Repeat Descemet Membrane Endothelial Keratoplasty

Secondary Grafts with Early Intervention Are Comparable with Fellow-Eye Primary Grafts

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Purpose: To evaluate the outcomes of secondary Descemet membrane endothelial keratoplasty (DMEK) after failed primary DMEK.

Design: Retrospective, interventional case series.

Participants: Fifty-five DMEK recipients 42 to 89 years of age.

Methods: An initial consecutive series of 1655 DMEK surgeries was reviewed to identify cases of secondary DMEK after failed primary DMEK (n = 55). A paired fellow-eye analysis was performed with a subgroup of 29 patients who underwent secondary DMEK in 1 eye and successful primary DMEK in the fellow eye.

Main Outcome Measures: Corrected distance visual acuity (CDVA), central corneal thickness, and 1-year endothelial cell loss.

Results: The median follow-up after DMEK regraft was 18 months (range, 3–61 months). All 55 regrafts cleared, 8 (15%) had air reinjected to promote attachment, 1 eye (2%) with trabeculectomy and progressive synechiae demonstrated late endothelial failure, and no rejection episodes occurred (0%). In the paired analysis, the median duration of endothelial decompensation before the regraft was 21 days (range, 2–133 days). At 1, 3, 6, or 12 months, CDVA did not differ between the primary and secondary grafts in fellow eyes (mean difference, ≤2 Snellen letters; P > 0.05 at all examinations). At 1 year, the visual acuity was ≥20/20 in 61%, ≥20/25 in 81%, and ≥20/40 in 100% of the secondary grafts in the paired analysis, excluding 1 eye with retinal problems. Vision differed by ≤1 line between fellow eyes in all but the 1 patient with the longest time to regraft (133 days), who demonstrated central haze and irregular astigmatism from anterior stromal scarring during that period. At 1 year, CDVA associated with the scarring was 20/40 versus 20/20 for the fellow-eye primary graft. The central corneal thickness was comparable between fellow-eye primary and secondary grafts at 3, 6, and 12 months (mean difference at 1 year, 2 μm; P = 0.57). The 1-year endothelial cell loss was comparable in primary and secondary grafts (27% vs. 31%, respectively; P = 0.58).

Conclusions: In patients who received prompt intervention to minimize the duration of central corneal decompensation, the visual outcomes with secondary DMEK matched the fellow-eye visual outcomes with primary DMEK. Ophthalmology 2015;[1–6] © 2015 by the American Academy of Ophthalmology.

Endothelial keratoplasty (EK) has become the preferred treatment for endothelial dysfunction because it is safer, provides faster visual recovery, and allows patients to resume daily activities sooner than penetrating keratoplasty (PK). The EK iteration known as Descemet membrane EK (DMEK) provides the quickest visual rehabilitation with the lowest risk of immunologic rejection. However, DMEK is more challenging to perform and somewhat more prone to partial detachment with delayed or incomplete corneal clearing, or both, than the popular Descemet stripping automated endothelial keratoplasty technique. Delayed corneal clearing has been described in some cases, so the optimal time to intervene by reinjecting air or replacing the graft has not been determined definitively.

Several centers that take a conservative approach of waiting and watching for a number of months before performing a regraft have reported that secondary DMEK results in poorer visual outcomes than primary DMEK. Our usual practice is to intervene promptly so that patients do not have to contend with poor vision, symptomatic bullae, and restricted activities for any extended period. The hypothesis of this study was that visual results after secondary DMEK are comparable with those after primary DMEK if the secondary DMEK is performed promptly to minimize the duration of corneal edema. When available, fellow eyes with primary DMEK served as the standard against which to compare the secondary DMEK visual outcomes.

Methods

Data collected prospectively at a single center from an initial consecutive series of 1655 DMEK procedures performed by 11
surgeons between March 2008 and October 2014 was reviewed retrospectively to identify patients who underwent secondary DMEK after failed primary DMEK with at least 3 months of follow-up. The first DMEK surgeries for all surgeons were included. A subgroup of patients who underwent secondary DMEK in one eye and successful primary DMEK in the fellow eye also was identified for a paired fellow-eye analysis. The study adhered to the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. Independent review board approval was obtained. All patients read and signed an informed consent document for the research as well as for the surgical procedures.

Surgical Technique

The surgical technique was described previously. In brief, a surgeon prepared the donor tissue at the surgical facility on the day of surgery or up to 2 days beforehand using the submerged cornea and a background away technique to isolate the endothelium and Descemet membrane. Patients received topical anesthesia with monitored intravenous sedation. The recipient epithelium was marked lightly with a trephine to indicate the planned graft diameter and location. The host endothelium and Descemet membrane were stripped from the marked area. A surgical inferior iridotomy was performed. The prepared donor tissue was stained with trypan blue (Vision Blue; DORC, Nuidland, The Netherlands) and was inserted into the eye through a 2.8-mm corneal incision with an intraocular lens injector (Viscoject; Medicel AG [Wolfhalden, Switzerland], Carl Zeiss Meditec [Jena, Germany], or Staar Surgical [Monrovia, CA]). As soon as the graft was determined to be in the proper orientation using a handheld slit beam, the graft was uncurled with a no-touch technique using short bursts of balanced salt solution. The graft was pressed against the posterior host cornea with an intraocular air bubble. Patients remained supine for 1 hour and then were examined with a slit lamp. If the intraocular pressure (IOP) was elevated or an air meniscus was occluding the iridotomy, some air was released using a 30-gauge needle on a 1-ml syringe inserted through the cornea. If the anterior chamber did not re-form spontaneously, balanced salt solution was injected to achieve physiologic pressure by palpation. The IOP was measured and patency of the peripheral iridotomy was confirmed at the slit lamp before the patient was released. In some cases, DMEK was combined with cataract extraction and intraocular lens implantation, as described previously.

After surgery, patients used topical antibiotics for 1 week. Prednisolone acetate 1% eye drops were used 4 times daily for the first 3 to 4 months, then tapered by 1 drop daily each month to once-daily dosing, which was continued through 1 year to prevent immunologic rejection.

Rebubbling

Examinations were performed at 1 day, 2 days, and 1 week after surgery to assess graft adherence. Air was reinjected to promote graft attachment if an area of detachment obscured the visual axis, continued to increase, or was large enough that it could lead to a complete detachment after air absorption. The procedure was performed in a minor operating room, as described previously.

Regraft Timing and Technique

Corneal clarity was assessed by slit-lamp examination. When a graft failed to clear initially and the surgeon suspected significant iatrogenic endothelial damage (e.g., difficult preparation, insertion, or positioning), the graft often was replaced within 1 week. When a graft failed to clear initially after routine surgery, the graft typically was monitored for several weeks before diagnosing primary graft failure, because DMEK sometimes exhibits delayed spontaneous clearing. The regraft timing took into consideration individual patient circumstances. Generally, we believe it is prudent to regraft promptly whenever bullae or microcystic edema are present over the pupillary area to ensure optimal visual outcomes.

When a regraft was required, the primary DMEK graft was removed carefully from the host posterior stroma with a reverse procedure using the Noncon Robo [Konan Medical, Inc., Hyogo, Japan] or automated analysis using the EM-3500 [Tomey Corp., Nagoya Japan]. The baseline donor ECD was measured by the provider eye bank (usually Indiana Lions Eye and Tissue Transplant Bank, Indianapolis, IN) with specular microscopy (KeratoAnalyser; Konan, Hyogo, Japan). Endothelial cell loss was calculated by subtracting the 1-year postoperative ECD from the baseline donor ECD, dividing by the baseline donor ECD, and multiplying by 100. In cases of late endothelial failure, the duration of corneal decompensation was defined as the interval between the regraft and the examination when corneal edema was documented first or the interval between the regraft and the date the patient first noted decreased vision, whichever was longer. Postoperative complications, including air reinjection, immunologic rejection, IOP elevation, and graft failure, were documented.

Outcome Measures

Corrected distance visual acuity (CDVA) was measured with Snellen projector charts, and data were converted to logarithm of the minimum angle of resolution (logMAR) units for statistical analysis. Central corneal thickness was assessed with ultrasonic pachymetry. The postoperative central endothelial cell density (ECD) was assessed by specular microscopy (manual centers method using the Noncon Robo [Konan Medical, Inc., Hyogo, Japan] or automated analysis using the EM-3500 [Tomey Corp., Nagoya Japan]). The baseline donor ECD was measured by the provider eye bank (usually Indiana Lions Eye and Tissue Transplant Bank, Indianapolis, IN) with specular microscopy (KeratoAnalyser; Konan, Hyogo, Japan). Endothelial cell loss was calculated by subtracting the 1-year postoperative ECD from the baseline donor ECD, dividing by the baseline donor ECD, and multiplying by 100. In cases of late endothelial failure, the duration of corneal decompensation was defined as the interval between the regraft and the examination when corneal edema was documented first or the interval between the regraft and the date the patient first noted decreased vision, whichever was longer. Postoperative complications, including air reinjection, immunologic rejection, IOP elevation, and graft failure, were documented.

Statistical Analysis

The paired Student t test was used for the fellow-eye analysis. The CDVA was converted from Snellen to logMAR units for the analysis, which was performed using Statistical Analysis Software version 9.3 (SAS Inc, Cary, NC). The tests were 2-tailed, and P values less than 0.05 were considered statistically significant.

Results

Demographics

Fifty-five patients (55 eyes) met the study inclusion criteria. Most had Fuchs’ endothelial dystrophy, and the median age was 69 years (range, 42–89 years; Table 1). Secondary DMEK was performed as a single procedure in the 55 eyes. After surgery, the youngest patient was phakic and the remaining 54 patients were pseudophakic (Table 1). The median duration of follow-up was 18 months (range, 3–61 months).

A subgroup of 29 patients who underwent secondary DMEK in one eye and successful primary DMEK in the fellow eye met the criteria for the paired analysis; all had Fuchs’ endothelial dystrophy (Table 1). The eye that required a secondary graft was the first treated eye in 11 patients (38%) and the second treated eye in 18 patients (62%). The median interval between the primary grafts in the fellow eyes was 18 weeks (range, 2 weeks to 2 years).

Reasons for Replacement of the Original Graft and Timing

The reasons for the 55 regrafts included unsuitable donor tissue (n = 5), surgical complications (n = 21), early failure to clear
for no identifiable reason \((n = 22)\), late endothelial failure \((n = 5)\), and refractive failure \((n = 2)\). Unsuitable donor tissue included 1 specimen from a donor younger than 20 years that was almost impossible to unfold and 2 specimens from donors with longstanding insulin-dependent diabetes that were used early in the series despite numerous tears. These grafts failed to clear and the median interval until the regraft was 7 days, range, 2–22 days. One tissue specimen from a 19-year-old donor cleared quickly, but the recipient had visual distortion resulting from a wrinkle across the visual axis because of unfolding difficulty. It was replaced after 205 days. One donor specimen proved to be unsuitable because of visually significant guttae and was replaced after 159 days. In the latter 2 cases, the host cornea did not experience any period of decompensation between the original graft and the regraft.

In 21 cases, the graft failed to clear after surgical complications. The median interval until the regraft was 9 days, range, 1–357 days. The regraft was performed as soon as the following day in a case in which the original graft was found to be upside down by anterior segment optical coherence tomography, and irreversible damage to the endothelium was suspected. The regraft was performed as late as 357 days in an eye that had mild persistent edema and central pachymetry of 567 μm. The central pachymetry did not increase with time, nor did the eye show microcystic changes or bullae. After the regraft, the central pachymetry decreased to 480 μm and the vision improved from 20/50 to 20/20.

In 22 cases that failed to clear with no identifiable reason, the median interval until the regraft was 32 days, range, 8–161 days. The longest interval between the original graft and the regraft was in an 89-year-old patient with macular degeneration who wanted to postpone further surgery.

In 5 cases of late endothelial decompensation, the median interval between the original graft and the regraft was 27 months, range, 9–54 months. The median duration of host corneal edema between the original graft and the regraft was 90 days, range, 43–149 days.

Two regrafts were performed to treat refractive failure of the original graft. These included 1 case with retained host Descemet membrane in the interface because of poor visualization from longstanding edema during the primary DMEK, and a case in which the donor age was suitable (>40 years), yet the original graft was difficult to unfold and ended up with a wrinkle that crossed the visual axis. The time to regraft was 147 and 205 days in these 2 cases, respectively. Neither host cornea experienced any period of corneal edema between the original DMEK and the regraft.

### Complications

All 55 regrafts cleared successfully (0% primary failure). Air was reinserted once in 7 eyes (13%) and twice in 1 eye (2%). Of the 22% experienced an immunologic rejection episode. One regraft (2%) had late endothelial decompensation in the absence of any documented rejection episodes and was replaced at 31 months in a patient with comorbidities of glaucoma, trabeculectomy, and progressive synechiae. Twelve patients (22%) experienced IOP elevation (defined as IOP ≥24 mmHg) and were treated by initiating or increasing glaucoma medication, reducing corticosteroid strength or dosing frequency, or both glaucoma medication and corticosteroid methods. At 1 year after secondary DMEK, the mean (± standard deviation) endothelial cell density was 1959±489 cells/mm², and the cell loss was 34±14% relative to the eye bank—reported baseline donor endothelial cell density (2942±247 cells/mm²).

### Visual Outcomes

Six of 55 patients (11%) were excluded from the visual acuity analysis because of significant retinal limitations. Three had age-related macular degeneration, 2 had diabetic retinopathy, and 1 had severe loss of retina nerve fiber layer from advanced glaucoma. At 1 year, the visual acuity was 20/20 or better in 43% of the eyes, 20/25 or better in 64%, and 20/40 or better in 100% \((n = 45)\). Four patients had not yet reached the 1-year time point; their vision ranged from 20/20 to 20/30 at the most recently completed examination.

Visual outcomes were assessed further through paired analysis in the subgroup of patients who underwent secondary DMEK in one eye and successful primary DMEK in the fellow eye. This design provided an opportunity to compare directly visual outcomes of secondary and primary DMEK without confounding from between-subject differences, such as a widely varying duration of endothelial decompensation before the original DMEK graft.

One fellow-eye patient was excluded from the paired visual acuity analysis because of severe retinal nerve fiber thinning.
resulting from advanced glaucoma. The remaining 28 fellow-eye patients all completed 6 months of follow-up and 26 completed 1 year of follow-up in both eyes (2 had not yet reached 1 year).

The CDVA was comparable in the fellow-eye primary and secondary grafts at every postoperative examination interval (Fig 1). The mean CDVA difference between the primary and secondary grafts was 0.04 logMAR units or fewer, corresponding to 2 Snellen letters or fewer on the eye chart, at every examination. The mean CDVA improved from 20/40 before DMEK (assessed before the primary graft was performed in each eye) to 20/30 at 3 months and 20/25 at 1 year after DMEK. At 1 year, vision was 20/20 or better in 61%, 20/25 or better in 81%, and 20/40 or better in 100% of the secondary grafts in the paired analysis.

The CDVA differed between fellow eyes by no more than 1 line in all but 1 patient, who consistently had vision that was 2 lines poorer in the eye with secondary DMEK. The initial graft in that eye failed to clear fully and a regraft was performed at 133 days. Central haze and irregular astigmatism from anterior stromal scarring developed during the period of corneal edema. At 1 year, the best spectacle-corrected vision was only 20/40 in the regrafted eye versus 20/20 in the fellow eye with primary DMEK.

Central Corneal Thickness and Endothelial Cell Density: Paired Analysis

The preoperative central corneal thickness (measured before the primary graft was performed in each eye) did not differ significantly between fellow eyes (635±71 vs. 631±81 µm; P = 0.78), suggesting that the corneal edema associated with Fuchs’ dystrophy had reached a similar stage in the fellow eyes of each patient before treatment (Table 2). The central corneal thickness did not differ significantly between fellow-eye primary and secondary grafts at 3 months (517±46 vs. 510±48 µm, respectively; P = 0.12) or at 6 or 12 months after DMEK (Table 2).

The baseline donor ECD was comparable for fellow-eye primary and secondary grafts (Table 2). After DMEK, the ECD did not differ significantly between the fellow eyes at 6 or 12 months, and the 1-year endothelial cell loss was comparable in fellow-eye primary and secondary grafts (30±13% vs. 31±14%, respectively; P = 0.66; Table 2).

Discussion

The key finding in this study was that the outcomes of secondary DMEK were comparable with those of primary DMEK when graft failure was treated promptly. The mean difference in CDVA between primary and secondary DMEK in fellow eyes was 1 to 2 Snellen letters at the 1-through 12-month examinations. The principal concern with postponing graft replacement for too long is that prolonged corneal edema can cause irreversible host stromal changes, which in turn may impair visual outcomes after secondary DMEK. This occurred in the patient in whom corneal haze and irregular astigmatism developed as a result of anterior stromal scarring during the 133-day interval between the failure of the primary DMEK and replacement with a secondary DMEK. However, prolonged corneal edema, when sufficiently mild, does not necessarily lead to changes that degrade the optical quality of the cornea, as evidenced by the patient who regained 20/20 vision despite having mild edema for 357 days between the original graft and the regraft. Because it is difficult to predict how rapidly corneal edema will produce stromal changes and which patients may be prone to have this happen, we believe it is prudent to regraft promptly whenever bullae or microcystic edema are present over the pupillary area to ensure optimal visual outcomes.

The findings in this study are consistent with reports that secondary DMEK provides superb visual outcomes when performed to treat unsatisfactory vision without corneal decompensation after Descemet stripping endothelial keratoplasty. However, when secondary DMEK has been used to treat a primary graft that was decompensated for a prolonged period, the visual outcomes have not matched those achieved with primary DMEK. Baydoun et al described a series of eyes in which the mean time to regraft was 16 months (range, 4–33 months). The CDVA was 20/25 or better in 5 of 13 eyes (38%) at 6 months and in 8 of 14 eyes (57%) at 1 year, but 5 eyes were using a contact lens at both intervals, presumably because of irregular astigmatism from anterior stromal scarring caused by long-standing corneal edema. Likewise, Cirkovic et al reported median CDVA of only 20/40 at 1 year in a series of DMEK regrafts performed at a median of 103 days (range, 7–497 days) after primary graft failure. Yoo and Bartz-Schmidt had better visual recovery (mean CDVA was between 20/25 and 20/30 at 3 months) in 6 eyes treated more promptly (1–5 months) with secondary DMEK.

Retention of the host stroma with EK is leading to a paradigm shift regarding when to proceed with transplantation. When PK was the procedure of choice, one typically would wait to perform surgery until the corneal edema became so pronounced it would not respond to treatments such as topical sodium chloride drops or ointment or the use of a hair dryer to dehydrate the cornea. Because the entire
corneal thickness was being replaced, it did not matter if degenerative changes occurred as a result of prolonged host corneal edema. Confocal microscopy studies by Patel et al.22,23 and Patel and McLaren18 have shown that host anterior stromal changes that occur with Fuchs’ dystrophy progression persist for years after EK. This suggests that for optimal vision, it is important to treat Fuchs’ endothelial dystrophy before the development of significant corneal edema and to avoid treatments such as Descemet membrane endothelial transfer or Descemet’s stripping alone without placement of a graft, both of which can be associated with prolonged corneal edema and degenerative stromal changes while the endothelium repopulates the central cornea.22,23 The results of this study suggest that it is likewise important to intervene promptly after EK graft failure to prevent prolonged, or possibly permanent, changes in the host cornea resulting from long-standing edema.

A report from the Australian Corneal Graft Registry found that EK had a substantially higher rate of early graft failure than PK during a period when many surgeons were early in the EK learning curve and the annual number of EK cases per surgeon was relatively low.24 Visual improvement after regrafts was not taken into consideration, and the results suggested that overall visual outcomes were poorer after EK than PK.24 In our experience, even if a patient has an early EK failure, they can have an EK regraft, recover excellent vision, and resume normal activities sooner than they would after primary PK.25 Unlike secondary PK, secondary EK grafts do not seem to be associated with inferior outcomes, such as a higher failure rate.2 In addition, the small EK incision is not susceptible to graft dehiscence or loss of the eye after minor trauma, which is a life-long risk after PK.26

The complication rates in this study of secondary DMEK were consistent with rates reported with primary DMEK.2,4–6,10,28,27 Air reinjection to promote graft attachment usually is the most common intervention after EK.2,4,10 The proportion of patients who experienced IOP elevation (24%) was similar to the proportions reported after other types of keratoplasty,27 and this complication is associated with the postoperative corticosteroid-dosing regimen.27 The endothelial cell loss at 1 year was consistent with primary DMEK cell loss in other studies.4,10,28 Descemet membrane endothelial keratoplasty has a remarkably low rate of immunologic graft rejection5; none of the 55 secondary DMEK grafts experienced a rejection episode over a median follow-up of 18 months (range, 3–61 months).

Among the strengths of this study was the intrasubject fellow-eye analysis, which eliminated intersubject and unpaired variations as potential confounders. A post hoc statistical power analysis indicated that our sample size provided 90% power to detect a mean difference of 3 Snellen letters or more of CDVA, 15 µm or more of pachymetry, and 300 cells/mm² or more of ECD between fellow eyes with the paired analysis. Study limitations included the retrospective nature and variation in the interval between graft failure and replacement.

In conclusion, this study showed that visual outcomes of secondary DMEK were comparable with primary DMEK outcomes in fellow eyes when regrafts were performed promptly to minimize the duration of host corneal dec complication rates with secondary DMEK were comparable with primary DMEK between graft failure and replacement.

Table 2. Central Corneal Pachymetry and Endothelial Cell Density in Fellow-Eye Primary and Secondary Descemet Membrane Keratoplasty

<table>
<thead>
<tr>
<th>Central corneal pachymetry (µm)</th>
<th>Primary Graft Eye</th>
<th>Secondary Graft Eye</th>
<th>P Value</th>
</tr>
</thead>
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<tr>
<td>Baseline (before initial transplants)</td>
<td>635±71</td>
<td>631±81</td>
<td>0.78</td>
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<tr>
<td>3 mos</td>
<td>517±46</td>
<td>510±48</td>
<td>0.12</td>
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<tr>
<td>6 mos</td>
<td>515±44</td>
<td>513±44</td>
<td>0.47</td>
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<tr>
<td>12 mos</td>
<td>514±42</td>
<td>512±40</td>
<td>0.97</td>
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<td>Endothelial cell density (cells/mm²)</td>
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<tr>
<td>Baseline donor</td>
<td>2985±225</td>
<td>2944±231</td>
<td>0.78</td>
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<td>6 mos</td>
<td>2135±336</td>
<td>2067±448</td>
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<tr>
<td>12 mos</td>
<td>2112±384</td>
<td>2032±490</td>
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<tr>
<td>Endothelial cell loss at 1 year (%)</td>
<td>30±13</td>
<td>31±14</td>
<td>0.66</td>
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References