Comparison of Endothelial Keratoplasty Techniques in Patients With Prior Glaucoma Surgery: A Case-Matched Study

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• PURPOSE: To compare the outcomes of Descemet membrane endothelial keratoplasty (DMEK) with those of Descemet's stripping endothelial keratoplasty (DSEK) in eyes with prior glaucoma surgery.

• DESIGN: Case-matched retrospective comparative case series.

• METHODS: Setting/study population: 46 DMEK procedures were matched with 46 DSEK procedures at a single institution. Observation procedures: cases were matched based on preoperative visual acuity, lens status, and surgical indication. Main outcome measurements: the outcome measurements included visual acuity improvement, primary and secondary graft failure, endothelial rejection, intraocular pressure (IOP) elevation, and the need for additional glaucoma intervention.

• RESULTS: Best-corrected visual acuity (BCVA) improved by −0.89 logMAR in the DMEK group and −0.62 logMAR in the DSEK group ($P = 0.005$) at 1 year follow-up. Visual acuity was significantly better in the DMEK group at postoperative months 1, 3, and 12 and at last follow-up. The percentage of patients achieving 20/40 or better best-corrected visual acuity was higher in the DMEK group at all time points, notably 47% in the DMEK group versus 15% in the DSEK group at 1 year ($P = 0.002$). Secondary graft failure was lower in the DMEK group (DMEK 0% vs. DSEK 17%; $P = 0.006$). Primary graft failure rates and rebubling rates were similar. There were no differences in the rates of postoperative IOP elevation or in the need for additional glaucoma intervention.

• CONCLUSIONS: In complex eyes with prior glaucoma surgery, DMEK offers faster visual recovery, better final visual acuity, and a lower rate of secondary graft failure compared to DSEK during the first postoperative year and beyond. (Am J Ophthalmol 2019;206:94–101. © 2019 Published by Elsevier Inc.)

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THE NUMBER OF GLAUCOMA PATIENTS IS EXPECTED to increase worldwide as populations age.[1–4] Prior glaucoma surgeries have been shown to have an adverse impact on corneal graft survival, in both penetrating keratoplasty (PK) and in Descemet's stripping endothelial keratoplasty (DSEK) patients. These patients exhibit a higher incidence of graft rejection and graft failure than patients without prior glaucoma surgery.[5–10]

Descemet membrane endothelial keratoplasty (DMEK) has been shown to produce effective visual rehabilitation[11–14] and has potential advantages in patients with prior glaucoma surgery. First, the decreased amount of transplanted tissue in DMEK incites a less robust immune response, potentially resulting in a decreased incidence of graft rejection.[15–17] Second, the thinner graft results in better visual acuity due to decreased interface reflectivity and haze.[17–19] This may be particularly beneficial in patients with reduced visual function from glaucomatous optic neuropathy. Third, the decreased requirement for postoperative immunomodulatory steroid drops reduces the risk of steroid-induced intraocular pressure (IOP) elevation in patients already sensitive to high pressures.[15,20]

Despite the advantages of DMEK, more surgeons still perform DSEK. However, the share of DMEK is growing, increasing from 0.7% of all transplantations in 2011 to 17.3% at the end of 2017, whereas DSEK has declined from 45.9% to 39.3% during this time period.[21,22] Previous studies by the present authors have shown that DMEK is feasible in eyes with prior trabeculectomy and/or glaucoma shunt.[11] The purpose of this study was to compare the outcomes of DMEK and DSEK in eyes with prior trabeculectomy and/or a glaucoma drainage device in a rigorous, case-matched manner.

SUBJECTS AND METHODS

INSTITUTIONAL REVIEW BOARD (IRB)/ETHICS COMMITTEE approval was obtained (University of California Los

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Angeles IRB 15-001250) prior to initiation of this case-matched retrospective comparative case series. All consecutive cases of endothelial keratoplasty performed at the authors' institute by 2 corneal surgeons (A.J.A. and S.X.D.) between August 2006 and December 2016 were reviewed to identify cases that had prior trabeculectomy and/or tube shunt implantation. Among these patients, cases of DMEK (S.X.D.) were matched with cases of DSEK (S.X.D. and A.J.A.) using preoperative visual acuity, lens status, and surgical indication. Vision-limiting comorbidities other than glaucoma were recorded.

• **CASE MATCHING:** DSEK and DMEK cases with prior glaucoma surgery were matched by the following factors: 1) indication for surgery: pseudophakic corneal edema, Fuchs endothelial corneal dystrophy, failed penetrating keratoplasty, failed endothelial keratoplasty (EK); 2) lens status: pseudophakic, and 3) preoperative best-corrected visual acuity (BCVA): 20/20, 20/25-20/40, 20/50-<20/200, 20/200 or worse. DSEK and DMEK cases were chosen within each matching subgroup containing identical values for all 3 matching factors.

• **SURGICAL PROCEDURE AND POSTOPERATIVE MANAGEMENT:** *DMEK procedure*. All DMEK surgeries were performed by S.X.D. with the patient under monitored anesthesia and retrobulbar block. Donor preparation and DMEK technique have been previously described.[11,23] Prestripped donor tissue prepared by eye banks was used in all DMEK cases. Surgical peripheral iridectomy was performed at 12- and 6-o'clock in all DMEK patients. A "touch, no touch" technique was used in which a 30-gauge cannula was used to manually unfold the Descemet membrane (DM) scroll on the DM side without touching the endothelium. A complete air fill was maintained for 8 to 10 minutes, and 80-90% fill with air or 20% SF_6 was left in place after the procedure.

DSEK procedure. Donor preparation and DSEK technique have been described previously.[5] Precut donor tissue was used for all except 1 case (98%). The donor cornea button was inserted through a clear corneal or scleral tunnel incision using Goosey forceps, needle push through, or Busin forceps and glide. A complete air fill was maintained for 8 to 10 minutes and an air or 20% SF_6 bubble 5-7 mm in diameter was left in place after the procedure.

• **SELECTION OF SURGICAL PROCEDURE:** Starting in 2013, DMEK has become the surgery of choice for author S.X.D. in all patients except for those with anterior chamber intraocular lenses and those who are aphakic. The presence of prior shunts, trabeculectomy, or anterior synechiae did not influence the decision of which endothelial keratoplasty procedure to perform.

• **TUBE MANAGEMENT:** If necessary, tube shunts were trimmed or anterior synechiae were lysed prior to tissue insertion in 11 of 46 DSEK cases and 22 of 46 DMEK cases. In combined endothelial keratoplasty and cataract surgery, cataract surgery was completed by phacoemulsification before insertion of the graft as previously described.[11]

• **POSTOPERATIVE MANAGEMENT:** Patients were instructed to remain supine for 1 to 2 hours in the recovery area and examination was performed to inspect for graft attachment, IOP elevation, and angle closure. If IOP was found to be high, a small amount of air was released from the paracentesis site. The patient was then instructed to remain supine for 24 to 48 hours and was examined in the clinic at postoperative days 1, 7, and 30 and every 2-3 months thereafter. Visual acuity, IOP, and slit lamp biomicroscopy examinations were performed at each visit. The Snellen chart was used for the visual acuity measurement. A topical fluoroquinolone was administered 4 times daily starting 2 days prior to surgery and continued for 1 week postoperatively or until any epithelial defect was healed. In addition, topical 1% prednisolone acetate was administered 4 times daily with slow taper to 3 times a week over the course of 4 to 6 months. Other drops, including glaucoma medications, were resumed the day after surgery. If the decision was made to perform rebubbling to facilitate graft reattachment, the procedure was performed under aseptic conditions in a minor procedure room.

Primary graft failure was defined as failure of the DSEK or DMEK graft to clear or as persistent corneal edema after postoperative month 1. Secondary graft failure was defined as irreversible cornea edema that developed after initial corneal clearing. Endothelial rejection was defined as the presence of keratic precipitates or a rejection line, with or without edema.

IOP was obtained using Goldmann tonometry, TonoPen, or pneumotonometer. When cornea edema was present, a TonoPen or pneumotonometer was used. Preoperative IOP was defined as the average measurements from the 2 most recent visits prior to the date of endothelial keratoplasty. Elevated IOP was defined as a postoperative measurement >8 mm Hg above preoperative IOP lasting more than 1 week or by the need for additional glaucoma surgery after postoperative week 1. Preoperative cup-to-disc ratio was recorded from the clinical visit immediately prior to corneal transplant surgery. In some cases, the view of the nerve was too hazy at this visit, and a clinical examination closest in time to the corneal transplant surgery was referenced.

Central corneal thickness (CCT) was obtained preoperatively and postoperatively with a handheld pachymeter. Post-cut CCT of DSEK graft was obtained from eye bank records.

• **STATISTICAL ANALYSIS:** Statistical analysis was performed by the statistician (F.Y.) using SAS software version 9.4 (SAS, Inc, Cary, North Carolina, USA). The

TABLE 1. Patient Demographics and Characteristics

	Total n (%)	DMEK n (%)	DSEK n (%)	*P*
Number of procedures	92	46	46	
Number of eyes	89	45	44	
Number of patients	85	42	43	
Surgical indications				
PCE	66 (72)	33 (72)	33 (72)	M
Failed EK	20 (22)	10 (22)	10 (22)	M
Failed PKP	4 (4)	2 (4)	2 (4)	M
FECD	2 (2)	1 (2)	1 (2)	M
Lens status				
Pseudophakic	92 (100)	46 (100)	46 (100)	M
Posterior chamber IOL	87 (95)	41 (89)	46 (100)	M
Sulcus IOL	5 (5)	5 (11)	0	M
Preoperative BCVA				
20/20	0	0	0	M
20/25-20/40	4 (4)	2 (4)	2 (4)	M
20/50-20/200	30 (33)	15 (33)	15 (33)	M
20/200 or worse	58 (63)	29 (63)	29 (63)	M
Length of follow-up (mo)	11.5 ± 1.9	11.6 ± 1.5	11.4 ± 2.2	0.68
Mean ± SD age (y)	72.3 ± 12.1	73.9 ± 10.6	70.7 ± 13.3	0.16
Sex				
Males	38 (41)	18 (39)	20 (43)	0.83
Females	54 (59)	28 (61)	26 (57)	0.83
Glaucoma				
Prior trabeculectomy	45 (49)	22 (48)	23 (50)	1.00
Prior tube shunt	70 (76)	36 (78)	34 (74)	0.81
Prior trabeculectomy and tube	23 (25)	12 (26)	11 (24)	1.00
Preoperative cup/disc ratio	0.77 ± 0.18	0.78 ± 0.17 (n = 40)	0.75 ± 0.19 (n = 40)	0.47
Cup/disc ratio range		0.3-0.99	0.3-0.99	
Preoperative IOP	11.6 ± 3.9	11.1 ± 4.0	12.2 ± 3.8	0.09
Number of preoperative glaucoma drops	1.50 ± 1.98	1.79 ± 1.89	1.26 ± 1.32	0.13
Preoperative ECC (cells/mm^2)		2935 ± 184 (n = 29)	3043 ± 154 (n = 16)	0.02
Other visual acuity limiting factors (LCSD, AMD, ERM, CME)	43 (47)	25 (54)	18 (39)	0.21

Values are mean ± SD or n (%) of 46, unless otherwise specified.

AMD = age-related macular degeneration; CCT = central corneal thickness; CME = cystoid macular edema; DMEK = Descemet membrane endothelial keratoplasty; DSEK = Descemet's stripping endothelial keratoplasty; ECC = endothelial cell count; EK = endothelial keratoplasty; ERM = epiretinal membrane; FECD = Fuchs endothelial corneal dystrophy; IOP = intraocular pressure; LCSD = limbal stem cell deficiency; M = matched criteria; PCE = pseudophakic corneal edema; PKP = penetrating keratoplasty.

Kruskal-Wallis test was used to compare differences in values of continuous variables including visual acuity, and the Fisher exact test was used to compare differences in categorical variables, including patient demographics and complications.

RESULTS

A TOTAL OF 161 CONSECUTIVE DMEK AND 597 CONSECUTIVE DSEK procedures were reviewed between August 2006 and December 2016. Among these procedures, 59 DMEK (36.6%) and 154 DSEK procedures (25.8%) were performed in eyes with prior trabeculectomy and/or tube shunt implantation, and 2 groups of 46 procedures each were matched by preoperative visual acuity, lens status, and surgical indication.

• CASE MATCHING: To minimize retrospective selection bias, starting visual acuity, surgical indication, and lens status were case matched between the 2 groups. In addition, additional analysis showed that these 2 groups had similar stages of pre-existing glaucoma, as the number of prior glaucoma surgeries, cup-to-disc ratios, preoperative IOPs, and the number of glaucoma medications were not significantly different between the 2 groups.

Although the differences did not reach significance, the DMEK group trended toward being more complex, with a

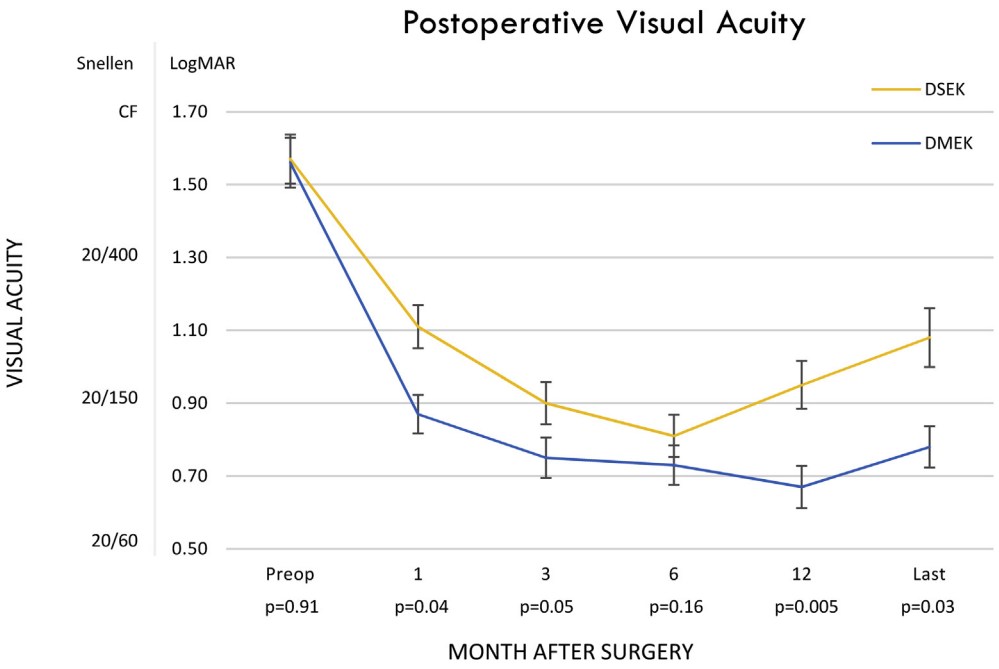

FIGURE 1. Visual acuity before surgery and at months 1, 3, 6, and 12 and last follow-up after DSEK and DMEK surgery. There were significant differences in visual acuity at months 1, 3, 12 and last follow-up favoring DMEK. DMEK = Descemet membrane endothelial keratoplasty; DSEK = Descemet's stripping endothelial keratoplasty.

higher preoperative CCT ($P = 0.07$), older patient population ($P = 0.16$), and higher number of comorbidities ($P = 0.21$). The higher complexity of the DMEK group gives added weight to the current study's finding that DMEK results in better postoperative outcomes.

One DMEK was performed by a fellow, and the remainder of DMEKs were performed by S.X.D. The DSEK surgeries were performed by S.X.D. and A.J.A. Fellows were not the primary surgeons in the DSEK cases. A subset analysis was performed comparing the 2 surgeons (S.X.D. and A.J.A.) who contributed DSEK data and no significant differences were found in visual acuity at 1 month ($P = 0.88$) or 1 year ($P = 0.98$).

• **PATIENT DEMOGRAPHICS:** Ninety-two procedures in 89 eyes of 85 patients were included in the analysis. The primary surgical indication was pseudophakic corneal edema (72%), followed by failed endothelial keratoplasty (22%), failed penetrating keratoplasty (4%), and Fuchs endothelial corneal dystrophy (2%). All patients were pseudophakic, and preoperative BCVA was most commonly 20/200 or worse (63%). There were no significant differences in the length of follow-up, age, sex, or type of prior glaucoma surgery. The cup-to-disc ratio, the number of glaucoma medications, and preoperative IOP were similar between the 2 groups (Table 1).

• **VISUAL OUTCOMES:** There were no differences in the preoperative BCVA between the 2 groups. There were no differences in the number of eyes in which vision might be limited by other comorbidities including age-related macular degeneration, limbal stem cell deficiency, macular edema, and epiretinal membrane ($P = 0.21$) (Table 1). Postoperative BCVA improved more rapidly in the DMEK group than in the DSEK group and was significantly better in the DMEK group at months 1, 3, and 12 (Figure 1).

Three eyes (7%) in the DMEK group achieved 20/20 or better visual acuity at 1 year follow-up compared with no eyes in the DSEK group. Twenty-two eyes (47%) in the DMEK group achieved 20/40 or better vision compared with only 7 eyes (15%) in the DSEK group ($P = 0.002$) (Figure 2). A greater proportion of patients achieved visual acuity of better than 20/40 vision at all time points during the first year of follow-up in the DMEK group (Figure 3).

At last follow-up (DMEK, 17.1 ± 7.9 months; range, 1-38 months; DSEK, 20.6 ± 13.5 months; range, 1-66 months), the visual acuity of the DMEK group was significantly better than that of the DSEK group ($P = 0.03$).

• **COMPLICATIONS:** The DMEK group had a significantly lower number of secondary graft failures at 1 year (n = 0; 0%) versus the DSEK group (n = 8; 17%; $P = 0.006$) (complications are summarized in Supplemental Figure and Table 2). There were no differences between the 2 groups in the rate of primary graft failure, endothelial rejection, rebubbling, postoperative IOP elevation, or glaucoma

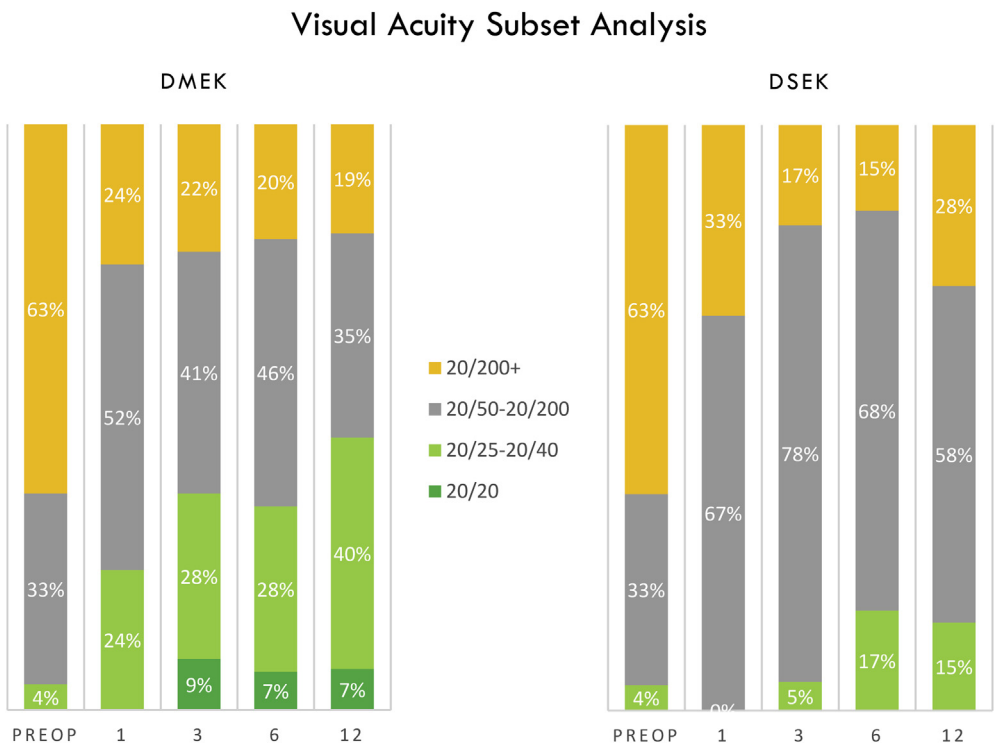

FIGURE 2. Visual acuity subset analysis prior to surgery and at months 1, 3, 6, and 12 after DSEK and DMEK surgery. The percentage of patients in each visual acuity group is shown at each time point. DMEK = Descemet membrane endothelial keratoplasty; DSEK = Descemet's stripping endothelial keratoplasty.

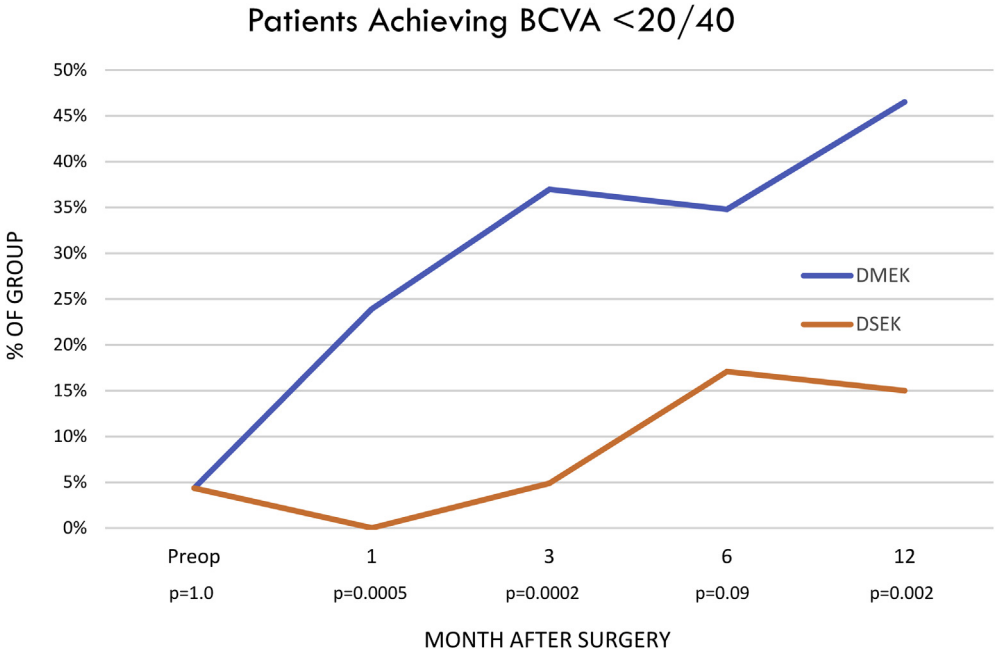

FIGURE 3. The percentage of patients achieving 20/40 vision at each time point following surgery is shown. The proportion of patients achieving this threshold was higher in the Descemet membrane endothelial keratoplasty (DMEK) group at all time points. BCVA = best corrected visual acuity.

TABLE 2. Postoperative Results and Complications

	Total n (%)	DMEK n (%)	DSEK n (%)	*P*
Primary graft failure	2 (2)	1 (2)	1 (2)	0.65
Secondary graft failure	8 (9)	0 (0)	8 (17)	0.006
Endothelial rejection	6 (7)	2 (4)	4 (9)	0.68
Rebubbling	14 (15)	10 (22)	4 (9)	0.14
Postoperative IOP elevation	30 (33)	14 (30)	16 (36), n = 45	0.66
Postoperative glaucoma operations	7 (8)	5 (11)	2 (4)	0.43
Preoperative CCT (μm)	753 ± 135	778 ± 121 (n = 39)	728 ± 145 (n = 41)	0.07
Postoperative CCT (μm)		519 ± 62	691 ± 112	<0.001

CCT = central corneal thickness; DMEK = Descemet membrane endothelial keratoplasty; DSEK = Descemet's stripping endothelial keratoplasty.

surgery (all $P > 0.05$) (Supplemental Figure). In the DMEK group, 5 patients needed postoperative glaucoma procedures (2 trabeculectomies and 3 glaucoma shunts). In the DSEK group, 2 patients needed glaucoma shunt implantation. This difference was not significant ($P = 0.43$). Endothelial cell count loss was available for 29 cases of DMEK and 16 cases of DSEK. Although no significant differences were observed in this incomplete data set ($P = 0.85$), the results were not complete enough to draw meaningful conclusions.

DISCUSSION

THIS IS THE LARGEST PUBLISHED STUDY COMPARING THE outcomes of DMEK with those of DSEK in patients with prior trabeculectomy and/or glaucoma drainage device. This study shows that even in these complex eyes, DMEK achieves faster visual recovery, a better final visual acuity, and a lower rate of secondary graft failure than DSEK.

Previous studies comparing DMEK and DSEK in eyes without glaucoma surgery showed that DMEK achieves a superior visual recovery compared with DSEK.[17,24–28] Given the complex surgical history of the eyes in the present study, preoperative visual acuity was considerably worse than that cited in other studies. This cohort of patients had a mean acuity of 1.57 logMar (20/800 Snellen equivalent) compared to a mean of 20/100 or better in other series.[25,29–32]

Despite the comorbitidies of this patient population, the 1-year BCVA improved to 20/40 and 20/20 in 40% and 7% of eyes, respectively, in the DMEK group, compared to 15% and 0% of eyes in the DSEK group, respectively. The preoperative CCT in the DMEK group was significantly thicker than that in the DSEK group, suggesting that the preoperative corneal edema was more severe in the DMEK group. Nevertheless, eyes in the DMEK group achieved a better visual acuity at 1 month than eyes in the DSEK group at 1 year. It is theorized that thinner postoperative corneal thickness along with decreased interface backscatter may contribute to the superior visual outcomes of DMEK.[18,19]

A faster visual recovery and a better final visual acuity are especially important for patients with advanced glaucoma who may be functionally monocular or may exhibit significant field defects. A final vision of 20/40 or better allows patients to be eligible for a driver's license,[33] to recognize faces,[34] to read efficiently,[24] and to live more independently. A significantly larger proportion of DMEK patients achieved BCVA of 20/40 or better at all time points compared to DSEK ($P = 0.0005$, 0.0002, 0.09, and 0.002, respectively).

In the present study, there were no secondary graft failures in the DMEK group, and 8 secondary graft failures in the DSEK group. Two of these 8 secondary graft failures occurred after a rejection episode. The remaining 6 secondary graft failures were due to endothelial failure. Disruption of the blood-aqueous barrier by prior glaucoma surgery can contribute to a less hospitable anterior chamber for a graft, with increased levels of complement and other immunomodulatory factors. Indeed, a higher rate of endothelial cell loss has been reported in eyes with prior glaucoma surgery.[15,16] In our study, the DMEK group demonstrated significantly lower secondary graft failures at 1 year than the DSEK group, which mirrors results found in other head-to-head comparisons.[15,17] In these eyes, the decreased amount of transplanted tissue in the DMEK procedure might be advantageous to graft survival.

The rebubbling rate was higher in the DMEK group than the DSEK group ($P = 0.14$). However, the difference was not statistically significant. No DMEK or DSEK graft required more than 1 rebubbling. The rebubbling rate in the DMEK group was slightly higher than that reported in other studies. This is perhaps due to a lower IOP during the 10 minutes full air fill periord during DMEK surgery to avoid optic nerve damage, and the increased difficulty of maintaining an anterior chamber air fill due to egress of gas through the trabeculectomy flap or tube shunt to the

subconjunctival space. SF_6 gas has been reported to reduce the need for rebubbling. However, late graft detachment (occurring after postoperative week 2) was observed in a few cases with SF_6. Whether SF_6 reduces the need for rebubbling to treat partial graft detachment in these complex eyes needs to be further investigated.

The average graft CCT implanted in our DSEK group was 132 μm, which nearly meets the <130-μm criteria for "ultra thin" DSEK. In our study, there were no differences between the outcomes in the <130-μm DSEK group and those in the >130-μm DSEK group. In addition, there remained significant differences in subset analysis comparing the "thin" <130-μm DSEK group with the DMEK group. The DMEK group visual acuity results were significantly better than those in the "thin" <130-μm DSEK group at 3, 6, and 12 months with *P* values of 0.03, 0.008, and 0.004, respectively. However, it may be worthwhile to perform further analysis with even thinner DSEK tissue.

Even though the current study is a case-matched retrospective comparative case series, there are several limitations. First, analysis was focused on the first year after surgery, although follow-up data are reported up to the last follow-up point. Second, the data for postoperative endothelial cell count was only available for a subset of patients. Finally, it would be beneficial to be able to survey a larger study group, as complications such as graft failure and rejection happen at a low rate.

DMEK achieves faster visual recovery, a better visual acuity, and a lower rate of secondary graft failure than DSEK in patients with prior glaucoma surgery. DMEK would be preferred in these patients to achieve the best possible visual rehabilitation. However, future study of the long-term outcomes are needed.

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