Risk of Corneal Transplant Rejection Significantly Reduced with Descemet's Membrane Endothelial Keratoplasty

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Purpose: To evaluate the relative risk of immunologic rejection episode in patients who underwent Descemet's membrane endothelial keratoplasty (DMEK), Descemet's stripping endothelial keratoplasty (DSEK), and penetrating keratoplasty (PK).

Design: Comparative case series.

Participants: One hundred forty-one eyes treated with DMEK at Price Vision Group, Indianapolis, Indiana.

Methods: The patients in the DMEK group were compared retrospectively with cohorts of DSEK (n = 598) and PK (n = 30) patients treated at the same center, with similar demographics, follow-up duration, and indications for surgery. The postoperative steroid regimen and rejection criteria were identical in the 3 groups. Kaplan–Meier survival analysis, which takes varying length of follow-up into consideration, was performed to determine the cumulative probability of a rejection episode 1 and 2 years after surgery. Proportional hazards analysis was used to determine the relative risk of rejection episodes between the 3 groups. $P<0.05$ was considered significant and calculated using the log-rank test.

Main Outcome Measures: Rejection-free survival and cumulative probability of a rejection episode.

Results: The mean recipient age was 66 years (56% females and 94% Caucasian) and median follow-up duration was 13 months (range, 3–40) in the DMEK group. Fuchs' dystrophy was the most common indication for surgery (n = 127; 90%) followed by pseudophakic bullous keratopathy (n = 4; 4%) and regrafts (n = 9; 6.4%). Only 1 patient (0.7%) had a documented rejection episode in the DMEK group compared with 54 (9%) in the DSEK and 5 (17%) in the PK group. The Kaplan–Meier cumulative probability of a rejection episode at 1 and 2 years was 1% and 1%, respectively, for DMEK; 8% and 12%, respectively, for DSEK; and 14% and 18%, respectively, for PK. This was a highly significant difference ($P = 0.004$). The DMEK eyes had a 15 times lesser risk of experiencing a rejection episode than DSEK eyes (95% confidence limit [CL], 2.0–111; $P = 0.008$) and 20 times lower risk than PK eyes (95% CL, 2.4–166; $P = 0.006$).

Conclusions: Patients undergoing DMEK had a significantly reduced risk of experiencing a rejection episode within 2 years after surgery compared with DSEK and PK performed for similar indications using the same corticosteroid regimen.

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There has been a rapid adoption of posterior lamellar corneal surgery in the form of Descemet's stripping endothelial keratoplasty (DSEK or DSAEK; hereafter DSEK) for the treatment of endothelial dysfunction given the advantages it offers over conventional penetrating keratoplasty (PK), including rapid and predictable visual recovery, enhanced tectonic integrity, and virtual elimination of ocular surface complications.

Despite the relative immune privilege enjoyed by the cornea, allograft rejection remains the leading cause of endothelial failure in PK in several reported series.[1–6] It was hoped that DSEK might lower rates of graft rejection, given the absence of donor epithelium and lack of sutures. However, in our recently reported large series of 598 cases of DSEK, the cumulative probability of experiencing a rejection episode was 8% at 1 year and 12% at 2 years; this was not significantly lower than PK with use of the same postoperative corticosteroid regimen ($P = 0.38$).[7]

Descemet's membrane endothelial keratoplasty (DMEK) is a newer iteration of endothelial keratoplasty techniques that involves selective transplantation of only Descemet's membrane and endothelium, without any accompanying stroma. It offers excellent visual outcomes with a greater proportion of eyes achieving ≥20/20 vision compared with DSEK.[8–10] We hypothesized that DMEK might reduce the incidence of allograft rejection substantially given the absence of not only the donor epithelium, but also the stroma. To test our hypothesis, the current study analyzed the probability of rejection in a cohort of 3 surgical groups (DMEK, DSEK, and PK) performed for similar indications and treated with the same postoperative corticosteroid regimen.

Methods

This retrospective analysis of data collected prospectively in an initial consecutive series of 150 DMEKs was performed between

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February 2008 and September 2010 at a tertiary referral center, Price Vision Group, Indianapolis, Indiana. An independent review board approved the study.

Inclusion and Exclusion Criteria

The study was limited to cases followed up at our center for ≥3 months, resulting in a total of 141 eyes. Patients in the study group (DMEK cases) were compared with a cohort of 598 DSEK cases performed at the same center between December 2003 and May 2007, and 30 PK cases performed at the same center between October 2002 and August 2003. The DSEK and PK cases included in this study have been described in a previous publication.[7]

Operative Technique

The DMEK technique of donor preparation and insertion has been detailed in an earlier publication.[8] The DMEK donor preparation was performed using the Submerged Cornea Using Backgrounds Away technique. The harvested Descemet's membrane and endothelium was inserted into the eye through a 2.8-mm corneal incision, using an intraocular lens injector (STAAR Surgical, Monrovia, CA). The donor was then unfolded in the correct orientation using a combination of balanced salt solution and air. Once unfolded, air was used to attach the donor against the recipient.

Postoperative Treatment Regimen

Patients undergoing DMEK were treated with the same steroid regime as described for PK as well as for DSEK.[7] In brief, patients were treated with tobramycin/dexamethasone ointment (Tobradex, Alcon, Fort Worth, Texas) 4 times daily for 1 week, after which it was substituted with prednisolone acetate 1% (Pred Forte, Allergan, Irvine, CA) 4 times daily. Typically, 4 times daily dosing was continued for 4 months and thereafter the steroid was decreased by 1 drop every month. If the patient did not develop steroid responsiveness, once-daily dosing of prednisolone acetate 1% was continued indefinitely. In eyes with steroid-responsive glaucoma, prednisolone acetate 1% was usually substituted for a milder steroid like flurometholone (FML, Allergan) or loteprednol etabonate (Lotemax, Bausch & Lomb, Rochester, NY).

Eyes with a rejection episode were treated with intensive topical prednisolone acetate 1% in a dose ranging from 8 times daily to hourly dosing, depending on the severity of rejection as described for DSEK in an earlier series.[7] The steroid was then gradually tapered, based on response to therapy, down to a maintenance dose of once daily.

Statistical Analysis

The criteria used for noting a rejection episode event in the database was the identification of keratic precipitates, an endothelial rejection line, subepithelial infiltrates, or an epithelial rejection line by slit-lamp examination. Descriptive statistics were reported as median values and ranges or mean values and standard deviations, as appropriate. The incidence of rejection episodes depends on duration of follow-up, so statistical methods were utilized that take variable follow-up into consideration by using the information collected on each patient for the length of time they were followed. Kaplan–Meier survival analysis and the log-rank test were used to measure the fraction of patients remaining rejection-free at 1 and 2 years. A proportional hazards analysis was also performed to determine the relative risk of rejection episodes between the groups. Some of the patients had bilateral grafts, so cluster analysis, which takes into consideration potential positive correlation between bilateral grafts, was included in the proportional hazards analysis. $P<0.05$ was considered significant. All analyses were performed using SAS version 9.1 software (SAS Inc, Cary, NC).

Results

Table 1 summarizes the demographics of the 141 DMEK eyes that were compared with 598 DSEK and 30 PK eyes. Recipient gender and race were comparable for the 3 groups ($P = 0.19$ and 0.44, respectively). Likewise, the indications for surgery were similar in the DMEK and DSEK groups, but the PK group did not include pseudophakic bullous keratopathy, regrafts, or iridocorneal endothelial syndrome, which tend to be more complicated eyes. The age distribution was similar for the DMEK and DSEK groups, whereas the PK group was somewhat older (mean, 73 vs 66 years, respectively), which was a clinically insignificant difference. The median follow-up duration was 13 months (range, 3–40) for DMEK, 11 months (range, 3–42) for DSEK, and 17 months (range, 1–35) for PK.

Cumulative Probability of a Rejection Episode

Only 1 eye (0.7%) in the DMEK group had a rejection episode compared with 54 eyes (9%) in the DSEK group and 5 eyes (17%) in the PK group. At 1 and 2 years after grafting, the Kaplan–Meier estimated probabilities of a rejection episode were 1% and 1%, respectively, for DMEK; 8% and 12%, respectively, for DSEK; and 14% and 18%, respectively, for PK. As seen in Figure 1, eyes with DMEK had a reduced risk of rejection compared with DSEK or PK and this was highly significant ($P = 0.004$). The DMEK eyes had 15 times lesser risk of rejection compared with the DSEK eyes (95% CL, 2.0–111; $P = 0.008$) and 20 times lesser risk of experiencing a rejection episode than the PK eyes (95% CL, 2.4–166; $P = 0.006$).

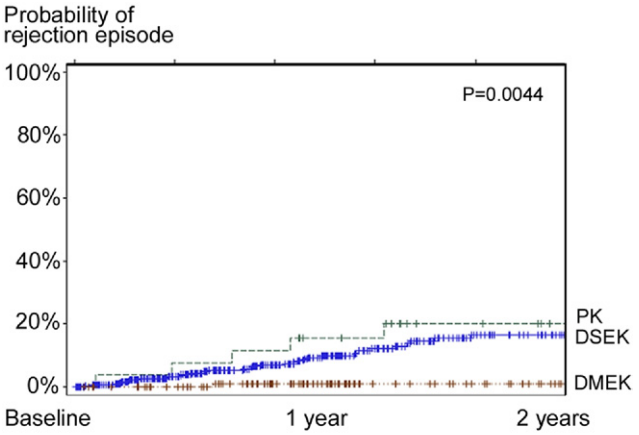
Clinical Profile of the DMEK Case with a Rejection Episode

The patient with the documented rejection episode was a 56-year-old Caucasian man with a history of cataract surgery followed by

Table 1. Demographics and Indications for Surgery in Patients Who Underwent Descemet's Membrane Endothelial Keratoplasty (DMEK), Descemet's Stripping Endothelial Keratoplasty (DSEK), or Penetrating Keratoplasty (PK)

	DMEK	DSEK	PK
Sample size (n)	141	598	30
Mean age (y)	66±11	66±12	73±12
Race			
Caucasian	126 (93%)	571 (95%)	29 (97%)
African American	5 (4%)	19 (3.2%)	1 (3%)
Other	4 (3%)	8 (1.3%)	0 (0%)
Gender (% female)	56	57	57
Indication for surgery, n (%)			
Fuchs' dystrophy	127 (90)	523 (87)	30 (100)
PBK	5 (3.6)	72 (12)	0 (0)
Regraft	9 (6.4)	0 (0)	0 (0)
ICE syndrome	0 (0)	3 (0.5)	0 (0)

ICE = iridocorneal endothelial; PBK = pseudophakic bullous keratopathy; PK = penetrating keratoplasty.



Rejection (%)	1 year	2 years
DMEK	1	1
DSEK	8	12
PK	14	18
Eyes still followed without rejection (n)		
DMEK	82	35
DSEK	246	79
PK	23	11

Figure 1. Kaplan–Meier survival curve depicting the significantly reduced probability of a graft rejection episode in eyes with Descemet's membrane endothelial keratoplasty (DMEK), when compared with Descemet's stripping endothelial keratoplasty (DSEK) and penetrating keratoplasty (PK) performed for similar indications and with the same steroid regimen ($P = 0.004$). The fraction that experienced a rejection episode and the number of eyes at risk (i.e., still being followed with no rejection episodes) is tabulated for each group at 1 and 2 years.

LASIK, arcuate keratotomy, and intraocular lens exchange in the right eye. He underwent uneventful DMEK surgery (graft diameter, 8 mm; baseline donor endothelial cell density, 3003 cells/mm^2) and his best-corrected visual acuity improved from counting fingers preoperatively to 20/40 at 2 weeks postoperative, with a clear and fully attached DMEK graft.

One month after surgery, he had a steroid-induced raised intraocular pressure (IOP) and so the follow-up doctor tapered off and discontinued prednisolone acetate 1%. One month after discontinuation, the patient presented with decreasing vision, pain, and redness in his right eye. On examination, best-corrected visual acuity was 20/200, and he was noted to have multiple keratic precipitates on the endothelium associated with an endothelial rejection line (Fig 2). He responded to intensive topical steroid therapy, with complete resolution of the rejection episode. When last reviewed, 3 months after the rejection episode, he had a clear graft with a best-corrected visual acuity of 20/50 and endothelial cell density of 1789 cells/mm^2. He was advised to continue prednisolone acetate 1% once daily indefinitely.

Discussion

This study confirms our hypothesis that DMEK is associated with a significantly reduced risk of graft rejection compared with DSEK and PK. Only 1 patient (n = 141) in the DMEK group experienced a rejection episode compared with 54 in the DSEK (n = 598) and 5 in the PK group (n = 30), resulting in an absolute rejection rate of 0.7% for DMEK, 9% for DSEK, and 17% for PK performed for similar indications and with the same steroid regimen ($P = 0.004$), DMEK eyes had 15 times lower risk of experiencing a rejection episode than DSEK eyes and 20 times lower risk than PK eyes.

Our findings of an extremely low (<1%) absolute rejection rate in DMEK eyes with median follow up of 13 months (range, 3–40) is consistent with a recent report by Cursiefen et al of no rejection episodes in 130 DMEK eyes with mean follow up of 9 months (Cursiefen C, Heindl L, Bachmann B, et al. Immune rejection after isolated transplantation of Descemet's membrane and endothelium (DMEK). Invest Ophthalmol Vis Sci 2011;52: E-Abstract 1155).

When compared with DSEK, DMEK provides excellent visual outcomes; if the results of this study are substantiated by other authors with long-term follow-up, it could have several implications: (1) Reduced rejection rates as seen with DMEK would lead to improved long-term graft survival and this in turn would lead to better patient care and management. (2) It would have a significant impact on eye banking and donor tissue availability, especially so in the developing world. (3) It may indicate that topical corticosteroids may be reduced after DMEK relative to PK and DSEK, thereby decreasing the risk of steroid responsiveness and glaucomatous damage. (4) Importantly, this may lead to a greater understanding of the immune privilege enjoyed by the cornea.

Glaucoma and steroid-induced IOP increases in PK eyes have been shown to range from 9% to 35%.[11–15] We have also shown that at least one third of eyes undergoing DSEK at our

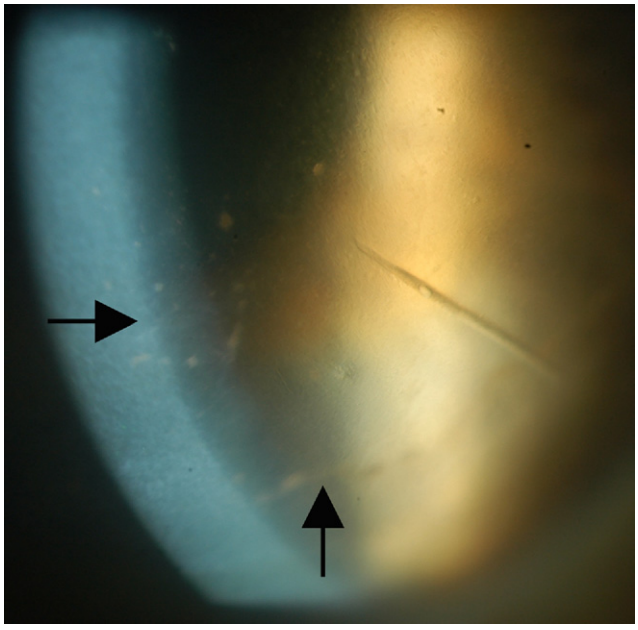


Figure 2. Slit-lamp photograph of the right eye of the only patient with Descemet's membrane endothelial keratoplasty (DMEK) who had a rejection episode showing a cluster of keratic precipitates (horizontal arrow) and an inferior rejection line (vertical arrow) associated with overlying corneal edema.

center experience steroid induced IOP spikes.[16] If indeed, DMEK eyes have a reduced risk of rejection relative to PK and DSEK, then there is a good likelihood that the steroid dosing may be reduced for DMEK eyes, allowing less risk of IOP spikes and related damage to the optic nerve and the graft itself. Reduced postoperative IOP spikes would also decrease the need for topical antiglaucoma medications and this would impact positively on health care costs.

In an elegant rabbit study, Khodadoust and Silverstein[17] demonstrated that all 3 corneal layers (epithelium, stroma and endothelium) are independently susceptible to rejection. They showed that eccentrically placed grafts as well as sutures encourage vessel ingrowth and initiate rejection. Evaluating endothelial rejection they suggested 2 origins for the cells responsible for rejection: From the uveal tract into the anterior chamber or from stromal vessels. In a murine model, Hori et al[18] have reported that alloimmunogenicity of the normal cornea resides within the epithelium and stroma and immune privilege arises from the endothelium. In a subsequent study, they also demonstrated that epithelium was more antigenic than stroma or the endothelium.[19]

The findings of these animal studies suggest that stromal vascularization increases risk of graft rejection. This was also confirmed in the collaborative corneal transplantation study, in which ≥2 quadrants of stromal vascularization were associated with the highest risk of rejection after PK.[5] Second, the presence of sutures acts as a triggering stimulus for new vessel formation and hence rejection, and last, epithelium provides the greatest antigenic stimulus.

The rate of rejection is time-dependent and influenced by the corticosteroid regimen. This is well illustrated in a report by Lee et al,[20] where the reported rate of graft rejection after DSEK ranged from 0% to 45.5% with an average of 10% with a follow-up ranging from 3 to 24 months. It has been suggested that DSEK may lower rates of graft rejection[21] and, in our report on rejection after DSEK, we have shown that although there was a lower risk of rejection compared with PK, it was not a significant difference.[7] Allan et al[22] in their series on rejection have, however, reported significantly reduced rates of rejection after endothelial keratoplasty techniques compared with PK ($P = 0.035$) and suggested this was probably related to the difference in corticosteroid regime in the compared groups.[22]

Based on findings from animal studies it would seem that DSEK, by eliminating sutures as well as donor epithelium and part of the stroma, would have a significantly lower risk of rejection compared with PK. How then do we account for this difference? The absence of epithelium as well as sutures reduces but does not eliminate the antigenic load in eyes with DSEK. Second, although there is an absence of direct contact between the host stromal vessels and donor tissue in DSEK, it is likely that effector cells in the anterior chamber may stimulate rejection in these eyes. In patients undergoing DMEK, not only is there a lack of sutures as well as donor epithelium, there is no donor stroma either. This may result in a greater reduction in antigenic load and hence reduced risk of rejection compared with DSEK, as well as PK, as seen in this study.

The strengths of this study are that it is the first to evaluate immunologic graft rejection episodes in a large series of DMEK grafts and compare it with both DSEK and PK. All DMEK cases were prospectively followed at our center using the same postoperative corticosteroid regimen and the same criteria for evaluating immunologic rejection that were used in the earlier DSEK and PK series. This eliminates significant confounding variables present when comparing rates of rejection between different sites. Study limitations that could introduce potential bias are that this was a retrospective comparison of cohorts treated during different time periods, with modest differences in the case mix, and a small number of eyes in the PK group. Although it would not be ethical at this point in time to conduct a randomized study between the 3 types of corneal grafting procedures owing to the vastly different rates of visual recovery and long-term complications, this study does support the need for prospective studies to evaluate the optimal dosing of topical corticosteroids[23] and further document the rate of rejection after DMEK as well other forms of corneal transplantation.

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Footnotes and Financial Disclosures

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