Clinical and Tomographic Outcomes of Intraoperative Descemet's membrane perforation in Deep Anterior Lamellar Keratoplasty

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Received: 27-5-2023, Accepted: 7-8-2023, Published online: 16-12-2023

EJO(MOC) 2023;3(4):183-192.

Running Title: Outcome of intraoperative DM perforation in DALK

Abstract:

AIM: To compare clinical and tomographic outcomes of patients with intraoperative descement membrane (DM) perforation during deep anterior lamellar keratoplasty (DALK) versus straightforward DALK surgery.

METHODS: This was a retrospective comparative study of 49 keratoconic patients who underwent DALK. They were subdivided into group I, which included patients with intraoperative DM perforation (n=13), and group II, included patients without perforation (n=36). Best Corrected visual acuity (BCVA), corneal tomographic parameters, and endothelial cell counts were recorded 12 months postoperatively.

RESULTS: Intraoperative DM perforation occurred in 13 (26.5%) eyes. BCVA became nearly similar in both groups at 12th month (0.30 ± 0.12 vs 0.31 ± 0.13, p=0.816). The mean Endothelial cell density (ECD) at 12 months postoperatively was 1732.62 ± 539.52 in group I compared to 2215.94 ± 265.62 cell/mm^2 in group II (P<0.001*). The mean value of the logarithm of contrast sensitivity (CS) was 0.77 ± 0.235 in group I compared to 1.04 ± 0.187 in group II (P<0.001*). In group I, intracameral air injection correlated with a decrease in postoperative CS and ECD (P=0.001 and 0.004, respectively).

CONCLUSIONS: DM perforation is a common complication of DALK surgery. Intracameral air injection is correlated with a decrease in ECD and quality of vision.

KEYWORDS: Descemet's membrane, microperforation, lamellar keratoplasty

INTRODUCTION:

DALK is the preferred option for treating anterior to mid-stromal corneal opacities, such as keratoconus, scars, dystrophies, and degeneration, due to the absence of endothelial rejection and optimal visual outcome [1-4]. Various techniques have been used to dissect the stroma from the underlying DM [5], including manual dissection [6], or dissection with a viscoelastic substance [7]. The commonest surgical technique used for DALK is the big bubble (BB), advocated by Anwar et Al [8, 9].

DALK has a slightly steeper learning curve than full-thickness procedures 10. It may be complicated by DM micro-perforation in 9.3% to 32% of cases [11]. Micro-perforation may occur during deep stromal air injection, dissection of the host cornea, or suturing of the donor graft [1]. Inadvertent DM micro-perforation, even if surgery is still successfully completed without the need for conversion to PK, has been reported to lead to an increased risk of early postoperative detachment of the recipient bed and consequent double AC formation. Although spontaneous resolution has been reported, this complication usually requires rebubbling of the AC with air or gas for successful management [12].

Despite sealing the micro-perforation, the use of intracameral air could increase the risk of further loss of endothelial cells. In other circumstances, DM macro-perforation due to excessive air injection or improper surgical maneuvers may warrant conversion of DALK into PK [1]. Few studies have compared the outcomes of patients who

underwent DALK with and without intraoperative DM perforation. This study aimed to compare the clinical and tomographic outcomes between patients with intraoperative DM perforation during DALK and those with straightforward DALK surgery.

SUBJECTS AND METHODS:

This retrospective, comparative study was conducted at the Mansoura Ophthalmic Center (MOC), Mansoura University, Egypt and included eyes that underwent DALK surgery between January 2021 and January 2022 due to keratoconus. This study followed the tenets of the Declaration of Helsinki and was approved by the local ethics committee (R.21.06.1360). Each patient provided written consent after being informed of the risks, benefits, and alternatives of surgery.

The study included eyes that underwent DALK surgery due to keratoconus that were not corrected by glasses or were intolerant to contact lenses. Patients with previous attacks of hydrops, corneal dystrophies, or stromal scars due to other causes (post-infectious or post-traumatic) were excluded. DALK patients were divided into two groups: Group I included patients with intraoperative DM perforation and group II included patients with straightforward DALK (without intraoperative DM perforation).

All patients underwent a complete ophthalmic examination before and after surgery; including visual acuity assessment, both uncorrected and best corrected visual acuity (UCVA and BCVA) were recorded using Landolt's charts and converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis, and slit-lamp examination. The corneal parameters were evaluated using the Pentacam® system (OCULUS, Wetzlar, Germany). Specular microscopy (Topcon SP-2000, Tokyo, Japan) was used for endothelial cell analysis in both groups postoperatively. Anterior segment optical coherence tomography (AS-OCT) (3D DRI OCT Triton; Topcon, Oakland, NJ, USA) was used for the postoperative assessment of the graft-host interface and detection of DM detachment (DMD).

Contrast sensitivity assessment was performed at 12 months postoperatively using the Pelli-Robson chart, which includes horizontal lines of capital letters arranged into groups of triplets, with two triplets per line. The contrast decreases from one triplet to the next, even within each line. All patients were assessed under monocular vision at a distance of 1 m from the chart, and under controlled photopic conditions. The data for both groups were retrieved and compared.

All surgeries were performed by the same experienced surgeon (HE) under general anesthesia using the big-bubble technique described by Anwar and Teichmann [8]. The surgery began with trephination up to 70–80% of stromal thickness (7.50 - 8 mm with a suction trephine (Hessburg- Barron vacuum trephine; Katena Products, Denville, NJ, USA). Air was injected intra-stromally using a 27-G bottom port cannula (Tan cannula, ASICO product) until a BB was formed, which was confirmed by an intra-cameral small bubble test [13] through peripheral paracentesis. In cases of successful BB, the superficial corneal stroma was removed using a crescent blade, followed by (Brave Slash) using a 15 ° knife.

The stromal layers were divided into four quadrants and excised completely using blunt-tipped micro-scissors. In cases of failed BB, manual layer-by-layer dissection was performed using blunt-tipped scissors. The dissection was completed as deep and as close as possible to the DM. In cases of DM perforation, the site of perforation (central 4 mm or mid-peripheral 4-6 mm), size (micro-perforations < 1 mm or macro-perforations (in this study, macro-perforations were defined as perforations > 1 mm and less than 2 mm, which were completed as lamellar surgery; however, perforations > 2 mm were converted to PK and were excluded from the study), and the step in which the perforation occurred were recorded.

When DM perforation was noted, air was first injected into the AC through paracentesis to seal the perforation, and then lamellar corneal dissection was completed starting away from the perforation in a centripetal direction. Dissection in the perforation region was always kept to the end to avoid any extension of the DM tears with preserving some lamellar tissue over the area of perforation. At the end of the surgery, the AC was inflated with air to allow the partially torn DM to adhere to the donor corneal button. In both groups, the DM and endothelium of a 0.25 mm oversized donor graft were

stained with 0.06% trypan blue dye (VisionBlue; D.O.R.C.) to enable identification and scraping using a dry sponge. Finally, the stromal graft was fixed to the host corneal bed using interrupted 10-0 nylon sutures.

Postoperatively, all patients received topical antibiotics (moxifloxacin 0.5%) discontinued after complete epithelialization, topical steroids (prednisolone acetate 1%) tapered slowly and discontinued by the end of the first six months, and preservative-free artificial teardrops. Patients were followed-up on the first day, first week, and 1, 3, 6, and 12 months postoperatively.

Postoperative double AC was diagnosed as localized corneal edema with the appearance of fluid between the posterior stroma and the residual host bed, or diffuse and severe corneal edema, making it impossible to visualize DMD clinically, which was confirmed with AS-OCT. Patients with double AC who underwent postoperative intra-cameral air injection ''re-bubbling'' were required to adapt to a supine position overnight and received acetazolamide 250 mg tablets three times a day (Diamox, Remedica Ltd, Cyprus) for 3 days to decrease the incidence of intraocular pressure spikes. Selective suture removal was performed to relax the steep meridian and reduce astigmatism 12 months postoperatively.

STATISTICAL ANALYSIS:

Statistical analyses were performed using SPSS version 25 (2017, Inc., Chicago, IL, USA). The Shapiro–Wilk test was used to check the normality of the data distribution. Quantitative variables are expressed as mean ± standard deviation (SD), while categorical variables are expressed as frequencies and percentages. For quantitative measures, we used independent T and Mann Whitney tests to compare parametric and non-parametric continuous data, respectively. Fisher's exact and chi-square tests were used for categorical data. All tests were conducted with a 95% confidence interval. Statistical significance was set at $P < 0.05$.

RESULTS:

This study included 49 eyes of 49 patients with keratoconus who underwent DALK. The patients were divided into two groups: group I included patients with intraoperative DM perforation (n=13), and group II included patients without perforation (n=36). The mean age was 28.73 ± 9.79 years in group I and 28.31 ± 7.57 years in group II (p=0.881). Group I included 10 females and 3 males, while Group II included 24 females and 12 males. In group I, type II BB was obtained in 3 cases (23.1%), with the cleavage plane between the DM and the posterior surface of Dua's layer (DL) [9]; the remaining 10 cases (76.9%) with failed BB were completed with manual layer-by-layer dissection, while in group II, type I BB, with the cleavage plane between stroma and DL [9], was achieved in 21 cases (58.3%) and failed BB with manual dissection occurred in 15 cases (41.7%).

Preoperatively, visual acuities were worse in group I compared to group II with statistically significant differences in both UDVA (1.76 ± 0.17 vs 1.59 ± 0.25; p= 0.029*), and CDVA (1.50 ± 0.0 vs 1.125 ± 0.12; p=0.014*). Keratometric readings (K1, K2, and Km) were higher in group I compared to group II, but didn't reach statistical significance except in mean K1 readings (61.97 ± 6.67 vs 55.82 ± 9.31 D; p=0.034*). The central corneal thickness was lower in group I than in group II, but the difference was not statistically significant. On the other hand, there was a statistically significant difference between both groups in the mean thinnest point (322.46 ± 30.56 vs 377.53 ± 90.70 um; p=0.038*).

Regarding endothelial cell density (ECD), preoperative specular microscopy could not be obtained in most patients because they had stage IV keratoconus according to the ABCD grading system (Km > 55D) [14] with severe central corneal conical protrusion. All the preoperative data are presented in Table 1. The mean diameter of the corneal graft used was (7.75 ± 0.25) in both groups with no statistically significant difference.

Table 1: Preoperative data of both groups

	Group I (DALK with perforation)	*Group II (DALK without perforation)*	*P*
Preoperative mean K1 reading (D)	61.97 ± 6.67	55.82 ± 9.31	***0.034****
Preoperative mean K2 reading (D)	68.06 ± 7.12	62.55 ± 10.57	0.089
Preoperative mean corneal curvature (D)	64.73 ± 6.58	59.02 ± 9.78	0.058
Preoperative Central corneal thickness (μm)	388 ± 53.89	412.06 ± 83.75	0.341
Preoperative mean thinnest point	322.46 ± 30.56	377.53 ± 90.70	***0.038****
Preoperative UCVA(LogMAR)	1.76 ± 0.17	1.59 ± 0.25	***0.029****
Preoperative BCVA (LogMAR)	1.50 ± 0.0	1.125 ± 0.12	***0.014****

Data are expressed as mean ± SD.

*Statistically significant (P <0.05)

DALK: deep anterior lamellar keratoplasty; D: diopters; UCVA: uncorrected visual acuity, BCVA: best corrected visual acuity; LogMAR: logarithmic of minimum angle of resolution.

Intraoperative DM perforation occurred in 13 (26.5%) eyes. Of the 13 eyes, ten eyes (76.9%) had micro-perforations and three (23.1%) had macro-perforations; three eyes (23.1%) had central perforations and ten (76.9%) had peripheral perforations. According to the surgical procedure, DM perforation occurred during needle insertion at the corneal depth (n=2, 15.4%) during scissor removal of the corneal stoma to leave a bare DM in type II BB (n=3, 23.1%) and during lamellar corneal dissection in the failed BB (n=8, 61.5%). Double AC was identified in nine cases (69.2%), and one single re-bubbling attempt was successful in resolving the double AC in all cases (figure 1).

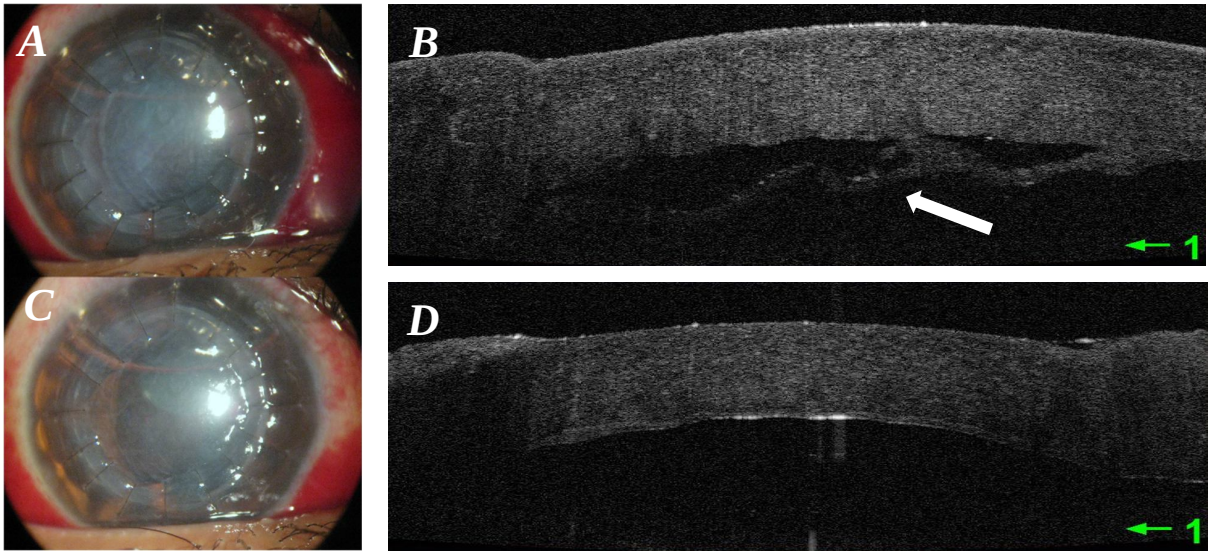

Fig.1 Slit lamp photography showing sever and diffuse corneal edema with AS-OCT showing DMD (white arrow) and increase in the corneal thickness (A and B), and slit lamp photography after intra-cameral air injection showing clear graft (by the end of the first week) with AS-OCT showing resolution of DMD (C and D)

Postoperatively, the CDVA was worse in group I than in group II, but the difference was not statistically significant at 1, 3, 6, and 9 months. The visual acuities (VAs) became nearly similar in both groups at 12 months (0.30 ± 0.12 vs

0.31 ± 0.13, p=0.816). At 1 year postoperatively, the mean value of log of contrast sensitivity (CS) was 0.77 ± 0.235 in group I compared to 1.04 ± 0.187 in group II, with a statistically significant difference between the groups (***p<0.001****).

As regard ECD at 12 months postoperatively, there was a statistical significant difference between both groups (1732.62 ± 539.52 in group I vs 2215.94 ± 265.62 cell/mm^2 in group II, ***p<0.001****). The mean keratometric values and pachymetry did not differ significantly between the groups during the follow-up period. Postoperative data are presented in Table 2.

Table 2: Postoperative data of both groups at 12 months

	Group I (DALK with perforation)	***Group II (DALK without perforation)***	***P***
Postoperative CDVA (LogMAR)	0.30 ± 0.12	0.31 ± 0.13	0.816
Postoperative mean Contrast Sensitivity (Log CS)	0.77 ± 0.235	1.04 ± 0.187	***<0.001****
Postoperative mean Keratometry (D)	42.12 ± 3.11	43.61 ± 2.59	0.099
Postoperative Central corneal thickness (μm)	536.62 ± 52.32	516.81 ± 58.51	0.326
Postoperative ECD (cell/mm^2)	1732.62 ± 539.52	2215.94 ± 265.62	***<0.001****

Data are expressed as mean ± SD.

*Statistically significant (P <0.05)

DALK: deep anterior lamellar keratoplasty; BCVA: best corrected visual acuity; LogMAR: logarithmic of minimum angle of resolution, Log CS: logarithmic of contrast sensitivity, D: diopters, ECD: Endothelial cell density.

Pupillary block glaucoma was reported in 4 out of 13 eyes (30.8%) in group I with double AC after intracameral air injection compared to no cases in group II. They were managed by administering 200 cc of 20% mannitol solution over 20 min, acetazolamide 250 mg three times daily, and topical anti-glaucoma medications for three days.

By the end of the first week, IOP had normalized in all four cases, however iris atrophy with dilated fixed pupil (Urrets-Zavalia syndrome) was observed. At 3 months postoperatively, two patients (15.4%) developed anterior subcapsular cataract, and both underwent cataract extraction with intraocular lens (IOL) implantation at 9 months postoperatively (figure 2). In both cases, the graft was clear but the pupil remained dilated and fixed. Detailed data of the cases with intraoperative DM perforation are illustrated in Table 3.

Table 3: Descriptive date of cases in group I (DALK with DM Perforation)

No	*Sex*	*Site of Perforation*	*Size of Perforation*	*Re-bubbling*	*BCVA 1 Year*	*CS 1 Year*	*ECD 1 Year*	*Complications*
1	Female	Peripheral	Micro	No	0.3	1.2	2231	No
2	Female	Peripheral	Micro	No	0.18	0.9	2138	No
3	Female	Peripheral	Micro	No	0.18	1.05	2541	No
4	Female	Central	Micro	No	0.18	1.05	2310	No
5	Female	Central	Micro	Yes	0.3	0.75	1998	No
6	Male	Central	Micro	Yes	0.3	0.75	1525	No
7	Male	Peripheral	Micro	Yes	0.3	0.75	1402	No
8	Female	Peripheral	Micro	Yes	0.18	0.5	1993	No
9	Female	Peripheral	Micro	Yes	0.3	0.5	1995	No
10	Female	Peripheral	Micro	Yes	0.3	0.75	831	UZS + Cataract
11	Male	Peripheral	Macro	Yes	0.6	0.9	1143	UZS
12	Female	Peripheral	Macro	Yes	0.48	0.5	1318	UZS
13	Female	Peripheral	Macro	Yes	0.3	0.5	1099	UZS + Cataract

DALK: deep anterior lamellar keratoplasty; DM: descement membrane; BCVA: best corrected visual acuity; CS: Contrast sensitivity, ECD: Endothelial cell density, UZS: Urrets-Zavalia syndrome

In group I, intracameral air injection (re-bubbling) was significantly correlated with a decrease in postoperative CS and ECD ***(P=0.001 and 0.004, respectively)***. This is presented in Table 4.

Table 4: Correlation between Intracameral air injection (Re-bubbling) with BCVA, CS and ECD

	Case with No Re-bubbling (n=4)	*Cases with Re-bubbling (n=9)*	*P value*
BCVA	0.21 ± 0.06	0.34 ± 0.123	P=0.075
CS	1.05 ± 0.122	0.656 ± 0.155	***P=0.001****
ECD	2305 ± 172.32	1478.22 ± 434.59	***P=0.004****

Data are expressed as mean ± SD.

*Statistically significant (P <0.05)

BCVA: best corrected visual acuity; CS: Contrast Sensitivity, ECD: Endothelial cell density.

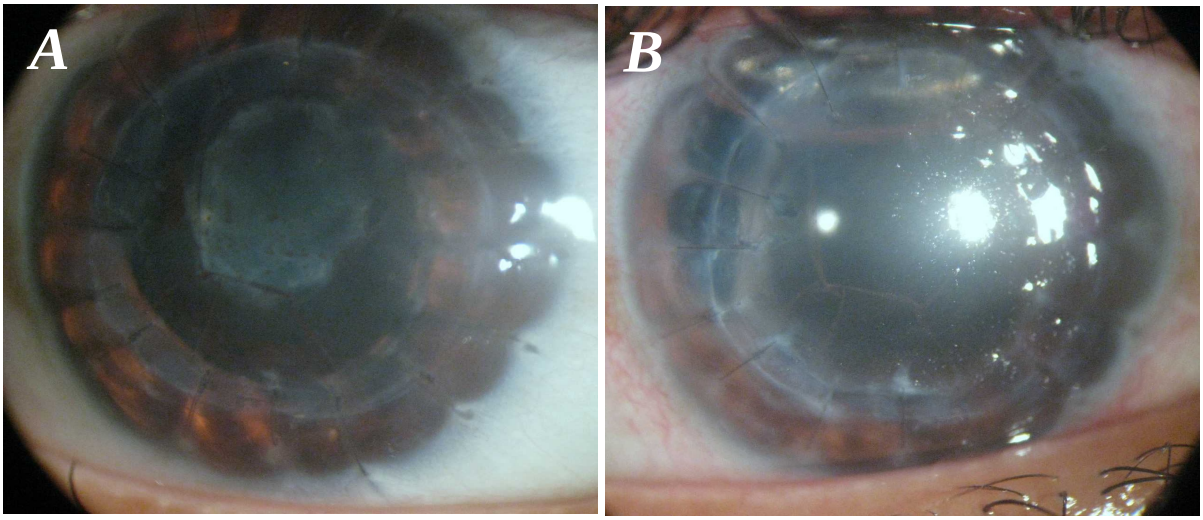

Fig.2 Slit lamp photography showing dilated fixed pupil, anterior sub-capsular cataract and DM folds 3 month postoperative (A), and after cataract extraction and IOL implantation 9 month postoperative (B).

DISCUSSION:

Big-bubble DALK, as described by Anwar and Teichmann, has provided good and safe DM bearing. In case of a failed BB, manual dissection may be required to complete stromal dissection [10]. DM perforation is a common intraoperative complication during DALK. In our study, it was reported in 26.5% (13/49) of the patients. This was comparable to the literature, which reported a range of 3.7 - 36% [15-18]. The choice of surgical technique and the surgeon's learning curve play the most important role in this variable rate of DM perforation [19].

In the present study, CDVA was lower in the perforated group than in the non-perforated group up to 9 months after surgery, in contrast to previous studies that reported differences between both groups at 1 week [20], and 3 months [21] postoperatively. However, there was no significant difference in CDVA between the two groups 1 year after DALK surgery, which is in agreement with previous reports [20-23]. Regarding Contrast sensitivity, it was significantly worse in the DM perforation group than in the no perforation group by the end of the first year postoperatively ($p<0.001$*). This could be attributed to interface irregularity in the perforated group, in addition to intracameral air injection, which may cause more scarring.

In the current study, postoperative DMD and double AC were identified in 69.2% (9/13) of the perforated cases, and a single re-bubbling attempt was successful in resolving the double AC in all cases. This suggests the significance of closer postoperative follow-up for the early diagnosis and management of double AC, which is considered the most feared complication in cases of perforation. Another clinical point worth highlighting is the importance of AS-OCT imaging in the early postoperative phase. The main sign of a double AC at the slit lamp is stromal edema, indicative of the loss of endothelial pump function, rather than an easily identifiable interface. Therefore, AS-OCT is imperative in the management of these patients [3].

In the present study, the DM perforation group showed a statistically significant decrease in ECD compared to the non-perforated group at 1 year postoperatively ($p<0.001$). This finding is consistent with a study conducted by Den et Al [21] and Leccisotti [22] who suggested an increase in endothelial cell loss in patients with DM perforation, which was aggravated by intracameral air injection. In contrast, several studies [1,5,23,24] showed that specular microscopy readings after DALK were comparable in both groups.

In this study, intracameral air injection was correlated with a decrease in CS and ECD ($P=0.001$ and 0.004, respectively). Endothelial cell loss in these patients may be the result of either direct trauma associated with perforation or postoperative double AC, which requires rebubbling. It has been proposed that leaving an air bubble inside the AC may cause trauma to the endothelium [25] and induce more endothelial cell loss [26].

In our study, there was no significant difference in graft survival between eyes with DM macro-perforations and those with DM micro-perforations. However, three patients with macro-perforation developed Urrtes-Zavalia (UZV) syndrome. This suggests that although macro-perforations are not common, they may have a worse prognosis than micro-perforations. Hence, it is important to minimize further endothelial trauma in cases of DM micro-perforation so that it is not converted into a macro-perforation.

Some strategies may include placing a small amount of ocular viscoelastic (e.g., Viscoat) to coat and protect the endothelium prior to placing air in the AC and also preventing the extension of a micro-perforation to a macro-perforation by keeping the AC not very shallow. In the setting of a macro- perforation, most studies recommended conversion of DALK to PK; however, we can see that it is based on the surgeon's experience, the exact size, and the site of the perforation.

In DM perforation, intracameral air injection may cause pupillary block, which in turn causes elevated IOP, leading to iris ischemia with fixed and dilated pupils with or without anterior subcapsular cataract (Urrtes-Zavalia syndrome). In our study, pupillary block glaucoma was reported in 30.8% (4/13) of perforated cases with double AC after intracameral air injection. They were managed with Mannitol 20% solution, systemic and topical anti-glaucoma medications for three days. By the end of the first week, the IOP had normalized in all four cases, but they developed iris atrophy with dilated fixed pupils, and two of them (15.4%) developed anterior subcapsular cataract.

Similarly, several studies [21,27,28] have reported dilated and paretic pupils following air injections in eyes with DM perforation during DALK. Therefore, it is important to avoid over-inflation of the AC with air and hourly monitoring of IOP to prevent this complication. In addition, the postoperative use of cycloplegic agents and strict supine posture of the patient play an important role in avoiding this complication.

The limitations of this study include the small sample size and short follow-up period, especially in patients with macro-perforations in whom a longer follow-up period is crucial for the assessment of long-term graft survival.

In conclusion, DM perforation is a common complication of DALK surgery. Intracameral air injection is associated with a decrease in ECD and visual quality. Close follow-up is needed in patients with air in the AC to avoid pupillary block and other complications.

ACKNOWLEDGEMENT: None

Data Availability: The authors declare that all data supporting the findings of this study are available within the article and its supplementary information file.

Competing interests: The authors declare no competing interests.

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Ethics declarations: All procedures performed in the study followed the 1964 Helsinki declaration and its later amendments, University Ethics Committee approved the project.

Conflict of interest

Aya M Hashish, Hatem E El-Awady, Eman A Awad, Amgad ElNokrashy. all authors have no conflicts of interest that are directly relevant to the content of this review.

Funding: No sources of funding were used to conduct this review.

Reviewer disclosures: No relevant financial or other relationships to disclose.

Declaration of interest: No financial affiliations or financial involvement with any organization or entity with a financial competing with the subject matter or materials discussed in the review.

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