Descemet Membrane Endothelial Keratoplasty With a Pull-Through Insertion Device: Surgical Technique, Endothelial Cell Loss, and Early Clinical Results

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Purpose: To describe a surgical technique for Descemet membrane endothelial keratoplasty (DMEK) using a pull-through, endothelium-in insertion device, the DMEK EndoGlide. We evaluated the endothelial cell loss (ECL) associated with the EndoGlide-DMEK (E-DMEK) technique in both ex vivo and prospective clinical studies.

Methods: The ex vivo study involved calcein acetoxymethyl staining and preparation of DMEK grafts, which were trifolded endothelium-in, loaded into the EndoGlide, pulled through, and unfolded in imaging dishes. Inverted fluorescent microscopy was performed, and ECL was quantified using trainable segmentation software. The prospective clinical series describes the outcomes of consecutive surgeries using the E-DMEK technique. Grafts were pulled through the EndoGlide with forceps and unfolded in the anterior chamber endothelium-down. Our main outcome measure was ECL in both studies.

Results: In the ex vivo study with 9 human donor corneas, mean ECL was 15.2% ± 5.4% (n = 9). In our clinical series of 69 eyes, leading indications for surgery were pseudophakic/aphakic bullous keratopathy (47.8%), previous failed grafts (23.2%), and Fuchs endothelial dystrophy (18.8%). Rebubbling and primary graft failure rates related to E-DMEK were 11.6% and 1.5%, respectively. Among eyes with at least 6 months of follow-up, mean preoperative endothelial cell density was 2772 (range 2457–3448) cells/mm^2, and postoperative endothelial cell density was 1830 (range 541–2545) cells/mm^2. Mean ECL was 33.6% (range 7.5–80.4; n = 32) at the 7.1 (range 6–11) months follow-up.

Conclusions: The ex vivo and pilot clinical studies suggest that E-DMEK shows acceptable rates of ECL, with safe and promising early clinical outcomes.

Key Words: DMEK, E-DMEK, EndoGlide, pull-through, endothelium-in

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Descemet membrane endothelial keratoplasty (DMEK) involves transplantation of only donor Descemet membrane and endothelium, whereas Descemet stripping endothelial keratoplasty (DSEK) also includes a layer of posterior stromal tissue.[1–3] DMEK holds significant advantages over DSEK, including better visual and refractive outcomes, faster visual recovery, and lower graft rejection rates.[3–7] Despite these advantages, DSEK still accounts for most endothelial keratoplasties performed.[8] In 2018, 64.4% of all endothelial keratoplasties performed in the United States were DSEK procedures, whereas 35.5% were DMEK procedures.[9] A major barrier to adoption of DMEK is the steep learning curve and technical difficulty, especially with regards to graft insertion and unfolding.[10,11] Currently, most surgeons use injection (as opposed to pull-through) techniques, adapting a variety of plastic intraocular lens (IOL) cartridges or glass tubes as injector devices.[10,12–17] These DMEK grafts are usually loaded and injected into the anterior chamber (AC) in an endothelium-out scroll configuration, and the surgeon is then faced with the uphill task of unfolding the graft against its natural tendency to remain scrolled up.[17] This can usually be achieved by tapping the corneal surface with cannulas, spurts of balanced salt solution (BSS), small air bubbles, or shallowing of the AC. However, graft unfolding becomes significantly more challenging in eyes with disarranged anterior segments.[3,12–14]

By contrast, the stromal component of DSEK tissue provides more structural rigidity, meaning that it more readily coils endothelium-in. DSEK is frequently performed with

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pull-through techniques and specifically designed DSEK inserters such as the EndoGlide (Network Medical Products Ltd, Ripon, UK) or Busin glide (Moria SA, Antony, France).[18] After insertion, DSEK grafts unfold spontaneously and are more easily maneuvered into position than DMEK grafts.[19–21] Because of these differences, most surgeons reserve DMEK only for simple, uncomplicated cases, such as early to moderate cases of endothelial decompensation. DSEK is usually performed instead of DMEK in more complex cases with anterior segment comorbidities, such as large iris defects or aniridia, aphakia, AC-IOLs, transscleral-fixated posterior chamber IOLs, glaucoma drainage devices, glaucoma filtering blebs, peripheral anterior synechiae (PAS), or previous failed penetrating keratoplasty or DSEK grafts.[3,12,13,22,23]

Considering the above limitations, we feel that a surgical technique for DMEK that makes use of a pull-through, endothelium-in approach confers many advantages. We have previously described such a technique for DMEK using the EndoGlide Ultrathin (Network Medical Products Ltd), which was originally designed for DSEK.[24] This was feasible but required a specially manufactured stromal carrier (the Descemet mat, or D-Mat) and a relatively large 4.5-mm scleral tunnel. In a further evolution of this technique, we now describe the use of a pull-through, endothelium-in insertion device designed specifically for DMEK (CORONET DMEK EndoGlide; Network Medical Products Ltd; Fig. 1), which does not require a stromal carrier and can be performed with a smaller, 2.75-mm, standard cataract incision. We evaluated the endothelial cell loss (ECL) associated with this EndoGlide-DMEK (E-DMEK) technique in an ex vivo laboratory-based study, and also examined the early clinical outcomes of E-DMEK in a prospective clinical series.

MATERIALS AND METHODS

Surgical Technique

The main incision for insertion is a 2.75-mm 2-plane clear corneal incision, created temporally in the recipient cornea with a standard cataract keratome. A 1.5-mm "pull-through" incision is created nasally, directly opposite, to allow entry of the curved 23G or 27G EndoGlide placement forceps (CORONET; Network Medical Products Ltd) (Fig. 2). Another paracentesis is created adjacent to this "pull-through" incision, for the placement of a small gauge (eg, 23G) AC maintainer (Fig. 2). A descemetorhexis is performed under air, using a reverse Sinskey hook (product number E3119, Bausch + Lomb Storz Ophthalmic Instruments, Heidelberg, Germany).[25] The descemetorhexis is over-sized by 0.5 mm to improve graft adhesion.[26] An inferior peripheral iridectomy is performed, unless there is already a preexisting large iris defect or functioning glaucoma drainage device or filtering bleb.

DMEK grafts are then prepared in an endothelium-in, trifold configuration and positioned at the edge of the donor corneoscleral button, which is placed in the donor well of the DMEK EndoGlide preparation base (Fig. 2).[17] The lumen of the DMEK EndoGlide cartridge is filled with BSS, and straight EndoGlide loading forceps (CORONET; Network Medical Products Ltd) are introduced into the anterior opening of the cartridge. The folded DMEK graft is grasped with the forceps and pulled into the EndoGlide cartridge, retaining its trifolded configuration (Fig. 2). The glide introducer is attached to the posterior end of the cartridge and locked in place. At this point, the EndoGlide cartridge is inverted 180 degrees so that the DMEK graft will unfold with the endothelium in the correct orientation in the AC.

With the AC maintainer running, the EndoGlide cartridge is inserted into the main temporal incision (Fig. 2). Curved EndoGlide forceps are introduced through the nasal "pull-through" incision and are used to grasp the trifolded DMEK graft within the cartridge, and slowly pull it into the AC (Fig. 2). Once the whole graft is free of the cartridge, without releasing it from the forceps, the EndoGlide cartridge is removed from the AC. Tapping on the main wound with the cartridge or a blunt instrument closes it and helps to reform the AC. Flow of BSS from the AC maintainer, which we usually place adjacent to the "pull-through" incision, helps with spontaneous unfolding of the graft, correctly orientated with the endothelial surface down. Unfolding can be further helped along by gentle taps on the corneal surface with a 30G cannula (Fig. 2). Once the graft is opened fully or partially, a bubble of 20% sulfur hexafluoride (SF_6) gas is injected below the graft to help to unfold and float it up. Once the graft is fully unfolded and tamponaded against the recipient cornea, it can be released from the forceps. A full gas tamponade is achieved while the main temporal and AC

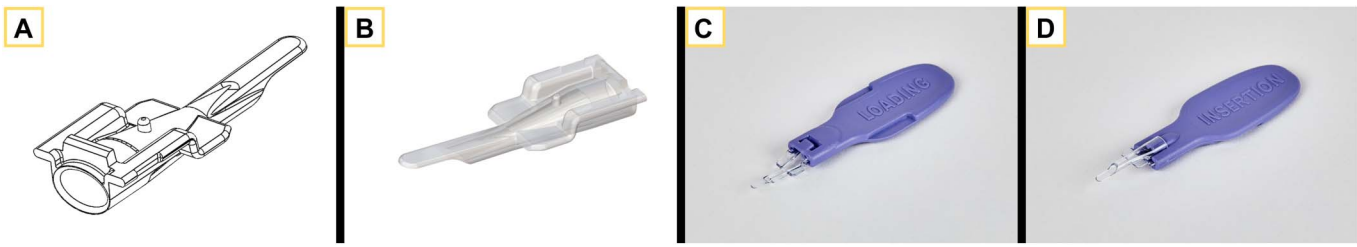

FIGURE 1. The CORONET DMEK EndoGlide (Network Medical Products Ltd). A, Schematic diagram of the DMEK EndoGlide cartridge, oriented for graft loading, showing the posterior lumen opening. B, Schematic diagram of the DMEK EndoGlide cartridge, oriented for graft loading, showing its longitudinal profile. C, Photograph of the DMEK EndoGlide cartridge, with the glide introducer locked in place, oriented for graft loading. D, Photograph of the DMEK EndoGlide cartridge, with the glide introducer locked in place, oriented for graft insertion.

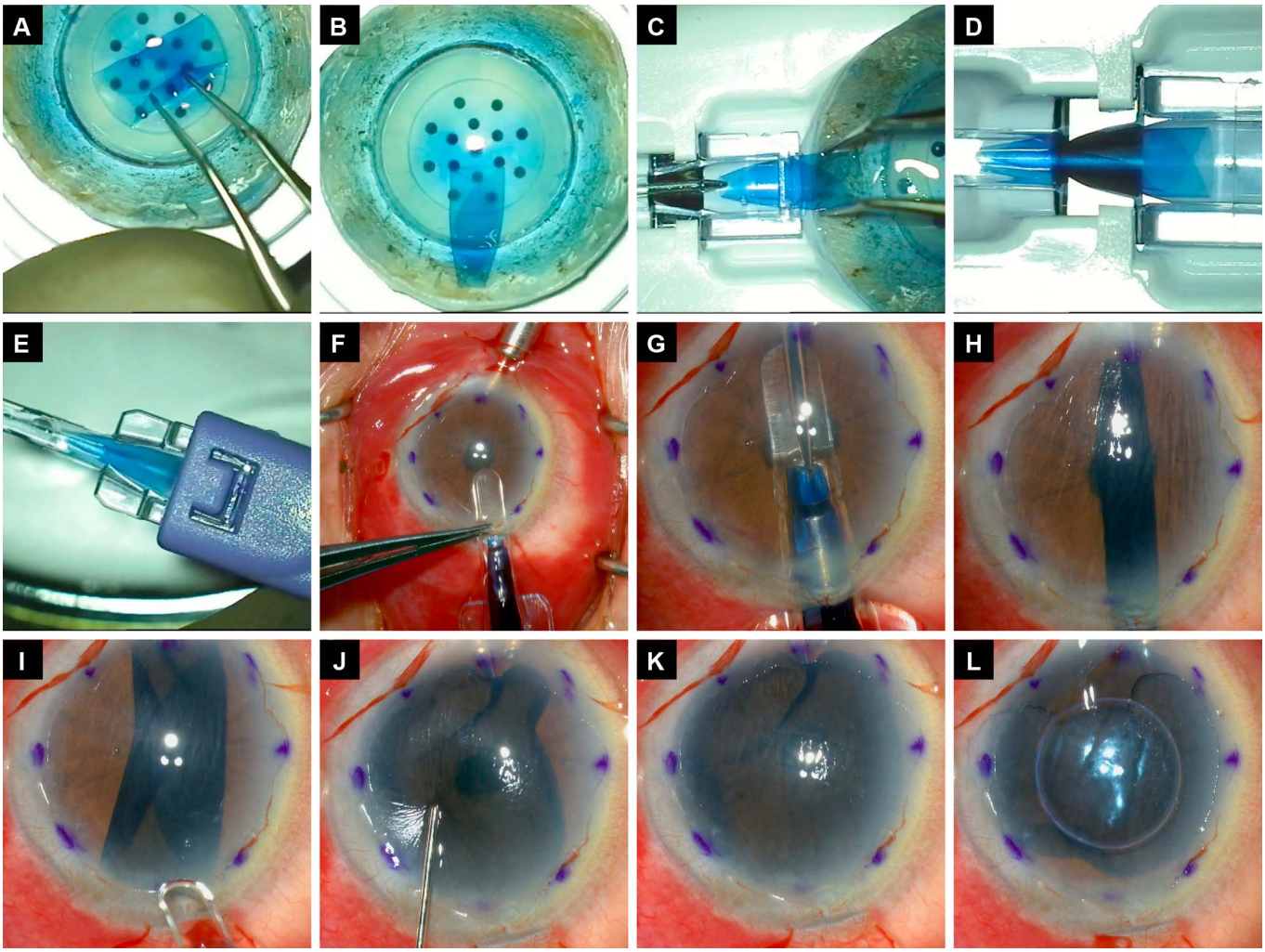

FIGURE 2. E-DMEK technique. A, Trifolding of DMEK graft using Kelman–Macpherson forceps. B, Trifolded endothelium-in configuration of the DMEK graft on the edge of the donor corneoscleral button before loading. C, Loading of the graft into the EndoGlide cartridge using straight EndoGlide forceps. D, DMEK graft curled endothelium-in within the EndoGlide cartridge. E, The EndoGlide cartridge with glide introducer locked in place. F, Insertion of EndoGlide through a 2.75-mm temporal clear corneal incision, and AC maintainer located nasally, just adjacent to the pull-through wound. G, Graft pull-through using curved EndoGlide forceps. H, Graft being held in AC by curved EndoGlide forceps, after removal of EndoGlide cartridge. I, Unfolding of the graft in the AC assisted by closure of the main wound. J, Unfolding of the graft in the AC assisted by tapping on the cornea with a blunt cannula. K, DMEK graft fully unfolded in the AC. L, Graft tamponade with 20% SF_6 gas.

maintainer incisions are sutured. The "pull-through" paracentesis does not usually require suturing. Thereafter, some gas is released from the AC, aiming for an 80% fill at the end of surgery. A video of this technique is included in Supplemental Digital Content 1 (see Supplemental Video, http://links.lww.com/ICO/A971).

Ex Vivo Study

We conducted an ex vivo laboratory-based study to evaluate the amount and patterns of ECL associated with E-DMEK pull-through. Nine human donor corneoscleral buttons were obtained from 2 eye banks—the Lions Eye Institute for Transplant & Research, Tampa, FL, and Saving Sight, Kansas City, MO. These were research-grade tissues, unsuitable for clinical transplantation for reasons unrelated to endothelial pathology. Consent was obtained for their use in research. Criteria for donor tissue used in this part of the study were as follows: donor age 40 to 80 years, storage time <14 days, and endothelial cell density (ECD) by specular microscopy >2000 cells/mm^2. Donors with diabetes mellitus or jaundice were not excluded.

Corneoscleral buttons were stained with calcein acetoxymethyl dye at a concentration of 2.67 μmol for 1 hour, at 37.0°C, as previously described.[27] Eight-millimeter DMEK grafts were prepared from all 9 corneoscleral buttons by a single surgeon (D.T.H.T.) using the lamellar dissection technique. Grafts were trifolded and loaded into the EndoGlide cartridges as described above, except that for the purposes of this laboratory study, the EndoGlide cartridges were not

inverted because it was desired for the grafts to unfold endothelium-up on the imaging dishes (μ-Dish 35 mm, high; ibidi GmbH, Grafelfing, Germany).[28] The anterior end of each EndoGlide cartridge was placed through an opening in the side of an imaging dish. Curved EndoGlide placement forceps were introduced into the anterior opening of the cartridge and used to grasp the edge of the trifolded graft. The graft was pulled through and unfolded endothelium-up on BSS on the base of the imaging dish. The endothelial surface of the DMEK graft was coated with dispersive ophthalmic viscoelastic device (Viscoat; Alcon, Fort Worth, TX). Grafts were then imaged using an inverted fluorescent microscope (Eclipse Ti; Nikon, Tokyo, Japan), equipped with a confocal spinning disc unit (CSU-W1; Andor Technology, Belfast, Ireland, UK) at ×4 magnification. Images were taken over 16 fields (4 × 4 fields), and at different focal depths, and then digitally stitched together to form a single composite image of each whole DMEK graft (Fig. 3). Image brightness and contrast were adjusted to achieve maximum contrast between areas of viable and nonviable endothelial cells, and image resolution was set at 1000 × 1000 pixels. Trainable segmentation software from an open source image processing package (Fiji; https://fiji.sc/) based on ImageJ (National Institutes of Health, Bethesda, MD) was used for the image analysis and to quantify ECL as a percentage of each whole DMEK graft.[29,30] Areas of spurious ECL caused by graft preparation or transfer into the imaging dish that were clearly unrelated to the E-DMEK procedure were excluded from the analysis (Fig. 3). Mean ECL and SD were calculated for all 9 grafts.

Clinical Case Series

This part of the study was aimed at examining the early clinical outcomes from a prospective series of the first 69 consecutive E-DMEK procedures performed by 2 surgeons (D.T.H.T. and J.S.M.) over 12 months from February 2018 to January 2019. This study received ethics approval from the local Institutional Review Board as part of the Singapore Corneal Transplant Study and was conducted in accordance with the tenets of the Declaration of Helsinki. Preoperative data collected included recipient patient demographics, indication for DMEK, best corrected visual acuity (BCVA), and donor tissue characteristics. Operative data included other surgical procedures performed and intraoperative complications. Postoperative data included complications such as rebubbling and primary graft failure (PGF). Outcome data including BCVA (n = 56) and ECD (n = 32) by specular microscopy were collected for patients with a minimum of 6 months of postoperative follow-up.

RESULTS

Ex Vivo Study

Nine human donor corneoscleral buttons were used in this study. The mean donor age was 58.8 (range 49–69) years. 4 of the 9 (44.4%) corneoscleral buttons were from donors with diabetes mellitus. The median death to preservation time was 9 (range 6–16) hours, and the median storage time was 7 (range 6–11) days. The mean starting ECD by specular microscopy was 2686 ± 406 (range 2079–3378) cells/mm^2. Details on donor tissue characteristics are provided in Supplemental Table 1 (see Supplemental Digital Content 2, http://links.lww.com/ICO/A972).

DMEK graft preparation by lamellar dissection, trifolding, and loading into EndoGlide cartridges was successfully performed in all 9 cases. In one case, a small midperipheral tear was inadvertently created during dissection. Nevertheless, the rest of the lamellar dissection could be successfully completed, and the graft was trifolded, loaded, and pulled

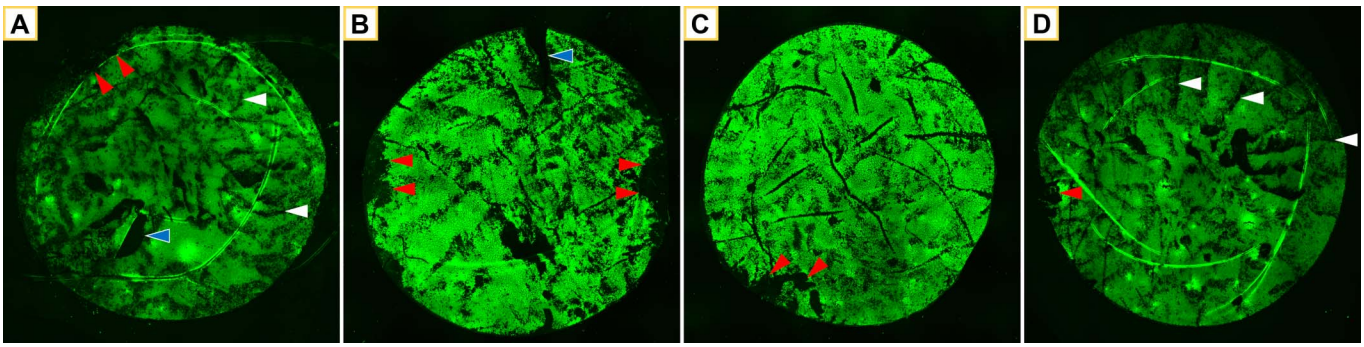

FIGURE 3. Fluorescent microscopy images of DMEK grafts after EndoGlide pull-through. A, DMEK graft with a small midperipheral tear at 7 o'clock created during graft preparation (blue arrowhead with white outline) that appears as an area of spurious ECL—this was deemed unrelated to the EndoGlide pull-through and was excluded from the analysis. This graft also shows peripheral areas of ECL from forceps pinch damage (red arrowheads) and a few irregular, linear, radially oriented areas of ECL in a wavy pattern (white arrowheads), which are related to the lamellar dissection graft preparation technique (not the pull-through). B, DMEK graft with a small radial tear at 12 o'clock (blue arrowhead with white outline) caused by a jet of OVD during flattening of the graft on the imaging dish—this was also unrelated to the EndoGlide pull-through and was excluded from the analysis. This graft also shows peripheral areas of ECL from forceps pinch damage (red arrowheads). C, DMEK graft showing peripheral areas of ECL from forceps pinch damage (red arrowheads). D, DMEK graft showing a peripheral area of ECL from forceps pinch damage (red arrowhead) and multiple irregular, linear, radially oriented areas of ECL in a wavy pattern (white arrowheads), which are related to the lamellar dissection graft preparation technique (not the pull-through).

through the EndoGlide cartridge without extension of the tear. Eventually, when this graft was flattened on the imaging dish, the small flap created by the tear folded on itself, resulting in an area of spurious ECL (Fig. 3). This area was excluded from the ECL analysis because it occurred during graft preparation and was clearly unrelated to the pull-through. In another case, a small radial tear was created during flattening of the graft on the imaging dish by a jet of ophthalmic viscoelastic device (Fig. 3). Again, because this occurred after the pull-through, it was excluded from ECL analysis.

The mean ECL associated with the E-DMEK pull-through was 15.2% ± 5.4% (95% confidence interval: 11.1%–19.3%; n = 9). Qualitatively, all 9 grafts had peripheral areas of ECL at the graft edges, related to forceps pinch damage from the straight and curved EndoGlide forceps during loading and placement, respectively (Fig. 3). In 4 of the 9 grafts, there were irregular, linear, radially oriented areas of ECL in a wavy pattern (Fig. 3), which we have previously reported to be associated with the lamellar dissection technique.[28] Otherwise, there were no identifiable linear areas of ECL that could be attributed to the loading or pull-through maneuvers.

Clinical Case Series

Sixty-nine consecutive E-DMEK procedures were performed by 2 surgeons (D.T.H.T. and J.S.M.) over 12 months from February 2018 to January 2019. Demographic characteristics of these patients and their indications for surgery are shown in Table 1. All patients were of Asian ethnicity. The most common indication for surgery was pseudophakic or aphakic bullous keratopathy (47.8%), followed by failed corneal grafts (23.2%; a more detailed breakdown of type of previous grafts can be found in Table 1) and Fuchs endothelial dystrophy (18.8%). In this series, DMEK grafts were prepared from donor corneoscleral buttons in the operating room by the operating surgeon using either the lamellar dissection technique (n = 49; D.T.H.T.) or the submerged cornea using backgrounds away (SCUBA) technique (n = 20; J.S.M.).[12,28] DMEK grafts ranged from 7.0 to 8.5 mm in diameter. Other significant ocular comorbidities and adjunctive surgical procedures performed in the same sitting are also shown in Table 1. Almost half of the cases (46.4%) had preexisting glaucoma, of which 9 (13.0%) patients had glaucoma drainage tubes and 5 (7.2%) had filtering blebs. Notably, there were 4 (5.8%) eyes that were aphakic. In total, 25 (36.2%) cases were complex cases, involving significant ocular abnormalities such as the presence of a glaucoma drainage tube, filtering bleb, aphakia, previous vitrectomy, AC-IOL, gross PAS, or anterior segment dysgenesis/iridocorneal-endothelial syndrome. A third of patients (33.3%) had combined phacoemulsification and IOL implantation together with DMEK. Duration of the postoperative follow-up in these cases ranged from 1 to 11 months.

In terms of intraoperative complications, in 1 case, the DMEK graft was unfolded and released from the forceps in the right orientation, but the AC maintainer flow was erroneously increased instead of being decreased. This resulted in the DMEK graft being ejected from the eye through the main corneal incision. The DMEK graft was reloaded into the EndoGlide cartridge and pulled through a second time, before being successfully attached to the recipient cornea. In another case, during pull-through, the surgeon grasped one of the trifolded graft edges instead of the central portion of the trifold. This resulted in graft inversion while it was pulled through into the AC. This was recognized immediately because of an asymmetric marker on the graft edge, and the surgeon was able to successfully manipulate and reinvert the graft in the AC. Both these cases did well postoperatively. Otherwise, there were no significant intraoperative complications in this series of 69 cases.

Postoperatively, there were 8 (11.6%) cases of partial graft detachment in the early postoperative period that required rebubbling with SF_6. There were 3 cases of PGF. However, 2 of these 3 cases were thought to be related to gas or rebubbling complications rather than the E-DMEK procedure itself. In 1 case, the SF_6 lasted an unusually long 2

TABLE 1. Demographic and Operative Characteristics of the First 69 Consecutive Cases of E-DMEK

Gender (%)	
Men	43 (62.3)
Women	26 (37.7)
Age, yrs	
Mean	65.9
Range	2–93
Indication for surgery (%)	
Pseudophakic/aphakic bullous keratopathy	33 (47.8)
Failed graft	16 (23.2)
Previous EK	10 (14.5)
Previous PK + EK	4 (5.8)
Previous DALK + EK	1 (1.4)
Previous DALK	1 (1.4)
Fuchs endothelial dystrophy	13 (18.8)
Glaucomatous bullous keratopathy	2 (2.9)
Post-laser peripheral iridotomy bullous keratopathy	2 (2.9)
Traumatic bullous keratopathy	2 (2.9)
Bullous keratopathy of unknown etiology	1 (1.4)
Other significant ocular comorbidity (%)	
Glaucoma	32 (46.4)
Glaucoma drainage tube	9 (13.0)
Gross PAS	9 (13.0)
Glaucoma filtering bleb	5 (7.2)
Aphakia	4 (5.8)
AC-IOL	3 (4.3)
ICE syndrome, anterior segment dysgenesis	2 (2.9)
Previous TPPV	1 (1.4)
Adjunctive procedures	
Phacoemulsification/IOL	23 (33.3)
Scleral-fixation of IOL	7 (10.1)
Release of PAS	6 (8.7)
Anterior vitrectomy	5 (7.2)
Repositioning/sulcus implantation of IOL	2 (2.9)
Trimming of glaucoma drainage tube	2 (2.9)
Pupilloplasty	2 (2.9)

DALK, deep anterior lamellar keratoplasty; EK, endothelial keratoplasty; ICE, iridocorneal-endothelial; PK, penetrating keratoplasty; TPPV, trans pars plana vitrectomy.

weeks in the AC, and the DMEK graft dried out. In the second case, the graft folded on itself during a rebubbling attempt and could not be unfolded because of fibrin in the AC. Therefore, after excluding these 2 cases, only 1 (1.5%) case of PGF could be attributed to the E-DMEK procedure. All 3 eyes subsequently underwent repeat E-DMEK procedures successfully.

Visual outcomes and ECL were analyzed for eyes with at least 6 months of postoperative follow-up (n = 56). Among 56 eyes with at least 6 months of follow-up, BCVA at the last follow-up ranged from 20/20 to hand movement. 40 of 56 eyes (71.4%) had BCVA of 20/40 or better. In the remaining 16 eyes with worse than 20/40 vision, visual prognosis was limited by other ocular comorbidities, such as end-stage glaucoma, macular pathology, and amblyopia. No eyes lost vision after E-DMEK. ECD by specular microscopy was available for 32 of 56 eyes with at least 6 months of follow-up. Among these 32 eyes, the mean preoperative donor ECD was 2772 (range 2457–3448) cells/mm^2, and the mean postoperative ECD was 1830 (range 541–2545) cells/mm^2. ECL was calculated as a percentage of donor ECD. Mean ECL at the last follow-up was 33.6% (range 7.5–80.4) at a mean follow-up duration of 7.1 (range 6–11) months postoperatively. Two cases had particularly high rates of ECL. The first was a 41-year-old patient with 65.6% ECL 11 months after surgery. This patient had had 2 previous failed corneal grafts (a penetrating keratoplasty and a DSEK), preexisting glaucoma, and gross PAS requiring intraoperative release. Postoperatively, this patient had a partial graft detachment that required rebubbling with SF_6. Eventually, the graft was attached and clear, but this high rate of ECL was likely because of a combination of the above factors. In addition, this eye had the longest postoperative follow-up, and the ECD was taken 11 months after surgery. The second case was a 78-year-old patient with 80.4% ECL at 7 months after surgery. This patient had pseudophakic bullous keratopathy with a previous failed DSEK, preexisting advanced glaucoma with a trabeculectomy, and a glaucoma drainage tube. Similarly, the high rate of ECL was likely multifactorial.

DISCUSSION

In this study, we describe a pull-through, endothelium-in technique for DMEK using a dedicated insertion device—the DMEK EndoGlide. We demonstrate in both an ex vivo laboratory-based study and a clinical series that this E-DMEK technique has acceptable rates of ECL, is safe, and shows promising early clinical results.

In our ex vivo study, the mean ECL with the pull-through technique was 15.2% ± 5.4%. This compares favorably with similar ex vivo studies evaluating other DMEK techniques in the published literature (Table 2). In these studies, DMEK graft loading and injection using glass tubes or plastic IOL cartridges showed a mean ECL ranging from 22.0% to 32.0%, using the same method of ECL quantification.[15,16,30] Qualitatively, the small peripheral areas of ECL we identified from forceps pinch damage are unlikely to be clinically significant. More importantly, we did not identify any linear patterns of ECL due to the pull-through.[31] Our clinical results were also promising. In our series, E-DMEK was associated with a rebubbling rate of 11.6% and a PGF rate of 1.5% (excluding the 2 cases thought to have failed for reasons unrelated to the surgical technique), whereas a recent large review of published data on DMEK found mean rebubbling and PGF rates of 28.8% and 1.7%, respectively.[3] Our mean ECL of 33.6% at a mean follow-up duration of 7.1 months was also very similar to the 33.0% mean ECL at 6 months reported in the same large literature review.[3] We did have 2 cases with unusually high ECL, but as detailed above, these were eyes with complex anterior segments and significant ocular comorbidity. When comparing against these published figures, it is also worth noting that most of the clinical studies cited included primarily patients with Fuchs endothelial dystrophy. Our series consisted of all Asian eyes, and almost half had DMEK performed for pseudophakic/aphakic bullous keratopathy, and almost a quarter for failed corneal grafts. Our series also included a significant proportion (36.2%) of complex cases, such as eyes with aphakia, glaucoma drainage tubes or filtering blebs, and gross PAS, which can be challenging with current endothelium-out techniques.[3,12,13] E-DMEK seems to be a promising technique for these "challenging" eyes.[32]

E-DMEK holds some theoretical advantages over current techniques, although these will need to be evaluated in future comparative studies. First, E-DMEK is an endothelium-in technique. It is postulated that such a configuration reduces the sheer stress on endothelial cells associated with passing through various insertion devices.[33] Perhaps more importantly, the endothelium-in configuration lends itself to easier unfolding of the graft in the AC, with less

TABLE 2. Published ECL Rates for Various Graft Insertion Devices Used for DMEK, Using Calcein Acetoxymethyl Staining and Quantification With Trainable Segmentation Software

Authors (Year of Publication)	Graft Insertion Device	Mean ECL (%)	Sample Size (No. of Eyes)
Schallhorn et al (2016)[15]	Modified Jones tube*	27.0	n = 9
	Viscoject IOL injector†	32.0	n = 9
Wolle et al (2017)[30]	Modified Jones tube*	22.0	n = 9
Downes et al (2018)[16]	Modified Jones tube*	23.0	n = 9
	DORC glass pipette injector‡	29.2	n = 9

*Gunther Weiss Scientific Glass, Portland, OR.
†Viscoject 2.2 IOL injection system; Medicel, Wolfhalden, Switzerland.
‡DORC International, Zuidland, Netherlands.

surgical manipulation than an endothelium-out configuration. As discussed above, this has to do with the natural tendency of DMEK grafts to scroll endothelium-out. A recent ex vivo study using paired donor tissue found that an endothelium-in approach had lower rates of ECL than an endothelium-out approach.[34] In contrast to this, a recent retrospective clinical study was unable to demonstrate a significant difference in ECL rates or graft unfolding time between endothelium-in and endothelium-out approaches.[33] However, this study only included eyes with Fuchs endothelial dystrophy and normal anterior segment anatomy—eyes with other ocular comorbidity such as glaucoma drainage devices or filtering blebs were excluded. In these "normal" eyes, the differences between the 2 approaches may not be significant, whereas in complex eyes, the advantages of an endothelium-in approach may be more readily apparent.

E-DMEK is also a pull-through technique, which provides more surgical control than injection techniques. This may be advantageous in complex eyes. The graft can be held onto with forceps while being unfolded, which minimizes the risk of graft inversion, ejection, or dislocation into the posterior segment (in eyes with aphakia or large iris defects). However, forceps pull-through does cause localized ECL and carries a small risk of graft tears, although this can be minimized by using smaller gauge (27G), nonserrated forceps. Other pull-through techniques for DMEK have been described, using the EndoGlide Ultrathin with either a specially manufactured stromal carrier (D-Mat), or donor stroma (Hybrid-DMEK or H-DMEK; manuscript in press).[24] However, E-DMEK is superior because it uses a smaller 2.75-mm (standard cataract) clear corneal incision instead of a 4.5-mm scleral tunnel and avoids the use of a stromal carrier, which can inadvertently enter the AC during pull-through, or adhere to the graft resulting in graft tears. Busin et al[17] also use an endothelium-in, pull-through approach with a contact lens carrier and an IOL injector device. This technique shares a number of similarities with E-DMEK. However, E-DMEK does not require an intermediate carrier for transfer of the graft to the insertion device. Rather, trifolded DMEK grafts can be loaded directly into the DMEK EndoGlide from donor corneoscleral buttons, which minimizes surgical time and graft manipulation. In addition, the DMEK EndoGlide is a dedicated device specifically designed for DMEK graft insertion, with a flatter, less rounded cross-sectional profile than IOL injectors, which may cause less wound distortion and provide better AC stability (Fig. 1). Lumen diameter is calculated from a mathematical formula to minimize overlap of endothelial surfaces, and except for the insertion tip, most of the device is wider than an IOL injector (which has a similar lumen diameter throughout its length).[35] This means that DMEK grafts spend less time in a "tight" configuration and may result in less endothelial damage. In addition, because of its flatter profile, grafts tend to remain trifolded within the DMEK EndoGlide, whereas in IOL injectors, they tend to adhere to the rounded internal lumen, which may make it harder to identify the graft edge and orientation correctly, and therefore increases the risk of graft inversion.

Some recent studies have suggested that DMEK grafts can be preloaded in modified Jones tubes before shipping for surgical use.[30,36,37] There is also potential for DMEK grafts to be preloaded into EndoGlide cartridges at the eye bank level in a similar manner, which could further simplify the surgical procedure and shorten the surgical time. However, this would require evaluation in a future study.

The limitations of this study should be acknowledged. Both the ex vivo and clinical studies lack comparative arms, although the methodologies used are well established in the literature. Our ex vivo study only evaluates ECL related to graft preparation, loading, and pull-through with the DMEK EndoGlide device. A more comprehensive approximation of the ECL from the entire E-DMEK procedure could be obtained by performing the full surgical procedure in cadaveric globes. However, this was beyond the scope of our study, and indeed, the ex vivo studies we compare against adopted a similar methodology to ours. In our clinical study, the method of graft preparation was not uniform—both lamellar dissection and SCUBA techniques were used. However, this is unlikely to have had significant impact on the results because the rates of ECL between the 2 techniques have been shown to be similar.[28]

In summary, we describe a surgical technique for DMEK using a pull-through, endothelium-in approach with the DMEK EndoGlide device. E-DMEK may allow an easier transition to DMEK for surgeons already familiar with DSEK and may also confer significant advantages in complex eyes. Future work should focus on longer-term clinical outcomes and evaluate the feasibility of preloaded E-DMEK grafts.

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