Three-Year Outcome Comparison Between Femtosecond Laser-Assisted and Manual Descemet Membrane Endothelial Keratoplasty

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Purpose: To evaluate 3-year outcomes of femtosecond laser-assisted Descemet membrane endothelial keratoplasty (F-DMEK) compared with manual Descemet membrane endothelial keratoplasty (M-DMEK) in patients with Fuchs endothelial corneal dystrophy (FECD).

Methods: A retrospective, interventional study, including eyes with FECD and cataract that underwent either F-DMEK or M-DMEK combined with cataract extraction at either the Toronto Western Hospital or Kensington Eye Institute, and that had at least 18 months' follow-up was conducted. Exclusion criteria: complicated anterior segments, previous vitrectomy, previous keratoplasty, corneal opacity, or any other visually significant ocular comorbidity.

Results: Included were 16 eyes of 15 patients in the F-DMEK group (average follow-up 33.0 ± 9.0 months) and 45 eyes of 40 patients in the M-DMEK group (average follow-up 32.0 ± 7.0 months). There were no issues with the creation of femtosecond descemetorhexis (in the F-DMEK group)—all descemetorhexis cuts were complete. Best spectacle-corrected visual acuity improvement did not differ significantly between the groups at 1, 2, and 3 years (P = 0.849, P = 0.465 and P = 0.936, respectively). Rates of significant detachment in F-DMEK and M-DMEK were 1 of 16 eyes (6.25%) and 16 of 45 eyes (35.6%) (P = 0.027). Rebubbling rates were 1 of 16 eyes (6.25%) and 15 of 45 eyes (33.3%) (P = 0.047). Cell-loss rates following F-DMEK and M-DMEK were 26.8% and 36.5% at 1 year (P = 0.042), 30.5% and 42.3% at 2 years (P = 0.008), 37% and 47.5% at 3 years (P = 0.057), respectively. Graft failure rate was 0% in F-DMEK and 8.9% in M-DMEK (all were primary failures; P = 0.565).

Conclusions: F-DMEK showed good efficacy with reduced detachment, rebubble, and cell-loss rates, compared with M-DMEK.

Key Words: DMEK, Descemet membrane endothelial keratoplasty, IEK, femtosecond laser, long-term, descemetorhexis, Fuchs dystrophy

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In recent years, Descemet membrane endothelial keratoplasty (DMEK) has become a favored treatment for Fuchs endothelial corneal dystrophy (FECD).[1–3] It has been shown that DMEK promotes faster and better visual recovery compared to Descemet stripping automated endothelial keratoplasty[4,5] with reduced rejection rates.[5]

In DMEK surgery, the recipient's Descemet membrane is peeled manually (descemetorhexis), to allow adherence of the donor DMEK tissue to the recipient's stroma. Complete removal of the recipient's Descemet membrane at the transplant site is crucial, since remnant tags and islands of Descemet's tissue might interfere with DMEK graft attachment.

Femtosecond laser has been increasingly used to create incisions in cataract, refractive, and corneal surgery.[6–9] Recently, the technique has been suggested as a novel tool for performing precise descemetorhexis in DMEK surgery.[10,11] We previously reported promising early outcomes with femtosecond laser-assisted-Descemet membrane endothelial keratoplasty (F-DMEK), showing efficacy similar to that of manual Descemet membrane endothelial keratoplasty (M-DMEK) with an apparently lower postoperative graft detachment rate.[11] In this study, we compared 3-year outcomes of F-DMEK and M-DMEK in FECD.

METHODS

A retrospective medical chart review was performed on consecutive patients who underwent either F-DMEK or M-DMEK combined with cataract surgery, secondary to FECD, at either Toronto Western Hospital or Kensington Eye Institute between September 2014 and September 2016 and who had at least 18 months of postoperative follow-up. All procedures were performed by a single experienced corneal surgeon (D.S.R.) or were directly supervised by him. All eyes included in the study were not among the first

150 DMEK surgeries performed by D.S.R. Excluded were eyes with either complicated anterior segments (presence of a glaucoma-drainage device, history of trabeculectomy or extensive peripheral anterior synechiae), previous vitrectomy, previous keratoplasty, corneal opacity, or any other visually significant ocular comorbidity. The cohort was divided into 2 groups: F-DMEK group and M-DMEK group. The 2 groups were chronologically matched to avoid chronological bias related to the surgeon's learning curve. Chronological matching was performed by first including all F-DMEK cases that met the inclusion criteria and then setting the time period of the study to be between the first (September 2014) and last (September 2016) DMEK surgery performed in the F-DMEK group. We then proceeded to include all M-DMEK eyes that met the inclusion criteria and were operated on during the same time period (September 2014 to September 2016). Sixteen eyes were included in the F-DMEK group, and 45 eyes were included in the M-DMEK group. In the F-DMEK group, the follow-up duration was 18, 24, and 36 months for 2 (12.5%), 2 (12.5%) and 12 (75.0%) eyes, respectively. In the M-DMEK group, the follow-up duration was 18, 24, and 36 months for 1 (2.2%), 13 (28.9%) and 31 (68.9%) eyes, respectively.

This retrospective interventional case series received Research Ethics Board approval by the University Health Network (Toronto Western Hospital, Toronto, Ontario, Canada) and was conducted in compliance with the tenets of the Declaration of Helsinki. The data collected in this study included demographic characteristics, best spectacle-corrected visual acuity (BSCVA), intraoperative and postoperative complications, corneal donor characteristics, and endothelial cell density (ECD) using a noncontact specular microscope (Robo, KSS 300; Konan Medical, Hyogo, Japan). All donor tissues used were stored in corneal storage solution (Optisol; Bausch & Lomb, Rochester, NY) and received from the Eye Bank of Canada, Ontario division.

Surgical Technique

DMEK grafts were prepared using a modification of the original Melles technique.[12] After preparation, the donor Descemet membrane was loaded into a glass cartridge (Gender Medical, Heidelberg, Germany). The descemetorhexis diameter was of same size as graft diameter in the F-DMEK group and was 0.25 mm larger than graft diameter in the M-DMEK group. Graft diameter in both groups was sized 3 mm less than the corneal diameter (graft diameter was 8.37 ± 0.19 mm in the F-DMEK group and 8.41 ± 0.15 mm in the M-DMEK group, $P = 0.562$). Table 1 details the donor characteristics of both groups. The surgical technique for F-DMEK has been previously described.[11] Briefly, descemetorhexis was performed using an Intralase iFS femtosecond platform (Abbott Medical Optics, Abbott Park, IL), creating a vertical ring cut whose depth extended from 100 μm above the thinnest measured corneal depth to 100 μm below the thinnest measured corneal depth. Corneal depth was measured using a Palmscan P2000U pachymeter (MicroMedical Devices, Calabasas, CA) at 8 points along the circumference of the planned descemetorhexis incision. In the M-DMEK group, a 360-degree separation of Descemet membrane was performed using the reverse Sinskey hook. This was followed in both groups by manual scraping and removal of the recipient's Descemet membrane. The rest of the procedure was similar to our standard, previously described technique for combined phacoemulsification, intraocular lens implantation, and DMEK.[13]

TABLE 1. Donor and Surgical Characteristics in the Femtosecond and Manual Descemet Membrane Endothelial Keratoplasty Groups

	F-DMEK	M-DMEK	*P*
Donor age (yr)	67.9 ± 3.5	64.1 ± 6.3	0.051
Graft diameter (mm)	8.37 ± 0.19	8.41 ± 0.15	0.562
Endothelial cell density (cells/mm^2)	2738 ± 260	2742 ± 203	0.476
Tamponading agent			
Air [N (%)]	14/16 (87.5%)	39/45 (86.7%)	0.932
SF6 [N (%)]	2/16 (12.5%)	6/45 (13.3%)	
Main surgeon			
Corneal surgeon	8/16 (50%)	18/45 (40%)	0.563
Clinical fellow and corneal surgeon	8/16 (50%)	27/45 (60%)	

All patients stayed strictly supine for 2 hours and then "as much as possible" at home until the next morning. All patients were examined 2 hours after surgery, and, if necessary, some of the air was released if the bubble was completely filling the anterior chamber likely resulting in pupillary block. The following day, 0.1% dexamethasone sodium phosphate and 0.3% tobramycin antibiotic (Tobradex; Alcon, Mississauga, Ontario, Canada) eye drops were administered 4 times daily for a week. Then, the antibiotic drops were discontinued and 0.1% dexamethasone sodium phosphate (Maxidex; Alcon) eye drops were tapered down from 4 times to once daily over a 3-month period.

Rebubbling was performed within 24 hours in eyes with Descemet membrane detachment spanning more than one-third of the DMEK graft area if no air bubble was present in the anterior chamber. Rebubbling was also performed later on if there was an unresolved Descemet membrane detachment that was causing persistent corneal edema either limiting rapid visual recovery or causing significant ocular surface discomfort.

Statistical Analysis

Data were recorded in Microsoft Excel (2016) and analyzed using SPSS version 23 (SPSS Inc, Chicago, IL). BSCVA results were converted to logarithm of the minimum angle of resolution (logMAR). Continuous variables were compared within subjects using the Wilcoxon nonparametric test and paired student's *t* test and between subjects using the Mann–Whitney test and nonpaired *t* test. Categorical variables were compared between subjects using Fisher's exact test. Multivariate linear regression was used to examine the independent effect of clinical variables on graft detachment rates. Variables included in the analysis were surgery type (F-DMEK vs. M-DMEK), surgeon's experience (corneal surgeon vs. clinical fellow supervised by a corneal surgeon), and tamponading agent (air vs. Sulfur hexafluoride [SF6]). All tests were 2-tailed, and the threshold for statistical significance was defined as a P-value <0.05.

RESULTS

Sixteen eyes of 15 patients in the F-DMEK group and 45 eyes of 40 patients in the M-DMEK group were included. Demographic and baseline characteristics of the 2 groups are shown in Table 2. There were no significant intraoperative complications and no issues with the creation of F-DMEK—all descemetorhexis cuts were complete.

Visual Outcome

In the F-DMEK group, preoperative BSCVA was 0.50 ± 0.33 logMAR (Snellen equivalent ~20/63) and improved significantly at 1, 2, and 3 years to 0.16 ± 0.14 logMAR (Snellen equivalent ~20/29, P = 0.001), 0.15 ± 0.12 logMAR (Snellen equivalent ~20/28, P = 0.002), and 0.14 ± 0.15 logMAR (Snellen equivalent ~20/28, P = 0.008), respectively. This represents an improvement of 0.32 ± 0.27, 0.30 ± 0.17, and 0.39 ± 0.37 logMAR at 1, 2, and 3 years, respectively.

In the M-DMEK group, preoperative BSCVA was 0.64 ± 0.49 logMAR (Snellen equivalent ~20/87) and improved significantly at 1, 2, and 3 years to 0.22 ± 0.13 logMAR (Snellen equivalent ~20/33, P < 0.001), 0.23 ± 0.23 logMAR (Snellen equivalent ~20/34, P < 0.001), and 0.16 ± 0.20 logMAR (Snellen equivalent ~20/29, P < 0.001), respectively. This represents an improvement of 0.40 ± 0.47, 0.43 ± 0.48, and 0.45 ± 0.48 logMAR at 1, 2, and 3 years, respectively.

BSCVA improvement did not differ significantly between the groups at any postoperative time point (P = 0.849, P = 0.465, and P = 0.936 for 1, 2, and 3 years, respectively). In the F-DMEK group, postoperative spherical equivalent changed by −0.28 ± 0.54 D (range −0.75 to +0.75 D) throughout the postoperative follow-up.

Safety

Significant graft detachment was seen in 1 of 16 eyes (6.25%) in the F-DMEK group and in 16 of 45 eyes (35.6%) in the M-DMEK group (P = 0.027). Rebubbling was performed in 1 of 16 eyes (6.25%) in the F-DMEK group and in 15 of 45 eyes (33.3%) in the M-DMEK group (P = 0.047). One eye in the M-DMEK group that had a significant detachment was not rebubbled at the patient's request with gradual visual improvement thereafter despite a partially detached graft and a final BSCVA of 20/40 at the last follow-up. Detachment and rebubble rates were also analyzed in the subgroup of patients where air was used as the tamponading agent (excluding eyes where SF6 was used), showing detachment and rebubble rates of 1 of 14 eyes (7.1%) in the F-DMEK group and 14 of 39 eyes (35.9%) in the M-DMEK group (P = 0.040). In a multivariate analysis, the type of surgery performed (M-DMEK vs. F-DMEK) was the only significant independent variable associated with graft detachment (P = 0.046, coefficient [B] = 2.170, standardized coefficient [β] = 0.526). Surgeon's experience and tamponading agent were not significantly associated with graft detachment (P = 0.515 and P = 0.860, respectively).

There were no primary graft failures in the F-DMEK group. In the M-DMEK group, there were 4 primary graft failures (8.9%): 2 failures secondary to complete graft detachment and 2 failures following partial detachment and rebubbling (P = 0.565). No secondary failures were observed throughout the follow-up in any of the groups. There were no episodes of immunologic graft rejection in the F-DMEK group and 1 rejection episode in the M-DMEK group, resolving completely with topical steroidal treatment.

Mean preoperative ECD in the F-DMEK and M-DMEK groups were 2738 ± 260 and 2742 ± 203 cells/mm^2, respectively. Cell-loss rates were 26.8% and 36.5% at 1 year (difference of 9.7% between the groups, P = 0.042), 30.5% and 42.3% at 2 years (difference of 11.8% between the groups, P = 0.008), and 37.0% and 47.5% at 3 years (difference of 10.5% between the groups, P = 0.057), respectively (Fig. 1).

Two eyes in the F-DMEK group had an intraocular pressure (IOP) spike 1 day after the procedure: The first (up to 35 mm Hg) resolved following paracentesis and IOP-lowering medications, and the second (up to 52 mm Hg) was due to a pupillary block and resolved with the administration of a topical cycloplegic and IOP-lowering medications. Two eyes in the M-DMEK group had IOP elevation during follow-up, attributed to steroid response. IOP normalized in the first eye following a change of the topical steroid and in the second eye following initiation of one topical IOP-lowering medication.

TABLE 2. Demographic and Baseline Patient Characteristics of the Femtosecond and Manual Descemet Membrane Endothelial Keratoplasty Groups

	F-DMEK	M-DMEK	P
Age (yr)	63.9 ± 9.3	69.1 ± 7.5	0.039
Gender: male eyes [n (%)]	7/16 (43.8%)	16/45 (35.6%)	0.565
Laterality: right eyes [n (%)]	4/16 (25.0%)	24/45 (53.3%)	0.079
Preoperative BSCVA (logMAR)	0.50 ± 0.33	0.64 ± 0.49	0.280
Follow-up time (mo)	33.0 ± 9.0	32.0 ± 7.0	0.289

DISCUSSION

This study evaluated 3-year outcomes of F-DMEK in patients with Fuchs endothelial dystrophy, showing excellent efficacy and safety in all parameters analyzed. This is in accordance with the short-term outcomes of F-DMEK published by our group and by others previously,[10,11] and to the best of our knowledge, this is the first study describing outcomes of F-DMEK beyond a short-term postoperative period.

Postoperative graft detachment is the most common complication following DMEK surgery, often requiring reinjections of air into the anterior chamber.[14,15] Rates of rebubble in the published literature average 12.8% (range 2.4%–82.0%)[16] and still constitute the most common postoperative issue in managing these patients. The rate of significant detachment and

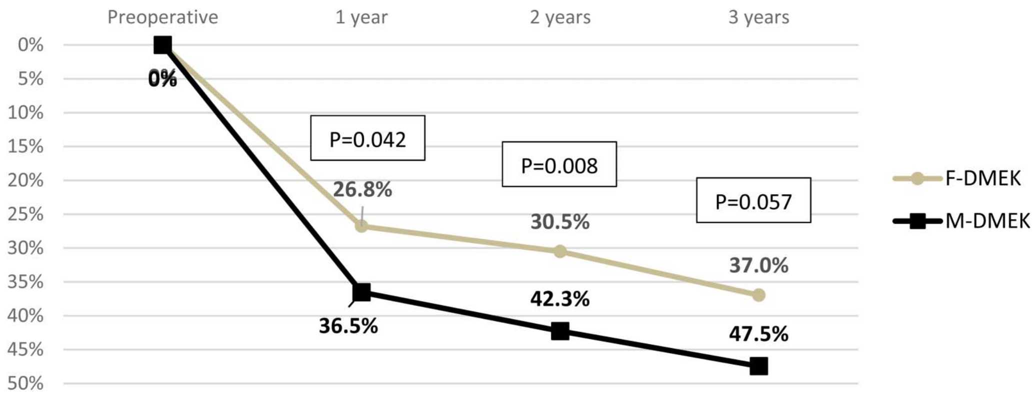

FIGURE 1. Cell-loss rate in the femtosecond DMEK (F-DMEK) and manual DMEK (M-DMEK) groups. *P*-values were calculated for the difference between the F-DMEK and M-DMEK groups.

rebubble in the current study was significantly lower in the F-DMEK group when compared with the M-DMEK group. One possible mechanism for this may be a more complete removal of Descemet membrane due to the deep and continuous Descemet incision performed by the femtosecond laser, which can reduce the number of remnant Descemet tags and islands in the planned interface. Other contributing factors could be either elevated subclinical postoperative inflammation in response to femtosecond laser stromal use that can promote better adherence of the graft or better alignment of the symmetric graft circular edge (created using the trephine) with the symmetric descemetorhexis edge (created using the femtosecond laser).

Endothelial cell loss following F-DMEK was consistently lower than M-DMEK throughout the 3-year follow-up period. The difference between the 2 groups appeared to be constant, with both groups having the largest cell-loss rate early, as expected from intraoperative and immediate postoperative cell loss, followed by a milder steady decline at the second- and third-year follow-ups. Although first- and second-year cell-loss rates were significantly different between the groups, third-year cell-loss rate difference was only borderline significant ($P = 0.057$), possibly due to a smaller number of patients completing 3 years of follow-up. The consistent difference in cell-loss rates between F-DMEK and M-DMEK could be a result of one or more possible factors. Feng et al[17] analyzed DMEK cell loss in relation to rebubbles and found that while their single-rebubble group did not have a significantly higher cell-loss rate compared with the no-rebubble group, there was a significantly higher cell-loss rate in eyes that had more than one rebubble attempt. They could not conclude whether a higher rebubble rate was the cause for increased cell loss or increased cell loss (intraoperatively) was the cause for a higher rebubble rate. Nevertheless, the proposed linkage between higher rebubble rates and increased cell loss may be one explanation for the reduced endothelial cell loss in the F-DMEK group. Additionally, the precise descemetorhexis performed by the femtosecond laser may help the surgeon to complete a more precise curvilinear stripping of Descemet membrane, avoiding accidental excess removal of peripheral host Descemet membrane, thereby decreasing the size of the bare area that needs to be repopulated by endothelial cells migrating off the graft. Also, same-sizing of the descemetorhexis and the graft in F-DMEK further reduces the bare area around the graft that needs to be repopulated by donor endothelial cells. In M-DMEK with an 8.25 mm graft, for example, oversizing the descemetorhexis by 0.25 mm would mean that donor endothelial cells will need to redistribute over an area that is approximately 6% larger than the graft area, thereby reducing ECD by 6%. Same-sizing the descemetorhexis and the graft in F-DMEK did not appear to induce graft detachment and may be another advantage of this procedure in reducing endothelial cell loss as discussed above.

Performing a femtosecond F-DMEK incision that extends 100 μm into the posterior stroma, raises the question of the influence of the posterior corneal incision on the postoperative refractive stability of the cornea. In the F-DMEK group, postoperative spherical equivalent remained stable, changing only by -0.28 ± 0.54 D (range -0.75 to $+0.75$ D) throughout follow-up. Further long-term studies can provide further insights into this topic.

In conclusion, F-DMEK showed good efficacy over a 3-year follow-up, with reduced detachment, rebubble, and cell-loss rates, when compared with M-DMEK. Additional prospective research is warranted to further investigate these issues.

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