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Factors Affecting Formation of Type-1 and Type-2 Big Bubble during Deep Anterior Lamellar Keratoplasty

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ABSTRACT

Purpose: To determine the factors associated with the formation of different types of big bubble (BB) during DALK.

Methods: In this retrospective study, 322 consecutive eyes of 307 patients with corneal stromal disorders who underwent DALK between January 2014 and June 2017 were included. Age, sex, corneal pathology, visual acuity, corneal curvature, corneal thickness, and adverse events were recorded. The main outcome measure was the success of BB formation with respect to the corneal pathology.

Results: Type-1 BB was achieved in 147 eyes (45.7%), whereas type-2 BB was formed in 109 eyes (33.9%). The overall success rate of BB formation was 82.9%. Type-1 BB formation in keratoconus patients was significantly higher than type-2 BB (83.8% vs 2.6%, $p < 0.001$). In contrast, type-2 BB formation was significantly higher than type-1 BB (61.0% vs 15.6%, $p < 0.001$) in patients with corneal scars. Type-1 BB was more likely to be seen in patients with superficial corneal scarring, granular, and lattice dystrophies, while corneas with deep scarring and macular dystrophy had more type-2 BB. The type of bubble was not associated with age and gender of the patients.

Conclusions: The overall success of big-bubble (BB) deep anterior lamellar keratoplasty (DALK) depends on the preoperative corneal pathology. Type −1 BB was more commonly seen in keratoconus patients whereas type-2 BB was observed in patients with deep corneal scars and other corneal pathologies affecting deeper layers of corneal stroma.

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DALK; big-bubble technique; type-1 big-bubble; type-2 big-bubble

Introduction

Deep anterior lamellar keratoplasty (DALK) has become the preferred surgical option for treatment of corneal stromal pathologies such as keratoconus, corneal scars, and corneal stromal dystrophies. The advantages of DALK over penetrating keratoplasty (PKP) include maintenance of globe integrity, absence of endothelial rejection, and a low rate of chronic endothelial cell loss.[1–3] In conventional anterior lamellar keratoplasty, only a portion of the corneal thickness is replaced whereas DALK involves the removal of central corneal stroma while leaving host corneal endothelium and Descemet's membrane (DM) intact.

Anwar and Teichmann described the big-bubble (BB) DALK. This surgical technique allows deep lamellar dissection and baring of Descemet membrane.[4] The big bubble is referred to as "type-1 big-bubble" when it is dome-shaped, well circumscribed, central, and has white margins. A second bubble type, or "type-2 big-bubble", is a thin-walled, "clear margin" big bubble, which leaves only DM beneath the bubble.[5] The tissue located between the type-1 and type-2 bubbles is now referred to as "pre-Descemet stroma" (PDS).[6] The posterior wall of a type-2 BB and the type-2 component of a mixed BB are composed of DM only. Consequently, these bubbles are more susceptible to large tears during surgery.[7] Goweida[8] evaluated the intraoperative complications of the two bubble types formed during DALK. The results showed that the rate of conversion to PKP in surgeries encountering type-2 BB was high (86%). In our study, we analyzed the factors associated with the formation of different bubble types during DALK.

Materials and methods

In this retrospective study, 322 consecutive eyes of 307 patients were included. All eyes underwent big-bubble DALK at the Eye Hospital of Wenzhou Medical University between January 2014 and June 2017 for corneal stromal disorders including keratoconus (KC), corneal dystrophies (CD) and corneal scarring (CS). Patients with infectious keratitis, scarring of DM, corneal edema, corneal perforation, bullous keratopathy, glaucoma, cataract, macular degeneration, and amblyopia were excluded.

Intraoperative bubble types were recorded, and videos were analyzed. Patients were divided into four groups by bubble type: type-1 BB, type-2 BB, mixed BB, and failed BB formation. Eyes with corneal scarring were divided into two groups, shallow scarring and deep scarring, according to whether evident corneal opacity was still observed after removal of the anterior 50–60% of the corneal stroma.

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All patients were followed after surgery for a minimum of three months. The bubble type and intraoperative complications for each case were documented. Additional data recorded included age, sex, corneal pathology, visual acuity, and Pentacam-based corneal curvature and thickness.

This study was approved by the Institutional Review Board of Wenzhou Medical University and adhered to the tenets of the Declaration of Helsinki. A written, informed consent was obtained from all subjects or their guardians prior to surgery.

Surgical procedure

All surgeries were performed by the same surgeon (WC) under retrobulbar or general anesthesia. The host cornea was trephinated up to approximately 50–60% of its thickness using a Hessburg-Barron vacuum trephine. After manual removal of the anterior lamella, a blunt 27-gauge air needle was inserted into the residual stromal bed to form a bubble. As reported by Tan et al.,[9] this modified BB DALK technique enables more predictable and deeper placement of the needle in corneal stroma. If the formation of a big-bubble fails during the primary attempt, the injection can be repeated at a different site. In addition, the recipient bed can be irrigated with sterile hypotonic water to induce stromal swelling for further dissection.

Following this procedure, one of the four previously mentioned bubble types would be seen. Corneal stromal separation was then performed for type-1 BB or mixed bubbles. In cases where a clear margin type-2 BB or failed BB occurred, additional deeper manual "wet-peeling" dissection was performed.[10] Iris forceps (Iris Forceps 4-101s; Rumex Inc., Clearwater, USA, each tooth of iris forceps is 0.063 mm long) were used to deepen the trephination groove to approximately 80–90% depth. Next, a modified blunt-tipped iris spatula (Xiehe Medical Instruments Company, Suzhou, China; the narrow tip is 0.24*0.50 mm and the wide tip is 0.12*0.80 mm) was inserted carefully into the pocket using slow gliding movements. The separated partial-thickness lamella was excised using a pair of blunt-tipped scissors. Significant edema of residual stromal fibers was observed above the type-2 BB after irrigation with sterile hypotonic water. This facilitates the creation of another stromal pocket and subsequent dissection. The small bubbles in stroma or stromal emphysema indicate the residual corneal stroma. Further dissection was undertaken to remove the residual corneal stroma until there was no corneal emphysema to reach the pre-Descemetic stromal level. The type-2 BB was then expelled using a 15-degree knife or iris forceps. To conclude the procedure, a DM-off donor corneal button with a diameter 0.25 mm larger than the recipient bed was sutured on to the host bed using 10–0 nylon sutures.

Postoperative management consisted of antibiotic-steroid combination eye drops 4 times daily for the first month. The eye drops were tapered off over a period of 6 months. Sutures were removed starting 3 months after DALK.

Statistical analyses

The categorical data comparisons were assessed by $\chi 2$ test, including gender, laterality, and incidence rates of different types of bubbles. The quantitative data was assessed by the unpaired t-test, including age, BSCVA. The statistical differences in trephination sizes were analyzed using Fisher's exact test and Wilcoxon rank sum test. SPSS 20.0 statistical analysis software was used to analyze the data. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

A total of 322 consecutive eyes were included in this study. The indications for surgery were, corneal scarring secondary to herpes simplex keratitis (HSK) (n = 102), KC (n = 117), CD (n = 64), and other corneal scars (n = 39). The average age of patients was 38.6 years (range, 14–72 years), with a median follow-up time of 17 months. The demographic data and operative details are summarized in Table 1. There were no significant differences in laterality or sizes of trephination among the three groups. However, gender and age were significantly different among the three groups. Keratoconus patients were more likely to be young males as compared to patients in CS and CD groups.

Four types of bubbles were observed during DALK as shown in Figure 1. Type-1 BB was seen in 147 eyes (45.7%), whereas type-2 BB was formed in 109 eyes (33.9%). Eleven eyes (3.4%) had mixed bubbles (Figure 2). Big bubble failed to form in 55 eyes (17.1%). Microperforation occurred in 12 (3.7%) eyes. A successful lamellar dissection was performed in all cases without conversion to PKP. Manual dissection using the wet-peeling technique was used in 50.9% of the eyes after type-2 BB formation or failed BB.

Overall, big-bubble formation (including type-1, type-2, and mixed bubbles) was observed in 82.9%, of which keratoconus, corneal scarring, and corneal dystrophies comprised 88.0%, 81.6% and 76.6%, respectively. The success rate was significantly different between keratoconus and corneal dystrophies, as well as between corneal scarring and corneal dystrophies. Table 2 shows the incidence of different intraoperative bubble types based on the primary diagnosis. Keratoconus patients had significantly higher number of type-1 BB compared to patients with corneal scar and corneal dystrophies, whereas patients with corneal scarring had higher number of type-2 BB compared to

Table 1. Demographic and surgical data.

	KC	CS	CD	p
Age (mean±SD, years)	24.2 ± 5.6	48.4 ± 12.1	41.5 ± 11.7	0.000
Male: female (n)	84:33	78:63	35:29	0.013
Left: right (n)	56:61	75:66	31:33	0.658
Host diameter [median (IQR), mm]	8.0 (8.0,8.25)	8.0 (8.0,8.25)	8.0 (8.0,8.25)	0.856
Donor diameter [median (IQR), mm]	8.25 (8.25,8.5)	8.25 (8.25,8.5)	8.25 (8.25,8.5)	0.829

KC = Keratoconus; CS = Corneal scar (HSK induced CS was 102 among them); CD = Corneal dystrophies; IQR = interquartile range; SD = standard deviation.

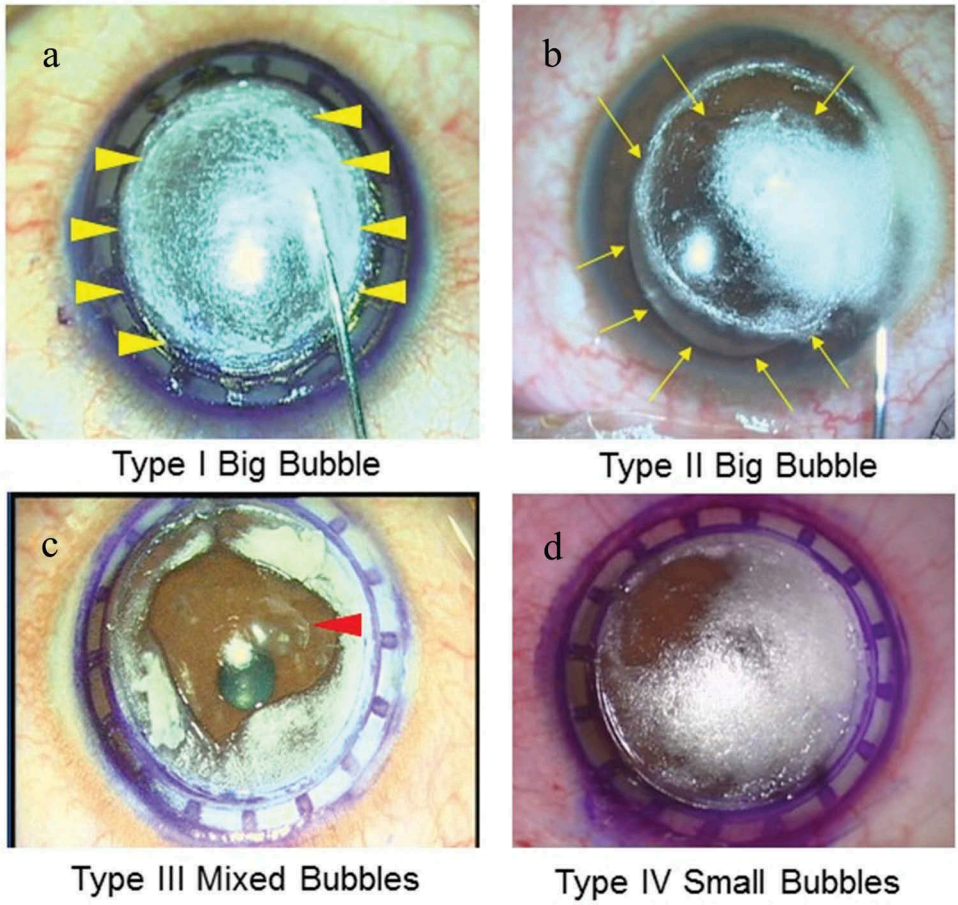

Figure 1. Four bubble types encountered during DALK using the big-bubble technique: **a**. Type-1 big-bubble is a well-circumscribed, white-bordered, central dome-shaped bubble (yellow arrows) between stroma and pre-Descemet stroma (PDS). **b**. Type-2 big-bubble is a clear-bordered, thin-walled bubble (yellow arrows) between PDS and DM. **c**. Mixed BB after removal of the stroma overlying a type-1 bubble; a type-2 bubble is evident between PDS and DM (red arrowhead). **d**. Small bubbles, or failure of big bubble formation, showing only small bubbles in stroma. Manual dissection by wet-peeling was performed in cases which resulted in type-2 BB or type-4 small bubbles.

KC and CD groups. In keratoconus patients, 83.8% of patients had type-1 BB and 2.6% had type-2 BB (p = <0.001). The corresponding numbers were 61.0% and 15.6%, respectively, in patients with corneal scarring (p = <0.001). Patients with corneal dystrophy had a comparable number of type 1 and type 2 BB (42.2% vs 31.3%, p = 0.199).

In the CS group, the depth of the scar was shown to be an important factor in BB formation. As shown in Table 2, corneas with superficial corneal scarring had higher chances of type-1 BB, while those with deep corneal scarring had more type-2 BB. Corneas with granular and lattice dystrophies were more likely to have type-1 BB, while type-2 BB was more likely to be encountered in macular dystrophy.

The mean preoperative BSCVA was 1.42 ± 0.55 LogMAR (0.5 ~ 2.3), which improved to 0.35 ± 0.21 logMAR (0.0 ~ 1.0) (P < 0.01) postoperatively. No significant difference was observed for BSCVAs in different BB groups (P > 0.05) (Table 3). A total of 18 (5.6%) eyes had temporary double anterior chambers (AC) which resolved spontaneously or by injection of sterile air into the AC. Episodes of stromal rejection occurred in 11 (3.4%) eyes and were managed successfully with topical corticosteroids. Recurrence of HSK was observed in 2 (0.62%) eyes, which resolved after treatment with oral antiviral agents.

Discussion

It is known that the cleavage plane during DALK with a white margin type −1 BB is intrastromal, as compared to the type-2 BB with a clear margin in which the cleavage plane is between stroma and DM.[6,11–13] The learning curve of DALK certainly influences the rate of surgical success.[14,15] The rate of formation of BB was 82.9% in the current study. In previous studies, the rate of BB formation varied from 35% to 95%.[16,17] The rate of BB formation in keratoconus varied from 61.4% to 90%,[8,18–22] however, the success rates of BB could drop to 38.2% in patients with CS.[8] In our study, the BB formation rates were 88.0% in KC, 81.6% in CS and 76.6% in CD. The results are similar to those reported in a study by Huang et al. which stated that DM was exposed successfully in 80.6% of the eyes with advanced keratoconus, 73.3% of the eyes with chemical or thermal burns, 71.4% of the eyes with corneal dystrophy, and 70% of the eyes with HSK induced scar. Arslan et al. also reported a complete Descemet membrane exposure via BB DALK in 79% cases with corneal stromal scars.[23] However, the authors did not differentiate type-1 from type-2 BB. In our study, type-1 BB was encountered in 83.8% of KC patients, 15.6% of CS patients and 42.2% of patients with CD. By contrast, type-2 BB was encountered in

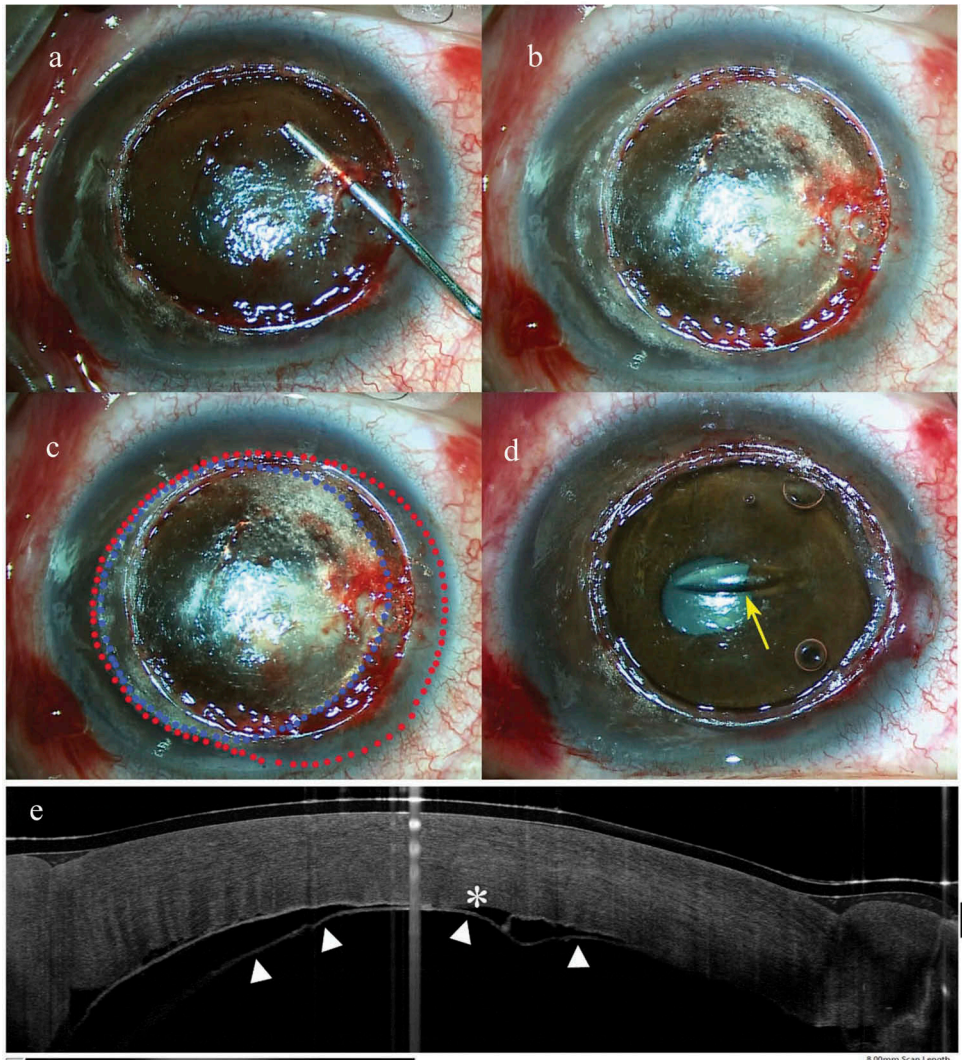

Figure 2. Big-bubble (BB) deep anterior lamellar keratoplasty with mixed bubbles. **a**. Corneal opacity can be observed after manual removal of the anterior corneal stroma. A blunt 27-gauge air needle was inserted into the residual stromal bed to form a bubble. **b**. Formation of combined type-1 and type-2 BB. **c**. Mark points indicating the borders of type-1 (blue) and type-2 (red) BB. **d**. Spontaneous fissure of pre-Descemet's stroma (PDS) and descemetocele (arrow) can be found after removal of pathological stroma by routine procedure of quartering separation (big bubble technique). In these cases, we did not open the interspace of type-2 BB and retain PDS. Air bubble leaked out from the fissure of PDS, but two small type-2 bubbles were retained. **e**. Anterior segment OCT immediately after surgery showed fissure in PDS (asterisk) and detached DM (arrowhead) which resolved spontaneously in three days.

2.6% of KC patients, 61.0% of CS patients and 31.3% of patients with CD.

The factors influencing different types of BB formation in various corneal pathologies are not clear. It may be attributed to the structural difference in PDS among individual eyes. The relatively high incidence of type 2 big bubble in this study may be attributed to the large number of eyes with corneal scars. Corneal edema during active HSK may weaken the adhesions between corneal stroma (including PDS) and DM. After stromal edema subsides, scarring may cause a firmer adhesion between stroma, PDS, and DM, leading to difficult separation from the overlying stroma via air injection when attempting to form a type-1 BB.

DM perforation is one of the main complications of DALK. Previous studies have reported DM perforation during DALK, ranging from 5% to 19%, needing a conversion to PKP in up to 12% of cases.[18–23] In our study, viscoelastic material was injected to maintain the space between PDS and posterior stroma after formation of a successful type-1 BB. No perforations occurred during any of the type-1 BB DALK procedures. We now know that a type-1 BB has a stronger posterior wall. It is, therefore, less likely to tear or burst during surgery. Dua et al. pointed out that the popping pressure of a type-2 bubble was about 2.42 times less than that of a type-1 bubble.[6] Lewis[24] revealed that the 8 μm posterior stroma anterior of the DM has a large amount of elastic fibers, whereas in other regions, the number of elastic fibers is extremely low. The net of elastic fibers anterior to the DM is expandable. It allows to hold the pressure of the air bubble. Despite the thinner collagen fibrils of the PDS arranged in an irregular interwoven lattice, a complex network of elastic fibers exists which crosses over the PDS and confers extensibility to type-1 bubble. Thus, when the posterior wall of a type-1 BB perforates, DALK can still be successfully completed as the tear does not extend. Goweida[8] reported a 10.4% rate of type-2 BB in their study along with DM rupture in 86% of the eyes needing conversion

Table 2. Different intraoperative bubble types during big bubble DALK (n, %).

	Type-1	Type-2	Mix	Failed	Subtotal
Keratoconus	98 (83.8%)	3 (2.6%)	2 (1.7%)	14 (12.0%)	117
Kmax≥65 D	46 (82.1%)	1 (1.8%)	1 (1.8%)	8 (14.3%)	56
Kmax<65 D	52 (85.2%)	2 (3.3%)	1 (1.6%)	6 (9.8%)	61
p	.649	.610	.951	.459	
TCP≥400 μm	56 (88.9%)	1 (1.6%)	0	6 (9.5%)	63
TCP<400 μm	42 (77.8%)	2 (3.7%)	2 (3.7%)	8 (14.8%)	54
p	.104	.470	.123	.379	
Corneal scarring	22 (15.6%)	86 (61.0%)	7 (5.0%)	26 (18.4%)	141
Shallow	18 (47.4%)	11 (28.9%)	1 (2.6%)	8 (21.1%)	38
Deep	4 (3.9%)	75 (72.8%)	6 (5.8%)	18 (17.5%)	103
p	.000	.000	.439	.627	
≥55 years	7 (16.7%)	26 (61.9%)	2 (4.8%)	7 (16.7%)	42
<55 years	15 (15.2%)	60 (60.6%)	5 (5.1%)	19 (19.2%)	99
p	.821	.885	.942	.724	
Corneal dystrophies	27 (42.2%)	20 (31.3%)	2 (3.1%)	15 (23.4%)	64
Granular	9 (75.0%)	0 (0)	0 (0)	3 (25.0%)	12
Lattice	14 (60.9%)	2 (8.7%)	0 (0)	7 (30.4%)	23
Macula	4 (13.8%)	18 (62.1%)	2 (6.9%)	5 (17.2%)	29
p	.000	.000	.288	.531	
Subtotal	147 (45.7%)	109 (33.9%)	11 (3.4%)	55 (17.1%)	322

KC = Keratoconus; HSK = Herpes simplex keratitis; CS = Other corneal scar; TCP = Thinnest corneal point.

Table 3. Intraoperative bubble types during big bubble DALK between males and females (n, %) and postoperative visual acuity in different bubble types.

	Type-1	Type-2	Mix	Failed	Subtotal
Male	94 (47.7%)	63 (32.0%)	6 (3.0%)	34 (17.3%)	197
Female	53 (42.4%)	46 (36.8%)	5 (4.0%)	21 (16.8%)	125
p	.351	.373	.646	.915	
Postoperative BSCVA (logMAR)	0.33 ± 0.25	0.35 ± 0.22	0.35 ± 0.30	0.37 ± 0.26	
p		.095			
Subtotal	147	109	11	55	322

to PKP. The high rate of Descemet rupture and conversion to PKP in a type 2 BB may be attributed to multiple attempts in order to try and bare the Descemet membrane. In our study, microperforation occurred in 3.7% eyes with type-2 BB. We managed type 2 BB using the wet-peeling technique[10]; which is a predescemetic technique used in failed BB and those with post hydrops corneal scars. This may explain the low number of eyes with microperforations in our type 2 BB cases. A similar surgical management for type 2 BB was suggested by Goweida in another study.[25] In contrast to type-1 BB, when the surgeon encounterstype-2 BB results, the conversion should be made to one of the manual dissection techniques and avoid baring of Descemet membrane.

Previous studies have analyzed the effect of severity of keratoconus on big-bubble creation. Huang et al.[26] and Fontana et al.[20] showed a higher success rate in advanced keratoconus or corneas with central mean keratometry >62D (80.6% vs. 36.4% and 73% vs. 55%). Michieletto et al.[27] reported that corneas thinner than 250 μm are more likely to get DM rupture. Feizi et al. found no association between big-bubble formation and corneal steepness, thickness, or anterior stromal scarring in KC.[28] In our study, the success rate of all four types of intraoperative bubbles in KC patients had no relationship to corneal curvature or thickness.

In conclusion, surgeons performing DALK should be familiar with different types of BB which can result following air injection. In our study, the success rate of type-1 BB was significantly higher in the KC group than in the CS and CD groups. The manual wet-peeling technique leaves PDS intact when encountering type-2 and can significantly decrease DM rupture rate.

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