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Low Dose Atropine in Preventing the Progression of Childhood Myopia: A Randomised Controlled Trial

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ABSTRACT

Purpose: To study the efficacy of low dose atropine (0.01%) eye drops in preventing myopia progression in children by comparing the mean change in spherical equivalent (diopter) and axial length (mm) over a period of one year to a control group and study its effect on near vision, pupil size, keratometry and pachymetry.

Methods: 200 eyes of 100 myopic children were randomized into two groups based on a computer-generated random number table. The treatment group was administered 0.01% atropine eye drop once at bedtime and control group was administered a placebo. The follow up was done 3-monthly for 12 months by assessing the mean change in spherical equivalent and mean change in axial length. Other parameters like near vision, pupil size, keratometry and pachymetry were assessed at each follow up.

Result: The study was age and sex matched. The mean change in spherical equivalent refraction and axial length was significantly lower in the treatment group (0.31 ± 0.55 D; 0.11 ± 0.22 mm) than the placebo group (0.80 ± 1.65 D; 0.23 ± 0.44 D) (p-value: 0.003). Less steepening of the corneal curvature was observed in the treatment group (0.16 ± 0.28 D vs 0.29 ± 0.3 D; $p < 0.001$) and the mean change in pachymetry was comparable between the groups (0.00 ± 0.01) (p-value 0.489). No significant change was seen in near vision (96% of the eyes with atropine had no change in near vision; 2% of the eyes had a change of near vision by one line (p-value 0.500); 2% had a change by 3 lines (p-value: 0.07) or pupil size following treatment.

Conclusion: The use of 0.01% atropine eye drop reduced the progression of myopia over the study period of one year with no significant changes in near vision, pupil size. No patient reported any systemic and local side effects with administration of 0.01% atropine eye drop.

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Atropine; myopia; childhood myopia; refractive error; axial length

Introduction

Myopia, commonly known as near-sightedness is a common refractive error. The current global prevalence of myopia and high myopia is estimated to be 28.3% and 4% respectively[1] with Asian countries sharing the largest burden.[2] Nearly half of the world's population is likely to be myopic by 2050 and 10% among these will suffer from high myopia owing to environmental factors including lifestyle changes which lead to a decreased time spent outdoors.[1] Sheeladevi et al. in 2018 stated that myopia had a prevalence of 5.3 per hundred in children under 15 years of age in India.[3] With increase in the severity of myopia, there is an increased risk of complications like chorioretinal degeneration, retinal detachment, myopic maculopathy, glaucoma and cataract and amblyopia.[4,5] Considering the global scenario, there is a huge socio-economic and psychological burden limiting the educational and employment opportunities,[6] deteriorating the quality of life of the affected population.[7]

Myopia management options using various optical and surgical methods are well known. However, the rising number of cases suggest that prevention, although difficult to achieve if exact cause of myopia is not established, should be emphasized upon besides the current approach of treating myopia, else the burden of this existing global public health issue may worsen. The options available to slow the progression include adapting healthy ocular habits, like increasing time outdoors and reducing the duration of near activities,[8] which requires immense amount of counselling and motivation and is difficult considering the busy parental schedules. Other options like orthokeratology,[9] soft contact lens[10] have shown to be effective, but the concerns of hygiene and patient compliance is an issue, more so in developing countries where such a preventive modality for reducing myopia progression may not be possible on a large scale.

Atropine in different concentrations is the most sought after antimuscarinic agent studied and compared with others like cyclopentolate[11] to establish the most effective dose and duration in retarding the myopic progression. The quest for atropine and its role on myopic progression dates to the nineteenth century.[12] Brodstein et al. in a long term prospective cohort study established the efficacy of 1% atropine in preventing the progression of myopia.[13] Initial landmark trials included higher concentration of 1% atropine to assess

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the effect on progression of myopia and it was established that higher doses of atropine were more effective in reducing the progression but also were associated with side effects due to mydriasis.[14–19.] Recent landmark trials include a five-year clinical trial published in 2015 on Atropine for the Treatment of Myopia (ATOM 2) conducted by Chia et al. on 400 Asian children receiving Atropine in concentrations of 0.5%, 0.1% and 0.01% in a ratio of 2:2:1 at bedtime in both their eyes. The study at the end of 2 years concluded that although higher concentrations of atropine administration were more effective in retarding myopic progression, 0.01% topical atropine administration was effective in retarding myopic progression with lesser adverse effects when compared with higher concentrations and less rebound after stopping treatment. Baseline refraction was -4.7 D (SD 1.8) in 0.5% group, -4.8 D (SD 1.5) in 0.1% group and -4.5 D (SD 1.5) in 0.01% group. The mean progression with different concentrations in terms of spherical equivalent at the end of phase 1 of this trial was 0.15 D/year, 0.19 D/year, and 0.25 D/year respectively for 0.5% atropine, 0.1% atropine, and 0.01% atropine, respectively. The mean increase in axial length was 0.27 ± 0.25, 0.28 ± 0.28, and 0.41 ± 0.32 mm in the 0.5%, 0.1%, and 0.01% groups, respectively. However, it also concluded that even though low dose atropine is effective in slowing the progression of myopia in terms of spherical equivalent, it does not have a significant effect in retarding the growth of the eyeball. Allergic conjunctivitis and dermatitis were seen in 16 cases in the 0.5% and 0.1% atropine group.[20] Another study called the LAMP (Low-concentration Atropine for Myopia Progression) study recruited a total of 438 subjects and they were randomized into four groups who were administered 0.05%, 0.025% and 0.01% atropine eye drops and a control group respectively at night to both eyes for 1 year. At the end of one year, they concluded that 0.05%, 0.025%, and 0.01% atropine eye drops reduced myopia progression along a concentration-dependent response with a change in spherical equivalent refraction being 0.27 ± 0.61 D, 0.46 ± 0.45 D, 0.81 ± 0.53 D respectively as compared to 0.81 ± 0.53 D in the placebo group. The change in axial length was found to be 0.20 ± 0.25 mm, 0.29 ± 0.20 mm, 0.36 ± 0.29 mm respectively in the 0.05%, 0.025% and 0.01% group as compared to 0.41 ± 0.22 mm in the placebo group. No adverse effect was observed on vision-related quality of life.[21] Hence, the studies that were conducted later included reduced concentration of atropine assess the efficacy and side effect profile.[19–27] In the second phase of the LAMP study, the placebo group subjects were administered 0.05% atropine eye drops and the other groups continued their respective treatment for another year. At the end of the second year, they found that the mean progression in spherical equivalent refraction was 0.55 ± 0.86D, 0.85 ± 0.73D, and 64 1.12 ± 0.85D in the 0.05%, 0.025%, 0.01% atropine groups, respectively and mean change in axial length was 0.39 ± 0.35 mm, 0.50 ± 0.33 mm, and 0.59 ± 0.38 mm in the 0.05%, 0.025% and 0,01% groups respectively. Based on their observations, they concluded that the efficacy of 0.05% atropine was double that of 0.01% atropine, and it is the most optimal concentration amongst the studied concentrations.[28] In the subsequent third phase of the LAMP study, the enrolled children were divided into two groups: the ones who continued treatment and the others being the washout group. It was observed that the progression of spherical equivalent refraction and axial length was more in the washout group in comparison to the group that continued treatment, although the differences in rebound effects were insignificant across the groups.[29]

Considering the variable range of concentrations of atropine used and paucity of literature signifying the effect of atropine in Indian children, this study was conducted by the authors to assess whether Indian eyes behave similarly or otherwise.

Methods

This prospective randomized controlled trial was conducted on a 112 children of the age group 5 to 12 years out of which 12 children were dropped out (as they were lost to follow up), with a baseline myopic spherical equivalent of -0.5 D to -10.0 D. Children having other congenital eye diseases, an astigmatism of >/= 1.5 D; children already undergoing myopia control, children with associated corneal opacity, glaucoma, strabismus, cataract; history of allergy to atropine; a previous history of intraocular surgery; any systemic illness (congenital heart disease, chronic respiratory disease, pyloric stenosis) were excluded from the study. Written informed consent was obtained from the parents and verbal assent was taken from the children before starting the trial. Ethical clearance was obtained for conducting the trial from the Institutional Ethics Committee- Human Research, University College of Medical Sciences, Delhi. All procedures were conducted abiding the Declaration of Helsinki.

During the baseline visit, history of the patient was elicited and at each visit, distant visual acuity (uncorrected and best corrected visual acuity) using Snellen's chart, near visual acuity using Roman test types, photopic and mesopic pupil size measurement using a ruler under ambient light conditions, cycloplegic refraction (attained using homatropine 2% eye drop for three doses 10 min apart) using an autorefractor (UNICOS, URK-800F) by considering an average of 5 readings, anterior and posterior segment examination, axial length measurement by A-scan (Biomedix Echorule Pro) by considering an average of 5 readings[30], keratometry (UNICOS, URK-800F) considering an average of 3 readings[31], pachymetry (TOPCON SP3000P) were done. All subjects were prescribed spectacles based on their post mydriatic testing. All the investigations were done by a single investigator. One group was given commercially available 0.01% atropine eyedrop (Eyedrop Myotry 0.01% Atropine sulphate ophthalmic solution, NRI Vision Care India Ltd) and the other was given artificial tear eye drop (hydroxypropyl methylcellulose 0.3%) in an identical vial, one drop in each eye at night in the allocation ratio of 1:1. The participants of the study were randomised into two groups based on a computer-generated randomisation. All participants

were examined at baseline and were followed up three monthly till one year. Compliance was assessed based on history and the number of empty vials brought back by the parents of the children being studied.

The outcome measures were to compare the progression of myopia between the groups in terms of mean change in spherical equivalent refraction (Diopters) and mean change in axial length (mm) and to analyse the changes in near vision, pupil size, corneal curvature, and corneal thickness. All ophthalmic parameters were monitored from baseline and if any ocular or systemic side effects were experienced by the child were noted.

Statistical analysis: Considering the mean value of -0.1 D in the treatment group and -0.6 D in the control group; and standard deviation of 0.6 in the treatment group and 0.4 in the placebo group, effect size of 0.98 was calculated.[16] Study was conducted to detect if the effect size is significant. This study was conducted on a sample size of a hundred children (200 eyes; 100 in each group) with a power of 80% and a type 1 error of 5%.

The quantitative variables were expressed as mean ± SD and compared between groups using the unpaired t-test and within groups across follow-ups using a paired t-test. Kruskal-Wallis test was employed where the number of groups is greater than two. A repeated measures ANOVA was used to detect any overall differences between related means. A p-value < 0.05 was considered statistically significant.

Results

A total of 100 children (200 eyes) were recruited in the study. 50 children were given 0.01% atropine eye drop and the other 50 children were given a placebo (lubricating eye drop). There was no significant difference between age and sex distribution of the sample; baseline parameters like mean spherical equivalent refraction, mean axial length, near vision, pupil size, corneal curvature, and central corneal thickness. (Table 1)

The mean age in the treatment group was 9.46 ± 2.65 years and the mean age in the control group was 9.66 years ±2.34 years (p-value 0.286). The sex ratio in this study was 1.22:1.

The mean change in spherical equivalent refraction and the mean change in axial length in the treatment group and in the placebo group over the study period of one year were statistically significant and have been mentioned in Table 2 (Table 2).

Table 2. Mean change in spherical equivalent refraction and axial length between the groups.

Group	Mean change in spherical equivalent refraction (D)	Mean change in axial length (mm/)
Atropine	0.31 ± 0.55	0.11 ± 0.22
Placebo	0.80 ± 1.65	0.23 ± 0.44
p-Value	**0.003**	**0.007**

The mean change in spherical equivalent refraction over the study period of one year was 0.31 ± 0.55D in the treatment group versus 0.80 ± 1.65 D in the placebo group. The mean change in axial length over one year was 0.11 ± 0.22 mm versus 0.23 ± 0.44 mm n the treatment and placebo group respectively (Figure 1) (Figure 2).The mixed two factor repeated measures ANOVA suggested that treatment groups significantly affect the spherical equivalent refraction over time (p-value: < 0.01) as well as the the axial length over the visits (p-value: < 0.01).

No change was observed in the scotopic and mesopic pupil size of the children, measuring an average of 4.48 mm (p-value: 0.468) and 2.10 mm respectively (p-value:1.00)

A significant increase in the keratometry readings was observed during the study (p-value: < 0.001) with the increase in corneal curvature of the treatment and the mean change in central corneal thickness was comparable between the groups. (p-value:0.489) (Table 3).

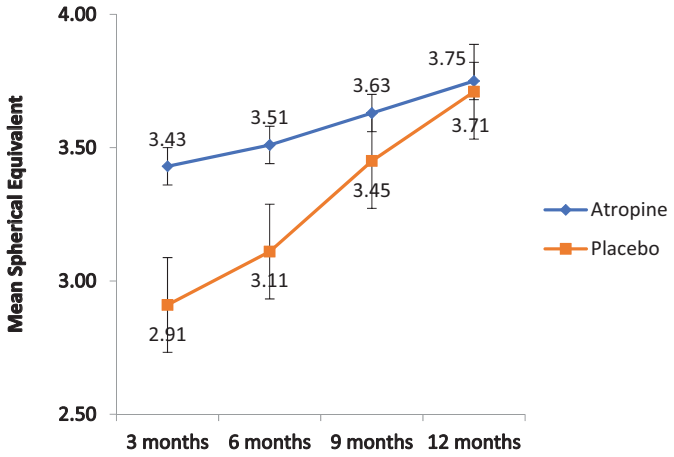

Figure 1. Graph depicting the mean spherical equivalent refraction in diopters during the follow up period of one year.

Table 1. Baseline characteristics of the study population.

	Atropine	Placebo	p-Value
Age (in years)	9.46 ± 2.65	9.66 ± 2.34	0.286
Gender			
Total no. of male eyes	58 ($n = 29$)	52 ($n = 26$)	0.197
Total no. of female eyes	42 ($n = 21$)	48 ($n = 24$)	
Spherical equivalent (diopters)	3.43 ± 3.32	2.91 ± 2.74	0.114
Axial length (mm)	24.36 ± 1.68	24.11 ± 1.32	0.120
Pupil size (scotopic)	4.48 ± 0.43	4.48 ± 0.44	0.468
Pupil size (mesopic)	2.10 ± 0.16	2.10 ± 0.32	1.00
Mean corneal curvature (diopters)	44.59 ± 1.74	44.42 ± 1.69	0.244
Central corneal thickness (mm)	0.52 ± 0.03	0.51 ± 0.03	0.322

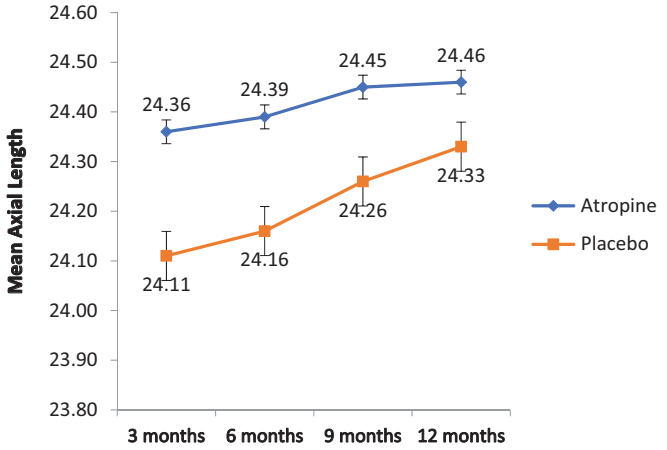

Figure 2. Graph showing the mean axial length in millimeters over the follow up period of 1 year.

Table 3. Mean change in corneal curvature and central corneal thickness.

Group	Change in corneal curvature(D)	Change in central corneal thickness(mm)
Atropine	0.16 ± 0.28	0.00 ± 0.01
Placebo	0.29 ± 0.3	0.00 ± 0.01
p-Value	**<0.001**	**0.489**

Discussion

Myopic refractive error in younger age group is usually due to a progressive increase in the axial length of the eyeball. In some cases, large increase in axial length may result in changes in the posterior segment resulting in a condition called pathological myopia.[1–4] Preventing the progression of myopia is a subject matter for a lot of ongoing research which leaves us to debate on which of the currently available options are better and at the same time yearning for newer and more effective options.

Among the options available to retard the progression of myopia, pharmacological methods are a good option as far as ease of administration is concerned which could be an important factor leading to better compliance. Various studies[13–29] with various concentrations have been conducted to evaluate the efficacy of this agent in halting the progression but the ideal concentration which can retard the progression of myopia without considerable side effects is still a concern.

Among the studies that exist in the literature, measures like spherical equivalent refraction and/or axial length were used as parameters to assess the progression of the myopic refractive error.[16,18]

Majority of the studies for the use of atropine in myopia have been concentrated in the east Asian countries like Singapore and Taiwan, owing to the large proportion of population suffering from myopia. It is also essential to determine the efficacy of atropine in other populations including the Indian subgroup of population as there may be a role of genetic factors determining the response to atropine.

This study at the end of twelve months using 0.01% of Atropine sulphate eye drops resulted in a mean change in the spherical equivalent in the treatment group of 0.31 ± 0.55 D and in the placebo group of 0.80 ± 1.65 D (*p*-value 0.003); and the mean change in axial length in the treatment group of 0.11 ± 0.22 mm and in the placebo group of 0.23 ± 0.44 mm (*p*-value 0.007) which was statistically significant. It is evident from the results of this study that the use of low dose atropine is efficacious in bringing about a retardation in progression of myopia which has also been the case in previous literature.[20,21,25–27]

Atropine in its commercially available therapeutic concentration of 1% causes mydriasis thereby impairing near vision and the quality of vision due to glare. The concentration of atropine used in this study is 1/100th of the commercially available therapeutic dose and hence did not lead to any change in pupil size and near vision as seen in some previously conducted studies.[21,25,26] Although lighting conditions were not monitored during the various visits in the study duration, an objective method of pupil size measurement in light controlled settings must be used to establish concrete results on pupil size. Yam et al. in 2019 reported a dose dependent change in pupil size measured using a corneal topographer following administration of atropine at various concentrations under photopic and mesopic conditions.[21] Also, Fu et al. in 2020 suggested that there was a significant increase in pupil diameter by 0.78 ± 0.42 mm, 0.69 ± 0.39 mm, with 0.02% and 0.01% atropine, respectively (*p*-value <0.001) as measured by an autorefractor.[27]

According to the Correction of Myopia Evaluation Trial (COMET) which measured physiological changes in corneal curvature over the years in children, an overall trend of slight flattening of the flatter meridian and slight steepening of the steeper meridian was observed between the age of 6–14 years. The rate of change observed in males (−0.0099 D/year) and females (−0.0114 D/year) [32] Also, the central corneal thickness increases with age from 1 to 11 years of age followed by plateauing; with a marked rise younger age groups.[33] In this study, it was observed that there is a significant change in the corneal curvature, steepening in the placebo group (0.29 ± 0.3D) being more than that of the treatment group (0.16 ± 0.28 D)(*p*-value <0.01) which could suggests that atropine could reduce myopic progression by influencing the corneal curvature. Such an effect has been also established by a study which was an extended study by the LAMP group.[34] Changes in central corneal thickness was assessed to see if the rate of progression in myopia was associated with any changes but did not show any statistical difference among the two groups. However, both these observations need to be strengthened with more evidence from further studies and extensive research is needed to assess if there is a direct mechanism of action of atropine on the cornea. The authors suggest that the effect of low dose atropine on corneal curvature may be an indirect one by means of an overall reduced rate of progression in axial length, lesser stretching of the eyeball and hence lesser changes in corneal curvature as well. The effect of atropine directly on cornea has not been established this far and this needs to be studied further.

This study observed that 0.01% atropine sulphate eye drops significantly retards the progression of myopia in

comparison to the controls. Since it is administered as once daily bedtime dosing, its use is less cumbersome, and a higher compliance can be achieved. Such bedtime dosing is also preferable to avoid any side effects owing to pupillary dilation which may occur. Parents of the affected children should be counselled regarding the safety and efficacy of the drug.

The strength of the study is that it is among the initial few studies on this issue in this subgroup of population where a prospective randomized placebo-controlled trial was conducted. However, a larger sample size using one eye of each participant in order to prevent correlation between the two eyes, an objective measure of pupil size and an objective control of lighting conditions during measurement of pupil size for a better and detailed evaluation of these parameters is desirable. A longer duration of study is needed to assess the efficacy and side effects of atropine better. This study also gives a thrust for further research based on cornea-based mechanism of action of atropine in retarding the progression of myopia.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The data that support the findings of this study are available from the corresponding author, Isha Sharma, upon reasonable request.

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