How to treat endothelial failure after PK or DMEK: is DMEK the way to go?

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Article

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Abstract

Background

Descemet membrane endothelial keratoplasty (DMEK) may be an elegant solution for endothelial failure after penetrating keratoplasty (PK). However, it is currently unclear whether this approach comes with any long-term drawbacks concerning chronic endothelial cell loss, rebubbling rates, graft survival and severity of immune reactions. We therefore herein compare the outcomes of DMEK to repair failed PK to the outcomes of DMEK to repair failed DMEK grafts.

Methods

This retrospective study included 117 patients with DMEK after keratoplasty (82 following DMEK and 35 following PK). Postoperative visual acuity, endothelial cell count, rebubbling rates, graft survival and rejection rates were recorded. Kaplan-Meier-analysis was used to assess survival rates.

Results

Visual acuity improved, but stayed at a lower level in PK patients. Endothelial cell loss was more severe in patients with DMEK as an initial procedure, whereas rebubbling rates, graft failure and immune reactions did not differ significantly between both groups. Ratios of graft diameters of the first and second graft did not influence survival or rejection of the graft.

Conclusions

Repeat DMEK is an appropriate method of treating endothelial graft failure after both DMEK and PK. The higher endothelial cell loss in the DMEK-DMEK group may be due to a different recipient endothelial reservoir and assimilate in the long term follow-up. These data may encourage treating endothelial graft failure with DMEK even in PK eyes.

Introduction

In comparison to penetrating keratoplasty (PK), Descemet membrane stripping endothelial keratoplasty (DMEK) has considerable advantages: intraoperatively, there is no open sky procedure with a consecutively lower risk for expulsive bleeding; postoperatively, the clinical course and aftercare are more comfortable for the patients as there are no sutures, as visual rehabilitation is faster and refractive stability is higher and rejection rate is lower.

It is therefore reasonable to consider DMEK as treatment option for endothelial graft failure following PK, Limbo-PK, Descemet stripping automated endothelial keratoplasty (DSAEK) or DMEK. However, according
to a recent and extensive European registry study, PK still is the favoured technique for repeat keratoplasties. Taking into account the recent success of DMEK, we can expect that repeat DMEK will outnumber repeat PK in the future. However, it is unclear whether there is a difference in the outcome of repeat keratoplasty depending on the initial technique. At present, only some reports exist about DMEK as a treatment option for graft failure after different keratoplasty techniques: DMEK-DMEK; PK-DMEK; DSAEK-DMEK. Only one study compares the outcome between different primary keratoplasty techniques (PK-DMEK and PK-DSAEK), showing superiority of DMEK in terms of visual acuity outcome.

Herein, DMEK following either PK or DMEK were compared concerning the endpoints best corrected visual acuity (BCVA), endothelial cell density (ECD), rebubbling rates, graft failure, and immune reactions in a consecutive cohort. We investigated the different outcomes following repeat DMEK depending on the initial keratoplasty technique by means of retrospective chart reviews.

**Subjects And Methods**

The group of 117 patients with repeat DMEK consists of 82 failed DMEK-grafts and 35 failed PK-grafts (including four Limbo-PK and two femtosecond laser-assisted PK). Analysis was performed retrospectively in consecutive patients between 2008 and 2020. Written consent for the scientific analysis of anonymised data was obtained from all patients who received a graft. The study was carried out in accordance to the Declaration of Helsinki and was approved by the local ethics committee (21-1407). Mean follow-up was 576 days (320-1147) in the DMEK and 1013 days (349-1739) in the PK group, respectively. No major demographic differences were detected between the two groups (for further details see table 1). Both groups are comparable with regard to manifest glaucoma and other ocular comorbidities (see table 1).

Table 1: Demographic factors and patients characteristics
<table>
<thead>
<tr>
<th></th>
<th>DMEK-DMEK (n=82)</th>
<th>PK-DMEK (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female</td>
<td>44:38 (54:46%)</td>
<td>15:20 (43:57%)</td>
</tr>
<tr>
<td>Age at surgery</td>
<td>77 years</td>
<td>71 years</td>
</tr>
<tr>
<td>Follow-up (mean)</td>
<td>576 days (320-1147)</td>
<td>1013 days (349-1739)</td>
</tr>
<tr>
<td>Manifest glaucoma</td>
<td>21 (26%)</td>
<td>13 (37%)</td>
</tr>
<tr>
<td>Comorbidities other than glaucoma</td>
<td>28 (34%)</td>
<td>12 (34%)</td>
</tr>
<tr>
<td>Indication of first keratoplasty</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fuchs endothelial dystrophy</td>
<td>64 (78%)</td>
<td>8 (23%)</td>
</tr>
<tr>
<td>• Bullous keratopathy</td>
<td>17 (21%)</td>
<td>10 (29%)</td>
</tr>
<tr>
<td>• Keratoconus</td>
<td>0</td>
<td>8 (23%)</td>
</tr>
<tr>
<td>• Infectious keratitis</td>
<td>0</td>
<td>6 (17%)</td>
</tr>
<tr>
<td>• Limbal insufficiency</td>
<td>0</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>• Others</td>
<td>1 (1%)</td>
<td></td>
</tr>
</tbody>
</table>

There are no significant differences in both groups. In the DMEK-DMEK-group, there was one patient with Cogan-syndrome-associated bullous keratopathy; PK-indications in the PK-DMEK-group include infections with fungi, viruses like Herpes simplex and different bacteriae, limbal insufficiency was caused by burns, autoimmune disorders or aniridia; in this group, the total percentage is 101% due to a rounding error. PK mainly was performed trephine-guided, four cases were Limbo-PK and two Femtosecondlaser-assisted PK.

Abbreviations: DMEK (Descemet membrane endothelial keratoplasty); PK (penetrating keratoplasty)

The PK-group is more heterogeneous in terms of the indication of the initial keratoplasty. This due to the stromal opacities in different infectious keratitis forms and in limbal insufficiency that only can be treated with penetrating keratoplasty procedures.

Initial PK and DMEK as first or second procedure and medical aftercare were performed as previously described with exclusively air tamponade in DMEK. The femtosecond laser-assisted PK was performed in Fuchs endothelial dystrophy using a “tophat”-profile with an inner diameter of 8.5 mm and an outer diameter of 8.0 mm. In DMEK surgery following PK, graft diameter for DMEK was always chosen 0.5 mm smaller than the PK graft to avoid overlapping of the stromal PK-wound and to allow better visualisation of the DMEK graft. In DMEK after DMEK, the same graft size was chosen in both surgeries which was 8mm.

For survival analysis unrelated to the follow-up, Kaplan-Meier-analysis was performed concerning the five endpoints mentioned above. Taking into account the heterogeneity of the PK-group and the relatively few
events, we decided not to use a proportional hazards model or a COX regression analysis. Nevertheless, we present p values from the log rank test.

**Results**

Visual acuity improved in both groups at a similar rate, but remained poorer in the PK group (see Fig. 1). About 70% of DMEK-DMEK patients gained two ETDRS (early treatment diabetic retinopathy study) lines or more after three years in contrast to 44% of PK-DMEK patients (see Fig. 1; p = 0.06).

Endothelial cell loss differed significantly between the keratoplasty-groups (see Fig. 2; p = 0.03): during the first three years, PK patients showed higher endothelial cell counts than DMEK patients. Beyond this period, ECD remained stable in both groups; PK patients having a loss below 1000 cells/mm² in 40%, DMEK patients in 60% of cases. This observation is remarkable, even though the statistical power is not sufficient for a valuable comparative test.

In terms of rebubbling rates, eyes with repeat DMEK following DMEK had to undergo a rebubbling procedure more often than the ones following penetrating procedures (30% versus 25% during the first four months postoperatively, see Fig. 3; p = 0.70).

Recurrent graft failure occurred in roughly 50% of the patients. 60% of these were DMEK patients and 40% had PK as the initial keratoplasty procedure (see Fig. 4; p = 0.03). PK-DMEK patients experienced the second graft failure faster than DMEK-DMEK patients.

There was no difference in immune-mediated graft rejection following DMEK as a rescue therapy in the different keratoplasty techniques (see Fig. 5; p = 0.50). Only few patients suffered from endothelial immune reactions of the second corneal graft.

Results were independent of the ratio diameters of the grafts (as in the first keratoplasty, different diameters were chosen and in DMEK following PK, diameter of the DMEK graft was 0.5 mm smaller than the initial PK graft; data not shown).

**Discussion**

DMEK has become the gold standard for the surgical treatment of endothelial diseases of the cornea. DMEK not only appears to be useful as a primary surgical procedure, but is also increasingly being considered for the surgical treatment of endothelial decompensation following prior corneal transplantation.

This study therefore investigated the outcome of repeat DMEK in case of endothelial graft failure following not just previous DMEK but also previous PK.

In our study, in terms of BCVA patients with initial DMEK benefit more from repeat DMEK than PK patients. It has been reported that an intact corneal surface provides better visual results in DMEK.
compared to PK \(^1\). According to our data (see Fig. 1) and the findings of another comparative study \(^{13}\), this seems also to be true for repeat DMEK and is consistent with the optical conditions before the graft failure.

However, as concerns ECD, PK patients show higher numbers during the first three years (see Fig. 2). This may be due to the surgical trauma to the peripheral endothelium of the host in initial DMEK, as well as to the additional air/gas contact during the first procedure. There are also more indications for PK where there is a healthy endothelial reservoir in the periphery (as in keratoconus for example). This may lead to longer graft survival rates \(^{15,16}\). In addition, ECD loss may become similar between DMEK and PK patients in the long-term follow-up of more than three years. Even though there are no comparative studies yet, long-term data from various large keratoplasty centers allow a valid overview. For DMEK, after initial ECD loss of about 34\% after six months (reflecting the surgical trauma), the annual loss rate decreases to 9\% \(^{17–19}\). For PK, an initial annual decrease of ECD of 20\% is reported \(^{20,21}\), consisting of a rapid and a slow component, the latter leading to slower decrease in the long-term period \(^{22}\). These data suggest that after three years, ECD numbers should balance between DMEK and PK. In addition, this difference in ECD does not seem to be relevant for the rate of a new graft failure, which is comparable between both groups (Fig. 4).

Looking at immune reactions, one could speculate that the higher alloantigen load grafted in PK-patients could lead to higher rejection rates, which is not supported by our data (Fig. 5). In contrary, repeat PK after failed PK is associated with a significantly higher graft rejection rate \(^{23}\) and therefore considered as high risk keratoplasty \(^{24}\) which seems not the case in DMEK after failed PK. First steps to elucidate the rejection/failure mechanisms in DMEK have been made recently, highlighting non-cellular components of the innate immune system \(^{25}\). Furthermore, rebubbling rates are comparable between PK and DMEK patients (Fig. 3), despite the fact that PK eyes show a more complex altered anatomy in comparison to DMEK eyes. There are often defects of iris, aphakia or glaucoma drainage devices are present, all of them complicating graft unfolding and adherence as well as hampering the presence of the air/gas tamponade. Additional factors such as incapability of the patient to stay supine for example, or the amount of the tamponade seem to be relevant in this context. Compared to rebubbling rates in primary and uncomplicated DMEK, about 20\% is consistent with our initial rebubbling rate during the first three years \(^1\), which decreased during the last few years to 11\% (data not shown).

According to these data, repeat DMEK is a considerable option in treating endothelial graft failure following PK and DMEK. Taking into consideration the current literature further helps to validate our findings and to answer the question if this success of DMEK is independent from the initial keratoplasty technique:

- Most studies have been published including patients with DMEK for DMEK failure \(^{4–6,25–29}\). Even though numbers of included patients differ (6–55) and reported clinical parameters are
heterogeneous, all studies confirm a fast visual rehabilitation and similar courses of ECD, rebubbling and immune reactions.

- Some studies address the results from DMEK for PK failure\textsuperscript{7–10,14,30,31}. Despite varying numbers of patients (5–93) and outcome parameters, all these papers highlight the fast rehabilitation following DMEK in PK eyes. The longest follow-up is three years which corresponds with the present study\textsuperscript{7}. Even in complicated, vascularized corneas with limbal insufficiency, comparable clinical courses of DMEK are reported\textsuperscript{32}.

- There are two studies reporting successful treatment of DSAEK-failure by DMEK\textsuperscript{11,12}.

These different studies are quite heterogeneous concerning cohorts and data analysis, but some of them conclude in common:

- Possible risk factors for graft failure following DMEK are glaucoma, complex preoperative anterior segment situations, and difficult primary DMEK surgery\textsuperscript{13,26,27}. One study states that a loss of endothelial cells is the main cause for graft failure following DMEK\textsuperscript{25}.

- Visual acuity improves in all mentioned studies (amount dependent on rate of extracorneal eye diseases limiting BCVA).

- Central corneal thickness decreases in successful repeat DMEK.

- There is an endothelial cell loss of about 30\% during the first 3–6 months postoperatively.

- Rebubbling rates vary between 15\% and 60\% in DMEK as repeat keratoplasty procedure\textsuperscript{4,7,27,28}.

As far as we know, the only comparative study that currently exists (PK-DSAEK versus PK-DMEK) is also retrospective and reports a favorable outcome in DMEK as treatment for graft failure; it comprises 52 cases in total\textsuperscript{13}.

Despite these results in favour of DMEK as treatment of graft failure, our study has some weaknesses: heterogeneity and limited size of both groups, and the retrospective character. In addition, we did not check for the increase in quality of life of the patients systematically as outcome measure of repeat DMEK. There are patients with low visual acuity after repeat DMEK who nevertheless are extremely enthusiastic about the relief of bullous keratopathy-complaints and the fast rehabilitation.

However, in spite of limited data availability and worldwide still widely spread DSAEK and PK\textsuperscript{2}, DMEK seems to be appropriate in treating graft failure even in complicated eyes. Especially when rapid visual rehabilitation and/or anatomical reconstruction and minimally invasive surgery are required (e.g. in the elderly or in eyes with comorbidities that limit visual prognosis and impending pain due to bullous keratopathy), DMEK is a reasonable alternative to repeat DSAEK or PK. In particular, patients with endothelial failure following successful Limbo-PK (restored limbal function and absence of graft rejection; 4/35 in our cohort) benefit from repeat DMEK as they retain their limbal function and stromal clarity\textsuperscript{32}. Given increasing surgical experience, more and more complex situations will be manageable.
Declarations

Acknowledgments: none

Conflict of interests: none for all authors

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References


**Figures**
Follow-up of BCVA following DMEK as regraft for DMEK failure (red line) or for PK failure (green line)

Depicted is the percentage of patients without BCVA-gain of two or more ETDRS lines. Velocity of BCVA gain is similar during the first three years (listed in days), but DMEK-DMEK patients reach higher BCVA than PK-DMEK patients (p=0.091). Below, numbers of participating patients for some time points are listed (in days).

Abbreviations: DMEK (Descemet membrane endothelial keratoplasty); PK (penetrating keratoplasty); BCVA (Best corrected visual acuity); ETDRS (early treatment diabetic retinopathy study)
Figure 2

Loss of ECD following DMEK-DMEK patients (red line) and PK-DMEK patients (green line)

During the first three years, DMEK-DMEK patients suffer from higher ECD loss than PK-DMEK patients do (p=0.031). Time is displayed in days.

Abbreviations: DMEK (Descemet membrane endothelial keratoplasty); PK (penetrating keratoplasty); ECD (endothelial cell density); pSQM (per square millimeter)
Figure 3

Percentage of rebubbling procedures following DMEK after DMEK (red line) and DMEK after PK (green line)

All rebubblings were performed during the first four months: in 40% of the DMEK-DMEK patients and in 30% of the PK-DMEK patients (p=0.73). Time is displayed in days.

Abbreviations: DMEK (Descemet membrane endothelial keratoplasty); PK (penetrating keratoplasty)
Figure 4

Rate of graft failure in DMEK-DMEK patients (red line) and in PK-DMEK patients (green line)

After three years, patients with initial PK suffered more often from graft failure (42%) than patients with initial DMEK (15%; difference 27%). After 3.5 years, the difference is reduced to 16% (52%:36%; p=0.014). Time is displayed in days.

Abbreviations: DMEK (Descemet membrane endothelial keratoplasty); PK (penetrating keratoplasty)
Figure 5

Patients with immune reactions after DMEK for graft failure following DMEK (red line) or PK (green line)

There is no difference between both groups with only a few single events during more than six years (p=0.52). Time is displayed in days.

Abbreviations: DMEK (Descemet membrane endothelial keratoplasty); PK (penetrating keratoplasty); IR (immune reaction)