMCO-010 Ototogenic Therapy in Subjects With Stargardt Disease		STARLIGHT	ACTIVE_NOT_R_ECRUITING	Stargardt Disease	BIOLOGICAL: Gene Therapy-vMCO-010	PHASE2	05-07-2022
Achromatopsia									
74	NCT02599922	Safety and Efficacy Trial of AAV Gene Therapy in Patients With CNGB3 Achromatopsia (A Clarity Clinical Trial)		ACTIVE_NOT_R_ECRUITING	Achromatopsia	BIOLOGICAL: rAAV2rTF-PR1.7-hCNGB3	PHASE1 PHASE2	11-04-2016	2026-07
75	NCT02610582	Safety and Efficacy of rAAV.hCNGA3 Gene Therapy in Patients With CNGA3-linked Achromatopsia	ColourBridge	RECRUITING	Achromatopsia	DRUG: rAAV.hCNGA3	PHASE1 PHASE2	2015-11	2027-04
76	NCT03001310	Gene Therapy for Achromatopsia (CNGB3)		COMPLETED	Achromatopsia	BIOLOGICAL: AAV - CNGB3	PHASE1 PHASE2	16-01-2017	25-10-2019
77	NCT03758404	Gene Therapy for Achromatopsia (CNGA3)		COMPLETED	Achromatopsia	BIOLOGICAL: adeno-associated virus vector AAV- CNGA3	PHASE1 PHASE2	12-08-2019	10-06-2021
78	NCT02935517	Safety and Efficacy Trial of AAV Gene Therapy in Patients With CNGA3 Achromatopsia (A Clarity Clinical Trial)		ACTIVE_NOT_R_ECRUITING	Achromatopsia	BIOLOGICAL: AGTC-402	PHASE1 PHASE2	03-08-2017	2026-08
79	NCT03278873	Long-Term Follow-Up Gene Therapy Study for Achromatopsia CNGB3 and CNGA3		ACTIVE_NOT_R_ECRUITING	Achromatopsia	BIOLOGICAL: either AAV - CNGB3 or AAV - CNGA3	PHASE1 PHASE2	29-06-2017	15-01-2026

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80	NCT02416622	Safety and Efficacy of rAAV-hRS1 in Patients With X-linked Retinoschisis (XRS)	COMPLETED	X-linked Retinoschisis	BIOLOGICAL: rAAV2TyF-CB-hRS1	PHASE1 PHASE2	2015-05 09-05-2023
81	NCT02317887	Study of RS1 Ocular Gene Transfer for X-linked Retinoschisis	ACTIVE_NOT_R_ECRUITING	Retinoschisis X-Linked	BIOLOGICAL: RS1 AAV Vector	PHASE1 PHASE2	11-02-2015 31-07-2025
82	NCT05878860	ATSN-201 Gene Therapy in RS1-Associated X-linked Retinoschisis	LIGHTHOUSE	RECRUITING	X-linked Retinoschisis	BIOLOGICAL: ATSN-201	PHASE1 PHASE2 22-08-2023 2029-10
83	NCT00001735	Gene Therapy for Gyrate Atrophy	COMPLETED	Gyrate Atrophy	PROCEDURE: Gene therapy	PHASE1	1998-04 2000-10
84	NCT03672968	EAP_GS010_single Patient	AVAILABLE	Leber Hereditary Optic Neuropathy (Optic, Atrophy, Hereditary, Leber)	GENETIC: GS010		????
85	NCT03293524	Efficacy & Safety Study of Bilateral IVT Injection of GS010 in LHON Subjects Due to the ND4 Mutation for up to 1 Year	REFLECT	ACTIVE_NOT_R_ECRUITING	Leber Hereditary Optic Neuropathy	GENETIC: GS010 DRUG: Placebo	PHASE3 12-03-2018 30-06-2024
86	NCT05607810	Long-Term Follow-up Study of ADV/M-022 in DME (INFINITY-EXT)	ENROLLING_BY_INVITATION	Diabetic Macular Edema Diabetic Retinopathy	GENETIC: ADVM-022		10-08-2022 2026-03
87	NCT05930561	4D-150 in Patients With Diabetic Macular Edema	RECRUITING	Diabetic Macular Edema Diabetic Retinopathy	BIOLOGICAL: 4D-150 IVT BIOLOGICAL: Afibercept IVT	PHASE2	09-08-2023 01-07-2028
88	NCT04418427	ADV/M-022 Intravitreal Gene Therapy for DME	INFINITY	COMPLETED	Diabetic Macular Edema Diabetic Retinopathy	BIOLOGICAL: 6E11 vg/eye of ADVM-022 BIOLOGICAL: 2E11 vg/eye of ADVM-022 BIOLOGICAL: Afibercept	PHASE2 28-05-2020 22-11-2022
89	NCT05916391	Gene Therapy for Diabetic Macular Edema	RECRUITING	Diabetic Macular Edema	GENETIC: FT-003	PHASE1	19-05-2023 01-05-2028
90	NCT05324592	Safety and Efficacy of 9MW0813 in Subjects With Diabetic Macular Edema	COMPLETED	Diabetic Macular Edema	DRUG: 9MW0813 DRUG: Afibercept	PHASE1	26-02-2021 25-01-2022
91	NCT05324774	Efficacy and Safety of 9MW0813 in Subjects With Diabetic Macular Edema	RECRUITING	Diabetic Macular Edema	DRUG: 9MW0813 DRUG: Afibercept	PHASE3	28-02-2022 30-07-2024
92	NCT05916391	Gene Therapy for Diabetic Macular Edema	RECRUITING	Diabetic Macular Edema	GENETIC: FT-003	PHASE1	19-05-2023 01-05-2028

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93	NCT05667810	Long-Term Follow-up Study of ADV/M-022 in DME (INFINITY-EXT)		ENROLLING_BY_INVITATION	Diabetic Macular Edema Diabetic Retinopathy	GENETIC: ADV/M-022	10-08-2022	2026-03
94	NCT05930561	4D-150 in Patients With Diabetic Macular Edema		RECRUITING	Diabetic Macular Edema Diabetic Retinopathy	BIOLOGICAL: 4D-150	09-08-2023	01-07-2028
95	NCT04418427	ADV/M-022 Intravitreal Gene Therapy for DME	INFINITY	COMPLETED	Diabetic Macular Edema Diabetic Retinopathy	IVT BIOLOGICAL: Aflibercept IVT		
96	NCT04418427	ADV/M-022 Intravitreal Gene Therapy for DME	INFINITY	COMPLETED	Diabetic Macular Edema Diabetic Retinopathy	BIOLOGICAL: 6E11 vg/eye of ADV/M-022 BIOLOGICAL: 2E11 vg/eye of ADV/M-022 BIOLOGICAL: Aflibercept	28-05-2020	22-11-2022
97	NCT05930561	4D-150 in Patients With Diabetic Macular Edema		RECRUITING	Diabetic Macular Edema Diabetic Retinopathy	BIOLOGICAL: 6E11 vg/eye of ADV/M-022 BIOLOGICAL : 2E11 vg/eye of ADV/M-022 BIOLOGICAL : Aflibercept	28-05-2020	22-11-2022
98	NCT05607810	Long-Term Follow-up Study of ADV/M-022 in DME (INFINITY-EXT)		ENROLLING_BY_INVITATION	Diabetic Macular Edema Diabetic Retinopathy	BIOLOGICAL: 4D-150	09-08-2023	01-07-2028
99	NCT04567550	RGX-314 Gene Therapy Administered in the Suprachoroidal Space for Participants With Diabetic Retinopathy (DR) Without Center Involved-Diabetic Macular Edema (CI-DME)	ALTITUDE	RECRUITING	Diabetic Retinopathy (DR)	GENETIC: RGX-314 Dose 1 GENETIC: RGX-314 Dose 2 GENETIC: RGX-314 Dose 3 DRUG: Topical Steroid	10-08-2022	2026-03
100	NCT04567550	RGX-314 Gene Therapy Administered in the Suprachoroidal Space for Participants With Diabetic Retinopathy (DR) Without Center Involved-Diabetic Macular Edema (CI-DME)	ALTITUDE	RECRUITING	Diabetic Retinopathy (DR)	GENETIC: RGX-314 Dose 1 GENETIC: RGX-314 Dose 2 GENETIC: RGX-314 Dose 3 DRUG: Topical Steroid	20-11-2020	2024-10
101	NCT00643747	Safety Study of RPE65 Gene Therapy to Treat Leber Congenital Anurosis	Retinal degeneration	COMPLETED	Retinal Degeneration	BIOLOGICAL: tgAAAG76 (rAAV 2/2,hRPE65p,hRPE65)	PHASE1 PHASE2	2007-01
		Retinoblastoma						

102	NCT03224268	Evaluate Safety and the Oncolytic Adenovirus VCN-01 Activity in Patients With Refractory Retinoblastoma	RTB	RECRUITING	Retinoblastoma, Recurrent	GENETIC: VCN-01	NA	06-09-2017	30-06-2022
	Bietti's Crystalline Dystrophy								
103	NCT04722107	Safety Study of rAAV2/8-hCYP4V2 in Patients With Bietti's Crystalline Dystrophy (BCD)	RECRUITING	Bietti's Crystalline Dystrophy	DRUG: rAAV2/8-hCYP4V2	EARLY_PHASE1	21-04-2021	29-04-2024	
104	NCT05399069	Safety and Tolerability of VGR-R01 in Patients With Bietti Crystalline Dystrophy	RECRUITING	Bietti Crystalline Dystrophy	DRUG: VGR-R01	EARLY_PHASE1	15-09-2022	2024-05	
105	NCT05832684	Safety and Efficacy of ZVS101e in Patients With Bietti's Crystalline Dystrophy	RECRUITING	Bietti's Crystalline Dystrophy	DRUG: ZVS101e	PHASE1 PHASE2	20-02-2023	2028-12	
106	NCT05694598	Safety and Tolerability of VGR-R01 for Patients With Bietti Crystalline Dystrophy	NOT_YET_RECRUITING	Bietti Crystalline Dystrophy	GENETIC: VGR-R01	PHASE1	01-03-2023	01-09-2025	
	Dry AMD								
107	NCT05984927	NG101 AAV Gene Therapy in Subjects With Wet Age-Related Macular Degeneration	RECRUITING	Age-Related Macular Degeneration	GENETIC: NG101 AAV gene therapy	PHASE1 PHASE2	2023-09	2030-01	
108	NCT05672121	Safety and Tolerability of KHK631 Gene Therapy in Subjects With Neovascular Age-related Macular Degeneration (nAMD)	NOT_YET_RECRUITING	Age-Related Macular Degeneration	DRUG: KHK631	PHASE1 PHASE2	2023-01	2026-12	
109	NCT05481827	ORACLE: A Long-term Follow-up Study to Evaluate the Safety and Durability of GT005 in a Gyroscope-sponsored Antecedent Study	ENROLLING_BY_INVITATION	Age Related Macular Degeneration (AMD)	GENETIC: GT005		12-07-2022	16-09-2028	
110	NCT03144999	Treatment of Advanced Dry Age Related Macular Degeneration With AAVCAG5CD59	COMPLETED	Dry Age-related Macular Degeneration	BIOLOGICAL: AAV/CAG5CD59	PHASE1	29-03-2017	09-12-2019	

Vitreous substitutes and tamponades – A review of types, applications, and future directions

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Vitreous substitutes and tamponades occupy the vitreous cavity following vitrectomy in the management of various conditions such as retinal detachment, macular hole, and diabetic retinopathy. Such replacements can be for the short term (gases such as sulfur hexafluoride (SF_6) and perfluoropropane (C_3F_8) or long term (such as silicone oils). Certain substitutes such as perfluorocarbon liquids are used only transiently during surgery as “a third hand” or rarely till a few days post surgery. Hydrogels and hyaluronan derivatives are among the newer vitreous substitutes that are showing promise for the future, albeit still under investigation. still being investigated for use as vitreous substitutes. These materials have properties similar to the natural vitreous and may offer advantages such as improved biocompatibility and biodegradability. Although vitreous substitutes are valuable tools in treating vitreoretinal conditions, they carry risks and potential complications such as cataract formation, glaucoma, and inflammation. The current communication extensively reviews the available literature on vitreous tamponades. It details the composition and properties of various vitreous substitutes and tamponades available for the clinician, highlighting the techniques of usage, indications, and limitations.

Key words: Vitreous tamponades, vitreous substitutes, vitrectomy

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The vitreous constitutes approximately 80% of the volume of the eye. The vitreous gel is an extracellular matrix composed of 99% of water. The remaining 1% comprises a complex mixture of proteins, collagens, hyaluronic acid, salts, and other substances.^[1] Collagen is the main protein component of the vitreous gel, precisely type II collagen. A network of collagen fibers helps maintain the structure and consistency of the gel. Other proteins in the vitreous gel include fibrillin, laminin, and fibronectin.^[2] Hyaluronic acid, a large carbohydrate molecule, is also crucial in the vitreous gel's structure and function. It binds to the collagen fibers and helps maintain the gel's consistency.^[3] Moreover, the vitreous gel contains electrolytes such as sodium,

potassium, chloride, and small amounts of glucose, ascorbic acid, and other nutrients.^[4] The vitreous has numerous roles, including structural support of the eye (maintaining the growth, volume, and elastic nature), providing nutrition and metabolic support, maintaining transparency, and aiding the accommodation reflex.^[5]

Modern vitreoretinal surgeries use various vitreous substitutes, which are used intraoperatively and postoperatively to replace the volume of native vitreous. All vitreous substitutes have their advantages and disadvantages. “Vitreous tamponade” is often used as a synonym for vitreous substitute. Vitreous tamponade agents are a subset of vitreous substitutes that provide surface tension across retinal breaks and holes to prevent fluid flow into the subretinal space. The tamponade is chosen based on its mechanical properties, personalized to the location of the break, features of RD, expected compliance of the patient to the postoperative positioning, and other factors. Balanced salt solution and hydrogels can be a vitreous substitute but cannot be called vitreous tamponade as they do not have the buoyancy of gas or oil required for the tamponade.

Vitreous substitutes are classified into three major categories^[6]:

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- Gases (air and expansile gases),
- Liquids (salt solution, perfluorocarbon liquids, semi-fluorinated alkanes, and silicone oil)
- Polymers (natural and synthetic hydrogels).

Method of Literature Review

A detailed literature search was done on PubMed and Google Scholar databases by using the following keywords: vitreous substitutes, vitreous tamponades, sulfur hexafluoride, perfluoropropane, perfluorocarbon liquid, silicone oil, and hydrogel. Additional articles were retrieved from the bibliography of the articles searched. More than 150 articles were reviewed, and 98 of them were included based on relevance and usefulness to the article. We did not exclude older publications that are commonly referenced. Non-English articles were excluded.

Ideal vitreous substitute

The structure and function of an ideal vitreous substitute should be structurally and functionally equivalent to the natural vitreous. It should tamponade both inferior and superior parts of the retina. It should be optically transparent, refractively neutral, preserve normal intraocular pressure (IOP), and support ocular structures. It has to be easy to use and would need self-healing as a replacement to require a single implantation. It should also be non-hazardous, biocompatible, non-biodegradable, accessible, and easy to store.^[7]

Intraocular gas

In 1911, Ohm first described using tamponade agents for retinal detachment; he successfully treated two patients with sterile air injections in the vitreous cavity [Table 1].^[8] In 1973, Norton described sulfur hexafluoride (SF_6) as a vitreous substitute. He found that SF_6 had a relatively longer duration of tamponade effect when compared with air.^[9]

Intravitreal gases can be expansile, such as sulfur hexafluoride (SF_6), perfluoroethane (C_2F_6), and octafluoropropane (C_3F_8), whereas air is a nonexpansile gas.

Physical properties of intravitreal gases

The gas injection behaves as an effective tamponade by preserving the IOP and the surface tension of the gas bubble.^[9] A gas bubble exerts surface tension to keep the bubble together; surface tension is exerted uniformly in all directions. Thus, the gas tamponade generates surface tension in all directions. And yet, this force will be more upward so that the head position can be adjusted accordingly. Gravity and buoyancy act on the gas bubble. Buoyancy pushes the bubble upward. This upward buoyancy is more significant with the silicone oil bubble. Perfluorocarbon liquids exert a similar downward force with a specific gravity. Tamponading agents block fluid flow through the retinal breaks, allowing retinal pigment epithelium (RPE) to absorb residual subretinal fluid. Blockage allows temporary retention of retinal detachment, while permanent chorioretinal adhesion develops in response to laser photocoagulation or cryotherapy.^[10]

The contact angle is the angle between the bubble of the tamponading agent and the retina. It is considered an essential indicator of the relative area of contact that the bubble contacts with the retina. Air and gas bubbles with a higher contact angle (38.8°) have additional contact area with the retina (the bubble tends to have a flat-bottomed shape) compared to silicone oil, which forms a more spherical shape (the bubble

resembles a flat bottom), inducing a smaller contact angle (16°) with the retina.^[11-13] Silicone oil provides less contact area with the retina than gas but remains in contact with the retina until removed. Instead, the gas dissolves in a few weeks. Dilution and keeping these gases can lead to complications such as elevated IOP, faster absorption than expected, and toxicity due to gas contamination. Visual recovery and recognition of surgical failure are quicker using air.^[14]

Indications

Intravitreal gases can be used in the following situations^[15]:

- (1) Pneumatic retinopexy is used in retinal detachment with the superior retinal breaks, where the breaks are isolated or grouped within 1 clock hour; there is no proliferative vitreoretinopathy and transparent ocular media. It is preferable in phakic eyes and when posterior vitreous detachment (PVD) is present.
- (2) Pneumatic retinopexy is also used for posterior retinal breaks,^[13,16] optic pits with macular detachment,^[17] and isolated tears under the superior rectus.^[10,18] Pneumatic retinopexy is also used in persistent detachment after scleral buckling^[13]; for instance, air could be used for superior breaks with minimal SRF. On the contrary, an expansile concentration of gas 0.3 mL of C_3F_8 can be used for inferior fishmouth breaks.^[13]
- (3) Intravitreal gas is injected in cases of macular holes (MHs).^[16] Both 20% SF_6 and 12% C_3F_8 have similar closure rates.^[19] A prospective randomized controlled trial found that air tamponade is inferior to SF_6 tamponade for MHs of $\leq 400\ \mu m$ in diameter. C_3F_8 gas injection can also treat early persistent MHs within 3 weeks of vitrectomy.^[20]
- (4) Displacement of subretinal hemorrhage: Pneumatic intravitreal gas is therapeutic in treating displacing submacular hemorrhages. It may allow quicker visual recovery and decrease the detrimental effect of heme on the photoreceptors. Before injection, careful patient selection must be made. The distinction between subretinal blood and blood elsewhere (preretinal, intraretinal, sub-RPE) is essential as injecting gas will not displace intraretinal or sub-RPE blood.^[21]

Advantages

Air tamponade

Air remains in the eye for a shorter time than gases, with tamponading characteristics similar to gas. Because of this, patients can see large letters and traverse in a familiar place in under 14 days, enabling faster postoperative rehabilitation.^[13,14,22] Air tamponade allows patients who live at higher altitudes to return home earlier, allows quicker visual rehabilitation air travel, and might decrease the risk of cataract development or progression.^[13,22,23] With the increasing use of an endolaser and complete drainage of subretinal fluid during modern pars plana vitrectomy surgery for rhegmatogenous retinal detachment (RRD), it is generally believed that chorioretinal adhesion around retinal breaks can form quickly, and extended duration of tamponade may be non-essential. This explains the reasons for using very short-acting air compared to longer-acting gases in cases of RRD.^[23]

Gas tamponade

Pneumatic retinopexy has transformed retinal detachment surgery into a walk-in procedure with considerably higher

Table 1: Comparison of various intravitreal gases can be

Intravitreal gases	Duration of action	100% gas expansion duration	Isoexpansile concentration
Perfluoropropane C ₃ F ₈	Long-acting	7.6 days	14%
Perfluoroethane C ₂ F ₆	Medium acting	3.5 days	16%
Perfluoromethane CF ₄	Short-acting	1.5 days	
Sulfur hexafluoride SF ₆	Short-acting	2.6 days	20%
Air	Short-acting	Immediate	

Table 2: Comparison of various silicone oils

Vitreous substitute	Molecular entities	Specific gravity (g/cm ³ @ 25°C)	Viscosity	Surface tension
Silicone oil (1000 cSt)	PDMS	0.97	1000	21.2
Silicone oil (5000 cSt)	PDMS	0.97	5000	21.3
Densiron 68	F6H8 (30.5%), Silicone oil (5000cSt) 69.5%	1.06	1349	19.13
Oxane HD	RMN3 (11.9%), OXANE 5700 (88.1%)	1.02	3300	-
Densiron 68 LV	Siluron 1000 & F6H8	1.05	300 mPas	
HWS46-3000	100000 cSt Silicone oil (45%)+F4H6 (55%)	1.118	2903 mPas	
HWS45-3000	100000 cSt Silicone oil (45%)+F5H5 (55%)		3108 mPas	

reattachment rates among a few patients.^[6,24] 23/25-G vitrectomy with a long-acting gas has improved success rates, especially in complex retinal detachment surgeries. Indications for intravitreal gases have expanded to MH repair and pneumatic displacement of submacular hemorrhage.^[15]

Disadvantages

Another disadvantage of gas tamponade is the need for precise postoperative positioning for a few weeks, which would be difficult in elderly patients.^[25] Intravitreal gases can cause temporary visual impairment due to the high difference in refractive index between gas and the lens.^[26] Expansile gas can cause lens opacities in the form of vacuoles, posterior capsular opacities, and posterior subcapsular cataracts. Overfill or excess expansile gas concentration can also cause ocular hypertension. Anterior chamber migration of gas is another complication seen intraoperatively or postoperatively.^[10,26] The gas bubble can leak from sclerotomies and migrate into subconjunctival space, causing hypotony.^[26] Mild hypotony needs to be observed. If prolonged, sclerotomies must be sutured with further gas reinjection. Subretinal gas migration can happen in conditions associated with large optic disc pit and coloboma involving the optic nerve.^[26] Usually, no surgical intervention is needed in cases of subretinal gas migration. The presence of proliferative vitreoretinopathy of grade C or greater and giant retinal tears can be a relative contraindication for the gas tamponade.^[23]

Gas may expand with changes in altitude. Thus, patients with intraocular gas are counseled against air travel. Air travel should be held up for approximately 2 weeks after the intravitreal injection of SF₆ and 6 weeks after the injection of C₃F₈.^[13,27] There might not be a specific volume of gas that can be deemed "safe" for intravitreal injection before air travel; some people may have decreased compensatory capacity for bubble expansion or may be extra sensitive to any IOP rise. Standard practice would be to advise all passengers not to fly in aircraft till the gas is completely absorbed.^[27,28] A sudden fall in the barometric pressure during flight can cause a rapid increase in IOP, which can cause the occlusion of the central retinal artery.^[13,27,29]

Recent advances

- (1) Shaving peripheral vitreous under air can be performed safely and effectively in cases with and makes scleral indentation needless. Shaving under air can be difficult for novice surgeons as there is compromised depth assessment.^[20,30]
- (2) Pneumatic vitreolysis (PVL) involves the injection of gas to release focal symptomatic vitreomacular traction with or without small stage 2 MHs. In eyes with FTMH, PVL resulted in hole closure in approximately one-third of the eyes.^[31,32]

Silicone oil

In 1962, Armaly^[33] and Cibis in 1962^[34] introduced silicone oil as a vitreous substitute [Table 2].(36) Silicone oil (polydimethylsiloxane, a.k.a. PDMS) has a specific gravity that is less than that of water (0.97 g/mL) and has a refractive index similar to the vitreous.^[7]

Upon the injection of silicone oil in the vitreous cavity, a solitary continuous bubble is formed and exerts high interfacial tension against residual vitreous, causing the aqueous humor to tamponade the retinal break.^[35] The most commonly used silicone oils are 1000, 1500, and 5000 centistokes (cSt). Both 1000 cSt and 5000 cSt oil have similar specific gravity and surface tensions but vary in their molecular weights (37 kDa and 65 kDa, respectively) and viscosities.^[36,37]

A higher-viscosity silicone oil has a lower tendency to emulsify.^[36] On the contrary, 1000 cSt silicone oil is easier and faster to inject and remove from the eye than 5000 cSt silicone oil. In addition, the vitreous cavity can be filled with 5000 cSt silicone oil quickly (5000 cSt silicone oil egresses slower than 1000 cSt silicone oil while closing sclerotomy).^[36] Other variants include Oxane 1300 and Oxane 5700 (Bausch and Lomb GmbH, Germany). Highly purified silicone oil is a long-term vitreous substitute with a constant volume.^[37] Heavy silicone oils, such as Densiron 68, Densiron Xtra (Fluoron), and Oxane HD (Bausch and Lomb), are denser than water.^[4,36]

Table 3: Comparison of various vitreous substitutes

Properties	Advantages	Disadvantages	Most useful situation
Air	<ul style="list-style-type: none"> • Large arc of contact • Colorless • Inert • Nontoxic 	<ul style="list-style-type: none"> • Inexpensive • Quicker visual recovery • Nontoxic <ul style="list-style-type: none"> • Short duration of action • Suboptimum in inferior RD • Air travel preferably restricted for 48 hours • Can cause transient cataract 	<ul style="list-style-type: none"> • As partial air fill to tamponade the port sites in sutureless vitrectomies • Primary uncomplicated retinal detachment with small superior holes • As an adjunct to glue-assisted retinal detachment surgeries • For fluid-air exchange following the removal of emulsified silicone oil • Pneumatic retinopexy • Macular Hole • Pneumatic displacement of subretinal hemorrhage • As an adjuvant to scleral buckling • Most preferred tamponade worldwide for uncomplicated retinal detachment surgeries
Gas	<ul style="list-style-type: none"> • Large arc of contact • Colorless • Inert • Nontoxic 	<ul style="list-style-type: none"> • Higher buoyancy • Stays in the eye for weeks <ul style="list-style-type: none"> • Raised IOP • Significant drop in vision post injection • Need for face-down positioning • Higher cataract rate • Expensive • Restricted air travel for weeks together • Difficult to assess the retina clinically through gas 	<ul style="list-style-type: none"> • Pneumatic retinopexy • Macular Hole • Pneumatic displacement of subretinal hemorrhage • As an adjuvant to scleral buckling • Most preferred tamponade worldwide for uncomplicated retinal detachment surgeries
Silicone oil	<ul style="list-style-type: none"> • Exerts high interfacial tension • Moderate tamponade effect • Immune tolerance 	<ul style="list-style-type: none"> • Long term stability • Longer duration of support • Control of postoperative vitreous hemorrhage • Patients who cannot posture are more suited to silicone oil over gas • Early visual rehabilitation • Single-eyed patients • Patients who need immediate air travel <ul style="list-style-type: none"> • Cataract formation • Corneal decompensation and band keratopathy formation in aphakes • Secondary glaucoma- which can be due to <ul style="list-style-type: none"> a) Secondary angle closure glaucoma (most commonly Pupillary block) b) Overfill of SO c) Trabeculitis because of emulsified SO d) Migration of silicone oil in AC • Can worsen retinal ischemia in cases with pre-existing retinal ischemia • Needs additional surgery for silicone oil removal 	<ul style="list-style-type: none"> • Most common use is rhegmatogenous retinal detachment complicated by PVR • Diabetic vitrectomy • Giant retinal tears • Traumatic retinal detachment • Endophthalmitis associated with retinal detachment • Endophthalmitis due to virulent organisms as silicone oil also has anti-microbial properties • Necrotizing retinitis like acute retinal necrosis and cytomegalovirus retinitis
PFCL	<ul style="list-style-type: none"> • Colorless • Odorless • High specific gravity 	<ul style="list-style-type: none"> • Flatten retina • Unroll the retinal fold • Easy injection • Easy removal <ul style="list-style-type: none"> • Inflammation especially if retained • Emulsification • Mechanical and chemical toxicity to the cornea, trabecular meshwork, retina • Usage in giant retinal tears can cause subretinal migration • If subfoveal migration occurs, needs additional surgery for removal 	<ul style="list-style-type: none"> • PVR • Giant retinal tear • Subluxated/dislocated lens • IOFB • Subretinal hemorrhage • Traumatic RD
Heavy Tamponade	<ul style="list-style-type: none"> • Higher viscosity 	<ul style="list-style-type: none"> • Tamponade effect is achieved in an upright position <ul style="list-style-type: none"> • Inflammation • Emulsification • Keratopathy • Secondary glaucoma 	<ul style="list-style-type: none"> • PVR in inferior peripheral retina • Myopic maculopathy • Inferior breaks • Complex RD

SO: Silicone oil. PFCL: Perfluorocarbon liquid. VEGF: Vascular endothelial growth factor. OCT: Optical coherence tomography. RD: Retinal detachment.
PVR: Posterior vitreoretinopathy

Rhegmatogenous retinal detachment

In eyes with severe proliferative vitreoretinopathy (PVR), studies have shown that silicone oil is just as effective as C_3F_8 and superior to SF₆ in reattaching the retina.^[38,39] Both silicone oil and C_3F_8 have been shown to improve visual function and have low complication rates. In a previous study, for eyes without prior vitrectomy that required retinotomy to flatten the retina, using silicone oil initially increased the likelihood of visual recovery and reduced the risk of hypotony at 6 months.^[38]

Silicone oil had better outcomes than C_3F_8 for cases requiring retinotomies, severe anterior proliferative vitreoretinopathy, patients with difficulty maintaining postoperative positioning, and those who need to fly or travel to higher altitudes. On the

contrary, using C_3F_8 is preferred in eyes with breaks at the edge scleral buckle, abnormal iris diaphragm, and breaks involving the superior retina.^[38,39]

Tractional retinal detachment

Silicone oil is often used when treating tractional retinal detachment with retinal breaks. This is especially true for monocular patients, patients with NVG or high risk for phthisis, and when all vitreoretinal traction could not be removed, or the retina could not be anatomically reattached during pars plana vitrectomy.^[40-42] In addition, silicone oil prevents the migration of vasoproliferative factors from the posterior segment to the anterior and prevents anterior segment neovascularization.^[43,44] McCuen *et al.*^[44] showed that

long-term use of silicone oil stabilized the neovascularization in 83% of eyes and achieved retinal attachment in 56% of patients with anterior proliferation and anterior segment neovascularization.

Trauma

When treating traumatic retinal detachment, silicone oil is often used during primary vitrectomy to prevent postoperative complications such as proliferative vitreoretinopathy, endophthalmitis, and postoperative hemorrhage.^[45,46] In addition, silicone oil as a long-term tamponade significantly improves visual outcomes. It is an effective substitute for vitreous and can effectively treat severe mechanical ocular trauma in patients with no light perception who believe their vision may improve.^[47]

Endophthalmitis

Aside from its role as a vitreous substitute, silicone oil has antimicrobial properties. An in-vitro study demonstrated that for 1000 cSt silicone oil, complete bactericidal action was reported by day 21 of exposure, and for 5000 cSt silicone oil, it was reported by day 30.^[48] Findings showed that it inhibited multidrug-resistant organisms. Both 1000 cSt and 5000 cSt silicone oils displayed similar fungistatic properties.^[48] Silicone oil can prevent the proliferation of fungi in fungal endophthalmitis and increase the efficacy of intravitreal antifungal agents.^[48]

Silicone oil is an effective vitreous substitute in myopic MHs and retinal detachment caused by MHs in a highly myopic eye.^[49] In addition, high myopic eyes might have an advantage from the hyperopic shift induced by the refractive index of the silicone oil.^[50]

Silicone oil is the tamponade of choice in complex retinal cases such as coloboma-related retinal detachment^[51] and breaks associated with viral retinitis.^[10] Such eyes often need long-term tamponade, mostly in monocular patients. Silicone oil can be a long-term vitreous substitute for chronic uveitis with hypotony and keep the eye from entering phthisis.^[52]

Heavy silicone oil

Heavy silicone oil (HSO) is a mixture of silicone oil with higher viscosity and semifluorinated alkane (SFA) such as F4H5, F4H6, and F6H8 used as a vitreous substitute. The newer HSOs are denser than water, more viscous, stable, and consequently well tolerated than their predecessors.^[53] HSO works well as a long-term tamponade agent with relative safety and tolerance for complex retinal detachments involving the inferior retina.^[54] HSO is associated with higher inflammation and IOP than conventional silicone oil.^[55,56]

Advantages

Silicone oil has higher surface tension and viscosity, ease of removal, low toxicity, and transparency. Due to its buoyancy, silicone oil has a tamponade force higher at the apex, facilitating the preservation of anatomical integrity. Silicone oil tamponade provides rapid visual rehabilitation, clear visualization of the fundus during the examination, shorter prone positioning duration, and better tamponade for those who cannot posture after the procedure.^[7] For these reasons, they are the only substance currently accepted for long-term vitreous replacement, especially in cases with complex retinal detachment.^[4,6,7]

Disadvantages

To achieve appropriate tamponade, adequate silicone oil fill is essential during the procedure. Overfill of silicone oil can result in elevated IOP and glaucoma. Dispersion of silicone oil causes emulsification.^[35] Silicone oil emulsification can cause detrimental effects on all parts of the eye, such as cataract, keratopathy, inflammation, and glaucoma.^[57] In a study conducted by Scott *et al.* comparing 1000 and 5000 cSt silicone oil, eyes with 1000 cSt had relatively higher IOP than eyes with 5000 cSt. On the contrary, eyes with 5000 cSt had a significantly lower tendency to emulsify but had significant corneal abnormality compared to the 1000-cSt group.^[37,36]

In vitrectomized aphakic eyes, the distorted or absent pupillary diaphragm causes silicone oil to bulge forward, causing anterior chamber migration and adherence to the endothelium.^[58] Specular microscopy is an excellent way to monitor early corneal decompensation caused by silicone oil. Silicone oil can migrate toward corneal stroma, incite inflammation, and cause keratopathy, manifesting as band-shaped keratopathy and progressive vascularization.^[58] Keratopathy progression can be arrested and occasionally reversed by silicone oil removal.^[59]

Silicone oil-induced ocular hypertension can occur at any time in the postoperative period. It may range from mild and transient to constant higher IOP, leading to vision loss.^[60] Glaucoma can be prevented by avoiding overfilling the oil and performing a lower peripheral iridectomy. Treatment options include IOP lowering medications, silicone oil from the anterior chamber, and partial removal from the vitreous cavity.^[61,62] IOP increased significantly in the eyes where silicone oil of 5000 cSt was used. Complication rates among 1000 versus 5000 cSt silicone oil were similar when used as a long-term vitreous substitute.^[36] Cyclodestructive procedures and glaucoma filtration surgery can manage refractory glaucoma associated with silicone oil.^[61,62] To lessen the complications, silicone oil removal has been recommended as soon as a stable situation in the retina has been achieved.^[59] Following silicone oil removal, visual loss may be observed due to retinal redetachment, glaucoma, hypotony, dense vitreous hemorrhage, and expulsive hemorrhage.^[59]

Unexplained visual loss following silicone oil tamponade can be due to vascular insufficiency in the deep capillary plexus (DCP) in the foveal avascular zone.^[63,64] Removing silicone oil as early as possible may help prevent keratopathy, cataract formation, glaucoma, and vascular insufficiency in the microvasculature, and improve visual acuity, probably due to better refraction acceptance and increased quality of life.^[59,63,64]

Although intracranial migration of silicone oil is uncommon, it can happen in eyes with anomalous optic discs and deeper optic cups. It can mimic intracranial lesions such as hematoma or tumors. Posterior migration of silicone oil in the visual pathway can cause loss of vision and central scotoma.^[4,50,65]

Perfluorocarbon liquid

Perfluorocarbon liquid (PFCL) was first described by Chang *et al.*^[66] for the treatment of giant retinal tears and proliferative vitreoretinopathy in 1987. It is a colorless, odorless synthetic fluorinated hydrocarbon liquid made up of carbon-fluorine bonds. Characteristic features of PFCL include high specific gravity and high viscosity. Multiple low-density PFCLs are being applied in vitreoretinal

surgeries, such as perfluoro-n-octane a.k.a. PFO (C8F18),^[67] perfluoroethylcyclohexane (C8F16),^[68] perfluorodecalin a.k.a. PFD (C10F18), perfluorotributylamide (PFTB), and perfluoroctylbromide (PFOB)^[10] [Tables 3 and 4].

Indications

1. Giant retinal tears

PFCL decreases the slippage of the tear edge and the chances of recurrence. It can unfold the folded flap of GRT.^[70]

2. Retinal detachment with proliferative vitreoretinopathy

PFCL injection helps open the closed funnel, aids in tackling membranes, and removes membranes in proliferative vitreoretinopathy.^[71]

3. PFCL tamponade prevents the vitrectomy cutter from engaging the retina by accident and can be helpful in base shaving. In addition, PFCL reduces the risk of iatrogenic retinotomies in retinal surgeries by stabilizing the retina.^[72]

4. PFCL helps remove dislocated crystalline lenses, dropped lens fragments, and intraocular lens implants. PFCL can provide a reflective surface against the ultrasonic stream of phacofragmentome and prevent the formation of retinal breaks.^[72,73]

5. Diabetic vitrectomy

PFCL stabilizes a retina for meticulous membrane peeling in conditions with combined traction and rhegmatogenous retinal detachment.^[74] PFCL is used to flatten the posterior retinal folds.^[72,75]

6. Macular surgeries

PFCL can be injected to stabilize the ILM flap and prevent these flap failures effectively.^[76]

PFCL can treat conditions such as MHs,^[76] myopic foveoschisis,^[69] and MH retinal detachment.^[77] The pressure exerted by PFCL shifts the SRF from subretinal space and drains the subretinal fluid.^[77]

7. Suprachoroidal hemorrhage

PFCL was used to extrude liquified blood from the suprachoroidal space via a sclerotomy incision.^[78]

8. In pediatric eyes, PFCL is used to induce PVD.^[79]

9. Intraocular foreign body removal

PFCL can protect the posterior pole during IOFB removal attempt. PFCL can also assist in managing retinal detachment, hemorrhage, and proliferative vitreoretinopathy changes associated with a foreign body.^[80]

10. Medium-term tamponade

PFCL was earlier meant for only intraoperative usage. A recent study done by Shukla *et al.*^[81] showed encouraging anatomical and functional outcomes with PFO tamponade in a unique group of very complex RDs which had a high probability of ending up with inoperable re-detachments or with prolonged silicone oil tamponade and its attendant complications. The study showed that medium-term PFO tamponade is a viable option in detachments with extensive proliferative vitreoretinopathy that cannot be satisfactorily

Table 4: Comparable usages of tamponades in various common clinical conditions

	Silicone oil	Gas	PFCL
Extensive PVR	<ul style="list-style-type: none"> Provides extended tamponade Can detect recurrent retinal detachment early due to good visualization through the oil As silicone oil tamponades the superior two-thirds of the retina well, it can provide a time margin of a couple of weeks before resurgery is planned 	<ul style="list-style-type: none"> Recurrence of RD is difficult to detect early due to the hazy view through gas Can develop postoperative hypotony^[10] 	<ul style="list-style-type: none"> Aids in dissection of proliferative membranes as a third hand Assists in performing retinectomy & Helps drain the SRF via retinotomy drainage Helps assess any residual stiffness in the retina to decide on retinotomy Assists post retinotomy to detect residual retinal stiffness
Giant retinal tear (GRT)	<ul style="list-style-type: none"> Most preferred in GRT >180° Lesser chances of retinal slippage.^[68] Can detect recurrent retinal detachment early due to good visualization through the oil 	<ul style="list-style-type: none"> More chances of retinal slippage^[68] Recurrence of RD is difficult to detect early due to the hazy view through gas 	<ul style="list-style-type: none"> PFCL can unroll the flap by acting as a valuable third hand during surgery Displaces the SRF effectively
Staphyloma RD	<ul style="list-style-type: none"> More prolonged tamponade Useful in single-eyed patients Higher risk of post-operative glaucoma as compared to gases 	<ul style="list-style-type: none"> Longer-acting gases provide a longer tamponade effect Recurrence of RD is difficult to detect early due to the hazy view through gas 	<ul style="list-style-type: none"> Role is controversial as it can migrate to the subretinal space
Myopic traction maculopathy	<ul style="list-style-type: none"> Helpful in cases with a detached macula Higher risk of post-operative glaucoma as compared to gases 	<ul style="list-style-type: none"> Longer-acting gases are preferred Recurrence of RD is difficult to detect early due to the hazy view through gas 	<ul style="list-style-type: none"> Stabilises ILM flaps & prevent flap failures.^[69]
Diabetic vitrectomy	<ul style="list-style-type: none"> Suitable in cases with extensive membrane Multiple breaks Tamponades early post-operative hemorrhage to maintain relatively clear media 	<ul style="list-style-type: none"> Reduces early postoperative vitreous hemorrhage 	<ul style="list-style-type: none"> Helps in removing the fibrovascular membranes on a thin retina by reattaching combined RD with better visibility
Macular hole	<ul style="list-style-type: none"> Suited for patients who are unable to maintain a prescribed prone position or need immediate air or high-altitude travel^[25] 	<ul style="list-style-type: none"> More preferred tamponading agent as has more surface tension; which enables glial proliferation and hole closure 	<ul style="list-style-type: none"> PFCL assists ILM peeling in the macular hole with retinal detachment

reattached intraoperatively, especially in young subjects with severely traumatized or infected eyes.^[81]

Advantages

The transparent nature of the PFCL allows for greater precision in performing manipulations. Its high density and specific gravity also help to flatten the retina and unroll retinal folds. In addition, it can displace subretinal fluid, which may eliminate the need for retinotomy. With a refractive index different from saline, it creates a visible PFCL-BSS interface that assists with intraocular maneuvers. Furthermore, it does not interfere with laser wavelengths and allows for endolaser under PFCL, and its lower surface tension and higher interfacial tension tend to keep it as a large bubble, reducing the risk of subretinal migration. Its lower viscosity allows easy injection and aspiration, even with small-gauge vitrectomies. Immiscibility resists mixing into BSS or blood, allowing for a clear operating field despite intraoperative bleeding.^[10] Lastly, the immiscibility and the difference in refractive index of the PFCL permits direct PFCL-silicone oil exchange, which is particularly helpful when treating giant retinal tears by decreasing the risk of slippage.^[68] The exchange can be performed with an active infusion of SO and passive efflux of PFCL by using a flute needle.^[10]

Disadvantages

Despite the great benefits of PFCLs, these molecules cause diverse complications during or after surgery. Intraoperatively, sudden rise in IOP rise during injection of PFCL can be avoided by using a dual-bore cannula. PFCL has to be removed completely at the end of surgery to prevent postoperative complications. Contaminants in PFCL have caused necrotizing inflammation, vascular occlusion, and optic atrophy in the past.^[82-84] Even without contaminants, PFCL is known to cause mechanical or chemical damage on contact with the cornea, and trabecular meshwork to increase IOP. It elicits an ocular inflammatory reaction, which increases with tamponade duration. PFCL tamponade may cause visual disturbance by migrating into the anterior chamber to obscure the visual axis or subretinal migration of PFCL, particularly when retained under the fovea.^[85] Overfill of PFCL without releasing adequate traction can cause subretinal migration of PFCL. Complications that PFCL causes are secondary glaucoma and mechanical or chemical retino-toxicity. Complications that perfluorodecalin causes are found to be less toxic in comparison to perfluoroctane.^[10,84-86]

Future research

The oxygenated PFCL-perfused vitrectomy technique can be beneficial in conditions with retinal ischemia. High oxygenated PFCL can help increase the IOP to a slightly higher level, which in turn helps achieve minimal bleeding during diabetic vitrectomy. As PFCL is immiscible with the blood and other fluids, it makes vitrectomy much easier. While PFCL is utilized as a perfusate, it can stabilize the detached retina simultaneously.^[72,87] Hydrogenated hydrofluorocarbon liquids (HFCLs) were introduced as an alternative to PFCLs, with lesser specific gravity and higher lipophilic properties.^[56,86,87]

Double fill

Treating multiple breaks in the superior and inferior retina and proliferative vitreoretinopathy by using conventional vitreous substitutes remains a clinical challenge. Double fill combines

silicone oil and heavy tamponade such as SFA^[56] and PFCL.^[88] Conventional silicone oil floats and tamponades the superior retina; however, heavy tamponade sinks and tamponades the inferior retina. It also decreases the sedimentation of cytokines and RPE cells that promote and reduce proliferative vitreoretinopathy changes. Silicone oil stabilizes the PFCL bubble, maintaining its effectiveness on the retina and preventing PFCL emulsification and migration to the anterior chamber.^[56,88]

Advantage

Double fill with PFCL and silicone oil is an effective treatment method for complex retinal detachments. The advantage is that it can be used in large inferior retinal breaks and acts as a single large tamponade agent with reduced dispersion. Furthermore, if the tamponade agents are withdrawn within 1 month, it is conceivable that double fill is safe for the retina.^[88,89]

Disadvantage

Combining silicone oil and semi-fluorinated alkane can cause inflammation and multiple complications, such as cataract formation. Although structural changes were not seen with OCT following double fill, altered retinal sensitivity is seen with microperimetry. The primary disadvantage is that they are not good at providing simultaneous tamponade as much as described theoretically.^[56,88]

Balanced Salt Solution (BSS)

A balanced salt solution (BSS) is commonly used intraoperatively as a vitreous substitute. BSS has a physiological pH of 7.5 and an osmolarity of 300 mOsm/kg, which is isotonic to ocular tissue. Corneal endothelium tolerates BSS Plus better, which contains bicarbonate, dextrose, and glutathione. BSS Plus (BSS Plus, Alcon Laboratories, Fort Worth, Texas, USA) is more physiological than BSS as its ionic concentration is appropriate for retinal electrical activity.^[6,90]

Advantage

BSS is used intraoperatively during vitrectomy to maintain intraocular volume and pressure after the drainage of subretinal fluid during retinal detachment surgery and choroidal detachments. In addition, it can transport medications needed for hemostasis, dilate pupil, and has anti-inflammatory effects.^[6,91]

Disadvantages

BSS is a short-term vitreous substitute with low surface tension. If there is a break at the end of the surgery, BSS has to be replaced with a vitreous substitute with higher surface tension.^[6]

Emerging substitutes

Foldable capsular vitreous body

Foldable capsular vitreous bodies (FCVBs) are a potential solution to the complications associated with the prolonged usage of SO as a vitreous substitute. The foldable capsule made of silicone elastomer is put into the eyeball, and saline or SO is injected through the tube valve system to inflate the capsule.^[47,92]

Indications

FCVB is used in retinal detachment caused by severe ocular trauma, a type of refractory vitreoretinal disease. FCVB can be

used in eyes where the retina cannot be attached and prevent the eye from going into phthisis. Treatment in these patients aims to preserve the globe rather than restore vision.^[47,92]

Advantages

Studies have shown that FCVB is a reliable treatment option for severe retinal detachment. FCVB can avoid the inconvenience caused by SO dependence and enucleation. After implantation surgery, FCVBs have maintained eyeball integrity and saved partial sight, demonstrating good stability and efficacy.^[47,92]

Disadvantages

FCVBs have not been used on a large scale; only some cases have been reported in the literature. In addition, there is a high incidence of cataracts in such eyes.^[47,92]

Hydrogels

Hydrogels are three-dimensional polymers with exceptional properties ideal for various biomedical applications. The hydrophilic nature of hydrogel allows it to maintain its shape to form materials that mimic natural tissue, making it perfect for drug delivery.^[84,93,94] Hydrogels can be categorized as

- A. Natural polymeric hydrogels: e.g. hyaluronic acid, chitosan, and polygeline
- B. Synthetic polymeric hydrogels: e.g. polyethylene glycol and polypropylene glycol/polycaprolactone
- C. Smart hydrogels: e.g. Gellan-HA, Pluronic F127, and WTG-127^[6,84]

Advantage

Natural polymers such as hyaluronic acid and its derivatives have excellent biocompatibility. Synthetic hydrogels have the advantage of ease of application and biomechanics compared to natural hydrogels but need to be more biocompatible for extensive use. Synthetic hydrogels can be programmed in their chemical and mechanical properties, which have the potential for drug delivery functions. Smart hydrogels react uniquely to physical, chemical, and biochemical responses.^[95,96] Possible uses of smart hydrogels are still only in the experimental stage, but if successful, they may be the centerpiece of the next generation of vitreous substitutes. In addition, regeneration-eliciting hydrogels may integrate the delivery of therapeutic cells or bioactive factors toward more efficient regeneration of the native vitreous body. Machine learning algorithms can be used to design hydrogel that can be used as artificial vitreous.^[84,97]

Disadvantage

Natural polymers with low mechanical strength, low surface tension, rapid biodegradation, and poor tamponade effect increase water solubility. Mechanical instability following the injection of synthetic hydrogel in the vitreous cavity causes the gel to shear and lose elasticity. It can have poor biocompatibility and can incite inflammation and phagocytosis.^[96] Higher osmotic pressure associated with synthetic hydrogel can induce retinal toxicity. Faster biodegradation can lead to decreased surface tension across retinal tears.^[97] A significant challenge lies ahead for smart hydrogels to become compatible with the immune system as they can cause vitritis, inducing phagocytosis and fragmentation within weeks of injection.^[84,96,97]

Cell culture

Natural polymers such as hyaluronic acid biodegrade very fast. Continuous culture of hyalocytes and fibroblasts for

implantation into the eye could enable constant hyaluronic acid and collagen production. Hyalocyte cultures have synthesized subcomponents that make vitreous, such as hyaluronic acid.^[94] Factors such as ascorbic acid and bFGF can stimulate hyalocyte proliferation.^[94] On the contrary, TGF- β 1 can cause inhibit hyalocyte growth.^[98] *In vivo* cell culture of hydrogel polymers can be the future of vitreous substitutes.

Conclusion

The vitreous substitute has to be selected based on patient/eye-specific details, such as the nature of the disease, duration of the disease, age of the patient, compliance of the patient, and duration involved in visual rehabilitation. Vitreous substitutes are materials used to replace the vitreous in cases where it has been removed or replaced due to disease, injury, or surgery. The ideal vitreous substitute should mimic the biological and physical properties of the natural vitreous, such as transparency, refractive index, mechanical stability, and biocompatibility. Currently, the most commonly used vitreous substitutes are silicone oil and gas. However, these materials have several limitations, such as migration, toxicity, degradation, and lack of long-term stability. Research is ongoing to develop more effective and safe vitreous substitutes. Some promising approaches include biomaterials, nanotechnology, and machine learning. Developing an ideal vitreous substitute is an active area of research, and using novel materials and technologies can significantly improve the outcomes of vitreoretinal surgeries.

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Hospital corneal retrieval program: A long way to go

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Purpose: The Hospital Corneal Retrieval Program (HCRP) aims to counsel and encourage the family of a critically ill or deceased person in the hospital for eye donation. Adequately sensitized health-care workers (HCWs) may play a pivotal role in boosting HCRP. **Study Design:** Multicentric, cross-sectional, descriptive study. **Methods:** Study participants included all HCWs of three medical colleges, including one with eye bank and corneal transplant services. A pretested, structured questionnaire was used to record the awareness, knowledge, and attitude about eye donation among HCWs. The expected outcome was to seek differences in awareness, if any, among medical and paramedical workers of medical colleges with (group A) or without (group B) eye bank and corneal transplant facilities. **Results:** Of the 4060 study participants, 2100 HCWs were in group A and the rest (1960) were in group B. For eight out of 13 questions assessing awareness and perception, a statistically insignificant difference in responses was observed between the two groups. Regarding questions related to attitude, although the majority of HCWs in both groups were comfortable talking about eye donation, they did feel that counseling relatives of a terminally ill patient about eye donation was insensitive. Less than half of HCWs showed a willingness to donate eyes, and about half of the participants wanted to acquire more knowledge about eye donation. **Conclusion:** Awareness regarding eye donation among HCWs was mostly found to be at dismal levels, irrespective of whether they worked in an institute with or without eye bank and corneal transplant services. This warrants an accelerated effort at sensitizing HCWs as a strengthening measure for HCRP.

Key words: Corneal blindness, corneal donation, eye donation, HCRP

Corneal blindness levies a substantial public health onus, affecting approximately 1.5 million people (4% of all cases of blindness) globally.^[1] Ninety percent of the global cases of ocular trauma and corneal ulceration leading to corneal blindness occur in developing countries.^[2] Further, in some parts of Africa and Asia, the incidence of cornea-related visual loss among children is 20 times higher than that in developed nations.^[2] The burden of corneal blindness on the individual and the community, as a whole, may be enormous. The younger productive population is more prone to corneal infections and injuries compared to the elderly, who are mostly affected by cataracts; hence, the socioeconomic impact of corneal blindness is greater than cataracts in terms of the total blind-person years.^[3]

Approximately 1.9 million corneal blind patients already exist across India, and about 20,000 get added to the tally each year.^[4,5] A major treatment option for restoring sight in those with corneal blindness is corneal transplantation, which can only be accomplished through cornea donation. A recent global survey on eye banking and corneal transplantation reckoned the severe mismatch between the supply and demand of donor corneas worldwide, with only one cornea available for

every 70 needed.^[6] Since not each of the donated corneas is healthy enough to be transplanted, India needs about 2,77,000 donor eyes to perform 1,00,000 corneal transplants each year as per the current rate of requirement.^[7] According to the Eye Bank Association of India (EBAI), about 56,000 corneas were procured in the year 2018–2019, while only 27,016 transplants were carried out in that same year.^[8] Therefore, the collection of the donor's eyes is the main concern in any organized effort to lessen corneal blindness. The establishment of robust eye bank and corneal transplant services as well as wilful corneal donation in ample numbers are required to tangibly combat corneal blindness.

Voluntary donation and Hospital Corneal Retrieval Program (HCRP) are the two modes of procuring donor corneas. Voluntary donations stand at negligible levels despite the rigorous efforts of National Program for Control of Blindness (NPCB), EBAI, and many nongovernment organizations at raising awareness of the general public and targeting social/religious taboos associated with corneal donations. HCRP, on the other hand, provides easy accessibility to potential donors and ready availability of a detailed medical history to assess the eligibility of the donor for corneal donation, enables swift procurement of tissues from younger donors, helps reduce

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death to corneal retrieval time, and improves cost-effectiveness. Hence, it improves both corneal collection and utilization rates in an eye bank. Literature suggests that awareness and training of health-care workers (HCWs) can appreciably increase the number of eye donations.^[9,10] A well-aware health-care professional/paramedical or nursing staff can aid in increasing voluntary donations by educating the common man about the importance of corneal donation, dispelling common myths and misapprehensions, and providing information on the donation process. Moreover, HCRP can get a boost if adequately aware health-care providers can identify potential donors, sensitize and support their families, address their concerns, and help them make an informed decision. This study was designed to evaluate the awareness of HCWs of three medical colleges, including one with functional eye bank and corneal transplant services.

Methods

A cross-sectional descriptive study was conducted among HCWs of three government medical colleges in northern India, including one medical college with functional eye bank and corneal transplant services for more than 10 years. The study population included all HCWs of the three medical colleges (interns, residents as well as consultant doctors, nursing and paramedical staff) who had been working in the hospital for more than 2 years. Residents and consultants from the ophthalmology department were excluded from the study. A prevalidated, structured questionnaire was prepared using Google Form, in English as well as vernacular language, to record the sociodemographic details and assess the awareness, knowledge, and attitude about eye donation. After seeking approval from the respective ethics committees of the three participating medical colleges, the link to the Google Form questionnaire was shared with all HCWs and was closed for responses after 7 days with two repeated reminders. The data was collected and compiled in MS Excel and analyzed by using Statistical Package for the Social Sciences (SPSS; version 20.0) software. Descriptive statistics were used as necessary, and all qualitative variables were presented as frequency and percentages. Quantitative variables were presented as mean and standard deviation. A Chi-square test of significance was applied. The expected outcome was to seek differences in awareness, if any, among medical and paramedical workers of medical colleges, with or without eye banks and corneal transplant facilities.

Results

All participants were categorized into two groups: group A, comprising HCWs in a medical college with functional eye bank and corneal transplant services, and group B, which consisted of health workers in medical colleges without transplant services.

Total number of study participants was 4060, with 2100 HCWs in group A and the remaining 1960 in group B. Table 1 shows the participant characteristics in the two groups. About one-fourth of the respondents in group A and one-fifth of the respondents in group B were medical, paramedical, or nursing students. Nursing staff formed the largest subgroup in both the study groups. Designation-wise distribution of study participants is shown in Fig. 1.

Table 2 presents the information regarding knowledge and perception of the participants about eye donation. For eight out of 13 questions assessing awareness and perception about eye donation, statistically insignificant difference in responses was observed between the two groups.

Majority of the participants knew that the eyes can be donated and no statistically significant difference was noted between the two groups. Very few respondents, with no statistical difference between the groups, knew that eyes could be pledged anytime during life or after death and that donated eyes must be retrieved within 6 h of death.

A statistically significant difference in the responses was recorded between the two groups when they were interrogated for the kind of blindness that can be ameliorated by eye donation, if only cornea or whole eyeball is retrieved, and if eye retrieval causes facial disfigurement. Group A participants, that is those who belonged to the medical facility with functional transplant services, exhibited better response rate to these questions. Similarly, compared to group B, statistically significant number of group A HCWs knew that the corneal retrieval can be carried out at the hospital as well as donor's home [Fig. 2].

Regarding questions related to attitude and practice [Table 3], although majority of HCWs in both the groups were comfortable to talk about eye donation, they did feel that counseling relatives of a terminally ill patient about eye donation was inhuman. Ironically, more group A HCWs were uncomfortable in counseling terminally ill patients for eye donation compared to group B participants

Table 1: Demographic characteristics of study participants

Characteristic	Group A n=2100 (%)	Group B n=1960 (%)	Total n=4060 (%)
Age, n (%)	<30	1158 (55.14)	1056 (53.88)
	>30	942 (44.86)	904 (46.12)
Gender, n (%)	Male	886 (42.19)	1033 (52.7)
	Female	1214 (57.81)	927 (47.29)
Designation	Student ^a	542 (25.80)	386 (19.69)
	Resident/faculty	313 (14.9)	293 (14.94)
	Nursing staff	583 (27.7)	614 (31.32)
	Paramedical staff	556 (26.47)	464 (23.67)
	Others	106 (5.04)	203 (10.33)
			309 (7.61)

^aMedical/nursing/paramedical student

and the difference was statistically significant. Less than half of HCWs showed willingness to donate eyes and about half

of the participants wanted to acquire more knowledge about eye donation [Fig. 3].

For most of the study participants in both the groups, source of information about eye donation was medical campaigns, medical personnel, or hospitals [Fig. 4]. Only a small role was played by electronic/print media and internet as the means of raising awareness among HCWs.

Discussion

The knowledge and attitude regarding eye donation among HCWs plays a primary role in promoting eye donation and thus ameliorating corneal blindness. Many opportunities of prospective eye donations may be lost if HCWs fail to counsel family members about the possibility of eye donation. Moreover, if the health personnel are not aware enough to answer the questions and concerns of public and family members of terminally ill patients, the eye donation drive remains hindered. HCRP, particularly, suffers a major setback in case of unaware and undersensitized HCWs.

Figure 1: Designation-wise distribution of study participants

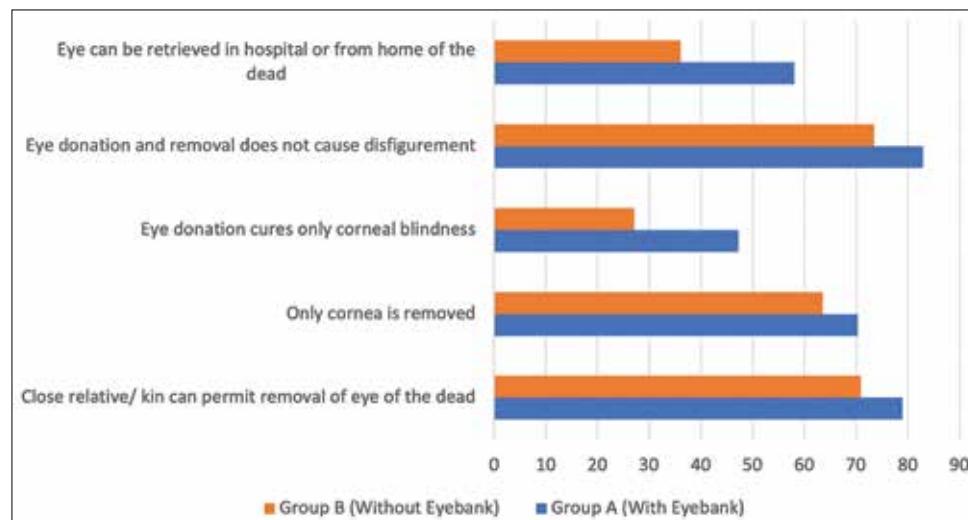
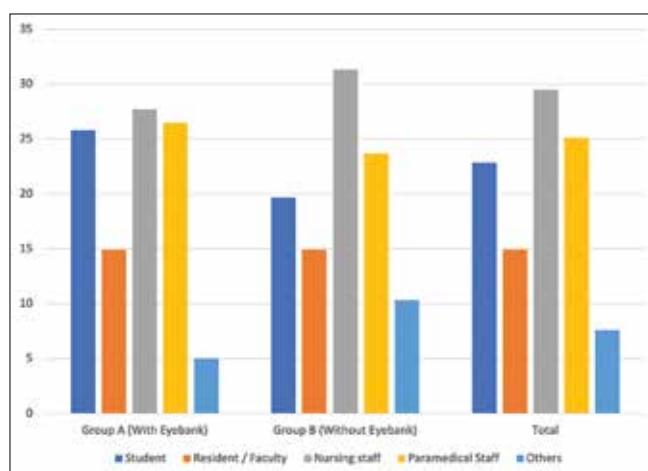


Figure 2: Difference in Knowledge and awareness between Group A and Group B. (P -value <0.05 for all the statements depicted in the bar graph)

Table 2: Awareness and knowledge regarding eye donation among HCWs

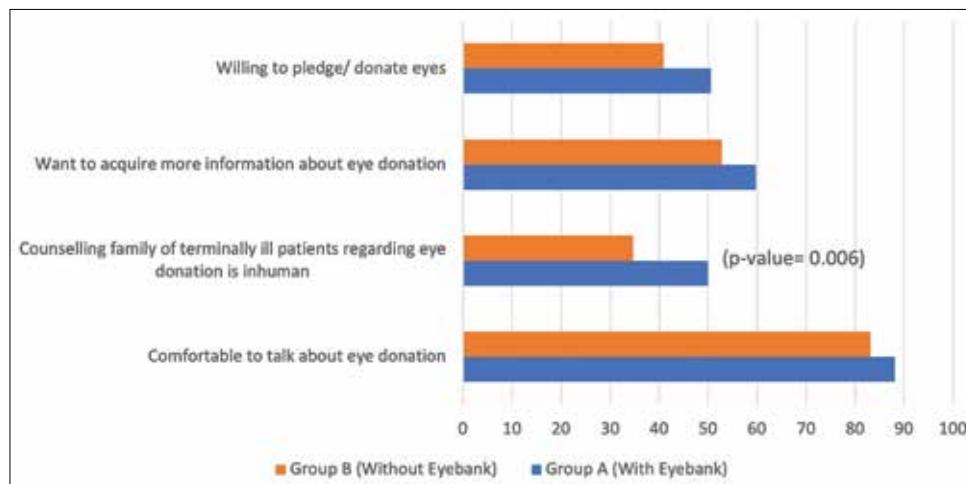
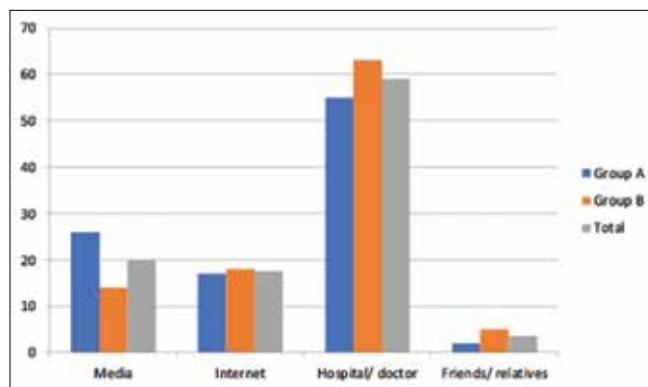
Knowledge and perception	Group A n=2100 (%)	Group B n=1960 (%)	Chi ² (P)	Total n=4060 (%)
Eyes can be donated	2022 (96.3)	1817 (92.7)	3.94 (0.139)	3839 (94.5)
Eyes can be pledged anytime during life and/or donated after death	138 (6.57)	130 (6.63)	2.42 (0.488)	268 (6.60)
Donated eyes should be removed within 6 h of death	251 (11.95)	182 (9.28)	4.94 (0.176)	433 (10.66)
Close relative/kin can permit removal of eye of the dead	1658 (78.95)	1389 (70.87)	8.87 (0.012)	3047 (75.05)
Person with communicable disease cannot donate eyes	990 (47.14)	1071 (54.64)	1.8 (0.396)	2061 (50.76)
Person with noncommunicable disease can donate eyes	1169 (55.67)	1033 (52.7)	2.32 (0.321)	2202 (54.24)
Only cornea is removed	1476 (70.28)	1245 (63.52)	10.51 (0.005)	2721 (67.02)
Eye donation cures only corneal blindness	992 (47.24)	531 (27.09)	16.65 (<0.001)	1523 (37.51)
Eye donation and removal does not cause disfigurement	1740 (82.86)	1441 (73.52)	14.88 (0.001)	3181 (78.35)
Eye can be retrieved in the hospital or from home of the dead	1218 (58.0)	709 (36.17)	36.67 (<0.001)	1927 (47.46)
Donated eyes can be preserved in eye bank	1249 (59.48)	1381 (70.46)	5.40 (0.066)	2630 (64.78)
Identity of donor and recipient is kept confidential	1303 (62.05)	1265 (64.54)	4.84 (0.089)	2568 (63.25)
Eye donation is not against religion	1976 (94.1)	1837 (93.72)	0.04 (0.519)	3813 (93.92)

*Statistically significant p-value (<0.05) is in bold

Table 3: Preferred practice regarding eye donation among HCWs

Practice	Group A n=2100 (%)	Group B n=1960 (%)	Chi ² (P)	Total n=4060 (%)
Comfortable to talk about eye donation	1850 (88.09)	1629 (83.11)	1.47 (0.146)	3479 (85.69)
Counseling family of terminally ill patients regarding eye donation is inhuman	1048 (49.90)	679 (34.64)	7.44 (0.006)	1727 (42.54)
Want to acquire more information about eye donation	1254 (59.71)	1034 (52.75)	1.50 (0.133)	2288 (56.35)
Willing to pledge/donate eyes	1061 (50.52)	800 (40.82)	4.47 (0.107)	1861 (45.84)

*Statistically significant p-value (<0.05) is in bold. HCW=health-care worker

**Figure 3: Difference in practice pattern between Group A and Group B****Figure 4: Frequency distribution of the preferred source of information about eye donation**

A comparative analysis of awareness and attitude was undertaken among HCWs of two kinds of medical facility, one with and the other without functional corneal transplant and eye bank services. Contrary to our expectation of having a better sensitized cohort of HCWs in group A, the awareness levels were mostly similar in both the groups. On the other hand, Robert *et al.* observed significantly better knowledge and practice levels regarding eye donation among fresh graduates from institutions with eye banks.^[11]

Awareness that the eyes can be donated was found to be fairly good at 94.5% among the total study participants (96.3% in group A and 92.7% in Group B), but it still lagging behind a perfect score as was reported in a study from India among a sample of medical students.^[12] Lowest awareness level

has been reported as 8.4% among eye patients of Ghana.^[13] Despite substantial awareness in our study participants that eyes can be donated, very few (6.60%) of them, with no significant difference between the two groups, knew that eyes could be pledged during life as well as can be donated after death with the consent of family. Knowledge that pledging is not mandatory and that cornea can be donated after death with the consent of kin was found among very few HCWs. It is imperative for HCWs to know that consent for donation is legally granted by any next of kin or close family member as detailed in the Transplantation of Human Organ and Tissue Act.^[14] Even if the eyes had been pledged by the deceased during his/her life, it is entirely the family's inclination and willingness to contact the eye bank for corneal donation.

Surprisingly, only about one-tenth of our study participants, irrespective of the study group, were aware of the ideal time of corneal retrieval after death. Previous studies conducted on medical students and HCWs have reported better cognizance of ideal time of corneal retrieval. Dave *et al.*^[15] recently found that 84.8% of medical and paramedical staff were aware of the ideal time of corneal retrieval, while Singh *et al.*^[16] reported that 44.1% of the medical students were aware of the same. Among HCWs, the knowledge of ideal time of eye donation is crucial, as a boost to HCRP as well as for procurement of usable corneas. Poor awareness related to ideal time of eye retrieval in our study participants may be seen as another setback to HCRP in the region.

Khandelwal and Katre^[17] found that only half of their participants were aware that corneal donation does not

cause disfigurement, but this awareness was significantly less in paramedical staff compared to interns and residents. In the present study, considerable number of HCWs (78.35%) were aware that eye donation does not lead to disfigurement and this awareness was statistically better among HCWs belonging to facility with eye bank. In addition, awareness that only cornea is retrieved from donors, only corneal blindness can be treated with eye/corneal donation, and cornea can be retrieved from either hospital or home of the deceased was found to be significantly better in group A participants. But still, the difference in awareness of the two groups was not as strong as reported by a previous study from South India. Narendran *et al.* had observed that having an eye bank or collection center in the hospital campus had a significant impact of 6 times higher knowledge scores than in those hospital staff who did not have an eye bank or a collection center in the campus.^[18]

About 85.69% of our total study participants, with no significant difference between the study groups, responded that they were comfortable to talk about eye donation. This may be attributed, partly, to their conscientiousness as health-care professionals. Also, since the question did not specify the target group and the expected outcome, the response was favorably good. At the same time, about 42% of participants regarded counseling the family of terminally ill patients about eye donation as inhuman, with ironically stronger feeling of inhumanity among participants of center with eye bank than those of center without eye bank. Literature suggests that HCWs' perception that discussing eye donation will cause distress to patients and kins is a major barrier to eye donation.^[19,20] A recent scoping review by Madi-Segwagwe *et al.*^[20] revealed that majority of HCWs, across the retrieved dataset, avoided discussions about eye donation unless the issue was primarily brought up by the patient or the kins. However, it is generally accepted that most of the families who give consent to donation consider this as a positive experience.^[21] A survey of in-patients found that it was not distressing to discuss eye donation for the majority (73%) of participants and that knowing about donation enabled them to make an informed decision about donation.^[22] Thus, a discrete discrepancy exists between the perception of service providers and that of services users.

Willingness to donate eyes in the present study was calculated to be 45.84%, with no statistical difference across the study groups. Williams and Muir, in their review analysis, mentioned that willingness to donate ranged from 7.3% among urban Pakistanis to 90% of patients at a tertiary eye institute in the USA, averaging 52% across all studies.^[23] However, it cannot be overemphasized that a disparity exists between having an interest in donation and being actually registered for the same. Further, not all the pledged eyes transform into actual donations, without robust eye banking services and effective HCRP. One of the commonly cited reasons for being unwilling to donate is lack of enough awareness regarding eye donation.^[23-25] Slightly more than half of HCWs in our study indicated that they were interested to acquire more information about eye donation.

In the present study, medical campaigns and hospital sources emerged as the preferred sources to acquire

information about eye donation. This is in congruence to the findings of other awareness surveys conducted among HCWs.^[9,15,24]

To combat corneal blindness, HCRP plays a fundamental role in meeting the corneal demands in a country like India, where majority of deaths occur in a hospital setting. EBAI further emphasizes on HCRP as approximately 72% of utilization of donated corneas is through HCRP model and 38% is through voluntary donation in eight eye banks of the country.^[26] An efficient HCRP ensures lesser death to enucleation time and preservation time, thereby improving the visual outcome after keratoplasty.^[27,28] Apart from raising awareness regarding corneal donation among HCWs, other measures to boost HCRP may include putting up posters and digital display units featuring eye donation information, in vernacular language, in intensive and critical care wards. Showing short videos of the experiences of the actual donor families and recipient patients in the waiting lounges can be another impactful measure. Further, organ donation sensitization can be made a "routine" inclusion in admission formalities in critical care and trauma units.

Conclusion

Frequent awareness lectures and campaigns, elaborating on the technical aspects of corneal donation and retrieval process, will result in better informed HCWs. A well-coordinated approach among the medical officers, nursing staff eye donation counselors, and technicians is warranted for an effective implementation of HCRP.

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Posterior corneal surface stability after femtosecond laser-assisted *in situ* keratomileusis in patients with myopia and myopic astigmatism

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Purpose: To evaluate the variation and stability of the posterior cornea surface parameters (posterior cornea curvature [PCC], posterior cornea astigmatism [PCA], and posterior cornea elevation [PCE]) after femtosecond laser-assisted *in situ* keratomileusis (LASIK) in patients with myopia and myopic astigmatism over a period of 6 months or longer. **Methods:** This retrospective study comprised 284 right eyes. Patients aged 18 years or older with myopia up to -12.00 D and/or astigmatism up to -6.00 DC and who underwent femtosecond LASIK were recruited. Patients were divided into three subgroups: low myopia (-0.50 to -3.00 D), moderate myopia (>-3.00 to ≤-6.00 D), and high myopia (>-6.00 D), according to their pre-LASIK spherical equivalent (SE). The variables included for analysis were PCC (central 0–3.0 mm, pericentral 3.0–6.0 mm, and peripheral region 6.0–9.0 mm), PCE, PCA, internal anterior chamber depth, intraocular pressure, and central cornea thickness at the pre- and post-LASIK stages. **Results:** The central PCC remained unchanged across all three myopia subgroups at 1 month when compared to the pre-LASIK stage and remained stable at 6 months. The pericentral regions became flatter across all myopia subgroups at 1 month postsurgery ($P < 0.001$) and remained unchanged at 6 months. This trend was not seen in the peripheral cornea regions, which remained unchanged at 1 and 6 months post-LASIK when compared to pre-LASIK mean readings. There were minimal changes in post-LASIK posterior cornea astigmatism throughout follow-up. There was no incidence of post-LASIK surgery ectasia in this study population. **Conclusion:** Post-LASIK, the different cornea subregions behaved differently. Overall, the posterior cornea surface remained stable post-LASIK across all myopia subgroups throughout follow-up.

Key words: LASIK, myopia, posterior cornea stability

Laser-assisted *in situ* keratomileusis (LASIK) is one of the most common surgical techniques used for correcting refractive errors. LASIK is known to be relatively safe and effective.^[1] Nevertheless, complications may arise. One of the most feared is postoperative ectasia, which can result in progressive myopic astigmatism.^[2] Accurate analysis of the cornea is, therefore, important during pre-LASIK assessment to reduce the chances of post-refractive surgery ectasia.^[3] Post-LASIK corneal shape, which determines the refractive outcome of LASIK, is affected by surgical parameters such as flap thickness, flap diameter and ablation depth, the wound healing process, and severity of postoperative inflammation.^[4]

Methods

Presently, surgical planning is based on population-based normative response. However, corneal reaction to surgical ablation (i.e., residual refractive error and refractive regression) is individualized. Consequently, customization of treatment has been gaining popularity. Thus, it is important to analyze

corneal shape changes at the pre-LASIK stage as well as the post-LASIK stage.

The primary objective of this study is to evaluate variation and stability of the posterior cornea surface parameters (posterior cornea curvature [PCC], posterior cornea astigmatism [PCA], and posterior cornea elevation [PCE]) after femtosecond LASIK in patients with myopia and myopic astigmatism over a period of 6 months or longer. The secondary objectives are to (i) evaluate the stability of internal anterior chamber depth, central cornea thickness, and intraocular pressure (IOP) post-LASIK surgery and (ii) assess the incidence of post-LASIK regression.

Most studies have analyzed the cornea as a whole.^[5–8] However, it has been shown that some variation in the posterior cornea surface after femtosecond LASIK surgery may be explained by variation in cornea subregions.^[9] Hence, we analyzed the central, pericentral, and peripheral regions of the posterior cornea surfaces separately. A literature search

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did not recover any studies in Southeast Asian countries that investigated the stability of posterior cornea surface post-LASIK. Furthermore, there is a paucity of data on refractive surgery in our country, and we found only two published papers to date with regards to LASIK.^[10,11] To the best of our knowledge, the present study is the first in this region that evaluates the stability of the posterior cornea surface subregions post-LASIK surgery.

The present study is retrospective and complies with the ethical principles outlined in the Declaration of Helsinki. The study protocol is approved by the Medical Research Ethics Committee. Data was collected between May 2020 and October 2021.

Patients aged 18 years or older with myopia up to -12.00 D and/or astigmatism up to -6.00 DC and who underwent femtosecond LASIK were recruited. The study subjects had stable refraction with no more than 1.00 D change within the previous year. Patients were divided into three subgroups, low myopia (-0.50 to -3.00 D), moderate myopia (>-3.00 to ≤-6.00 D), and high myopia (>-6.00 D), according to their degree of myopia calculated from their pre-LASIK spherical equivalent (SE). The ocular variables included for analysis were PCC (central 0–3.0 mm, pericentral 3.0–6.0 mm, and peripheral 6.0–9.0 mm region), PCE, PCA, internal anterior chamber depth, IOP, and central cornea thickness at the pre- and post-LASIK stages.

All patients underwent a complete ophthalmic examination preoperatively. Those wearing soft and hard contact lenses were asked to stop wearing their lens for 1 and 2 weeks, respectively, before surgery. Trained optometrists performed all cornea topography scans. Pre- and post-LASIK cornea topography was done using the GALILEI G6 Lens Professional[®] 2024 Ziener Ophthalmic Systems. All measurements were made under identical lighting condition with nondilated pupil. The best dual Scheimpflug tomography scan was selected to be used for analysis.

In this study, we used the Galilei G6, which has a dual Scheimpflug rotating camera and an integrated Placido's disc for imaging of the anterior segment. A Scheimpflug system images the anterior segment in three dimensions with a camera perpendicular to a slit beam, creating an optical section of the cornea. It provides anterior and posterior surface topography of the cornea that is derived from true elevation measurements, in contrast to the Orbscan IIz (Bausch and Lomb, Rochester, NY, USA), which derives its posterior elevation map mathematically. The Galilei G6 uses a monochromatic slit-light source (blue light-emitting diode [LED] at 470 nm). The whole scan takes less than a minute to complete, giving information about more than 122,000 data points. Placido and Scheimpflug images of the cornea were simultaneously obtained in a single scan and used for anterior corneal measurements. The measurements from the Galilei have been found to have good repeatability in normal subjects and post-refractive surgery patients.^[12,13]

Every patient was subjected to a standard surgical procedure. A corneal flap with a diameter of 8.8 mm and a superior hinge was made at a depth of 110 μ m with the femtosecond laser (FEMTO LDV Z8, Ziener Ophthalmic Systems AG). This step was followed by tissue ablation using an excimer laser (Visx STAR S4 IR[™], Advanced Medical Optics). The cornea flap was then replaced. Post-LASIK surgery, patients were given gutt Vigamox QID and gutt Pred Forte

1% every 2 h for 1 week. The medications were tapered and discontinued at 2 weeks. Patients who completed a minimum follow-up period of 6 months were included in the study. This duration was used as the cutoff as corneal wound healing is expected to have stabilized around 6 months after surgery.^[8]

To summarize, the present study involved 286 patients, of whom 280 had bilateral femtosecond-assisted LASIK and six underwent unilateral eye LASIK. There were 566 observations of operated eyes, where 282 were left eyes and 284 were right eyes. As reported previously, measurements in bilateral corneas are strongly correlated and behave with mirror symmetry.^[14] Hence in this study, only the right eyes were used for statistical analyses.

Descriptive statistics was expressed as mean \pm standard deviation unless otherwise stated. For testing whether mean PCC at the three ocular regions differed significantly among the three myopia subgroups, one-way analysis of variance was used. Paired *t*-tests for differences in mean for comparisons of ocular variables at different time stages were done. Bonferroni adjustment for multiple comparisons was done at a nominal 5% level of significance. All statistical analyses were done using R version 4.0.4 (R Core Team, 2021).

Results

Of the 284 patients, 111 (39.1%) were men and 173 (60.9%) were women. The mean age of subjects was 30 ± 6 years. In terms of ethnicity, 64% (183/284) of the patients were Chinese, 22% (62/284) were Malay, 6% were Indians (17/284), and 8% were other ethnicities (22/284). In the present study, the median of post-LASIK follow-up duration was 6.8 months (interquartile range: 6.1–7.7 months).

The mean pre-LASIK SE was estimated to be -2.32 ± 0.54 D in the low myopia group (80 eyes), -4.31 ± 0.87 D in the moderate myopia group (152 eyes), and -8.18 ± 1.18 D in the high myopia group (52 eyes). The difference in mean post-LASIK SE between 1-week post-LASIK and pre-LASIK was 2.23 ± 0.69 D ($P < 0.001$) in the low myopia group, 4.25 ± 0.90 D ($P < 0.001$) in the moderate myopia group, and 8.08 ± 2.01 D ($P < 0.001$) in the high myopia group. These improvements are clinically as well as statistically significant. Subsequently, mean SE remained close to emmetropia at 1-month and the final post-LASIK follow-up across all myopia subgroups. Refractive regression was most pronounced in the high myopia subgroup.

Mean preoperative PCC at the central and the pericentral regions was approximately the same: -6.26 ± 0.22 and -6.25 ± 0.19 D, respectively, in the low myopia group, -6.28 ± 0.21 and -6.27 ± 0.20 D, respectively, in the moderate myopia group, and -6.31 ± 0.32 and -6.33 ± 0.18 D, respectively, in the high myopia group. In the peripheral region, the mean was slightly steeper [Table 1.1]. No statistically significant differences in mean PCC for central, pericentral, and peripheral regions were found across all myopia subgroups during all stages of review (P values >0.05) [Table 1.2, 1.3 and 1.4].

Across all myopia subgroups, mean PCC at the pericentral region showed statistically significant flattening at 1-month and the last post-LASIK follow-up, compared to the pre-LASIK values ($P < 0.001$) [Table 1.3]. In the moderate myopia subgroup, although a statistically significant difference in mean PCC at the pericentral region ($P < 0.001$) was detected between 1-month and the last post-LASIK follow-up, the difference of 0.01 D is

Table 1.1: Mean±SD of PCC axial of three regions (central, pericentral, peripheral; in diopter, D)

Myopia subgroup	Region	Stage		
		Pre-op	1-month post-op	Last post-op follow-up
Low	Central	-6.26±0.22	-6.26±0.22	-6.25±0.23
	Pericentral	-6.25±0.19	-6.29±0.19	-6.27±0.19
	Peripheral	-6.08±0.19	-6.07±0.19	-6.07±0.19
Moderate	Central	-6.28±0.21	-6.29±0.21	-6.27±0.21
	Pericentral	-6.27±0.20	-6.32±0.20	-6.31±0.19
	Peripheral	-6.10±0.20	-6.10±0.19	-6.09±0.19
High	Central	-6.31±0.32	-6.33±0.19	-6.33±0.22
	Pericentral	-6.33±0.18	-6.45±0.17	-6.44±0.17
	Peripheral	-6.15±0.18	-6.14±0.18	-6.15±0.17

PCC=Posterior cornea curvature, SD=Standard deviation

Table 1.2: Result of paired t-tests for central axial PCC between the follow-up stages for each myopia subgroup^a

Myopia subgroup	Comparison between stages		
	Pre-LASIK versus 1-month post-LASIK	Pre-LASIK versus last post-LASIK follow-up	1-month post-LASIK versus last post-LASIK follow-up
Low	0.00±0.08 (1.000)	0.01±0.08 (0.882)	0.01±0.08 (1.000)
Moderate	-0.01±0.09 (0.348)	0.01±0.10 (0.321)	0.02±0.09 (0.006)
High	-0.02±0.26 (1.000)	-0.02±0.28 (1.000)	0.00±0.10 (1.000)

^aActual threshold for statistical significance is 0.05/9=0.006 after Bonferroni adjustment; P values are indicated in brackets; LASIK=Laser-assisted *in situ* keratomileusis

Table 1.3: Result of paired t-tests for pericentral axial PCC between the follow-up stages for each myopia subgroup^a

Myopia subgroup	Comparison between stages		
	Pre-LASIK versus 1-month post-LASIK	Pre-LASIK versus last post-LASIK follow-up	1-month post-LASIK versus last post-LASIK follow-up
Low	-0.03±0.04 (<0.001)*	-0.02±0.04 (<0.001)*	0.01±0.04 (0.011)
Moderate	-0.05±0.04 (<0.001)*	-0.04±0.04 (<0.001)*	0.01±0.04 (<0.001)*
High	-0.12±0.09 (<0.001)*	-0.12±0.09 (<0.001)*	0.01±0.04 (1.000)

^aActual threshold for statistical significance is 0.05/9=0.006 after Bonferroni adjustment; P values are indicated in brackets; *indicates statistically significant result. LASIK=Laser-assisted *in situ* keratomileusis

Table 1.4: Result of paired t-tests for peripheral axial PCC between the follow-up stages for each myopia subgroup^a

Myopia subgroup	Comparison between stages		
	Pre-LASIK versus 1-month post-LASIK	Pre-LASIK versus last post-LASIK follow-up	1-month post-LASIK versus last post-LASIK follow-up
Low	0.02±0.07 (0.073)	0.01±0.08 (0.333)	0.00±0.06 (1.000)
Moderate	0.00±0.08 (1.000)	0.01±0.08 (0.278)	0.01±0.08 (0.213)
High	0.01±0.08 (0.990)	0.00±0.09 (1.000)	-0.01±0.08 (1.000)

^aActual threshold for statistical significance is 0.05/9=0.006 after Bonferroni adjustment; P values are indicated in brackets; LASIK=Laser-assisted *in situ* keratomileusis

of no clinical importance. For the low and the high myopia subgroups, no statistically significant differences were found between 1-month and the last post-LASIK follow-up ($P>0.006$).

Mean PCA remained stable from pre-LASIK to 1-month and the last post-LASIK follow-up for the low and high myopia subgroups (P values >0.006) [Table 2.1]. In the moderate myopia subgroup, there was a statistically significant change ($P<0.001$) in mean PCA at 1-month and the last post-LASIK follow-up relative to pre-LASIK measurement [Table 2.2]. However, the decrease of 0.06 D at 1-month post-LASIK was not clinically significant.

The mean of the highest PCE was estimated to be about 12.5 ± 4 and 15 ± 5 μm at pre-LASIK and at 1-month post-LASIK, respectively, for all myopia subgroups. There was a statistically significant increase of the highest PCE in post-LASIK stages compared to the pre-LASIK stages across all myopia subgroups ($2.5 \mu\text{m}$; P values <0.001) [Table 3]. However, the magnitude of increase was not clinically significant. Change in mean of highest PCE between 1-month and the last follow-up stage was not statistically significant (P values >0.006).

Pre-LASIK surgery, subjects with higher refractive errors had, on average, thicker corneas ($548 \pm 27 \mu\text{m}$ in the low myopia group, $553 \pm 30 \mu\text{m}$ in the moderate myopia group, and $565 \pm 31 \mu\text{m}$ in the high myopia group). There was a statistically and clinically significant reduction in central cornea thickness (CCT) at 1-month post-LASIK. Mean CCT decreased by 40, 74, and 125 μm from 548, 553, and 565 μm pre-LASIK in the low, moderate, and high myopia subgroups, respectively (P values <0.001). Mean CCT then stabilized around 510 μm in the low myopia subgroup, 480 μm in the moderate myopia subgroup, and 440 μm in the high myopia subgroup at 1-month post-LASIK. The mean values remained stable at the last follow-up.

In the moderate myopia subgroup, a statistically significant thickening of CCT was seen at the last post-LASIK follow-up when compared to 1-month post-LASIK (P values <0.001). The difference in mean CCT was +4 μm . Similar result was observed in the high myopia subgroup (difference in mean CCT = +5 μm). For the low myopia subgroup, the difference in mean CCT was +2 μm , but this was not statistically significant ($P > 0.006$) [Table 4].

The mean internal anterior chamber depth (IACD) was approximately the same in all three myopia subgroups pre-LASIK: $3.12 \pm 0.29 \text{ mm}$ in the low myopia group, $3.12 \pm 0.24 \text{ mm}$ in the moderate myopia group, and

$3.07 \pm 0.28 \text{ mm}$ in the high myopia group. A statistically significant decrease of about 0.05 mm ($P < 0.001$) was observed at 1-month post-LASIK. Subsequently, mean IACD remained relatively stable throughout the follow-up period.

Mean IOP was approximately $15 \pm 3 \text{ mmHg}$ pre-LASIK for all three myopia subgroups. Post-LASIK, there was a mean decrease of about 1 mmHg per diopter refractive error correction in the low and moderate myopia subgroups and about 0.7 mmHg per diopter correction in the high myopia subgroup.

Discussion

Due to coronavirus disease 2019 travel restrictions imposed in the country during the study period, not all patients were able to attend their follow-up at exactly 6 months post-LASIK. Consequently, some degree of heterogeneity in ocular measurements at the 6-month post-LASIK period is expected. A follow-up period of 6 months was used as the minimal cutoff as previous studies have reported that cornea wound healing generally stabilizes at 6 months post-LASIK.^[8,15] Furthermore, Christiansen *et al.*^[16] found that visual outcome in terms of SE refraction only changed minimally after 6 months. In their study of moderate myopes, only 2% (steeper corneas) and 5% (flatter corneas) experienced a change in SE greater than 0.50 D between 6 and 12 months post-LASIK.^[16] Generally, we observed that PCC remained stable 6 months post-LASIK.

Interestingly, we observed regional changes in PCC that differ from what was reported previously [Table 5]. In Bao *et al.*,^[9] the curvature of the posterior cornea surface was reported to be slightly flatter in the central region and slightly steeper in both the pericentral and peripheral regions at 6 months post-LASIK, compared to pre-LASIK measurements, across all myopia subgroups. Possible mechanisms for these differences are given by three conceptual models for post-LASIK cornea wound healing.^[9] Firstly, weakening of the central cornea leads to easier pushing out of the peripheral region under IOP and

Table 2.1: Mean±standard deviation of posterior cornea surface astigmatism (in D)

Myopia subgroups	Stage		
	Pre-LASIK	1-month post-LASIK	Last post-LASIK follow-up
Low	-0.33±0.15	-0.34±0.14	-0.35±0.16
Moderate	-0.36±0.12	-0.41±0.14	-0.41±0.14
High	-0.40±0.16	-0.43±0.15	-0.44±0.16

LASIK=Laser-assisted *in situ* keratomileusis

Table 2.2: Result of paired t-tests of posterior cornea astigmatism between the follow-up stages for each myopia subgroup^a

Myopia subgroups	Comparison between stages		
	Pre-LASIK versus 1-month post-LASIK	Pre-LASIK versus last post-LASIK follow-up	1-month versus last post-LASIK follow-up
Low	-0.02±0.09 (0.450)	-0.02±0.1 (0.148)	-0.01±0.09 (1.000)
Moderate	-0.06±0.09 (<0.001)*	-0.06±0.11 (<0.001)*	0.00±0.12 (1.000)
High	-0.03±0.14 (0.387)	-0.05±0.14 (0.057)	-0.02±0.08 (0.444)

^aActual threshold for statistical significance is 0.05/9=0.006 after Bonferroni adjustment; P values are indicated in brackets; *indicates statistically significant result. LASIK = laser-assisted *in situ* keratomileusis

Table 3: Result of paired t-tests for highest PCE (in μm) between the follow-up stages for each myopia subgroup^a

Myopia subgroup	Comparison between stages		
	Pre-LASIK versus 1-month post-LASIK	Pre-LASIK versus last post-LASIK follow-up	1-month post-LASIK versus last post-LASIK follow-up
Low	1.8±2.9 (<0.001)*	1.3±3.0 (<0.001)*	-0.5±2.9 (0.483)
Moderate	3.0±5.6 (<0.001)*	3.0±3.5 (<0.001)*	0.0±5.5 (1.000)
High	2.3±4.3 (<0.001)*	3.1±3.6 (<0.001)*	0.7±3.7 (0.492)

^aActual threshold for statistical significance is 0.05/9=0.006 after Bonferroni adjustment; P values are indicated in brackets; *indicates statistically significant result. LASIK=Laser-assisted *in situ* keratomileusis, PCE=Posterior cornea elevation

Table 4: Result of paired t-tests of central cornea thickness between the follow-up stages for each myopia subgroup^a

Myopia subgroup	Comparison between stages		
	Pre-LASIK versus 1-month post-LASIK	Pre-LASIK versus last post-LASIK follow-up	1-month post-LASIK versus last post-LASIK follow-up
Low	-40±13 (<0.001)*	-37±12 (<0.001)*	2±8 (0.012)
Moderate	-74±19 (<0.001)*	-70±19 (<0.001)*	4±7 (<0.001)*
High	-125±21 (<0.001)*	-20±21 (<0.001)*	5±6 (<0.001)*

^aActual cutoff level is 0.05/9=0.006 after Bonferroni adjustment; P values are indicated in brackets; *indicates statistically significant result. LASIK=Laser-assisted *in situ* keratomileusis

Table 5: Cornea healing biomechanics in this study versus Bao *et al.*'s (2019) study

This study	Posterior cornea curvature changes	Bao <i>et al.</i> 's study, 2019 ^[9]
Remains the same postoperatively and stays stable throughout the follow-up period	Central region	Becomes flatter at 6 months postsurgery
Becomes flatter at 1-month postsurgery, then remains stable	Pericentral region	Becomes steeper at 6 months postsurgery
Remains the same postoperatively and stays stable throughout the follow-up period	Peripheral region	Becomes steeper at 6 months postsurgery

flattening of the anterior central region. Secondly, the weaker central region is curved under IOP, pulling the peripheral region toward the center. This results in the central cornea becoming steeper while the periphery becomes flatter. The third mechanism shows intermediate behavior between the first two mechanisms. In Bao *et al.*, cornea shape changes are best explained by the first mechanism. In contrast, the third mechanism appears to be the most plausible in this study.

Here, we suggest several explanations to account for the differences observed in the present study and Bao *et al.*^[9] Firstly, the population in this study is more diverse, comprising subjects from different ethnic groups; in contrast, the Chinese population in Bao *et al.*'s study is homogeneous. This difference may account for different cornea healing biomechanics and post-LASIK posterior cornea changes. Next, instrumentation difference may also be a source of variation. The cornea tomography machine used in our study was Galilei G6, whereas Bao *et al.* used Pentacam HR. The Pentacam system uses a monochromatic blue LED at 475 nm and a single Scheimpflug camera that rotates around the optical axes of the eye to analyze the anterior segment. Shetty *et al.*^[17] assessed the repeatability and agreement of three rotating Scheimpflug cameras, the Pentacam, Galilei G6, and Sirius, in measuring the mean keratometry, thinnest corneal thickness, anterior chamber depth, and mean posterior keratometry in keratoconus patients. They concluded that there are significant differences in measurements obtained using these three devices. Hence, anterior segment measurements from these machines are not interchangeable.

With regards to PCE changes, there was no incidence of surgery-induced ectasia in present study. The femtosecond laser allows the cornea flap to be made at a lower depth, with greater predictability and homogeneity in thickness, which reduces loss of corneal tensile strength.^[18] Patients could still develop late-onset corneal ectasia with a mean time of onset between 57±24 months.^[19] Hence, post-LASIK patients should be followed up for longer duration. PCA remained stable at 6 months post-LASIK. Mean PCA ranged between -0.33 and -0.44 D throughout follow-up period. On average, patients

in the high myopia subgroup exhibited higher PCA.

We found that patients with higher refractive errors pre-LASIK had thicker corneas. This is in agreement with several previous studies that also reported a positive correlation between the degree of myopia and CCT.^[20-22] However, there are also reports of negative correlation^[23] or no correlation^[24,25] between CCT and degree of refractive error. Two hypotheses have been put forth to explain the elongation of the human globe. Pedersen *et al.*^[26] argued that the overall growth of the eye coupled with axial elongation in myopia accounted for the findings of their study, where a greater degree of myopia was observed to be associated with higher CCT. In contrast, the "stretching theory" postulates a passive thinning of all the layers of the eye as it elongates, analogous to a balloon being inflated.^[27] The stretching theory thus accounts for the negative correlation. Wang *et al.*^[8] reported that the immediate reduction in cornea thickness measurements caused by ablation was followed by slight increases over a 6-month follow-up period due to epithelial thickening at the center of the cornea as a result of myopic ablation. In the present study, we too found a slight increase in CCT during the last post-LASIK follow-up across all myopia subgroups. However, we are unable to conclude that the increase is purely due to cornea epithelial thickening as we did not measure the epithelium and stroma thickness separately.

There was an average decrease of 1 mmHg per diopter of refractive error correction in the low and moderate myopia subgroups and a 0.7 mmHg drop per diopter in the high myopia subgroup post-LASIK surgery. This is consistent with the study by Ajazaj *et al.*^[28] who found a postsurgery reduction of about 1 mmHg per diopter in their LASIK patients. One of the clinical implications of this observation is that post-LASIK patients may have a delayed diagnosis of glaucoma due to the artificially low IOP.

We observed a statistically significant decrease of ~0.05 mm in IACD at 1-month post-LASIK, which then remained stable. Wang *et al.*^[8] observed a similar reduction in IACD, which they attributed, at least partly, to the backward shift in the posterior cornea surface observed in their study cohort. This could not

be the reason for the apparent decrease in IACD in the present study as the central cornea subregion remained unchanged throughout follow-up with no significant forward or backward shift. Overall, the post-LASIK IACD remained stable across all myopia subgroups. This observation may be useful for deriving new intraocular lens (IOL) calculation formulae for post-keratorefractive surgery eyes. As the current post-refractive surgery population ages, the need for cataract removal surgery will eventually arise. IOL power calculations in eyes with previous corneal refractive surgery are challenging as refractive surprise can occur. There are three possible reasons: (i) the altered ratio between the anterior and posterior corneal surfaces makes the keratometric index invalid; (ii) the corneal curvature radius is measured out of the optical zone; and (iii) the effective lens position is erroneously predicted if such a prediction is based on post-refractive surgery cornea curvature.^[29] Various IOL power calculation formulae are currently available, with 60%–70% eyes showing a prediction error within 0.50 D postsurgery.^[29] Currently, some IOL formulae, for example, Maloney's method, incorporate the posterior cornea power with a mean value of −4.90 D, whereas the Haigis-L formula uses anterior chamber depth.

Wang *et al.*^[8] also compared the changes in ocular biometric parameters after femtosecond LASIK versus small-incision lenticule extraction (SMILE) over a 6-month period. They found that the cornea became thicker during follow-up after both surgeries and the posterior corneal surface became slightly flatter with a posterior shift; these effects were lower in low myopia patients than in high myopia patients, and the effects were larger and more consistent in femtosecond LASIK than in SMILE. They concluded that femtosecond LASIK caused more pronounced topographic changes postsurgery than SMILE, possibly due to more structural changes taking place in the corneal tissue in the former procedure.^[8] Similarly, Ryu *et al.*^[30] reported that postoperative changes in epithelial thickness were larger after femtosecond LASIK surgery than after SMILE.

Conclusion

To summarize, the posterior cornea subregions showed differences in characteristics after femtosecond-assisted LASIK. Overall, the posterior cornea surface remained stable post-LASIK surgery across all myopia subgroups throughout follow-up.

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Conflicts of interest: Dr Adeline Low declares that one of the surgeons in the eye center where current study was conducted is her father. The eye center was neither involved in nor influenced the conduct, result interpretation, result analysis and preparation of manuscript for this study. All other authors have none to declare.

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Outcomes of keratoplasty in a cohort of *Pythium insidiosum* keratitis cases at a tertiary eye care center in India

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Purpose: To assess outcomes of keratoplasty performed in patients diagnosed with keratitis caused by *Pythium insidiosum* (PI). **Design:** Retrospective review. **Methods:** Preoperative, intra operative and post operative data of patients diagnosed with PI keratitis and who underwent keratoplasty for their condition from January 2020 to December 2021 were collected from the central patient database of a tertiary eye care hospital in India. The data were analyzed for anatomic success, elimination of infection, graft survival, incidence of repeat keratoplasty, final visual acuity and varied complications. **Results:** In total, 16 eyes underwent penetrating keratoplasty for PI keratitis during the study period. Mean time to keratoplasty from onset of symptoms was 31.3 days and mean graft size was 10.4 mm. Nine out of the 16 cases had recurrence of infection following surgery, seven of which required a repeat keratoplasty for elimination of infection. Mean graft size for repeat keratoplasty performed in recurrent cases was 11.7 mm. Globe was successfully salvaged in 14 out of 16 patients (87.5%). Three grafts remained clear at 6-month follow up while 11 grafts failed. Mean improvement in uncorrected visual acuity from 2.32 to 2.04 logMAR was observed at last follow up. Endo-exudates, graft infiltration, graft dehiscence, secondary glaucoma and retinal detachment were the various complications noted after keratoplasty. **Conclusion:** PI keratitis is a tenacious and potentially blinding condition. Keratoplasty remains the choice of treatment in this condition, however recurrence of disease and graft failure are common. Large sized grafts, meticulous per-operative removal of infection, adjuvant cryotherapy, and intraoperative and post operative use of antibiotics can help in improving outcome of keratoplasty in these patients.

Key words: Corneal blindness, microbial keratitis, *Pythium insidiosum*, therapeutic penetrating keratoplasty

Microbial keratitis is one of the leading causes of corneal blindness in tropical belts of the world, particularly in developing nations of South and East Asia.^[1] It is estimated that in India, approximately 2 million cases of corneal ulcer occur yearly, most of which are attributed to some form of antecedent injury.^[2] While fungi and bacteria are the most common etiological agents of keratitis, sophisticated microbiologic techniques such as DNA sequencing have revealed the existence of newer pathogens. It is estimated that 10% of cases of microbial keratitis are associated with these novel organisms.^[3] *Pythium insidiosum* (PI) is one such new pathogen of the 21st century. It is an aquatic oomycete, which exists in two forms, mycelium and zoospore.^[4] Infection has been reported to be acquired through motile zoospores present in freshwater.^[5]

Classical clinical features of PI keratitis are described as reticular dot infiltrates, tentacular projections, and peripheral furrowing; however, these hallmark signs may be absent in majority of the cases.^[6] Microbiologically, it mimics fungus due to the presence of branching hyphae on smear examination, but unlike fungus, its growth on culture is delayed and it lacks ergosterol in its cell wall.^[7]

Since PI keratitis was first reported in 1993, diagnostic techniques and management guidelines for this condition

have evolved.^[8] Published reports indicate that it is a fulminant condition and therapeutic keratoplasty is warranted in most of the patients.^[9–11] Owing to the obstinate nature of the disease, loss of globe and failure of keratoplasty with eventual loss of vision are the commonly reported outcomes in PI keratitis.^[6,10] Herein, we report outcomes of keratoplasty in a cohort of PI keratitis patients from a tertiary eye care institute in India, with an emphasis on surgical techniques to eliminate infection.

Methods

This is a retrospective review of outcomes of keratoplasty in culture-proven cases of PI keratitis treated between January 2020 and December 2021 at a tertiary eye care institute in India. The study approval was obtained from the institutional review board, and the study complied with the tenets of the Declaration of Helsinki.

The clinical and the microbiologic case records of all culture-proven cases of PI keratitis which underwent keratoplasty were retrieved from the electronic central patient database of the hospital. Patients with incomplete medical records or those treated for PI keratitis on clinical suspicion alone were excluded.

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Preoperative data such as demographic profile, predisposing risk factors, systemic comorbidity, previous clinical or microbiologic diagnosis, visual acuity at presentation, medical therapy received, and time to therapeutic penetrating keratoplasty (TPK) from the onset of symptoms were recorded.

Intraoperative data recorded included the size of the graft, special techniques employed during keratoplasty, use of adjuvant intraocular antibiotics, combined posterior segment surgery (if performed), and lens status at the end of the procedure.

Postoperative data were collected to assess the outcomes of keratoplasty and its complications. Parameters noted were globe integrity, graft survival, best corrected visual acuity (BCVA), and recurrence of infection. Recurrence was further elaborated as the type of recurrence, medical or surgical intervention for recurrence, and period of disease-free follow-up.

Corneal scraping was performed in all patients and sent for potassium hydroxide (KOH), Gram stain, and culture. Patients with a microbiologic diagnosis of PI keratitis were treated with topical linezolid 0.2% eyedrops hourly, azithromycin 1% eye ointment twice a day, topical cycloplegic (homatropine 2%) eyedrops twice a day, and oral azithromycin (500 mg twice a day). TPK was performed in patients, with worsening of disease defined as an increase in size and depth of infiltration, involvement of the limbus, corneal perforation, and corneal thinning. Excised corneal button/tissue was sent for microbiologic (bacterial and fungal) cultures and histopathology examination in every case.

Postoperatively, the eyes were treated with topical linezolid 0.2% eyedrops hourly, topical azithromycin 1% eye ointment twice a day, topical cycloplegic (homatropine 2%) eyedrops twice a day, and oral azithromycin (500 mg twice a day). Patients were prescribed steroid prednisolone acetate 1% eyedrops four times a day when the button culture report was found to be negative for fungal growth. Patients were followed up at close intervals. Repeat keratoplasty was performed in patients with recurrence not responding to topical and intracameral linezolid treatment.

Data analysis was performed using the Statistical Package for the Social Sciences statistics program (version 29.0; IBM, Chicago, USA). Continuous data are reported as mean \pm standard deviation with range, while categorical data are presented as frequencies (*n*) and percentages (%). BCVA data were converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analysis. Vision categories of counting fingers, hand motion, light perception, and no light perception were assigned logMAR values 2.1, 2.4, 2.7, and 3.0, respectively. Survival analysis was done to estimate the average time to repeat penetrating keratoplasty following the first surgery for *Pythium* keratitis.

Results

A summary of the clinical characteristics of the cohort is provided in Table 1. A total of 16 eyes of 16 patients were included in the study. The mean age at the time of presentation was 33.9 ± 13.2 years (range 19–58 years). Out of the 16 patients, 10 were males (62.5%) and six (37.5%) were females. A history of injury with vegetative matter was found in one patient, and one patient reported the onset of symptoms following contact lens use. None of the patients had preexisting ocular comorbidity. One patient had a history of hypertension and coronary artery disease.

Table 1: Baseline characteristics of *Pythium insidiosum* keratitis patients (*n*=16)

Characteristic	N=16
Sex	
Male/female	10/6
Mean age	33.9 years
Predisposing risk factors	
Injury	1
Contact lens use	1
Previous microbiologic diagnosis	
Fungus	7
Bacteria	1
Viral	1
Fungus and bacteria	6
Bacterial	1
Visual acuity at presentation	
1.5–1.8 logMAR	2
<1.8–2.1 logMAR	5
<2.1–2.4 logMAR	3
<2.1–2.7 logMAR, accurate projection of rays	4
Perception of light +, inaccurate projection of rays	2
Mean duration of symptoms at the time of presentation	23.1 days

LogMAR=Logarithm of the minimum angle of resolution

The mean duration of symptoms was 23.1 ± 9.9 days (range 10–45 days) at the time of presentation to the hospital. All patients had a history of previously receiving treatment from elsewhere. Seven (43.75%) patients had been diagnosed with fungal keratitis and were on antifungal treatment. Seven (43.75%) patients were on a cocktail therapy of antibacterial and antifungal drugs, while two patients were receiving antiviral therapy. None of the patients had been previously diagnosed as cases of PI keratitis. The mean visual acuity at presentation was 2.32 ± 0.36 logMAR (approximately counting fingers close to face). The range of visual acuity at presentation was 1.5–2.7 logMAR (20/600- light perception Snellen). Figs. 1 and 2 show representative photographs depicting the clinical features and course of disease of patients from the study cohort.

Corneal scraping and microbiologic examination were performed for all patients. Long, sparsely septate hyaline hyphae with numerous vesicles suggestive of PI species were observed on KOH with calcofluor white smears in 11 patients [Fig. 3a and b]. In addition, Gram staining of the smear showed a thick cell wall, few septae, and a mass of vesicles within the hyphae. Flat, feathery-edged, partially submerged, colorless, or light brown glabrous colonies with filiform margins on blood agar were grown with the corneal scrapings from all patients in the cohort [Fig. 3c and d].

The diagnosis was further confirmed on histopathologic analysis of the growth. Periodic acid Schiff (PAS) staining was negative for fungal hyphae and showed only unstained fragments of sparsely septate hyphae, which were broad and unfolded. Grocott-Gomori's methenamine silver stain showed distinctly stained oomycetes on iodine potassium iodide-sulfuric acid (IKI-H₂SO₄) treatment suggestive of *Pythium* species. Following TPK, the excised corneal button was cultured and processed for species identification for all cases. Six of the 16 (37.5%) corneal button cultures showed *Pythium* growth after first surgery, while three out of seven (42.9%) corneal button cultures from repeat keratoplasty patients showed *Pythium* growth.

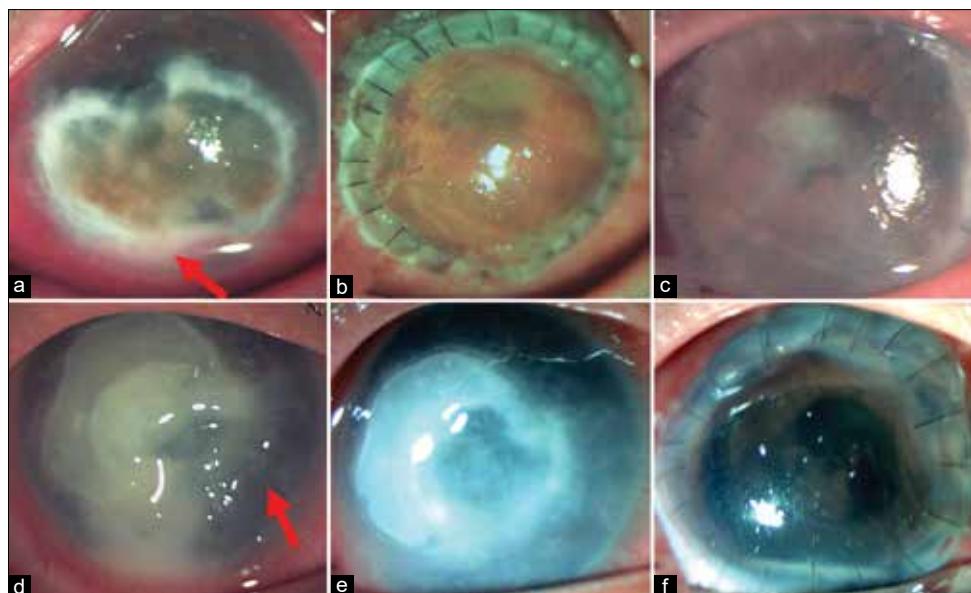


Figure 1: (a) Clinical photograph of a 58-year-old man with *Pythium* keratitis with limbal involvement (red arrow). (b) Large graft with complete removal of infection on postoperative day 1. (c) Failed graft with no recurrence seen at a 2-month follow-up. (d) Slit-lamp picture of a 19-year-old girl with mid-stromal tentacle-like lesions (red arrow) characteristic of *Pythium* keratitis. (e) Progression of disease leading to central corneal perforation with flat anterior chamber despite medical management of *Pythium*. (f) Postoperative day 4 picture following therapeutic keratoplasty, showing clear graft with no recurrence

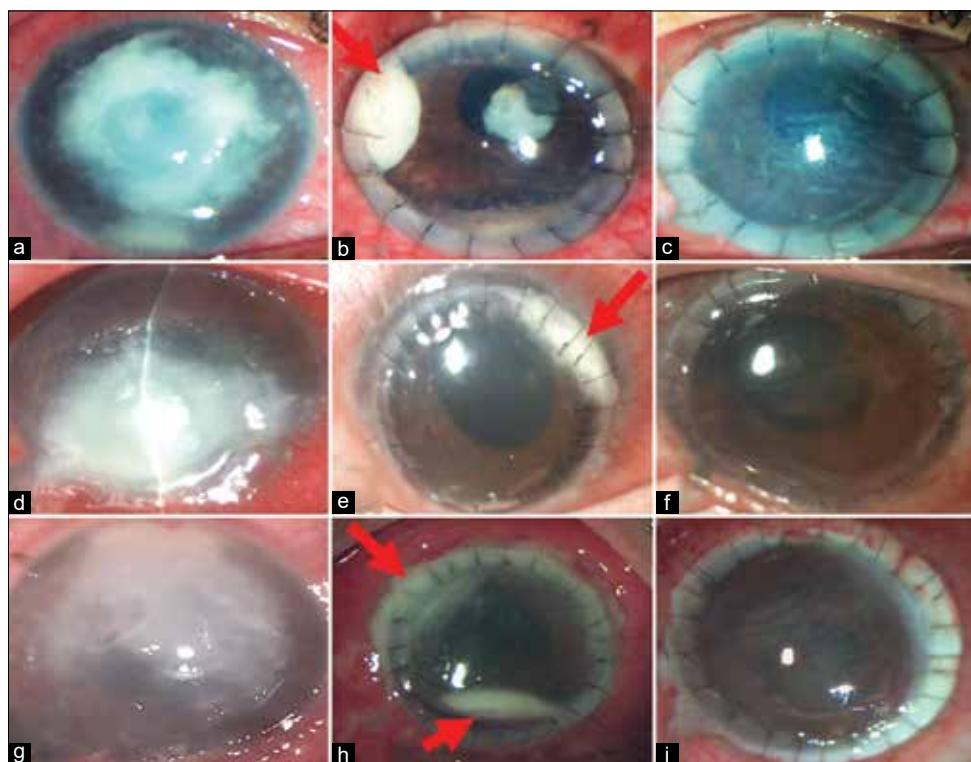


Figure 2: (a) Clinical picture of a 21-year-old girl with *Pythium* keratitis. (b) Graft dehiscence and endoexudates (red arrow) observed on postoperative day 26. (c) Hazy graft with no recurrence of disease seen after 1 month. (d) Slit-lamp examination of a 24-year-old male with *Pythium* keratitis. (e) Recurrence observed on fourth postoperative day (red arrow). (f) Clear and compact graft with no recurrence of infection at postoperative week 3. (g) Clinical presentation of a 34-year-old man with *Pythium* keratitis. (h) Recurrence noted at 1 week as infiltration at the graft-host junction and hypopyon (red arrows). (i) Postoperative Day 22 of repeat keratoplasty shows clear and healthy graft

Eleven patients underwent TPK under local anesthesia with facial block by a surgeon from the cornea team. General anesthesia was administered to five patients. The mean time to the first or primary keratoplasty from the onset of symptoms

was 31.3 ± 8.6 days (range 16–49 days). Mean primary graft size was 10.34 ± 0.87 mm (range 9.5–12 mm). Infection resolved with primary keratoplasty in nine patients (56.25%), while seven patients (37.5%) required repeat keratoplasty.

One patient required three keratoplasties for elimination of infection.

Trephination of the host bed was performed with the diameter of trephination enough to include more than 1 mm of the surrounding normal cornea. Careful dissection of the corneal tissue was done while separating the adherent tissue from all sides. Peripheral iridectomy was performed in all cases. A 1-mm difference between donor and host trephination size was ensured. Sixteen to 24 well-spaced, interrupted sutures were placed depending on the donor graft size. In one patient, who had scleral infiltration, an incision was made at the site of infiltration to partially deroof the sclera and drain the infiltration. The deroofed area was left uncovered to allow better penetration of antibiotics postoperatively. Intracameral linezolid (200 µg in 0.1 ml) was administered to all patients at the end of surgery. Double freeze-thaw cryotherapy at the site of scleral infiltration was done in addition to TPK in one patient.

The lens was preserved in 14 out of 16 patients after the first TPK. Three out of 6 patients who underwent repeat TPK had spontaneous expulsion of the lens during the procedure. Anterior vitrectomy was performed in all cases of lens expulsion.

All patients were kept under close follow-up postsurgery. Nine patients (56.25%) had a recurrence of infection. The mean time to presentation with recurrence was 8.9 days (range 2–34 days). Seven patients (43.8%) had one episode of recurrence, while two patients (18.8%) had two episodes of recurrence. Endoexudates were the most common form of recurrence being found in six of the nine cases. Recurrence of the disease additionally manifested as graft infiltration (one patient), graft-host junction infiltration (one patient), both graft-host junction infiltration and endoexudates (one patient),

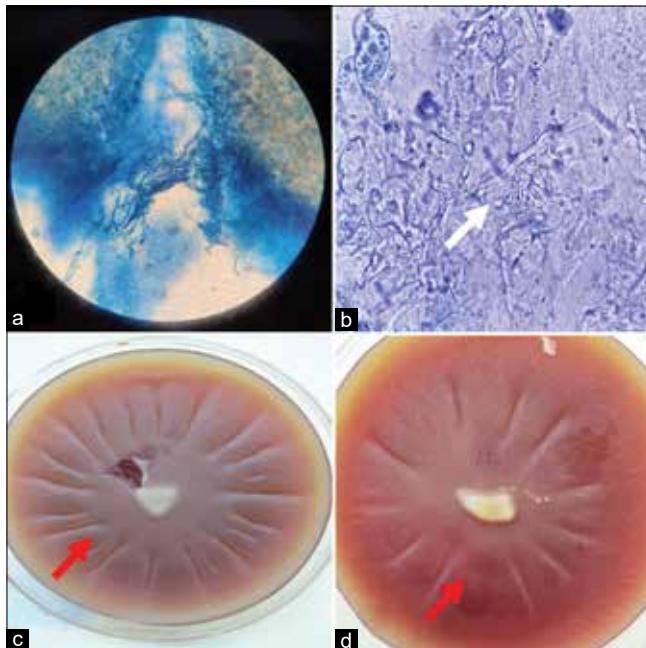


Figure 3: (a and b) Potassium hydroxide with calcofluor white smear showing septate, broad, acute-angled, nonfilamentous hyphae from corneal scraping. (c and d) Blood agar showing radiating colonies with flat planes, feathery edges, partially submerged, glabrous growth suggestive of *Pythium insidiosum*

graft dehiscence along with endoexudates (one patient), and graft melt (one patient).

Recurrence of infection was managed by repeat penetrating keratoplasty in seven patients, application of cryotherapy to the graft-host junction in one patient, and intracameral linezolid (200 µg in 0.1 ml, thrice over 4 days) in one patient. The mean graft size for the first TPK in patients who presented with recurrence was 10.06 ± 1.15 mm (range 8.5–10 mm), while the mean graft size of the repeat TPK was 11.7 ± 1.56 mm (range 10–14 mm). Two of the seven patients who underwent a repeat keratoplasty received up to four doses of intracameral linezolid before the second surgery. Topical steroid (prednisolone acetate 1%) eyedrops were prescribed two hourly to all patients after repeat keratoplasty, in addition to antibiotics.

The mean postoperative follow-up period in the study was 8.9 ± 9.8 months. Graft outcome was assessed at 6 months from the last surgery. Out of the seven patients who did not have a recurrence of infection after the first keratoplasty, one patient had a clear graft, five patients had graft failure, and one patient progressed to phthisis bulbi. The mean time to graft failure was 12.16 ± 4.54 weeks (range 2–32 weeks). Two of the five patients with graft failure underwent optical keratoplasty after 6 months of disease-free period.

Infection was controlled in all patients who underwent repeat keratoplasty. Out of the seven patients in whom repeat keratoplasty was performed, one patient had a clear graft, five patients had graft failure, and one patient progressed to phthisis bulbi. Fig. 4 depicts graft survival following repeat penetrating keratoplasty. Out of the five patients with graft failure, one patient underwent optical keratoplasty and another patient underwent Descemet's stripping automated endothelial keratoplasty (DSAEK) for visual rehabilitation. Secondary glaucoma (one patient) and retinal detachment (one patient) were the additional complications observed along with graft failure in this group. Retinal detachment was managed by vitrectomy and endolaser application, along with a repeat keratoplasty. Two patients who developed recurrence and were managed with the application of cryotherapy or administration of intracameral linezolid (200 µg in 0.1 ml) had clear grafts after the infection was controlled.

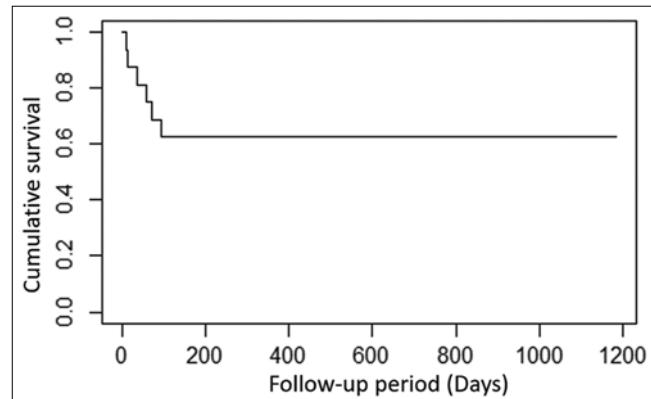


Figure 4: Kaplan-Meier survival curve of grafts which developed recurrence of *Pythium insidiosum* keratitis and underwent repeat keratoplasty. The average time between two surgeries in these cases was estimated to be 47 days (range 11–93 days). Patients with no recurrence of the disease were followed up for 497 days on average

The mean uncorrected visual acuity at 6-month follow-up was 2.04 ± 0.77 logMAR (20/2000 Snellen) in the study. Table 2 summarizes the intraoperative and postoperative details of patients.

Discussion

The study describes the demographic details, clinical course, and detailed outcomes of TPK in a cohort of patients with culture-proven PI keratitis. PI keratitis was observed to afflict patients in young and

Table 2: Intraoperative and postoperative details of therapeutic penetrating keratoplasty

Characteristic	N=16
Mean time to keratoplasty	31.3 days
Mean graft size in first keratoplasty	10.3 mm
Mean graft size in repeat keratoplasty	11.7 mm
Surgical procedure (n=16)	
Keratoplasty alone	14
Keratoplasty with scleral deroofing	1
Keratoplasty with cryotherapy	1
Graft outcome after first keratoplasty (n=16)	
Clear graft at 6 months	1
Failed graft	5
Phthisis bulbi	1
Recurrence of disease	9
Mean time to presentation with recurrence	8.9 days
Time to recurrence for each patient	
Patient 1	7 days
Patient 2	34 days
Patient 3	2 days
Patient 4	3 days
Patient 5	7 days
Patient 6	2 days
Patient 7	7 days
Patient 8	8 days
Patient 9	10 days
Type of recurrence (n=9)	
Endoexudates	6
Graft infiltration	1
Graft-host junction infiltration	1
Graft melt	1
Graft infiltration + endoexudates	1
Graft dehiscence + endoexudates	1
Treatment of recurrence of disease (n=9)	
Repeat keratoplasty	7
Cryotherapy alone	1
Intracameral administration of linezolid (200 µg in 0.1 ml)	1
Complications after repeat keratoplasty (n=6)	
Recurrence of disease (n=4)	
Endoexudates	2
Hypopyon	1
Graft-host junction infiltrates	1
Secondary glaucoma	1
Retinal detachment	1
Graft outcome after repeat keratoplasty (n=7)	
Clear graft at 6 months	1
Failed graft	5
Phthisis bulbi	1
Treatment for failed graft after repeat keratoplasty (n=2)	
Optical penetrating keratoplasty	1
DSAEK	1

middle age groups and was found to be more common in males compared to females, as has been reported in other studies.^[4,12] Swimming in water bodies, contact lens wear, and trauma have been commonly reported as the risk factors for developing *Pythium* keratitis in literature.^[4,13-15] While most patients in the study did not report a specific predisposing event, a history of corneal injury with vegetative matter and contact lens use was found in two of the patients respectively. The mean time for patients to present to the hospital was 23 days from the onset of symptoms, and none of the patients had been diagnosed as cases of PI keratitis or had been receiving specific therapy for their condition at presentation. Time to presentation to hospital for patients with PI keratitis has been reported to range between 2 and 60 days in various studies.^[4,6] Delay in presentation and accurate diagnosis subsequently adversely affect the clinical outcomes in this condition.

All patients in the cohort presented with visual acuity worse than counting fingers at 2 m. Interestingly, all 16 patients had received nonspecific medical treatment for microbial keratitis before presentation to the center. Administration of empirical antibiotic therapy without confirmatory microbiologic diagnosis continues to be widely practiced at the primary care level.^[16] Unfamiliarity with clinical features and common misdiagnosis as fungal keratitis due to overlapping features are some of the other challenges in managing these patients. Clinically, rapid progression of disease is the hallmark of PI keratitis.^[17,18] Large size of infiltration, involvement of limbus, dense vascularization, and endothelium and anterior chamber infiltration at presentation were the high-risk factors responsible for the rapid deterioration of keratitis in the present study. A favorable response in PI keratitis on treatment with the antibiotic combination of linezolid eyedrops and azithromycin eye ointment has been reported in literature.^[18-20] However, keratoplasty has been stated as the mainstay in the management of severe, refractory, and rapidly worsening cases of PI keratitis.^[6,21]

Even though the primary aim of TPK in these patients is the eradication of infective foci and restoration of globe integrity, achieving a good visual outcome with an optically clear graft is desirable. The long-term success of keratoplasty also depends on the development of various postoperative sequelae, causative agents, preoperative medications, timing of surgery, quality of donor tissue, and size of the graft.^[22] In the present study, the mean sizes of the graft in primary keratoplasty and repeat keratoplasty were 10.4 and 11.7 mm, respectively, indicating a large extent of infiltration in the cohort of patients. Meticulous clearing of infiltration with a disease-free margin of at least 1–2 mm was ensured in all cases to prevent recurrence. Scleral spread has been frequently reported in this condition, as was seen in two patients in the study.^[23] A wide peritomy and thorough exploration of the sclera beyond the limbus were carried out and on evidence of scleral infection, partial deroofing of the sclera and drainage of infection were performed in one patient. Cryotherapy of the infected sclera was another technique employed to treat scleral infiltration in one patient, as has been described by Agarwal *et al.*^[24] In addition, intracameral linezolid was administered at the end of surgery in all cases for maximal benefit.

Postoperative period management can be challenging in cases of PI keratitis. More than half of the patients in the study presented with recurrence of disease in varied forms

such as graft infiltration, endoexudates, or graft dehiscence. Recurrence of disease after keratoplasty has been reported to be more common in cases of PI keratitis, compared to other causes of microbial keratitis.^[4,24,25] Agarwal *et al.*^[24] reported post-TPK recurrence in seven out of 10 patients, who underwent evisceration eventually. Repeat keratoplasty with a larger graft size and meticulous clean-up of infiltration were performed in seven patients in the study for recurrence of the disease. In addition, topical steroids were prescribed two hourly in the postoperative period in view of the increased inflammation observed in the postoperative period in these patients.

Enucleation and evisceration for endophthalmitis in PI keratitis are devastating outcomes and have been commonly reported before.^[9,12,26,27] In recent times, Vishwakarma *et al.*^[12] have reported the anatomical success of TPK in 72.2% of patients with PI keratitis in their study, with three patients requiring evisceration for infection control. The globe was successfully salvaged (eyes which did not need evisceration or progressed to phthisis bulbi) in 14 out of 16 patients (87.5%) in this study. None of the eyes developed endophthalmitis or required evisceration for infection control. This can be attributed to a better understanding of the disease over the years, taking adequate surgical precautions, administration of adjuvant antibiotic therapy, and early control of postoperative inflammation with vigorous administration of topical steroids. While successful salvage of the globe and control of infection are steps in the forward direction in managing these patients after therapeutic keratoplasty, the rate of graft failure continues to be high in this cohort as was observed in the present study.^[4,28] For visual rehabilitation, optical keratoplasty (penetrating or DSAEK) was performed in failed grafts. Mean uncorrected visual acuity improved marginally from 2.32 to 2.04 logMAR after surgery, which is comparable with reports in literature.^[6,12]

Conclusion

PI keratitis is a challenging condition which often presents with severe infiltration that is refractory to medical treatment, necessitating management with therapeutic keratoplasty. Recurrence of infection after surgery is the main concern in managing these patients. Careful intraoperative inspection, appropriately large-sized grafts, and meticulous cleanup of infiltration are advised peroperatively. Furthermore, surgeons must be prepared for repeat surgeries and a prolonged and arduous postoperative course. The pearls of management include being vigilant, providing timely and appropriate intervention, and aggressive control of postoperative inflammation in patients of PI keratitis.

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Clinical perspective and outcome of culture-negative microbial keratitis: A retrospective study

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Purpose: To study the risk factors, clinical features, and treatment outcomes of patients with culture-negative keratitis (CNK). **Methods:** A retrospective data review of 933 patients with CNK was performed from January 2018 to December 2020. The variables such as the history of injury, visual acuity, slit-lamp findings with measurements of size and depth of ulcer, microbiological evaluation, duct patency, blood glucose levels, and treatment were considered, and clinical outcome was analyzed. **Results:** Of the 933 patients with CNK, 763 (81.8%) were medically managed, with a mean treatment duration of 2.08 ± 1.7 weeks. Among them, 622 (66.7%) were both smear and culture-negative, and 311 (33.3%) showed only smear positivity. Smear-positive patients showed a positive correlation with the history of injury. A higher incidence of fungal growth on repeat culture was observed. Surgical interventions were done only in 18.2% of the patients; the rest were treated with topical medications alone. **Conclusion:** High clinical suspicion, differentiation of causative organisms based on clinical findings, and initiating empirical therapy with broad-spectrum antibiotics and antifungals improve the ultimate prognosis in patients with CNK, even though a standard protocol for empirical medical treatment may differ among institutions and surgeons based on their clinical experience and geographical variations.

Key words: Culture-positive keratitis, culture-negative keratitis, microbial keratitis

Microbial keratitis (MK) is one of the most common causes of preventable blindness globally. In developing countries like India, the annual incidence of MK may exceed 2 million cases per year.^[1,2] It also affects the economic burden of the healthcare system in developed countries; 175 million dollars are spent annually on MK in the United States.^[1,3] Timely diagnosis with microbiological examination and culture is the key to prompt and successful management of MK.^[4] The diagnosis is intrinsically made by corneal scraping with smear examination, culture, and antibiotic sensitivity tests. Even though the culture is considered the gold standard approach, it has a positive rate of about 40–60%.^[4–6] The predisposing factors for culture negativity (CN) include delayed presentations of patients to the clinic, average being 19–20 days, depth of the infiltrates, usage of multiple self-topical medications before first corneal scraping, and infection with rare or fastidious pathogens with indistinguishable clinical features such as *Acanthamoeba*, atypical mycobacteria, and fungi.^[6–8] Hence, in such scenarios, corneal biopsy to reach the deeper infiltrates and performing other molecular diagnostic modalities such as polymerase chain reaction (PCR), in-vivo confocal microscopy (IVCM), immunohistochemistry (IHC), and histopathological examination (HPE) of the tissue after therapeutic keratoplasty would aid in appropriate diagnosis depending upon the availability of resources.^[9] The history

and clinical features often elucidate the possible underlying causative organisms.^[10] This might need clinical expertise. The management in such cases is primarily an empirical antimicrobial therapy, close follow-up, and its clinical response, which aids in determining the prognosis of the disease.^[9] Delay initiating appropriate medical treatment of infective keratitis might lead to the progression of the ulcer, perforation, and even visually blinding conditions like endophthalmitis.^[8] The clinical course of CNK is often overlooked, and its management outcomes should be more frequently explored in the literature. This study aims to comprehensively review the patients with CNK, its clinical course, and visual and treatment outcomes.

Methods

A retrospective review of 933 patients with culture-negative microbial keratitis presenting at a tertiary eye care center in Tamil Nadu, South India, was assessed for over 3 years, from January 2018 to December 2020. Demographic data, mode of injury, duration of symptoms, visual acuity, infiltrate size (largest diameter in mm), smear and culture report, course of treatment, time of resolution of symptoms, surgical interventions (therapeutic penetrating keratoplasty), duration

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of follow-up, and outcome (corneal scar, clear or failed graft) of all the study patients were collected from electronic medical records and entered in the Microsoft Excel for analysis. The study was conducted as per the tenets of the Declaration of Helsinki and after obtaining institutional ethical committee approval (IEC/R/CS/2022/008).

Sample collection and diagnosis: Patients presenting to the hospital with clinical features suggestive of MK with no growth detected on the first corneal scraping culture were included in the study. Patients with presumed viral keratitis, neurotropic ulcers, interstitial keratitis, atheromatous ulcers, and any ulcer associated with autoimmune conditions were excluded. After slit-lamp examination and documentation of clinical findings such as size, shape, depth, and extent of the ulcer, all the patients were subjected to corneal scraping. Corneal scrapings were collected under topical anesthesia using 0.5% proparacaine. Scraping specimens included two scrapings for smear examination (one each for Gram stain and 10% potassium hydroxide wet mount), followed by a subsequent scraping for culture on potato dextrose agar, 5% sheep blood agar, chocolate agar, and non-nutritive agar plates. Culture positivity (CP) was defined as the growth of at least three confluent colonies on one solid medium within 2 weeks of incubation. The absence of growth on any culture plates, even after 2 weeks, was considered culture negativity. A repeat microbiological examination was done in 339 (36.3%) patients with nonhealing keratitis.

Treatment

Treatment for patients was started based on the clinical appearance of the ulcer and initial smear reports. Later, patients with culture positivity were treated according to the organism identified. All patients with culture-negative reports and who were not responding to treatment and showing signs of worsening, repeat cultures, and smears are performed by either corneal biopsy or scraping after 72 hours of treatment after discontinuing the medical therapy for 12 hours. Table 1 depicts the treatment approach adopted in our institution based on the clinical appearance of the ulcer and literature reference.^[11-18]

The daily examination was done until the ulcer improved, gradually reducing the frequency of drops and follow-up over 2 weeks. Continue using eye drops four times daily for 2 more weeks after healing the ulcer. Cases unresponsive to medical therapy with worsening of symptoms for >3 weeks, an increase in the size of the ulcer/exudates/hypopyon, limbal involvement, and impending perforation [Fig. 1] were managed surgically with therapeutic penetrating keratoplasty (TPK). Treatment success was defined as complete healing of the ulcer with scar formation within 12 weeks of presentation with medical therapy. Progressive corneal ulceration, perforation, and the need for urgent therapeutic keratoplasty constituted treatment failure.

Statistical analysis

Statistical analysis was performed using STATA software version 14.2 (StataCorp, USA). Descriptive qualitative variables were reported using frequencies (n) and percentages (%). Quantitative variables were declared using the mean with standard deviation (SD) and median with interquartile range (IQR). The Chi-square test was used for categorical variables, and the Wilcoxon rank sum test was used for



Figure 1: Slit-lamp image showing clinical worsening of infiltrate with signs of impending perforation

continuous variables to compare the variables between the trauma group and the no-trauma group. Snellen's visual acuity values were converted into a logarithm of the minimal angle of resolution (log MAR) for statistical analysis. The Wilcoxon sign rank test compared postoperative visual acuity with baseline data. The treatment duration was compared with different infiltrate sizes, and the significance was analyzed using the Kruskal-Wallis test. A Spearman rank correlation was used to examine the correlation between infiltrate size and treatment duration. Two-tailed hypothesis testing was used, and the results with $P < 0.05$ were considered statistically significant.

Results

A total of 2347 patients of microbial keratitis, excluding clinical viral keratitis, were registered during the study period from January 2018 to December 2020 [Fig. 2]; of these 2347 patients, 933 culture-negative keratitis (CNK) (39.7%) cases were included in the study. The duration of the mean follow-up was 15.63 (19.0) months. The demographic and clinical findings of the study patients are summarized in Table 2. The median (IQR) age at the presentation was 41 years (range 7–66 years). There was male preponderance in the study population as 678 (72.7%) were male patients, and only 255 (27.3%) were female. A history of ocular trauma with vegetative matter (wooden stick/thorn) was noted in 340 (36.4%) patients. Use of prior topical ocular medications was recorded in 667 eyes (71.4%) before presentation to the hospital.

During the initial visit, 157 (16.8%) patients had an infiltrate size of >5 mm, 323 (34.6%) had an infiltrate size between 3 and 5 mm, and 453 (48.6%) had an infiltrate size less than 3 mm. Emphatically, the duration of treatment

Table 1: Treatment approach based on the clinical appearance of the ulcer

Clinical findings of the corneal ulcer	Empirical treatment
Oval, yellowish white opaque stromal abscess associated with dacryocystitis; clinically suspected as Gram-positive bacteria ^[6]	Topical moxifloxacin 1% Fortified vancomycin 5%
a) Ulcer size <5 mm and anterior depth of involvement b) Ulcer size >5 mm with deep stromal involvement	
Corneal ulcer with copious discharge with severe inflammation, and the ulcer progresses rapidly with marked stromal melt, ring infiltrate, hypopyon, and later descemetocele formation or perforation. ^[11]	Topical ciprofloxacin 1% and fortified amikacin 1% (with caution: adverse events: persistent epithelial ulcers and ocular surface toxicity) Fortified ceftazidime 5%
a) Small ulcers <5 mm b) Large size >5 mm	
Patchy anterior stromal pin-head-like infiltrates in a wreath-like configuration; clinically suspected as <i>Nocardia species</i> ^[13]	Fortified amikacin 1% eye drops
Dry, raised ulcers with feathery margins, satellite lesions, endothelial plaque, and an immune ring; clinically suspected as fungal keratitis ^[18]	Natamycin 5% or amphotericin 0.15% with or without voriconazole 1%, depending upon the size of the ulcer Topical polyhexamethylene biguanide (PHMB)
Epithelial irregularities with ring-shaped stromal infiltrates and radial keratoneuritis; clinically suspected as <i>Acanthamoeba</i> keratitis ^[17,19]	
Stromal infiltrate with hyphenated edges, multifocal lesions with tentacular projections, and peripheral furrowing with thinning, guttering, and a tendency to spread toward the limbus; clinically suspected as <i>Pythium</i> keratitis ^[14,15]	Linezolid 0.2% and azithromycin 1%
In case of clinical dilemma or polymicrobial suspect cases-, empirical therapy with broad spectrum antibiotics and antifungals was started ^[9]	Topical moxifloxacin 1% and natamycin 5%
Adjuvant therapy ^[9]	Cycloplegics, antiglaucoma medications, lubricating eye drops, and systemic anti-inflammatory drugs.

Table 2: Demographic characteristics and clinical findings of the study participants

	Frequency (%)
Age (in years)	
Median (IQR)	41.0 (7.0 to 66.0)
Gender	
Male	678 (72.7)
Female	255 (27.3)
Laterality	
Right eye	593 (63.6)
Left eye	340 (36.4)
Ocular trauma	
Yes	340 (36.4)
No	593 (63.6)
Previous usage of ocular medications	667 (71.4)
Infiltrate size (in mm)	
<3 mm	453 (48.6)
3 to 5 mm	323 (34.6)
>5 mm	157 (16.8)
Treatment duration (in weeks)	
Mean (SD)	2.08 (1.7)
Median (IQR)	1.43 (1.0 to 2.8)
Surgical intervention	
TPK	170 (18.2)
Nil	763 (81.8)

was prolonged with an increase in infiltrate size [$\rho = 0.55$, $P < 0.001$, Fig. 3].

All patients were started on empirical therapy based on the clinical findings and positive smear report. Treatment was later modified depending on the treatment response. Out of the 933 patients with CNK, 763 (81.8%) were medically managed with a mean treatment duration of 2.08 (± 1.7) weeks. Among

them, 622 (66.7%) were both smear and culture-negative, and 311 (33.3%) showed only smear positivity. The smear-positive patients were studied further regarding their history of trauma [Table 3]. The smear-positive patients following trauma showed a higher incidence of fungal hyphae in 81 (23.8%) and Gram-negative bacilli in 32 (9.4%) patients. Those patients without a history of trauma had a higher incidence of Gram-positive cocci on smear, amounting to 99 (16.6%) cases. In contrast, fungal hyphae and Gram-negative bacilli were noted in 49 (8.3%) patients each.

A repeat microbiological examination was done in 339 (36.3%) patients with nonhealing keratitis. Of these, 169 (50%) patients showed positive culture reports on resampling. In 104 (61.5%) patients, the culture showed fungus growth; 6 (3.5%) patients were positive for *Acanthamoeba*, 58 (34.3%) had mixed growth (bacterial and fungal), and one (0.05%) patient was positive for *Pythium* sp. The treatment was modified according to the repeat culture and sensitivity report in 35 (10.3%) patients, and the same treatment was continued in the rest of the cases as the clinical judgement was correlating with the culture positivity.

About 170 (18.2%) patients underwent therapeutic keratoplasty (TPK) for various indications, such as a perforated ulcer or impending perforation, progressive ulcer with involvement of limbus, and nonhealing ulcer for more than 3 weeks of medical therapy. After TPK, the infected corneal button was sent for culture and sensitivity testing. Among them, 114 (67.1%) eyes were positive for fungus (unidentified hyaline fungus), 3 (1.8%) were positive for *Pythium* sp., and 53 (31.2%) were once again culture-negative. Post TPK, the graft remained clear for at least 6 months in 61 (35.9%) cases, failed, and remained opaque with quiet eyes in 53 (31.2%). The remaining 37 (21.8%) had failed opaque grafts with secondary glaucoma and were on long-term antiglaucoma

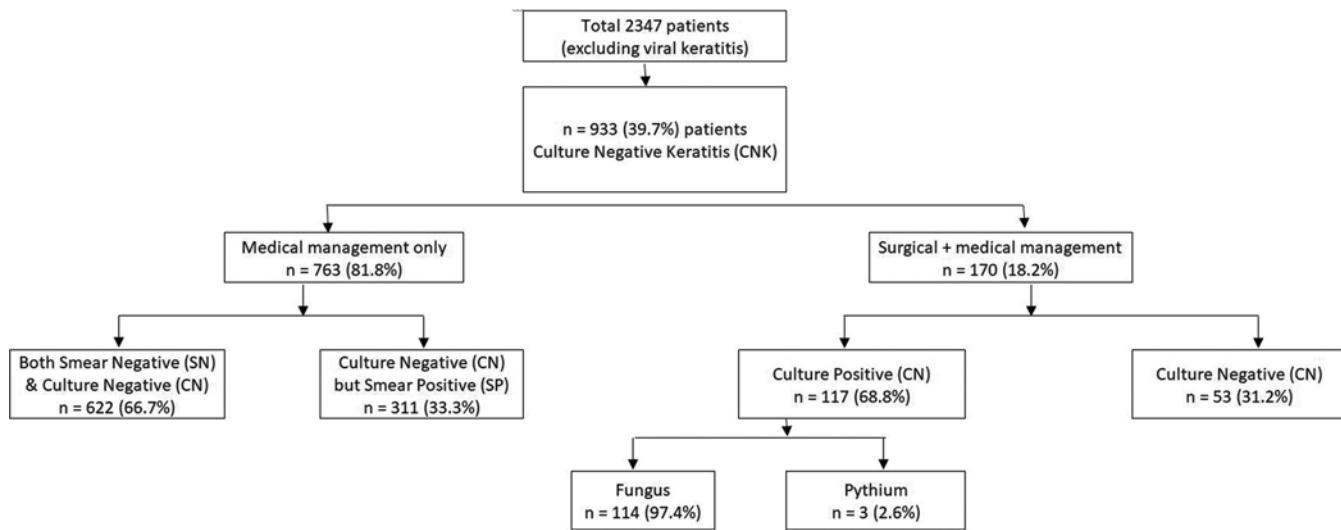


Figure 2: Breakup of total number of study patients with CNK based on the culture and smear results

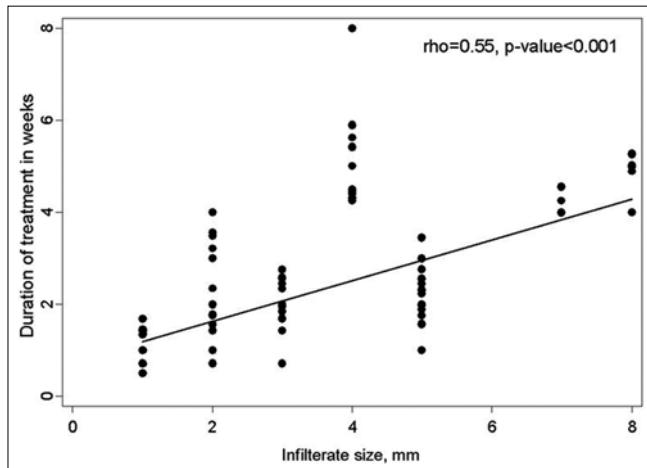


Figure 3: Correlation of infiltrate size and duration of treatment using a scatter diagram

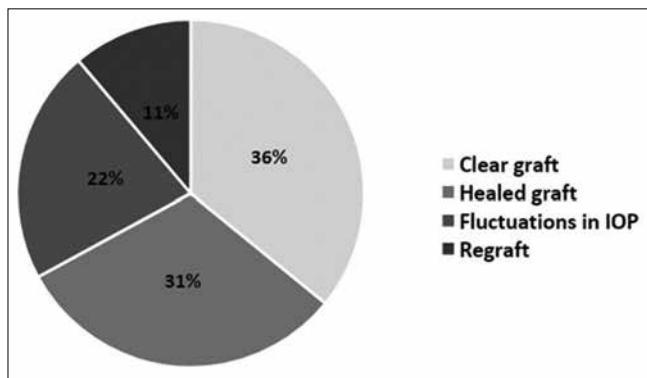


Figure 4: Final clinical outcomes following TPK

medications [Fig. 4]. A total of 19 (11.1%) cases underwent regraft for graft melt or graft reinfection, out of which 3 (15.7%) eyes with pythium keratitis had graft melted even after resurgery and went for phthisis bulbi, and the remaining 16 (84.2%) eyes were lost to follow-up. Collectively, 286 (30.6%) cases out of a total of 933 CNK cases were found

to be culture-positive on re-evaluation (169 resampling cases and 117 button cultures post TPK) [Fig. 5]. Post-treatment visual acuity (VA) was compared with baseline VA at presentation using the Wilcoxon sign rank test [Fig. 6]. There was a statistically significant difference in the post-treatment visual acuity (median VA = 0.18, i.e., 6/9) compared to baseline VA (median VA = 0.30, i.e., 6/12, $P < 0.001$).

Discussion

Infective keratitis (IK) is the major culprit behind corneal blindness in our country. The incidence of IK varies from 5.3 per one lakh population in USA to 113 per one lakh population in South India.^[8,16] From these statistics, it is clear that developing countries like India are under significantly more burden of IK than developed countries.

Microbiological smear and culture evaluation are necessary for the appropriate management of IK since the prognosis depends on the accuracy of treatment based on the identification of the infective organism. But, the microbiological culture sensitivity is only 60–70%.^[6,9] Due to various reasons such as inadequate sample collection, growing a minuscule sample on a culture plate, difficulty in collecting samples from uncooperative patients, pretreatment with antimicrobial agents, and contamination of the culture plates might lead to the technical difficulty in identifying the causative organisms and a few organisms like fungi, *Acanthamoeba*, and *Microsporidia* have the propensity for penetrating deep into the cornea, which requires deep corneal scrapings or corneal biopsy for an adequate sample.^[19–22] Gram-negative organisms are more difficult to identify on Gram staining due to their lighter color.^[10,11,23] The sensitivity of Gram staining is only 36–40% for bacteria, 42.1% for fungus, and 91% for *Acanthamoeba* with KOH wet mount.^[19–22] The overall specificity of staining methods in diagnosing MK is only between 29 and 62%.^[19,22,23] Prior use of antimicrobial agents, mechanical damage to the cell wall, an insufficient sample, poor staining techniques, failure to examine the whole slide, excessive heat fixation, and contamination of the stain or culture plates used are some of the laboratory-associated factors leading to adverse sensitivity reports. Hence, in such scenarios, experienced clinicians prefer treating MK based on

Table 3: Comparison of age, size of the infiltrate, and the culture report with the history of ocular trauma

	Trauma	No trauma	Total	P ^a
Number of subjects	340	593	933	-
Age (in years)				
Mean (SD)	10.22 (7.1)	14.82 (10.7)	13.15 (9.7)	<0.001 ^b
Median (IQR)	8.0 (7 to 12)	14.0 (10 to 17)	11.0 (7 to 16)	
Infiltrate size (in mm)				
<3 mm	171 (50.3)	282 (47.6)	453 (48.6)	<0.001
3 to 5 mm	91 (26.8)	232 (39.1)	323 (34.6)	
>5 mm	78 (22.9)	79 (13.3)	157 (16.8)	
Culture report				
Negative	227 (66.8)	396 (66.8)	622 (66.7)	<0.001
Fungus	81 (23.8)	49 (8.3)	170 (18.2)	
Gram-positive bacteria	0	99 (16.6)	56 (6.0)	
Gram-negative bacteria	32 (9.4)	49 (8.3)	85 (9.1)	

^aChi-square test; ^bWilcoxon rank sum test; SD, standard deviation; IQR, interquartile range

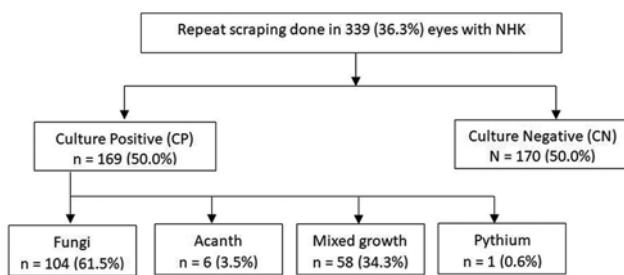


Figure 5: Results of repeat corneal scraping results of our study patients with nonresolving keratitis

the clinical picture alone.^[7,8] Grant Carlisle *et al.*^[22] noted very high CNR in 69% of his study subjects and attributed it to prior topical antibiotics. Similarly, among our patients, 71.4% used prior topical drops. In such instances, repeat culture helped us to modify the empirical antimicrobial therapy according to the infective agent identified.^[22] We had repeated cultures in 36.3% of the patients; among them, CPR was 50%, which was quite significant. The appropriate therapy was changed depending on the repeat culture reports, which ranged from 5 to 15%, comparable to our observations (10.3%).^[24] Thirty-five patients (10.3%) is the subset of the 169 who required treatment modification compared to the 134 patients who did not require treatment modification as clinical suspicion matched with the positive culture report on repeat scraping.

The culture positivity rate also depends on the size of the infiltrate and the amount of scraping material available. Morlet *et al.*^[24] found that ulcers larger than 5 mm had 2.68 times the chance of a positive culture result, but we observed only 16.8% of our patients with infiltrate size >5 mm, which was probably the reason for the culture-negative results. Higher incidences of fungus were observed with repeat cultures (61.5%). Hence, it is a requisite to perform repeat cultures in patients with nonhealing keratitis promptly.

Many studies have documented the association of a higher incidence of fungal keratitis with trauma.^[18,25,26] Likewise, we also identified fungus in 71.6% of smears of the patients (113) with a positive history of trauma. Henceforth, detailed history taking relating to trauma is mandatory in patients with CNK.

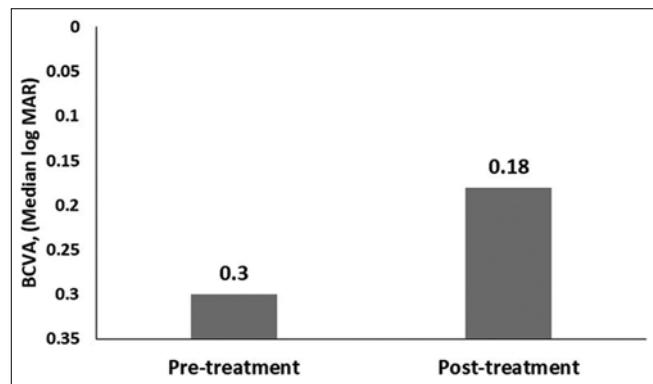


Figure 6: Post-treatment median BCVA (log MAR) was plotted using bar graph against pretreatment

TPK remains the ultimate option for clinically uncontrolled infectious keratitis, with the primary goal being eradicating the infection process and preserving globe integrity.^[27] Song *et al.*^[28] reported a high incidence of surgical intervention (74%) in patients living in rural areas exposed to agricultural activities with a high fungal infection rate (48.7%). Even though we had a higher incidence of fungal keratitis in our study patients, the surgical intervention was less (18.2%), likely due to the early addition of antifungals as the empirical therapy in our patients. Hence, it becomes pivotal to add antifungals to the empirical treatment at the time of presentation in the case of CNK to achieve a good prognosis. The post-treatment improvement in visual acuity was statistically significant in our patients, which might be due to the small-sized infiltrates, around 48.5% (n = 453). This might be one of the reasons behind the high culture negativity rate in our study. PCR and confocal microscopy are an attractive diagnostic modality for microbial keratitis; it has higher specificity and sensitivity. Moreover, the procedure is complicated, needs technical support, and is expensive, impeding its use in developing countries. Performing molecular methods, if feasible to improve the diagnosis in cases of CNK, would aid in improving the culture positivity rate and thereby be helpful in initiating an appropriate therapy for the microbe identified^[29] since the accurate diagnosis of the organisms and focused treatment on the target microbes carries good prognosis.

Ours was a retrospective observational study; the authors have used the microbial smear and culture methods as a diagnostic tool; the advanced diagnostic modalities like PCR/confocal microscopy were not considered, and we have not included the description of species for studying the results in our study. These are some of the limitations.

Conclusion

CNK is a challenging scenario when further molecular diagnostic methods are not available. As a clinician, it is mandatory to achieve high culture yield by doing repeat corneal scrapings and corneal biopsies in deep-seated keratitis with the aim to identify the inciting microbes in these eyes. Furthermore, clinical acumen of identifying the type of microbial keratitis along with microbiological reports benefits management of MK. Also, aiming for newer diagnostic modalities whenever it is feasible would help in accurate therapy and help in achieving good prognosis in these cases.

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Tear meniscus particle analysis with anterior segment optical coherence tomography in keratoconus

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Purpose: To perform tear meniscus particle analysis using anterior segment spectral domain-optical coherence tomography (SD-OCT) and ImageJ software in keratoconus patients. **Methods:** A total of 76 participants (76 eyes) were included in the study. A comprehensive analysis of tear meniscus parameters, including tear meniscus height (TMH), tear meniscus depth (TMD), tear meniscus turbidity (TMT), and percentage of area occupied by particles (PAOP) within the meniscus, was performed in keratoconus patients and healthy controls. **Results:** TMT was significantly higher in the keratoconus group, while PAOP was significantly lower ($P < 0.05$). However, TMH and TMD did not show significant differences between the two groups ($P > 0.05$). There was a negative correlation observed between TMT and PAOP. In binary logistic regression analysis, TMT and Schirmer score were found to be the most influential factors in predicting keratoconus (odds ratio [OR] = 0.995, $P = 0.039$ and OR = 1.143, $P = 0.021$, respectively). **Conclusion:** This study revealed novel findings on analysis of the tear film in keratoconus patients, with higher TMT and lower POAP levels in the keratoconus group compared to the healthy control group.

Key words: Keratoconus, optic coherence tomography, tear meniscus, turbidity

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Keratoconus is a bilateral and asymmetrical disease that causes irregular astigmatism and decreased visual acuity as a result of progressive thinning and steepening of the cornea.^[1] Although classically thought of as a noninflammatory disease, several studies have reported that keratoconus is associated with significant changes in inflammatory mediators.^[2-6] Therefore, it is proposed that keratoconic eyes often experience some form of ocular inflammation.^[3,7,8] It is known that patients with keratoconus experience more tear instability than healthy individuals without keratoconus.^[9] In studies investigating the immunologic profile of tear fluid in keratoconus patients, high levels of matrix metalloproteinases (MMPs), interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha (TNF- α), increased expression of proteolytic and lysosomal enzymes, and decreased protease inhibitor concentrations were reported.^[6] These authors reported that all of these immunologic changes may be associated with corneal tissue damage in keratoconic eyes.^[3,6-8]

Anterior segment spectral domain-optical coherence tomography (SD-OCT) has been widely used to evaluate anterior segment structures of the eye, such as the cornea, conjunctiva, and tear film.^[10-17] The primary uses of anterior segment optical coherence tomography (OCT) are the investigation of dry eye,

tear film measurement, and keratoconus screening. Lately, an increasing number of studies have used anterior segment OCT to evaluate tear meniscus dynamics in various diseases.^[13-17] Research has demonstrated that OCT, with its superior depth resolution, enables a more accurate assessment of the tear meniscus compared to conventional methods.^[18-20] In previous studies, anterior segment SD-OCT was used to evaluate quantitative features of the tear meniscus in keratoconic eyes.^[14] However, as far as we know, there is no study that has performed particle analysis of the tear meniscus in keratoconus. The effect of increased inflammatory mediators in the tears of patients with keratoconus on tear meniscus particle analysis is thus an intriguing and unanswered question.

In this study, the tear menisci of patients with keratoconus were evaluated using anterior segment SD-OCT and ImageJ software. The number of particles per square millimeter (mm^2), that is, tear meniscus turbidity (TMT), and the ratio of the area percentage of area occupied by particles (POAP) to the total meniscus area were analyzed.

Methods

In this prospective study, a comprehensive analysis of tear meniscus parameters was performed in 39 keratoconus patients who attended a tertiary-level university referral hospital

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and 37 age- and sex-matched healthy peers. The study was approved by the University Ethics Committee and conducted in accordance with the principles of the Declaration of Helsinki. Informed consent was obtained from all participants.

Each participant was required to complete the ocular surface disease index (OSDI) questionnaire, their tear break-up time (TBUT) was determined, the Schirmer I test for 5 min without topical anesthesia was performed, and their corneal-conjunctival staining scores (Oxford scheme)^[21] were determined. Dry eye was diagnosed by the Schirmer tear test (without anesthesia) at <10 mm/5 min and TBUT <10 s.^[14] Those diagnosed with dry eye were excluded from the study for both groups. Assessment of the meibomian gland dysfunction (MGD) score was conducted utilizing the Foulks-Bron scoring system, which examines the coherence of meibomian gland secretion and assesses the presence of inflammation in the lid margins. A specific threshold value of 5 was determined as the cutoff point for diagnosing MGD.^[22] Those with an MGD score above 5 were excluded from both groups.

In addition, all individuals underwent a comprehensive ophthalmologic examination, which included visual acuity measurement, intraocular pressure measurement with a pneumatic tonometer, a slit-lamp examination, and a fundoscopic examination. The diagnosis of keratoconus was made by clinical examination (biomicroscopy findings such as Fleisher ring, corneal thinning, Vogt striae, characteristic external clinical findings such as shear reflex on retinoscopy, and Rizzuti and Munson findings) by an experienced corneal specialist (AM) and validated by Scheimpflug camera with a Placido disc topographer (Sirius; Costruzione Strumenti Oftalmici, Florence, Italy). The Amsler-Krumeich classification for keratoconus was used to categorize all keratoconic eyes into four groups.^[23]

One week after the first ophthalmologic examination, tear meniscus parameters were measured using anterior segment SD-OCT, RTVue-XR (Optovue, Inc., Fremont, CA, USA). Vertical images were captured at the 6 o'clock position of the cornea, precisely 2 s after blinking, with the purpose of ensuring measurement accuracy. The tear meniscus height (TMH) was determined by measuring the length from the point where the meniscus intersects with the cornea at the highest point to the lower eyelid. The tear meniscus depth (TMD) was calculated as the vertical distance between the apex of the fornix and TMH. For the analysis of TMT, images obtained through SD-OCT and processed using ImageJ software (National Institutes of Health, Bethesda, MD, USA) were utilized. The images underwent editing and conversion to binary format, resulting in black-and-white images [Figs. 1-3]. Subsequently, a threshold was applied to segregate particles from the background in all images [Figs. 1-3]. Following the protocol outlined by Carracedo *et al.*,^[24] the relationship between the percentage of area occupied by particles (PAOP), the number of particles, and the total area of the tear meniscus (expressed as the number of particles per mm²) was examined. During OCT examination, the environmental conditions, including temperature (24°C–27°C) and humidity (40%–50%), were carefully controlled. An experienced ophthalmologist (GGS) captured each photograph within the time frame of 8:30 a.m. and 10:00 a.m. in a dimly illuminated room.

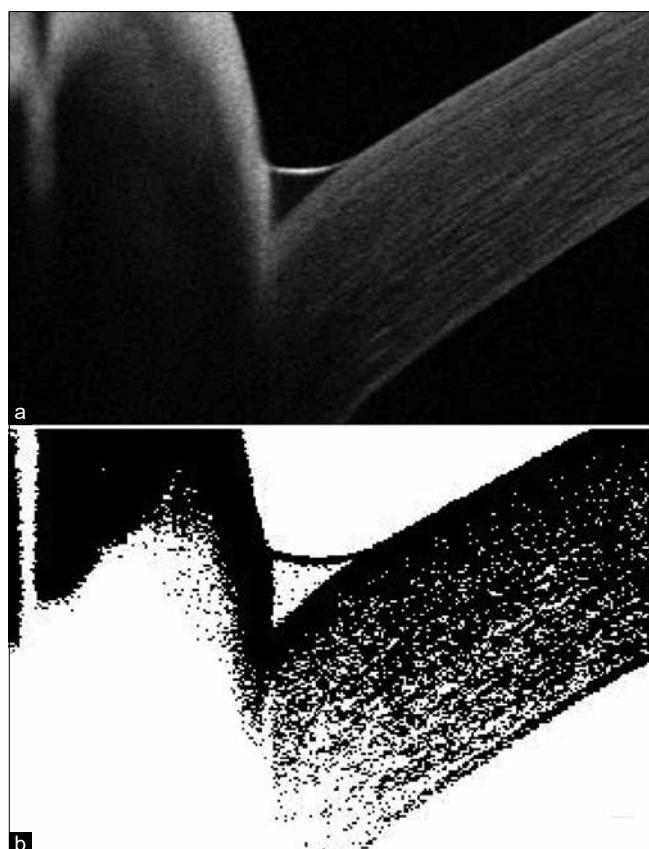


Figure 1: Optical coherence tomography image of the tear meniscus in a patient with keratoconus (a); the tear meniscus after software processing, to calculate turbidity (b)

Participants who had dry eye, corneal scarring, or any other ophthalmic or systemic disease in the last year, had undergone any ocular surgery, or used contact lenses were excluded from the study. Participants with evidence of any ocular infection, epiphora, blepharospasm, entropion, ectropion, blepharochalasis, or conjunctivochalasis, and those who have used any eye drops in the past 12 h were also excluded. As a result, all participants had clear conjunctiva and cornea, no epithelial erosion of the cornea or conjunctiva on fluorescein staining, and normal results on the Schirmer and TBUT tests (>10 mm and >10 s, respectively). They also had normal OSDI scores and MGD scores (<12 and <5, respectively).

Statistical analyses

Data was analyzed using Statistical Package for the Social Sciences, version 25.0 for Windows (IBM Inc., Armonk, NY, USA). Based on the results of the study, *post hoc* power analysis was performed for the difference between two independent mean values for TMT. The power level was 0.96. G Power version 3.1.9 software was used for power analysis. The assumption of normality was evaluated using the Shapiro-Wilk test. Numerical variables are presented as mean \pm standard deviation in the case of a normal distribution and as median (25th–75th percentile) in the absence of a normal distribution. Categorical variables are presented as numbers (percentages). An independent sample *t*-test or Mann-Whitney *U* test, as appropriate, was used to compare numerical variables between groups. The relationship between two

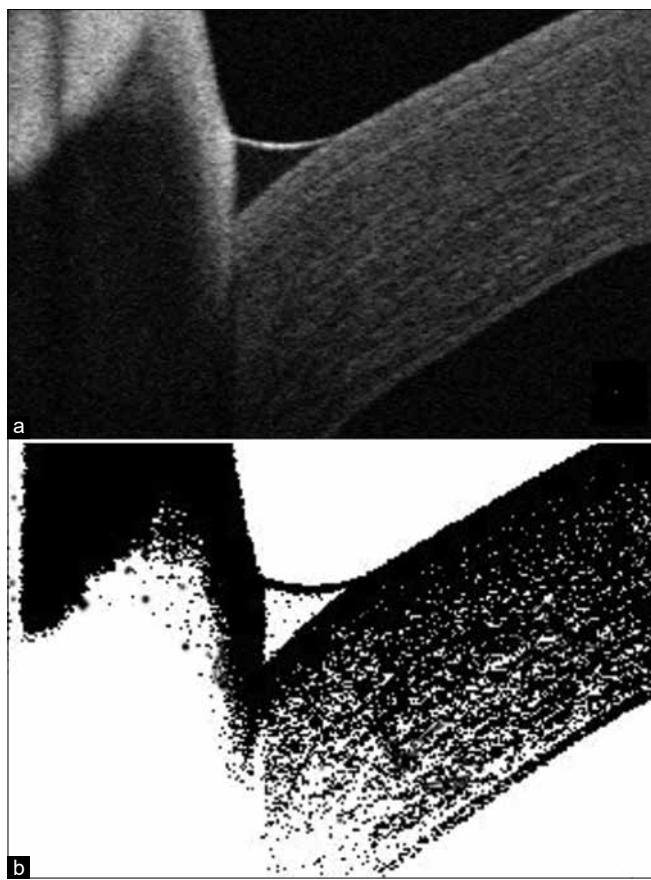


Figure 2: Optical coherence tomography image of the tear meniscus in a healthy participant (a); the tear meniscus after software processing, to calculate turbidity (b)

categorical variables was examined with the Chi-square test. Relationships between continuous variables were determined by Spearman correlation analysis. The factors significantly associated with keratoconus in the univariate analyses were also assessed using binary logistic regression analysis to determine the most influential factors. Statistical significance was defined as $P < 0.05$.

Results

Patient characteristics

The study group consisted of a total of 39 participants with keratoconus, consisting of 15 men and 24 women, and the control group consisted of a total of 37 healthy participants, consisting of 16 men and 21 women. There was no significant difference in age and gender distribution between the groups ($P = 0.625$ and $P = 0.672$, respectively). According to the Amsler-Krumeich classification, 16 of the keratoconus patients were stage 1, 14 were stage 2, five were stage 3, and four were stage 4.

Clinical outcomes and measurements

The OSDI score was higher and Schirmer and TBUT scores were lower in the keratoconus group ($P < 0.05$ for all). When the tear meniscus parameters were examined, although TMH and TMD did not differ significantly between the groups ($P = 0.182$ and $P = 0.084$, respectively), TMT was significantly higher in the keratoconus group compared to the control group and PAOP

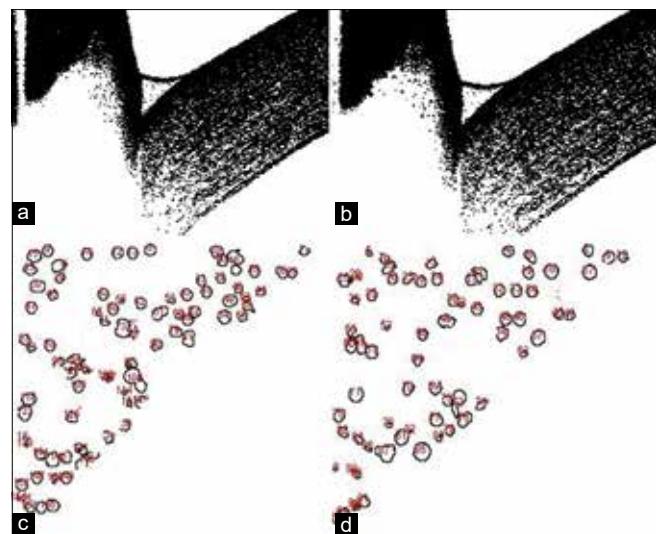


Figure 3: Optical coherence tomography image (a) and the image taken from the ImageJ software system, which includes the particle analysis of tear meniscus in a healthy participant (b). Optical coherence tomography image (c) and the image taken from the ImageJ software system, which include particle analysis of tear meniscus in a patient with keratoconus (d)

was significantly lower than the healthy group ($P = 0.001$ and $P = 0.021$, respectively). No statistically significant difference was observed in terms of TMD, TMH, TMT, and POAP values in different keratoconus stages ($P > 0.05$ for all). All the analyzed and compared parameters for the groups are presented in Table 1.

Relationship between dry eye and tear meniscus parameters

The OSDI score was negatively correlated with TBUT and Schirmer scores ($\rho = -0.283$, $P = 0.013$ and $\rho = -0.233$, $P = 0.043$, respectively), while TBUT and Schirmer scores were positively correlated with each other ($\rho = 0.430$, $P < 0.001$). There was a positive correlation between TMH and TMD ($\rho = 0.871$, $P < 0.001$). PAOP-Schirmer, PAOP-TMH, PAOP-TMD, and PAOP-TMT were all negatively correlated ($\rho = -0.228$, $P = 0.047$, $\rho = -0.332$, $P = 0.003$, $\rho = -0.374$, $P = 0.001$, and $\rho = -0.305$, $P = 0.007$, respectively). The correlation between study parameters is presented in Table 2.

Binary logistic regression analysis was also used to determine the dry eye parameters with the strongest effect (OSDI, TBUT, and Schirmer scores) and tear meniscus parameters with the strongest effect (TMD, TMH, TMT, and PAOP), which were significantly associated with keratoconus in univariate analyses. In the binary logistic regression analysis, the factors with the strongest effect for keratoconus were TMT and Schirmer score (odds ratio [OR] = 0.995, $P = 0.039$ and OR = 1.143, $P = 0.021$, respectively). Binary logistic regression predicting the likelihood of keratoconus is presented in Table 3.

Discussion

In light of the studies in which increased inflammatory mediators were detected in the tears of keratoconic eyes and suggesting that keratoconus may be associated with an inflammatory component, we hypothesized that there may be various changes in the tear meniscus of patients with keratoconus due to increased inflammation. We compared

Table 1: Comparison of ocular surface and tear meniscus parameters between keratoconus and control groups

	Keratoconus group n=39 (51%)	Control group n=37 (49%)	P ^a
Median (Q1–Q3)			
Age (years)	24 (20–29)	24 (20–26)	0.625
Sex			
Female	24 (61%)	21 (56%)	
Male	15 (39%)	16 (44%)	
SE (D)	-4 (-7/-2)	-0.50 (-1.50/0.25)	<0.001
IOP (mmHg)	12 (11–14)	14 (12–18)	0.005
OSDI score	8 (7–11)	7 (5–9)	0.030
TBUT (s)	15 (12–17)	17 (16–18)	0.001
Schirmer test I (mm)	24 (19–27)	28 (26–30)	<0.001
Staining score (Oxford) (0–5)	0 (0–0)	0 (0–0)	1.000
MGD score	4 (3–4)	3 (3–4)	0.094
TMH (μm)	221.44 (164.0–298.1)	198.57 (162.7–231.0)	0.182
TMD (μm)	227.10 (162.1–298.5)	185.79 (163.6–221.0)	0.084
TMT (particle number/mm ²)	493.92 (430.5–595.3)	399.84 (282.2–488.4)	0.001
PAOP (%)	1.576 (0.746–2.414)	2.076 (1.236–2.857)	0.021

Bold indicates significant differences. ^aMann–Whitney U test. IOP=intraocular pressure, MGD=meibomian gland dysfunction, OSDI=ocular surface disease index, PAOP=percentage area occupied by particles, SE=spherical equivalent, TBUT=tear break-up time, TMD=tear meniscus depth, TMH=tear meniscus height, TMT=tear meniscus turbidity

Table 2: Correlation between the study parameters

	OSDI	TBUT	Schirmer	MGD	TMH	TMD	TMT	PAOP
OSDI	—	r=-0.283 P=0.013	r=-0.233 P=0.043	r=-0.123 P=0.290	r=0.017 P=0.885	r=0.031 P=0.793	r=0.093 P=0.423	r=-0.145 P=0.211
TBUT		—	r=0.430 P=0.000	r=-0.153 P=0.186	r=-0.128 P=0.271	r=-0.086 P=0.460	r=-0.113 P=0.332	r=0.070 P=0.546
Schirmer			—	r=-0.084 P=0.470	r=-0.082 P=0.479	r=-0.049 P=0.676	r=-0.152 P=0.189	r=-0.228 P=0.047
MGD				—	r=0.064 P=0.583	r=0.034 P=0.771	r=0.209 P=0.069	r=-0.029 P=0.800
TMH					—	r=0.871 P=0.000	r=-0.002 P=0.986	r=-0.332 P=0.003
TMD						—	r=0.029 P=0.802	r=-0.374 P=0.001
TMT							—	r=-0.305 P=0.007
PAOP								—

Spearman correlation. Bold results indicate significant correlation. MGD=meibomian gland dysfunction, OSDI=ocular surface disease index, PAOP=percentage area occupied by particles, TBUT=tear break-up time, TMD=tear meniscus depth, TMH=tear meniscus height, TMT=tear meniscus turbidity

particle analyzes of the tear meniscus of keratoconic and healthy eyes. There were no significant differences observed in terms of TMH and TMD between the groups. We found that TMT was higher in keratoconic eyes, but PAOP was reduced. Although there were no participants with a definite diagnosis of dry eye in either group, the measurements of dry eye parameters (OSDI, TBUT, and Schirmer) in keratoconic eyes were worse. TMT and PAOP were negatively correlated with each other. This study revealed a new, previously unexplored aspect of the tear films of patients with keratoconus.

A previously published study found that patients with keratoconus showed more pronounced indications of dry eye, MGD, and symptoms of tear instability than a healthy group.^[25] Therefore, we deliberately excluded keratoconus patients with

dry eye and MGD from the study. Our results showed that keratoconic menisci were not different in terms of depth and length. However, surprisingly, TMH and TMD were higher in the keratoconus group, although they were not significantly different. Similarly, Sarac *et al.*^[14] evaluated TMD and TMH in keratoconus patients without dry eye and did not report any difference between TMD and TMH levels of keratoconus patients and healthy controls.

At present, although the etiopathogenesis of keratoconus is not fully understood, it is thought that cytokines, proteases, inflammatory activity, and oxidative stress impair the corneal tissue and stimulate ectasia progression.^[7] Lema and Durán^[4] showed higher levels of proinflammatory cytokines, IL-6, TNF- α , and MMP-9 in the tears of patients with keratoconus.

Table 3: Binary logistic regression predicting the likelihood of keratoconus

	<i>B</i>	SE	Wald	<i>P</i>	OR	95% CI for OR	
						Lower	Upper
OSDI	-0.121	0.114	1.123	0.289	0.886	0.708	1.108
TBUT	0.233	0.141	2.722	0.099	1.262	0.957	1.665
Schirmer	0.134	0.065	4.253	0.021	1.143	1.007	1.298
TMT	-0.005	0.002	5.317	0.039	0.995	0.990	0.999
PAOP	0.223	0.257	0.752	0.386	1.250	0.755	2.068
Constant	-4.317	3.005	2.065	0.151	0.013		

B=unstandardized regression weight, CI=confidence interval, OR=odds ratio, OSDI=ocular surface disease index, PAOP=percentage area occupied by particles, SE=standard error, TBUT=tear break-up time, TMT=tear meniscus turbidity. Bold values are statistically significant outcomes with P-value <0.05

Later, the same group reported that IL-6 and TNF- α levels were increased in both eyes in patients with unilateral keratoconus and subclinical disease in the contralateral eye, but MMP-9 levels were increased only in keratoconic eyes.^[5] Balasubramanian *et al.*^[6] showed an increase in cathepsin B levels and a decrease in polymeric immunoglobulin receptor, fibrinogen, cystatin SN, and cystatin S levels in keratoconic tears. In line with these findings, they reported that tear proteins expressed differently in keratoconus contain increased proteases and decreased protease inhibitors. As a result of the increased expression of inflammatory mediators such as proinflammatory cytokines, cell adhesion molecules, and MMPs in the tear fluid, an increase in the number of particles in the tear meniscus is expected. In line with this inference, we found higher TMTs in keratoconic eyes than in healthy eyes. If TMT is the number of particles per square millimeter and there is no difference in TMH and TMD measurements in keratoconus compared to healthy subjects, it is clear that the number of particles in the meniscus has increased. Recently, Dogan and Arslan^[26] reported that TMT was higher in patients with MGD than in healthy eyes, and they related this to inflammation in MGD.

Our findings showed that while TMD and TMH of patients with keratoconus do not change, the number of particles per square millimeter increases, but the total area occupied by these particles decreases. In this case, the relatively larger particles in healthy tears appear to have been replaced by smaller particles. Balasubramanian *et al.*^[6] reported that total tear protein levels decreased in patients with keratoconus compared to controls, and high gelatinolytic and collagenolytic activity was observed in keratoconic tears. In 2012, Balasubramanian *et al.*^[27] reported that the amount of lactoferrin and secretory IgA was significantly reduced in the tears of patients with keratoconus. Lema *et al.*^[28] found that there was lower expression of immunoglobulin kappa chain protein, zinc- α 2-glycoprotein, and lactoferrin in the tears of bilateral keratoconus patients than in the tears of healthy individuals. In light of these studies, we hypothesize that the particles in the tear meniscus of keratoconus patients are affected by the changes due to these destructive processes. In addition, keratoconus and dry eye syndrome share a similar mechanism and both have adverse effects on the meibomian gland.^[29] The surface lipid layer of the tear film, produced by the meibomian glands, reduces the surface tension and delays

evaporation of the tear film. It is known that the tear lipid layer thickness decreases in keratoconus patients.^[20] Considering that the tear lipids in keratoconus are relatively large particles but are reduced in keratoconus, the decrease in PAOP can be explained despite the increase in inflammatory particles. Our results showed that MGD scores were higher in keratoconus patients, although this was not significantly different from healthy controls. It is obvious that further evaluations and more detailed studies are needed to clearly understand the seemingly complex mechanisms underlying these findings.

In the correlation analysis, there was no surprising result in the relationships between the measurements of dry eye parameters (OSDI, TBUT, and Schirmer). As expected, a positive correlation was also found between TMH and TMD. TMH and TMD are indicators of tear meniscus area, and both show a negative correlation with PAOP, based on our results. The Schirmer test, which is a quantitative method for diagnosing tear area, also shows a negative correlation with PAOP. According to the findings of Arita *et al.*,^[30] it was proposed that despite the reduction in the tear lipid layer, a crucial component of tears, the overall volume of tear fluid could be preserved through augmented compensatory secretion of fluid. From this point of view, the preservation of TMD and TMH and the increase in Schirmer score can be explained despite the decreasing PAOP.

This study has some limitations, mainly due to the relatively small number of participants in both groups. In addition, the participants in the keratoconus group were not homogeneously distributed according to the severity of keratoconus. Ultimately, we did not assess tear meniscus alterations in real time. Despite the aforementioned limitations, we firmly believe that this study contributes to the literature on OCT-imaging lower tear meniscus particle analysis. In the future, further studies with larger sample sizes are needed to evaluate the effect of the keratoconus stage on meniscus particle analysis.

Conclusion

This study evaluated previously unexplored parameters for keratoconic tear film. It was found that the ratio of the total number of particles in the tear meniscus (TMT) and the sum of the volumes of the particles in the meniscus to the entire meniscus volume (POAP) was different in keratoconic eyes than in healthy eyes. Evaluation of keratoconus from various aspects, whose pathogenesis is not currently fully elucidated, will help to understand its pathogenesis, perhaps to prevent its progression or to develop less-invasive treatment options.

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Conflicts of interest: There are no conflicts of interest.

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Evaluation of the effect of atorvastatin on corneal endothelial cells during the initial 12-month period after acute coronary syndrome

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Purpose: It was aimed to compare corneal endothelial changes during the initial 12-month period in which patients started using atorvastatin after a diagnosis of acute coronary syndrome (ACS). **Methods:** Forty-six participants (group 1) who underwent cardiac angioplasty and stenting for ACS and started using 80 mg atorvastatin in the early period were included in the study. In the study, a control group comprising 71 healthy adults (group 2) was included. These individuals did not use medication for any known systemic disease, had never taken statins, had no history of ocular surgery, and did not have any cornea-related eye diseases. Baseline and 12th month endothelial evaluations of group 1 and 2 participants were compared using specular microscopy. **Results:** There were 28 female and 18 male participants in group 1 and 48 female and 23 male participants in group 2 ($P = 0.455$). The mean baseline corneal endothelial cell density (CECD) was not significantly higher in group 1 compared to group 2 (2471.4 ± 200 cells/mm² vs 2428.2 ± 539.8 cells/mm², $P = 0.230$). When the change between baseline and 12th month CECD was examined, the decrease in group 2 was significantly different from that in group 1 (-15.2 ± 31.9 and -44.8 ± 49.6 , $P = 0.002$). Although the percentage of hexagonal cells decreased significantly in group 2 participants, no significant change was observed in group 1 (respectively; $P < 0.001$, $P = 0.073$). The endothelial cell coefficient of variation did not differ significantly in group 1 participants over a 1-year period ($P = 0.192$), and a significant increase was observed in group 2 ($P < 0.001$). **Conclusion:** This study revealed that atorvastatin may have a positive effect on corneal endothelium cell density and morphology.

Key words: Atorvastatin, coefficient of variation, corneal endothelial cell density, hexagonality, specular microscopy

The corneal endothelium is critical for maintaining the transparency of the cornea. A number of factors that cannot be changed, such as genetics, race, and age, and factors that can be changed, such as drug use, infection, trauma, previous surgery, and ultraviolet exposure, are relevant to the preservation of the structural and functional integrity of the cornea.^[1,2] Moreover, clinical observations indicate that a corneal endothelial cell density (CECD) of approximately 500 cells/mm² represents the critical value at which endothelial decompensation develops.^[3] Therefore, CECD is an important parameter to be followed clinically. Wound healing within the corneal endothelium is primarily mediated by cell spreading, resulting in increased cellular pleomorphism and a decreased percentage of hexagonal cells with increasing age.^[1,3] As a consequence, these values provide insight into the functional capacity of the endothelium. Indeed, data concerning the CECD and endothelial cell morphology facilitate the assessment of patients' endothelium functional reserve.

Statins are inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co-A) reductase. They are used to reduce both low-density lipoprotein (LDL) cholesterol and the risk of atherosclerotic cardiovascular

disease, and their side effects are generally minimal in most patients.^[4,5] Additionally, statins exert pleiotropic effects, namely, anti-inflammatory, antiapoptotic, antiproliferative, and immunomodulator effects.^[6] Clinical trials have shown a significant reduction in cardiovascular problems among patients treated with statins.^[7] Thus, statins are currently approved for the treatment of patients with hyper- and dyslipidemia, acute coronary syndrome (ACS), peripheral vascular disease, a history of ischemic stroke, and other cerebrovascular diseases. At least some of the benefit derived from the use of statin therapy is thought to be related to its cholesterol-lowering effect. Furthermore, recent studies have shown that the clinical benefits of statins are related to improved endothelial dysfunction, the existence of anti-inflammatory properties, and reduced blood thrombogenicity effects.^[8]

Exploring the potential impact of statin use on corneal specular microscopy and topography findings has been a subject of thorough investigation within the literature. The evidence thus far has pointed toward favorable effects associated with statin administration. Specifically, in the context

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of hyperlipidemia, there has been a noteworthy study of higher levels of CECD, as assessed through specular microscopy, during the course of long-term statin treatment.^[9] However, it is crucial to note the existing research gap concerning baseline corneal specular microscopy assessment and the impact of statin use in individuals lacking a history of prior statin use. The current literature predominantly focuses on the effects of statins in those already undergoing statin therapy, leaving unexplored the potential preventive or modulatory effects of statins on CECD in statin-naïve individuals. Further investigations into the baseline corneal specular characteristics and subsequent changes associated with statin initiation in individuals without a prior history of statin use are imperative for a comprehensive understanding of the broader implications of statins on CECD. Early and intensive statin therapy is the required standard of intensive care for patients with ACS, and it is recommended in various guidelines.^[10,11] Hence, the present study sought to evaluate the corneal endothelial cell changes during the initial 12-month period in which patients started using statins after a diagnosis of ACS.

Methods

This cross-sectional comparative study was performed retrospectively following ethics committee approval. Moreover, the study was conducted in accordance with the principles of the Declaration of Helsinki.

The study population included 46 patients who underwent cardiac angioplasty and stenting for ACS and then started using atorvastatin (group 1). In group 1, none of the patients had a prior history of statin use. In addition, 71 healthy adults without a history of statin use were included in the study as the control group (group 2). The sample size calculation was performed using the G*Power 3.1.9.7 software. A minimum of 45 patients per group was determined to be necessary, considering an effect size of 0.6, a significance level of 0.05, and a power of 80%, resulting in a total sample size of 90. Corneal endothelial evaluation was performed by means of specular microscopy at baseline and after 12 months, and the results were compared between group 1 and group 2. The participants who used 80 mg of atorvastatin for the first time after undergoing cardiac angioplasty and stenting underwent routine ophthalmological examinations prior to discharge, and the results of their corneal endothelium examination under a noncontact specular microscope were included in the study. Participants with a best corrected visual acuity of at least 1.0 (on the logarithm of the minimal angle of resolution scale) in both eyes and a refractive error (in the spherical equivalent) within ± 2.00 diopters were included in the study. The exclusion criteria included a history of intraocular surgery, ocular trauma, glaucoma, uveitis, or corneal opacity; evidence of endothelial dystrophy on slit lamp biomicroscopy; and/or a family history of corneal decompensation, contact lens use, or diabetes mellitus. Participants who discontinued the use of atorvastatin were not followed up, had no specular microscopy evaluation after 12 months, and/or had a history of disease or surgery that could affect the corneal endothelium during the study period were also excluded from the study.

The participants' specular microscopy values were automatically evaluated using a Tomey EM-4000 noncontact specular microscope (Tomey Corporation, Nagoya, Japan),

which was set to examine the central cornea, as determined by the fixation of the individual participant. The parameters recorded from the system included the central corneal thickness (CCT), mean CECD (cells/mm²), coefficient of variation in the cell area (CV), and percentage of hexagonal cells (Hex (%)) by an examiner blinded to the group. The CECD was recorded as the number of cells per square millimeter, the CV was used as an index of the variation in the cell area (polymegathism), and the Hex (%) in the analyzed area was used as an index of the variation in the cell shape (polymorphism).

Statistical analysis

In this study, statistics concerning the continuous variables were reported as the mean \pm standard deviation/median (minimum–maximum) values, whereas descriptive statistics concerning the categorical variables were reported as numbers and percentages. The conformity of the continuous variables to a normal distribution was evaluated using the Kolmogorov–Smirnov test. Comparisons between groups were performed using the *t*-test or Mann–Whitney U-test in the independent groups, depending on the distribution structure. Pre- and postprocedure comparisons were also performed using the paired-samples test or Wilcoxon test, again depending on the distribution structure. The relationships between the categorical variables were examined using the Chi-square test. The IBM SPSS Statistics (Version 28) program was used for all the statistical analyses. The level of significance was considered to be 95% in the analyses, and the results were interpreted as statistically significant if the *P*-value was ≤ 0.05 .

Results

In this study, data concerning the 46 participants in group 1 and the 71 participants in group 2 were analyzed. The ages of the participants in group 1 ranged from 42 to 79 years (mean: 63.8 ± 10.4 years), while the participants in group 2 were aged between 41 and 87 years (mean: 64.1 ± 12.2 years). There was no significant difference between the groups in terms of the participants' age, gender, best corrected visual acuity, or intraocular pressure. Descriptive statistics concerning the participants in both groups are presented in Table 1.

As shown in Table 2, the respective baseline and specular microscopy values of both groups were compared after 12 months. The CECD levels of the participants in group 1 were not significantly higher than those of the participants in group 2 at the baseline evaluation (*P* = 0.230). When compared with baseline, the mean rate of change (decrease) in the CECD levels of the participants in group 1 after 12 months was statistically significantly lower than the rate seen in relation to the participants in group 2 (*P* = 0.002). When the intragroup evaluations were performed, a significant decrease was observed in both groups in terms of the CECD values at baseline and after 12 months.

When the CV values of the groups were examined at the baseline and after 12 months [Table 2], we observed that the CV value of group 2 was significantly higher than that of group 1 after 12 months (*P* = 0.042). While no significant change occurred in the CV values of the group 1 participants during the 12-month period (*P* = 0.192), a statistically significant increase was observed in group 2 participants (*P* < 0.001). As shown in Table 2, the mean Hex% values of the groups were significantly

Table 1: Descriptive statistics

Parameter		Group 1 (n=46)	Group 2 (n=71)	P
Age		63.8±10.4/63 (42-79)	64.1±12.2/64 (41-87)	0.640 ^a
Sex	Male	28 (60.9)	48 (67.7)	0.455 ^b
	Female	18 (39.1)	23 (32.3)	
BCVA (logmar)	Baseline	0.1±0.1/0.0 (0.0-0.4)	0.1±0.1/0.1 (0.0-0.4)	0.154 ^a
	First Year Follow up	0.1±0.2/0.1 (0.0-1.0)	0.1±0.1/0.1 (0.0-0.7)	0.176 ^a
IOP (mmHg)	Baseline	14.9±2.9/14 (11-22)	14.6±2.1/14 (10-19)	0.116 ^a
	First Year Follow up	14.7±3/15 (10-23)	14.8±1.7/15 (11-19)	0.201 ^a

Categorical variables were presented as numbers and percentages (%); continuous variables were presented as mean±standard deviation/median (minimum–maximum) values. ^aMann Whitney U test. ^bPearson Chi-square test

Table 2: Corneal specular microscopy characteristics

Parameter		Group 1 (n=46)		Group 2 (n=71)		P
		Avg±SD	Median (Min-Max)	Avg±SD	Median (Min-Max)	
Corneal Endothelial Cell Density	Baseline	2471.4±200	2450.5 (2124-3027)	2428.2±539.8	2418 (1978-3209)	0.230 ^a
	12 th month Follow up	2456.2±212.5	2420 (2100-3025)	2383.3±536.6	2408.5 (1886-3103)	0.036 ^{a,*}
	Difference (decrease)	-15.2±31.9	-8.0 (-103.0-98.0)	-44.8±49.6	-21 (-259-102)	0.002 ^{a,*}
	P (Baseline-12 th month Follow up)	<0.001 ^{b,*}		<0.001 ^{b,*}		
Coefficient of Variation (CV)	Baseline	40±5.1	39 (31-55)	40.6±7.2	40 (32-49)	<0.101 ^a
	12 th month Follow up	40.2±5.2	39.5 (30-54)	41.1±7.2	40 (33-50)	0.042 ^{a,*}
	Difference (decrease)	0.2±1.0	0.0 (-2-2)	0.5±1.6	0.5 (-9-5)	0.145 ^a
	P (Baseline-12 th month Follow up)	0.192 ^c		<0.001 ^{b,*}		
Hexagonality	Baseline	44.7±6.9	46 (32-58)	44.5±10.5	45.5 (31-56)	0.780 ^a
	12 th month Follow up	44.4±6.7	45 (32-56)	42.7±9.5	44.5 (29-55)	0.044 ^{d,*}
	Difference (decrease)	-0.35±1.29	0 (-3-2)	-1.85±3.49	-1 (-17-4)	0.001 ^{a,*}
	P (Baseline-12 th month Follow up)	0.073 ^c		<0.001 ^{b,*}		
Central Corneal Thickness	Baseline	545.1±32.5	542 (477-611)	526.2±41.4	524 (456-660)	0.006 ^{d,*}
	12 th month Follow up	544.8±33.6	543 (460-620)	527.1±41.7	524 (455-656)	0.011 ^{d,*}
	Difference (decrease)	-0.3±5.4	0.5 (-18-9)	0.9±14.3	1.0 (-99 - 45)	0.240 ^d
	P (Baseline-12 th month Follow up)	0.724 ^c		0.575 ^c		

Avg: Average, SD: Standard Deviation. ^aMann–Whitney U-test, ^bWilcoxon signed rank test, ^cPaired samples t-test, ^dIndependent-samples t-test *P<0.05

different at the end of the 12-month period. The Hex% change rate (decrease) in group 2 participants was also statistically significantly higher than that in group 1 participants ($P = 0.001$). Upon examining the groups' CCT values [Table 2], there was no significant difference between the start and end of the 12-month period ($P = 0.240$).

Discussion

Data on the potential effects of atorvastatin on the corneal endothelium are still unclear. Unlike the corneal epithelium's capacity to regenerate, CECDs cannot be renewed and regress throughout life.^[12] Previous studies have reported that CECDs and CCT decrease with age,^[13,14] with most studies showing a trend toward decreased Hex% and increased CV with age as well.^[13-15] Although a high CECD (>4200 cells/mm²) has been reported in infants, these values decrease rapidly during childhood, with this acceleration slowing upon reaching 18 years of age. The rate of CECD loss exhibits variability across different age brackets, ranging from 0.3% to 2.9% annually.^[16,17] Advancing age is associated with a multitude of factors contributing to CECD loss. First, the regenerative capacity of remaining endothelial cells diminishes with age, thereby

impeding efficient self-repair mechanisms and precipitating a gradual decline in cell density.^[13-15] Additionally, the corneal endothelium is subject to various insults over an individual's lifespan, encompassing oxidative stress, mechanical trauma, and metabolic alterations. Furthermore, aging correlates with a reduction in the efficacy of endothelial pump function, potentially resulting in corneal edema and subsequent CECD loss.^[17] Concomitantly, age-related alterations in endothelial cell morphology, characterized by the loss of hexagonal shape and increased irregularity, may compromise their ability to uphold corneal transparency and function. Moreover, environmental factors such as prolonged exposure to ultraviolet radiation, tobacco use, and poor dietary habits may expedite age-related changes in the corneal endothelium.^[13-17] Understanding the interplay of these factors is critical for elucidating the mechanisms underpinning age-related corneal endothelial cell loss and informing strategies to preserve corneal health and visual acuity across the lifespan. In our study, we observed a significant decrease in CECD value after 12 months in the healthy control group, while no significant change was observed in CCT value. The concurrent increase in CV value and the decrease in Hex% value were statistically

significant, which may be associated with the decrease CECD values.

The clinical benefits of statin therapy after acute coronary syndrome undoubtedly result, at least in part, from effects on low-density lipoprotein (LDL) cholesterol. Atorvastatin in particular is a commonly used inhibitor of 3-hydroxy-3-methyl-glutaryl-CoA reductase and has been reported to not only lower LDL cholesterol levels but also have anti-inflammatory effects.^[18] Studies have suggested that the benefits of statins may be partly due to their pleiotropic effects.^[19] In addition, statins are believed to grant significant therapeutic contributions in autoimmune disease treatment through their pleiotropic immunomodulatory effects.^[20] One study showed that the use of statins in normotensive glaucoma patients may be associated with reduced visual field loss.^[21] In addition, statins have reduced uveitis-related ocular inflammation in animal studies and decreased the development of uveitis in observational studies.^[21] Shirinsky *et al.*^[22] reported that different statin subtypes may have a therapeutic effect in noninfectious uveitis. Moreover, in a study on cultured endothelium, statins were shown to upregulate the endothelial nitric oxide synthase enzyme and increase nitric oxide production from vascular endothelial cells.^[23]

The pivotal role of transforming growth factor-beta (TGF- β) proteins in orchestrating signaling pathways that govern fibrosis is well-established, and inhibition of TGF- β activity has been demonstrated to impede the fibrotic phenotype, fostering a more regenerative cellular milieu.^[24] Emerging evidence from preliminary data suggests a potential link between statins and the promotion of corneal regeneration through modulation of the TGF- β pathway.^[25] In a specific *in vitro* study, a quantitative human corneal cell-based screening assay was conducted to discern compounds with pharmaceutical potential for enhancing the regenerative capacity of the cornea. Statins emerged as noteworthy candidates in this context.^[26]

What inspired our study is statins' beneficial effect on specifically vascular endothelial cells. He *et al.*^[27] highlighted the potential protective role of atorvastatin in contrast-induced nephropathy, suggesting its association with the antiapoptotic pathway. Moreover, a separate investigation demonstrated the protective effect of atorvastatin against doxorubicin-induced hepato-renal toxicity through an antiapoptotic mechanism.^[28] Chen *et al.*^[29] revealed the neuroprotective properties of atorvastatin through the antiapoptotic pathway, evidenced by its ability to improve neurological outcomes and reduce neuronal death in the context of neuroinflammation. To the best of our knowledge, there is no other study in the literature that has examined endothelial changes after statin use for a certain period of time.^[9] However, there is research suggesting that statins may protect the vascular endothelium against the worsening prognoses of various retinal disorders, such as age-related macular degeneration and diabetic retinopathy.^[30-34] Zheng *et al.*^[35] showed that simvastatin protects apoptosis in retinal capillary endothelial cells in animal models. Likewise, Ho *et al.*^[36] reported that simvastatin treatment regulates ultraviolet B-dependent corneal endothelial cell apoptosis through caspase-3 activity; of note, there is no study on the effect of atorvastatin on the endothelium. Another study using different statin subtypes reported that thrombin-induced barrier degradation was slowed in bovine

corneal endothelium.^[37] In addition, statins have shown positive effects in different cell types, such as retinal pigment epithelium, by preventing reactive oxygen-induced damage through NADPH oxidase-dependent mechanisms.^[38] In contrast, other researchers have associated statin use with an increased risk of developing lens opacities.^[39] Because of these contrasting results, the ocular benefits and side effects of statins remain unclear.

In our study, we aimed to reveal whether statins, which have been shown to reduce barrier dysfunction in the vascular endothelium,^[40,41] have a parallel effect on the corneal endothelium. We correlated our results with those of the abovementioned studies on the ocular beneficial effects of 12-month atorvastatin use. Our results showed that 12 months of atorvastatin use was significantly effective in reducing CECD loss upon corneal specular microscopy evaluation. CCT did not show significant changes in either of our two study groups in the 12-month period, which we attribute to CCT's lower sensitivity in demonstrating the function of the corneal endothelium. The decrease in Hex% value in the control group was also higher than that in the atorvastatin group, which is in line with the preservation of the CECD value of atorvastatin group. CV values showed a higher increase in the control group as well but not at a statistically significant level. A previous study reported that there is a decrease in CECD, an increase in CV, and a decrease in Hex% with increasing age in the Turkish population.^[15] Although our study indicated atorvastatin's positive prognostic effects on the corneal endothelium, we do not have strong evidence of the mechanism by which it does this. When the reported studies are considered together, we believe that our results stem from statin use's antioxidant, pleiotropic, and antiapoptotic effects on the corneal endothelium. Further prospective randomized controlled studies with larger patient series are needed to provide stronger data in defense of this claim.

Conclusion

Findings from various studies have shown that besides inhibiting cholesterol synthesis, statins have different mechanisms whereby they reduce cardiovascular risk by acting on the vascular endothelium, even at normal cholesterol levels.^[42,43] Similarly, our study supports that statin therapy in the treatment of ACS diseases may protect the corneal endothelium. It is imperative to bear in mind that medications administered for ACS, aside from statins, may also exert an impact on the corneal endothelium. The relatively small number of participants and 12-month follow-up form limitations, however. Given the retrospective design of our study, randomization was lacking, and potential confounding factors associated with the use of multiple medications after a diagnosis of ACS were not accounted for in the analysis. Future investigations with extended follow-up periods and comprehensive consideration of confounding variables may yield a more nuanced understanding of the subject matter. Long-term studies with large series are thus necessary to better evaluate the detailed effects of atorvastatin on the corneal endothelium. Furthermore, in this study, CECD was not assessed in distinct regions of the cornea.

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Transzonular moxifloxacin and dexamethasone delivery in phacoemulsification: A novel dropless regimen

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Purpose: To assess the safety and efficacy of transzonular moxifloxacin and dexamethasone versus standard postoperative topical drug regimen in phacoemulsification. **Design:** Nonrandomized prospective study. **Methods:** The study included 100 eyes of 100 age and gender-matched individuals with senile cataract undergoing routine phacoemulsification. The patients were consecutively divided into transzonular (TZ = 50) and topical (TP = 50) groups. Both the groups were followed up for 4 weeks and assessed for intraocular inflammation, visual acuity, changes in intraocular pressure (IOP), and any adverse events. **Results:** The grades of inflammation were significantly lower in TZ as compared to the TP group ($P < 0.001$). The IOP remained normal and comparable in both the groups. Most of the patients in the two groups attained a visual acuity of 0.2 or better at the end of the follow-up. No adverse effects and increased rate of endophthalmitis were noted in TZ group. **Conclusion:** A one-time peroperative TZ moxifloxacin and dexamethasone combination is a safe and effective method to control postoperative inflammation after cataract surgery. A word of caution though, due precautions to be exercised to prevent the risk of inflammation and endophthalmitis.

Key words: Phacoemulsification, postoperative inflammation, topical, transzonular

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Cataract surgery is continuously evolving with innovative surgical techniques, devices, and drug formulations; and all these factors have immensely enhanced the refractive and visual outcomes.^[1] Despite all the advancements, the patient still has to rely on topical antibiotics and steroids for the control of postoperative inflammation. Though quite effective in controlling inflammation, the topical route is frequently associated with improper administration, poor compliance, and contamination of bottle tip, which often leads to complications like endophthalmitis, breakthrough inflammation, and ocular surface disturbances related to preservatives.^[2] Lately, many approaches to drug delivery, viz., intracameral antibiotics, triamcinolone, subconjunctival triamcinolone, etc., have been tried to minimize these issues. In recent years, a newer transzonular administration has been used wherein the drug is placed in the vitreous through the zonules much like an intravitreal injection, though less invasively. The drug remains in the matrix of the vitreous body for relatively longer duration with sustained release. It, thus, offers medication-free postoperative recovery.^[3]

Reports have suggested that this approach provides similar effectiveness in terms of inflammation control, visual acuity, and patient comfort as provided by topical drops.^[4] In one of the study, intravitreal triamcinolone acetonide-moxifloxacin injection has been found to reduce the severity of anterior chamber cell reaction by 34.0 and 35.7% at 1 week and 1 month as compared to standard topical therapy.^[5] However, many of these studies have reported some visual disturbances like blurring and floaters due to the suspension nature of triamcinolone.

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We set out to study the safety and efficacy of per-operative transzonular moxifloxacin-dexamethasone injection as a substitute for standard postoperative topical antibiotic-steroid regimen. The use of dexamethasone is advantageous as it is a clear solution and, thus, lacks the transient blurring of vision associated with triamcinolone.

Methods

After approval from the institutional ethical committee in accordance with tenets of the Declaration of Helsinki and obtaining an informed consent, this prospective, nonrandomized controlled study was conducted on 100 eyes of 100 cases of age-related cataract in the age group of 45–65 years. The sample size was calculated using an alpha of 0.05 and power of 80% with a large effect size. The cases were further divided into Group 1 [transzonular group (TZ): ($n = 50$) in which 0.15 ml combination of transzonular preservative-free moxifloxacin (0.05 ml of 0.5%) + dexamethasone (0.1 ml of dexamethasone 4 mg/ml) was given with no postoperative topical administration and Group 2 [Topical group (TP): ($n = 50$) which was followed up with standard postoperative topical drug regimen (moxifloxacin 0.5% + dexamethasone 0.1% 4 times and naphenac 0.1% 2 times for 4 weeks)].

Individuals with age-related cataracts suitable for cataract surgery were included and those with prior history of

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vitrectomy, secondary, or complicated cataract, i.e., traumatic cataract, uveitis, diagnosed glaucoma, known steroid responders, cataract surgery combined with any other ocular surgery, patients with unstable capsular bags/zonular support system, patients not willing to follow-up, and not willing to give informed consent were excluded.

All cases were operated by a single experienced surgeon using a standard phacoemulsification technique under topical anesthesia. After intraocular lens (IOL) implantation, preservative-free combination of moxifloxacin and dexamethasone (0.15 ml) was injected through the zonules using a 27-gauge cannula in the study group. The tip of the cannula was passed underneath the iris, and once it reached the root (a resistance is felt), the tip was rotated toward the zonules and pushed slightly posteriorly; the medication was then slowly injected. The medication in most cases can be visualized as a fluid wave as it enters the anterior vitreous space. The viscoelastic was subsequently removed from the anterior chamber and the section closed with stromal hydration.

A thorough baseline evaluation including best-corrected visual acuity (BCVA), IOP, and slit-lamp biomicroscopy was done in all patients. Patients were followed up on 1, 3, 7, and 28th day postoperatively, and were evaluated for any change in IOP, BCVA, anterior chamber inflammation (cells/flare) graded according to Standardization of Uveitis Nomenclature Working Group criteria, and any intraoperative and postoperative complications.

Statistical analysis

Descriptive statistical measures were given as mean and percentages. Paired *t*-test within the groups and unpaired *t*-test between the groups were used. Statistically significance was set at < 0.05.

Results

The mean age (in years) was 58.98 (± 8.33) in TZ and 59.92 (± 11.72) in the TP group; both groups were comparable in other baseline characteristics [Table 1]. Most patients in the TZ group showed lower grades of inflammation as compared to the TP group ($P < 0.001$) from day 1 to day 7, and no inflammation was seen in either of the group on day 28 [Fig. 1]. The IOP remains normal throughout the follow-up (mean range: 9–20), and no significant difference was noted between the groups ($P = 0.221$) [Fig. 2]. The final BCVA at day 28 was better in the TZ group ($P = 0.023$); however, majority of patients (99%) in both the groups attained LogMAR acuity of 0.2 or better [Fig. 3]. In the TZ group, three patients had breakthrough cellular inflammation on day 7 visit while none was reported in the TP group ($P = 0.24$). Consequently, they were put on topical steroids until the inflammation subsided (5–7 days). None of the patients in either group had any episode of corneal edema, cystoid macular edema, endophthalmitis, or any other adverse event.

Discussion

Cataract surgery is the most commonly performed ocular procedure worldwide; it has evolved from simple visual rehabilitation to purely refractive surgery. Despite all the advancements, postoperative inflammation still warrants the use of multiple postoperative eye drops which create confusion and significant financial burden, especially for elderly patients. Recently, there has been a shift from the current topical to more convenient approaches to provide postoperative drug delivery safely and effectively. Various approaches have been tried like

Table 1: Demographics of study population

	Study Group [TZ] (n=50)	Control Group [TP] (n=50)	P
Age in years			
Mean \pm SD	58.98 \pm 8.33	58.92 \pm 11.72	
Range	40–78	33–80	0.977
Male	29	22	$\chi^2=1.96$
Female	21	28	0.161
Cataract grade			
NS I	07	12	
NS II	31	23	$\chi^2=5.59$
NS III	07	13	0.134
NS IV	05	02	
Pre-Op IOP (mmHg)			
Mean \pm SD	15.10 \pm 2.53	15.60 \pm 3.003	
Range	10–22	10–25	0.370

periocular and intracameral drug injections with similar or better effectiveness compared to the topical regimen. A newly introduced technique wherein antibiotics and steroids are injected into the vitreous through the transzonular route showed very promising outcomes. In this study, we used dexamethasone and moxifloxacin combination for transzonular intravitreal injection as a substitute for the standard topical regimen.

Our study shows that the mean aqueous cells/flare were consistently lower in the TZ group as compared to the TP group on postoperative days 1, 3, and 7 ($P < 0.001$); however, at day 28 no difference was seen between the groups. This was consistent with the results of Simaraj *et al.*^[6] where anterior chamber cell counts were significantly lower in the injection group as compared to the topical group ($P = 0.006$). Gungor *et al.*^[7] compared the postoperative inflammation management between intracameral dexamethasone (0.4 mg/0.1 mL) and intracameral triamcinolone acetonide (2 mg/0.05 mL) and conclude that the two treatment regimens reduced anterior chamber cells and flare equally and effectively. Tyson *et al.*^[8] evaluated the clinical outcomes following a transzonular intravitreal injection of a compounded triamcinolone–moxifloxacin–vancomycin formulation and found the rate of breakthrough inflammation at days 14–21 to be very low (9.2%). Another study by Singhal *et al.*^[9] found a higher incidence of breakthrough inflammation with transzonular injection of triamcinolone and moxifloxacin as compared to topical therapy ($P = 0.048$).

In our study, the mean IOP during the follow-up was similar to the baseline value on days 3, 7, and 28 in both groups ($P > 0.05$). Also, there was no difference seen in the mean IOP between the two groups ($P > 0.05$). In a study by Chang *et al.*,^[10] the IOP after phacoemulsification was not significantly altered by intracameral dexamethasone treatment regardless of time after surgery, with or without glaucoma ($P = 0.12$). In fact, there was a slight decline of 1.9 ± 1.2 mmHg rather than a rise in IOP. A study conducted by Gills *et al.*^[11] showed the injection of low-dose triamcinolone acetonide (up to 3 mg) had been associated with a lower incidence of IOP spikes than seen with postoperative drops. Nassiri *et al.*^[5] found no statistically significant difference in the rate of high IOP between the two groups at any time postoperatively. Other studies being done using low-dose intracameral triamcinolone acetonide also reported no significant rise in IOP in the postoperative period.

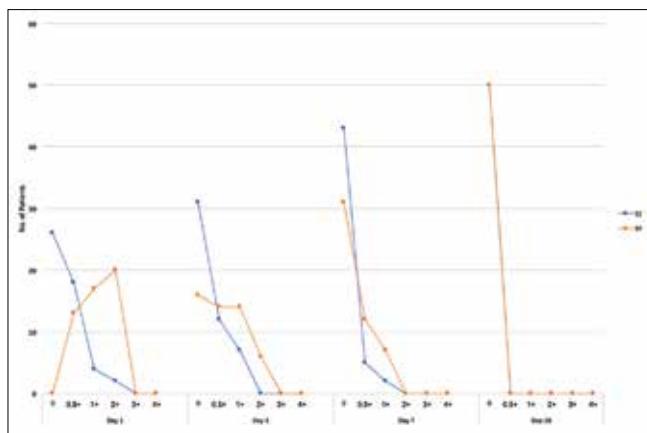


Figure 1: Analysis of anterior chamber cells in the groups

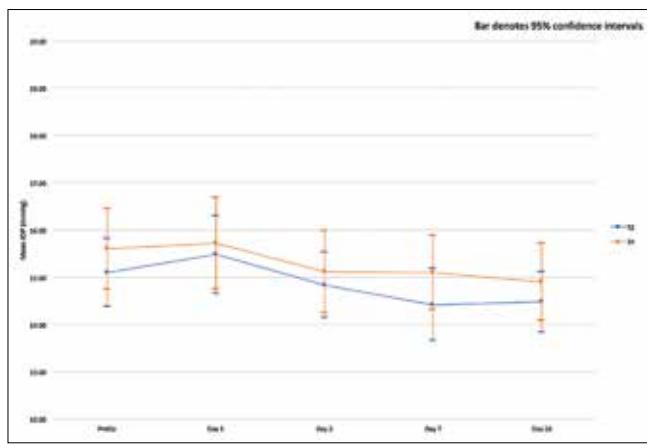


Figure 2: Change in IOP in the two groups over the follow-up

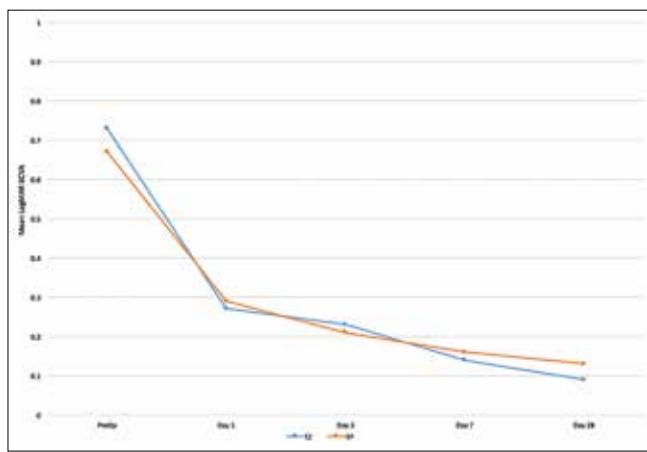


Figure 3: LogMAR visual acuity in the two groups

Almost all patients in our study gained postoperative BCVA of 6/9 or better on day 28 in both groups and they were comparable ($P > 0.05$) [Fig. 3]. Similarly, in a study by Fisher and Potvin^[3] the BCVA of subjects at 1 week and 1 month postoperatively improved significantly ($P < 0.01$). In our study, no intraoperative complication like zonular dialysis and posterior capsule rupture was observed in the TZ group, and in either of the groups, no serious intraoperative or postoperative complication like endophthalmitis has occurred.

Conclusion

The dropless approach like per-operative transzonular injection of antibiotics and corticosteroids to manage postoperative inflammation is emerging as a promising modality in modern ophthalmic surgery. This drug delivery system may reduce the risk of postoperative infection and inflammation, simplify therapeutic compliance, and reduce the expenses of the patient with a single intraoperative injection that adds value to an already outstanding and life-changing procedure.

In this study, we conclude that the transzonular drug deliverance (moxifloxacin and dexamethasone) in cataract surgery has a greater therapeutic and tolerance response as compared to the conventional topical regimen in controlling the risk of infection and postoperative inflammation. Moreover, this approach could prove more efficacious in terms of better compliance and cost-effectiveness particularly for the rural population of India for whom instilling eye drops is challenging and unsafe due to various reasons. However, extreme caution should be exercised pertaining to the drug quality, asepsis, and injection technique as the drug is to be directly injected into the vitreous and, thus, poses a theoretical risk of inflammation and endophthalmitis.

Further randomized controlled studies on a larger population could possibly establish the effectiveness of this approach so that patients can be relieved of tedious postoperative drug instillations and associated morbidities.

The possible limitations of this study are (a) small sample size, (b) nonrandomized design, and (c) grading flare on slit lamp rather than using a flare meter, a more objective method.

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Indocyanine green-enhanced transpupillary thermotherapy for juxtapapillary retinal capillary hemangioblastoma

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Purpose: To study the clinical presentation and treatment outcomes of indocyanine green-enhanced transpupillary thermotherapy (ICG-TTT) for treatment-naïve juxtapapillary retinal capillary hemangioblastoma (JRCH). **Methods:** A prospective interventional case series. The technique involved ICG dye infusion 45 seconds prior to application of TTT. The main study outcomes were local tumor control, resolution of subretinal fluid (SRF), and improvement in best-corrected visual acuity (BCVA). **Results:** Eight eyes of seven patients (5 males and 2 females) were included. The mean age was 26 years (range: 5–56 years). Systemic evaluation revealed von-Hippel Lindau (VHL) disease in five patients. The most common location was the temporal aspect of the optic disc (5 eyes). The mean basal diameter was 2.9 mm (range: 1–8 mm), and tumor thickness was 1.4 mm (range: 1–4 mm). All eight eyes were treated with multiple sessions of ICG-TTT (mean: 3 sessions). Six eyes received adjuvant intravitreal injection of dexamethasone implant (4 eyes) and/or bevacizumab (4 eyes). Post treatment, six eyes (75%) had tumor regression with reduction of SRF. One eye had a partial response with persisting SRF, and one eye showed poor response to TTT for which external beam radiotherapy was performed. At the last follow-up (median: 11 months; range: 6–29 months), the BCVA remained stable in seven eyes and improved in one eye (hand motion to 20/40). **Conclusion:** Multiple ICG-TTT sessions can be considered as an alternative treatment option for JRCH with effective local tumor control and SRF resolution.

Key words: Indocyanine green angiography, juxtapapillary retinal capillary hemangioblastoma, transpupillary thermotherapy, treatment

Retinal capillary hemangioblastomas (RCH) are benign retinal vascular tumors presenting as round, sessile orange-red vascular lesions in the mid-peripheral retina or rarely in the juxtapapillary area.^[1,2] They can manifest either sporadically or as a part of von Hippel-Lindau (VHL) syndrome.^[3] Juxtapapillary RCH (JRCH) are small nodular vascular hamartomas seen over the optic disc or located in the juxtapapillary region. Isolated RCH is usually stable and unassociated with vision-threatening complications and hence can be safely observed.^[4] However, RCH associated with VHL is usually progressive and complicated by associated vitreous hemorrhage, secondary exudative retinal detachment due to tumor exudation, or tractional retinal detachment due to glial proliferation around the tumor.^[3,5] Because of their location, JRCH are easily misdiagnosed before they exhibit endophytic growth protruding into the vitreous cavity, resulting in visual impairment secondary to macular exudation, subretinal fluid accumulation, macular edema, epiretinal membrane formation, and exudative or tractional retinal detachment.^[6]

Various treatment modalities such as laser photocoagulation, photodynamic therapy, transpupillary

thermotherapy (TTT), or a combination of these modalities along with the use of intravitreal agents have been tried for small tumors located at the posterior pole.^[7–11] The treatment for JRCH is challenging due to collateral laser-induced damage to the optic nerve and surrounding retinal blood vessels. Photodynamic treatment with/without the use of intravitreal antivascular endothelial growth factor (VEGF) has been the standard of care for the treatment of JRCH with good anatomical and functional outcomes.^[12–14] However, with the current unavailability of verteporfin dye in many countries, we explored the option of indocyanine green-enhanced TTT (ICG-TTT), which would enable a more selective vascular occlusion with less damage to the optic disc. ICG-TTT has been in use for treatment of various intraocular tumors such as RCH, choroidal hemangioma, retinoblastoma, and choroidal melanoma with good tumor control and dose-dependent decrease in TTT fluence threshold as compared to standard TTT.^[10,15–19]

In this study, we aimed to report the clinical presentation and investigate the efficacy and safety of ICG-TTT in a series of patients diagnosed with JRCH.

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Methods

Study patients

Institutional review board approval was obtained for this study. A prospective, interventional, treatment-naïve case series of patients diagnosed with JRCH at a tertiary eye institute from May 2019 to October 2022 were included in this study. The diagnosis was based on a combination of past medical and/or family history of VHL disease, clinical examination, and use of ancillary imaging studies such as fundus photography, fluorescein angiography, optical coherence tomography, and ultrasonography.

Patient characteristics

The following baseline demographic features were recorded for all patients: age, gender, location of the tumor in relation to the optic disc, and presenting best-corrected Snellen's visual acuity. Tumor dimensions, including the base diameter and height of the lesion, were estimated during clinical examination and confirmed using B-scan ultrasonography. Optical coherence tomography (OCT) scan was performed over the tumor to study its configuration, involvement of retinal layers, growth pattern (endophytic or exophytic), and presence of associated features such as subretinal fluid (SRF), macular edema, and tractional maculopathy. Fluorescein angiography was performed to demonstrate the leakage pattern of the lesion as well as detect any subclinical small lesions located at the posterior pole or in the periphery.

Treatment regimen

All the patients were treated with ICG-TTT along with anti-VEGF injection or dexamethasone implant depending on the tumor location and presence of macular SRF. The dosage was calculated based on 0.5 mg/kg of body weight. Under sterile conditions, 2-mL ICG dye (Aurogreen injection, Aurolabs, India) was injected 45 seconds prior to the application of TTT (Iris Medical OcuLight SLx; Iridex Corporation, Mountain View, CA, USA). Laser settings were adjusted to give retinal greying over the tumor area following 1-minute exposure time by using a spot size of 1.2 mm and power ranging 300–400 mW. The final endpoint was graded in terms of SRF resolution at the macula and reduction in tumor thickness. The patients were examined at 6–8 weeks intervals post laser for determining the tumor response, resolution of SRF, and need for additional interventions. Complete response was defined as a reduction in tumor thickness with or without scarring/fibrosis and absence of SRF; partial response was defined as the presence of SRF at the macula with minimal reduction in tumor thickness. At the last follow-up, final visual acuity and multimodal imaging using fundus photography and OCT were performed to document and grade the treatment response. Treatment-related complications such as an increase in tumor thickness, persistent or recurrent SRF, exudative retinal detachment, and foveal atrophy were noted at the last follow-up.

Outcome measures

The main outcome measures were local tumor control, SRF resolution, and final visual acuity at the last follow-up.

Results

Eight eyes of seven patients (5 males and 2 females) diagnosed to have JRCH were included in the study. The mean age

at presentation was 26 years (median: 24 years; range: 5–56 years). Bilateral RCHs were seen in five patients (71%), of which one patient had bilateral JRCH, while in the other four eyes, one eye had small focal RCH and three eyes were pre-phthisical. A positive finding of VHL disease was seen in five patients (71%). The most common presenting complaint was diminution of vision (100%) and floaters (29%). Patient characteristics and clinical features are described in Table 1.

The most common tumor location was on the temporal aspect of the optic disc (5 eyes), while in two eyes, the tumor extended >270° in the parapapillary area. Tumors exhibited endophytic growth in four eyes and exophytic growth in four eyes. The mean largest basal diameter was 2.9 mm (range: 1–8 mm) and tumor thickness was 1.4 mm (range: 1–4 mm). The best corrected visual acuity ranged from no perception of light (NPL) to 20/20. OCT demonstrated involvement of outer retinal layers in four eyes, with the presence of SRF involving the macula in all eight eyes (100%). Fluorescein angiography performed in four eyes showed extensive peripapillary leakage and pooling in the macular area in the late phases.

All eight eyes were treated with multiple sittings of ICG-TTT after a minimum interval of 6–8 weeks. A mean of three sessions of TTT was required during the study for tumor control (range: 1–7 sessions). Of the eight eyes, six eyes received adjuvant intravitreal injections, including anti-VEGF (bevacizumab) in four eyes and intravitreal dexamethasone implant in two eyes [Table 2]. Post treatment with multiple sittings of ICG-TTT, regression of the tumor with resolution of SRF was seen in six eyes (75%). In two patients (case no. 2 and 3), because of the larger size of the tumor and exudative fluid, there was a suboptimal treatment response with persistent SRF. At the last follow-up (median: 11 months; range: 6–29 months), the best corrected visual acuity remained stable in seven eyes and improved in one eye (hand motion to 20/40). The representative case illustrations showing the fundus photograph and OCT are highlighted in Figs. 1a-l, 2a-h, 3a-h, and 4a-h.

Discussion

The longitudinal progression of retinal capillary hemangiomas over the course of the disease has been shown to result in progressive loss of vision, usually from exudation, macular edema, serous retinal detachment, or secondary glial proliferation leading to epiretinal membrane formation or tractional maculopathy.^[5,6,20]

The prevalence of JRCHs has been reported to be between 15% and 20% among VHL patients, with a higher likelihood in younger patients.^[6,21] In our series, of the eight eyes, four patients (5 eyes) with VHL disease had JRCH (71%), with one having bilateral JRCH. The mean age of presentation in our series was 26 years (median: 24 years), with the youngest patient being 5 years. Both patients 2 and 3 (aged 5 and 11 years, respectively) had a large JRCH involving more than 270° of the parapapillary retina. The majority of JRCH affects the temporal aspect of the optic nerve, thereby leading to serous macular detachment and progressive loss of vision.^[1,6] In our series also, the most common tumor location was on the temporal aspect of the optic disc (63%), with associated retinal features of macular exudation and edema seen in seven eyes and serous detachment in all eight eyes. The tumor growth pattern was endophytic and exophytic in four eyes each with exophytic

Table 1: Demography and clinical presentation of juxtapapillary retinal capillary hemangioblastoma (JRCH)

Patient	Age (years)	Gender	Eye	VHL disease	Growth	Tumor dimensions (mm)	Optic disc involvement	Angiographic features	OCT features	
									Subretinal fluid	Macular edema
1	34	M	BE	Yes	RE-Endophytic LE-Exophytic	RE- 3x2.5x2 LE- 2x1.5x1	RE-Inferotemporal LE-nasal	Early and late leak	Yes (BE)	Yes (BE)
2	5	F	LE	Yes	Exophytic	LE- 8x7 x 4	>270-degree involvement	Peripapillary leakage	Yes	Yes
3	11	M	LE	No	Exophytic	4x3.5x2.5	>270-degree involvement	Not done	Yes	Yes
4	28	M	LE	Yes	Endophytic	2x2 x 1	Temporal	Peripapillary leakage	Yes	Yes
5	24	F	LE	Yes	Exophytic	1.5x1 x 1	Temporal	Not done	Yes	No
6	56	M	RE	No	Endophytic	3x2 x 2	Superotemporal	Not done	Yes	Yes
7	22	M	LE	Yes	Endophytic	1.5x1 x 1	Inferotemporal	Peripapillary leakage	Yes	No

M: male; F: female; BE: both eyes; RE: right eye; LE: left eye

Table 2: Treatment and visual outcomes

Patient	Eye	TTT parameters		Number of ICG-TTT sessions	Adjuvant treatment: first line	Treatment response		At presentation BCVA	Final BCVA	Follow-up (months)
		Power (mW)	Counters (1 min duration)			Tumor	OCT feature (SRF)			
1	BE	350	RE- 9 LE- 5	2	Intravitreal Bevacizumab (BE)	Regressed (BE)	Reduced	RE- 20/60 LE- 20/20	RE- 20/60 LE- 20/25	6
2	LE	350	17	7	Intravitreal dexamethasone implant	Partial	Persisting	LE- CF CF	LE- HM	15
3	LE	400	15	2	Intravitreal dexamethasone implant	Partial	Persisting	LE- CF CF	LE- CF CF	11
4	LE	300	6	3	Intravitreal dexamethasone implant	Regressed	Reduced	LE-20/20	LE- 20/20	6
5	LE	300	8	1	None	Regressed	Reduced	LE-20/20	LE- 20/20	29
6	RE	300	9	2	None	Regressed	Reduced	RE- HM	RE- 20/40	10
7	LE	400	2	2	Intravitreal bevacizumab	Regressed	Reduced	LE- 20/20	LE- 20/20	11

M: male; F: female; BE: both eyes; RE: right eye; LE: left eye; SRF: subretinal fluid; BCVA: best-corrected visual acuity; CF CF: countinf fingers close to face; HM: hand motions

tumors associated with larger base diameter and thickness and exudative retinal detachment.

The treatment for JRCH remains challenging particularly due to its anatomic location close to the optic disc, macula, and major retinal blood vessels as well as less clearly defined efferent and afferent feeder vessels. Various treatment modalities such as observation, laser photocoagulation, TTT, photodynamic therapy, anti-VEGF, and intravitreal steroid injections in combination or alone have been tried with limited success. Laser photocoagulation is used to treat small tumors of up to 1.5 mm in the peripheral retina but carries additional risk for JRCH because of its proximity to the optic nerve and macula, leading to a large central scotoma in the visual field. Because of inadvertent collateral damage to surrounding structures, PDT due to its selective vascular occlusion of tumor vessels is the standard of care for treatment of JRCH. Studies have reported good anatomical and functional outcomes following the use of PDT for the treatment of JRCH.^[8,12,13,22] However, since July 2021, a worldwide shortage of verteporfin (Visudyne®) occurred,

resulting in a major impact on the care of ophthalmic patients across the world, thereby disrupting the treatment option of PDT.^[23] As an ocular oncologist, we felt an urgent need to look for alternative treatment strategies for various intraocular tumors such as choroidal hemangioma, choroidal melanoma, and JRCH. TTT, a modified laser photocoagulation technique, has been tried in the past for the treatment of RCH by using a low-level heat and a modified diode laser.^[10,11,24-26] TTT works on the principle of thermotherapy and not direct coagulation of tumor vessels, as seen with argon laser photocoagulation. The effect of thermotherapy leads to the dilation of capillaries and an increase in exudation, which is not a desirable effect; hence, very high power (500–1200 mW) is needed to prevent such complications. However, the high-power usage of TTT, especially for JRCH, would damage the sensory retina and increase retinal traction, thereby compromising final visual acuity. ICG-enhanced TTT has been tried in the past for the treatment of choroidal neovascularization and small choroidal melanomas with good efficacy and safe outcomes.^[15,16,25,27] ICG increases the laser uptake within the tumor without



Figure 1: (a–l): A 34-year-old male presented with bilateral JRCH with macular edema with BCVA of 20/60 and 20/20 in OD and OS, respectively. Fluorescein angiography (FA) demonstrated early hyperfluorescence of the tumor vessels and progressive leakage in the late phase of the angiogram, as shown in Figs. 1(b), 1(c), 1(h), and 1(i). He underwent ICG-guided TTT with intravitreal bevacizumab in both eyes. At 6 weeks follow-up, SRF was persisting; hence, a repeat sitting of ICG-TTT with intravitreal dexamethasone implant was given. At 12 weeks, the BCVA was stable with complete resolution of SRF and tumor control

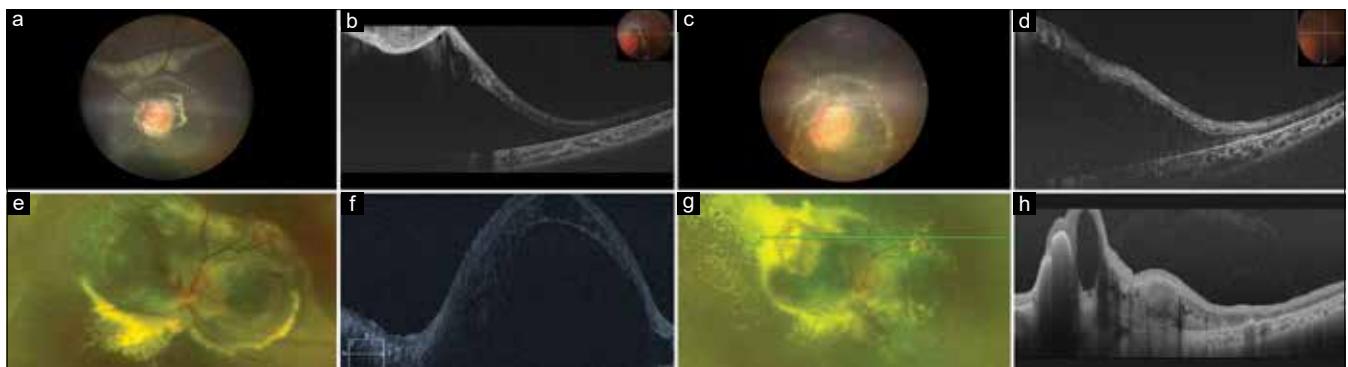


Figure 2: (a–d): A 5-year-old girl presented with small focal peripheral RCH in the right eye and a large JRCH involving >270° of parapapillary area with SRF. Her BCVA was 20/30 in the right eye and CF CF in the left eye. There was complete regression of lesion in the right eye following one sitting of TTT, while multiple ICG-TTT sessions (a total of 7) were required for the left eye every 8–10 weeks interval along with intravitreal injection of dexamethasone. At the last follow-up, the BCVA remained stable with partial regression of lesion and persisting SRF. (e–h): An 11-year-old boy presented with a large JRCH in the left eye. At presentation, his BCVA was CF CF in the left eye. He underwent one sitting of ICG-TTT with intravitreal bevacizumab, following which there was increase tumor exudation and massive inferior exudative retinal detachment. Considering the size, location, and inferior exudative RD, he was referred for external beam radiation treatment (EBRT). At 2 months post treatment, BVCA remained stable with resolving exudative RD and partial tumor regression

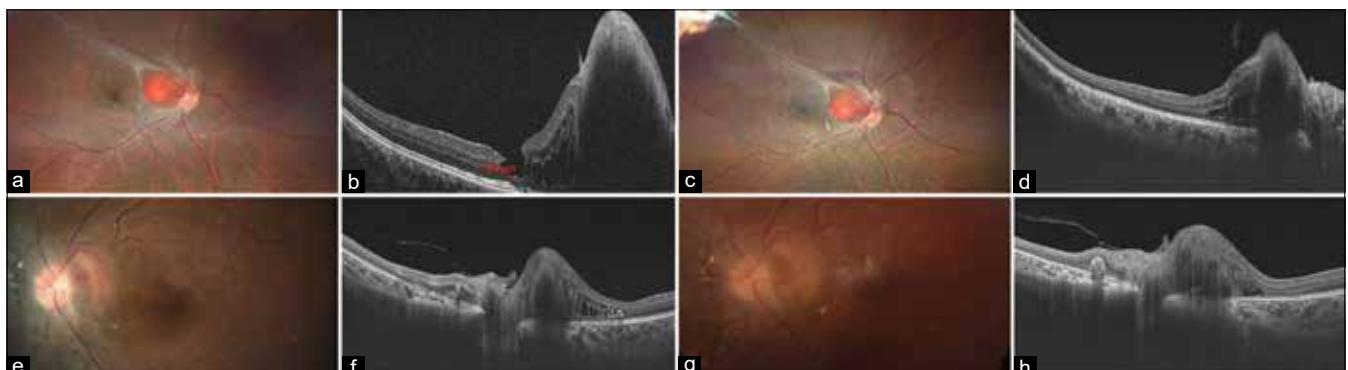


Figure 3: (a–d): A 28-year-old male presented with a small JRCH in the left eye. His BCVA was No PL in the right eye and 20/20 in the left eye. He underwent three sittings of ICG-TTT with an intravitreal dexamethasone implant in the left eye at an interval of 2 months. At the last follow-up, the tumor showed regression with resolution of SRF and stabilization of vision. (e–h): A 24-year-old female was diagnosed to have left eye JRCH with presence of SRF and intraretinal fluid. Her BVCA was No PL in the right eye and 20/20 in the left eye. She was treated with one sitting of ICG-TTT, following which the tumor remained stable with resolution of SRF and stable vision

increasing the laser intensity, thereby minimizing the diffuse heat generation from the RPE. In our study, we used a very low

power (300–400 mW) and used the ICG dye as a photosensitizer to achieve the desired effect without causing any collateral

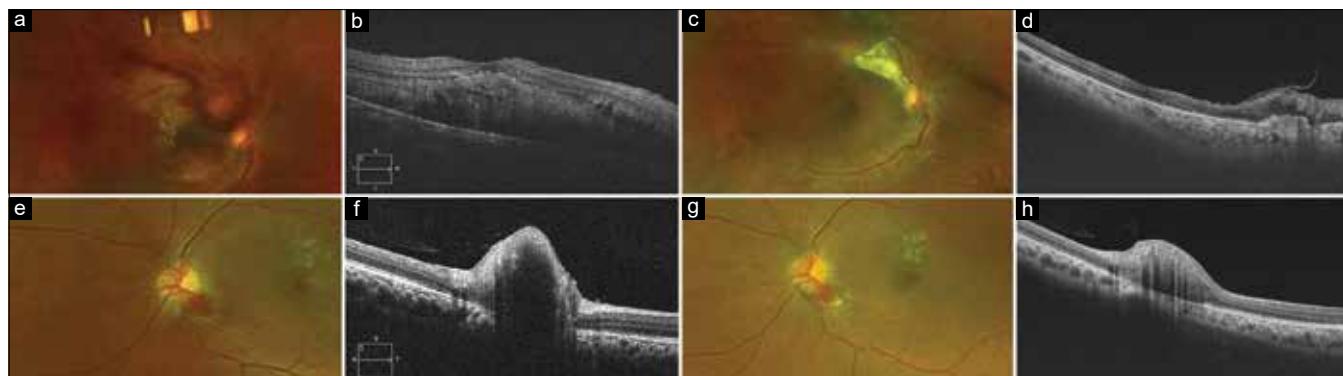


Figure 4: (a–d): A 56-year-old male presented with exudation and subretinal hemorrhage involving the macula in the right eye. A detailed evaluation showed the presence of an exophytic variant of JRCH with BCVA of hand motions in the right eye. The patient was treated with two sittings of ICG-TTT. At the last follow-up, BCVA improved to 20/40 with complete resolution of SRF and regression of the tumor. (e–h): A 22-year-old male presented with a small, solitary JRCH in the left eye involving the inferotemporal quadrant of the optic disc. He has lost vision in the right eye following a failed vitreoretinal surgery for RCH. His BCVA was No PL in the right eye and 20/20 in the left eye. He underwent two sittings of ICG-TTT with intravitreal bevacizumab in the left eye. At last follow-up, the tumor regressed with stabilization of vision

damage to the surrounding structures. Costa *et al.*^[28] studied the effects of photodynamic therapy by using ICG and 810-nm light irradiation on the choriocapillaris and retinal pigment epithelium at different threshold levels with a power of 230 mW/cm² that caused laser-induced endothelium-bound intraluminal photothrombosis, with no obvious alteration in retinal and choroidal architecture and minimal loss of visual cells, whereas power density >630 mW/cm² caused choriocapillaris occlusion and endothelial cell cytoplasmic alteration with disruption of retinal pigment epithelium cells and photoreceptor outer segment. Similarly, Peyman *et al.*^[18] demonstrated that intravenous ICG pretreatment can reduce the TTT threshold fluence and irradiance needed to create angiographically visible lesions in normal rabbit choriocapillaris. Kim *et al.*^[29] studied the effect of thermal injury to the optic nerve head by using TTT, which led to increased expression of heat shock proteins (Hsps), thereby demonstrating a neuroprotective effect of TTT on retinal ganglion cells.

In our series, six eyes (75%) showed tumor regression with resolution of SRF following a mean of three sessions of TTT. These results are comparable to PDT treatment, which has shown excellent tumor control and good visual outcomes.^[8,13,14] A recent study of nine cases highlighted the use of PDT for the treatment of JRCH, wherein tumor control was achieved in seven of nine tumors (78%), with subretinal fluid resolution in six of nine eyes (67%) and stable or improved visual acuity in seven of nine eyes (78%).^[12] In our series also, BCVA remained stable in seven eyes (88%) and improved in one eye till last follow-up. Recent studies have shown increased VEGF expression in patients with RCH, thereby exploring the use of adjuvant anti-VEGF injections in the treatment of RCH and its associated tumor-related sequelae such as macular edema, SRF, or exudation.^[12,30-33] However, the long-term results have been variable with a transient reduction in SRF. In our series, six eyes received adjuvant intravitreal injections of either anti-VEGF (4 eyes) or sustained-release dexamethasone implant (4 eyes) at various time points, showing temporary reduction in the SRF and macular edema. Unfortunately, in two of our patients, there was a dramatic increase in SRF post ICG-TTT despite receiving adjuvant intravitreal injections. This has been reported previously related to an increase in

intraocular tumor leakage (exudative response) following laser or PDT treatment.^[12,34] One of our patients had massive exudative retinal detachment following two sessions of ICG-TTT and hence was referred for external beam radiation treatment (22.5 Gy dose delivered in 7.5 Gy/fraction). At 3 months follow-up, the tumor showed partial tumor regression with resolution of exudative detachment.

This study has several limitations, including a small sample size and surgeon-related variability of treatment combinations. TTT is known to cause damage to the optic nerve and macula structures; however, we have not performed optic nerve function tests such as HVF, which could have provided some insights related to ONH function, and we accept this as a limitation of the paper. Considering the rare nature and presentation of JRCH, this prospective interventional case series highlights the clinical presentation and treatment outcomes. Furthermore, our series provides a novel opportunity to study the efficacy of ICG-TTT in a prospective cohort of treatment-naïve patients.

Conclusion

In this prospective interventional case series, we analyzed the potential use of multiple sessions of ICG-TTT along with adjuvant anti-VEGF agents as an alternative treatment option for JRCH with effective local tumor control, SRF resolution, and vision stabilization. However, larger tumors associated with severe exudation and leakage have an overall poor prognosis. In the future, larger studies are necessary to study the long-term outcomes of this novel treatment.

Statement of ethics

Institutional Review Board approval was obtained at L V Prasad Eye Institute (LEC -BHR-P-10-21-762).

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Brolucizumab-associated intraocular inflammation in Indian patients by VRSI study group

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Context: Concerns about brolucizumab's (Pagenax®) association with intraocular inflammation (IOI) limit its use despite its cost-effectiveness and efficacy. This multicentric study analyzes IOI incidence across 21 tertiary eyecare centers in India since its introduction in October 2020. **Purpose:** To determine the real-world incidence rate of IOI in Indian patients secondary to intravitreal brolucizumab across 21 tertiary eye care centers in India. **Settings and Design:** Retrospective multicentric, survey-based study. **Methods:** Data including number of patients treated, clinical indications, side effects encountered, and IOI case details was collected via Google Forms in 21 Indian tertiary eye care centers since October 2020. Mean, median, frequency, and standard deviation were calculated for statistical analysis. **Results:** All centers used pro re nata protocol for brolucizumab injections with a minimum injection interval of 8 weeks. The incidence of IOI was 0.79% (21 events out of 2655 eyes). Treatment indications included idiopathic polypoidal choroidal vasculopathy, neovascular age-related macular degeneration, diabetic macular edema, and off-label uses. IOI was experienced after the first injection (57%) in majority of cases with a median onset of 14 days (range: 1–65 days). IOI was mild in 28.5%, moderate in 33%, and severe in 38% of cases. Eighteen out of 21 IOI eyes recovered preinjection best corrected visual acuity or better. **Conclusions:** Our study found a lower IOI incidence (0.79%) with brolucizumab (Pagenax) in Indian patients compared to previously reported literature. IOI events were mostly mild to moderate, and post-treatment, most patients improved or maintained BCVA. Larger prospective multicentric studies with PRN dosing protocol are needed to confirm these findings.

Key words: Brolucizumab, intraocular inflammation, Indian population

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Intravitreal anti-vascular endothelial growth factor (anti-VEGF) drugs are the mainstay of treatment for various retinal pathologies such as neovascular age-related macular degeneration (nAMD) and diabetic macular edema (DME). Phase III trials have demonstrated their efficacy with either monthly or two-monthly dosing schedules.^[1,2] However, in real-world clinical practice, it is difficult to have good patient compliance with monthly follow-up or injections. Thus, an effort is being made to come up with drugs which have more durable action, thereby reducing the frequency of visits of the patients to the clinic without compromising the efficacy or the final visual outcome.

To address the challenges associated with frequent dosing, a novel humanized single-chain antibody fragment named RTH258, later known as brolucizumab, has been introduced. In the first human trial with this drug, it was found to be non-inferior to ranibizumab and it also offered the advantage of

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an extended duration of action, reducing the need for frequent injections.^[3] Brolucizumab's small molecular size (26 kDa), high stability, and solubility allow the administration of 6 mg in a single 50 µl intravitreal injection, enabling the delivery of a higher molar dose within the same volume as current vascular endothelial growth factor (VEGF) inhibitors in clinical use, thereby ensuring a longer duration of action.^[4,5] Marketed as Beovu® by Novartis (Basel, Switzerland), brolucizumab received Food and Drug Administration (FDA) approval for nAMD in October 2019 and for DME in June 2022. The Drug Controller General of India granted approval for the drug, which has been available as Pagenax® (Novartis India Ltd, Mumbai, India) since October 2020.

Despite the favorable outcomes demonstrated in the HAWK and HARRIER Phase 3 trials, where brolucizumab showed superior anatomic results and noninferior visual outcomes compared to aflibercept in nAMD patients, there was a concern regarding its association with intraocular inflammation (IOI).^[6] A *post hoc* analysis of these trials reported an IOI rate of 4.5%, with 2.1% of eyes experiencing concomitant vascular occlusions.^[7] Consequently, FDA approved a label update for brolucizumab on June 11, 2020, including additional safety information.^[8]

The largest real-world analysis, which included 10,654 and 11,161 eyes from the Intelligent Research in Sight (IRIS) Registry and Komodo Health database, respectively, found an overall incidence of IOI and/or retinal occlusion to be 2.4%, with certain risk factors such as prior ocular inflammation, occlusion, and female sex associated with higher risk.^[9] This lower incidence of IOI, compared to the controlled clinical trials like HAWK and HARRIER, highlighted the significance of real-world data in assessing the safety of brolucizumab. A recent multicentric study conducted in centers across eastern India by Chakraborty *et al.*,^[10] involving 758 injections of brolucizumab for nAMD, reported the incidence of IOI as 1.7% (13 IOI events out of 758 injections), with vascular occlusion in one eye. The above study predominantly reported data from eastern India; in contrast, our study had centers across various parts of the country. Secondly, they calculated the IOI incidence out of the total number of brolucizumab injections used rather than the total number of eyes treated by brolucizumab as reported by the global clinical trials such as HAWK and HARRIER, and KESTREL and KITE.^[7,11]

This is a retrospective multicentric survey-based study conducted to determine the real-world incidence of IOI secondary to intravitreal brolucizumab used in Indian patients across 21 tertiary eye care centers located at different geographic locations of the country.

Methods

The study was approved by the ethics committee of the respective participating centers, and it adhered to the tenets of the Declaration of Helsinki. This was a multicentric survey-based study performed by the VRSI (Vitreo-Retinal society-India) study group amidst its members/member institutions. The survey was circulated across 21 tertiary eye care centers located in various states and union territories of India (New Delhi [6], Rajasthan [1], Uttar Pradesh [2], Karnataka [3], Kerala [2], Maharashtra [2], Telangana [1], and West Bengal [3]).

To collect the data of the patients who received intravitreal brolucizumab (Pagenax, Novartis India Ltd) from October 2020

to January 2023, a structured questionnaire was developed using Google Forms and an online survey platform was used and sent via email to all the participating centers. The questionnaire included a section on the number of eyes injected and the clinical indications for which Pagenax was given. Another section of the form was dedicated to the observed side effects. The last section included the clinical details of the eyes with IOI, which included the clinical presentation with visual acuity, relevant past ocular and systemic history, the time interval between the injection and the onset of IOI, laterality of inflammation, grade of inflammation, management done, and the final visual outcome and if the treatment plan with anti-VEGF drugs was modified after IOI was encountered.

The grade of inflammation was classified as per the criteria for adverse events (AEs) used in the HAWK and HARRIER study as follows:^[6,7]

1. mild: when the patient is aware of the AE, but can easily tolerate the sign or symptom;
2. moderate: if the sign or symptom results in discomfort significant enough to cause interference with the patient's usual activities; and
3. severe: if the sign or symptom is incapacitating and results in inability of the patient to work or engage in their usual activities.

Statistical analysis was performed using the Microsoft® Excel for Mac, version 16.66.1. The mean, median, frequency, and standard deviation were calculated.

Results

A total of 21 centers across India participated in this survey-based study, comprising 13 private centers, six nongovernmental organizations, and two government centers. A total of 5046 brolucizumab injections were administered in 2655 eyes from October 2020 to January 2023. The indications for treatment were idiopathic polypoidal choroidal vasculopathy (PCV), nAMD, and DME. Other off-label indications were idiopathic macular neovascularization (MNV), retinal venous occlusions, pachychoroid neovasculopathy, post-vitrectomy macular edema, Coats disease, vitelliform degeneration with cystoid macular edema, and chronic central serous chorioretinopathy (CSCR). In 14 out of the 21 centers, brolucizumab was administered for both treatment-naïve eyes and the eyes unresponsive to other anti-VEGFs, while in the remaining seven centers, it was administered to resistant cases.

The average follow-up duration was 6 months (range: 3–9 months). All participating centers followed a pro re nata protocol from the initiation of injection, with an interval of at least 8 weeks between two consecutive injections irrespective of the indication.

The percentage prevalence of IOI during the study period was 0.79% (21 events out of 2655 eyes). None of the eyes had vascular occlusion.

Among the eyes with IOI, one had a history of prior cataract surgery 1 month back. Two had a history of prior IOI with other anti-VEGFs, one with ranibizumab and the other with bevacizumab. Intravitreal brolucizumab was given unilaterally in 17 eyes (81%) and bilaterally in four eyes. In all patients, IOI occurred unilaterally. There was history of diabetes mellitus, hypertension, and coronary artery disease in one patient each.

The clinical indications for using brolucizumab in the eyes which had IOI were nAMD (12 eyes), PCV (five eyes), DME (one eye), Coats disease (one eye), idiopathic choroidal neovascular membrane (CNVM) (one eye), and branch vein occlusion-related macular edema (one eye). Thirteen eyes (62%) had a history of previous anti-VEGFs, whereas eight eyes (38%) were treatment naïve. The median number of anti-VEGF injections received before brolucizumab was 10 (range: 3–30 injections).

IOI related AE occurred after the first injection in 12 eyes (57%), after the second injection in six (28%) eyes, after the third injection in two eyes (9%) and after the fourth injection in one eye.

The median number of days between IOI and brolucizumab injection was 14 days (range: 1–65 days). The time interval between brolucizumab injection and the onset of mild inflammation was 32 days (range: 4–60 days) and for moderate inflammation, it was 30 days (range: 2–65 days). For eyes with severe grade of inflammation, the median number of days between injection and the onset of IOI was 14 days (range: 1–21 days).

The presenting complaints were blurring or diminution of vision in 16 eyes (76%), floaters in five eyes (24%), redness in three eyes (14%), and ocular pain in four eyes (19%). IOI was noted to be mild in six eyes (28.5%), moderate in seven eyes (33%), and severe in eight eyes (38%). Figs. 1 and 2 highlight the various clinical presentations of IOI and their response to treatment.

The median best corrected visual acuity (BCVA) at baseline before brolucizumab injection was 0.6 log of minimum angle of resolution (logMAR; range: 0.2–1 logMAR), that is, Snellen's equivalent of 6/24.

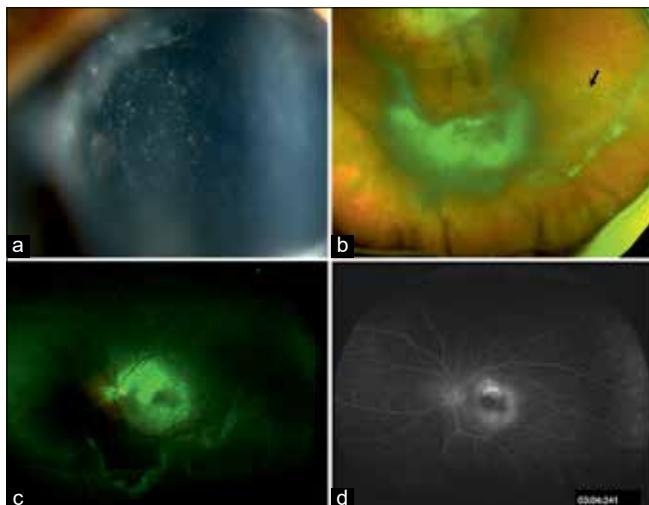


Figure 1: (a) slit lamp photograph showing AC cells at presentation (b) wide field fundus photograph showing dense central vitritis with vasculitis in peripheral vessels (black arrow) at presentation (c) wide field fundus photograph showing resolving vitritis after receiving oral and topical steroid for 3 weeks (d) Wide-field angiography (mid-phase) images showing mid disc hyperemia but no signs of vasculitis at 3 weeks. (Image Courtesy:Dr Khushboo Chandra, Disha Eye Hospitals, Kolkata, India)

Among the six eyes with mild inflammation, the median preinjection BCVA was 0.6 logMAR (6/24) (range: 0.5–1) and the median post-IOI BCVA at 1 month was 0.7 logMAR (6/30) (range: 0.5–1.8). At the end of 3 months, BCVA in all mild IOI eyes was equal to or better than pre-IOI BCVA.

In the seven eyes with moderate inflammation, the median preinjection BCVA was 0.6 logMAR (6/24) (range: 0.2–0.8) and the median post-IOI BCVA at 1 month was 0.3 logMAR (6/12) (range: 0.2–0.8). At the end of 3 months, BCVA for six out of seven moderate IOI eyes was equal to or better than pre-IOI BCVA. The eye which experienced a one line drop in vision from a preinjection BCVA of 0.2 logMAR (6/9) to a post-IOI BCVA at 3 months of 0.3 logMAR (6/12) was a case of treatment-naïve branch retinal vein occlusion associated macular edema, which was treated with topical steroids. One eye with moderate inflammation experienced intraocular pressure (IOP) rise, which was controlled with topical IOP-lowering drops.

In the eight eyes with severe inflammation, the median preinjection BCVA was 0.8 logMAR (6/36) (range: 0.5–1.2) and the median post-IOI BCVA at 1 month was 1.3 logMAR (6/120) (range: 0.8–1.3). At the end of 3 months, BCVA for six out of eight eyes was equal to or better than pre-IOI BCVA. In patients with vision drop, one eye was a treatment-naïve PCV with preinjection BCVA of 1 logMAR (6/60), which dropped to a BCVA of 1.8 logMAR (Finger counting at 1 metre [FC-1 m]) immediately post-IOI. Prompt vitrectomy and oral steroids were given, but the patient was lost to follow-up. The second eye was a treatment-naïve nAMD with preinjection BCVA of 0.6 logMAR (6/24), and the patient presented with intense inflammation with BCVA 1.8 logMAR (FC-1 m). The patient was treated with oral and topical steroids and regained a BCVA of 0.8 logMAR (6/36).

Five out of six eyes with mild inflammation were treated with topical steroids, and one patient received additional oral steroids.

Five out of seven eyes with moderate inflammation were treated with oral as well as topical steroids, with one eye requiring vitrectomy and one eye treated with topical steroids only.

One eye experienced IOP rise, requiring IOP-lowering drugs.

Five out of eight eyes were treated with oral and topical steroids, with two eyes requiring additional vitrectomy and one eye treated with posterior sub-Tenon triamcinolone injection.

Most eyes (15 out of 21 eyes) were shifted to another anti-VEGF after the occurrence of IOI with brolucizumab. Of

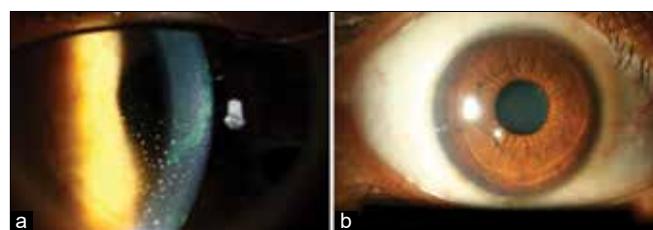


Figure 2: (a) Magnified slit lamp photograph showing keratic precipitates (KPs) (b) Slit lamp photograph after 2 weeks showing reduction of intra-ocular inflammation

the remaining eyes (six eyes), one eye with treatment-naïve PCV did not require further injections post-IOI episode, whereas one patient was lost to follow-up. Interestingly, four eyes, one with mild IOI and three with severe IOI, were continued with brolucizumab without any modification of treatment such as combining brolucizumab with oral or topical or intravitreal steroids. One out of the three eyes with severe inflammation was being treated for resistant nAMD with a history of cataract surgery 1 month before the first brolucizumab injection and presented with an endophthalmitis-like appearance, which was treated with prompt vitrectomy and switched to other anti-VEGF post-IOI. However, this eye had to be switched back to brolucizumab because of poor response to the other anti-VEGF given.

On further follow-up, none of these four eyes experienced a recurrence of IOI on repetition of brolucizumab during subsequent visits.

Discussion

Brolucizumab is the new anti-VEGF drug for the management of various retinal pathologies. This retrospective, multicentric, survey-based study reports the real-world incidence of IOI following intravitreal brolucizumab injection given for both approved indications such as nAMD, DME

and off-label indications such as CSC, retinal venous occlusions, Coats disease, post-vitrectomy macular edema, idiopathic MNV, vitelliform degeneration with macular edema in patients of Indian origin.

This study shows an incidence of IOI as 0.79%, which is much lesser than that reported previously.^[7,9,10,12,13] Large clinical trials such as HAWK and HARRIER, and KESTREL and KITE reported an IOI incidence of 4.5% and 5.3%, respectively.^[7,11] The OCTOPUS and SWIFT trials for nAMD reported an even higher incidence rate of 10.5%, which they attributed to proactive monitoring for IOI-related signs and symptoms.^[14] Real-world studies from Caucasian populations report IOI rates of 2.4% (IRIS registry and Komodo database) to 4.6%.^[9,13] Higher incidence rates of IOI ranging from 10% to 22% were reported from Asian studies (Japan and Korea).^[15-18] A brief summary of major Asian studies is presented in Table 1.

Most of the clinical trials followed a regimen of initial monthly or six-weekly loading dose of brolucizumab injections, followed by 12-weekly or Pro re nata (PRN) basis injections.^[6,11,14] This has been questioned by certain real-world studies from India, such as the PROBE study, which followed a PRN regimen from the start in 27 treatment-naïve neovascular AMD eyes and found good visual and anatomic outcomes with no IOI occurrence.^[19] A recent series of 758 injections by

Table 1: A summary of major Asian studies on brolucizumab-induced intraocular inflammation

Citation	Country	Treatment naïve/ resistant ^a	Total no. of eyes	Clinical indication	Treatment regimen	IOI events	Visual outcome
Chakraborty et al. 2023 ^[13]	India	NA	NA	nAMD	Pro re nata	13 (758 injections, 1.7%)	11/13 recovered vision
Kim et al. 2023 ^[15]	Korea	20 eyes (6.8%) treatment naïve and 274 eyes (93.2%) resistant	294	nAMD	Loading dose	41 (13.9%)	39 out of 41 recovered vision
Bae et al. 2022 ^[16]	Korea	All resistant	34	nAMD	Pro re nata	5 (14.7%)	All recovered vision
Yeom et al. 2023 ^[17]	Korea	All resistant	81	nAMD	Treat and extend	8 (9.9%)	All recovered vision
Matsumoto et al. 2022 ^[18]	Japan	All treatment naïve	68	nAMD	Treat and extend	15 (22.1%)	All recovered vision
Bilgic et al. 2021 (PROBE study) ^[19]	India	All treatment naïve	27	nAMD	Pro re nata	0	NA
Hirano et al. 2023 ^[20]	Japan	All resistant	23	DME	Single injection	0	NA
Kikushima et al. 2023 ^[21]	Japan	All resistant	60	nAMD	Treat and extend	12 (20%)	All recovered vision
Hsu et al. 2022 ^[22]	Taiwan	All resistant	10	nAMD and PCV [§]	Single injection	0	NA
Nam et al. 2022 ^[23]	Korea	All resistant	26	PCV	Pro re nata	0	NA
Fukuda et al. 2021 ^[24]	Japan	All treatment naïve	14	PCV	Loading dose	2 (14%)	One had persistent field loss due to BRAO
Maruko et al. 2021 ^[25]	Japan	43 eyes treatment-naïve and 84 eyes resistant	127	nAMD	Loading dose	12 (9.4%)	All recovered vision
Bilgic et al. 2021 (REBA study) ^[26]	India	25 were treatment naïve rest resistant	105	nAMD	Loading dose for treatments naïve and monthly for resistant group	0	NA
Chakraborty et al. 2021 (BRAILLE study) ^[27]	India	20 eyes treatment naïve, 74 eyes resistant	94	nAMD	Pro re nata	0	NA

DME=Diabetic macular edema, IOI=Intraocular inflammation, nAMD=Neovascular age-related macular degeneration, PCV=Polypoidal choroidal vasculopathy.

^aResistant refers to cases that were switched to brolucizumab after poor response to other anti-VEGFs, BRAO=Branch retinal artery occlusion

Chakraborty *et al.*^[10] which followed a PRN protocol from the start, found an IOI-related incidence of 1.7% (per injection).

As recommended by Bilgic *et al.* in the PROBE study and Chakraborty *et al.*, all the participating centers in our study used a PRN protocol from the time of initiation of treatment and there was a minimum interval of 8 weeks between two subsequent injections of brolucizumab, irrespective of the retinal pathology.^[10,19] The lower dosing used may possibly cause lesser immunogenicity, and hence is possibly safer.

Racial variation in ocular inflammation has been previously reported. For instance, the Pacific Ocular Inflammation Study found a significantly higher prevalence of uveitis in white populations.^[28] Asian-Pacific countries, including Japan, China, and Taiwan, show a high prevalence of noninfectious and idiopathic uveitis conditions.^[29] These differences may explain higher incidence of IOI observed in Caucasian populations and Asian studies, particularly in Japan, in comparison to our study.

Another cause for the lower incidence rate of IOI in our study may be the lack of a proactive approach in early diagnosis of IOI as followed by OCTOPUS and SWIFT trials, leading to underdiagnosis of mild IOI following brolucizumab, which may be asymptomatic.^[14] All participating centers also followed a strict protocol of excluding patients with a history of uveitis or underlying autoimmune conditions in accordance with the guidelines issued for patient selection for treatment with brolucizumab.^[30-32] This may also have resulted in lower IOI incidence. A recent post-marketing survey analysis showed decline in overall retinal vasculitis and/or retinal vascular occlusion cases after the safety signal was issued, which further supports this reasoning.^[33]

The majority of IOI cases in our data (12 out of 21, or 57%) experienced it after the first injection, with 28% experiencing it after the second injection (six eyes), two eyes experiencing IOI after the third injection, and one eye having it following the fourth injection. Our results were similar to those of Khanani *et al.*^[9] who found 49% (256 out of 523) IOI events after the first injection, 39% (205 out of 523) IOI events after the second injection, and 12% IOI events after the third or more than three injections (combined IRIS registry and Komodo data). Similar findings were reported by Bodaghi *et al.*^[14] in the OCTOPUS and SWIFT trials, which involved proactive screening for IOI and found most IOI-related events (81.1%) occurring during the loading phase after a mean of 2.6 (standard deviation [SD] = 1.3) brolucizumab injections.

Preexisting local serum antibodies to brolucizumab have been noted in 36%–52% of treatment-naïve patients, which is higher than that observed with other anti-VEGF agents such as ranibizumab, where it is 4%–5%.^[34] These preexisting antibodies cause a type 3 hypersensitivity reaction causing inflammation in patients receiving the first dose of the injection.^[35,36] Since the median number of days between the injection and IOI in our study was 14 days (range: 1–65 days), this supports the hypothesis of a delayed hypersensitivity reaction.^[35]

Majority of the cases were mild to moderate IOI (13 out of 21 eyes), with eight eyes reported as having severe IOI. As reported in literature that eyes with mild to moderate IOI resolve without any sequelae, in our series also 12 eyes with mild to moderate IOI and six eyes with severe IOI resolved completely with recovery of vision to pre-injection BCVA.^[7,12]

One eye with moderate IOI and one eye with severe IOI experienced a one line drop of vision from pre-injection BCVA at 3 months and one eye which presented with severe inflammation was lost to follow-up. In our series, occlusive vasculitis was not reported in any case.

As per the prescribing information, brolucizumab is to be discontinued during active IOI.^[34] However, there are no clear guidelines on resuming anti-VEGF treatment after resolution of the IOI episode. Singer *et al.*^[7] in their post hoc analysis of the HAWK and HARRIER study, reported that after the first IOI-related AE, approximately 74% of eyes in the trial received further brolucizumab injections, and most of these eyes (24/36 eyes [approximately 67%]) completed the study with brolucizumab only and achieved an overall BCVA gain by the end of study. Recurrence, worsening of IOI, and/or occlusive vasculitis have been reported in literature following the switch back to another anti-VEGF.^[14,35,37] In our study, the 15 eyes that were switched to another anti-VEGF did not have recurrence or worsening of IOI during the follow-up period. The four eyes that were continued on or switched back to brolucizumab following resolution of the IOI episode also reported no recurrence of IOI during the follow-up period.

To the best of our knowledge, this study has the largest number of eyes of Indian origin treated with brolucizumab for various indications and analyzed for the incidence of IOI. The other strength of the study is that it was a multicentric study including centers from different geographic locations of the country.

The limitations of this study are that it is a survey-based retrospective study. Secondly, the follow-up of our patients ranged between 3 and 9 months, which may not include the incidence of late IOI or recurrence of IOI on subsequent follow-up visits. Thirdly, it included patients in whom brolucizumab was used in off-label indications. Lastly, risk factor analysis could not be carried out due to the small number of IOI cases as well as lack of detailed clinical information of the non-IOI patients.

Conclusion

To conclude, the incidence of IOI in our study was found to be much lesser (0.79%) in Indian eyes in comparison to that reported in Caucasians (2.4%), and we hypothesize that this possibly could be related to a different immune response in Indian patients.^[9] The IOI-related AEs were mild to moderate in majority of the patients, and nearly all eyes after treatment of IOI regained or became better than preinjection BCVA at 3 months follow-up visit. Larger multicentric prospective studies maybe required in future to further confirm the incidence of IOI in patients treated with brolucizumab, including a proactive monitoring of the treated patients.

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Evaluation of an AI algorithm trained on an ethnically diverse dataset to screen a previously unseen population for diabetic retinopathy

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Purpose: This study aimed to determine the generalizability of an artificial intelligence (AI) algorithm trained on an ethnically diverse dataset to screen for referable diabetic retinopathy (RDR) in the Armenian population unseen during AI development. **Methods:** This study comprised 550 patients with diabetes mellitus visiting the polyclinics of Armenia over 10 months requiring diabetic retinopathy (DR) screening. The Medios AI-DR algorithm was developed using a robust, diverse, ethnically balanced dataset with no inherent bias and deployed offline on a smartphone-based fundus camera. The algorithm here analyzed the retinal images captured using the target device for the presence of RDR (i.e., moderate non-proliferative diabetic retinopathy (NPDR) and/or clinically significant diabetic macular edema (CSDME) or more severe disease) and sight-threatening DR (STDR, i.e., severe NPDR and/or CSDME or more severe disease). The results compared the AI output to a consensus or majority image grading of three expert graders according to the International Clinical Diabetic Retinopathy severity scale. **Results:** On 478 subjects included in the analysis, the algorithm achieved a high classification sensitivity of 95.30% (95% CI: 91.9%–98.7%) and a specificity of 83.89% (95% CI: 79.9%–87.9%) for the detection of RDR. The sensitivity for STDR detection was 100%. **Conclusion:** The study proved that Medios AI-DR algorithm yields good accuracy in screening for RDR in the Armenian population. In our literature search, this is the only smartphone-based, offline AI model validated in different populations.

Key words: Artificial Intelligence, deep learning, diabetic retinopathy, eye screening

Diabetic retinopathy (DR), a microvascular complication of diabetes mellitus (DM), is one of the leading causes of preventable blindness. It is estimated that 642 million people would be living with diabetes by 2040 worldwide.^[1] The global prevalence of DR among people with diabetes is 34.6%, and it is 10.2% for sight-threatening diabetic retinopathy (STDR).^[2] Over the past decade, the number of people with diabetes has increased.^[1] Such high numbers not only pose a great economic burden but also create an ever-increasing demand for accessible eye care. Artificial intelligence (AI) can help bridge the otherwise widening gap between ophthalmologists and patients.

Current deep learning (DL)-based AI algorithms have shown performances approaching that of clinicians in detecting DR.^[3–7] This encourages the deployment of such systems to reduce the burden on ophthalmologists. There is a requirement across all geographies to tackle the global problem of preventable blindness. It is thus important to focus on unbiased and robust

AI systems, which work equally well across ethnicities and populations.

Patient attributes, such as race/ethnicity, can introduce biases in AI systems, and these biases pose significant challenges in the development of AI-based models for DR screening. It is crucial for effective solutions deployed in different geographies to demonstrate consistent accuracy across diverse populations.^[4,8,9] It should be noted that ethnic groups with darker skin tend to have higher melanin content within their uveal melanocytes, resulting in darker fundus pigmentation.^[10,11] Consequently, although DR lesions are similar across all ethnic groups, the background color of the fundus can make these lesions more or less distinct. Thus, fundus pigmentation may also impact the interpretation of AI systems.^[10]

We hypothesize that an AI algorithm can generalize across different populations. This should hold true even if the population is not represented in the training set. This assumption relies on an ethnically balanced and diverse

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dataset. The Medios AI-DR is an offline, smartphone-based algorithm trained on a diverse dataset that did not include Armenian eyes. We report here the accuracy of this algorithm on an Armenian population for the detection of referable diabetic retinopathy (RDR). The scope of the DR screening program in Armenia falls under the aegis of the Armenian Eye Care Project (AECP) team in cooperation with the Armenian Ministry of Health and the World Diabetes Foundation with an aim to end preventable blindness due to DR.^[12] The AECP project is part of a larger initiative led by this team to ensure accessible eye care for all Armenians.

Methods

This retrospective study was approved (IRB approval no.: N4-3/2020) by the institutional ethics committee. It was performed according to the tenets of the Declaration of Helsinki.

Study Population Sampling and Imaging Protocol: Patients with established diabetes attending the polyclinics of Armenia for DR screening were included in this study. The images were captured using the Fundus-on-Phone (FOP NM-10, Remidio Innovative Solutions), a smartphone-based fundus camera with a field of view of 40°, and collected over a 10-month period between July 2019 and April 2020. The study population included 550 consecutive subjects. Subjects with no established ground truth diagnosis were excluded.

Retinal image acquisition: The images were captured by non-medically trained operators in real-world conditions. The imaging protocol consisted of acquiring one disc and one macula-centered image per eye of each patient without dilation. This was performed during routine DR screening. Repeat images were captured when required to ensure sufficient image quality.

Image Grading: The consensus or majority image grading of three expert graders, two fellowship-trained ophthalmologists, and one certified optometrist formed the reference standard for assessing the AI algorithm. One grader, a fellowship-trained ophthalmologist, provided image-based diagnosis during the screening program. In total, 53 patients had no consensus after grading by the three graders. They were presented to two senior retina specialists, whose adjudicated diagnosis was deemed final. All graders were masked to the Medios AI-DR output and to each other's grading. The de-identified images were graded for the stage of DR and the presence of diabetic maculopathy. The International Clinical Diabetic Retinopathy classification was used to grade images. The images were graded as either no DR, mild non-proliferative DR (mild NPDR), moderate non-proliferative DR (moderate NPDR), severe non-proliferative DR (severe NPDR), proliferative DR (PDR), or ungradable. The graders also looked for hard exudates within 1 disc diameter of the fovea center. This was used as a surrogate marker for the presence of clinically significant diabetic macular edema (CSDME), which is considered a standard guideline in a screening context in the absence of stereo imaging.^[13-15] An image was deemed ungradable if a reliable diagnosis of DR was not possible. This could happen in two distinct scenarios: 1) if major vessels could not be clearly identified, or 2) due to blurring, artifacts, under/over-exposure, or glare spanning half or more of the image. The patient-level diagnosis was inferred by the DR stage of the more affected eye. The consensus grading for each patient formed the final diagnosis. RDR was defined

as moderate NPDR or higher severity and/or the presence of CSDME. STDR was defined as severe NPDR or higher severity and/or the presence of CSDME.

AI-based software architecture: The Medios AI-DR consists of an ensemble of two convolutional neural networks based on the Inception-V3 architecture. It classifies color fundus images for the presence of RDR. The detailed software architecture has been previously published.^[6] In brief, the training set consisted of 52,894 images as follows: 34,278 images were obtained from the Eye Picture Archive Communication System telemedicine program (EyePACS LLC, Santa Cruz, California). In total, 14,266 mydriatic images were captured using a Kowa VX-10α (Kowa American Corporation, CA, USA) at a tertiary diabetes center in India, and 4350 non-mydriatic images were taken in mass screening camps in India by using the Remidio FOPNM-10. The dataset was curated to contain as many referral cases as healthy ones.

Automated image analysis: The analysis was performed on the FOP NM10 with offline Medios AI-DR that does not require internet to provide a report. The de-identified images were loaded through Remidio's secure cloud connectivity system. The Medios AI-DR was manually run as per standard protocol. Following an automated analysis of image quality, each patient underwent an automated analysis for DR. The AI output No RDR or RDR, as well as the image quality analysis results, were noted. The "proceed anyway" override option was used for images that failed the AI quality check but received a consensus grading by the experts.

Outcome measure: The primary outcome measures were the sensitivity, specificity, false positives, false negatives, and predictive values (positive and negative) of the Medios AI-DR algorithm for detecting RDR on images captured using FOPNM-10 on this population. The secondary outcome measures were the sensitivity, specificity, and predictive values (positive and negative) of the algorithm for detecting any grade of DR. In addition, the sensitivity for detecting STDR was reported.

Statistical analysis: Considering a sensitivity of at least 80% with a precision of 10% and a prevalence of RDR of 20%, the required sample size was 308 patients for a 95% confidence interval.^[16] We, however, looked at a larger sample size of 550 patients imaged over 10 months.

Next, 2 * 2 confusion matrices were used to compute the sensitivity (true positive [TP] rate) and specificity (true negative [TN] rate) to detect RDR, any stage of DR, and STDR. The positive predictive value (PPV) and the negative predictive value (NPV) were evaluated. Furthermore, 95% confidence intervals (CI) were calculated for sensitivity, specificity, NPV, and PPV. The false positive (FP) rate was calculated as FP/FP + TN. The false negative rate was calculated as FN/FN + TP. The kappa statistic was used to determine the agreement between each expert grader to the consensus grading. A kappa value of above 0.8 was considered as high agreement, between 0.5 and 0.79 as moderate, and below 0.5 as poor agreement. Data were analyzed using the pandas (1.1.0), NumPy (1.19.5), and scikit-learn (0.23.1) libraries in Python (ver 3.7.7).

Results

The mean age in this study cohort of 550 subjects was 61.6 ± 9.94 years (range: 12–83 years). Among them,

63.45% ($n = 349$) were females. In the final analysis, 478 subjects were included after excluding duplicate entries ($n = 6$) and patients deemed ungradable ($n = 66$) [Fig. 1].

Based on consensus image diagnosis by experts, any DR was present in 159 (33.26%) patients, RDR was seen in 149 patients (31.17%), and STDR in 62 patients (12.97%). The intergrader agreement (quadratic weighted kappa) between the individual certified experts and the majority diagnosis was moderately good (0.56–0.72).

In total, 478 subjects were fed to the AI to generate outputs for the presence or absence of RDR. The sensitivity for RDR was 95.30% (95% CI: 91.9%–98.7%) and specificity was 83.89% (95% CI: 79.9%–87.90%). The NPV, that is, the probability of a subject with a negative screening test by the AI to truly not have RDR, was high (97.53%, 95% CI: 95.7%–99.3%). The key performance metrics for Medios AI-DR on the Armenian population are listed in Tables 1A and 1B.

The AI made a false diagnosis of RDR in 53 subjects. Four subjects had a consensus grading of mild NPDR, and the other 49 subjects had a consensus grading of no DR by the graders. Thus, the false positive rate was 16.11%. Among the 53 subjects, 17 were graded with AMD by at least one of the graders, while another nine were graded as having another pathology.

Table 1A: Confusion matrix to evaluate Medios AI- DR performance for RDR

<i>n</i> =478	Image grading RDR positive	Image grading RDR negative
AI RDR positive	142 (29.7%)	53 (11.1%)
AI RDR negative	7 (1.5%)	276 (57.7%)

All the seven subjects falsely diagnosed as RDR-negative cases by the AI were moderate NPDR cases. The false-negative rate was 4.70%. No cases of STDR were missed (100% sensitivity). Fig. 2 shows examples of subjects diagnosed correctly and incorrectly by the AI for RDR.

Discussion

This study showed the clinical effectiveness of the Medios AI-DR algorithm in detecting RDR in an Armenian population, reproducing its results from previous validation studies on the Indian population [Table 2]. The study highlighted the generalizability of this offline system in an ethnic population unseen during training. The study revealed excellent sensitivity (95.30%) and acceptable specificity (83.89%) for RDR.

The current study demonstrated a 100% sensitivity for sight-threatening DR. This subgroup entails patients at immediate risk of blindness if left untreated. Hence, this result supports the use of the Medios AI-DR as an aid in the early diagnosis of RDR. Thus, the specialists could focus on the treatment of patients with sight-threatening diseases rather than on screening. This is particularly valuable in regions with low density of ophthalmologists. This conclusion is further supported by a low false negative rate of 4.70% (7 cases of moderate NPDR missed), a parameter critical to denote the safety of the AI system. DR is understood to progress slowly in its early stages. The risk of missing such cases is mitigated by a recommendation for follow-up screenings every year.

The study showed 53 false positives (49 with no DR and 4 with mild NPDR). Furthermore, among the 53 subjects, 17 were graded with AMD by at least one of the graders, while another nine were graded as having another pathology. The accuracy is comparable to our findings on Indian cohorts.^[6,7,17]

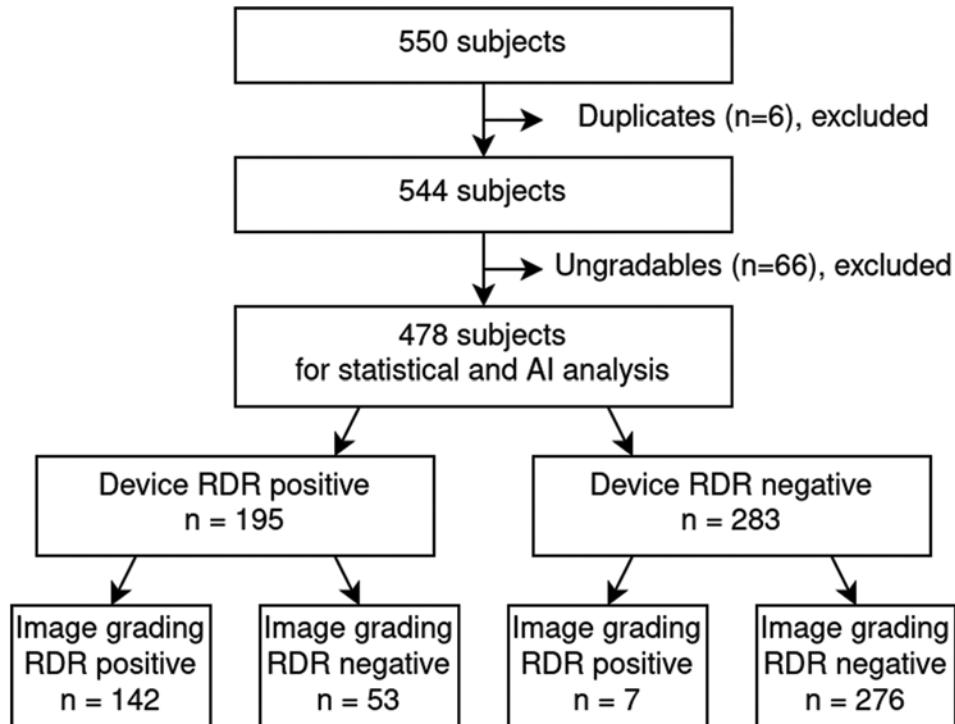


Figure 1: STARD Diagram for Medios AI-DR output for RDR

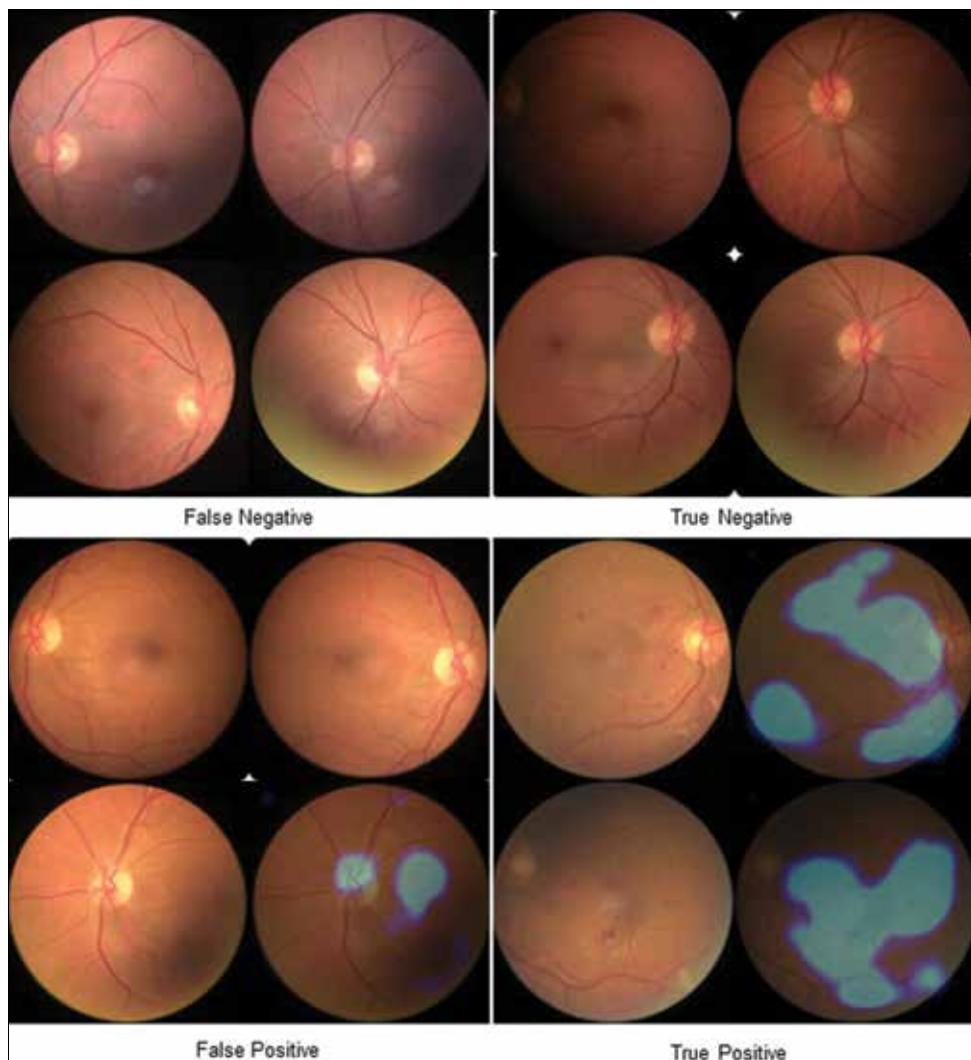


Figure 2: Examples of False Negative, True Negative, False Positive and True Positive patient images analyzed for RDR using Medios AI- DR. Activation maps are shown for images with positive AI diagnosis

Table 1B: Performance of Medios AI-DR on the Armenian population

	RDR	Any DR	STDR
Sensitivity (95% CI)	95.30% (91.9%–98.7%)	91.82% (87.6%–96.1%)	100.00 (1.0–1.0)
Specificity (95% CI)	83.89 (79.9%–87.9%)	84.64% (80.7%–88.6%)	NA
PPV (95% CI)	72.82% (66.6%–79.1%)	74.87% (68.8%–81.0%)	NA
NPV (95% CI)	97.53% (95.7%–99.3%)	95.41% (93.0%–97.8%)	NA

Table 2: Performance of Medios AI-DR in screening for RDR in previous studies

Study	Ethnicity	Sensitivity	Specificity
Natarajan et al. ^[6]	Indian	100.0% (95%CI: 78.2%–100.0%)	88.4% (95% CI: 83.2%–92.5%)
Sosale et al. ^[7] (SMART Study)	Indian	93% (95% CI: 91.3%–94.7%)	92.5% (95% CI: 90.8%–94.2%)
Sosale et al. ^[17]	Indian	98.84% (95% CI: 97.62%–100%)	86.73% (95% CI: 82.87%–90.59%)
Current Study	Armenian	95.30% (91.9%–98.7%)	83.89% (79.9%–87.9%)

We hypothesize that retinal pigmentation did not affect the system's performance. The large and diverse dataset used during development ensured representation across dark to lightly pigmented retinas. Here, the misdiagnosis is rather

explainable by the presence of other pathologies being picked up by the AI (26/53, 49%) as referable diseases. We are currently in the process of deploying other disease-specific models such as AMD, which will address this in the near future. Graders,

however, only reported the status of DR. The presence of another retinal disease warranting a referral to a specialist and triggering a positive report by the AI thus cannot be ruled out. The false positive rate is within acceptable limits. The FDA-mandated superiority endpoints of 85% sensitivity and 82.5% specificity for an autonomous RDR AI were surpassed in this study.^[14,15]

Previous studies have reported that a lack of ethnic diversity in training data impacted the performance of AI-based systems across ethnicities.^[10] Varying concentrations of melanin in different ethnic groups affect the pigmentation of uveal melanocytes as well.^[11] A different contrast between fundus and DR lesions due to a varying color of fundi may affect the performance of AI algorithms. AI systems should thus be trained on data from various ethnic groups to reduce bias toward a particular group. This is of particular importance when considering the deployment of systems across many geographies.

The Medios AI-DR had previously been validated in cohorts visiting primary and tertiary care centers in India only. Most studies relied on real-world images captured by minimally trained operators. They showed a sensitivity of 93%–100% and a specificity of 86.7%–92.5% [Table 2].^[6,7,17] Though these studies demonstrated the consistency of the algorithm in different clinical settings and the community, these had not assessed its consistency across different ethnicities. The current study complements the earlier one and demonstrates generalizability to a new population, with good sensitivity and specificity. There are some reports of the use of ethnically diverse training datasets on the AI-based detection of RDR. Bellemo *et al.*^[9] reported a sensitivity of 92.25% and a specificity of 89.04% in detecting RDR in an African cohort by using an AI algorithm trained with images predominantly from Chinese, Malay, and Indian populations. The system showed consistency and generalizability in detecting RDR in patients with dark fundi of the African population.^[9] We are unsure if the good sensitivity and specificity were related to the AI training dataset that also included the Indian eyes. Both Indian and African groups rank higher in melanin synthesis and have nearly similar dark-colored fundi. Similarly, Ting *et al.*^[4] reported a sensitivity of 90.5% and a specificity of 91.6% in identifying RDR in a multi-ethnic population. Again, these investigators had included images from Indian, Chinese, and Malay populations. The validation set further comprised African-American, Caucasian, and Hispanic populations with additional multi-ethnic validation datasets. All these studies indicate a common pattern: a sufficiently diverse training set can lead to generalizability beyond the ethnic groups included during training. While this hypothesis is reinforced in this study, we evaluated the AI performance in a different low-resource population that has significant accessibility issues for DR screening. To our knowledge, there is no peer-reviewed published evidence (MEDLINE literature search) on the performance of AI on images captured in a real-world diabetic screening program in Armenia. In addition, on the technical front, the Medios AI-DR is a lightweight ensemble architecture that utilizes a low processor environment of a smartphone-based fundus camera, allowing it to be deployed on the edge on the device. This could overcome barriers of internet connectivity and cloud-based inferencing in limited resource settings.

Strengths: First, the Medios AI-DR algorithm for RDR has been developed with over 50,000 images, which also included 34,278 images from the Kaggle-EyePACS dataset. The Kaggle-EyePACS dataset includes populations of indigenous American, African, European, Asian, and Indian subcontinent descent by design. It does not have any inherent issues with diversity or bias.^[18,19] This could partly explain the absence of bias in this algorithm when used on both dark and lightly pigmented fundi. The results of this study further strengthened this statement. Second, this study truly captured real-world data where images were captured by minimally trained operators. Thus, the AI was subject to test on images of poor quality unlike the pristine images obtained in the clinic where the performance will be far better.

Limitations: This is a retrospective study with inherent limitations attributable to any retrospective study. A notable limitation was the absence of a “live” AI quality check and feedback to the operator to recapture images. This implied that the study did not follow the exact protocol of two sufficient quality images per eye (one disc and one macula centered) in all patients, as required for optimum AI performance results. Instead, the study used all images captured (up to 7 images per patient) from multiple capturing attempts giving the worst-case scenario results. Inclusion of all available images might have also adversely affected the sensitivity and specificity. In addition, an accurate assessment of the image quality algorithm was not possible. A prospective trial would have been ideal to assess the best performance of the algorithm. The DR AI algorithm and image grading at least relied on two 40° fields of view per eye – one macula and one disc-centered image (covering approximately 60° field of view), potentially overlooking a few instances of severe DR extending beyond the captured area, particularly affecting the nasal region or extending beyond major blood vessel arcades. However, utilizing non-mydriatic single or two-field fundus photography for DR screening aligns with the acceptable practices recommended by the International Council of Ophthalmology as well as the American Academy of Ophthalmology Guidelines.^[20,21]

Conclusion

There is evidence that a training set biased against a specific ethnic group does not generalize well beyond that group.^[10] However, others and we have shown that an AI algorithm trained with an ethnically diverse dataset overcomes this deficiency.^[4,9] In addition, we feel that additional investigations are needed to evaluate variations of fundus pigmentation across ethnicities and understand the similarities and differences to develop robust AI solutions by using retinal images.

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Conflicts of interest: Divya Parthasarathy Rao, Florian M. Savoy, Anand Sivaraman, Sreetama Dutt are employees of Remidio Innovative Solutions Pvt. Ltd. All the other authors declare no known financial interests.

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Electroretinographic changes in the inner and outer retinal layers before and after intravenous chemotherapy for retinoblastoma

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Purpose: To study the inner and outer retinal functions using a full-field electroretinogram (ERG) before and after intravenous chemotherapy (IVC) in children with retinoblastoma (RB). **Methods:** Of the 11 eyes, seven had RB and four were normal. All children were examined under anesthesia using a handheld ERG machine with a standard protocol – light-adapted single-flash ERG (fERG), photopic single-flash 3.0- and 30-Hz flickers, and photopic negative response (PhNR) amplitudes at 72 ms (P72). The amplitudes and peak times were compared before and after IVC. **Results:** Post-chemotherapy tumor regressed in all seven eyes. Of the seven eyes, the fERG peak time (a-wave) was delayed in two eyes (29%), whereas the b-wave was delayed in six eyes (86%). The fERG amplitude height for a- and b-waves decreased in five eyes (71%) and six eyes (86%), respectively. In addition, photopic flicker 30-Hz b-wave peak time delayed in five eyes (71%), whereas the b-wave amplitude height decreased in six eyes (86%). Simultaneously, the P72 amplitude height decreased in six eyes (86%), whereas the P-ratio increased in all seven eyes (100%). In comparison, the ERG responses improved in three of the four contralateral normal eyes. Overall, the cone function improved in two eyes (29%), whereas cone bipolar cell and retinal ganglion cell (RGC) function improved in one eye (14%) each. **Conclusion:** Comparison of light-adapted ERG changes before and after IVC showed reduced amplitudes and delayed peak times for both a and b waveforms, as well as reduced PhNR amplitude attributable to bipolar and RGC injury.

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Retinoblastoma (RB) is the most common intraocular tumor in children, accounting for approximately 11% of all cancers occurring in the first year of life.^[1] In the last two decades, chemotherapy has become the mainstay of RB treatment delivered primarily through intravenous chemotherapy (IVC).^[2-5] Because of concerns for systemic toxicity, such as neutropenia, infections, ototoxicity, and second cancers later in life, and to achieve higher globe salvage rates, there has been a paradigm shift in the management of RB, evolving toward chemotherapy delivered through various routes: intra-arterial chemotherapy (IAC) and intravitreal chemotherapy (iVitC).^[6,7] Although globe salvage rates have improved with newer delivery routes, visual outcomes in these children are limited, particularly because of the primary location of the tumor in the macular area, presence of retinal detachment, and side effects following the use of IAC and iVitC.^[8-12] Direct chemotoxicity following the use of IAC or iVitC causes retinal pigment epithelial and choroidal atrophy, sectoral or diffuse iris atrophy, and intraocular inflammation.^[13] Electrophysiologic tests, particularly electroretinogram (ERG), have been used in the past for the early detection of such functional changes in the retina or optic nerve following IAC or iVitC.^[13-18]

Compared to Western countries, in India, IVC remains the mainstay in the management of RB. As these children are under

the age of 5 years, visual acuity (VA) recording in this preverbal group remains a challenge. ERG recording can be a surrogate marker for VA testing and can help detect any alterations in the retinal function. Consequently, the macula, which has a larger pigment density than the peripheral retina, may be prone to chemotherapeutic agent toxicity.^[19] Full-field ERG (FF-ERG), which represents global retinal function, may not detect macular toxicity, necessitating the need for ERG tests that are selective to macular function, such as pattern ERG (PERG) and multifocal ERG. In a study by Liasis *et al.*,^[20] investigating macular toxicity following the use of intraarterial melphalan, they concluded that PERG rather than FF-ERG should be used to monitor baseline macular function and potential toxicity in children undergoing chemotherapy for RB using skin electrodes. However, in children in the age group of 1–4 years, performing standard PERG may not be feasible. Preiser *et al.*^[21] compared both photopic negative response (PhNR) and PERG to detect glaucoma, and concluded that both test protocols complement each other and the results are reproducible. There are numerous reports of ERG monitoring of retinal function following IAC or iVitC, but studies reporting ERG recording following IVC have been limited.^[14-16,18,20] A study by

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Brodie *et al.*,^[22] in a series of four patients (eight eyes), showed improvement in 30-Hz flicker ERGs recording post-IVC in six of eight eyes. The 30-Hz flicker ERG assesses cone pathway functions and provides very little information about the overall function of retinal ganglion cells. Herein, we studied ERG monitoring of retinal function using photopic flash and flicker ERG to assess cone photoreceptor and cone bipolar cell function as well as PhNR to provide insights into retinal ganglion cell function before and after IVC for RB.

Methods

This was a prospective observational study conducted at the Operation Eyesight Universal Institute for Eye Cancer, LV Prasad Eye Institute, Hyderabad, India, after obtaining approval from the institutional review board. The study adhered to the tenets of the Declaration of Helsinki. The inclusion criteria were children diagnosed with unilateral or bilateral RB on the basis of clinical examination and ancillary imaging modalities such as ultrasonography and magnetic resonance imaging. Informed consent was obtained from each patient's parent or guardian for clinical examination and ERG recordings under sedation/anesthesia (laryngeal mask airway) pre- and post-chemotherapy. Children presenting with extraocular RB or orbital RB at the first visit and those lost to follow-up during the study period were excluded.

Patients' demographic details such as age, gender, family history of RB, presenting signs, symptoms, and tumor laterality were recorded. Photographic documentation was performed in all cases using a RetCam 2 wide-field imaging system, and all tumors were documented with fundus drawings. Fundus drawings and RetCam images were reviewed for accurate tumor details such as location, size, number, distance from the optic nerve and fovea, presence of subretinal fluid (SRF), and associated features such as vitreous seeding, vitreous hemorrhage, and retinal detachment. All eyes with intraocular tumors were classified according to the International Classification of Intraocular Retinoblastoma (ICRB).^[23]

As per the institute protocol, during the study period, all patients were treated with only standard IVC (VEC protocol- standard dose: [every 3–4 weeks, six cycles]: vincristine 1.5 mg/m² [0.05 mg/kg for children <36 months of age and maximum dose <2 mg], etoposide 150 mg/m² [5 mg/kg for children <36 months of age], carboplatin 560 mg/m² [18.6 mg/kg for children <36 months of age]) as the first-line treatment.^[24] Children treated with adjuvant focal treatment during the study period were excluded.

Every child underwent examination under anesthesia (EUA) before each chemotherapy cycle. The retinal functions of children diagnosed with RB were studied during EUA using the RETeval™ system before and after the completion of six cycles of chemotherapy. RETeval (LKC Technologies, Gaithersburg, MD, USA) is a system for recording ERGs that consists of a handheld stimulator with a small Ganzfeld dome of 6 cm in diameter. The stimuli were delivered as white presented by a combination of three-colored light-emitting diodes (red: 622 nm, green: 530 nm, and blue: 470 nm) and a signal recorder clip coupled with disposable electrodes (Sensor Strip, LKC Technologies, Inc.). In a single adhesive sensor strip, three electrodes are embedded: an active (positive), a reference (negative), and a ground. The amplitudes and

implicit times were automatically measured and displayed using the RETeval system.

This study used a certain protocol for recording retinal functions following the standardization published by the International Society for Clinical Electrophysiology of Vision (ISCEV), which included photopic flash (light-adapted), photopic flicker, and PhNR, which uses different flash frequencies and background illumination in the RETevalTM device. Before the test, the pupils were dilated to standardize the amount of light reaching the retina and the placement of electrodes that adhered to the skin 2 mm below the lower eyelid, after the skin was cleaned with a mild dermabrasion gel (Nuprep).

Under sedation, the eyelids were kept open with a speculum, and the fundus was examined using an indirect ophthalmoscope. Subsequently, under room light adaptation, ERG tests were performed using an ISCEV photopic flash/flicker using 3.0 cd s/m² with chromaticity at 2 and 28.3 Hz at a background luminance of 30 cd/m² less than the 1-ms pulse duration, which provides cone system function. PhNR protocols have a red flash (1.0 cd·s/m²) on a blue background (10 cd/m²), which obtains the function of ganglion cells, and the stimulus frequency is 3.4 Hz.^[25] Both eyes were tested simultaneously by observing the pupil using the RETeval device. Each eye was tested twice in each participant.

All participants who came for follow-up after six cycles of chemotherapy were retested using the same protocols under sedation. All children were evaluated to document tumor control with regression pattern, persistence, or resolution of retinal detachment and any tumor recurrences. Where applicable, subjective VA was tested using teller acuity cards (age 1–3 years) and HOTV cards (age 3–5 years). Resultant flash ERG values of amplitudes and peak times of a-wave and b-wave were compared pre- and post-chemotherapy to study global retinal function in RB-affected eyes and normal contralateral eyes in cases with unilateral RB. In addition, the measurement of PhNR amplitude and P-ratio (PhNR/b-wave) at 72 ms was considered.^[26]

All data were entered into an Excel file, and the results were extrapolated in the form of percentage change in the waveform pattern. The outcome was taken as the mean change in amplitude and peak time for all individual tests before and after chemotherapy. Statistical differences between study and normal eyes were calculated using unpaired *t*-test. *P* value < 0.05 was considered statistically significant.

Results

Six children (12 eyes) were included in the study. Four children had unilateral RB, whereas two children had bilateral RB. Of eight eyes with RB, one eye (case 4) diagnosed with unilateral advanced disease underwent primary enucleation and was therefore excluded from the study [Table 1]. Histopathology revealed high-risk features, for which six adjuvant cycles of chemotherapy were initiated; hence, the contralateral normal eye was included. The mean age at presentation was 3 years (range: 1–5 years). Based on ICRB, one eye belonged to Group B, three to Group C, and four to Group D. All eyes had macular involvement of the tumor, except one eye. Retinal detachment was noted in five eyes. All patients were treated with six cycles of primary IVC at 3-week intervals. The results

of the photopic flash, flicker, PhNR, and P-ratio parameters studied in all eyes pre- and post-chemotherapy are shown in Tables 2 and 3.

At the end of six cycles of IVC, all seven eyes showed good response in terms of tumor regression. On comparison, post-chemotherapy, of the seven eyes with regressed RB, light-adapted single-flash ERG peak time (a-wave) was shortened in four eyes (57%) and delayed in two eyes (29%). In one eye, the readings were unmeasurable. Similarly, the peak time of the b-wave was shortened in one eye (14%) and delayed in five eyes (71%). The light-adapted single-flash ERG amplitude height for the a-wave increased in two eyes (29%) and reduced in five eyes (71%), whereas for the b-wave, the amplitude increased in one eye (14%) and reduced in six eyes (86%) [Table 4]. The left eye of case 3 had nondetectable ERGs posttherapy, case 5 had nondetectable photopic ERGs in both eyes pretherapy, and the left eye of case 6 had nondetectable ERGs both pre- and posttherapy. Similarly, the photopic flicker 30-Hz b-wave peak time was shortened in two eyes (29%) and delayed in four eyes (57%), whereas the b-wave amplitude height increased in one eye (14%) and decreased in six eyes (86%). The left eye of cases 3 and 6 had nondetectable photopic flicker before and

after therapy. Post-chemotherapy PhNR recordings at 72 ms amplitude height increased in one eye (14%) and reduced in six eyes (86%), whereas the PhNR P-ratio increased in all seven eyes (100%). Overall, cone photoreceptor function (by a wave amplitude measurement) improved in two of seven eyes (29%) and cone bipolar cell function (by b-wave amplitude measurement) improved in one of seven eyes (14%). Despite complete tumor regression in all eyes, retinal ganglion cells or inner retinal function improved in one of seven eyes (14%). After treatment, subjective VA tested in one child (case 1) showed improvement in terms of central fixation, whereas it showed poor fixation in two children (cases 2 and 3). Of the four contralateral normal eyes, two had a VA of 20/30, which was appropriate for their age, whereas the other two had a VA of 20/60. An illustrative case example is highlighted in Fig. 1 (case 5) and Fig. 2 (case 1) showing tumor and ERG responses before and after chemotherapy.

Specific analysis of normal contralateral eyes (case 1: left eye, case 5: left eye, and case 6: right eye) revealed improved ERG responses compared to baseline values, except in case 4. Case 4 was a patient with unilateral RB who underwent primary enucleation and was detected to have high-risk histopathologic features necessitating adjuvant IVC. This child showed normal

Table 1: Demography and clinical characteristics of children diagnosed with retinoblastoma

Cases	Age (years)	Laterality	Eye	Gender	ICRB staging	Location	Retinal detachment	Post-chemo tumor response	Post-chemo retinal detachment
1	3	Unilateral	RE	Female	Group C	Macula	No	Regressed	No
2	1	Bilateral	RE	Male	Group C	Macula	No	Regressed	No
			LE	Male	Group C	Macula	Subtotal	Regressed	Shallow
3	2	Bilateral	RE	Male	Group B	Non macula (equator)	No	Regressed	No
			LE	Male	Group D	Posterior pole	Total	Regressed	Persistent
4	3	Unilateral	RE	Female	Group D	Macula to equator	Total	Underwent primary enucleation ^a	NA
5	4	Unilateral	RE	Male	Group D	Macula to equator	Subtotal	Regressed	No
6	5	Unilateral	LE	Male	Group D	Macula to equator	Total	Regressed	Persistent

^aCase 4 (right eye) was excluded because the eye was primarily enucleated; however, the contralateral normal eye was included. ICRB=International Classification of Intraocular Retinoblastoma, LE=left eye, RE=right eye

Table 2: Photopic flash (light-adapted 3.0) ERG parameters in the retinoblastoma group

Cases	Photopic flash ERG	Implicit times (ms) – RE		Amplitudes (mv) – RE		Implicit times (ms) – LE		Amplitudes (mv) – LE	
		a-wave	b-wave	a-wave	b-wave	a-wave	b-wave	a-wave	b-wave
1	Pre	17.7	29.7	-1.7	11.5	12.1	23.7	-0.34	8.6
	Post	14.6	43.9	-2.1	8.1	9.1	21.6	-1.1	6
2	Pre	14.1	36.1	-7.6	23	14.1	34.5	-2.7	10.6
	Post	13.7	36.6	0.07	15.1	15	34.8	-2.6	9.2
3	Pre	15	29.2	-8	12.8	13.2	38.2	-4.1	6.3
	Post	13.3	31.7	-2.5	5.3	NM	NM	NM	NM
4	Pre	One eyed				14.9	33.5	-7	27.1
	Post	One eyed				15.2	36.6	-1.9	14.2
5	Pre	NM	NM	NM	NM	NM	NM	NM	NM
	Post	14.4	38.5	-1.7	3.8	11.7	30.3	-4	11.5
6	Pre	16.1	32	-4.3	11.4	NM	NM	NM	NM
	Post	12.6	30.2	-3.5	17.2	NM	NM	NM	NM

ERG=electroretinogram, LE=left eye, NM=not measurable, RE=right eye

Table 3: Photopic flicker and PhNR ERG parameters in the retinoblastoma group

Cases	Photopic flicker ERG	Implicit times (ms) – RE	Amplitudes (mv) – RE	Implicit times (ms) – LE	Amplitudes (mv) – LE	PhNR at 72 ms (mv) – RE	P-ratio – RE	PhNR at 72 ms (mv) – LE	P-ratio – LE
1	Pre	37.4	7.4	32.9	9.9	-0.92	0.14	-2.3	0.4
	Post	38	4.5	33.9	5.8	-0.58	0.28	-0.66	0.21
2	Pre	35.5	32.8	17.4	12	-1.7	0.18	-1.8	NM
	Post	34	12.3	34.7	7.2	-1.5	0.28	-1.7	0.52
3	Pre	26.5	17.8	NM	NM	-0.77	0.06	0.56	-0.24
	Post	27.5	6.6	NM	NM	-0.51	0.12	-0.33	1.29
4	Pre	One eyed	One eyed	28.8	22.5	One eyed	One eyed	-2	0.18
	Post	One eyed	One eyed	32.7	15.4	One eyed	One eyed	-2.1	0.33
5	Pre	NM	NM	NM	NM	NM	NM	NM	NM
	Post	41.9	2	26.7	15.7	0.1	0.1	-0.22	0.03
6	Pre	28.4	15.7	NM	NM	-0.85	0.16	-0.10	NM
	Post	27.4	16.6	NM	NM	-0.06	0.01	-0.05	1.51

ERG = electroretinogram, LE = left eye, NM = not measurable, PhNR = photopic negative response, RE = right eye

Table 4: Comparative differences in various ERG parameters before and after systemic chemotherapy for study and normal eyes

Cases	Eye	Flash ERG (post vs. pre) a-wave	Flash ERG (post vs. pre) a-wave	Flash ERG (post vs. pre) b-wave	Flash ERG (post vs. pre) b-wave	Flicker ERG (post vs. pre)	Flicker ERG (post vs. pre)	PhNR amplitude (72 ms) (post vs. pre)	PhNR P-ratio (post vs. pre)	Post-chemo tumor response
		Peak time	Amplitude	Peak time	Amplitude	Peak time	Amplitude			
1	RE	Shortened -3.1	Increased -0.4	Delayed 14.2	Reduced -3.4	Delayed 0.6	Reduced -2.9	Reduced 0.34	Increased 0.14	Regressed
	LE	Shortened -3	Increased -0.76	Shortened -2.1	Reduced -2.6	Delayed 1	Reduced -4.1	Reduced 1.64	Reduced -0.19	Non-tumor eye
2	RE	Shortened -0.4	Reduced 7.67	Delayed 0.5	Reduced -7.9	Shortened -1.5	Reduced -20.5	Reduced 0.2	Increased 0.1	Regressed
	LE	Delayed 0.9	Reduced 0.1	Delayed 0.3	Reduced -1.4	Delayed 17.3	Reduced -4.8	Reduced 0.1	Increased 0.52	Regressed
3	RE	Shortened -1.7	Reduced 5.5	Delayed 2.5	Reduced -7.5	Delayed 1	Reduced -11.2	Reduced 0.26	Increased 0.06	Regressed
	LE	Delayed NM	Reduced NM	Delayed NM	Reduced NM	NM	NM	Reduced -0.89	Increased 1.53	Regressed
4	RE	One eyed								Enucleated
	LE	Delayed 0.3	Reduced 5.1	Delayed 3.1	Reduced -12.9	Delayed 3.9	Reduced -7.1	Increased -0.1	Increased 0.15	Non-tumor eye
5	RE	Shortened 14.4	Increased -1.7	Shortened 38.5	Increased 3.8	Shortened 41.9	Increased 2	Increased 0.1	Increased 0.1	Regressed
	LE	Shortened 11.7	Increased -4	Shortened 30.3	Increased 11.5	Shortened 26.7	Increased 15.7	Increased -0.22	Increased 0.03	Non-tumor eye
6	RE	Shortened -3.5	Reduced 0.8	Shortened -1.8	Increased 5.8	Shortened -1	Increased 0.9	Reduced 0.79	Reduced -0.15	Non-tumor eye
	LE	NM	NM	NM	NM	NM	NM	Reduced 0.05	Increased 1.51	Regressed

ERG=electroretinogram, LE=left eye, NM=not measurable, PhNR=photopic negative response, RE=right eye

ERG before chemotherapy, but showed delayed responses in flash and flicker ERG after chemotherapy. However, the child had a normal macula and a vision of 20/30 on subsequent testing. Comparing mean and median differences between study and normal eyes using unpaired *t*-test for various ERG parameters showed no statistical differences at the last follow-up [Table 5].

Discussion

In this study, we objectively measured the retinal function using photopic flash and flicker waveforms, which have been traditionally used in previous ERG studies in patients with RB as per the ISCEV protocol.^[22] However, the 30-Hz photopic flicker waveform provides information about the

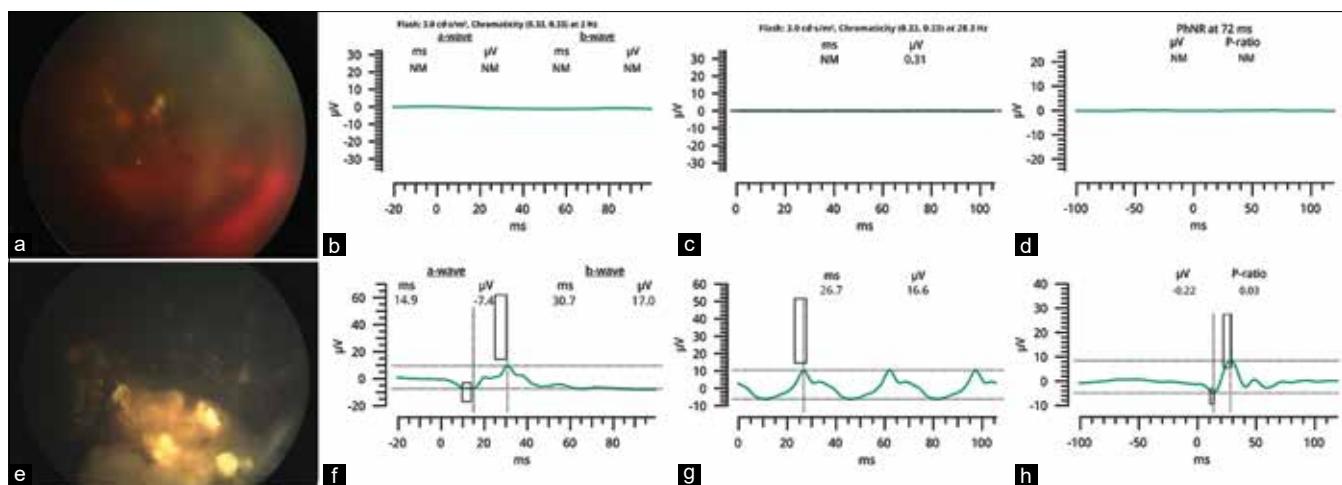


Figure 1: Fundus photograph of the right eye (case 5) showing Group D retinoblastoma with vitreous hemorrhage and retinal detachment (a). All ERG waveforms (photopic flash, 30-Hz flicker and PhNR) were nondetectable at baseline (b-d). After six cycles of intravenous chemotherapy, the tumor regressed with type 3 regression pattern and attached retina (e). All the ERG waveforms, photopic flash (a- and b-wave) and 30-Hz flicker (b-wave) amplitudes, increased, and the peak times shortened compared to baseline visit (f and g). Similarly, the PhNR amplitude at 72 ms and the P-ratio (PhNR/b-wave) also increased from the baseline visit (h). ERG = electroretinogram, PhNR = photopic negative response

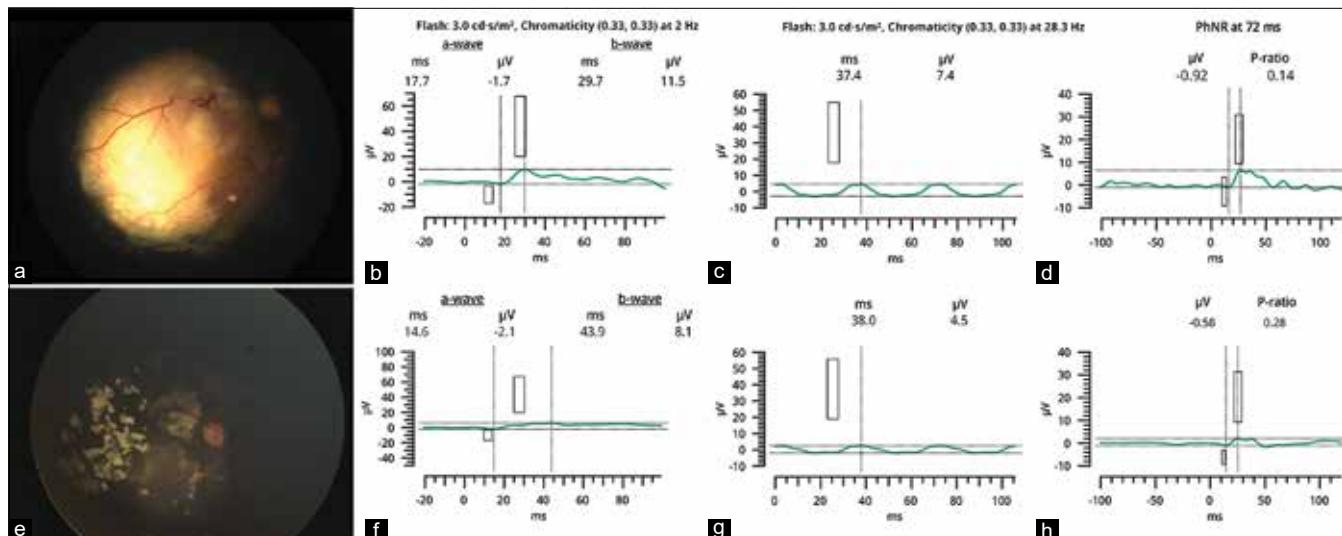


Figure 2: Fundus photograph of the right eye (case 1) showing Group C retinoblastoma with no retinal detachment (a) and post-chemotherapy regressed tumor (e). Before and after chemotherapy, the ERG waveforms of photopic flash (a-wave) showed a shortened peak time and increased amplitude height (b and f), whereas photopic flash and 30-Hz flicker (b-wave) peak times were delayed and amplitude height was reduced (b, c, f, and g). Similarly, the PhNR amplitude height at 72 ms was reduced and the P-ratio (PhNR/b-wave) was increased from the baseline visit (d and h). ERG = electroretinogram, PhNR = photopic negative response

cone on and off bipolar cells and is dependent on L and M cone photoreceptors, with little information regarding the inner retinal function, especially the retinal ganglion cells and the amacrine cells. Ideally, we would like to perform PERG, which provides information about the functional integrity of retinal ganglion cells and macular photoreceptors.^[27] However, in children aged 5 years and under anesthesia, this would not be possible. To overcome this, we studied a newer protocol developed in a handheld LKC ERG model named PhNR. The PhNR waveform originates and represents the function of the inner retinal layers, especially the retinal ganglion cells and the amacrine cells, or perhaps through mediation by the glial cells.^[28,29] This waveform is believed to be a surrogate marker and can complement the PERG waveform.^[21] The results of this

study address the following three important questions: (i) Does tumor regression in RB have any impact on retinal function? (ii) Does IVC have any impact on retinal cone photoreceptors/bipolar cells and ganglion cell function due to chemotherapy toxicity if any? and (iii) Does associated retinal detachment impact the overall retinal function?

This study demonstrated delayed responses in more than 50% of eyes in both protocols (photopic flash and flicker) following IVC despite complete tumor regression. Both IAC and iVitC cause dose-dependent retinal toxicity, particularly to the retinal pigment epithelium, leading to retinal and choroidal atrophy.^[15,30,31] Brodie *et al.*^[22] studied ERG changes following the use of IVC and showed significant improvement

Table 5: Comparison between study and normal eyes for various ERG parameters after intravenous chemotherapy

ERG parameters	Study eyes (n=5) (mean/median)	Normal eyes (n=4) (mean/median)	P (unpaired t-test)
Flash ERG a-wave (peak time)	-3.7/-1.7	-4.4/-3.2	0.8
Flash ERG a-wave (amplitude)	2.2/0.1	0.2/0.02	0.4
Flash ERG b-wave (peak time)	-4.2/0.5	-7.7/-1.9	0.7
Flash ERG b-wave (amplitude)	-3.2/-3.4	0.4/1.6	0.5
Flicker ERG (peak time)	-4.9/0.6	-5.1/0	0.9
Flicker ERG (amplitude)	-7.4/-4.8	1.3/-1.6	0.2
PhNR (P-ratio)	0.51/0.14	-0.04/-0.06	0.1

ERG=electroretinogram, PhNR=photopic negative response

in six of eight eyes. However, the drug used was single-agent carboplatin, whereas in our series, all the children received a standard three-drug combination of vincristine, etoposide, and carboplatin every 3 weeks for a total of six cycles. Although retinal toxicity following the use of IVC is largely unexplored, studying ERG waveforms would not only assess the retinal function, but also provide an objective assessment of vision. In particular, the inner retinal function test PhNR waveforms improved in one eye (14%) after chemotherapy, thereby suggesting abnormal retinal ganglion and amacrine cells. In our previous publication of macular RB,^[8] we speculated on compromised final VA in two-thirds of the eyes due to associated foveal atrophy. In this study, cases 2 and 3 showed marked delayed and reduced responses for both FF-ERG b-wave and flicker ERG waveforms following chemo-regression because of the presence of advanced disease (groups C and D) and macular tumor at presentation, suggestive of poor VA.

Westall *et al.*^[32] reported a time course of 2 years before the maturation of ERG waveforms from infancy to adult forms. As age advances, there is maturation and an increase in the amplitude of the waveforms. In our series, of the seven eyes with RB, only three eyes showed improvement in the flash and flicker photopic waveforms post-chemotherapy, suggesting that the presence of a macular tumor and associated total or subtotal retinal detachment might have a detrimental effect on overall ERG waveforms. Cases 2, 3, and 6 with macular tumors had persistent RD at the last follow-up and showed delayed responses of all waveforms despite tumor regression. In contrast, in case 5, the waveforms improved post-regression of the tumor. In this case, the tumor did not involve the macula, and RD completely regressed at the last follow-up. Abdelhakim *et al.*^[33] reported a positive correlation between retinal reattachment and ERG recovery following IAC, thereby increasing the probability of a favorable visual outcome.

Our study showed that IVC had no detrimental effect on normal contralateral eyes. In three of four eyes, ERG responses showed improvement compared to baseline values, suggesting normal age maturation of the retinal function and ERG waveforms. However, delayed responses in flash and flicker ERG were noted in one case (case 4). The reason for such an abnormal response in a normal eye could be either because of general anesthesia or faulty technique in terms of using skin electrodes.^[34,35] However, the same child at the 1-year follow-up showed a normal macula with 20/30 VA in the normal eye, suggesting error in ERG recording under anesthesia.

In our series, despite complete regression of the tumor in all eyes, PhNR amplitudes showed improvement in only one

eye (14%), suggesting poor inner retinal function, especially in the retinal ganglion and amacrine cells. This is important because studies have shown amacrine cells as the cells of origin of RB with the presence of Rb-1 gene mutations^[36] and amacrine cell differentiation,^[37] thereby highlighting the importance of studying the function of inner retinal cells, especially the ganglion cells and the amacrine cells. In our study, PhNR amplitudes were reduced in most eyes, and the P-ratio (PhNR/b-wave) at 72 ms improved. This can be explained as the P-ratio is dependent on the b waveform, and any abnormality of the b waveform can lead to an error in interpreting the P-ratio.

The strength of our study was that it was a prospective study in which various photopic ERG protocols were studied in children with RB to study the effects of IVC on overall retinal function, particularly retinal ganglion cells. A few limitations of our study are that as known ERG waveforms do get affected if performed under anesthesia, these changes would have occurred in all subjects and would not affect the results of the comparative analyses. In addition, as it is known, the LKC handset uses a skin contact electrode compared to standard corneal contact electrodes, which could have affected the ERG amplitudes. We accept the limitations of the absence of normative age-matched and ethnic population data for ERG recording using the handheld LKC model as well as the lack of definite cut-off values (>25 µV) considered significant for improvement or reduction of ERG waveforms. The majority of patients were not reassessed to determine the repeatability of measurements because of reduced anesthesia duration. The 30 Hz cone flicker ERG using RETeval under EUA usually had a smaller amplitude and prolonged peak time response than the wake conditions. We do accept the limitation of our study as VA was not measured in all eyes. In an ideal scenario, the correlation of ERG with subjective/objective VA would be the best approach. However, this was beyond the scope of this study. A future prospective larger cohort study would be appropriate to study such a correlation. In addition, as there was no significant difference in ERG parameters pre- and post-chemotherapy in normal eyes, there might be factors other than IVC alone, such as location, size of tumor, and presence of RD and SRF, which might affect the overall function of retina and need to be studied in future.

Conclusion

Post-IVC, in children with RB, light-adapted ERG showed reduced amplitudes and delayed peak time, especially in eyes with advanced disease at presentation and associated retinal detachment. The inner retinal function protocols, especially

PhNR waveforms, improved in only <one-fifth of the eyes, suggesting long-term effects on vision development and the need for early rehabilitation. We propose further longitudinal studies to evaluate the overall retinal function and vision development in this subset of children.

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Optical coherence tomography characteristics and prognostic predictors of acute macular neuroretinopathy following SARS-CoV-2 infection

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Purpose: To analyze the characteristics of optical coherence tomography in acute macular neuroretinopathy (AMN) following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and discuss the prognostic predictors. **Methods:** Patients with AMN following SARS-CoV-2 infection were divided into two groups according to the presence or absence of hyperreflective outer nuclear layer (ONL) lesion involving the fovea. **Results:** The first visit included 14 eyes in the fovea-involved group and 20 eyes in the no fovea-involved group. Ellipsoid zone (EZ) hyporeflection and interdigitation zone (IZ) interruption were detected in all eyes. Other common manifestations were myoid zone (MZ) hyperreflection (76.5%), ONL hyperreflection (73.5%), outer plexiform layer (OPL) thickening (64.7%), and EZ interruption (50%). The follow-up period was 48.4 ± 55.3 days. At the last visit, 12 eyes were in the fovea-involved group and 13 eyes in the no fovea-involved group. IZ interruption was detected in all eyes. Other common manifestations were EZ hyporeflection (92.0%), ONL atrophy (40.0%), OPL thickening (36.0%), OPL linear (32.0%), and MZ hyperreflection (32%). The improvement of visual acuity (VA) was -0.5 ± 0.5 and -0.2 ± 0.4 in the fovea-involved group and the no fovea-involved group, respectively, with a statistically significant difference between them ($P = 0.045$). Initial VA, initial cotton wool spot, initial ONL cyst, final ONL cyst, and final OPL linear were associated with final VA ($P = 0.000$, $P = 0.029$, $P = 0.044$, $P = 0.049$, $P = 0.049$, respectively). **Conclusions:** In the early stage of AMN following SARS-CoV-2 infection, IZ interruption and EZ hyporeflection were the most common manifestations, and pathology of IZ was more serious than that of EZ. Subsequently, OPL and ONL atrophied, and ONL atrophied faster. Regardless of whether hyperreflective ONL involved the fovea, VA improved, with a more noticeable improvement found in the fovea-involved group. The presence of initial ONL cyst and initial cotton wool spot, rapid atrophy of OPL, and poorer initial VA indicating poorer VA outcome.

Key words: Acute macular neuroretinopathy, optical coherence tomography, prognostic predictor, SARS-CoV-2 infection

Acute macular neuroretinopathy (AMN), first described by Bos and Deutman in 1975,^[1] is characterized by acute paracentral scotoma resulting from dark reddish, wedge-shaped intraretinal lesions on the macula.^[1] Previous studies suggested that AMN is associated with viral infections, and that nearly half of the AMN patients have a pre-symptom of nonspecific flu-like illness or fever.^[2] Recent case reports have linked severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or coronavirus disease 2019 (COVID-19) vaccine injection to AMN. Ischemia of deep retinal capillary is considered as a pathogenic mechanism of AMN.^[3] Viral infections, including SARS-CoV-2, could potentially impair retinal microvasculature, leading to AMN.^[4,5]

Visual outcome of AMN is not clear so far. Only half of the patients with AMN achieved a visual acuity (VA) of 20/40 (log of minimum angle of resolution [logMAR] 0.3) or better at the last follow-up.^[2] Some patients with AMN following SARS-CoV-2 infection or COVID-19 vaccine injection had

good prognosis including improved VA, reduced scotoma, and recovery of retina structure, while others experienced persistent symptoms.^[6,7]

This study aims to provide a comprehensive investigation into the visual outcomes and optical coherence tomography (OCT) characteristics of AMN following SARS-CoV-2 infection.

Methods

Patients diagnosed with AMN following SARS-CoV-2 infection and followed up in our hospital between December 2022 and Jun 2023 were enrolled. The study was conducted in adherence with the guidelines established by the Declaration of Helsinki, and it was approved by the Institutional Review Board.

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The diagnosis of AMN was primarily based on the structural findings seen on OCT (AAO EyeWiki): hyperreflective plaque at the outer nuclear layer (ONL) and outer plexiform layer (OPL), disruption of ellipsoid zone (EZ) and interdigitation zone (IZ), dark gray and petaloid lesion in the infrared (IR) image that was obtained when OCT was performed [Fig. 1]. When the diagnosis of AMN is uncertain, other diseases such as acute multifocal placoid pigment epitheliopathy, retinal pigment epithelitis, and multiple evanescent white dot syndrome should be excluded using multimodal imaging.

VA and OCT images of the first and last visits were collected. The duration period of follow-up was the interval between the dates of the first and last visits. VA was recorded in the form of logMAR. OCT images were from the examinations

of spectral-domain OCT (Spectralis; Heidelberg Engineering, Heidelberg, Germany), and OCT parameters were from the 6-mm-diameter Early treatment diabetic retinopathy study (ETDRS) ring centered on the fovea. Definitions of OCT parameters are as follows (Fig. 2a1-a3 were FP, IR image, and OCT image of the same eye respectively. The same applied to Fig. b1-b3, c1-c3, and d1-d3, e1-e3 and f1-f3): OPL thickening – OPL was thicker than normal [Fig. 2a3]; OPL linear – OPL was thinner than normal and appeared as a linear form [Fig. 2b3]; ONL atrophy – ONL was thinner than normal [Fig. 2b3]; ONL hyperreflection – the reflection of ONL was higher than normal [Fig. 2c3 and d3]; ONL cyst – one or more cysts were detected in ONL [Fig. 2e3]; myoid zone (MZ) hyperreflection – the reflection of MZ was higher than normal [Fig. 2c3–e3]; EZ hyporeflection – EZ was visible, but the

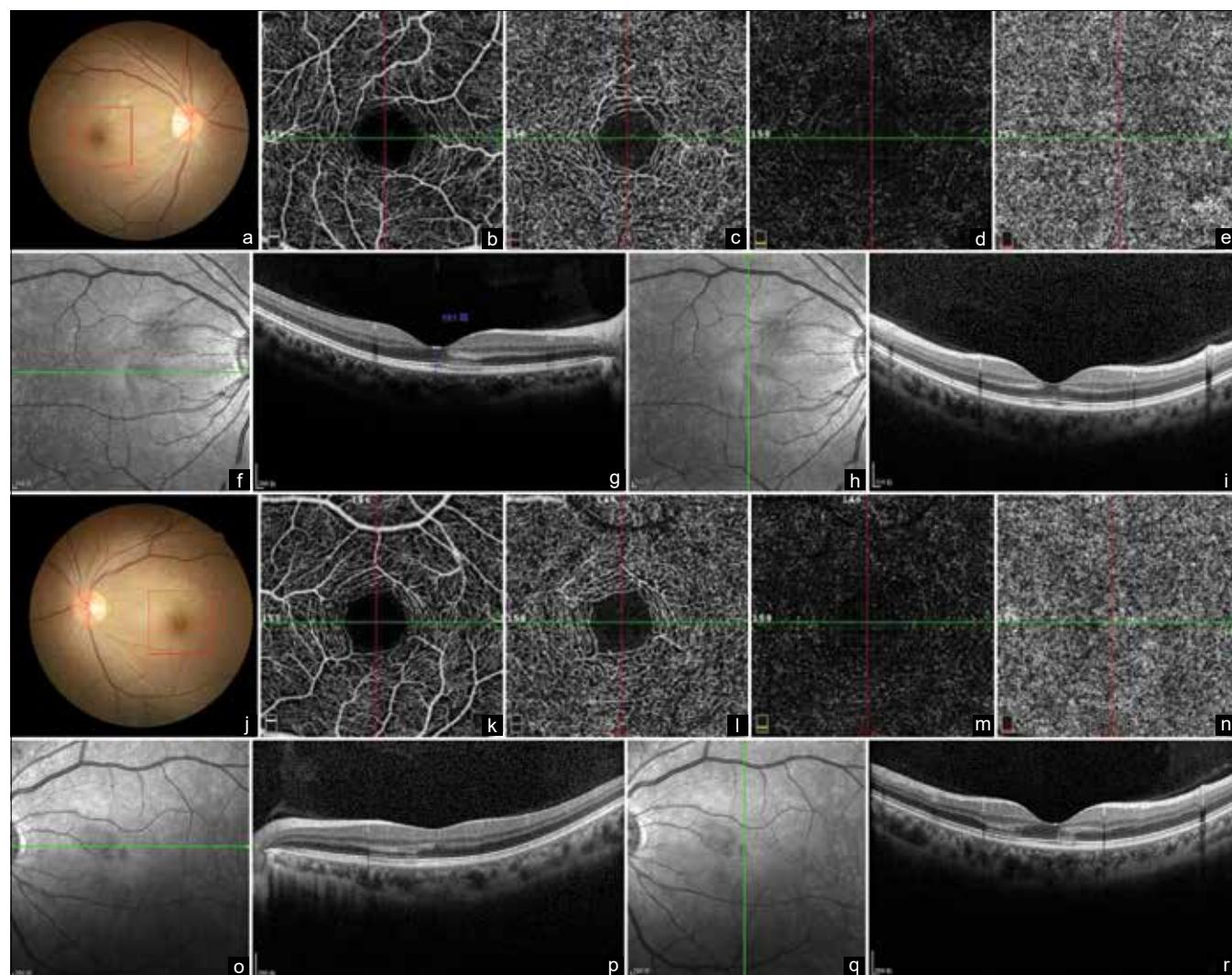


Figure 1: Multimodal imaging at the initial visit of a patient with binocular AMN, who was a 27-year-old woman. There was a blurring of vision in both eyes after the fever caused by SARS-CoV-2 infection subsided. (a–i) Multimodal imaging of the right eye. (a) Fundus photograph (FP), the red-boxed area was the OCTA scanning area (b–e, 3 mm × 3 mm). (b–e) OCTA image of the superficial retina (inner limiting membrane–inner plexiform layer), deep retina (inner plexiform layer–OPL), outer retina (OPL–Bruch–retinal pigment epithelium membrane), and choriocapillaris (Bruch–retinal pigment epithelium membrane–Bruch–retinal pigment epithelium membrane + 30 µm) in the macular. (f), (h) IR images. (g), (i) OCT images of horizontal and vertical scans, respectively, corresponding to the green line of (f) and (h). (j–r) Multimodal imaging of the left eye. (j) FP, the red-boxed area was the OCTA scanning area (k–n, 3 mm × 3 mm). (k–n) OCTA image of the superficial retina, deep retina, outer retina, and choriocapillaris in the macular. (o), (p) IR images. (q), (r) OCT images of horizontal and vertical scans, respectively, corresponding to the green line of (o) and (p). AMN = acute macular neuroretinopathy, OCTA = optical coherence tomography angiography, OPL = outer plexiform layer, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

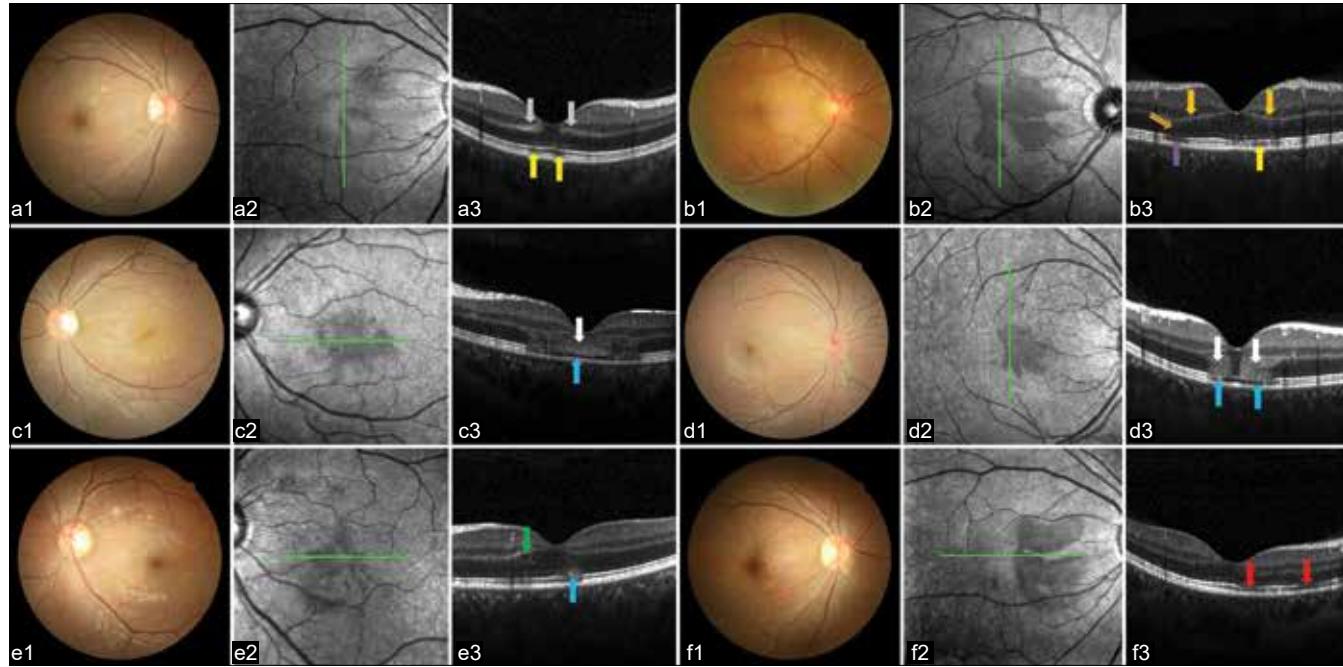


Figure 2: Multimodal imaging. (a1–a3) FP, IR image, and OCT of the right eye of the same patient in Figure 1 at the initial visit. OPL thickening (gray arrow), IZ interruption (yellow arrow) on OCT (a3). (b1–b3) FP, IR image, and OCT of the right eye of one patient. OPL linear (orange arrow), ONL atrophy (brown arrow), EZ and IZ interruption without MZ hyperreflection (purple arrow), IZ interruption (yellow arrow) on OCT (b3). (c1–c3) FP, IR image, and OCT of the left eye of one patient. ONL hyperreflection involving the fovea (white arrow), EZ and IZ interruption with MZ hyperreflection (blue arrow) on OCT (c3). (d1–d3) FP, IR image, and OCT of the right eye of one patient. ONL hyperreflection not involving the fovea (white arrow), EZ and IZ interruption with MZ hyperreflection (blue arrow) on OCT (d3). (e1–e3) FP, IR image, and OCT of the left eye of one patient. ONL cyst (green arrow), EZ and IZ interruption with MZ hyperreflection (blue arrow) on OCT (e3). (f1–f3) FP, IR image, and OCT of the right eye of the same patient in Figure 1 during the third-week follow-up. EZ hyporeflection with IZ interruption (red arrow) on OCT (f3). EZ = ellipsoid zone, IZ = interdigitation zone, MZ = myoid zone, OCT = optical coherence tomography, ONL = outer nuclear layer, OPL = outer plexiform layer

reflection was lower than normal [Fig. 2f3]; EZ interruption–EZ was partially interrupted and invisible [Fig. 2b3–e3]; IZ interruption–IZ was partially interrupted [Fig. 2a3–f3]. According to whether ONL hyperreflection lesion involved the fovea, we divided the eyes into two groups: ONL hyperreflection lesion involved the fovea group (fovea-involved group) and ONL hyperreflection lesion did not involve the fovea group (no fovea-involved group).

All values are presented as mean \pm standard deviation. Statistical analyses were performed using Statistical Package for the Social Sciences 24.0 (IBM, Chicago, IL, USA) with a two-sided alpha level of 0.05 for statistical analyses. Chi-square tests were applied for OCT parameters, and *t*-tests were employed for VA and follow-up period comparisons between the two groups. Spearman tests were utilized to examine the relationship between final and initial VA and various OCT parameters.

Results

A total of 17 patients were included; 11 (64.7%) of them were females and the other six patients (35.3%) were males. The average age was 31.8 ± 10.8 years, ranging from 16 to 50 years. All patients had bilateral AMN, and 34 eyes were enrolled. Initial VA was 0.7 ± 0.7 . Fourteen eyes (41.2%) were in the fovea-involved group and the other 20 eyes (58.8%) were in the no fovea-involved group. The average initial VA of the fovea-involved group (0.9 ± 0.8) was lower than that of the no fovea-involved group (0.6 ± 0.7).

Four patients had systemic diseases, including lower level of white blood cells (WBC), kidney disease, and

hypertension [Table 1]. One patient had both lower level of WBC and kidney disease.

In the first visit, EZ hyporeflection and IZ interruption were detected in all 34 eyes. Other common manifestations included MZ hyperreflection (76.5%), ONL hyperreflection (73.5%), OPL thickening (64.7%), and EZ interruption (50%). There were statistical differences in EZ interruption and ONL cyst between the two groups [Table 2].

Thirteen patients (26 eyes) were followed up in our hospital: 12 eyes (46.2%) in the fovea-involved group and the other 14 eyes (53.8%) in the no fovea-involved group. The mean duration period of follow-up was 48.4 ± 55.3 (2–173) days, and there was no statistical difference between the two groups ($P = 0.208$) [Table 3]. In the last visit, the average VA improved to 0.5 ± 0.5 and 0.3 ± 0.3 for the fovea-involved group and the no fovea-involved group, respectively, and there was no statistical difference in the final VA between the two groups ($P = 0.176$). The improvement of VA was greater in the fovea-involved group (-0.5 ± 0.5) compared to the no fovea-involved group (-0.2 ± 0.4), and the difference was statistically significant ($P = 0.045$).

The OCT image of a right eye in the no fovea-involved group was not available, so the OCT images of the other 25 eyes were analyzed in the last visit [Table 4]. In the last visit, IZ interruption was also detected in all 25 eyes. The other common manifestations were EZ hyporeflection (92.0%), ONL atrophy increased from 23.5% to 40.0%, OPL thickening decreased from 64.7% to 36.0%, OPL linear increased from 23.5% to 32.0%,

MZ hyperreflection decreased from 76.5% to 32.0%, and ONL hyperreflection and EZ interruption both decreased to 28%. There was no statistical difference in all OCT parameters between the two groups [Table 4].

The relationship between final VA and other parameters including initial VA, initial OCT parameters, cotton wool spot, final OCT parameters, and the duration period of follow-up was analyzed. Five parameters were found to be statistically related to final VA, including presence of initial ONL cyst ($P=0.044$), initial VA ($P=0.000$), initial cotton wool spot ($P=0.029$), OPL linear of the last visit ($P=0.049$), and ONL cyst of the last visit ($P=0.049$).

Table 1: Basic information of patients

Finding	n (%)
Age (n=17)	
11–20 years	3 (17.6%)
21–30 years	6 (35.3%)
31–40 years	3 (17.6%)
41–50 years	5 (29.4%)
Sex (n=17)	
Male	6 (35.3%)
Female	11 (64.7%)
Systemic diseases (n=17)	
Lower level of WBC	2 (11.8%)
Kidney disease	2 (11.8%)
Hypertension	1 (5.9%)
Onset of eye symptoms (n=34)	
Just after fever subsided	34 (100%)

WBC=White blood cells

Discussion

Demographic insights

SARS-CoV-2 infection or COVID-19 vaccine injection might be linked to AMN.^[6–8] All the patients enrolled in this study suffered AMN just after the fever caused by SARS-CoV-2 infection subsided. Dutta Majumder and Agarwal^[9] reported that patients administered COVID-19 vaccine might experience an earlier onset of AMN compared to those with SARS-CoV-2 infection.^[9]

A review of previous studies of AMN showed that only 15.8% of AMN patients were male.^[2] This is inconsistent with the result of our study. About one-third of patients were male in our study. The inconsistency might result from the different sources of patients. All the patients enrolled in our study had experienced SARS-CoV-2 infection, while the inducing factors of AMN patients in previous cases or studies were multifarious, including use of oral contraceptives, exposure to either epinephrine or ephedrine, and so on.^[2] Nearly one-third of AMN patients in previous studies had a history of using oral contraceptives.^[2] This might be a reason of more female AMN patients in previous cases or studies than those in our study. All the female AMN patients in our study did not have the history of using oral contraceptives.

A review also reported the mean age of initial presentation of AMN was 29.5 years, and nearly half of them had it in the third decade of life.^[2] The average age was 31.8 ± 10.8 years old in our study, which is a little higher than that in previous cases. There were two peaks of age in our study [Table 1]: 21–30 years old (35.3%) and 41–50 years old (29.4%). So, people in these two age groups suffering from SARS-CoV-2 infection should pay more attention to their vision.

Table 2: OCT and other characteristics in the first visit

	All eyes (n=34)	Fovea-involved group (n=14)	No fovea-involved group (n=20)	P
VA	0.7±0.7	0.9±0.8	0.6±0.7	0.327
Eye				
Right eye	17 (50%)	7 (50%)	10 (50%)	1.000
Left eye	17 (50%)	7 (50%)	10 (50%)	1.000
Eye symptoms				
VA reduced	26 (76.5%)	10 (71.4%)	16 (80.0%)	0.562
Visual occlusion	8 (23.5%)	4 (28.6%)	4 (20.0%)	0.562
OPL				
Thickening, n (%)	22 (64.7%)	9 (64.3%)	13 (65.0%)	0.966
Linear, n (%)	8 (23.5%)	2 (14.3%)	6 (30.0%)	0.288
ONL				
Hyperreflection, n (%)	25 (73.5%)	12 (85.7%)	13 (65.0%)	0.178
Atrophy, n (%)	8 (23.5%)	3 (21.4%)	5 (25.0%)	0.809
Cyst, n (%)	10 (29.4%)	7 (50%)	3 (15.0%)	0.027*
MZ hyperreflection, n (%)	26 (76.5%)	12 (85.7%)	14 (70.0%)	0.288
EZ				
Hyporeflection, n (%)	34 (100%)	14 (100%)	20 (100%)	
Interruption, n (%)	17 (50%)	11 (78.6%)	6 (30.0%)	0.005*
IZ interruption, n (%)	34 (100%)	14 (100%)	20 (100%)	
Cotton wool spot, n (%)	5 (14.7%)	1 (7.1%)	4 (20%)	0.298

EZ=Ellipsoid zone, IZ=Interdigitation zone, MZ=Myoid zone, OCT=Optical coherence tomography, ONL=Outer nuclear layer, OPL=Outer plexiform layer, VA=Visual acuity

Table 3: Final VA, change of VA, and duration of follow-up

	All eyes (n=26)	Fovea-involved group (n=12)	No fovea-involved group (n=14)	P
VA of the last visit	0.4±0.4	0.5±0.5	0.3±0.3	0.176
Change of VA	-0.3±0.4	-0.5±0.5	-0.2±0.4	0.045*
Duration of follow-up (days)	48.4±55.3	63.3±62.8	35.6±46.5	0.208

VA=Visual acuity

Table 4: OCT characteristics in the last visit

	All eyes (n=25)	Fovea-involved group (n=12)	No fovea-involved group (n=13)	P
OPL				
Thickening, n (%)	9 (36.0%)	5 (41.7%)	4 (30.8%)	0.571
Linear, n (%)	8 (32.0%)	4 (33.3%)	4 (30.8%)	0.891
ONL				
Hyperreflection, n (%)	7 (28.0%)	2 (16.7%)	5 (38.5%)	0.225
Atrophy, n (%)	10 (40.0%)	6 (50.0%)	4 (30.8%)	0.327
Cyst, n (%)	2 (8.0%)	2 (16.7%)	0 (0.0%)	0.125
MZ hyperreflection, n (%)	8 (32.0%)	2 (16.7%)	6 (46.2%)	0.114
EZ				
Hyporeflection, n (%)	23 (92.0%)	10 (83.3%)	13 (100%)	0.125
Interruption, n (%)	7 (28.0%)	5 (41.7%)	2 (15.4%)	0.144
IZ interruption, n (%)	25 (100%)	12 (100%)	13 (100%)	

EZ=Ellipsoid zone, MZ=Myoid zone, IZ=Interdigitation zone, OCT=Optical coherence tomography, ONL=Outer nuclear layer, OPL=Outer plexiform layer

Two patients had kidney diseases in our study, including renal failure and nephritis, and one patient had a lower level of WBC. One study reported that a patient with kidney disease had symptoms of Central retinal artery occlusion (CRAO) and Paracentral acute middle maculopathy (PAMM) after injection of COVID-19 vaccine.^[10] However, currently, there is no research available to confirm whether kidney disease or abnormal levels of WBC are risk factors of AMN.

Clinical observations

A review reported that 54.4% of AMN patients had bilateral involvement,^[2] while in this study, all AMN patients had bilateral involvement. The inconsistency may be due to the differences in patient sources. We speculated that AMN following SARS-CoV-2 infection is more likely to involve both eyes.

The average initial VA (0.7 ± 0.7) was poorer in our study than that reported in previous studies.^[2] Dark reddish, wedge-shaped intraretinal lesions pointing to the fovea were considered the characteristic manifestations of AMN in the past.^[1] However, AMN was not always paracentric; about 40% eyes involved the fovea, which resulted in a significant decline of central vision in our study. Initial VA in the no fovea-involved group was poorer than that in the fovea-involved group.

OCT parameter analyses

OCT could be well used for the observation of AMN lesions. We analyzed the OCT parameters in this study. EZ hyporeflection and IZ interruption were most common in AMN following SARS-CoV-2 infection. IZ disruption might represent a subclinical alteration in retinal pigment epithelium melanin.^[11] EZ interruption decreased from 50% in the first visit to 28% in the last visit. This might suggest that pathology of IZ was more serious than EZ and the recovery of IZ was later than EZ.

ONL hyperreflection and OPL thickening resulted from deep retinal capillary ischemia in the early stage.^[4,12] About one-third of the eyes of AMN patients had hyperreflectivity of ONL and about 5% had hyperreflectivity of OPL in a previous study.^[2] In our study, ONL hyperreflection was detected in 73.5% eyes and OPL thickening in about two-thirds of the eyes in the first visit, which were much more than those in the previous study. ONL atrophy and OPL linear resulted from the development of ischemia. Only 28.0% eyes had ONL hyperreflection in the last visit, which decreased fast; however, the proportion of OPL linear increased slightly from 23.5% to 28.0% during follow-up. This might suggest that OPL atrophy due to ischemia is slower than ONL atrophy. OPL atrophy was statistically related to final VA, which means that rapid atrophy of OPL indicated poorer visual prognosis.

MZ was between external limiting membrane and EZ, showing hyporeflection owing to the lower packing density of mitochondria in the myoid as opposed to the ellipsoid region of the photoreceptor, and current evidence supports MZ was the myoid portion of the inner segments.^[13] MZ had not been discussed separately in previous studies or cases of AMN. MZ hyperreflection was a common characteristic of OCT in the early stage in our study. The proportion was up to 76.5%, even surpassing ONL hyperreflection and OPL thickening. MZ recovered during the follow-up; the proportion of MZ hyperreflection decreased significantly to 32% in the last visit. EZ also recovered during the follow-up; the proportion of EZ interruption gradually decreased from 50% to 28% and the proportion of EZ hyporeflection decreased from 100% to 92%.

There were statistical differences in EZ interruption and ONL cyst between the two groups. The proportions of EZ interruption and ONL cyst were much higher in the

fovea-involved group than those in the no fovea-involved group. The eyes with fovea involvement had more severe lesions. We speculated that EZ interruption and ONL cyst might suggest more serious lesions. Initial ONL cyst was statistically related to final VA.

Previous studies on AMN following SARS-CoV-2 infection had predominantly consisted of case reports, with some including follow-up data. However, the follow-up periods varied significantly among different case reports, and the prognosis of AMN also varied considerably. A case reported that scotomas of one patient improved significantly within 2 weeks,^[14] while another case reported that symptoms of one patient persisted for 15 weeks.^[15] In this study, 13 patients (26 eyes) had follow-up data, with an average follow-up period of 48.4 ± 55.3 days.

The result of this study showed a statistically significant correlation between OPL linear and final VA ($P = 0.049$), implying that faster OPL atrophy is indicative of a poorer visual outcome. Faster OPL atrophy was associated with more severe deep retinal capillary ischemia. In addition, final VA was significantly associated with both initial ONL cyst ($P = 0.044$) and final ONL cyst ($P = 0.049$). The presence of cyst indicated the presence of intraretinal fluid. The presence of intraretinal fluid was associated with a greater impairment of the intraretinal vascular network, and the intraretinal fluid localization at the level of OPL-ONL was associated with the worst functional and anatomic outcome.^[16] Cotton wool spots comprised localized accumulations of axoplasmic debris within adjacent bundles of unmyelinated ganglion cell axons and were widely held to reflect focal ischemia from terminal arteriolar occlusion.^[17] In our study, the results showed that the presence of initial cotton wool spot suggested a poorer final VA ($P = 0.029$). Furthermore, initial VA was found to be related to final VA ($P = 0.000$), with poorer initial VA indicating a poorer visual outcome in AMN following SARS-CoV-2 infection.

Conclusion and Limitations

In conclusion, our study sheds light on the complex interplay between SARS-CoV-2 infection, demographic factors, and OCT parameters in AMN. While the findings provide valuable insights, it is essential to acknowledge limitations such as sample size constraints. The rarity of AMN cases with follow-up data and heterogeneous follow-up periods necessitates cautious interpretation. Future studies with larger cohorts and standardized follow-up durations will contribute to a more robust understanding of AMN dynamics following SARS-CoV-2 infection.

The relatively small sample size and the single-center nature of the study may constrain the generalizability of the results. As with any retrospective analysis, the potential for selection bias cannot be entirely excluded. Future research should incorporate diverse patient populations and collaborative efforts to enhance the robustness of conclusions drawn from investigations into AMN post-SARS-CoV-2 infection.

Ethics statement

We obtained the ethics approval of Eye Hospital of Wenzhou Medical University (No. 2023-020-K-15).

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Ocular dominance and its association with retinal thickness profile – A cross-sectional study

Farnaz Ahamed Khan, Nirupama Kasturi, Amit Kumar Deb

Purpose: The retinal thickness profile is essential for detecting ocular diseases like glaucoma and other optic neuropathies. The retinal nerve fiber layer (RNFL) thickness is affected by age, ethnicity, axial length, optic disc area, and inter-eye differences. Ocular dominance has a strong functional correlation with cerebral cortical activity. However, its relationship with RNFL thickness profile is yet to be fully established. **Methods:** A cross-sectional study was conducted in 136 healthy adults to study the association between ocular dominance and RNFL parameters measured by Spectral domain optical coherence tomography (SD-OCT) and to study the association of ocular dominance with other parameters such as handedness, intraocular pressure, average axial length, average keratometry, and refractive error. Sighting ocular dominance was detected using the Miles test, and sensory ocular dominance was detected using the fogging test. Visual acuity and refraction assessment were done, and the patients underwent ocular biometry using the Lenstar 900 machine to measure the axial length and keratometry. The RNFL thickness was measured using the Cirrus HD optical coherence tomographer. **Results:** One hundred and thirty-two (97.06%) individuals were right-handed, four (2.94%) were left-handed, 108 (79.41%) participants were right eye dominant, and 28 (20.59%) were left eye dominant. There was 100% agreement between sighting and sensory ocular dominance. The average RNFL thickness and other measured ocular parameters were comparable in the dominant and nondominant eyes. Regardless of dominance, the left eyes in the study cohort had a greater statistically significant difference in superior RNFL thickness ($P < 0.05$), which correlated with increased central macular thickness. **Conclusion:** Ocular dominance occurred mostly in the right eye. The RNFL thickness profile is not associated with ocular dominance in emmetropic and mild myopic individuals with normal best corrected visual acuity.

Key words: Handedness, ocular dominance, retinal nerve fiber layer thickness

The anatomical and functional development of the right and left hemispheres of the human brain has a high degree of symmetry. However, there are differences between the two sides; each is dominant in processing specific cognitive tasks. Studies have shown that functional asymmetry for spatial orientation exists in the cerebral hemispheres.^[1,2] This asymmetry of the brain may affect handedness and verbal and spatial cognition.^[3-8] The ocular system exhibits laterality like the brain system, known as ocular dominance.^[9] Ocular dominance is the tendency to prefer visual input from one eye over another. The dominant eye is the one that a person usually uses in monocular behavior coordination while looking through a keyhole or a telescope.^[10] It has been said that eye dominance might be related to cortical hemispheric specialization to visual attention.^[11] The importance of eye dominance in daily life is not clearly understood, yet it is clinically crucial in sports vision, vision therapy, and monovision treatments.^[12] The functional role of the dominant eye is vital in ophthalmology as patients might suffer more significant visual handicaps if a macular disease affects the dominant eye rather than the nondominant eye. In ocular mechanisms like strabismus, the nondominants are more likely to develop amblyopia.^[13] This

concept must also be considered while providing presbyopia correction by refractive surgery, intraocular lens implantation, or contact lenses. Greater patient satisfaction might result from correcting the dominant eye for distance and the nondominant eye for near vision.^[14-16] It is also known that the dominant eye is related to cerebral laterality with significantly higher cortical activation than the nondominant eye.^[17,18] Earlier, detecting structural differences between dominant and nondominant was difficult, as no technology was available to utilize *in situ*. With the advent of optical coherence tomography (OCT), it is now possible to measure the morphologic structure of the eye. OCT is a widely used imaging tool for measuring retinal nerve fiber layer (RNFL) thickness and macular thickness parameters. The development of spectral domain OCT has resulted in faster scanning and high-resolution images to interpret RNFL. Previous studies by Choi *et al.* have shown the associations between ocular dominance with inferior retinal nerve layer thicknesses and macular ganglion cell-inner plexiform layer (GCIPL) which differed by few microns, which may not be clinically significant.^[19,20] Hence, this study was

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undertaken to identify any structural differences in the retinal layers between the dominant and nondominant eyes.

Methods

This cross-sectional study consisted of patients between 18 and 35 years of age with a best corrected visual acuity of 6/6, who attended the ophthalmology outpatient department in a tertiary care center in South India between January 2021 and July 2022. The sample size was calculated assuming the proportion of dominance as 85%, with respect to the study of Samarawickrama *et al.* in 2008, with an alpha error of 0.05, a beta error of 0.2, and a power of 80%.^[21] Both eyes of the patient were considered for the study, and the total sample size was 136. Patients with high hyperopia (axial length [AL] <21 mm) and high myopia (AL >27 mm) were excluded as short and long ALs play a role in increasing or decreasing the average AL. Patients with retinopathies, diseases affecting the optic nerve, including glaucoma, chronic smokers, alcoholics, patients with past intraocular surgery, and those with trauma were excluded. The dominant hand used for writing was noted.

Measurement of ocular dominance

Sighting ocular dominance was determined using Miles test, where the participant was asked to extend both arms in front of the body and both hands together to create a small triangle between the thumb and the first knuckle. With both eyes open, the participant was asked to view a distant object (on a single 6/12 letter at 6 m) through the triangle. Then, the participant was asked to alternate closing of the eyes to determine which eye was viewing the object, and this eye was considered the dominant eye [Fig. 1]. Sensory ocular dominance was



Figure 1: Clinical photograph showing the Miles test for ocular dominance when viewed through the dominant eye

determined by the fogging test, where the subject was asked to fixate at a 6/12 letter at 6 m with both eyes open. A +/- 1.50 D lens was alternated in front of each eye for a few seconds. The dominant eye was the one in which the subject reported more blurred vision with the positive lens under binocular conditions. Then the visual acuity, with and without correction, was determined by the Snellen acuity chart and converted into log of minimum angle of resolution (logMAR) values. After collecting ocular and systemic history, slit-lamp examinations were conducted for patients to look for anterior segment pathology. Patients underwent cycloplegic refraction and dilatation to check for lens opacity and fundus examination. The optical biometer was used for ocular biometry (Lenstar 900; Haag-Streit, Koeniz, Switzerland). The Lenstar LS 900 was calibrated before obtaining the measurements, and a minimum of five readings were taken with a standard deviation (SD) of <0.2. Parameters studied using the biometer were average AL and average keratometry (K) values. Optic nerve head and ganglion cell complex evaluation by the Cirrus HD OCT 500 (Carl Zeiss Meditec, Dublin, CA, USA) was performed by a single imaging technician after cycloplegia. The optic disc cube and macular cube protocols were done for the SD-OCT to provide RNFL and Ganglion cell complex (GCC) thickness measurements. Images with a signal strength ≤6 were excluded.

Results

The study included 136 individuals between 18 and 35 years of age; the mean age was 24.4 ± 3.08 years. Sixty-seven (49.26%) of them were males and 69 (50.73%) were females. In the study population, 132 (97.06%) individuals were right-handed and four (2.94%) were left-handed, of which 108 (79.41%) participants were right eye dominant and 28 (20.59%) were left eye dominant [Fig. 2]. There was 100% agreement between sighting and sensory ocular dominance. Among the right-handed individuals, 105 (79.54%) were right eye dominant and 27 (20.45%) were left eye dominant. Among the left-handed individuals, three (75%) were right eye dominant and one (25%) was left eye dominant. Among the study participants, 109 individuals were emmetropic with an uncorrected visual acuity of 0 in the logMAR chart in both eyes and 27 individuals were myopic with vision better than 0.1 in the logMAR chart in both eyes. The myopic patients had a mean spherical equivalent of 0.61 ± 1.40 D for the right eye and 0.62 ± 1.39 D for the left eye among right eye-dominant participants and 0.56 ± 1.33 D for the right eye and 0.48 ± 1.12 D for the left eye among left eye-dominant participants. The baseline intraocular pressure, cup-disc ratio, average AL, average K (Avg K), average RNFL, Ganglion cell

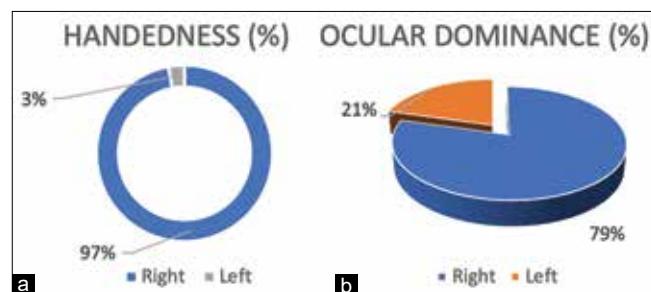


Figure 2: (a) Distribution of percentage of handedness and (b) percentage of ocular dominance in the study population

layer- inner plexiform layer (GCL-IPL), and central macular thickness (CMT) data for all study participants ($N=136$) were comparable between the right and left eyes [Table 1]. In our study, the right eye RNFL parameters, except the superior one, were slightly higher than those of the left eye among the right eye-dominant participants, but this was not statistically significant [Table 2]. Similarly, the, left eye RNFL parameters were slightly higher than those of the right eye among the left eye-dominant participants [Table 3]. Overall, the superior quadrant RNFL thickness of the left eye was higher in both right eye- and left eye-dominant individuals, which was statistically significant [Fig. 3] and correlated with the high CMT.

Discussion

This study investigated the possible associations between ocular dominance and handedness, refractive error, and other ocular biometry parameters like average AL, average keratometry, and retinal thickness profile, including the average GCL-IPL and CMT. There was no difference in gender distribution or any specific pattern in the RNFL thickness between the genders. The study participants were predominantly right-handed and only four were left-handed. There was no association found between handedness and ocular dominance. This was comparable to the systematic review by Moreno *et al.*,^[22] in which the relationship between hand-eye laterality and sports performance was looked into in various studies on this subject over the last decade. The dominance of the eyes has different types, like sighting, sensory, and acuity dominance.^[23,24] The dominant sighting eye is the one that can swiftly move toward a target and stay fixed on it.^[25] If the dominant eye has better visual acuity, it will be preferred as the predominant eye for a better quality image and becomes the acuity dominance. The dominant sensory eye is the one that has stronger vision than the other, and while testing for blur with a small plus lens, it is relatively easy to

get more blurred than the nondominant eye.^[26,27] The exact difference between sighting and sensory ocular dominance stays unresolved.^[28] In our study, there was 100% agreement between sighting and sensory ocular dominance among the participants. Mwanza *et al.* and Huynh *et al.*^[29,30] found that the superior quadrant RNFL was thicker in the left eye than in the right eye. Budenz *et al.* and Park *et al.*^[31,32] found that the average RNFL of the right eye was significantly thicker than the

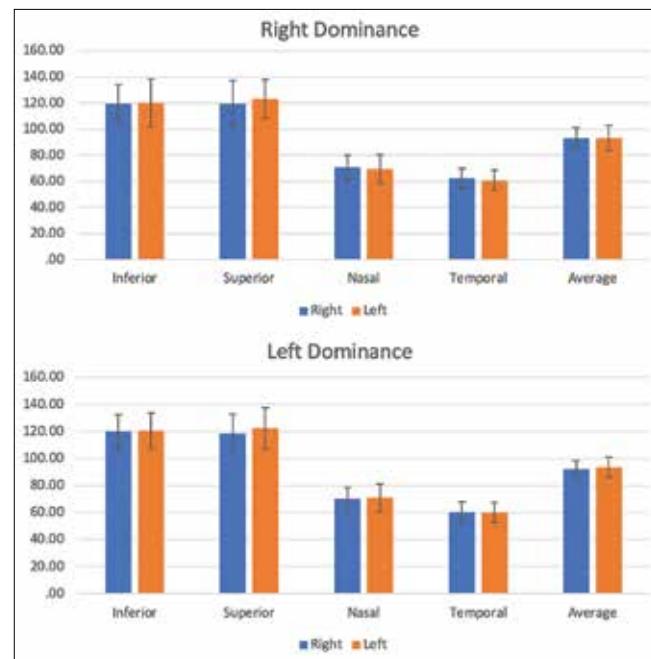


Figure 3: Bar graph showing the average and quadrant retinal nerve fiber layer thickness comparison between the right eye and the left eye in right eye dominance and left eye dominance

Table 1: IOP, CDR, average AL, Avg K, average RNFL, GCL-IPL, and CMT data for all study participants ($n=136$)

Characteristic	Right eye Mean±standard deviation	Left eye Mean±standard deviation
IOP (mmHg)	13.45±2.16 (10–18)	13.73±1.88 (10–18)
CDR	0.33±0.07 (0.2–0.5)	0.32±0.07 (0.2–0.5)
Average AL (mm)	23.94±1.19 (21.97–26.95)	23.96±1.20 (21.98–26.94)
Avg K (D)	44.09±1.62 (39.73–48.19)	45.60±1.67 (40.29–48.16)
Average RNFL thickness (μm)	93.18±7.42 (78–113)	93.40±9.25 (67–126)
Average GCL-IPL thickness (μm)	81.60±5.17 (65–91)	81.88±5.13 (62–92)
CMT (μm)	240.83±20.48 (193–272)	242.80±18.70 (207–276)

AL=axial length, Avg K=average keratometry, CDR=cup–disc ratio, CMT=central macular thickness, IOP=intraocular pressure, RNFL=retinal nerve fiber layer

Table 2: Comparison of RNFL parameters of the right eye and the left eye among the right eye-dominant participants ($n=108$)

Characteristic	Right eye	Left eye	Mean difference	P
Inferior RNFL thickness (μm)	118 (109.25–128.00)	118 (106.25–130.00)	0.00	0.274**
Superior RNFL thickness (μm)	119.78±17.22	123.33±14.51	-3.55	<0.001*
Nasal RNFL thickness (μm)	70.73±9.45	69.45±9.45	1.27	0.196*
Temporal RNFL thickness (μm)	61 (56.25–69.50)	61 (55.00–67.00)	0.00	0.100**
Average RNFL thickness (μm)	93 (88.00–98.00)	92.50 (88.00–99.00)	1.50	0.420**

Values are given as mean±standard deviation/median (IQR). *Paired t-test for parameters that followed a normal distribution. **Wilcoxon signed-rank test for parameters that did not follow a normal distribution. IQR=interquartile range, RNFL=retinal nerve fiber layer

Table 3: Comparison of RNFL parameters of the right eye and the left eye among the left eye-dominant participants (n=28)

Characteristic	Right eye	Left eye	Mean difference	P
Inferior RNFL thickness (μm)	120.21 \pm 12.18	120.68 \pm 13.18	-0.464	0.815*
Superior RNFL thickness (μm)	118.61 \pm 14.38	122.43 \pm 15.32	-3.821	0.048*
Nasal RNFL thickness (μm)	70.32 \pm 8.47	70.93 \pm 10.43	-0.607	0.652*
Temporal RNFL thickness (μm)	57 (56.00–70.00)	58.50 (56.00–67.00)	-1.500	0.599**
Average RNFL thickness (μm)	92.43 \pm 5.92	93.64 \pm 7.46	-1.214	0.128*

Value in bold shows statistical significance. Values are given as mean \pm standard deviation/median (IQR). *Paired t-test for parameters that followed a normal distribution. **Wilcoxon signed-rank test for parameters that did not follow a normal distribution. IQR=Interquartile range, RNFL=Retinal nerve fiber layer

left eye. Cehver *et al.* compared the macular and peripapillary RNFL thicknesses of the dominant eye and nondominant eye using OCT. They found the same results in average and superior quadrant analysis. In the other three quadrants (nasal, temporal, and inferior), RNFL thickness was more in the right eyes than in the left, but there was no significant difference.^[33] Cehver *et al.* hypothesized that the RNFL profile might be affected by ocular dominance.^[33] Still, their results showed that ocular dominance does not statistically affect the differences in interocular and intraocular RNFL thickness, and this was consistent with our study. Anisometropia refers to the condition of unequal refractive errors between the two eyes, and this occurs due to an interocular difference in ALs.^[34] In anisometropia, the interocular difference in refractive errors leads to constant or intermittent defocused retinal image and, thereby, a decline in the clarity and contrast of the image in the affected eye or a difference in the size of the retinal image between the eyes. This leads to two different signals of a single object to the visual system, which causes a decline in the visual function.^[35,36] Maintaining a balance between the signals from the two eyes is important in developing the visual system. So, during anisometropia development, it is believed that the neural system, part of the visual system, develops some form of asymmetry to overcome this interocular asymmetry to bring about balance. It is accepted in a few studies that ocular dominance plays a major role in adapting to this asymmetry and, thereby, it becomes important to identify the dominant and nondominant eyes.^[37,38] Jhiang *et al.* elucidated the role of laterality, ocular dominance, and anisometropic magnitude in the more myopic eye in anisometropia. They found that when the magnitude of anisometropia was less than moderate (4 D in either eye), the neural asymmetry, probably ocular dominance, favored the more myopic eye and thereby reduced the effect of the interocular optical asymmetry, so that the signals from the two eyes were close to balance. But when the magnitude of anisometropia was beyond a particular threshold, the neural asymmetry could overcome the optical asymmetry, thereby the probability of the myopic eye being dominant dropped. Ocular dominance increased the interocular optical difference instead of overcoming it.^[39] Chia *et al.* studied the effect of eye laterality and dominance on refraction in Singaporean children. They found that ALs in the right eyes were significantly longer, and that the dominant eyes were significantly less astigmatic. Still, these differences were small and of little clinical significance.^[40] In our study, no clinically significant difference was found between the dominant and nondominant eyes in terms of AL, average K, or refractive error. Observation of various retinal layers, such as the macular GCIPL and the macular and circum papillary RNFL, in OCT is useful in the evaluation of diseases like glaucoma. The macular GCIPL cells are primarily

involved in glaucoma, so their thickness assessment becomes important. Although RNFL measurements assess almost all the axons arising from ganglion cells, the circum papillary region is likely to be affected by high myopia.^[41,42] Based on this, Shoji *et al.* evaluated the effect of high myopia on the SD-OCT parameters in glaucoma. They found that the circum papillary RNFL measurements are significantly affected by refractive errors, making it inferior in detecting glaucoma in high myopia compared to emmetropia. They also found that the GCC measurements and related parameters were not significantly affected, even in high myopia.^[43] Patients suffer more visual handicaps if there is a macular pathology in the dominant eye than in the nondominant eye. Cehver *et al.*^[33] compared the macular and peripapillary RNFL thicknesses of the dominant eye and nondominant eyes using OCT and concluded that there was no significant association between both. In the Sydney Myopia Study, Samarawickrama *et al.* evaluated CMT and ocular dominance in children and found no statistically significant difference.^[21] In our study, no significant association was found between ocular dominance, ganglion cell thickness, and CMT.

Limitations

The number of right-handed and right eye-dominant individuals in the study was lower than that of left-handed and left eye-dominant individuals. Only a single SD-OCT device was used, and error characteristics may differ in other systems. Since none of the patients had significant anisometropia, the effect of refractive error on the interocular difference in RNFL could not be evaluated.

Conclusion

We found handedness and dominance to be predominantly on the right side. Overall, the superior RNFL thickness was higher in the left eye in both right eye-dominant and left eye-dominant individuals, which correlated with increased CMT in the left eye. No other ocular characteristic studied was also found to be associated with dominance.

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Correlation of glycosylated hemoglobin (HbA1c) with retinal nerve fiber layer (RNFL) thickness and central macular thickness (CMT) in the diabetic population in North India

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Purpose: The current study was aimed to find correlation of glycosylated hemoglobin with retinal nerve fiber layer thickness (RNFLT) and central macular thickness (CMT) in the diabetic population in North India. **Methods:** This was a cross-sectional observational study of 300 diabetic patients divided equally in two groups with and without retinopathy, and 150 people were included as control. The study was conducted from October 2020 to August 2022. All patients underwent slitlamp fundoscopy with a +78 D lens, and spectral-domain (SD) optical coherence tomography was performed to measure the RNFLT and CMT, and the staging of retinopathy was done as per the ETDRS classification. Along with that, blood investigations were ordered, including fasting (FBS) and post-prandial (PPBS) blood sugar and glycosylated hemoglobin (HbA1c). Quantitative variables were compared using one-way analysis of variance, or Kruskal-Wallis test was applied for inter-group comparison, followed by a Student Newman Keuls Test. **Results:** The mean age of the patients in the diabetic group with retinopathy was 52.62 ± 9.38 years. The overall male: female ratio was 3:2. The mean FBS in the diabetic group with retinopathy was 146.54 ± 45.40 mg/dl; the PPBS and HbA1c in the same were 210.39 ± 63.71 mg/dl and $7.85 \pm 1.33\%$, respectively. RNFL thinning was found in all four quadrants in diabetics irrespective of the status of retinopathy (P -value = 0.000) with a significant weak negative ($r < 0.4$) correlation of glycosylated hemoglobin values with RNFLT in the inferior (r value = -0.300, P -value = 0.000) and superior (r value = -0.236, P -value = 0.004) quadrants of right eyes and in inferior (r value = -0.176, p -value = 0.031), superior (r value = -0.222, P value = 0.006), and nasal quadrants (r value = -0.166, p -value = 0.043) of left eyes in diabetics with retinopathy. However, in diabetics without retinopathy, no correlation was found. On correlating HbA1c with CMT, a weak positive ($r < 0.3$) association existed in both eyes in the diabetic group without retinopathy (r = 0.020 and 0.048 for OD and OS, respectively) and diabetics with retinopathy (r = 0.152 and 0.127 for OD and OS, respectively). However, the association was not found to be significant in either of the groups (P -value > 0.05). **Conclusion:** The study concluded that neurodegeneration occurs in diabetic retinopathy as evident with nerve fiber layer thinning, and it is negatively correlated with glycosylated hemoglobin (HbA1c).

Key words: Central macular thickness (CMT), diabetes mellitus (DM), glycosylated hemoglobin (HbA1c), retinal nerve fibre layer (RNFL), retinal nerve fibre layer thickness (RNFLT), SD-OCT (spectral-domain optical coherence tomography)

Diabetic patients are in general seen to be more prone to develop associated nephropathy, neuropathy, retinopathy, and cardiac diseases as the four major complications when compared with the non-diabetic population.^[1] The most common complication of this chronic disease is diabetic retinopathy (approximately 90%).^[2] In most developing countries, diabetic retinopathy is one of the most common contributing factors of blindness.^[3] Diabetic retinopathy clinically presents as retinal ischemia, intraretinal microvascular abnormalities, hemorrhages, neovascularization, and increased vascular permeability.^[4]

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It can progress from mild, non-proliferative to moderate or severe non-proliferative disease, which may further progress to proliferative disease if the insulting factors are not put to control.^[5] Since times immemorial, diabetic retinopathy has been thought primarily as a retinal vascular disease since the microvascular theory has been the most accepted mechanism in the pathophysiology of development of diabetic retinopathy. However, today, it is known that diabetes mellitus induces apoptosis in ganglion cells, horizontal cells, amacrine cells, and Müller cells, in accordance with activation of microglial cells,^[6-8] and this has evidenced with the functional abnormalities in

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electroretinograms, perimetries,^[9-11] visual evoked potentials, dark adaptation, contrast sensitivity,^[12-14] and color vision before the clinical appearance of diabetic retinopathy.^[15-17] Thus, all these experimental, clinical, and functional findings point toward the possible role of neuro-retinal degeneration to the pathogenesis of diabetic retinopathy. Therefore, it is a misunderstood concept that diabetic retinopathy is simply a microvascular complication of diabetes, when it has its roots interlinked with initiating neuronal degenerative processes as well. In 2015, the American Diabetes Association reported that according to the Clinical Practice, glycosylated hemoglobin (HbA1c) was recommended as an excellent predictive marker for the diagnosis of diabetes.^[18] Each 1% reduction in HbA1c is seen to minimize the risk of developing systemic and ocular complications of diabetes by about 40%. The measurement of HbA1c is thus considered to be as important as blood glucose measurement, and it can facilitate the accomplishment of improved glycaemic control. HbA1c reflects average plasma glucose over the past 2–3 months and does not require patients to fast and thus can be measured at any time. The obtained data through this study might support the usefulness of this non-invasive marker for establishing severity of diabetic retinopathy as well as can help throw light on its primal neurodegenerative process.^[19] To the best of our knowledge, this is the first study in northern India correlating the HbA1c with the RNFLT and CMT with a large study population.

Methods

This cross-sectional observational study was conducted over 2 years, from October 2020 to August 2022, at a tertiary eye care referral center in northern India. The study followed the tenets of the Declaration of Helsinki, and study approval was obtained from the Institutional Ethics Committee (IEC). Informed consent was taken from all the patients. Nine hundred eyes of 450 patients were evaluated prospectively. Inclusion criterion for diabetic patients was type 2 DM. Group 1 (n = 150) included 150 healthy control who had no systemic or ophthalmologic problems, group 2 included 150 diabetic patients who had no DR (n = 150), and group 3 included 150 patients who had mild-moderate NPDR (n = 150 patients). All patients in the control group were evaluated for undiagnosed DM [Table 1]. The retina in all participants was evaluated through slitlamp bio-microscopy using +78 D lens, indirect fundoscopy, and fundus fluorescein angiography. Mild NPDR was defined as microaneurysms only; moderate NPDR was defined more than just microaneurysms, but less than severe NPDR as classified by ETDRS scale.^[20]

Exclusion criteria were non-consenting uncooperative patients, a best corrected visual acuity below 1 logMar unit, myopic patients with a spherical equivalent >3D, and patients with severe and very severe non-proliferative diabetic retinopathy and proliferative diabetic retinopathy were excluded because RNFL loss is already established in such patients. Those with pre-existing glaucoma, intraocular inflammation, optic nerve pathology, vitreous hemorrhage, previous retinal laser treatment, significant media opacities such as dense cataracts, corneal opacities, and any history of previous intraocular surgery except for uneventful surgery for uncomplicated cataract. One-eyed patients and those with hypertension were also excluded. All subjects underwent pupillary dilation (tropicamide 0.8% + phenylephrine 5%) and an ophthalmologic examination, including slitlamp bio-microscopy (SL, Appasamy, India) with a +78 dioptres handheld lens and SD-OCT. Fundus fluorescein angiography was performed in diabetic patients for excluding severe non-proliferative or proliferative retinopathy. Blood investigations including FBS, PPBS, and glycosylated hemoglobin (HbA1c) at the time of visit were evaluated. HbA1c was calculated by high-performance liquid chromatography (HPLC) using a D-10 Machine developed by BIO-RAD Company. RNFL thickness and central macular thickness (CMT) were measured using SD-OCT with Cirrus HD-OCT 500 (Carl Zeiss Meditec AG Goeschwitzer Str. 51-52 07745 Jena Germany).

Statistical analysis

Statistical analyses were performed with SPSS 25.0 (developed in California in US, based on IBM). Categorical variables were presented in number and percentage (%), and continuous variables were presented as mean ± SD, median, and inter-quartile range. Quantitative variables were compared using one-way analysis of variance (ANOVA), or Kruskal Wallis test was applied for inter-group comparison, followed by a Student Newman Keuls test. A P-value <0.05 was considered to be statistically significant. FBS, PPBS, and HbA1c were compared using the unpaired t-test between patients with no DR, mild-moderate NPDR, and control group, and later, any correlation if present between HbA1c and four-quadrant RNFLT and CMT was found, and correlation graphs were plotted.

Results

Four hundred and fifty patients (900 eyes) were analyzed. The characteristic features of participants in three groups are summarized in Table 1. The participants were similar as per age and gender characteristics for homogeneity of the

Table 1: Characteristic features of participants in three groups

Parameters	Group 1(n=150)	Group 2(n=150)	Group 3(n=150)	P
Mean age (years)	50.93±9.95	51.57±9.75	52.62±9.38	NS
Male/Female	84/66	91/59	95/55	NS
OD BCVA (log Mar)	0	0.16±0.11	0.38±0.26	S
OS BCVA (log Mar)	0	0.15±0.10	0.37±0.25	S
FBS (mg/dl)	89.02±9.12	129.61±23.72	146.54±45.40	S
PPBS (mg/dl)	127.86±5.58	176.37±45.56	210.39±63.71	S
HbA1c (%)	5.18±0.30	7.08±1.00	7.85±1.33	S

NS=Non-significant (P>0.05), S=Significant (P<0.05)

three groups; FBS, PPBS, and HbA1c levels were significantly higher (P -value <0.05) in the patients with DM compared to the controls. The values of RNFLT and CMT as measured across the three groups are given in Tables 2 and 3, respectively, and any significant difference in data is represented in the form of P -value <0.05. Correlation of HbA1c with quadrant-wise RNFLT and CMT is depicted in Tables 4 and 5, respectively, and based on that, the correlation graphs of HbA1c with four quadrant RNFL thickness of RE and LE of group 3 are represented in Fig. 1 (Graphs A-D) and Fig. 2 (graphs E-H), respectively, and correlation graphs of bilateral eye CMT with HbA1c of group 3 are represented in Fig. 3 (graphs I and J), respectively. The RNFL was found to be thinner in patients with DM when they were compared to control with a statistically significant difference [Table 2], and the CMT was found to be thicker in diabetic patients with statistically significant difference [Table 3].

The above differences were irrespective of the development of retinopathy. When looked for any correlation, the study indicated a weak negative correlation ($r<0.4$) between HbA1c and 4 quadrant RNFLT in diabetics with retinopathy except for the temporal quadrant of the left eye [Table 4, Figs. 1 and 2], whereas in diabetics without retinopathy, no significant correlation was seen [Table 4]. HbA1c was found to correlate weakly positive($r<0.3$) with CMT in diabetics [Table 5 and Fig. 3].

Discussion

We conducted a study to find correlation if any between HbA1c and RNFLT as well as CMT in diabetic North Indian population. The study included 300 diabetics (divided equally into 150 patients with and without retinopathy) and 150 healthy control population, making a total of 450 patients (900 eyes). Dhasmana *et al.*^[21] conducted a study to find out RNFLT in 115 diabetics and 50 healthy control (total of 165 study population). Fahmy *et al.*^[22] conducted a study comprising of 32 healthy control and 31 diabetic patients (total of 126 eyes of 63 total study population) and attempted to evaluate correlation between HbA1c and peripapillary RNFLT like

ours. In our study, the mean age group of healthy control was 50.93 ± 9.95 years, 51.57 ± 9.75 years in diabetic group without retinopathy, and 52.62 ± 9.38 years in diabetic group with retinopathy. Similar to our study, Dhasmana *et al.*^[21] in their study included subjects in healthy controls with a mean age of 45.4 ± 7.96 years. Diabetics without retinopathy had a mean age of 51.16 ± 9.49 years, and in diabetics with retinopathy, the mean age was 55.10 ± 9.06 years.

In our study, we included 270 males (60%), while females were 180 (40%). Similar to our study, Dhasmana *et al.*^[21] in their study included 101 males (61.21%) and 64 females (38.79%). Fahmy *et al.*^[22] in their study had more females with 46 females (73.02%) and 17 males (26.98%). In our study, we found RNFL to be significantly thinned out in each of the four quadrants of both eyes in diabetic patients (P -value = 0.000), irrespective of the status of retinopathy. Like our study, Mehboob *et al.*^[23] in their study found out the mean RNFLT as well as RNFLT of all four quadrants to be thinned out significantly in diabetic population (P -value = 0.001). Contrary to our study, Dhasmana *et al.*^[21] found out statistically significant RNFL thinning only in the supero-temporal (p - value = 0.001) and upper nasal sectors (P -value = 0.031) in patients with diabetic retinopathy. Fahmy *et al.*^[22] in their study found thinning of RNFL in diabetics when compared with healthy controls; however, the RNFL was found to be significantly thinned out only in the superior quadrant (p - value = 0.002). The difference in results could be due to greater susceptibility to damage in retinal nerve fibers distributed in superior and inferior quadrants with less supporting tissue. Our study found that in diabetics without retinopathy, the HbA1c had no correlation with peripapillary RNFLT. In diabetics with retinopathy, the HbA1c was correlated weakly negative (with Pearson's correlation, $r < 0.4$) with peripapillary RNFLT in all except the temporal quadrant of left eye. However, correlation was found to be significant only in inferior (r value = -0.300, p - value = 0.000) and superior (r value = -0.236, P -value = 0.004) quadrants of right eye and in inferior (r value = -0.176, P -value = 0.031), superior (r value = -0.222, P -value = 0.006), and nasal (r value = -0.166, P -value = 0.043) quadrants of left

Table 2: Four quadrant RNFLT among 3 groups

Parameters	Group 1($n=150$)	Group 2($n=150$)	Group 3($n=150$)	P
OD RNFLT				
Inferior (μm)	118.26 ± 8.53	114.43 ± 9.27	108.64 ± 12.07	0.000*
Superior (μm)	123.34 ± 10.03	119.59 ± 10.55	110.68 ± 13.10	0.000*
Nasal (μm)	70.38 ± 7.45	69.46 ± 6.35	64.62 ± 8.03	0.000*
Temporal (μm)	63.00 ± 7.16	59.09 ± 8.48	58.60 ± 8.18	0.000*
OS RNFLT				
Inferior (μm)	118.60 ± 7.66	114.86 ± 9.83	109.98 ± 11.94	0.000*
Superior (μm)	122.94 ± 10.47	117.66 ± 13.62	110.26 ± 13.46	0.000*
Nasal (μm)	67.70 ± 6.38	67.62 ± 7.50	63.12 ± 7.26	0.000*
Temporal (μm)	62.76 ± 6.27	57.20 ± 7.58	58.12 ± 7.15	0.000*

*Denotes significance, $P<0.05$

Table 3: CMT among 3 groups

Parameters	Group 1($n=150$)	Group 2($n=150$)	Group 3($n=150$)	P
OD CMT (μm)	219.10 ± 10.40	225.36 ± 13.52	241.57 ± 25.10	0.000*
OS CMT (μm)	218.97 ± 10.78	225.58 ± 13.45	240.59 ± 23.99	0.000*

*Denotes significance, $P<0.05$

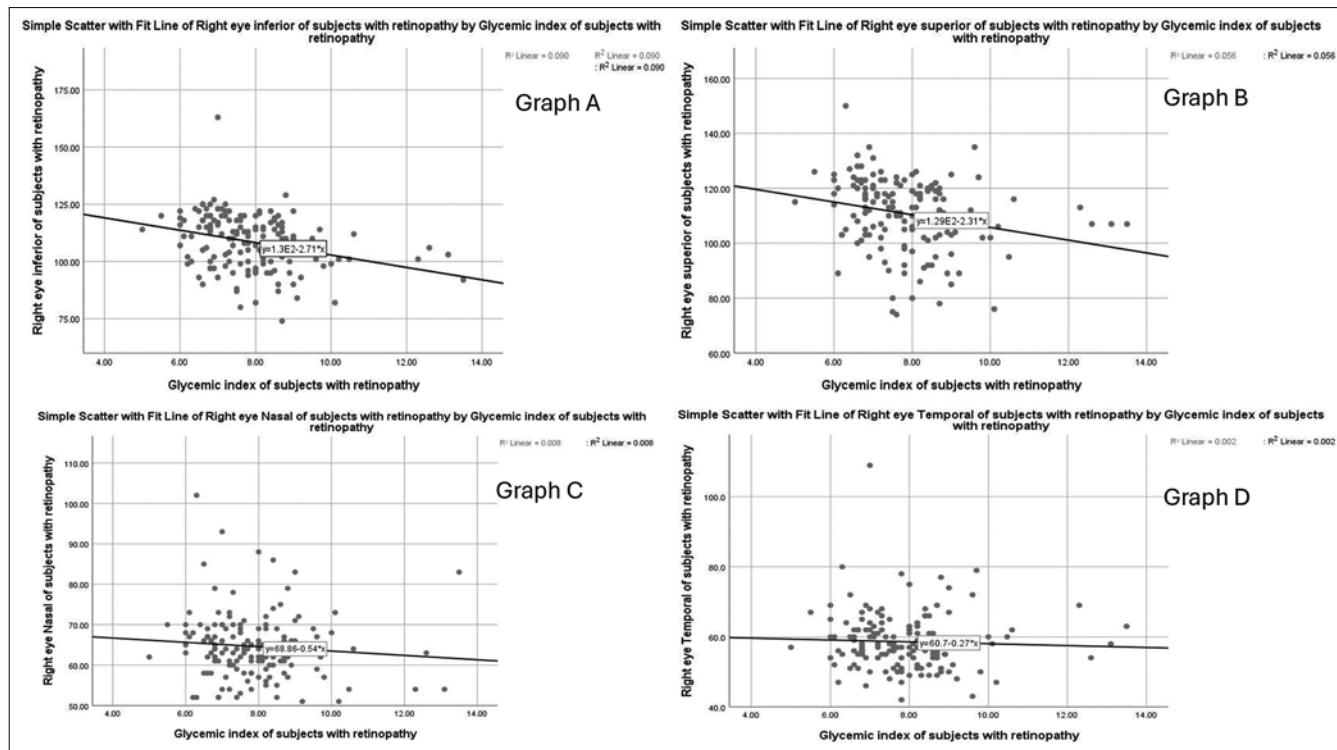


Figure 1: Correlation graphs between RE four-quadrant RNFL thickness and HbA1c of Group 3. Graph A: Correlation graph between RE Inferior quadrant RNFL thickness and HbA1c. Graph B: Correlation graph between RE Superior quadrant RNFL thickness and HbA1c. Graph C: Correlation graph between RE Nasal quadrant RNFL thickness and HbA1c. Graph D: Correlation graph between RE Temporal quadrant RNFL thickness and HbA1c

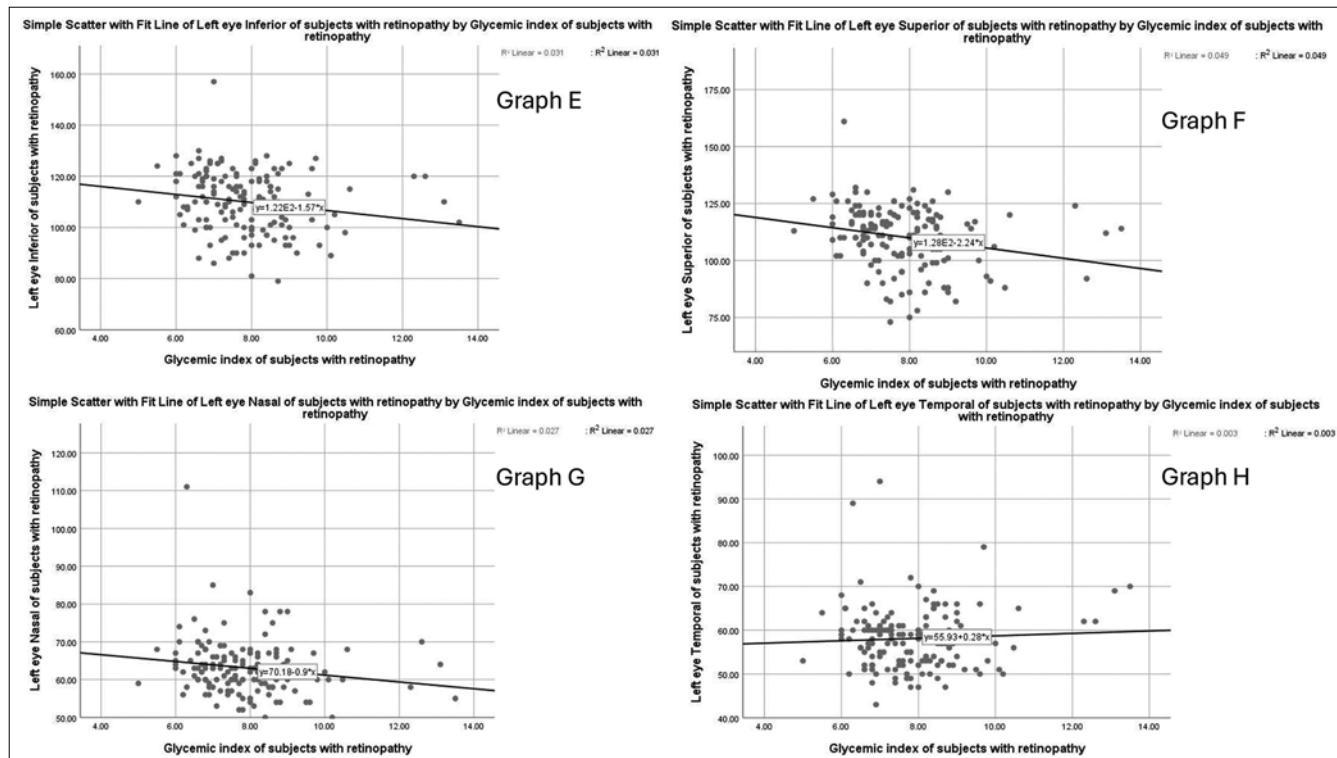


Figure 2: Correlation graphs between LE four-quadrant RNFL thickness and HbA1c of Group 3. Graph E: Correlation graph between LE Inferior quadrant RNFL thickness and HbA1c. Graph F: Correlation graph between LE Superior quadrant RNFL thickness and HbA1c. Graph G: Correlation graph between LE Nasal quadrant RNFL thickness and HbA1c. Graph H :Correlation graph between LE Temporal quadrant RNFL thickness and HbA1c

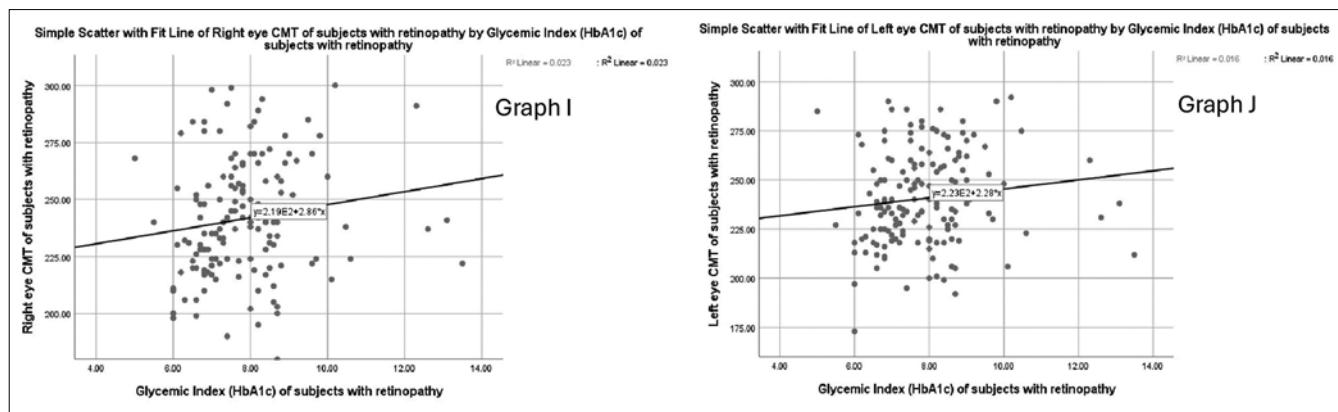


Figure 3: Correlation graphs between Bilateral eye CMT and HbA1c of Group 3. Graph I: Correlation graph between RE CMT and HbA1c. Graph J: Correlation graph between LE CMT and HbA1c

Table 4: Correlation between HbA1c and Four Quadrant RNFLT among diabetics

Parameters	r (Pearson's correlation)	P
OD RNFLT (Diabetics without retinopathy, n=150)		
Inferior (μm)	0.030	0.716
Superior (μm)	0.025	0.758
Nasal (μm)	0.005	0.951
Temporal (μm)	0.021	0.801
OS RNFLT (Diabetics without retinopathy, n=150)		
Inferior (μm)	0.191	0.019*
Superior (μm)	0.006	0.945
Nasal (μm)	0.139	0.090
Temporal (μm)	-0.096	0.243
OD RNFLT (Diabetics with retinopathy, n=150)		
Inferior (μm)	-0.300	0.000*
Superior (μm)	-0.236	0.004*
Nasal (μm)	-0.090	0.275
Temporal (μm)	-0.044	0.595
OS RNFLT (Diabetics with retinopathy, n=150)		
Inferior (μm)	-0.176	0.031*
Superior (μm)	-0.222	0.006*
Nasal (μm)	-0.166	0.043*
Temporal (μm)	0.052	0.526

*Denotes significance, P<0.05

Table 5: Correlation between HbA1c and CMT among diabetics

Parameters	r (Pearson's correlation)	P
Diabetics without retinopathy (n=150)		
OD CMT (μm)	0.020	0.812
OS CMT (μm)	0.048	0.557
Diabetics with retinopathy (n=150)		
OD CMT (μm)	0.152	0.063
OS CMT (μm)	0.127	0.121

eye. Contrary to our study, Fahmy *et al.*^[22] in their study found peripapillary RNFLT to be negatively correlated with HbA1c

in the superior, inferior, and nasal quadrants but positively correlated in the temporal quadrant. This correlation was significant in the superior quadrant only. Karakahya^[24] found in their study only the thickness of average RNFL ($r = -0.234$, P -value = 0.014) along with inferior ($r = -0.237$, P -value = 0.013) and nasal quadrants ($r = -0.216$, P -value = 0.023) to be correlated significantly negatively with HbA1c. Dhasmana *et al.*,^[21] Nor-Sharina Y *et al.*,^[25] and Oshitari T *et al.*^[26] contrary to above, however, found no correlation between HbA1c and RNFLT. We also found CMT to be significantly increased in diabetics irrespective of the status of retinopathy (P -value = 0.000). Like our study, Oshitari *et al.*^[27] also found that in the pre-proliferative retinopathy group, the macular thickness of the center sector was significantly thicker than that of the no retinopathy group (Fisher's PLSD; $P \leq 0.0006$, Games-Howell and Student-Newman-Keuls).

Thus, CMT was found to increase with advancing retinopathy most likely due to deranged glycemic control-mediated vascular hemodynamics.

When HbA1c was correlated with CMT, we found weak positive ($r < 0.3$) correlation in diabetic group without retinopathy ($r = 0.020$ OD, $r = 0.048$ OS) and with retinopathy ($r = 0.152$ OD, $r = 0.127$ OS). However, it was not significantly correlated. Jamali *et al.*^[28] divided groups on the basis of HbA1c 7% and tried to correlate them with CMT, and they found that CMT increased with increasing stages of diabetic retinopathy and bad glycemic control.

Limitations

Our study did not incorporate the duration of diabetes, which may also have individual effect on RNFL thickness. RNFLT and CMT of both eyes were evaluated at one point of time in all the participants in our study, but since the level of diabetes control and retinopathy are dynamic entities, these may subject to change with time. Our study did not keep the patients in long-term follow-up.

Conclusion

Hence, from the results of our study, it would be fair enough to not consider diabetic retinopathy solely as a microvascular complication of diabetes, when it has its roots to neurodegenerative processes as well. Who precedes whom is still under discussion, and research is in progress, but

till then, a conclusion drawn with certainty would be that like disease processes including migraine, glaucoma and pathological myopia, diabetic retinopathy also has a setting in of neuronal disturbance as is evident with RNFL thinning. Therefore, monitoring of RNFL thickness in recently diagnosed diabetics can help in determining the progress and severity of disease, even before the actual retinopathy sets in. Also, an increase in HbA1c is found to be correlated negatively with RNFL thickness, in diabetics with retinopathy; therefore, tight glycemic control can prevent RNFL thinning and similarly, RNFL thinning can reflect upon the glycemic control. RNFLT can thus be used as a probable non-invasive marker of retinopathy in diabetic patients prior to development of actual clinically evident retinopathy that may aid us in preventing future sight threatening complications. However, more studies are further needed to consolidate this finding. CMT increase in diabetic patients as found in our study has been seen in previous studies as well, and hyperglycemia-mediated alterations in vascular permeabilities of capillaries around fovea have a role in it.

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Ethical clearance

The study followed the tenets of the Declaration of Helsinki, and study approval was obtained from the Institutional Ethics Committee (IEC) of Institute Of Medical Sciences, BHU, Varanasi.

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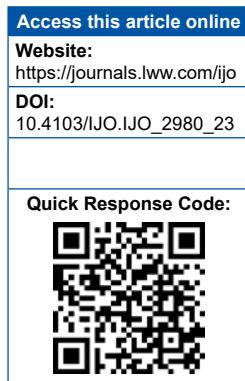
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Ophthalmologic profile of patients with systemic sclerosis

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Purpose: To study the ophthalmologic manifestations of systemic sclerosis (SSc) and its correlation with autoantibody profile. **Methods:** A cross-sectional study on 200 eyes of 100 consecutive adult patients diagnosed with SSc was performed at a tertiary care center in Northern India. The examination of ocular adnexa, anterior segment, and posterior segment with slit-lamp biomicroscopy, tear film break-up time (TBUT), Schirmer's II test, and choroidal thickness measurement by swept-source ocular coherence tomography was done. Autoantibody profile was available for 85 patients, and its statistical association with the ocular examination findings was analyzed. **Results:** In total, 100 patients (93 females and 7 males) were included. The mean age was 45.11 ± 11.68 years, and the mean disease duration was 6.93 ± 3.68 years. Meibomian gland disease was more commonly found in patients with the diffuse subtype of SSc ($P = 0.037$). Choroidal thickness was increased in 34% and decreased in 7% (reference range = 307 ± 79 μm) patients. Reduced TBUT, meibomian gland dysfunction, and eyelid stiffness had a statistically significant association with the presence of anti-Scl-70 antibody ($P = 0.003$, <0.0001 , and 0.004, respectively). These patients had ocular fatigue, foreign body sensation, and burning sensation. No significant association was noted with the presence of SS-A/Ro and SS-B/La antibodies. **Conclusion:** This study highlights the need for an active comprehensive ophthalmic evaluation. Approximately 75% of the patients in our cohort had ocular involvement to varying extent. An isolated presence of anti-Scl70 antibody was also found to have a positive association with dry eye disease.

Key words: Anti-Scl-70-autoantibodies, autoantibodies, dry eye disease, MG dysfunction, scleroderma, systemic



Systemic sclerosis (SSc) is a connective tissue disease usually affecting middle-aged (30–50 years of age) adults, with women being affected about three times more often than men.^[1,2] The literature discussing the ophthalmic involvement in SSc is limited, probably due to the rarity of the disease. In previous studies, various eye involvements, including dry eyes, reduced choroidal thickness, astigmatism, posterior subcapsular cataract, raised intraocular pressure, eyelid abnormalities, and retinal microcirculatory impairments, have been reported to be seen in association with SSc.

Szucs *et al.*^[3] categorized ophthalmic manifestations of SSc as primary, secondary, or coincidental. They hypothesized that generalized vasculopathy affects the retinal and choroidal vasculature, whereas fibrosis-related mechanisms involve the ocular adnexa and orbit. A cross-sectional observational study by Gomes *et al.*^[4] on 45 patients with SSc reported that eyelid skin changes occurred commonly

in the diffuse variant of SSc. This study also concluded that older age and a severe capillaroscopic pattern were associated with retinal microvascular changes, though they were not distinguishable from manifestations of systemic hypertension. Eye involvement may herald the onset or exacerbations of an immune reaction in connective tissue diseases. These may be in the form of intraocular inflammation and uveitis or eyelid, ocular adnexal involvement, and dry eye.

The limited availability of data on the prevalence and variety of ocular symptoms in patients with SSc, especially in the Asian population, has been an important lacuna in clinical knowledge. In addition, the association of autoantibody profile with ocular symptoms is not very well established in available literature probably due to the lack of a large study cohort. Thus, this study was designed to assess the ophthalmologic profile in patients with SSc and correlate the ophthalmic findings with the duration of disease, the subtype of SSc, and the autoantibody profile.

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Methods

A cross-sectional study was conducted at a tertiary care center in Northern India from July 2018 to June 2019. Consecutive adult patients presenting to the rheumatology specialty clinic of our hospital and who were diagnosed with SSc, as per the American College of Rheumatology Criteria for SSc,^[5] were taken up for a detailed ophthalmic evaluation. Patients with coexisting ocular diseases diagnosed before the onset of SSc, history of ocular trauma, uncontrolled diabetes mellitus, and uncontrolled systemic hypertension were excluded.

Data regarding age, gender, SSc subtype, disease duration, systemic involvement, and the presence or absence of ocular symptoms were recorded. The same ophthalmologist (SC) did a comprehensive ophthalmic examination of all the patients. Visual acuity was assessed on Snellen's chart, and the best-corrected visual acuity was documented. Intraocular pressure (IOP) was measured with Goldmann applanation tonometry. A disinfected prism was used for the process, and after putting topical anesthetic eyedrop, fluorescein dye was used for staining the eye. A slit beam with a cobalt blue filter was projected onto the head of the prism, and the patient was asked to look straight ahead. This made visualizing the fluorescein rings easier. Two fluorescein semicircles in the prism head were seen to meet and form a horizontal "S" shape, and the IOP readings were noted. The normal range for intraocular pressure (IOP) was taken as 10–20 mmHg.^[6] Slit-lamp biomicroscopy examination was performed for anterior segment evaluation (eyelids, conjunctiva, cornea, sclera, anterior chamber, iris, and lens) and posterior segment evaluation with a +90-D lens. Eyelid examination also included assessment for determining the presence or absence of meibomian gland dysfunction (MGD), eyelid telangiectasia, and blepharitis.^[7,8]

Dry eye disease (DED) evaluation also included tear film break-up time (TBUT) and the Schirmer test. A value of ≤ 10 seconds was considered as evaporative dry eye.^[9] Schirmer's test with topical anesthesia (Schirmer's II) was done, and patients with a value of ≤ 10 mm at 5 minutes were considered to be affected with dry eyes. Three measurements were taken, and a mean of all three was recorded.

Subfoveal choroidal thickness was measured on a swept-source optical coherence tomography device- Triton DRI (Topcon Corporation, Tokyo, Japan). A 5-line cross-scan centered on the fovea was analyzed. The choroid thickness was measured by caliper tool from the posterior edge of the retinal pigment epithelium to the choroid-scleral junction beneath the fovea by the same ophthalmologist (SC); the normal reference range was $307 \pm 79 \mu\text{m}$.^[10]

Modified Rodnan skin score (MRSS) was tested by the same rheumatologist (AC). This score measures cutaneous involvement in SSc by summing skin thickness scores of seventeen sites.^[11]

Autoantibody profile and antinuclear antibody (ANA) pattern analysis were done. Extracted nuclear antigen (ENA) of anti-dsDNA, nucleosomes, histones, SmD1, PCNA, Rib-P0, SS-A/Ro52kD, SS-A/Ro60kD, SS-B/La, CENP-B, Scl-70, U1-snRNP, AMA M2, Jo-1, PM-Scl, Mi-2, and Ku was done using line blot assay.

The patients were examined for the presence of systemic disorders such as pulmonary arterial hypertension and interstitial lung disease by the same rheumatologists (SKS and AC). Pulmonary arterial hypertension (PAH) was defined as the presence of precapillary pulmonary hypertension, including an end-expiratory pulmonary artery wedge pressure (PAWP) of ≤ 15 mmHg and a pulmonary vascular resistance of > 3 Wood units. Interstitial lung disease (ILD) was defined as a heterogeneous collection of distinctive lung disorders classified on the grounds of shared clinical, radiographic, physiologic, or pathologic factors. The pathogenetic sequence involves a series of inflammation and fibrosis that extends beyond disrupting the interstitial bed to changing the parenchyma (alveoli, alveolar ducts, and bronchioles).

The study protocol adhered to the Principles of the Declaration of Helsinki, and the institutional ethics committee's approval was obtained before the commencement (INT/IEC/2018/001492).

Patient and public involvement statement: The study participants were included in the study at the stage of recruitment after obtaining written and informed consent. The research questions were informed in the language best understood by the study participants. It was a cross-sectional design, and patients were asked the research questions and underwent intervention during the same visit; they were asked to report freely if they assessed that the burden of time required to participate in research was overwhelming. The results of the study will be discussed with participants and relevant wider patient communities to help them reveal the ophthalmic complaints to their primary physician so that timely examination and resolution can be planned.

Statistical analysis

A sample size of convenience was taken for the study. The statistical analysis was performed by SPSS v23 (IBM Corp.) software. The continuous variables were recorded and analyzed as mean \pm standard deviation and median \pm interquartile range. The categorical variables were analyzed in terms of frequencies and percentages. The independent sample *t*-test was used to compare groups having data with continuous distribution. Non-parametric tests such as the Wilcoxon-Mann-Whitney U test were used for data that did not have a normal distribution. The comparison of groups with categorical data was made using the Chi-square test. Fisher's exact test was used in the case of contingency tables having a frequency of less than 5 for more than 25% of the cells. The level of statistical significance was kept at $P < 0.05$. Logistic regression was used for analyzing the relationship of an outcome or dependent variable to one or more predictors or independent variables when the dependent variable was dichotomous, having only two categories.

Results

Demographics

In total, 100 consecutive patients with SSc were enrolled in this study. The majority (93) were females, and the mean age at presentation was 45.11 ± 11.68 years. The mean duration of illness was 6.93 ± 3.68 years. SSc was categorized as the diffuse subtype in 76 and limited in 24 patients [Table 1].

Systemic profile

Clinical signs and symptoms of dysphagia were present in 29%. Pulmonary arterial hypertension and interstitial

lung disease were noted in 25% and 57%, respectively. Treatment details included systemic corticosteroids in 65%, phosphodiesterase-5 inhibitors in 38%, hydroxychloroquine in 9%, and cyclophosphamide in 35% of the patients. These drugs were prescribed individually to the patients by the rheumatologist as per the need during the course of the disease.

Ocular profile

The mean best-corrected visual acuity (BCVA) in the study population was 0.02 on the LogMAR scale, which approximates between 6/7.5 and 6/6 on the Snellen chart scale. Seven patients had BCVA poorer than 6/9 and were noted to have cataractous changes in the lens. All patients had an intraocular pressure of ≤ 18 mmHg with a mean of 11.55 ± 2.23 mmHg.

Ocular symptoms

Of the 100 patients, 32 (32%) did not have eye involvement and were asymptomatic. Sixty-eight patients (68%) had ocular symptoms, including burning sensation (51), itching (48), foreign body sensation (42), and floaters (1). Most of the patients (78%) in our cohort had never consulted an ophthalmologist in the past for their ocular symptoms, likely because of more pressing systemic symptoms.

Eyelids and ocular surface

Eyelid stiffening was noted in 62 of 200 eyes (31%). Associated findings included a woody texture (on palpation), difficulty in upper eyelid eversion, and shallow fornix. Incomplete eyelid closure with lagophthalmos ≥ 2 mm was present in six out of 200 eyes [Fig. 1], and two patients developed exposure keratopathy with corneal scarring. Eyelid telangiectasia was noted in 118 eyes (59%). MGD was noted in 113 of 200 eyes (56.5%). These patients had variable findings of eyelid thickening and rounding of the eyelid margin, telangiectasia, plugging of orifices of meibomian glands, and blepharitis [Fig. 2]. All of them had itching, burning sensations, and foreign body sensations. The TBUT was abnormal in 104 eyes (52%). The Schirmer's II test scores were abnormal in 76 eyes (38%). The average Schirmer's II score was 15.73 ± 10.84 mm, and the TBUT value was 9.22 ± 3.81 seconds.

MGD was more prevalent in patients of the diffuse subtype than the limited subtype ($P = 0.037$). No statistically significant association was seen between the subtype of SSc and the prevalence of eyelid stiffness, TBUT, and Schirmer's test positivity ($P = 0.27, 0.13$, and 0.70 , respectively). Patients with eyelid stiffening were more likely to have MGD ($P = 0.001$). However, eyelid stiffening did not correlate with Schirmer's test score ≤ 10 mm and TBUT ≤ 10 seconds [Table 2].

There was no statistically significant association of qualitative Schirmer's test, TBUT, or MGD with disease duration. The average Schirmer's II test score was higher in patients with a disease duration of up to 5 years than in those with a disease duration of more than 5 years. However, the difference was not statistically significant ($P = 0.759$). Similarly, the average TBUT for those with a disease duration of up to 5 years was higher than for those with a disease duration of more than 5 years. However, the difference was not statistically significant ($P = 0.459$). One patient presented with subconjunctival hemorrhage; on systemic examination, the patient was noted to be hypertensive, which likely was the etiology for the subconjunctival hemorrhage.

Slit-lamp biomicroscopy

Conjunctiva: Conjunctival congestion was noted in 11 out of 200 eyes (5.5%). Three eyes had a pterygium; the duration of SSc in these patients was >7 years.

Cornea: Corneal changes in the form of superficial punctate keratitis were seen in nine eyes. Two eyes had corneal scarring in the inferior one-third secondary to lagophthalmos and exposure keratopathy. One patient (a 41-year-old female) was detected to have bilateral keratoconus on corneal topography after refraction indicated high astigmatism. She had a history of seasonal allergic conjunctivitis in childhood, managed with topical medication.

Iris: The iris architecture was normal and did not reveal transillumination defects in any patient.

Lens: Cataract was noted in 20 eyes (10 patients), and eight eyes had already undergone cataract surgery before the presentation. Fourteen eyes had nuclear sclerosis type of cataract, the mean age at presentation of patients with cataract was 54.6 ± 11.92 years, and the duration of the disease was 8.5 ± 4.24 years. Six eyes of three patients had posterior subcapsular cataracts; they presented with cataracts at an earlier age of 42 ± 14.42 years as compared with the nuclear sclerosis subtype group, although the difference was not statistically significant ($P = 0.147$). The average disease duration in the posterior subcapsular cataract group was 7 ± 4 years, comparable with the nuclear sclerosis subtype group ($P = 0.696$).

Uveitis: None of the 100 patients had any signs of active uveitis.

Posterior segment: Two patients had choroidal scars near the vascular arcades [Fig. 3a and 3b], but did not give any history of ocular symptoms suggestive of uveitis or choroiditis, likely

Table 1: Demographic features of the study population

Characteristics	Study population	
Average age (years \pm SD)	45.11 ± 11.68	
Gender	93:7	
Female:Male	76 (76%)	
SSc [#] subtype, n (%)	24 (24%)	
Diffuse	$76 (76\%)$	
Limited	$24 (24\%)$	
Average duration of disease (years \pm SD)	6.93 ± 3.68	

[#]Systemic sclerosis

Table 2: Association between eyelid stiffening and the presence or absence of meibomian gland disease, positive Schirmer's II test, and positive TBUT test

	Meibomian gland dysfunction present		Schirmer's test value ≤ 10 mm		TBUT* ≤ 10 sec	
	n	P	n	P	n	P
Eyelid stiffening						
Present	24	0.005**	15	0.197	24	0.177
Absent	33		24		14	

*TBUT: Tear film break up time, **Statistically significant

as the visual acuity was unaffected because of sparing of the macular area. One patient had bilateral pigment epithelium detachment near the inferior vascular arcade [Fig. 3c and 3d]. Angioid streaks were noted in one patient (case number 20, 46 y/M, duration of illness nine years; Fig. 4). His BCVA was 6/6 in both eyes (OU) with a refractive error of +1.00 DS OU, thus ruling out myopia. He also did not give any history of diabetes or hypertension.

Swept Source-Optical Coherence Tomography (SS-OCT): SS-OCT was performed to study the subfoveal central choroidal thickness (CCT). The average choroidal thickness was $344.13 \pm 73.32 \mu\text{m}$; the normal reference range was $307 \pm 79 \mu\text{m}$. The choroidal thickness was increased in 68 eyes (34%) and decreased in 14 eyes (7%).

OCT-angiography (OCT-A): OCT-A images were available for eight eyes (four patients) who also had Raynaud's phenomenon. The scans were performed in the winter when the cold is expected to exacerbate peripheral ischemia. The findings were within normal limits.

Modified Rodnan skin score (MRSS): MRSS was available for 84 patients. The score ranged from 0 to 46 with a median of 9 ± 15 and a mean of 11.78 ± 10.66 years. Eyelid stiffness was found to be associated with the MRSS score on univariate logistic regression analysis ($P = 0.0004$; odds ratio: 1.08; 95% confidence interval: 1.03–1.14), and no significant association was seen between MRSS and MGD, qualitative Schirmer's test, and TBUT ($P = 0.67, 0.81$, and 0.73, respectively).

Immunological profile

Antinuclear antibody (ANA): ANA test reports were retrieved from the rheumatology clinical database for all patients; out of these, 97 were positive (97% positivity rate).



Figure 1: Lagophthalmos (right > left) due to eyelid involvement in a 47-year-old female

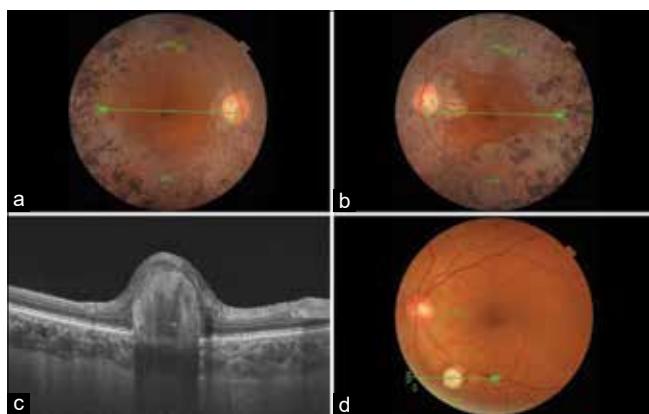


Figure 3: (a and b) Fundus photograph of a patient with retinochoroidal scarring. (c and d) OCT through the lesion and fundus photograph of the patient with pigmentary epithelial detachment

Autoantibody profile: The autoantibody profile was available for all the patients. The abnormal Schirmer's II test did not correlate with any specific antibody subtype. In contrast, decreased TBUT and MGD correlated with the anti-Scl-70 antibody ($P = 0.0001$ and 0.003, respectively). No statistically significant association of TBUT, MGD, or Schirmer's II test score was found with anti-SS-A/Ro60kD, SS-A/Ro52kD, and SS-B/La antibodies [Table 3].

Discussion

The information on the ophthalmologic profile in SSc is sparse and has been derived from case reports or studies with small sample sizes. Ophthalmic manifestations in SSc are characterized by marked heterogeneity. Our study on 200 eyes in 100 patients aims to provide a comprehensive ophthalmological profile of SSc. To the best of the authors' knowledge, the analysis of demographic, clinical, and serological data and their association with ophthalmologic manifestations has not been described in the literature.

A review on ocular manifestations of SSc by Tailor *et al.*^[12] reported eyelid skin abnormalities and keratoconjunctivitis sicca as the most common ocular manifestations. The involvement of eyelids and adnexa was noted in the form of eyelid stiffening in 31% of the eyes in our study. There was a high incidence of MGD (56.5%), eyelid telangiectasia (59%), reduced TBUT (52%), abnormal Schirmer's (38%), and eyelid stiffening (31%). The diffuse subtype of SSc was found to have MGD more frequently than the limited subtype. These patients were symptomatic of burning, itching, dry eye, and foreign body sensation.

The average TBUT score was affected more than the average Schirmer's II score, indicating that lipid tear film abnormality

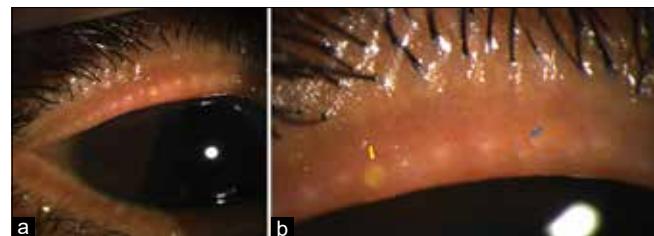


Figure 2: (a) Meibomian gland dysfunction, (b) Enlarged view of eyelid margins showing capping of the opening of the meibomian gland (yellow arrow) and telangiectasia (blue arrow)

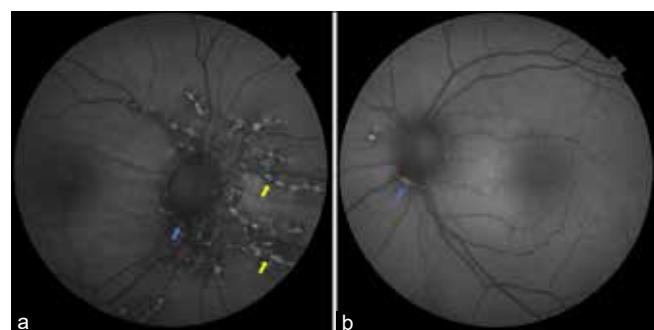


Figure 4: Red free fundus photographs of a 46-year-old male (a: Right eye, b: Left eye) showing the presence of a peripapillary ring of atrophy (blue arrows), with numerous, narrow, irregular streaks radiating in a centrifugal pattern (yellow arrows)

Table 3: Autoantibody profile and its association with the presence or absence of eyelid stiffness, meibomian gland dysfunction, qualitative Schirmer's II, and TBUT[#]

	Meibomian gland dysfunction present		Schirmer's test value <10 mm		TBUT <10 sec		Eyelid stiffness present	
	n	P	n	P	n	P	n	P
Disease duration								
<5 years (44)	23	0.50	15	0.475	22	0.722	13	0.780
>5 years (56)	33		23		30		18	
SSc[#] subtype								
Limited (n=24)	13	0.835	9	0.953	14	0.476	5	0.21
Diffuse (n=76)	43		29		38		31	
Autoantibody positive (n, %)								
Scl-70 (43, 50.58%)	39	0.003**	22	0.125	33	<0.0001**	22	0.004**
SS-A/Ro60kD (16, 18.82%)	13	0.387	8	0.339	12	0.05	7	0.346
SS-A/Ro52kD (13, 15.29%)	9	0.320	8	0.112	8	0.392	5	0.551
SS-B/La (1, 1.17%)	1	0.776	0	0.576	1	0.541	0	0.635
ds DNA (1, 1.17%)	1	0.776	0	0.576	1	0.541	1	0.364
Nucleosome (1, 1.17%)	0	0.223	0	0.576	0	0.458	0	0.635
Histones (1, 1.17%)	1	0.776	1	0.423	1	0.541	1	0.364
SmD1 (4, 4.7%)	1	0.033**	1	0.432	1	0.248	1	0.535
PCNA (4, 4.7%)	3	0.201	1	0.432	3	0.373	2	0.464
CENP-B (3, 3.52%)	2	0.536	1	0.615	0	0.092	0	0.251
U1-snRNP (7, 8.23%)	2	0.005**	3	0.637	2	0.154	0	0.035**
AMA M2 (1, 1.17%)	1	0.776	1	0.423	1	0.541	0	0.635
PM Scl 9 (2, 2.35%)	2	0.600	0	0.329	0	0.207	1	0.599

[#]Tear film break-up time, ^{*}Systemic Sclerosis, **Statistically significant

is the more prominent cause of DED. DED is a multifactorial condition that affects and results from both – abnormalities of tear production and the ocular surface. Inflammation in CTD has been shown to affect both the lacrimal gland (aqueous deficiency DED) and the eyelids (lipid tear dysfunction DED), resulting in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface.^[13] Gurlevik *et al.*^[14] demonstrated that patients with Sjogren's syndrome were at a higher risk of meibomian gland loss, which caused severe dry eye symptoms due to evaporative DED. Pflugfelder *et al.*^[15] hypothesized that conjunctival epithelium may be a direct immunological target in CTD leading to lipid tear film dysfunction. SSc patients show lipid tear dysfunction related to the severity and duration of the disease due to ongoing inflammation and subsequent atrophy of the meibomian glands.^[16] Meibomian glands are sebaceous glands in the eyelids and contribute to lipid secretion, forming the superficial layer of the tear film and thus delaying its evaporation. A diffuse dysfunction of the terminal ducts of these glands results in quantitative abnormalities in its secretions, resulting in evaporative dry eyes and symptoms such as ocular irritation. MGD, eyelid telangiectasia, and reduced TBUT were high in our study cohort, thus indicating that lipid dysfunction is the cause of DED symptoms. However, there was no association between MGD, qualitative and quantitative Schirmer's test, and TBUT with disease duration or the MRSS score.

Sequelae of ocular surface inflammation and DED-like conjunctival congestion (5.5%), superficial punctate keratitis (4.5%), pterygium (1.5%), and corneal scarring secondary to exposure keratopathy (1%) were noted in our

study. Corneal ectasia in the form of keratoconus, diagnosed on corneal topography, was noted in one patient (1%). However, the patient had a history of seasonal allergic conjunctivitis in childhood. Corneal ectatic disorders, such as keratoconus may be associated with SSc.^[17] Though these diseases are non-inflammatory, progressive ectasias, strong associations with various immune-related conditions have been described.^[17,18]

Cataractous lens changes may coexist (age-related nuclear sclerosis variant) or manifest as a result of corticosteroid therapy (posterior subcapsular (PSC) variant). Gomes *et al.*^[4] reported the presence of cataracts in 42.2% of patients with SSc in a cross-sectional observational study of 45 patients. Aging and steroid treatment were presumed to be the causes of cataracts in their research. In our study, cataract was noted in 20 eyes of 10 patients: 14 eyes had nuclear sclerosis, and six had a posterior subcapsular type cataract. The latter is known to be associated with systemic steroid use and presents at an earlier age.^[19] A similar pattern was noted in our study, with the mean age of patients with posterior subcapsular cataracts being 42 ± 14.42 versus 54.6 ± 11.92 for those with nuclear sclerosis type of cataract. Eight patients had already undergone surgery for cataract extraction before presentation to our center; thus, the type of cataract could not be ascertained in these patients.

The adverse effects of other drugs used in the treatment of SSc are well documented in the literature. Phosphodiesterase inhibitors are known to cause defects in color vision, light perception, transient alterations in electroretinogram, conjunctival hyperemia, and photophobia.^[20]

Hydroxychloroquine is known to cause retinopathy in the form of bull's eye maculopathy, and corneal toxicity in the form of intraepithelial deposition of the drug in the cornea.^[21,22] However, none of the patients in our study group showed these adverse effects.

In our study, none of the patients had raised IOP or optic nerve changes suggestive of glaucomatous optic neuropathy. However, glaucoma in patients with SSc has been reported previously.^[4]

The evidence of retinal involvement in SSc is equivocal; retinal and choroidal changes resulting from associated systemic hypertension have been reported. Parafoveal telangiectasias are a part of the limited SSc variant- the CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia); their presence warrants an evaluation for SSc.

None of the patients in our study demonstrated parafoveal telangiectasias. Choroidal thickness was increased in 68 eyes (34%) and decreased in 14 eyes (7%). This did not statistically correlate with the presence of Raynaud's phenomenon. Coşkun *et al.*^[23] compared the choroidal thickness in 46 patients with scleroderma with 31 controls. In contrast with our findings, subfoveal CCT was significantly reduced in the scleroderma group. The assessment of the status of choroidal perfusion by fundus fluorescein angiography (FFA) might help provide a clue about the reason for such a contradiction. A comparative analysis of choroidal perfusion with a control group might provide a better insight.

In our study, OCT-A was performed in eight eyes of four patients who also demonstrated Raynaud's phenomenon. The scans were performed in the winter when the cold is expected to exacerbate peripheral ischemia. The findings were within normal limits and did not reveal retinal vascular abnormalities. Rothe *et al.*^[24] studied the retinal microvascular blood flow by using OCT-A of 24 eyes of 12 patients with SSc without renal involvement. They compared the same number of age-matched controls. Though not statistically significant, they provided a proof of concept and demonstrated retinal microvasculature involvement in OCT-A even in ophthalmologically asymptomatic patients. In addition, the best-corrected visual acuity correlated significantly with perfusion in the superficial and deep retinal capillary plexus.

Angiod streaks result from fractures in Bruch's membrane and radiate from the optic nerve head in a centrifugal pattern, along force lines exerted by extraocular muscles. Angiod streaks are bilateral, irregular lines deep to the retina arranged in a centrifugal pattern coming out from the optic disc. They are typically configured as radiations from a ring-like area of peripapillary pigment mottling.^[25] One patient in our study had angiod streaks. Refraction ruled out associated myopia, and there were no other systemic diseases except SSc. Involvement was asymmetric, with the right eye showing more prominent changes [Fig. 4]. To the best of the authors' knowledge, this study is the first report of angiod streaks associated with SSc. We propose that the SSc-associated fibrosis process may weaken the ocular coats, including the Bruch's membrane, predisposing it to stretching. The second insult may result from the choroidal vasculopathy associated with SSc.

The autoantibody profile and its association with systemic symptoms such as Raynaud's phenomenon in SSc have been extensively described in the literature.^[26,27] However, the association between autoantibody subtype and ophthalmic manifestation has not been reported well. Szucs *et al.*^[3] reported a weak association between laboratory parameters and ocular findings. In their study, there was a significant difference between SS-A positivity and tear parameters and substantial (but not statistically significant) differences between objective signs and subjective symptoms of DED in SS-B positive and negative cases. We correlated the autoantibody subtype with the ocular findings. In our study, decreased TBUT, MGD, and eyelid stiffening correlated with positivity for anti-Scl-70 antibodies. No statistically significant association was seen with SS-A/Ro60kD, SS-A/Ro52kD, and SS-B/La antibodies, suggesting that patients with isolated Scl-70 positivity should also be screened for dry eyes.

A prospective study with serial monitoring of ophthalmic findings may help formulate a more reliable, measurable ophthalmic score that eventually monitors disease activity. Though this study has a large sample size of 200 eyes of 100 patients diagnosed with SSc with a diverse ophthalmological profile, the main limitation of this study is the absence of an age-matched control group. As with cross-sectional observational studies, there was data heterogeneity, which may mask some associations and conclusions.

Conclusion

Ocular manifestations in SSc are heterogeneous. This study provides a descriptive ophthalmic database for 200 eyes of 100 patients with SSc. DED of both the evaporative and aqueous deficient types were prominent, with a high incidence of evaporative variant, MGD, eyelid telangiectasia, reduced TBUT, and abnormal Schirmer's II scores. These manifestations also correlated with isolate antibody Scl-70 positivity. This study highlights the need for a comprehensive ophthalmic evaluation in patients of SSc, even without ocular symptoms.

Limitations of the study

Though the authors attempted to conduct a thorough study with definitive answers, some aspects may have remained unexplored, such as the study of conjunctival fluorescein staining pattern, measurement of interpalpebral aperture and lid length, and correlation of ocular findings with the duration of systemic disease on and off treatment.

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To compare horizontal strabismus deviation as assessed from photographs with that in the strabismus clinic using the prism bar

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Purpose: To compare the deviation in cases of horizontal strabismus as assessed from photographs with the measurements as obtained in the strabismus clinic. **Methods:** After obtaining informed consent, we recruited subjects with manifest horizontal strabismus. We took a frontal flash photograph from a distance of 50 cm using smart-phone-based cameras with the flash light vertically aligned with the lens. After projecting the photograph on a laptop and using a vernier caliper, we measured the horizontal corneal diameter of the non-strabismic eye and the decentration of reflex in the strabismic eye taking limbus as the reference point. We converted these values to degrees by using a conversion factor of 7.5°/mm and further to prism diopters (PD) by the standard mathematical formula $100 \times \tan\theta$. **Results:** We included 74 subjects aged between 5 and 40 years with manifest horizontal deviation from 20 to 85 PD. We found a statistically significant correlation of 82.6% (P value < 0.001) between the clinic and photographic measurements. Agreement analysis suggested that the photographic measurements measured on average 7 PD less (95% confidence interval: 4.6 to 9.2) than clinical measurements along all values of misalignment, although the difference between the two methods decreased as the quantum of deviation increased. Linear regression revealed an r^2 of 68% and provided a predictive equation to derive clinic equivalent measurements from photographic estimates. **Conclusion:** We believe our simple method provides robust evidence that a photographic estimation can provide the basic information of the size of the deviation to plan possible surgeries, especially in situations of a tele-consultation. This is an easy approach to both understand and master and should form the armamentarium of most orthopticians and strabismologists.

Key words: Corneal light reflex, flash photograph, smartphone camera, strabismus

Strabismus involves a misalignment of the eyes, which apart from cosmetic issues is often accompanied by amblyopia, and both contribute to adverse psycho-social and visual experiences, often hampering education, eventually affecting development and maturity of growing children.^[1-3] Timely treatment, which may include spectacles, prisms, anti-amblyopia patching, and surgery, either in combination or in isolation, may abort many problems.

Strabismus is measured in prism diopters (PD) by an orthoptist or eye surgeon using prisms, either as bars or free. Three approaches are commonly employed:^[4-7] the prism and alternate cover test (PACT), the modified Krimsky test if an eye has poor fixation, and the Hirschberg test, which estimates the deviation in degrees the light reflex is off-centered in the deviating eye.

Attempts had been made to estimate the deviation from clinical photographs,^[8-10] but the coronavirus disease 2019 (COVID-19) pandemic provided further impetus to such options. These methods are simple, use geometric concepts and trigonometry, and need only minimal training. In the digital world, with the ubiquitous smart-phone cameras, good-quality snaps are easily obtained and shared. An ability

to estimate ocular deviation using flash pictures would help in pre-operative planning. These could be boosted by using smartphone apps like 9-Gaze,^[11] which allow eyes to be snapped in the nine-directions of gaze, and Snellen app, which permits a reasonable assessment of vision in children at home.^[12]

Based on an earlier preliminary study done at our center (unpublished, Sharma R, personal communication) on 40 strabismus patients, we devised a simple method to quantify horizontal strabismus by assessing photographs taken with a flash and evaluating the eccentricity of the corneal reflex. This was then compared with the formal measurement of the magnitude of strabismus in the clinic using prisms. We subsequently looked for how well they compared: by performing correlation and agreement.

Methods

After obtaining ethical clearance from the institutional review board of our university, we included consenting patients (or

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children whose parents gave consent) with manifest horizontal strabismus for obtaining frontal photographs. Children less than 12 months of age and patients who had intermittent horizontal deviation or were non-cooperative for the clinical measurement and/or photography were excluded. Our method comparison study was conducted at the Strabismus Clinic of our institute over a period of August 2020 to December 2022.

Using the PS: Power and sample size calculator,^[13] we calculated the sample size needed for the correlational analysis using an alpha error as 0.05 and a power of 0.80 and assuming a correlation between the two methods to be 50%. The calculated sample size needed is 29 pairs. To calculate the sample size for the Bland Altman plot, we used MedCalc for Windows, version 19.4 (MedCalc Software, Ostend, Belgium).^[14] With expected mean of differences kept as 3.5 PD (unpublished data, Sharma Richa, Personal Communication), the standard deviation as 5 PD, and the maximum allowed difference between methods as 16, the sample size was found to be 85 pairs. Though we recruited a larger sample size of 100 patients, the final analysis was performed only on 74 pairs due to incomplete data [Fig. 1].

In our study, we used flash photographs taken using either standard cameras or smart-phone-based cameras with the flash light vertically aligned either below or above the lens, from a distance of 50 cm, with the patient directed to look into the camera lens. Only digital copies were provided to the assessor, who was masked to the clinic measurement done by a trained orthoptician, of more than a decade of experience in the orthoptic clinic.

We adopted the following method to quantify strabismus measurements from the photographs. We assumed the normal horizontal (white to white) corneal diameter to be 11.7 mm.^[15] Using a laptop, we zoomed in till the ocular landmarks were well discernible without the pixels breaking up. We physically measured the actual horizontal corneal diameter on the eye which was facing the camera and had the flash reflex in the corneal center using the vernier caliper with a digital display providing 1/10th of a mm precision. From these two, namely, the assumption and the photograph measurement, we derived a magnification or minification factor. For instance, if the measure of corneal diameter on the photograph was A mm, then A mm (on the photograph) ≈ 11.7 mm (actual), and therefore, each 1 mm (in the photograph) = 11.7/A mm (actual). Once the off-set

of the corneal reflex was ascertained in the deviated eye, we arrived at an estimate of its deviation as shown.

It is established knowledge that 1 mm of ocular rotation implies an angular shift of 7.5 degrees (the average of Hirschberg and Krimsky values)^[4,5] for an average-sized globe of 23 mm axial length, while assuming the eye to be a perfect sphere. Next, on the strabismic eye, we measured the horizontal distance from the corneal reflex to the nearest limbus. A symmetrical measurement was made in the non-strabismic eye: the difference providing us a measure of deviation in mm on the photograph. This was then converted to actual by multiplying by 11.7/A to get the actual difference in mm, and the value so obtained was converted to degrees by multiplying by 7.5 and then to PD by the standard mathematical formula $PD = 100 \times \tan\theta$ (degrees).^[16]

Once we estimated the strabismus from photographs in PD, we obtained the clinic record which was obtained using the modified Krimsky test where needed and the PBCT where that was possible. We used the near measurement for comparison with the photographs since their distances were a better match. After obtaining the paired data, we used JASP 0.16.0.0^[17] and Medcalc^[14] to perform a Pearson's correlation and a paired *t*-test and looked for agreement using the Bland-Altman graphic method. Additionally, we performed exploratory logistic regression analysis to derive a relation for prediction of clinical values from the photographic measurements.

Results

We included 74 patients with manifest horizontal strabismus, with 45 exotropes and 29 esotropes. Of these, 43 (58.1%) were males and 31 (41.9%) were females. The mean (SD) age was 14 (6.9) years and ranged from 5 to 40 years. The mean (SD) best corrected visual acuity (BCVA) of our subjects was 0.24 (0.41) logMAR in RE and 0.36 (0.58) in the LE. The logMAR BCVA ranged from 0 to 2.3 in RE and from 0 to 3 in LE [1].

The mean (SD) deviation on Hirschberg corneal reflex was 24 (10) degrees, ranging between 10 and 45. The clinical measurements of angle of deviation in PD ranged between 20 and 85 with a mean (SD) value of 44 (15), while the photographic measurements in PD were between 11 and 81 with a mean (SD) value of 37 (17) [Table 1].^[18] In the clinic, we performed the Krimsky test on 21 patients, while 53 were measured by the prism and alternate cover test.

Correlational analysis

We found a statistically significant correlation of 82.6% (Pearson's *P* value <0.001) between the clinic and photographic measurements of 74 subjects in our sample. The heatmap showed that most of the clinical and photographic measurements in our study lay in the zone of 20 to 35 PD [Fig. 2].

Comparative analysis

We compared the measurements obtained by the photographic method with that of the clinical measurements done by performing alternate prism cover test.

We did the paired *t*-test to evaluate the difference of mean measurement obtained by each method. Compared to the clinic method, the photographic method measured on average less by 6.9 (± 9.9) PD; 95% CI: 4.7 to 9.3 PD; *t* (73 df) = -6.03; *P* value: <0.001. While being statistically significant, the small difference may not be of much clinical importance.

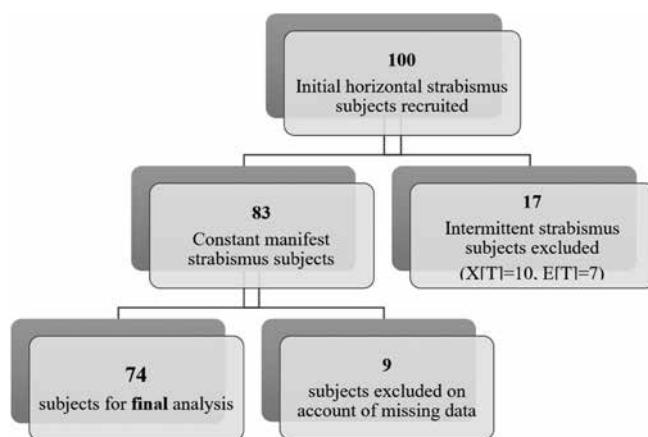


Figure 1: Flowchart of subjects flow in the study

Table 1: Descriptive data for demographic and study parameters of 74 subjects in our study

Statistical Variables	Age (years)	BCVA (RE) (logMAR)	BCVA (LE) (logMAR)	HBCR (Degree)	Clinical (PD)	Photographic (PD)
Mean	14.4	0.2	0.4	24.3	44.054	37.065
Std. Deviation	6.9	0.4	0.6	10.9	15.432	17.621
Minimum	5.0	0.0	0.0	10.0	20.000	11.340
Maximum	40.0	2.3	3.0	45.0	85.000	81.500

Note: LogMAR 2.3=Perception of hand movement and LogMAR 3=No light perception.^[18]

We then looked for agreement between the measurements, which revealed a similar difference and 95% CI: see Fig. 3. The regression line slopes gently to the right and up toward 0, the line of no difference, indicating that the difference between the two measurements decreases with the increasing size of the deviation, that is, beyond 40 PD [Fig. 3].

Linear regression analysis suggests that 68% of the variation of the clinic measurement can be explained by the variation of the photographic measurement ($r^2: 0.68$) and yields a prediction formula to compute the clinical measurement from that obtained by the photographic estimate: [Fig. 4].

$$\text{Clinical measurement (PD)} = 0.7 * \text{Photographic estimate (PD)} + 17$$

Discussion

In our prospective method comparison study on 74 subjects, from 5 to 40 years, with manifest horizontal deviation between 20 and 85 PD, we found a statistically significant correlation of 82.6% (P value < 0.001) between the clinic and photographic measurements. Although compared to the clinic measurement the photographic one was statistically significantly less (-6.98 ± 1.15 PD; paired t -test P value < 0.001), it does not seem to be a clinically meaningful difference.

Agreement analysis reinforced this difference but further suggested that the difference between the two methods decreased as the quantum of deviation increased [see Fig. 3]. A possible explanation lies in the fact that with the increasing quantum of deviation, the corneal reflex lies closer to our reference point, that is, limbus, and the distance between these two becomes more linear instead of curvilinear and therefore more likely to be correctly estimated in a two-dimensional picture. While the correlation was excellent and significant, the linear regression yielded a simple formula to calculate the equivalent clinic measurement from the photographic estimate [Fig. 4].

In a somewhat similar effort, Yang *et al.*^[19] in 2011 used a 3D strabismus photo-analyzer on 100 subjects in Japan (32 exotropes, 30 esotropes, and 38 orthotropic) for analyzing binocular alignment using full face photographs. Though the authors stated their method as test-retest reliability, they seem to test the agreement between their method and the Krimsky test through the Bland–Altman Plot akin to us. They concluded that there was no overall tendency for any specific test result to be higher or lower than the other test value (the half-width of 95% limit of agreement being 2.8° or 4.9 PD). Prism cover test (PCT) was performed on a few of their subjects ($n = 33$), but the authors did not provide any comparative data for this. However, in our study, we have drawn conclusions based on clinical measurements obtained by performing PCT, which

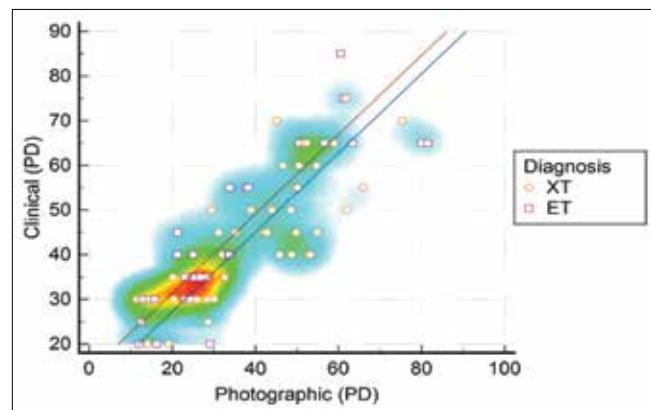


Figure 2: Heatmap correlation plot for clinical and photographic measurements of Exotropes (XT) and Esotropes (ET) in our study

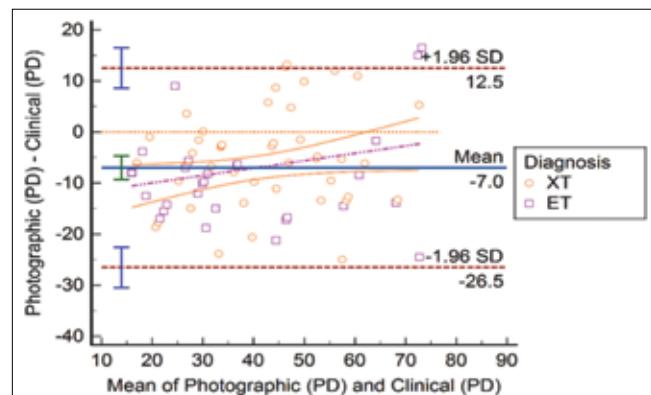


Figure 3: Bland-Altman agreement plot between clinical and photographic method

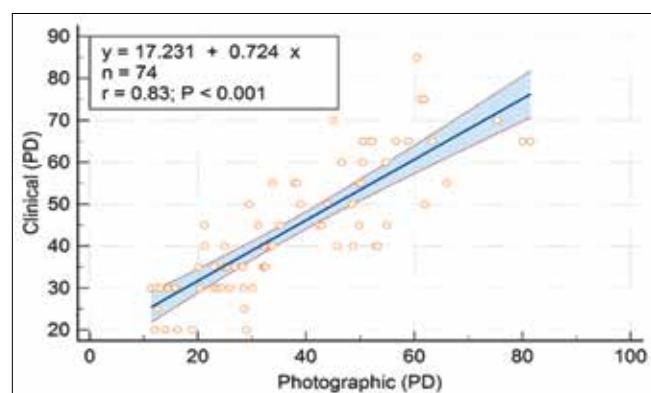


Figure 4: Scatter diagram with regression line to predict the clinical measurements by using the photographic technique

is the gold standard for assessing binocular misalignment. Unlike our study, they had two different observers and also deduced inter-observer variability, which was found to be good (within 6 PD). On eyeballing the agreement analysis plots, the variation of values between the two methods looks similar to our study, though they have plotted the measurements in degrees while we have used PD. Also, going by the description of their equipment and software, it appears to be costly and not easily accessible in a developing country like ours wherein a simple smartphone camera like the one described in our study would prove to be more useful. We assume that since our data were not adjusted for angle κ as opposed to theirs, it might be a reason for some of the variation found between the two methods in our study.

Tengtrisorn *et al.*^[20] conducted a cross-sectional study in Thailand enrolling 33 horizontal strabismus subjects, 14 males and 19 females, with a mean age of 16.42 ± 15.64 years. Having excluded five intermittent tropias, their sample had 18 esotropes and 11 exotropes. The remaining 28 subjects [sic] were photographed for analysis by Photo-Hirschberg testing using computer software. The corneal light reflex displacement, converted into PD, was compared to the angle of deviation measured with PACT, and the data so obtained were analyzed using Pearson correlation. The correlation between the two methods was found to be moderately strong for 1 m, the correlation coefficients (r) of the angle of deviation for ET and XT being 0.443 and 0.637, respectively, while in our study, the value of r was found to be 0.826 for ET and XT overall. In their study, the error while using Hirschberg's ratio was minimized by using different conversion factors for near and distance as derived by previous research done by the same authors in 2015,^[21] while in our study, we used the traditional conversion factor derived by Hirschberg and Krimsky and analyzed photographs taken only at near (50 cm), which is largely the distance of face-to-face interaction considering the cosmetic aspect of strabismus correction. The sample size in this study was quite small ($n = 28$) as compared to our study ($n = 74$). Importantly, it is not the correlation but the agreement that should have been tested as was done in our study.

In another study done in Thailand by Duangsang S *et al.*,^[22] they enrolled 104 subjects including 51 females and 53 males, with a mean age of 18.35 years (range of 17.17 to 19.84 years), to calculate the range of central corneal light reflex ratio (CCLRR), which is the ratio of the summed distances from the inner corneal margins to the corneal light reflex of the right and left eyes to the horizontal diameter of the right and left eyes, as estimated using digital photography with the camera flash as the light source. The alternate prism and cover test at near/distance revealed orthophoria in 44 (42.3%)/99 (95.2%), exophoria in 59 (56.7%)/4 (3.8%), and esophoria in one (1%). The mean CCLRR (+ SD) from near/distance measurements was estimated to be 0.468 (0.012)/0.452 (0.019). They used a digital camera equipped with a telephoto lens with a flash attachment placed directly above the lens that was used to obtain corneal light reflex similar to that in our study. Interestingly, the authors considered that the use of the ratio from both eyes may be a superior approach, compared to the methods used in previous studies, because the ratio is not affected by magnification of the images, variation of the corneal diameter, or slight deviations in the position of the subject's face. In our view, it does seem a

complicated way of doing something and since uncertainty still exists since the horizontal corneal 'diameter' would anyway be in error when eyes would be deviated.

Conclusion

At present, the alternate prism cover test is the gold standard to measure the quantum of deviation in patients with strabismus. However, this is time-consuming, needs special sets of prisms and patient co-operation, and needs a level of expertise on the part of the orthoptician.^[20] Choi *et al.*^[23] reported that compared to measurements with the prism and alternate cover test, even strabismus sub-specialists showed under-estimation with the Hirschberg method, and over-estimation with the Krimsky method, by at least 10 PD.

In our study, we have explored the possibility of estimating the deviation through digital photographs and compared it with the clinic measurements. We believe our simple method provides robust evidence that a photographic estimation can provide the basic information of the size of the deviation, especially in case of a tele-consultation.

Clearly, real-time clinic measurements with prisms using accommodating targets for both distance and near would remain the basis to decide the surgical plan and dosage: This provides solid measurements, including near-distant disparity, and identifies and grades the alphabet phenomena, along with over- and under-actions. Our simple photographic estimate not just correlates well with the clinic measurements, and that is understandable, but the agreement is off by less than a mere seven degrees. Complemented with the 9-gaze pictures, now available on smartphone apps, we believe that this approach can find a place for a preliminary discussion of a tentative surgical plan: whether more than one surgery is likely or whether two muscles or more are likely to be needed, along with the likely costs. We propose that a photo-tele-ophthalmology approach could be a way for first contact between patients of strabismus and the surgical team, providing estimates which allow more informed tele-consultation, and may also reveal gross under- or over-corrections post-operatively. We recommend that strabismologists and orthopticians consider it as a reasonable option at first tele-contact.

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Pencil push-up training compared with binocular vision training in the management of slight post-operative under-correction of intermittent exotropia: A prospective study

Desheng Song*, Tao Pan*, Lu Zhou, Jiaona Jing

Purpose: This study aims to compare the effectiveness of pencil push-up training and binocular vision training in treating post-operative mild under-correction in patients with intermittent exotropia. **Methods:** A prospective cohort study was conducted, including patients who underwent surgery for intermittent exotropia at Children's Hospital of Nanjing Medical University between June 2022 and January 2023 and experienced post-operative mild under-correction (-8 $^{\circ}$ to -15 $^{\circ}$). Patients were divided into two groups: pencil push-up training group and binocular vision training group. All patients underwent measurements of exodeviation and stereoacuity at distance and near, sensory fusion, and fusion convergence amplitude. The data were analyzed using independent sample t-tests, repeated measures analysis of variance, and Chi-square tests. **Results:** There were no statistically significant differences in exodeviation at distance and near between the two training groups before the training. After 6 months of training, the exodeviation at distance and near achieved a significant decrease in both groups ($P < 0.05$), and the pencil push-up training group showed a similar distance and near exodeviation compared to the binocular vision training group ($t = 1.58$, $P > 0.05$; $t = 0.43$, $P > 0.05$). After 6 months of training, the binocular vision training group exhibited significantly superior stereoacuity and fusion convergence amplitude compared to the pencil push-up training group ($P < 0.001$). **Conclusion:** Both pencil push-up training and binocular vision training are effective in reducing exodeviation in patients with post-operative mild under-correction of intermittent exotropia. However, binocular vision training demonstrates superior efficacy in restoring stereopsis and fusion convergence amplitude compared to pencil push-up training.

Key words: Intermittent exotropia, pencil push-up, vision therapy

Intermittent exotropia is the most prevalent form of strabismus in clinical practice, representing 50% to 90% of all exotropia cases.^[1] Surgical intervention constitutes the primary approach for managing this disease. The occurrence rate of residual and recurrent exotropia after surgery ranges from approximately 25.8% to 35.5%,^[2-5] significantly impacting the long-term effectiveness of surgical treatment. Post-operative deviations in the range of -8 $^{\circ}$ to +5 $^{\circ}$ (+ indicating esotropia, - indicating exotropia) are indicative of successful IXT surgery.^[6] Surgical intervention is recommended when the angle of exotropia is equal to or greater than 15 $^{\circ}$. Exodeviations between -8 $^{\circ}$ and -15 $^{\circ}$ following surgery represent a transitional phase between successful surgery and the potential need for reoperation, often requiring a secondary procedure. Clinical observations indicate that a second surgery not only imposes physical and psychological burdens on the affected child and their family but also places a psychological burden on the operator. Additionally, research suggests that binocular visual function plays a critical role in preserving post-operative eye alignment,

and the recurrence of IXT surgery is mainly caused by a decrease in binocular vision function. If the post-operative exodeviation is less than 15 $^{\circ}$, appropriate binocular visual training can be provided to enhance the child's control over exotropia and potentially obviate the need for further surgery.

Common methods of visual function training in clinical practice include pencil push-up training and hospital-and-home-based binocular vision training. Pencil push-up training is straightforward to perform, but the efficacy lacks empirical support. Conversely, hospital-and-home-based binocular vision training has demonstrated clinical effectiveness.^[7,8] However, this training method is time-consuming and challenging to perform. The present study aimed to comparably analyze the outcomes of pencil push-up training and binocular vision training in 162 cases of mild under-correction exotropia following IXT surgery at the Ophthalmology Department of Children's Hospital of Nanjing Medical University from June 2022 to

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January 2023. Our investigation observed the therapeutic effects of these two training methods on patients with post-operative exodeviation ranging from -8° to -15° , aiming to assess the potential of promoting pencil push-up training as a standard training approach.

Methods

Objectives

The study aimed to include individuals who met the following criteria: 1. Age between 5 and 18 years. 2. Best corrected visual acuity (BCVA) ≥ 0.8 and anisometropia $\leq 1.50\text{D}$. 3. Stereopsis ≤ 3000 seconds of arc. 4. Basic or convergence insufficiency-type IXT with residual exodeviation of 8° to 15° at distance or near. 5. Willingness to strictly adhere to training requirements and cooperate with all examinations. 6. Absence of functional or organic ocular diseases affecting binocular vision.

Exclusion criteria involved: 1. Constant exotropia. 2. Concurrent dissociated vertical deviation (DVD), A or V patterns, paralytic or restrictive factors, and nystagmus. 3. Moderate to severe amblyopia.

A total of 162 patients who had previously undergone IXT surgery at our hospital and experienced under-correction were included in the study. Informed consent was obtained from a parent and/or legal guardian of all subjects. This study was approved by the Nanjing Children's Hospital Review Board and complied with the principles outlined in the Declaration of Helsinki.

Pre-operative examinations

Prior to training, all patients underwent a series of examinations, including BCVA, cycloplegic autorefraction, slit-lamp biomicroscopy, indirect ophthalmoscopy, ocular motility, presence of amblyopia, lateral incomitance, prism and alternative cover test (monocular occlusion for 1 hour), and evaluation of distance and near stereopsis, sensory fusion and fusion convergence amplitude. Deviation measurements were conducted using the prism and alternate cover test. Near deviation measurements were performed with the target placed 33 cm in front of the eyes, while distance deviation measurements were conducted with the target positioned at 6 m. These measurements were carried out by the same examiner. Amblyopia was defined as a difference of two or more lines in terms of the BCVA between each eye. Patients were considered to have a lateral incomitance if exotropia shows a difference of at least 5 PD between central and lateral fixation. Distance stereopsis was measured using a random dot stereogram. Stereopsis ≤ 80 seconds of arc was considered normal foveal stereopsis, while values >80 seconds of arc were classified as abnormal. Participants who did not pass the 800 seconds of arc stereogram but passed the stereoblind screening test were recorded as having 3000 seconds of arc. Near stereoacuity was evaluated using a Titmus stereo test. Sensory fusion was tested using four Worth dots at 40 cm and 5 m fixation. The amplitude of fusional convergence was assessed using a 1 to 40 PD fixed horizontal prism bar both at distance (3 m) and then near (1/3 m).^[9]

Training methods

The training methods used were as follows:

Pencil push-up training group: Patients held a pencil between their eyes, with the tip positioned at one arm's length from the root of the nose at the same height as the root. They performed repetitive movements from far to near until diplopia occurred and then returned to the original position. This exercise was performed for 20 cycles, constituting one set. Three sets were completed consecutively, taking approximately 15 minutes. The exercise was conducted twice daily, 5 days a week, for a duration of 6 months.

Binocular vision training group: Patients received a 60-minute session of in-hospital training once a week administered by an optometrist. Additionally, they performed 15 minutes of home-based training five times a week. The training duration was also 6 months. The specific details of in-hospital and home-based training were based on references,^[10] and individualized training guidelines were provided to each patient. During in-hospital treatment, patients practiced under supervision for 4–5 periods following the standard protocol provided by the therapist.

Follow-up

Follow-up examinations were conducted at 1, 3, and 6 months to measure deviation and stereopsis at near and distance, sensory fusion, and fusional convergence amplitude. Post-operative ocular alignment was classified as follows: post-operative horizontal strabismus angle ranging from -8° to $+5^\circ$ (including -8° and $+5^\circ$) is considered satisfactory, exodeviation $>8^\circ$ indicated under-correction, and esodeviation $>5^\circ$ indicated over-correction.

Adherence to the treatment plan

Parents were responsible for recording the daily time of home-based training on a provided calendar and evaluating the patient's compliance with the treatment plan. Weekly reviews were conducted to confirm completion of the exercises. For patients showing poor compliance, interventions such as alternative rewards were employed.

Statistical methods

A prospective cohort study was conducted to analyze the data using SPSS 20.0. The observed data primarily consisted of measurement data, expressed as mean \pm standard deviation, following a normal distribution. For the multi-timepoint observation data, two factor repeated measures ANOVA was utilized, along with the Chi-square test to compare the differences in the rates of attaining distant stereopsis and sensory fusion between the two groups. When comparing within groups, the adjusted significance level is $P_1 < 0.05/3 \approx 0.017$, and the significance level for other comparisons is $P < 0.05$.

Results

Basic information

A total of 162 patients who completed their follow-up were enrolled in this study, with 78 assigned in the pencil push-up training group (48 males and 30 females) and 84 in the binocular vision training group (36 males and 48 females). Three patients from each group were lost to follow-up. Prior to the training, there were no statistically significant differences observed in terms of age, BCVA, equivalent spherical diopter, deviation and stereopsis at distance and near, sensory fusion,

and fusional convergence amplitude between the pencil push-up training group and the binocular vision training group ($P > 0.05$) [Table 1].

Comparing the effects of two training methods on post-operative exodeviation at distance

The interaction between training methods and duration has a statistically significant impact on the exodeviation at distance ($F_{\text{interaction}} = 5.59, P = 0.002$). Consequently, separate assessments were conducted to evaluate the individual effects of the training methods and duration on the two groups. There was no significant overall difference observed between the groups ($F_{\text{grouping}} = 0.01, P = 0.86$). At baseline, 1 month, and 6 months, no statistically significant differences were found in the angle of distant exotropia between binocular vision training group and Pencil push-up training group ($t = -1.15, -1.63, 1.58$, all $P > 0.05$). However, binocular vision training group exhibited significantly lower exodeviation at distance compared to the pencil push-up training group at 3 months ($t = 3.44, P < 0.001$). A significant overall variation was noted in terms of duration ($F_{\text{time}} = 5.60, P < 0.001$), indicating a decrease in exodeviation at distance over time in both pencil push-up training group ($F = 172.20, P < 0.001$) and binocular vision training group ($F = 235.37, P < 0.001$), as displayed in Table 2 and Fig. 1. The difference in exodeviation at distance between 3 months and 1 month was significantly higher in binocular vision training group when compared to pencil push-up training group ($t = -3.17, P = 0.003$). No significant differences were found between 1 month and baseline as well as 6 months and 3 months, in comparison to pencil push-up training group ($t = 0.27, P = 0.79; t = -1.94, P = 0.06$), as shown in Fig. 2.

Comparison of the effects of two training methods on post-operative exodeviation at near

The comparison between binocular vision training group and pencil push-up training group in terms of exodeviation at near before and after training at different time points revealed statistically significant differences in both grouping and duration ($F_{\text{grouping}} = 4.36, P = 0.04; F_{\text{duration}} = 234.70, P < 0.001; F_{\text{interaction}} = 2.44, P = 0.08$). Both groups exhibited a decrease in exodeviation at near as the training duration increased ($F = 117.06, P < 0.001; F = 119.43, P < 0.001$). No statistically significant differences in exodeviation at near were observed between binocular vision training group and pencil push-up training group at baseline, 1 month, and 6 months ($t = -0.32, 1.18, 0.43$, all $P > 0.05$). However, binocular vision training group demonstrated significantly lower exodeviation at near compared to the pencil push-up training group at 3 months ($t = 2.55, P = 0.01$), as depicted in Table 2 and Fig. 1. The difference in exodeviation at near between 1 month and 3 months was significantly greater in binocular vision training group than in pencil push-up training group ($t = 2.32, P = 0.02$). There were no significant differences between 1 month and baseline or between 3 months and 6 months ($t = -1.03, P = 0.31; t = -1.26, P = 0.21$) when compared to pencil push-up training group (as presented in Table 2, Fig. 3).

Under-correction and over-correction after training

Nine patients in the pencil push-up training group still exhibited distant and near exotropia greater than -8° after 6 months of training, whereas all patients in the binocular vision training group achieved the success criteria. No cases

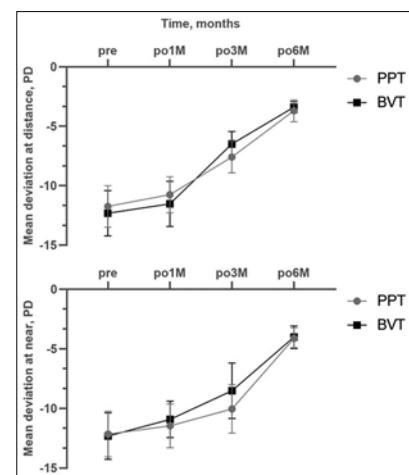


Figure 1: The mean angle of deviations at distance and near at pre-training (pre) and each post-training (po) time with the pencil push-up therapy group and the binocular vision training group. The negative values on the vertical axis represent exodeviation

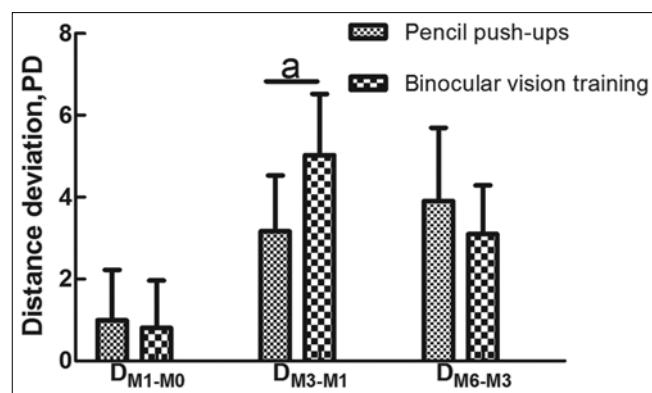


Figure 2: Comparison of differences in distance deviation at each follow-up time point

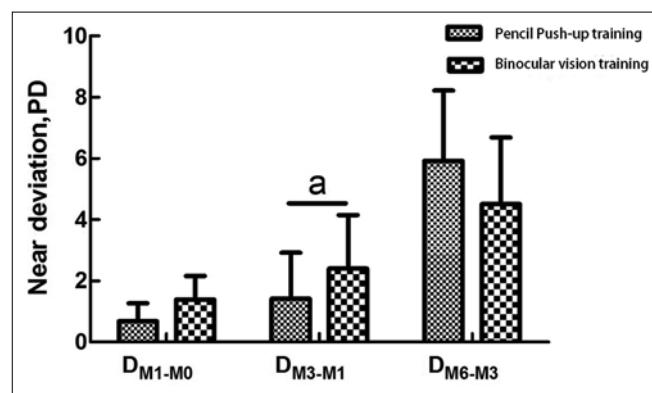


Figure 3: Comparison of differences in near deviation at each follow-up time point

of over-correction were observed in either group following the training.

Comparison of the effects of two training methods on post-operative stereopsis at distance

The interaction between training methods and training time showed statistically significant differences in the effects on

stereopsis at distance ($F_{interaction} = 5.30, P = 0.003$). Consequently, separate analyses were conducted to examine the individual effects of training methods and time within each group. There were no significant overall differences between the groups ($F_{grouping} = 0.03, P = 0.89$). At baseline, 1 month, and 3 months, no statistically significant differences in stereopsis at distance were found between binocular vision training group and pencil push-up training group ($t = -1.04, -0.59, 0.36$, all $P > 0.05$). However, binocular vision training group demonstrated superior distant stereopsis compared to the pencil push-up

training group, with a statistically significant difference at 6 months ($t = 9.33, P < 0.001$). A significant overall difference was observed in terms of time ($F_{time} = 74.71, P < 0.001$), indicating that both pencil push-up training group and binocular vision training group experienced an improvement in distant stereopsis over time ($F = 136.21, P < 0.001; F = 200.35, P < 0.001$), as presented in Table 3. Neither pencil push-up training group nor binocular vision training group exhibited cases of normal stereopsis at baseline. However, after 6 months of training, 2 cases in pencil push-up training group and

Table 1: Baseline data of the patients

Characteristic	Pencil Push-up training (78)	Binocular vision training (84)	P
Age (years)	7.00±2.50	7.00±2.30	0.94 ^a
Sex (Male:Female)	35:43	40:44	0.42 ^b
Stereoacuity (arcsecond)	1149.24±789.42	1245.56±800.37	0.66 ^a
SER (D)			
OD	-1.1±1.3	-1.4±1.5	0.44 ^a
OS	-1.1±1.4	-1.2±1.3	0.75 ^a
Deviation (PD)			
At distance	-11.58±1.60	-11.71±1.74	0.76 ^a
At near	-11.78±1.88	-12.11±1.67	0.50 ^a
Fusional convergence amplitude			
At distance	18.2±9.46	17.9±9.86	0.78 ^a
At near	13.21±8.96	13.3±9.32	0.86 ^a
Sensory fusion (suppression)			
At distance	11	12	0.97 ^b
At near	3	4	0.78 ^b
Amblyopia (n, %)	3/78 (3.85%)	5/84 (5.95%)	0.32 ^b
Lateral incomitance (n, %)	8 (10.26%)	6 (7.14%)	0.22 ^b

PD, Prism diopters; D, Diopters; OD, Right eye; OS, Left eye. ^aAnalysis of variance. ^bChi-squared test

Table 2: Comparison of distance and near deviation in the pencil push-up and binocular vision training groups

	At distance		At near	
	PPT	BVT	PPT	BVT
Before training	-11.75±1.75	-12.32±1.90	-12.15±1.90	-12.32±1.95
After training				
1 month	-10.76±1.52 ^a	-11.53±1.90	-11.46±1.83	-10.92±1.53 ^a
3 months	-7.60±1.32 ^b	-6.49±1.04 ^b	-10.04±2.03 ^b	-8.52±2.33 ^b
6 months	-3.70±0.92 ^c	-3.39±0.47 ^c	-4.12±0.89 ^c	-4.01±0.93

PPT: Pencil push-up therapy. BVT: Binocular vision training. Compare with distance deviation before training, ^a $P < 0.05$; Compare with distance deviation after 1 month training, ^b $P < 0.05$; Compare with distance deviation after 3 months training, ^c $P < 0.05$

Table 3: Comparison of distance and near stereoacuity in the pencil push-up group and binocular vision training groups

	At distance		At near	
	PPT	BVT	PPT	BVT
Before training	1103.33±651.05	1295.38±704.48	135.89±78.65	148.49±84.33
After training				
1 month	976.75±363.16	1056.86±600.23	132.46±75.52	140.65±72.34
3 months	707.41±390.06 ^b	672.80±300.39 ^b	127.44±69.84	102.13±69.58 ^b
6 months	440.79±150.13 ^c	160.44±51.78 ^c	125.89±52.56	79.43±32.46 ^c

PPT: Pencil push-up therapy. BVT: Binocular vision training. Compare with distance deviation after 1 month training; ^b $P < 0.05$; Compare with distance deviation after 3 months training; ^c $P < 0.05$

9 cases in binocular vision training group achieved normal stereopsis, with a statistically significant difference ($\chi^2 = 5.02$, $P = 0.03$).

Comparison of the effects of two training methods on post-operative stereopsis at near

After 6 months of training, the pencil push-up group did not show any change in stereopsis at near ($F = 0.93$, $P = 0.35$), while the binocular vision training group demonstrated a significant improvement ($F = 7.00$, $P < 0.001$). Results from 1-month training indicated no notable difference between the binocular vision training and pencil push-up training groups ($t = -0.70$, $P = 0.48$). In the case of the data from the 3-month and 6-month visit, the binocular vision training group exhibited a significantly better near stereopsis compared to the pencil push-up training group ($t = 2.31$, $P = 0.02$; $t = 6.82$, $P < 0.001$) [Table 3].

Sensory fusion

Before the training, there were 11 children in the pencil push-up training group and 12 children in the binocular vision training group who experienced monocular suppression at distance. After 6 months of training, all children in the binocular vision training group achieved normal sensory fusion, whereas 4 children in the pencil push-up training group still exhibited monocular suppression ($\chi^2 = 5.28$, $P = 0.02$). In terms of near sensory fusion, prior to the training, 3 children in the pencil push-up training group and 4 children in the binocular vision training group had monocular suppression. Following 6 months of training, all children in the binocular vision training group regained normal sensory fusion, while 2 children in the pen push-up training group continued to experience monocular suppression ($\chi^2 = 3.73$, $P = 0.05$).

Comparison of the effects of two training methods on fusion convergence amplitude

The fusion convergence amplitude was significantly improved from the pretraining to 6-month follow-up visits in the pencil push-up training group and binocular vision training group at both near and distance (at near: $F = 16.77$, 31.19 , both $P < 0.001$; at distance: $F = 24.44$, 33.40 , both $P < 0.001$). According to 1-month training results, there was no significant difference between the binocular vision training and pencil push-up training groups at distance ($t = 0.19$, $P = 0.84$). In the case of the data from the 3-month and 6-month visit, binocular vision training group showed a significantly higher fusion convergence amplitude than pencil push-up training group ($t = -2.98$, $P < 0.001$; $t = -2.42$, $P = 0.016$). Similar results were observed for the fusion convergence amplitude at near [Table 4].

Discussion

IXT is a common eye disease, but there is still a lack of unified standard for surgical treatment. Different researchers have proposed various criteria for defining the success of surgery. Chia *et al.*^[11] and Figueira *et al.*^[12] defined success as maintaining postoperative horizontal strabismus angle in the primary position within $\pm 10^\circ$. Lee *et al.*^[13] suggested that a range of $\pm 8^\circ$ would be more appropriate. On the other hand, Maruo *et al.*^[14] even considered a range of $\pm 20^\circ$ as successful in their studies. Wang *et al.*^[2] and PEDIG^[15] stated that a postoperative esotropia degree $\leq 5^\circ$ and exotropia degree $\leq 10^\circ$ would be considered satisfactory. Wang *et al.*^[6] found that an exotropia degree $\leq 8^\circ$ can lead to extramacular binocular vision. In this study, we adopt the definition of surgical success proposed by Wang *et al.*^[6] Another aspect of defining surgical success is that the angle of exotropia $\leq 8^\circ$ does not require external intervention.

Horizontal exotropia $\geq 15^\circ$ after IXT is the threshold for considering surgery. It is not recommended to undergo training at this stage as the purpose of training is to enhance the patient's autonomous vergence, enabling them to overcome exotropia through voluntary vergence when experiencing fatigue or neurological instability. However, in cases where the degree of exotropia is significant, foveal suppression is persistent, and fusion ability is poor, relying solely on training to strengthen convergence may lead to excessive convergence after surgery without the ability to control it, resulting in esotropia and subjective diplopia. Managing the resulting diplopia is more challenging than dealing with the original exotropia symptoms. Patients with mild undercorrection (between -8° and -15°) after IXT surgery, who do not meet the surgical criteria, may experience recurrence of IXT due to exodrift if timely intervention is not provided. Studies have revealed a wide range of long-term recurrence rates after exotropia surgery.^[2,3,6] Implementing functional training or timely interventions can potentially help prevent the need for secondary surgeries.

Pencil push-up training method has gained popularity in clinical practice due to its simplicity, ease of learning, lack of cost, and absence of follow-up requirements. Internal training within the hospital should be conducted once a week. If clinical trials demonstrate that pencil push-up training is as effective as in-hospital training, it could substantially reduce healthcare expenses and alleviate the burden on patients.

In clinical settings, patients diagnosed with convergence insufficiency frequently necessitate binocular vision training. Moreover, the training process and evaluation system have achieved a commendable level of comprehensiveness. Despite

Table 4: Comparison of fusional convergence amplitude at distance and near in the PPT group and BVT groups

	At distance		At near	
	PPT	BVT	PPT	BVT
Before training	13.21 \pm 8.96	13.3 \pm 9.32	18.2 \pm 9.46	17.9 \pm 9.86
After training				
1 month	15.4 \pm 9.37	15.86 \pm 9.96	19.4 \pm 10.36	19.6 \pm 10.12
3 months	17.65 \pm 10.66	21.77 \pm 10.05 ^b	21.45 \pm 11.40	26.64 \pm 10.65 ^b
6 months	21.34 \pm 11.22 ^c	25.4 \pm 11.84	24.2 \pm 11.56 ^c	28.8 \pm 12.42

PPT: Pencil push-up therapy. BVT: Binocular vision training. Compare with distance deviation after 1 month training; ^b $P < 0.05$; Compare with distance deviation after 3 months training; ^c $P < 0.05$

the differences in patient sources between this study and those with convergence insufficiency, both groups share a common training objective of enhancing binocular visual function, and the training methods employed are identical. The training in this study strictly adheres to the established process for patients with convergence insufficiency and has been proven to be effective.

Prior to training, there were no statistical differences in the angle of exotropia between the two groups at distance and near; however, binocular vision training group exhibited a higher angle of exotropia than the pencil push-up training group. At 3 months, the angle of exotropia in binocular vision training group was smaller than that in pencil push-up training group, and this difference was statistically significant. Furthermore, the difference in the angle of exotropia between 1 month and 3 months in binocular vision training group was greater than that in pencil push-up training group, with statistical significance. This disparity may be attributed to the simplicity and ease of understanding of the pencil push-up training method, which lacks a learning curve, whereas binocular vision training method is more intricate and influenced by the learning curve, resulting in lesser early effectiveness when compared to the pencil push-up training group. After 6 months of training, there were no statistical differences in the angle of exotropia between the two groups, suggesting that both training methods reached a stable level. Extending the training duration might further diminish the angle of exotropia. However, considering that the majority of individuals have exophoria, the impact might not be readily apparent. No statistically significant difference between the stereopsis before training and 1 month after training was observed; however, after 3 months of training, a difference became apparent, albeit without significant variation between the two groups. After 6 months of training, binocular vision training group showcased superior stereopsis compared to the pencil push-up training group, with statistical significance. The improvement in deviation decrease may be temporary if there is still suppression and poor convergence amplitudes. In this study, both training methods showed improvement in sensory fusion and fusion vergence amplitude, but binocular vision training resulted in greater improvements.

The comparison may not be fairly balanced as the binocular vision training group is having repeated reinforcement and supervision by the optometrists. Nonetheless, pencil push-up training showed a similar effect to binocular vision training in reducing exodeviation at both distance and near. We believe that pencil push-up training is worth popularizing.

In summary, both pencil push-up training and binocular vision training methods can decrease the postoperative degree of exotropia and maintain it at a stable level. However, if binocular vision training method is mastered early, it can lead to a faster reduction in exotropia angle. While both methods are effective at reducing exodeviation, binocular vision training surpasses the effectiveness of pencil push-up training in terms of functional recovery. It has been observed that if the

role of physiological diplopia is explained to the patients, the pencil push-ups do very well.^[16] So, ophthalmologists should consider explaining physiological diplopia as an integral part of convergence exercises. When selecting training methods, it is crucial for clinical physicians or vision trainers to consider various factors, including cost, efficiency, and effectiveness. They should opt for the most beneficial method for individualized training of the target population.

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Comparison of intraocular lens power prediction by American Society of Cataract and Refractive Surgery formulas and Barrett True-K TK in eyes with prior laser refractive surgery

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Purpose: To evaluate the prediction accuracy of various intraocular lens (IOL) power calculation formulas on American Society of Cataract and Refractive Surgery (ASCRS) calculator and Barrett True-K total keratometry (TK) in eyes with previous laser refractive surgery for myopia. **Methods:** This retrospective study included eyes with history of myopic laser refractive surgery, which have undergone clear or cataractous lens extraction by phacoemulsification followed by IOL implantation. Those who underwent uneventful crystalline lens extraction were included. Eyes with any complication of refractive surgery or those with eventful lens extraction procedure and those who were lost to follow-up were excluded. Formulas compared were Wang–Koch–Maloney, Shammas, Haigis-L, Barrett True-K no-history formula, ASCRS average power, ASCRS maximum power on the ASCRS post-refractive calculator and the IOLMaster 700 Barrett True-K TK. Prediction error was calculated as the difference between the implanted IOL power and the predicted power by various formulae available on ASCRS online calculator. **Results:** Forty post-myopic laser-refractive surgery eyes of 26 patients were included. Friedman's test revealed that Shammas formula, Barrett True-K, and ASCRS maximum power were significantly different from all other formulas ($P < 0.00001$ for each). Median absolute error (MedAE) was the least for Shammas and Barrett True-K TK formulas (0.28 [0.14, 0.36] and 0.28 [0.21, 0.39], respectively) and the highest for Wang–Koch–Maloney (1.29 [0.97, 1.61]). Shammas formula had the least variance (0.14), while Wang–Koch–Maloney formula had the maximum variance (2.66). **Conclusion:** In post-myopic laser refractive surgery eyes, Shammas formula and Barrett True-K TK no-history formula on ASCRS calculator are more accurate in predicting IOL powers.

Key words: American Society of Cataract and Refractive Surgery, Barrett True-K TK, intraocular lens calculator, LASIK, PRK

Millions of patients have undergone refractive surgery in the last decade, and many of them are now at the stage of cataract development requiring cataract extraction or refractive lens exchange, the latter in view of spectacle independence.^[1,2] Keratorefractive procedures lead to modified corneal architecture, which is the principal element that propels errors during intraocular lens (IOL) power calculation. IOL power calculation after prior myopic laser *in situ* keratomileusis (LASIK) and photorefractive keratectomy (PRK) leads to erroneous keratometry reading as well as estimation of IOL power for emmetropia, resulting in postoperative hyperopic outcomes.^[3-7] Error in the estimation of the correct post-LASIK keratometry values is one of the major contributory factors, as is the error in estimated lens position prediction in inaccurate IOL power calculations in these eyes.^[8] Accuracy in IOL power calculation eyes status post-LASIK and PRK has been documented previously with the aid of specially developed regression formulae and corneal powers obtained from different corneal topographers like the Orbscan,^[9] Pentacam,^[10] and Atlas.^[11]

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The American Society of Cataract and Refractive Surgery (ASCRS) has provided a calculator online ([www.iolcalc.ascrs.org](http://iolcalc.ascrs.org)), which incorporates various modules for calculation of powers in eyes with prior Radial Keratotomy (RK), myopic PRK/LASIK, and hyperopic PRK/LASIK. The updated version (4.7, 2015) of this post-refractive surgery calculator includes optical coherence tomography (OCT)-based IOL calculation formula and the Barrett True-K formula. Several studies have reported favorable outcomes after using ASCRS post-refractive surgery calculator in eyes with prior laser refractive surgery.^[12-16]

IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany), is an optical biometer based on swept-source OCT. A unique parameter it measures is the total keratometry (TK) – TK1 and TK2 – using telecentric three-zone keratometry along with swept-source OCT, and it has provisions for calculation of IOL powers in eyes subjected to refractive surgery – the

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LASIK/PRK and RK modes. IOLMaster 700 Barrett Suite offers a true-keratometry (True-K) TK formula, which is specifically designed for use in IOLMaster 700 for calculation of IOL power in post-refractive surgery eyes.^[17,18]

In this study, we aim to compare the accuracy of various IOL calculation formulae available on the ASCRS online IOL calculator and the Barrett True-K TK formula from IOLMaster 700 with respect to IOL power prediction in eyes with previous myopic laser refractive surgery.

Methods

Study design and setting

A retrospective comparative analysis was undertaken in a tertiary eye care center after obtaining ethical clearance from the Institutional Review Board. This study adhered to the tenets of the Declaration of Helsinki.

Study participants

Sample size was estimated based on the proportion of 2.5% of eyes that underwent cataract surgery with a history of refractive surgery between 2018 and 2022 and a confidence interval (CI) of 95% with a margin of error of 5%. All patients who had an uneventful cataract extraction or clear lens exchange with at least 1-month follow-up were included. Those with a prior complicated LASIK or PRK procedure or with an eventful cataract extraction or clear lens exchange and those who were lost to follow-up after surgery were excluded.

Biometry and IOL power calculation

Optical biometry values were obtained from either Lenstar LS900 (Software EyeSuite i9.6.3.0; Haag Streit Diagnostics, Bern, Switzerland) or IOLMaster 700 (version 1.07, Carl Zeiss Meditec AG). Keratometry values for 1–4-mm and 4.5-mm zones were obtained from the Holladay equivalent keratometry reading (EKR) report of the Pentacam HR (version 1.22r05; Oculus Inc, Wetzelar, Germany). The myopic LASIK/PRK module available on ASCRS post-refractive IOL calculator (www.iolcalc.ascrs.org) was used for the purpose of calculating IOL powers in these eyes. In the IOLMaster 700 (version 1.07, Carl Zeiss Meditec AG), LASIK and PRK modes were used, and the IOL power recommended by Barrett True-K TK mode for the planned IOL with the least residual spherical equivalent (SE) with target refraction as zero was taken into consideration for comparison. Formulas compared in this study were Wang–Koch–Maloney, Shammas, Haigis-L, Barrett True-K no-history method, ASCRS average power, and ASCRS maximum power from the ASCRS post-refractive surgery calculator and the Barrett True-K TK from IOLMaster 700.

Surgical technique

Phacoemulsification was performed in all cases with a 2.8 temporal clear corneal incision by five surgeons using the Alcon Centurion phacoemulsification system (Alcon Laboratories, Fort Worth, TX, USA). IOLs implanted in the capsular bag were Tecnis ZCB00 (Johnson and Johnson), Tecnis Eyhance (Johnson and Johnson), Acrysof IQ (Alcon), and Acriol (IO Care, Care Group).

Outcome measures

Postoperatively, data were obtained at 1 month after surgery. Prediction error (PE) was calculated by subtracting the IOL power predicted by each of the six formulas on ASCRS calculator taken into consideration in this study and the Barrett True-K TK in IOLMaster 700 from the implanted IOL power. A positive value of

PE (predicted IOL power lesser than the power of the implanted IOL) would lead to a hyperopic outcome. Conversely, a negative value of PE would lead to a myopic outcome. Median absolute error (MedAE) was calculated for each formula by obtaining the absolute values of the arithmetic PE and then deriving the median of those values.

Statistical analysis

Statistical analysis was performed using MedCalc® Statistical Software version 20.112 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2022). All calculated values were medians with 95% CI. Normality of data was checked using the Kolmogorov–Smirnov test, and since the data was not normally distributed, nonparametric Friedman's test was used to compare the PEs of different formulas on the post-RK module of ASCRS post-refractive calculator. Snellen's visual acuity was converted to and presented as log of minimum angle of resolution (logMAR) acuity. Results calculated for each formula were: median arithmetic IOL PE (with 95% CI), median absolute IOL PE (with 95% CI), MedAE (with 95% CI), sample variance (SV), and refractive error within ±0.50 D, ±1.00 D, ±1.50 D, ±2.00 D, and ±2.50 D. A smaller variance signifies less variability in IOL predictions. Wilcoxon signed-rank test was used to analyze the level of significance between the preoperative and postoperative SE. Using the assumption that every 1.00 D of error in IOL power causes 0.7 D error in refractive error at the spectacle plane, a *P* value of less than 0.05 was considered statistically significant.^[18]

Results

Forty eyes of 26 patients were included in this study. Twenty (50.0%) eyes were right eyes and 20 (50.0%) eyes were left eyes. There were 12 males (46.2%) and 14 females (53.9%). Demographic data of the patients are presented in Table 1. Median difference between preoperative and postoperative SE was 3.06 (1.88, 4.25) D, which was statistically significant (*P* < 0.0001) [Fig. 1].

SV was also calculated for each formula. Table 2 summarizes the arithmetic median error with 95% CI and absolute median error with 95% CI along with their respective ranges, and SV for each formula considered in this study.

Multiple comparison analysis of Friedman's test revealed that Shammas formula, Barrett True-K, and ASCRS maximum power were significantly different from all other formulas (*P* < 0.00001 for each) [Fig. 2].

We calculated the percentage of eyes within IOL power PE of ±0.5 D, ±1.00 D, ±1.5 D, and ±2.00 D, and these are summarized in Table 3.

Table 1: Demographic characteristics of participants

n=40 eyes	Median (95% CI)	Range
Age at cataract surgery (years)	52.00 (47.00, 57.00)	29–79
Pre-cataract surgery SE (D)	-2.75 (-4.31, -1.81)	-10.13 to 3.50
Post-cataract surgery SE (D)	0 (0, 0)	-1.38 to 0.75
Axial length (mm)	27.08 (26.33, 28.18)	23.84 to 31.95
Implanted IOL power (D)	17.25 (15.50, 18.83)	6.5 to 29

CI=confidence interval, IOL=intraocular lens, SE=spherical equivalent

Table 2: Arithmetic and absolute median prediction errors with their respective ranges and sample variance for each formula

	IOL prediction error post-LASIK (n=40)				
	Arithmetic median (95% CI)	Arithmetic range (D)	Absolute median (95% CI)	Absolute range (D)	Variance
Wang-Koch-Maloney	0.74 (0.25, 1.45)	-5.49 to 3.61	1.29 (0.97, 1.61)	0.10 to 5.49	2.66
Shammas	-0.11 (-0.32, -0.02)	-1.00 to 0.96	0.28 (0.14, 0.36)	0.01 to 1.00	0.14
Haigis-L	0.32 (0.12, 0.58)	-0.96 to 1.56	0.34 (0.26, 0.64)	0.03 to 1.56	0.30
Barrett True-K	0.11 (-0.05, 0.25)	-0.52 to 1.25	0.28 (0.21, 0.39)	0.01 to 1.25	0.15
ASCRS average IOL power	0.21 (0.12, 0.46)	-1.21 to 3.21	0.34 (0.21, 0.48)	0.04 to 3.21	0.43
ASCRS maximum IOL power	-0.42 (-0.67, -0.30)	-5.49 to 0.96	0.44 (0.33, 0.68)	0.02 to 5.49	0.92
IOLMaster Barrett True-K TK	0.50 (0.50, 0.50)	-3.50 to 1.50	0.50 (0.50, 0.83)	0 to 3.50	0.63

ASCRS=American Society of Cataract and Refractive Surgery, CI=confidence interval, IOL=intraocular lens, LASIK=laser *in situ* keratomileusis, TK=total keratometry

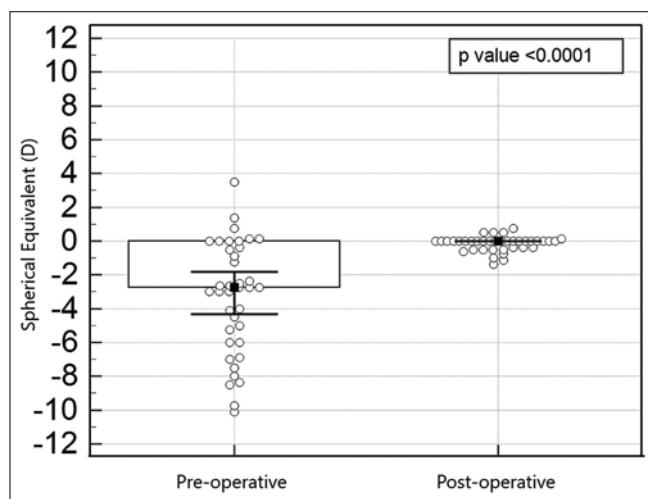


Figure 1: Results of Wilcoxon signed-rank test for preoperative and postoperative spherical equivalent (D = diopters)

Discussion

Accuracy of IOL power calculation is known to be hampered by prior myopic keratorefractive procedures, which tend to underestimate the IOL power, leading to hyperopic outcomes in these eyes.^[6] Various regression formulas have been developed in a bid to minimize the errors in IOL power calculation in these eyes by striving to accurately measure central corneal power as well as estimate the effective lens position in these eyes.^[8] ASCRS post-refractive surgery IOL power calculator incorporates many formulas (www.iolcalc.ascrs.org) and is freely available for use online; it provides three separate calculators for prior RK, prior myopic LASIK/PRK, and prior hyperopic-LASIK/PRK. The current study compared six formulas provided by the ASCRS post-refractive calculator (myopic LASIK/PRK mode) and the IOLMaster 700 Barrett True-K TK.

The results of the present study revealed that Shammas formula had the least SV (0.14) and Wang-Koch-Maloney formula had the maximum SV (2.66). Shammas formula had 100% of eyes within ± 1.00 D, while Barret True-K had 100% of eyes within ± 1.50 D. MedAE was the least for Shammas and Barrett True-K formulas (0.28 [0.14, 0.36] and 0.28 [0.21, 0.39], respectively) and the highest for Wang-Koch-Maloney formula (1.29 [0.97, 1.61]).

Menon *et al.*^[19] compared the predictability and accuracy of ASCRS calculator with the Haigis-L formula in post-myopic

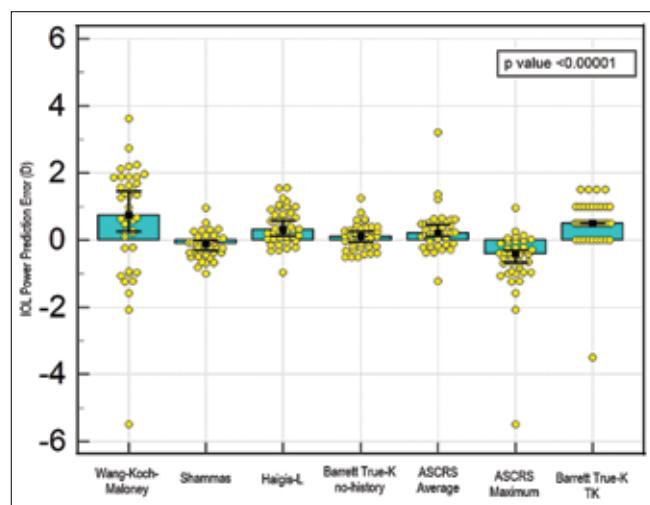


Figure 2: Results of multiple comparison analysis of Friedman's test for analysis of IOL prediction errors (D = diopters). IOL = intraocular lens

LASIK eyes. They found the ASCRS calculator to be better or equally accurate compared to the Haigis-L formula. They also concluded that the ASCRS maximum or average powers are better when compared to minimum power due to more inclination toward hyperopia with the latter. In the present study, we found that Shammas formula followed by Barrett True-K formula were more accurate compared to others on the ASCRS post-refractive surgery calculator. ASCRS average power and ASCRS maximum power had 90% and 67.5% of eyes, respectively, within ± 0.5 D. This study did not include ASCRS minimum power in the analysis.

A comparative analysis of refractive PE was done by Lawless *et al.*^[20] in post-myopic LASIK eyes, and they found that the Barrett True-K TK showed the lowest mean refractive PE compared to ASCRS average anterior K, Barrett True-K no history, Haigis-L anterior K, Haigis TK, Holladay double K TK, and Shammas anterior K. Barrett True-K TK exhibited the highest percentages of eyes within ± 0.50 D, ± 0.75 D, and ± 1.00 D of RPE compared to other formulae in these eyes.

Yeo *et al.*^[21] compared PE in different formulas in 64 eyes with previous myopic laser refractive surgery and found that emmetropia verifying optical formula TK followed by Barrett True-K TK and Haigis TK achieved the highest percentages of patients with absolute PE within 0.50 and 1.00 D. They concluded that formulas with TK lead to better or similar

Table 3: Percentage of eyes within refractive prediction error of ± 0.5 D, ± 1.00 D, ± 1.5 D, ± 2.00 D for each method

Status post-LASIK/PRK (n=40)				
	Percentage of eyes within refractive error of			
Formula	± 0.5 D	± 1.0 D	± 1.5 D	± 2.0 D
Wang-Koch-Malone	27.5%	57.5%	87.5%	95.0%
Shammas	92.5%	100.0%	100.0%	100.0%
Haigis-L	67.5%	95.0%	100.0%	100.0%
Barret True K	95.0%	100.0%	100.0%	100.0%
ASCRS average	90.0%	97.5%	97.5%	97.5%
ASCRS maximum	67.5%	92.5%	97.5%	97.5%
IOLMaster Barret	65.0%	87.5%	97.5%	97.5%
True-K TK				

ASCRS=American Society of Cataract and Refractive Surgery,

IOL=intraocular lens, LASIK=laser *in situ* keratomileusis,

PRK=photorefractive keratectomy, TK=total keratometry

results as the existing no-history post-myopia LASIK formulas.

In the current study, IOLMaster Barrett True-K TK formula had 65% of eyes and 87.5% of eyes within ± 0.5 D and ± 1.00 D, showing that Barrett True-K TK was inferior to all other formulas, except Wang-Koch-Malone formula to which it was superior. Similarly, SV for Barrett True-K (0.63) was higher than all other formulas, but lower than that of Wang-Koch-Malone formula.

Arithmetic median with 95% CI was negative for Shammas formula ($-0.11 [-0.32, -0.02]$) and ASCRS maximum power ($-0.42 [-0.67, -0.30]$), indicating that these formulas may lead to more myopic outcomes compared to the rest.

One limitation of the present study is the shorter follow-up. EyeSys 3000 Corneal Atlas System was not used in our evaluation before surgery in the RK module. Humphrey Atlas (Carl Zeiss Meditec, Dublin, CA, USA) was not used in our pre-cataract evaluation. Another limitation is the use of two different machines for biometry. In addition, in this study, we have used the Pentacam EKR zone values for Atlas ring values due to the nonavailability of the latter at the time the included patients were operated. However, this method has continued to provide accurate IOL power prediction and consequent favorable results. The present study could not include all the formulas on the ASCRS calculator due to the lack of other devices required for IOL power calculations, like EyeSys 3000 topographer. However, this is unlikely to have significant impact as this device is not routinely used in most clinics; so, our data may be more pertinent practically.

Conclusion

Shammas formula and Barrett True-K no-history formula were more accurate than other formulas on ASCRS post-refractive surgery calculator and IOLMaster Barrett True-K TK formula. Further research is warranted to improve the current methods of IOL power calculation in eyes with prior refractive surgery.

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Exploring associations between blue light filtering intraocular lenses and dementia risk

Previous studies have reported that cataract surgery is significantly associated with a lower risk of developing dementia and Alzheimer's disease (AD).^[1,2] Hypothesized mechanisms include improved visual function leading to less social isolation and/or healthier lifestyle, increased visual stimuli resulting in better neuronal connections, and stimulation of intrinsically photosensitive retinal ganglion cells (ipRGCs),^[3,4] which are associated with mood and cognitive function.^[5,6] We hypothesized that blue-filtering intraocular lenses (BF-IOLs) may be associated with increased risks of dementia compared to non-blue-light filtering IOLs (non-BF-IOLs) because ipRGCs are exquisitely sensitive to blue light (400–500-nm wavelength) and their stimulation may differ depending on the type of IOL placed after cataract surgery.

To investigate this question, we performed a retrospective cohort study of patients in the Taiwan National Health Insurance Program who underwent bilateral cataract surgery between 2008 and 2013. Patients were identified using surgery

payment codes and followed from first cataract surgery until dementia, loss to follow-up, death, or December 31, 2018, and assigned to BF-IOL and non-BF-IOL groups. Patients with a history of dementia, AD, age-related macular degeneration, glaucoma, or diabetic retinopathy before cataract surgery were excluded. Clinical and demographic data included age, sex, urbanization of residence, occupation, income, and Charlson comorbidity index (CCI). Propensity score matching (PSM) on all demographic and clinical variables and CCI was performed. Similar methods are described in our previous works.^[7] Outcomes were diagnosis of dementia or AD based on International Classification of Diseases (ICD) codes. We computed the incidence rate of dementia and AD in each group and used Cox proportional hazard models to determine the hazard ratios (HR) of dementia or AD, comparing the two groups.

Among 139,708 enrolled patients, 18,632 received BF-IOLs and 121,076 received non-BF-IOLs. The median follow-up was 6.9 years (range: 0.04–10.99 years). After PSM, there were 16,552 participants each in the BF-IOL and non-BF-IOL groups, with no significant differences in demographic, comorbidity, and CCI between the two groups (absolute standardized mean difference < 0.1).

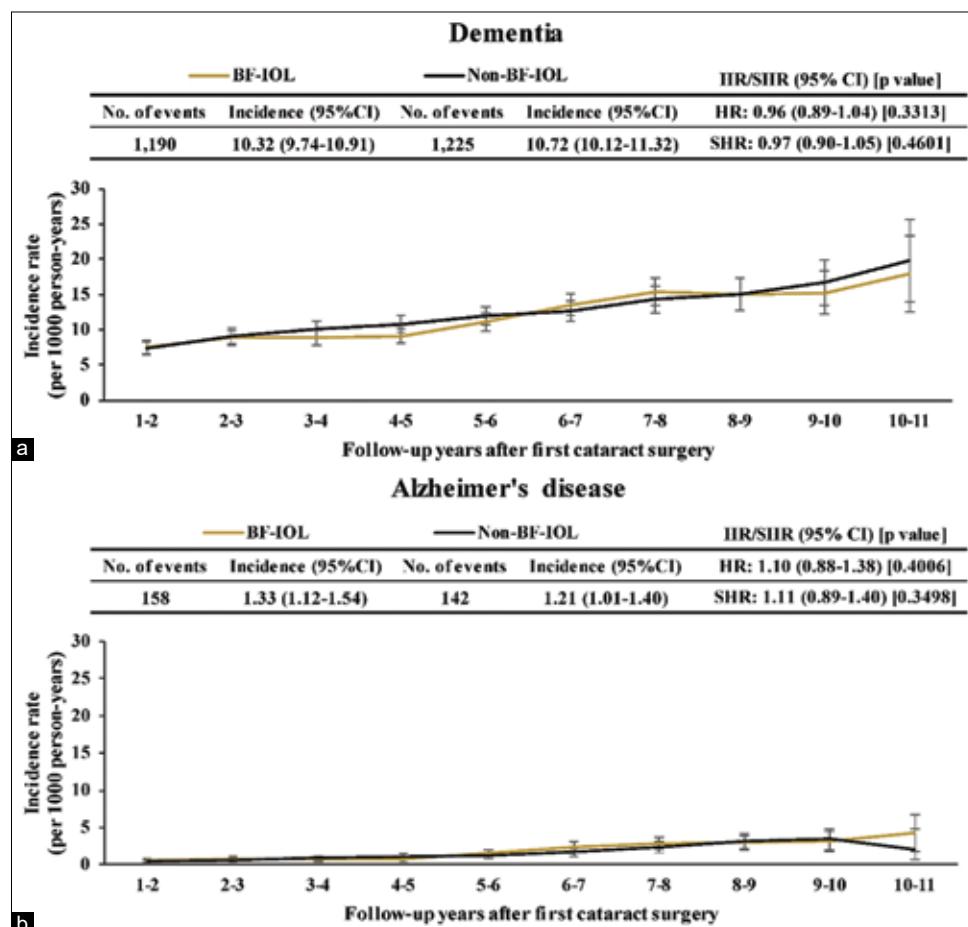


Figure 1: 2-year moving average incidence rate of dementia (a) and Alzheimer's disease (b) after cataract surgery after propensity score matching. BF-IOLs: blue light-filtering intraocular lenses, HR: hazard ratio; SHR: subdistribution hazard ratio

We found no difference between BF-IOL and non-BF-IOL groups in the incidence rate of dementia (10.32 per 1000 person-years, 95% confidence interval [CI]: 9.74–10.91 vs. 10.72, 95% CI: 10.12–11.32), and there were no differences in the risk of dementia between the BF-IOL and non-BF-IOL groups (HR = 0.96, 95% CI: 0.89–1.04) [Fig. 1]. Results were similar for AD: there was no significant difference in incidence rates and no difference in the risk of AD in the BF-IOL group versus the non-BF-IOL group (HR = 1.10, 95% CI: 0.88–1.38) [Fig. 1].

Unlike our original hypothesis, we found no statistical difference in dementia or AD development risks between the BF and non-BF-IOL groups. Two possible reasons may explain our results. First, BF-IOL filters only some blue light, and residual blue light transmission may be sufficient for ipRGC output streams.^[8] Second, a similar recovery of visual function may occur between the two groups after cataract surgery regardless of the BF capability. Improved visual function may lead to better neuronal connections and/or secondary benefits such as a healthier lifestyle. Further research into the interactions between ipRGCs, circadian rhythm, and cognition is warranted.

Lower education level, lower income, and rural residential settings have been linked to increased dementia risk.^[9] We controlled for these, although income, occupation, and residential setting may not sufficiently represent the overall social determinants of health in evaluating dementia risks. A recent study comparing 9108 participants who underwent bilateral cataract surgery found that non-BF-IOLs were associated with lower all-cause mortality compared to BF-IOLs (HR = 0.80, 95% CI: 0.66–0.96; $P = 0.02$) in a univariable Cox proportional hazards model. However, results did not reach statistical significance in the multivariable model controlling for demographics, insurance status, comorbidities, other health-related risk factors, and location/timing of surgeries (HR = 0.87, 95% CI: 0.73–1.03; $P = 0.11$).^[10]

Limitations exist with our study. Our data may not be generalizable in non-Taiwanese populations. Due to national health care coverage in Taiwan, the average age at which people receive cataract surgery is lower than in most countries, which may impact the role of cataract surgery in dementia development. We used healthcare claim records, for which the accuracy of ICD coding may vary, and relied on ICD codes for dementia/AD diagnoses instead of research criteria. Although we controlled for multiple comorbidities and demographic factors by using PSM, residual confounders may exist.

In this Taiwanese health claim database study, BF-IOL use was not associated with higher risks of developing dementia or AD compared to non-BF-IOL. These findings may have implications for patients, physicians, and policymakers weighing the cost/benefit analysis of BF-IOLs. Further research is needed into the role of ipRGCs and their potential relationship with the development and progression of dementia and AD.

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Hypersensitivity reaction to injection hyaluronidase after multiple eye surgery: Presentation, management, and preventive strategies

Allergic reaction to local anesthetic agent is rare.^[1] On literature review of cases scheduled for eye surgery under regional anesthesia, a total of four cases have been reported to have allergic reaction to lignocaine, whereas around 40 cases have been reported for allergic reaction to hyaluronidase.^[2-5] The incidence of local allergic reaction to hyaluronidase ranges from 0.05% to 0.69%.^[5-8] Most of the cases were caused by the IgE-mediated Type I hypersensitivity reactions (HSRs), while some of them were caused by Type IV T-cell-mediated reactions. Type I-mediated HSR requires pre-sensitization to the allergen. Thus, in these HSR patients, following an uneventful first eye surgery under regional anesthesia, during the second eye surgery, they might present with either localized or systemic reactions. Also, in these patients, history of environmental, food, or tablet allergy might be present.

At our institution, between July 2021 and November 2023, a total of nine patients developed HSR following multiple injections of hyaluronidase. None of these patients had any previous history of allergy to medicine, food, or environmental agents. All of them had undergone uneventful eye surgery under regional anesthesia previously. The demographic details of these nine patients, details of the surgery, signs and symptoms developed, and the treatment given are shown in Table 1. Local anesthetic solution used was either 0.5% bupivacaine with methylparaben as a preservative (Anawin, Neon Laboratories Ltd.) or 0.75% ropivacaine without preservative (Ropizuva, Abbott Ltd) along with freshly reconstituted Inj. hyaluronidase (Hynidase) at a dose of around 15 IU/ml. Hyaluronidase was stored inside the operation theater at a temperature of less than 25°C. In all the above patients, following HSR, intradermal skin test was performed separately both for the local anesthetic solution used and for the Inj. hyaluronidase. The skin test result was found to be positive for Inj. hyaluronidase, while it was negative for the local anesthetic solution used. It was caused mainly by the multiple exposure to *per se* Inj. hyaluronidase.

Following second, third, and fourth eye surgery, three patients in each developed HSR to Inj. hyaluronidase. The incidence rate was calculated based on the number of incidences that occurred and the percentage of third, fourth, and fifth time eye surgery. Within the above time period, total number of patients who underwent third, fourth, and fifth time eye surgery was 871, 222, and 56, respectively. The incidence rate for hyaluronidase HSR occurring for the third, fourth, and fifth time eye surgery was 0.34%, 1.35%, and 5.36%, respectively. For the third time eye surgery, symptoms were detected at the end of surgery and the time of onset of reaction was between 90 and 150 min. Mostly, it was an unilateral swelling involving the conjunctiva, periorbital region, and forehead, but no systemic manifestations occurred. Symptoms were controlled with Inj. hydrocortisone and tablet pheniramine. For the fourth time eye surgery, reaction occurred immediately in one patient and for the other two patients, it occurred between 90 and 110 min. Swelling involved both the periorbital region, cheek,

and face, but without any systemic manifestations. It was treated with Inj. hydrocortisone and tablet pheniramine. In the fifth eye time surgery, for two patients, reactions occurred between 80 and 150 min and for one patient, it occurred at his residence around 6 h later. Apart from the localized symptoms, systemic manifestations like itching involving the face and palms occurred and rashes were seen over both the arms and forearms. In two patients, swelling was seen over the lips and tongue. One patient even required oxygen supplementation via face mask and his vitals were constantly monitored in the postoperative care area for nearly 3 h. All of them were managed with Inj. hydrocortisone and Inj. pheniramine.

The incidence rate of HSR for both third and fourth time exposure was found to be less than 1.35%, but for the fifth time exposure, the incidence rate increased to around 5.5%. This is somewhat similar to HSR that has been reported to occur following multiple cycles of intravenous (IV) infusion of chemotherapeutic agents like asparaginases, taxanes, platinum compounds, and epipodophyllotoxins.^[9] During the first five cycles of carboplatin IV infusions, the risk is around 1%.^[10] It rises to 6.5% with the sixth cycle^[11] and increases sharply to 27% in patients receiving more than seven cycles of treatment, although the previous infusions were uneventful.^[12,13]

Thus, the incidence rate of hyaluronidase HSR for the fourth time exposure was found to be similar to the incidence rate of HSR for chemotherapeutic agents exposed for the fifth time (both around 1.35%). Also, the incidence rate of hyaluronidase HSR for the fifth time exposure was found to be similar to the incidence rate of sixth time exposure to the chemotherapeutic agent, that is, around 5.5% and 6.5%, respectively. The number of eye surgery cases done for more than five times was very small to report for any HSR to occur. Hence, there is no data available to compare the same with the incidence rate of seventh time exposure to the chemotherapeutic agents.

Signs and symptoms of HSR for the initial infusion of chemotherapeutic agents were mild, such as skin rash, urticaria, itching over the palms, edema of the face and hands, diarrhea, and pruritus.^[13-15] They usually get resolved with steroids and antihistamines. In our study too, it was found that mild, localized reactions occurred for the third and fourth time exposure and they were treated with Inj. hydrocortisone and tablet pheniramine. With subsequent IV infusions of the chemotherapeutic drugs, more severe reactions like tachycardia, hypotension or hypertension, bronchospasm, seizures, chest pain, and life-threatening anaphylaxis reactions have been reported.^[14-16] In hyaluronidase exposure for the fifth time, apart from the localized symptoms, systemic reactions occurred; all of them required Inj. hydrocortisone and Inj. pheniramine. One patient even required oxygen supplementation via face mask and monitoring in the postoperative care unit for nearly 3 h. Hence, it is very important for the surgeons to be aware of this Inj. hyaluronidase HSR following multiple injections, especially for the fifth time exposure or above, and to take adequate preventive measures to prevent this from happening.

Some successful preventive strategies are adopted to prevent HSR from occurring in multiple time IV infusions of chemotherapeutic agents. First and foremost is the identification of high-risk group of patients who can develop

Table 1: Details of demography, surgery, signs and symptoms that occurred, and treatment given to the nine patients

Age in years/ sex	Surgery details/ no. of times of eye surgery	Signs and symptoms	Treatment	Previous h/o eye surgery details
51/F	Scleral fixation of intraocular lens (OS)/third eye surgery	Around 150 min, at the end of surgery, following removing of surgical drapes, swelling over both eyelids and minimal forehead swelling were noted	Inj. hydrocortisone 100 mg IV and tablet chlorpheniramine oral were given	14 months ago – vitrectomy (OS) 12 months ago – AGV (OS)
36/M	SOR + ReSOI (OD)/third eye surgery	Around 120 min, at the end of surgery, following removal of drapes, swelling of the right periorbital region and right side of the face and forehead was noted	Inj. dexamethasone 8 mg IV and Inj. chlorpheniramine 25 mg IV were given	9 months ago – V + MP + FGE + EL + SOI (OD) 2 months ago – SOR + MP + SOI (OD)
59/F	PE + IOL (OD)/ third eye surgery	Around 90 min, following surgery in the ward, right periorbital swelling was noted. On examination, eyelids were swollen, conjunctival chemosis with EOM restrictions (-2 in all gazes) was found. Recovered on the third postoperative day	Oral tablet prednisolone and tablet chlorpheniramine started. Next day, Inj. Decadron 8 mg IV for 2 days and tablet chlorpheniramine were continued	7 years ago – V + BB + SOI (OS) 6 years ago – PE + IOL + SOR (OS)
56/M	SOR (OS)/fourth eye surgery	Around 90 min, following removal of surgical drapes, contralateral (right) periorbital swelling was noted	Inj. hydrocortisone 100 mg IV and tablet chlorpheniramine were given	15 years ago – V + BB + EL + SOI (OD) 16 years ago – SOR + ERM removal (OD) 1 year ago – V + BB + EL + SOI (OS)
44/F	PE + SOR (OD)/ fourth eye surgery	Immediately following inferolateral block, swelling occurred over the right eyelid and cheek. Gradually, swelling was noted over the left periorbital region and cheek	Inj. hydrocortisone 100 mg IV and Inj. chlorpheniramine 25 mg IV were given. Surgery was deferred and 2 days later, surgery was performed with Inj. ropivacaine without hyaluronidase	4 years ago – V + BB + EL + SOI (OS) 3 years ago – PE + IOL + SOR (OS) 4 months ago – V + EL + FGE + SOI (OD)
48/M	SOR (OS)/fourth eye surgery	Around 110 min, following removal of surgical drapes, swelling over the face and contralateral periorbital (right) swelling were noted	Inj. hydrocortisone 100 mg IV and tablet chlorpheniramine oral were given	3 years ago – V + EL + SOI (OS) 2 years ago – SOR + EL + C3F8 (OS) 1 year ago – Encirclage + ReSOI (OS)
48/F	Buckle removal (OD)/fifth eye surgery	Around 80 min, following removal of drapes, contralateral periorbital swelling and urticaria over the chest were noted	Inj. hydrocortisone 100 mg IV and Inj. chlorpheniramine 25 mg IV were given	20 years ago – SB (OD) 7 years ago – L + V + BB + EL + SOI (OD) 6 years ago – SOR (OD) 2 years ago – L + V (OS)
61/M	DMEK (OS)/fifth eye surgery	Around 150 min following surgery, itching over the palms and tightness over the face occurred. Swelling was noted in the upper lip and tongue. Rashes were seen over both the arms and forearms. Contralateral periorbital (right) swelling was also noted	Inj. hydrocortisone 100 mg IV and Inj. chlorpheniramine 25 mg IV were given Oxygen via face mask through Bain's circuit was given. Gradually, about 3 h later, swelling subsided and no itching was present	4 years ago – DSEK (OD) 2 years ago – PE + IOL + DMEK (OS) 1 year ago – AGV (OD) 3 months ago – AGV (OS)
60/M	SOR (OD)/fifth eye surgery	Around 6 h later in the night, patient developed swelling over the periorbital (right) region, face, and tongue. Patient also had itching over the face	Itching reduced with tablet chlorpheniramine oral stat. Then, on the first post-op day, Inj. hydrocortisone 100 mg IV was given and tablet chlorpheniramine was continued for two more days	4 years ago – PE + IOL both eyes 1 year ago – V + EL + SOI (OD) 3 months ago – V + EL (OS)

AGV=Aحمد glaucoma valve, BB=belt buckle, DMEK=Descemet membrane endothelial keratoplasty, DSEK=Descemet stripping endothelial keratoplasty, EL=endolaser, FGE=fluid gas exchange, h/o=history of, IOL=intraocular lens, IV=intravenous, MP=membrane peeling, OD=right eye, OS=left eye, SOR=silicone oil removal, V=vitrectomy, ReSOI=Re-silicone oil injection, SOI=silicone oil injection, PE=Phacoemulsification, EOM=extraocular muscle, Encirclage=Encircling buckle, L=Lensectomy, SB=Scleral buckling

such reactions. Hence, a thorough detailed history of any reactions that occurred during the previous exposure to the drug and history of any allergy to food and environment is taken.^[19] If there is any positive history, then they are subjected to allergic intradermal skin test to the drug. At our institution, we administer preoperative intradermal skin test with Inj. lignocaine along with Inj. hyaluronidase for patients with history of allergy to medicine, allergic rhinitis, bronchial asthma, food allergy, insect bite allergies, or skin allergic conditions. For the above patients requiring multiple surgeries, we repeat the skin test before every surgery, even if the skin test result was negative for earlier eye surgery. In many studies, authors have predicted the occurrence of HSR using the intradermal skin tests.^[17] Skin tests are reported to have a 99% negative predictive value, and they have been recommended for every patient before administration of eight cycle of platinum compounds.^[18]

But performance of intradermal skin test requires certain special skills, and reactions have occurred in spite of negative skin tests results.^[19] So, another additional preventive strategy method was followed with the use of premedicants like corticosteroids and histamine 1 antagonist (pheniramine).^[19] But no standard premedication regimens have been developed so far.^[19] Often, patients are able to tolerate a rechallenge of a taxane if they are pretreated with a corticosteroid and an antihistamine, even if they have previously experienced HSRs.^[20]

As practiced in IV infusions of chemotherapeutic agents, it would be a wise and safe practice to adopt such preventive method strategies for multiple exposure to Inj. hyaluronidase. Hence, identification of high-risk group of patients through a detailed history, subjecting them to intradermal skin test, and administering premedicants like steroids and/or pheniramine, especially for the fifth time exposure, can be considered. Apart from this, emergency preparedness like crash cart with necessary medicines, airway equipment, and adequately trained staff in basic and advanced cardiac life support care must be looked upon.

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A case of severe diffuse lamellar keratitis after small-incision lenticule extraction operation

Dear Editor,

Diffuse lamellar keratitis (DLK) is a normal reaction of the corneal healing process following a stimulus. This reaction is intensified by the swift and unobstructed movement of inflammatory cells originating from the bone marrow through the cornea, especially within the lamellar interface. The most common cause is intraoperative or late injury to the epithelium. When the corneal epithelium is damaged, IL-1a, IL-1b, and TNF-a are immediately released from the epithelium into the underlying stroma. These cells not only have a chemotactic effect on bone marrow-derived cells themselves but also attract other bone marrow-derived cells such as monocytes, macrophages, and neutrophils from corneal blood vessels into the cornea. Cytokines and chemokines produced by these cells also attract other bone marrow-derived cells, thereby enhancing the inflammatory response.^[1,2] Based on the severity and location of the inflammatory reaction, DLK can be categorized into four grades^[3]: grade I, white granular cells in the periphery with

sparing of the visual axis; grade II, white granular cells in the visual axis; grade III, clumping of granular cells with haze and reduced vision; and grade IV, stromal necrosis and melt, often leading to secondary hyperopia and irregular astigmatism. In this case, we describe in detail the complications of DLK after small-incision lenticule extraction (SMILE) and the related diagnosis and treatment process.

Case Report

A 27-year-old woman came to our hospital for SMILE surgery due to myopia in her right eye. Her medical history was unremarkable, as was her preoperative eye examination. Before the operation, the diopters were -2.25 DS/-0.50 DCx50 for the right eye and +0.50 DS/+0.25 DCx40 for the left eye; both eyes had a best corrected visual acuity (BCVA) of 20/16. On the first postoperative day, a sand of Sahara reaction appeared between the corneal layers of the right eye on a slit-lamp examination, and the BCVA was 20/40. The patient used antibiotic eye drops, eye ointments, and glucocorticoid eye drops postoperatively. The treatment process is shown in Table 1. Over the next 5 months, the patient's central corneal opacity narrowed and the central corneal maximum optical density value improved [Fig. 1]. The Pentacam (OCULUS

Table 1: Changes in patient condition and treatment process

Time after surgery	UDVA/BCVA (Snellen)	IOP (mmHg)	Densitometry values	Cornea	Treatment
1 day	20/60-20/40 (-0.50 DS/-2.00 DC x175)	14	/	DLK grade II	1. 0.3% LED qid 2. 1%PAED Q1h 3. TDEO bid 4. 0.1% SHED qid
2 day	20/16	15	/	DLK grade II	1. 0.3%LED 6 times/day 2. 1%PAED 12 times/day 3. TDEO bid 4. 0.1%SHED qid
7 day	20/63-20/32 (-1.00 DS)	14	84.7	DLK grade III	1. 0.3% LED 6 times/day 2. 1%PAED q1h 3. TDEO bid 4. 0.1% SHED qid 5. DT qd (5 days)
2 weeks	20/50-20/32 (-1.50 DC x165)	11	36.9	Stromal opacity (3±3 mm ²)	1. 0.3% LED qid 2. 1%PAED 8 times/day 3. 0.3% SHED qid 4. TDEO qn
1 month	20/32-20/32 (-1.25 DC x165)	12	25.9	Stromal opacity (2±2 mm ²)	1. 0.1% FED qid (2 week) Tid (2 week) 2. 0.1% SHED qid
2 month	20/50-20/25 (+3.00 DS)	15	21.2	Milder stromal opacity (2±2 mm ²)	1. 0.1% FED tid (3 days) bid (3 days) qd (3 days) 2. 0.1% SHED qid
3 month	20/40-20/20 (+2.50 DS)	11	20.4	Corneal cloudiness	None
4 month	20/40-20/20 (+2.00 DS)	12	20.3	Corneal cloudiness	FT
5 month	20/25-20/20 (+1.75 DS)	13	21.6	Corneal cloudiness	FT

LED: Levofloxacin eye drops PAED: Prednisolone acetate eye drops; TDEO: Tobramycin dexamethasone eye ointment DT: Dexamethasone tablets; SHED: Sodium hyaluronate eye drops; FED: Fluorometholone eye drops; q1h: 1 time per hour; qd: 1 time per day; bid: 2 times per day; tid: 3 times per day; qid: 4 times per day; qn: 1 time before going to bed; FT: Flipper training

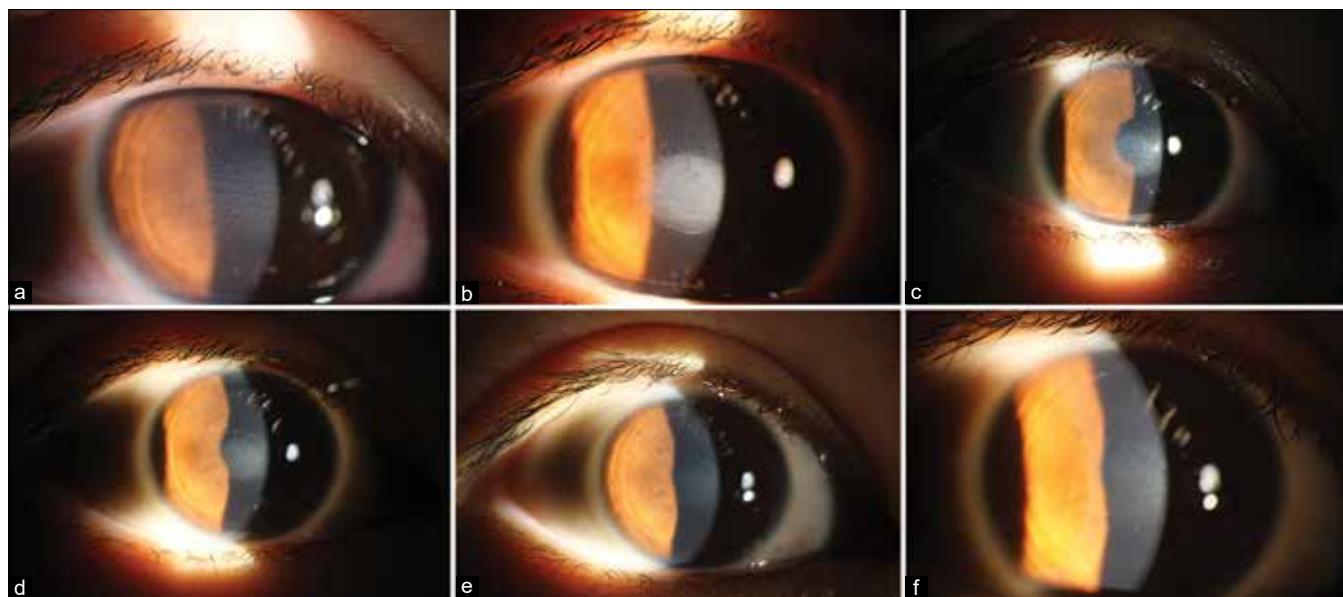


Figure 1: Changes in the patient's cornea under the slit lamp. a: On the 1st day after surgery, there was diffuse, sand-like opacity and mild edema between the layers within 6 mm in the central area of the cornea, which became more severe closer to the pupil area; b: One week after surgery, there was interlaminar inflammation within 4 mm of the pupil area of the cornea. The degree of reaction opacity was dense; c: Two weeks after surgery, the stromal opacity within 3 mm of the pupil area was less severe than before; d: One month after surgery, the stroma was slightly opaque within 2 mm of the pupil area; e: Two months after surgery, the stroma was slightly opaque within 2 mm of the pupil area; f: Three months after the operation, the center of the cornea basically returned to transparency, with only slight cloudiness remaining

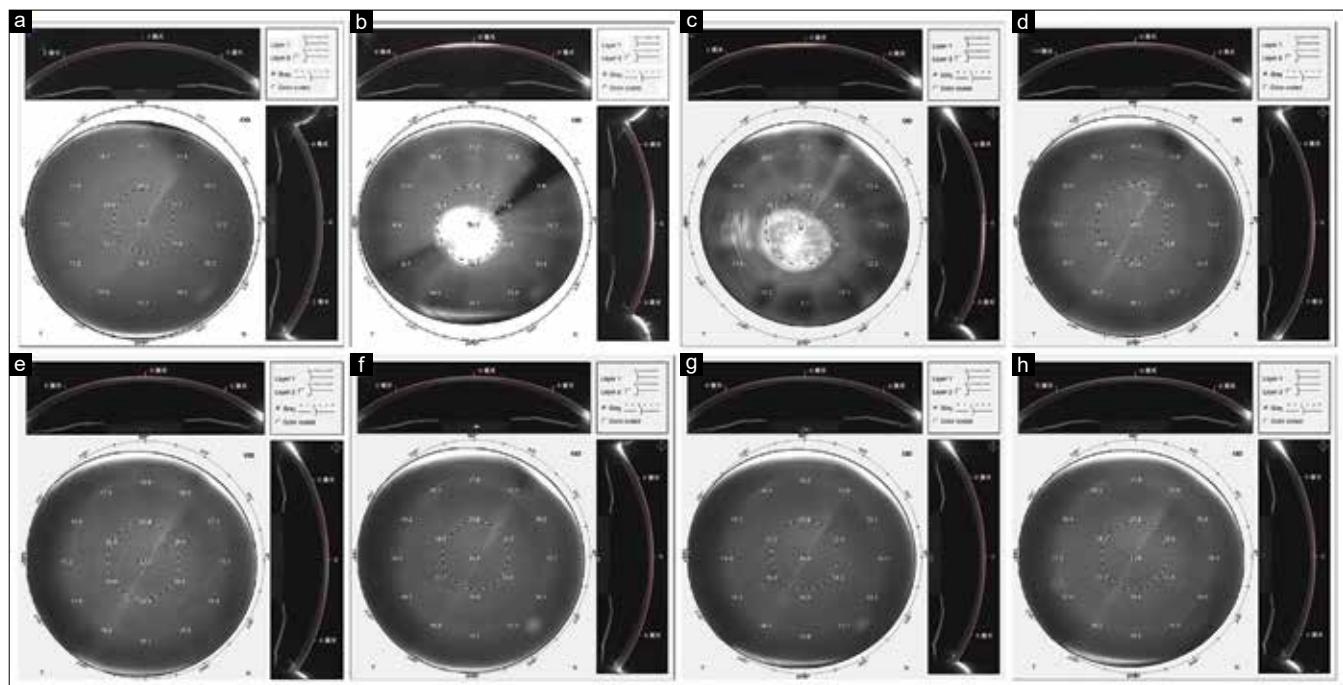


Figure 2: Corneal optical density change chart. This picture shows the changes in optical density before surgery (a) and at 1 week (b), 2 weeks (c), 1 month (d), 2 months (e), 3 months (f), 4 months (g), and 5 months after surgery. The optical density continued to decrease after surgery, and the corneal stroma gradually returned to transparency, especially within the 2-mm range of the center of the pupil

PENTACAM, GERMANY) optical density function was used to evaluate the degree of corneal interlayer opacity, and the optical density of the patient gradually decreased [Fig. 2]. This patient's corneal curvature first decreased and then increased after surgery [Fig. 3], and she developed hyperopic drift. Optical coherence tomography (VG2001, CHINA) was used

to measure central corneal epithelial thickness, and it was found that epithelial thickening following surgery reduces the hyperopic shift during the healing period [Fig. 4]. Four months post-surgery, the uncorrected visual acuity (UDVA) of the right eye was 20/40 and BCVA was 20/20. After the visual function examination, it was found that the positive relative

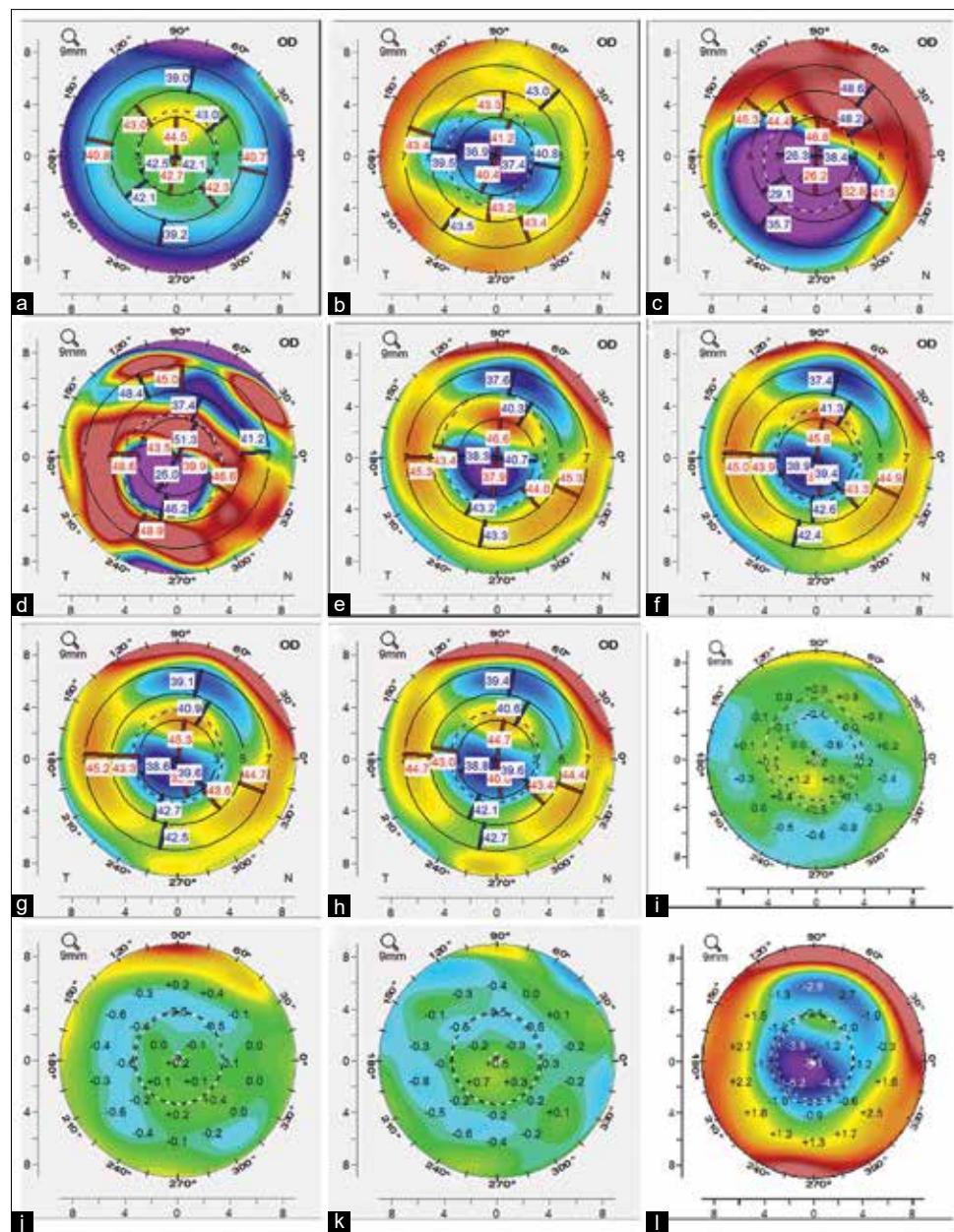


Figure 3: Changes in corneal curvature before and after surgery. (a) Preoperative corneal curvature map; (b) Corneal curvature map 1 week aftersurgery; (c) Corneal curvature map half a month after surgery: the curvature was lower than that at 1 week after surgery; (d) Corneal curvature map 1 month after surgery; (e and f) Corneal curvature 2 and 3 months after surgery, respectively; (g and h) Corneal curvature 4 and 5 months after surgery, respectively; (i) difference in corneal curvature between 2 months and 1 month after surgery, showing that the central corneal curvature increased; (j) difference in corneal curvature between 3 months and 2 months after surgery, showing that the central corneal curvature increased; (k) difference in corneal curvature between 5 months and 4 months after surgery, showing that the central corneal curvature increased; (l) difference in corneal curvature between 5 months and before surgery, showing that the central corneal curvature decreased

accommodation (PRA) of the right eye was -0.50 D, prompting the patient to practice with a ± 2.00 D flipper. After one month of practice, the UDVA improved to 20/25, and BCVA remained at 20/20, essentially returning to normal.

Discussion

SMILE has a low incidence of DLK, with an incidence rate of 0.45% in the population.^[4] DLK after SMILE typically presents

as grade I or II, with mild disease and short duration, which may be related to the high precision of the femtosecond laser and minimal damage to the surrounding tissues.^[5] The DLK classification for this patient was grade II and III, which is relatively rare. The cause of DLK is not fully understood, but it may result from endotoxins released by Gram-negative bacteria in sterilized containers, irrigation fluids used during surgery, the temperature and humidity in the operating

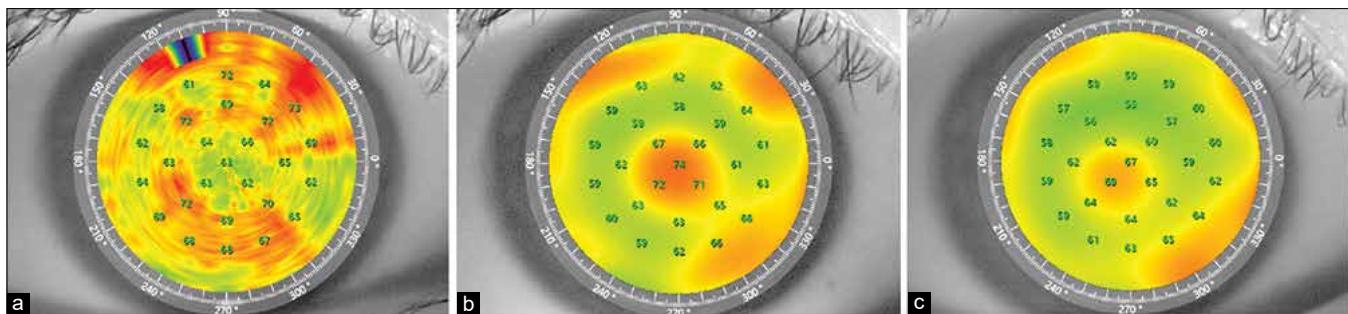


Figure 4: Changes in epithelial thickness after surgery. a: Corneal epithelial thickness 1 week after surgery; b: Corneal epithelial thickness 2 months after surgery; c: Corneal epithelial thickness 5 months after surgery, showing that the central corneal epithelial thickness first increased and then decreased

room, talc in surgical gloves, and oily secretions from the meibomian glands. A corneal flap that is too thin or too large in diameter, among other factors, may also contribute.^[5-7] This patient had normal meibomian gland function before surgery, and powder-free gloves were used; the surgery was smooth with no significant bleeding. Other patients who underwent SMILE surgery in the same batch did not develop DKL; thus, the equipment, talc, hemoglobin, and other causes can be ruled out. It is important to distinguish DKL from interface fluid syndrome (IFS), which often presents as diffuse opacity and edema between corneal layers, mainly due to prolonged steroid use.^[8] This patient's postoperative intraocular pressure was normal, and no interlayer corneal edema was observed under the slit lamp; thus, IFS could be excluded.

Early diagnosis and the application of glucocorticoids after DKL are critical. After the patient's condition worsened 1 week after surgery, she was prescribed oral dexamethasone tablets for 5 days and responded well to steroid treatment. Post surgery, corneal curvature changes first decreased and then increased. The curvature changes during the healing response were the result of inflammation resolution and scarring. Postoperative hyperopia was the result of excessive flattening of the pupil area, exceeding the expected curvature value after SMILE of -2.5 D. The mechanism is possibly due to the release of collagenase and metalloproteinase by inflammatory cells and corneal fibroblasts/keratinocytes within the layers. These enzymes can alter the matrix around the lamellar interface and even promote the melting of the DKL matrix, thereby reshaping the cornea.^[9] Contrary to the changes in corneal curvature, the thickness of the central corneal epithelium first increased and then decreased after surgery. It can be seen that the proliferation of the corneal epithelium has a certain compensatory effect on the reduction of curvature.

During the 3-month postoperative follow-up, the patient's corneal optical density continued to decrease, with the most significant change in the pupil diameter range of 0–2 mm. Although corneal transparency gradually improved, the UDVA did not significantly improve, which may be related to the postoperative hyperopia. The patient had anisometropia in both eyes before surgery and myopia in the right eye. Long-term myopia may lead to insufficient accommodation, resulting in decreased distance vision after surgery. To confirm this, the patient's visual function was examined 4 months after

surgery, and the right eye's relative accommodation was -0.50 D, indicating insufficient accommodation. After 1 month of flipper training, the patient's UDVA improved to 20/25 and PRA to -1.25 D, despite a persistent +1.75 DS in her right eye. The significant hyperopia remaining after DKL from the SMILE takes 3–6 months to stabilize, and surgery is not advisable before then. Thus, refraction should be monitored to be stable before considering vision enhancement surgery.

Conclusion

Corticosteroid treatments for DKL after SMILE surgery are generally successful. Severe DKL repair can engender hyperopia. If the patient's accommodation is not sufficient, hyperopic drift could degrade UDVA. Vision function training may enhance this and waiting until refraction stabilizes before considering vision augmentation surgery is advised.

Ethical approval

This study complied with the tenets of the Declaration of Helsinki. Written informed consent was obtained from the patient's mother for publication of this case report and any accompanying images.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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A case series of uveitis in patients with multiple sclerosis

Dear Editor,

Multiple sclerosis (MS) is an immune-mediated, chronic inflammatory disorder of the central nervous system (CNS) that primarily affects young adults (20–40 years).^[1] Once considered uncommon in the Indian population, MS has been increasingly reported in recent years.^[2,3] This rise has been attributed to improved accessibility and availability of radiological imaging such as magnetic resonance imaging (MRI), consultation with neurologists, and increased public awareness.^[2,3] Similarly, there is a dearth of ophthalmic literature that associates uveitis

with MS patients from India, although there have been a few case reports published from India. We present a case series involving five patients with MS who developed uveitis.

While the most common ocular manifestation of MS remains optic neuritis, uveitis in MS is relatively rare and includes anterior uveitis, intermediate uveitis, and retinal vasculitis. The prevalence of uveitis associated with MS varies, with rates ranging from 0.058% in the general population to 0.65%–1.09% in large cohorts.^[1] A female predominance is observed in MS as well as in uveitis linked to the disease, and the majority of the involvement is bilateral.^[1,2] All our patients were female, and the majority of them had bilateral involvement. Except for one, all our patients had peripheral retinal peri phlebitis. Among all subtypes of uveitis, intermediate uveitis is more common, and concomitant history or evidence of optic neuritis is common in these MS patients with uveitis as evidenced in the index study.^[4,5]

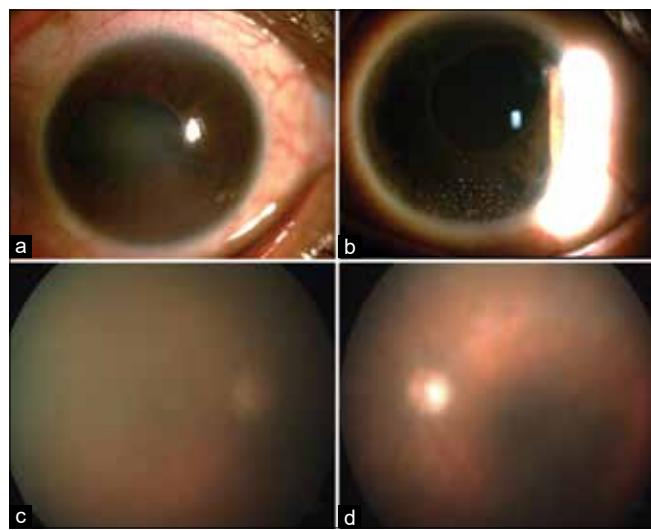


Figure 1: (a and b) Slit-lamp photograph showing granulomatous anterior uveitis in patient 1; (c and d) Fundus photograph in the same patients showing vitritis

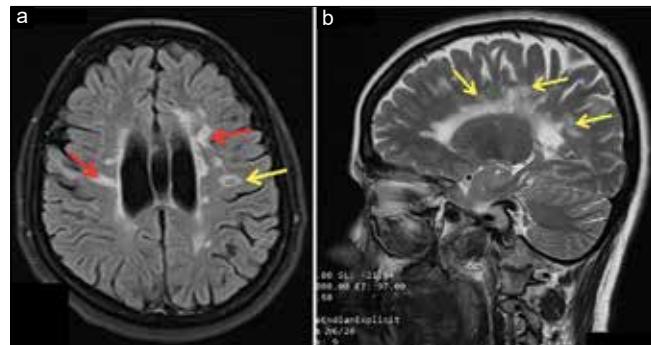


Figure 2: (a) MRI brain (T2 coronal) showing hyperdense white matter lesions perpendicular to the body of lateral ventricle (red arrow) and central hypodense with rim of hyperdense lesion indicating chronicity of MS (yellow arrow); (b) MRI brain (T2 sagittal) of patient 4 showing periventricular white matter lesions perpendicular to the body of the lateral ventricle (yellow arrow)

Table 1: Clinical profile of patients presenting with uveitis and multiple sclerosis

Patient number	Age	Sex	Eye	Anterior Segment	Posterior Segment	Follow-up (in years)
1	49	F	OU	Mutton fat KPs, AC 2+cells, Posterior synechiae, complicated cataract	Vitreous	7
2	18	F	OU	Mutton fat KPs, AC cells 1+Flare 1+, Peripheral anterior synechiae	Vitritis, snowballs, and snow banking, peripheral periphlebitis	12
3	36	F	OS	AC cells 2+	Optic neuritis, vitritis, snowballs, peripheral peri phlebitis	3
4	40	F	OU	AC cells 1+, Koeppe nodule, Posterior synechiae, secondary open-angle glaucoma	Vitritis, snowballs, peripheral periphlebitis	20
5	46	F	OS	Medium-sized KPs, AC cells 2+, Flare 2+, Posterior synechiae and complicated cataract	Healed perivasculitis, glaucomatous cupping	7

F=Female, KP=Keratic Precipitates, AC=Anterior Chamber, OU=Both eyes, OS=Left eye

One of our patients developed granulomatous anterior uveitis [Figs 1 and 2] with pars planitis and peripheral retinal vasculitis initially, and 1 year later, a diagnosis of MS was established when she developed bilateral optic neuritis and systemic symptoms. Uveitis can manifest as an initial presentation of MS, with systemic and CNS involvement potentially being absent or subclinical initially. In the absence of neurological symptoms, an episode of uveitis in these patients might initially be managed as idiopathic, and without proper follow-up, ophthalmologists could overlook such associations if the patient does not return for visits.

In conclusion, the report describes five patients with uveitis in MS [Table 1], a clinical association that has been sparsely reported from India. Granulomatous anterior uveitis with peripheral retinal vasculitis and vitritis is common among these patients, and uveitis can rarely present as the initial presentation of MS.

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Conflicts of interest: There are no conflicts of interest.

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Short-term postoperative perfluorocarbon liquid-silicone oil combination tamponade for chronic rhegmatogenous retinal detachment: Initial experience

Sir,

We intend to share our initial experience evaluating the efficacy and safety of short-term postoperative perfluorocarbon liquid-silicone oil (PFCL-SO) combination tamponade for

chronic rhegmatogenous retinal detachment (RRD) and advanced proliferative vitreoretinopathy (PVR) changes. All the patients underwent 23-gauge pars plana vitrectomy, posterior vitreous detachment induction, vitreous base shaving, pre- and subretinal PVR membrane removal, internal limiting membrane peeling, endolaser, and PFCL-SO tamponade (PFCL till ora serrata, and rest with 1000-centistoke SO). The second stage of the surgery was performed after 2 weeks with PFCL-SO removal, multiple fluid-air exchanges, and a postoperative tamponade (5000-centistoke SO).

The mean age of eight patients (eight eyes) was 43.4 ± 10.1 years. The mean duration of symptoms was 3.6 ± 2.5 months. Two

Table 1: Details of the patients who underwent two-stage surgery with short-term postoperative perfluorocarbon liquid-silicone oil combination tamponade for chronic rhegmatogenous retinal detachment

Age/ Gender	Present BCVA	Lens status	PVR Grade	Other Present CF	Retine-ctomy	SOR	Anat Outcome	Final BCVA
36/M	20/600	Phakic	CA4	-	Inferior 6-o'clock hour	Yes	Attach	20/120
42/F	HMCF	Pseudo-phakic	CP3	-	No	No	Attach	20/80
47/M	HMCF	Pseudo-phakic	CA6	-	Inferior 6-o'clock hour	Yes	Attach	20/200
38/M	HMCF	Phakic	CA8	-	No	Yes	Attach	HMCF
60/F	HMCF	Pseudo-phakic	CA2	-	No	No	Attach	20/200
45/F	HMCF	Phakic	CA	Massive 360° CDs	Inferior 3-o'clock hour	No	Attach	20/300
27/M	FCCF	Phakic	CA6		No	Yes	Attach	FCCF
52/M	FCCF	Aphakic	CA3	MMD, My MH	Inferior 4-o'clock hour	No	Posterior pole detached	FCCF

Present BCVA=Presenting best-corrected visual acuity, PVR=Proliferative vitreoretinopathy, Present CF=Presenting clinical features, SOR=Silicone oil removal, Anat Outcome=Anatomical outcome, HMCF=Hand movement close to face, FCCF=Finger counting close to face, CD=Choroidal detachment, MMD=Myopic macular detachment, My MH=Myopic macular hole

eyes had already undergone an unsuccessful vitreoretinal surgery elsewhere for RRD. The presenting BCVA was logMAR 2.39 ± 0.39 (Snellen equivalent: finger counting). The presenting clinical features of all the patients are highlighted in Table 1. Relaxing retinectomy was required in four eyes (50.0%). The mean duration of postoperative PFCL-SO combination tamponade was 15.9 ± 2.4 days. The retina was attached in all the eyes during the second stage of surgery.

The retina was completely attached in 87.5% of eyes after 6 months of follow-up. Four eyes underwent successful SO removal (SOR) till the end of the study, while SO was still *in situ* in the other four eyes. Three patients were advised SOR; however, they did not undergo it, while one patient was advised to avoid SOR due to recurrent posterior pole RD under oil. The retina remained attached in all these eyes even after SOR. BCVA improved to logMAR 1.47 ± 0.79 (Snellen equivalent: 20/590). Visual improvement was seen in 62.5% of eyes, while the rest retained their preoperative vision. Five (62.5%) eyes developed BCVA $\geq 20/200$.

Three patients developed intraocular pressure rise, which was well controlled with topical antiglaucoma medications. Complications such as postoperative retained PFCL, exaggerated inflammation, posterior synechiae formation, granulomatous precipitates on the intraocular lens, corneal decompensation, macular changes, optic atrophy, or intractable IOP rise were not seen in any patient.

The anatomical and functional success rate (final BCVA $\geq 5/200$) of eyes with advanced PVR changes undergoing conventional surgery has been reported to be 45%–85% and 26%–67%, respectively.^[1–4] Enders reported that the relative risk ratio for recurrent detachment in the presence of preoperative PVR changes was 1.46, while 3.5% of eyes developed ≥ 2 recurrent detachments, and SO had to be left *in situ* in 3.7% of eyes.^[5]

The anatomical and visual success rate of eyes undergoing a two-stage surgery has been reported to be 76%–93.3% and 46.7%–86.6%, respectively, while SO had to be retained *in situ* in 32.8%–52.9% of eyes.^[6–14]

Although there is a potential risk of inflammation and raised IOP, the good anatomical and visual success as well as the lack of clinically apparent toxicity seen in the pilot study shows that the two-staged surgery with short- to intermediate-term PFCL-SO combination tamponade is a safe and effective approach for the management of chronic RRD

with advanced PVR changes. The combination prevents direct oxidative damage to the retina as SO engulfs the PFCL bubble and prevents direct PFCL-retina contact. However, there is no study to date to prove the superiority or inferiority of the novel PFCL-SO sandwich technique over the conventional technique.

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Author's Response to Comments on "Efficacy of low-vision devices in the elderly population with age-related macular degeneration"

Dear Editor,

At the outset we would like to thank the authors for their letter to the editor,^[1] appreciating our work.^[2]

In reply to the same

- a. Concur that follow-up time of 1 month was less; however, this was done as per study protocol, keeping in mind the difficulty these patients have in travelling long distances to hospital for follow-up. The follow-up at 1 month was physical and not by telephonic interview, as done in prior studies. This was done considering our patient cohort's poorer socioeconomic status and learning ability.
- b. Low vision aids (LVA) selection was based on these geriatric patients' ability and willingness to use LVA, to study effectiveness and feasibility of LVA (aim of our study). Our study design was not comparative.
- c. Patient satisfaction was assessed by modified questionnaire of Nhung for vision-related quality of life. (Pg 2810, paragraph 5). Adherence could not be assessed, as long-term follow-up was not envisaged.^[2]

As per the definition of low vision, the better eye was only provided with the visual aid. The patient himself/herself was the control, as the parameters of speed of reading, fluency of reading, and Quality of life (QOL) change were evaluated at baseline and postrehabilitation.

The Low Vision Rehabilitation Outcomes Study by Goldstein JE *et al.*^[3] across 28 outpatient centers in Untied States evaluating 468 patients used a similar study design.

Once again appreciate your interest and comments on this poorly discussed and less implemented, yet extremely relevant aspect of ophthalmology.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Kirti Singh, Arshi Singh, Priyanka Chaudury¹, Divya Jain²

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Authors' Response: Possible dose-dependent effect of eplerenone on intraocular pressure

Dear Editor,

We sincerely appreciate the thoughtful comments on our article.^[1] The discussion surrounding an alternate pathway for aqueous drainage is indeed intriguing, and the article by Smith *et al.*^[2] provides excellent models for explaining its potential existence. Building upon this foundation, we hypothesized that medications impacting the retinal pigmented epithelium pump function or choroidal vasculature, such as eplerenone, could influence the intraocular pressure (IOP).

We acknowledge the limitations of our study design, as outlined in the article itself. A retrospective analysis cannot demonstrate causality, but rather suggests a possible association between eplerenone use and IOP changes. Confounding factors, including over-the-counter (OTC) medications potentially interacting with eplerenone's metabolism, remain a challenge to control for in this setting.

As the authors rightly point out, eplerenone is metabolized by cytochrome P450 3A4. Many agents which can affect the cytochrome P450 3A4 function are OTC medications like omeprazole or dietary agents like black pepper, grapefruit, and green tea. While prescribing providers likely consider potential interactions, our retrospective study could not fully account for all agents that might affect effective eplerenone dosage. This limits our interpretation of the dose-response association.

We agree that the lack of observed side effects in our study population does not preclude their possibility. Since eplerenone was prescribed at standard doses for its established indications, we anticipate its safety profile would be consistent with previously reported data. We used average IOP measurements to minimize the impact of daily fluctuation. All patients had IOP measured at least 1 week after starting eplerenone, though treatment duration varied, affecting the homogeneity of our population.

We reanalyzed the subgroup receiving a daily eplerenone dose of 25 mg or less (31 patients). The mean \pm standard deviation IOP before treatment was 14.05 ± 3.57 mmHg, which decreased to 13.56 ± 3.66 mmHg after starting eplerenone ($P = 0.44$). The correlation between dose and IOP reduction percentage was 0.0157, suggesting a potential dose-related trend as seen in Table 2.^[3]

Finally, we concur with the authors that our study highlights a potential new target for glaucoma management, especially

in cases of low-tension glaucoma. We believe further research is warranted to explore this promising avenue.

Sincerely,

Ramin Daneshvar, MD, MSc

Seyedeh Mehrsa Sadat Razavi

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

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Navigating the challenges of infective keratitis: A critical analysis of treatment and diagnostic approaches

Dear Sir,

The recent study by Agarwal *et al.*^[1] titled "Depth, size of infiltrate, and the microbe – The trio that prognosticates the outcome of infective keratitis" published in the Indian Journal of Ophthalmology provides a significant contribution to our

understanding of microbial keratitis. The retrospective analysis brings forward the crucial interplay between the depth and size of corneal infiltrates and the type of infecting organism in predicting treatment outcomes. However, several areas could be addressed further to enhance the study's impact on clinical practice and future research directions.

Firstly, the study underlines natamycin's omission in the initial treatment regimen for fungal keratitis cases, raising questions about therapeutic choices. Given natamycin's prominence as a first-line treatment for fungal infections,^[2]

elaborating on the rationale behind its exclusion could offer deeper insights into decision-making processes, especially in settings with high fungal prevalence. Moreover, the potential for mixed infections involving fungi and *Pythium* keratitis, as highlighted by recent case series,^[3] suggests a need for comprehensive diagnostic approaches to differentiate between these pathogens effectively. The study briefly discusses microbiologic evaluation techniques; however, it could benefit from a more detailed exploration of how mixed infections were ruled out and how fungal and *Pythium* keratitis were distinguished on smear results.

Another area for enhancement is the timing and role of therapeutic scraping. While the study mentions microbiologic evaluation, further details on whether therapeutic scraping was performed, and its influence on treatment outcomes, would provide valuable clinical insights.^[4]

In addition, the timing of culture report readings could be clarified. Understanding the interval between sample collection and definitive organism identification could inform about potential delays in initiating targeted therapy, a critical factor in managing aggressive infections.^[5] For future directions, this study sets the groundwork for longitudinal research to observe long-term outcomes based on initial treatment decisions and diagnostic findings. It also opens avenues for exploring the effectiveness of various antifungal agents, including natamycin, in different fungal species and infection depths. Comparative studies examining the efficacy of medical versus surgical interventions across different infective keratitis types could further refine treatment algorithms. In conclusion, while Agarwal *et al.*'s work significantly advances our knowledge, addressing these aspects could further tailor clinical management strategies and guide future investigations in microbial keratitis.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

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Author's Response to Comments on "Depth, size of infiltrate, and the microbe – The trio that prognosticates the outcome of infective keratitis"

Dear Editor,

We would like to thank the authors Gurnani and Kaur.^[1] for their keen interest in our article "Depth, size of infiltrate, and the microbe – The trio that prognosticates the outcome of infective keratitis."^[2]

The limited understanding of the impact of the causative organism on outcome based on the size-depth dynamics of

the infiltrate carved the need for our retrospective study. The primary aim of this manuscript was to analyze the response to treatment with specific emphasis on understanding the size-depth dynamics of the infiltrate on the outcome between various causative organisms. The diagnosis was based on clinical features and microbiologic evaluation, which included stains, culture, and/or polymerase chain reaction (PCR) if the earlier two were negative. In case of negative scraping and the culture showing no growth after 48 h, a repeat scraping was advised, which included PCR based on our institute protocol. As mentioned in the methodology, only microbiologically proven cases were included in the study, and cultures were reported after 48 h of the initial scraping and thereafter checked every 2–3 days or during every clinical visit. The mixed infections in our series were diagnosed based on the above-described

microbiologic evaluation, and all were noted to be bacterial with fungal coinfections.

The outcome of infective keratitis is based on multiple factors, and the factors which make them refractory have been well described by Agarwal *et al.*^[3] which include misdiagnosis and inadequate or delayed treatment as mentioned by Gurnani and Kaur.^[1] Though these factors do have a role in influencing the outcome, analyzing them in a retrospective study might in itself be a limitation and was not the primary aim of the study. Natamycin is the drug of choice in filamentous fungal keratitis and is our preferred drug, too but the study did not analyze the outcomes based on the treatment initiated elsewhere at the time of presentation. The treatment outcome was based on the medical management initiated at our center.

We observed that between larger infiltrate size and deeper involvement, the former was a higher risk factor for surgery, except in bacterial keratitis where an increased depth was associated with a significantly higher need for surgical intervention. Other organisms like *Acanthamoeba* had a good response to medical management, whereas *Pythium* keratitis ended up requiring surgery, irrespective of the size and depth.

Our study thus provides a new insight into the dynamics of size and depth in relation to the infecting organisms.

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Shweta Agarwal, Bhaskar Srinivasan, Geetha Iyer, Sunita Pandey, Manokamma Agarwal, Richa Dhiman, Janani Surya, Appakkudal R Anand¹

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Advertisement**Training Programs (As per information provided by various centers)**

Name	Ant.Segment Cornea/Cat	Glaucoma Uveitis	Orbit & Plastics	Ped Ophthal	Retina Vitreous	Gen Ophthal	Short Term Fellowship	Observership.
A. B. Eye Institute	b,c,n,p	-	-	-	f	m	b,c,f,n,p,m,z	a,b,c,f,h,l,m, n,p,z,TY
ASG Eye Hospital	3- PHACO + Medical Retina (24 Months) 1- PHACO+Refractive (24 Months)	-	-	-	3 (24 Month)	-	-	-
Aditya Jyot Eye Hospital	Cornea Fellowship (12 Month)	-	-	-	VR Fellowship (18 Months)	Fellowship (12 Months)	Medical Retina Fellowship (12 Months)	-
Advanced Centre for Eyes	-	-	-	-	✓	-	-	-
Advanced Eye Hospital & Institute	2 (6 Months)	-	-	-	1	1	A,F	A,F,H,O
Ahalia Foundation Eye Hospital	10/year	02	-	-	01	-	-	-
Anuradha Eye Hospital	-	-	-	-	✓	-	-	-
Arasan Eye Hospital	a,b, NP, Ty	2d, Ty	-	-	F(OR)	2D, 2PD	a,b,d,g,k, Ty	a,b,d,h,i,o,p,q
Aravind Eye Hospital & P.G. Institute of Ophthalmology	Anterior Segment – IOL Microsurgery: – 20 Nos. (24 months), Cornea – 6 Nos (18 months)	Glaucoma - 8 Nos (24 months), Uveitis – 1 No. (18 months)	3 Nos (18 months)	6 Nos (18 months)	10 Nos (24 months)	6 Nos (18 months)	Small Incision Cataract Surgery – (1 month) : 72 (6 per – Madurai, Tirunelveli, Coimbatore & Pondicherry) Phacoemulsification – (1 month) : 72 (6 per - Madurai, Tirunelveli, Coimbatore & Pondicherry) Lasers in Diabetic Retinopathy Management – (8 weeks) : 60 (5 per – Madurai, Coimbatore, Tirunelveli & Pondicherry) Diagnosis and Management of Glaucoma – (4 weeks) : 72 (6 per – Madurai, Tirunelveli, Coimbatore & Pondicherry) Instrument Maintenance – (4 weeks) : 36 (6 – alternate month) Community Outreach – (3weeks): 20 (10 - twice a year)	-
Arora Eye Hospital & Retina Centre	1	-	-	-	-	-	Phacoemulsification: 6 intakes in a year Medical retina: 2 intakes in a year	-
Aso Palav Eye Hospital	2	-	-	-	6	-	-	20
Aurangabad Chikalthana Lions Eye Hospital	✓	-	-	-	-	-	✓	-
B.W. Lions Superspeciality Eye Hospital	2q, 4a	4d	-	-	-	3D + 3PD + 8	a, b	8
Centre for Sight Eye Institute	Cataract (1 year 6 months) – 1 every year Cataract + Refractive (2 years) + 1 every year Cataract + Cornea (2 years) - 1 every year Cataract + Cornea + Refractive (2 years 6 months) - 1 every year Advanced Phacoemulsification (3 months) - 2 every 3 months	Glaucoma (2 years) - 3 every year Glaucoma Diagnostics (3 months) - 3 every 3 months	Oculoplasty and Ocular Oncology International Fellowship (1 year at CFS Hyderabad and 1 year at Wills Eye Institute, Philadelphia, USA or New York Eye Cancer Centre, New York, USA) - 1 every 6 months Oculoplasty observership at CFSEI, Dwarka (3 months) - 2 every 3 months	-	Vitreoretina (2 years) - 2 every year Medical Retina Hands-on + Surgical Retina Observership (3+1 months) - 3 every 3 months	Comprehensive Ophthalmology (2 years) - 2 every year	-	As specified in each subspecialty
Chaithanya Eye Hospital & Research Institute	3 Short term	2 Long Term	4 Short Term	2 Long Term	3 Long Term	3	3	-
C.L Gupta Eye Institute	✓	✓	-	✓	✓	✓	✓	✓
Darshan Eye Care and Darshan Surgical Centre	✓	-	-	-	-	-	1 year Fellowship	-
Dr. Agarwal's Eye Hospital & Eye Research Center	2 Years	1 Year	1 Year	1 Year	2 Years	18 Months	Medical Retina - 6 Months	Nill
Divyajyoti Trust	a-TY, b-TY, q-1	d-1	-	e - 1	f-TY, h-TY, k-1	m-1, i-TY, j-TY	a,b,d,f,h, s-TY	a,b,c,d,f,g,m
Drashti Nethralaya	4	0	2	2	2	2	12	custom
Drishti Eye Institute & Dehradun Wave Lasik Centre	1 (l)	1t + 1d	-	-	1f+1g	1	f,h,t,w,z (TY) Refractive Surgery	a,d,f,g,h,k,p,t,w,z (TY) Refractive Surgery
DD Eye Institute	12	-	-	-	-	-	-	2
DR.Gadre Eye Care and Laser Center	-	-	-	-	1	1	-	-
Eye Microsurgery & Laser Centre	Cat 1	1	-	-	-	1	-	-
Giridhar Eye Institute	Cornea-1 Cataract-1	Glaucoma 1	1	1	4	0	Medical Retina 2 Months	Ms Final year Studenten for 4 weeks
Isha Netralaya Institution	NA	NA	NA	NA	1	NA	F,G,H, Z	F,G,H, Z
Indira Gandhi Eye Hospital & Research Centre	Cornea & Refractive Surgery-No-2- (24 Months), Lucknow	Glaucoma Services-No-2- (24 Month), Lucknow	Orbit & Oculoplasty -No-1- (18 Month), Lucknow	Paediatric ophthalmology-2 No(18 Month), Lucknow	Vitreo- Retina Services-No-2- (24 Months), Lucknow, Gurugram, Amethi	Comprehensive ophthalmology- No-8- (24 Months), Lucknow, Gurugram, Amethi	1. Cataract:- SICS (4 Week), Phacoemulsification (4 Week), Combined (2 Months) 2. Glaucoma Services: Medical- Surgical Training (2 Months) 3. Orbit & Oculoplasty:- DCR, Lid Surgeries (15 Days) Observership: (15 Days) 4. Medical Retina: Diagnostic, Laser and intra vital injections-(2 Months)	a,b
Jayapriya Eye Hospital	-	-	-	-	-	1-seat	SICS 2 seat Phaco 1seat	-
Laxmi Eye Institute	4	2	-	1	1f, h, z	2D, 2PD	6	6

Name	Ant.Segment Cornea/Cat	Glaucoma Uveitis	Orbit & Plastics	Ped Ophthal	Retina Vitreous	Gen Ophthal	Short Term Fellowship	Observership.
Lions Nab Eye Hospital	12 a,o,Ty, 12b,o,Ty, 2l, 1q	-	-	1 e,r	2l,1g,k	2m,2D,2PD, 4DO	12a,o,Ty, 12b,o,Ty	-
Lotus Eye Hospital	SICS/Phaco 2	1	-	1	1f	1	a b c e p	-
MM Joshi Eye Institute	6a	2d	-	2e	4g	4m	-	-
Mahatme Eye Bank & Eye Hospital	✓	✓	-	-	-	✓	✓	✓
MGM Eye Institute	0	1	0	0	1	3	30	15
M. N. Eye Hospital	2	-	-	-	1	2	a,b,c,d,e,f,g,h,o,s	-
Nandadeep Eye Hospital	1	-	-	-	-	1	-	-
Narayana Netralaya	2	2	2	2	2	-	-	-
National Institute of Ophthalmology	1	1	-	1	1	1	-	2
Nethradham Super Specialty Eye Hospital	04	04	-	-	04	06 DNB	24	12
Ojas Eye Hospital	2 Seats, 1 Year	-	-	-	2 Seats, 1 Year	-	-	-
PBMA'S H. V. Desai Eye Hospital	2	2	1	2	2	6	1 per in each	4
Prasad Netralaya, Super Specialty Eye Hospital	4a, b, c, n, p	-	-	-	4f, g, h	-	-	6a, b, 6f, h, 6z
Rani Menons Eye Care Centre	Phaco (12 Month) 2 No	-	-	-	-	-	-	-
Ratan Jyoti Netralaya	-	-	-	-	-	2	1 (a, p), 1d, 1(f, h)	-
Regional Institute of Ophthalmology, Eye Hospital Sitapur	6	0	0	0	1	0	0	0
Retina Hospital, Rajkot	-	-	-	-	2k	-	-	-
Retina Institute of Karnataka	-	-	-	-	2	-	2f	-
Retina Foundation Hospitals Pvt. Ltd.	-	-	-	-	✓	-	-	-
Retina Speciality Hospital	1 nos. (Cat.) (24 months)	-	-	-	2 nos. (24 months)	-	-	-
The Palampur Rotary Eye Foundation	✓	✓	-	✓	✓	✓ Long term	Medical Retina 3 Month & 6 Months	✓
Sankar Foundation Eye Institute	2+2	2	1	1	2	Nil	Nil	Nil
Sankara Eye Foundation A unit of Sri Kanchi Kamakoti Medical Trust	6	4	2	3	6	14	34	15
SBH Eye Hospital	Long term fellowship of 12 months	-	-	-	RV-Long term fellowship (12 months)	Long term fellowship (12 Months)	30 days paid fellowship programme on SICS	YES 30 DAYS -Medical Retina -Glaucoma -Pediatric Ophal
Sharat Maxivision Eye Hospitals	1 Year Fellowship in Cataract Surgery -2 Seats				1 Year Fellowship in Medical Retina - 2 Seats		1 SICS/PHACO IMONTH FELLOWSHIP	
Shanti Saroj Netralay	-	1	-	-	2	-	-	-
Shri Ganapati Netralaya	2	0	1	0	4	2	1 Month paid SICS/Phaco Training (2 per month)	0
Shri Ganesh Vinayak Eye Hospital	y	-	-	-	y	-	y	y
Sheth Shri C.H. Nagri Eye Hospital, Nagri Eye Research Foundation Trust	1	-	1	-	2	-	-	-
S. B. Dr. Sohan Singh Eye Hospital Pvt. Ltd.	-	-	-	-	✓	-	-	-
Srikriran Institute of Ophthalmology	2 Positions per Year 2 Years	1 Positions per Year 2 Years	-	1 Positions per Year 2 Years	1 Positions per Year 2 Years	-	1 Per month	-
Sri Sankaradeva Netralaya	Fellowship (18 Months)	Fellowship (18 Months)	Fellowship (18 Months)	Fellowship (18 Months)	Fellowship (18 Months)	Fellowship (18 Months)	Vitreoretina & Medical Retina [2-3 Months], Paediatric Ophthal [3 Months], SICS [2 Months], Phacoemulsification [2 months]	Medical Retina, Paediatric ophthal, [1-3 Months]
Suraj Eye Institute	Cornea One every year (duration 21 months)	Glaucoma-Two every year (duration 18 months)	-	Paed Ophthalmol One every year (duration 18 months)	Ret and Vit One every year (duration 24 months)	Gen Ophthal One every year (duration 21 months)	-	
Tirupati Eye Centre & Research Institute	I. Cataract 10- 30days 2. Refractive Surgery- 3 days		Facial Aesthetic - 2 days			Yes	Cataract - 6/12 months 2. Refractive 3/6 months Facial Aesthetic 10 days	Cataract - 10 to 30 days 2. Refractive - 7 days Facial Aesthetic- 2 days
Dr. Om parkash Eye institute	-	-	-	-	Retina Vitreous	-	-	-
Dr Shroff's Charity Eye Hospital	8q	2d	2op	2r	2g	-	4f, 20a, 4f, 4q	2d, 2e, 2q, 2op, 10u, 20w
Dr. Sohan Singh Eye Hospital	-	-	-	-	✓	-	-	-
Dr. Thakorhai V. Patel Eye Institute	2 years Every 6 months	15 months 1/year	Avail in Jan 18	15 months 1/year	2years 2/year	-	-	4/year
Venu Eye Institute & Research Centre	2	2	01	-	2	2 Intensive IOL - 6	24abc, 24uv, 3PD, 3D, 6f, 12jx, 20w, 24y, Adv. Phaco Tr.-12	Eye Bank Observership-24 (Director / Manager) + Foreign Graduates Observership-24
Vision Eye Centre	-	-	1	-	-	-	-	-

(a) Phacoemulsification, (b) SICS, (c) ECCE, (d) Glaucoma-Diagnosis & Mgmt, (e) Paediatric Ophthalmology, (f) Medical Retina, (g) Vitreo Retina, (h) Lasers in Diab. Retinopathy, (i) Community Outreach, (j) Instrument Maintenance, (k) Retina Vit Surgery, (l) Ant. Segment, (m) Gen. Ophthal, (n) IOL Microsurgery, (o) Surgical Training, (p) Cataract, (q) Cornea, (r) Squint, (s) Anterior Segment Microsurgery, (t) Uveitis, (u) Contact Lens, (v) Low Vision Workshop, (w) Optometrist, (x) Eye Bank Course, (y) Eye Donation Counsellor, (z) Indirect Ophthalmoscopy, (D) DNB, (PD) Post DO DNB, (DO) DOMS, (TP) Training Programme, (OR) On Request, (TY) Throughout the year, (OP) Orbit and Oculoplastics, (OL) Ocularist, (OT) Ophthalmic Technology. (*) Mark Training Programs are affiliated by Srimanta Sankaradeva University of HealthSciences and the certificate would be provided by the university following exit examination. (the list of institute address can be seen online & in print copy of Jan, April, July, Oct issues)

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HOYA

Combining outdoor time and spectacle lenses for myopia management

Spending time outdoors is paramount to myopic children's wellbeing, eye health included.^{1,2} However, they also need protection from harmful UV rays and intense sunlight.³⁻⁵

Spending time outdoors may slow down myopia progression in myopic children,^{1,2} and as such it is the most common recommended behavioral myopia management solution given by Eye Care Professionals.⁶

However, children are more susceptible to eye damage from UV light than adults, as the majority of lifetime sun exposure occurs under the age of 21.³⁻⁵ Moreover, children's pupils are larger and the crystalline lenses of their eyes are more transparent, which allows more UV rays to reach the retina.⁴ Myopic children on atropine treatment are particularly likely to experience light sensitivity, due to atropine dilating the pupil.⁷⁻⁹

Therefore, children who wear spectacle lenses need a solution that will correct the myopic refractive error and slow myopia progression, as well as protecting them from harmful UV rays and intense sunlight.

That is why HOYA Vision Care developed MiYOSMART Chameleon, a 2-in-1 photochromic spectacle lenses, which adopted Defocus Incorporated Multiple Segments (D.I.M.S.) Technology for effective myopia management and correction of myopic refractive error, while protecting from intense sunlight.¹⁰⁻¹³

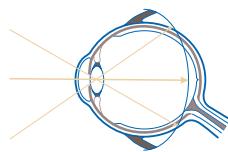
Recent post-marketing surveillance, the Early Experience Program, gained insight directly from



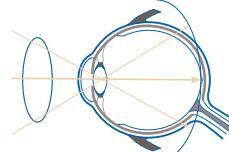
the young patients. The results showed that 80% of children adapted to the photochromic spectacle lenses within one day (n=65, at 2 weeks) and 98% were overall satisfied with MiYOSMART Chameleon (n=55, at 3 months).¹⁴

Furthermore, children who used these photochromic spectacle lenses alongside their atropine treatment had a significant reduction in light sensitivity after 2 weeks of concurrent wear (n=12).¹⁴

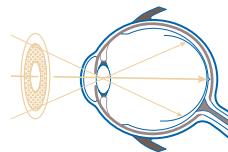
With patient satisfaction and benefits outlined above, MiYOSMART Chameleon has the potential to improve the outcomes of myopia management in children, indoors and outdoors.



Uncorrected myopia



Standard single-vision correction



D.I.M.S. Technology correction

*MiYOSMART Chameleon spectacle lenses adopted the same D.I.M.S. Technology as MiYOSMART clear spectacle lenses. Average of 60% myopia progression reduction in children aged 8-13 when using MiYOSMART clear spectacle lenses (n=79).¹⁴

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MiYOSMART comes with an extended warranty of 9 months