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Long-term outcome of descemet membrane endothelial keratoplasty (DMEK) following failed penetrating keratoplasty (PK)

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ABSTRACT.

Purpose: **To assess the long-term outcome of Descemet membrane endothelial keratoplasty (DMEK) following failed penetrating keratoplasty (PK).**

Methods: **Retrospective review of 1840 consecutive DMEK surgeries from the prospective Cologne DMEK database performed between 07/2011 and 08/2017 at the Department of Ophthalmology, University of Cologne.**

Results: **Fifty-two eyes received a DMEK surgery after failed PK. Main indications for initial PK were Fuchs endothelial corneal dystrophy (23.1%), keratoconus and herpetic keratitis (each 15.4%). Best-corrected visual acuity (BCVA) at 3, 6 and 12 months was 0.72 ± 0.39 (n = 33), 0.56 ± 0.36 (n = 32) and 0.38 ± 0.28 (n = 23), respectively. Two- and 3-year BCVA was 0.37 ± 0.21 (n = 21) and 0.32 ± 0.18 (n = 10). Mean improvement in visual outcome in logMAR lines was +4.3 ± 3.4 at 6 months, +5.0 ± 3.6 at 12 months, +6.0 ± 2.3 at 24 months and +5.4 ± 2.7 at 36 months, respectively. 59.6% received at least one rebubbling and 40.4% did not necessitate a rebubbling. Endothelial cell density (ECD)-decrease at 6 months was 36% (n = 17), 37% at 12 months (n = 17), 40% at 2 years (n = 8) and 32% at 3 years (n = 2). 34.6% of transplants needed a regraft.**

Conclusion: **Descemet membrane endothelial keratoplasty (DMEK) is a feasible treatment option after failed PK having a relatively good long-term outcome.**

Key words: DMEK – cornea – PK

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Introduction

Until a few years ago, the only option for treating failed penetrating keratosplasty (PK) grafts was the repeated transplantation of full-thickness corneas or implanting a keratoprothesis. Both of these procedures carry the increased risk for a variety of complications such as thinning of the recipient cornea, scarring, increased risk of infections and immune reactions, slow visual recovery, loose sutures, increased risk of corneal surface disease and poor innervation (Claesson & Armitage 2013; Lee et al. 2015).

Since Descemet stripping automated endothelial keratoplasty (DSAEK) was introduced later on, more and more centres used DSAEK instead of repeated PK to rescue a failed PK. The success of DSAEK over a failed PK regarding the graft survival rate and the visual recovery was positive and was reported in many studies (Anshu et al. 2011; Price et al. 2011; Hoerster et al. 2016). Descemet membrane endothelial keratoplasty (DMEK) has become the treatment of choice for Fuchs endothelial corneal dystrophy (FECD) in many countries (Melles et al. 2006; Cursiefen & Kruse 2010; Flockerzi et al. 2018). When comparing to DSAEK, DMEK results in a more rapid visual recovery, fewer higher-order optical aberrations, improved contrast sensitivity and lower rates of immune reactions compared to DSAEK (Price et al. 2009; Rudolph et al. 2012; Hos et al. 2017; Hos et al. 2019).

Price et al. reported a series of 93 eyes with a mean follow-up of 21 months and concluded that DMEK is an effective option in managing secondary graft failure after PK with good visual outcomes and mid-term graft survival (Pasari et al. 2019). Heinzelmann et al. examined the mid-term outcome of 19 eyes over almost one year with mostly bullous keratopathy as primary indication and also concluded that DMEK is a feasible

option even in eyes with limited visual potential (Heinzelmann et al. 2017). Einan-Lifshitz et al. (2018) depicted the mid-term outcome over almost two years of 28 eyes and concluded that DMEK is a viable option for cases of failed PKP, although associated with lower visual acuity and higher number of rebubbling interventions. Another study by Lavy et al. (2017) examined a small cohort of 11 eyes using DMEK as a secondary option after failed PK over 36 months and reported acceptable outcomes in many cases.

Longer-term outcome data after DMEK for a failed PK are still missing. Therefore, the aim of this study is to report the long-term outcome in a relatively large cohort of DMEK following failed PK.

Patients and methods

Out of clinical records of 1840 eyes from the prospective *Cologne DMEK database*, 52 eyes with DMEK following failed PK could be determined. Donor tissue parameters, preoperative status and clinical outcome parameter were reviewed. All 52 DMEK surgeries were performed by two experienced surgeons (CC and BB) with comparable techniques between July 2011 and August 2017 at the Department of Ophthalmology, University of Cologne, Cologne, Germany (Bachmann et al. 2010; Kruse et al. 2011).

The data have been collected prospectively within the *Cologne DMEK database*, using the REDCap (Research Electronic Data Capture) electronic data capture tool, which is a secure, web-based application designed to support data capture for research studies (Stanzel et al. 2016). The study was conducted in adherence to the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board (No. 14-373).

Collection of clinical data

Demographic data of all recipients were collected, including age, gender, indication for keratoplasty and previous surgery.

Baseline donor central ECD was measured by the cornea eye bank. The postoperative central ECD was measured with specular microscopy (Tomey EM-3000 Specular Microscope). Endothelial cell density (ECD) images were analysed by taking one automated reading (serial photographs of 15 shots) with manual correction on a photographic range of 0.25×0.54 mm.

The central corneal thickness (CCT) was measured by Pentacam HR, Oculus GmbH, Wetzlar, Germany, preoperatively, at 3, 6, 12, 24 and 36 months postoperatively.

Intraoperative and postoperative complications, including postoperative Descemet detachments requiring air reinjection into the anterior chamber (rebubbling), were documented.

Furthermore, the following data of donor tissue were assessed: age (years), gender (male/female), endothelial cell density (cells/mm^2), source of tissue (Germany/USA) and preservation time until grafting (days).

Descemet membrane endothelial keratoplasty (DMEK) surgery alone in phakic or pseudophakic eyes, as well as triple procedures (DMEK combined with phacoemulsification and posterior chamber lens implantation for coexistent cataract), was included.

Donor preparation and surgical technique

Two experienced surgeons (CC and BB) performed DMEK in a standardized fashion as described previously (Bachmann et al. 2010; Kruse et al. 2011). Out of the 52 eyes, one surgeon (CC) performed the surgery on 32 eyes and the other one (BB) on 20 eyes. The first surgeon (CC) used slightly oversized DMEK grafts whereas the second surgeon (BB) used same-sized or slightly undersized DMEK grafts. Corneas cultured under both storage conditions, warm or cold storage, were used for transplantation. Donor graft preparation was always performed by the surgeon directly before the surgery.

In all patients, the day before surgery an iridotomy with a neodymium-doped yttrium aluminium garnet (Nd:YAG) laser at 6 o'clock was performed to avoid postoperative angle block. The iridotomy was surgically extended during DMEK surgery.

During surgery, corneoscleral buttons were mounted onto a suction block (Moria SA, Antony, France). Trypan blue staining was performed for 5–10 seconds overall to allow visualization of the mark. The peripheral Descemet membrane was peeled off, and afterwards the central margin was lifted with a round blade and then peeled off using a single forceps in both groups. Descemet's membrane was punched by the first surgeon (CC) with a 8 or 8.5 mm trephine; thus, a slightly oversized graft was obtained. In the case of the second surgeon (BB), the Descemet membrane was punched with a 7.5 or 8.0 mm trephine; thus, a same-sized or a slightly undersized graft was obtained. The DMEK graft was then transferred into an injector cartridge (AT. Smart Cartridge, Zeiss meditec, Jena, Germany) commonly used for lens implantation during cataract surgery (Kruse et al. 2011). In eyes showing coexistent cataract formation, a combined procedure (triple-DMEK) with phacoemulsification and posterior chamber lens implantation was performed directly before DMEK. For removal of the endothelium-Descemet membrane layer, the anterior chamber was filled with air. The descemetorhexis was performed by both surgeons within an area of about 0.5 mm smaller than the interface using a Price hook. Following descemetorhexis, the injector cartridge in combination with the injector AT Shooter A2-2000 (Zeiss meditec, Jena, Germany) was used to insert the graft into the anterior chamber. To maintain the anterior chamber depth during graft implantation, a bimanual technique was used, stabilizing the anterior chamber with an irrigation handpiece (0.8 mm; Geuder GmbH, Heidelberg, Germany). Then, unfolding of the graft lamella was performed either by insertion of an air bubble into the inner lumen of the roll, by gentle tapping of the cornea with the tip of a cannula, or by the combination of both. After centring the graft, an air bubble was placed underneath the donor lamella and the anterior chamber was filled completely with 100% air or sulphur hexafluoride 20% (SF_6 20%) to secure the graft at the recipient's posterior corneal surface (Kruse et al. 2011). The decision for each anterior chamber tamponade was independent of patient-related factors. SF_6 20% was used routinely since January 2015.

Postoperative course

Postoperative medication included topical prednisolone acetate 1% in tapering doses over 12 months and

topical antibiotics approximately 2 weeks as well as lubricant eyes drops during the first week hourly to reduce the occurrence of postoperative cystoid macular oedema and then tapered to five times a day (Hoerster et al. 2016). Pilocarpine 2% eye drops were applied three times a day as long as the anterior chamber was filled with air or gas covering the pupil's bottom margin. Patients were instructed to keep a strict supine position postoperatively, at least for three days under continuous monitoring of intraocular pressure (Stanzel et al. 2016).

A rebubbling was performed when a significant dehiscence of a DMEK lamella was detected by slit lamp biomicroscopy or by optical coherence tomography of the anterior segment.

Statistical analyses

Data were analysed by SPSS (version 24.0; SPSS, Inc, Chicago, IL) using ANOVA for interval scale parameters. Best-corrected visual acuity (BCVA) results were converted to logMAR. The level of significance was set at $p < 0.05$.

Results

Demographics

A total of 52 eyes which underwent DMEK surgeries after previous penetrating keratoplasty (PK) between July 2011 and August 2017 at the Department of Ophthalmology, University of Cologne, Cologne, Germany, with sufficient follow-up information were included for further analysis. The mean follow-up was 21.98 ± 13.02 months (range 3–36 months).

The mean age was 67.3 ± 14.7 years. 36.5% were female and 63.5% were male subjects.

Most of the eyes received a pseudophakic DMEK (78.8%), followed by triple-DMEK (11.5%) and phakic DMEK (9.6%).

The main indication for the previous PK surgery was FECD (23.1%) followed by keratoconus and herpetic keratitis (each 15.4%). Other indications included keratopathy associated with juvenile glaucoma/Axenfeld-Rieger syndrome (9.6%), stromal corneal dystrophy (5.8%), trauma (5.8%), keratoconus associated with trisomie 21 or psoriasis (3.8%), keratopathy after pseudophakic decompensation (3.8%), bacterial keratitis/corneal ulcera (3.8%), congenital cataract (1.9%) and ICE syndrome (1.9%).

Visual outcome

The BCVA was determined either by spectacles or by contact lenses. We did not exclude eyes having a visual limitation caused by extracorneal eye diseases. The preoperative BCVA (Mean ± SD; logMAR) was 1.07 ± 0.33. The 3-, 6- and 12-month BCVA (Mean ± SD; logMAR) was 0.72 ± 0.39 ($n = 33$), 0.56 ± 0.36 ($n = 32$) and 0.38 ± 0.28 ($n = 23$), respectively. Further on, the 2- and 3-year BCVA was 0.37 ± 0.21 ($n = 21$) and 0.32 ± 0.18 ($n = 10$), respectively (Figs 1 and 2; $p < 0.001$). When comparing the incipient postoperative period (3–6 months) with the later postoperative period (12–36 months), there is a significant difference in VA outcome ($p < 0.001$) meaning that the visual acuity takes longer time to recover.

When represented as the number of logMAR lines gained or lost compared to the preoperative logMAR, following values resulted the following: at 3 months postoperatively the mean logMAR lines gained was +2.9 ± 2.3, at 6 months +4.3 ± 3.4, at 12 months +5.0 ± 3.6, at 24 months +6.0 ± 2.3 and at 36 months +5.4 ± 2.7, respectively. A total of 21/24 (87.5%) of the documented 12-month values achieved a better VA than before the DMEK surgery. Failed transplants were not included in this analysis.

Donor characteristics

The mean donor age was 66 ± 10 years, and the mean culture time was 15.7 ± 6.1 days. Regarding the donor gender, 38% were male, 26.8% female and in 35.2% of the cases there was no information about the donor gender. The mean ECD was 2723 ± 226 cells/mm^2.

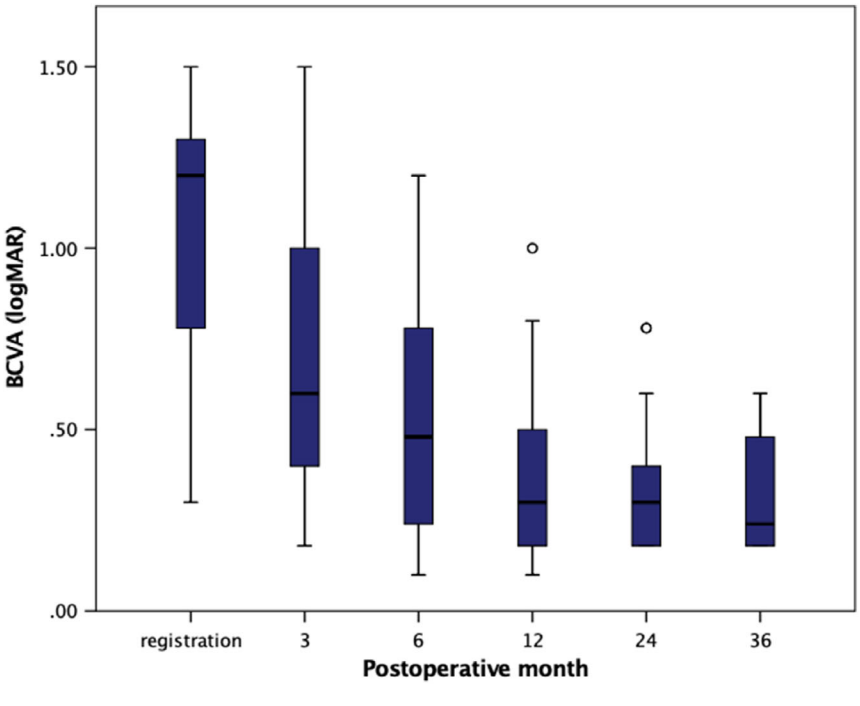

Fig. 1. Mean ± SD of the pre- and postoperative BCVA (logMAR) outcome over 3 years follow-up after DMEK for failed PK. The preoperative BCVA was 1.07 ± 0.33. 3-, 6- and 12-month BCVA was 0.72 ± 0.39 ($n = 33$), 0.56 ± 0.36 ($n = 32$) and 0.38 ± 0.27 ($n = 23$), respectively. Two- and 3-year BCVA was 0.37 ± 0.21 ($n = 21$) and 0.32 ± 0.18 ($n = 10$). There was a significant difference between the postoperative BCVA values ($p < 0.001$). When comparing the early postoperative period (3–6 months) with the later postoperative period (12–36 months), there was a significant difference in VA outcome ($p < 0.001$) meaning that the visual acuity takes longer time to recover. We did not exclude eyes having a visual limitation. Failed transplants including immune reactions were not being taken into consideration for this analysis.

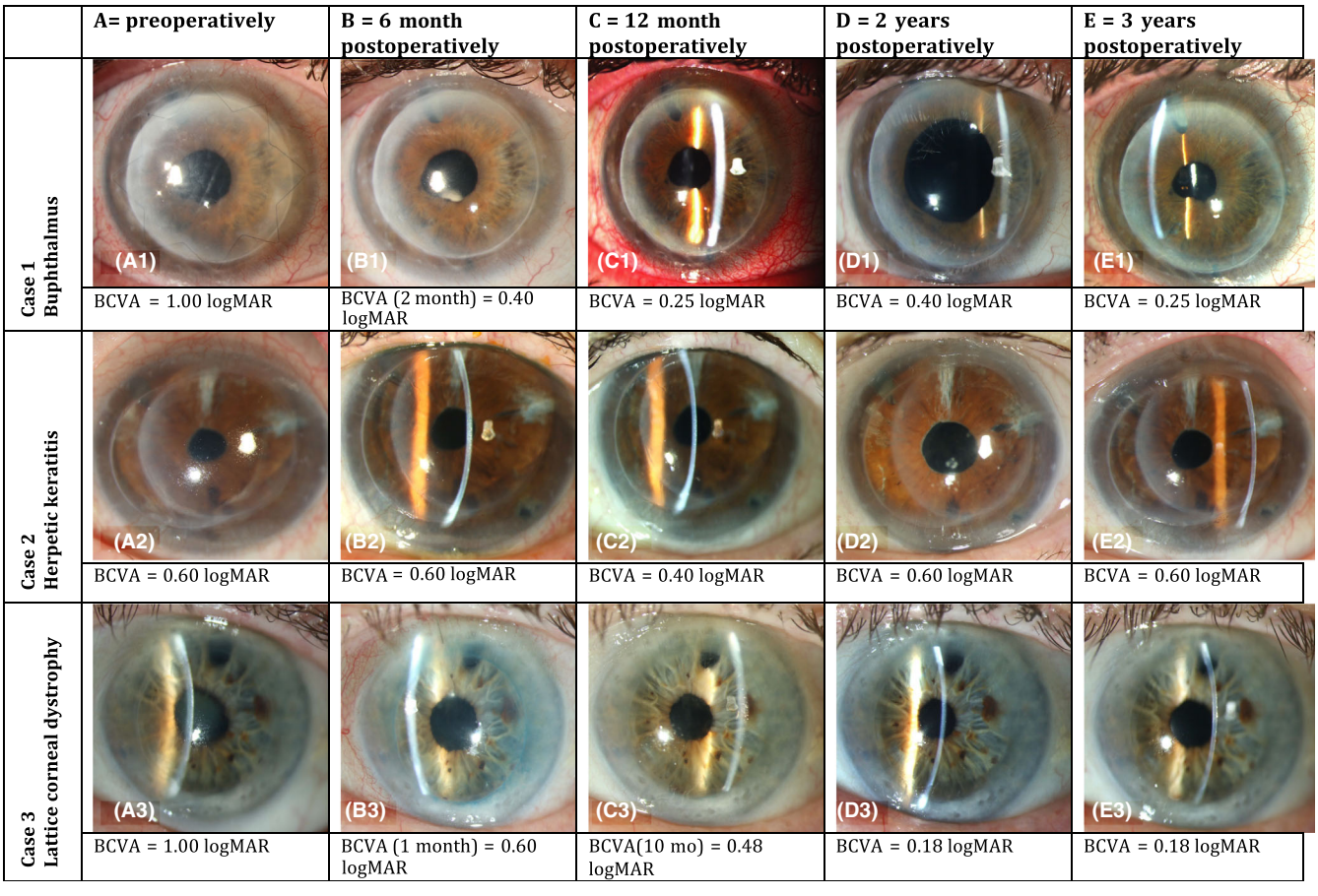

Fig. 2. The picture series depicts three cases of DMEK after failed PK with different primary corneal diseases over a follow-up of three years. The best-corrected visual acuity (BCVA) is delineated under the respective picture. Case 1: DMEK after failed PK in buphthalmus. The conjunctival hyperaemia in picture 1C is due to glaucoma medication. Case 2: DMEK after two failed PKs in herpetic keratitis. Patient also suffers from age-related macular degeneration, which explains the lacking VA increase. Case 3: Triple-DMEK after three failed PKs in lattice corneal dystrophy. BCVA = best-corrected visual acuity; DMEK = Descemet membrane endothelial keratoplasty; VA = visual acuity; PK = penetrating keratoplasty.

Postoperative endothelial cell density

The 6- and 12-month ECD was 1676 ± 394 cells/mm^2 (n = 17) and 1625 ± 404 cells/mm^2 (n = 17), respectively. The 2- and 3-year ECD was 1641 ± 363 cells/mm^2 (n = 8) and 1745 ± 44 cells/mm^2 (n = 2), respectively (Fig. 3; p = 0.965). This resulted in a ECD-decrease of 35.9 ± 12.8% at 6 months, 37.1 ± 16.5% at 12 months, 40.0 ± 16.7% at 2 years and 32.4 ± 5.35% at 3 years (p = 0.901).

Intraoperative tamponade and rebubbling rate

61.5% of the eyes received intraoperatively air and 38.5% received sulphur hexafluoride (SF_6) in a concentration of 20% for intracameral tamponade. 59.6% (n = 31) needed at least one rebubbling whereas 40.4% did not necessitate a rebubbling. Out of the 31 eyes that were rebubbled, 38.5% received one, 11.5% received two, 5.8% received three and 3.8% received four rebubblings. The decrease in the postoperative rebubbling rate since replacing room air by SF_6 20% for intracameral tamponade in January 2015 was significant (p = 0.033).

Central corneal thickness and postoperative astigmatism

The preoperative mean ± SD central corneal thickness (CCT) of the recipients was 770 ± 213 µm (n = 25). The postoperative mean ± SD CCT was 584 ± 101 µm (n = 9), 537 ± 68 µm (n = 14), 536 ± 61 µm (n = 11), 643 ± 109 µm (n = 6) and 569 ± 92 µm (n = 5) at 3, 6, 12, 24 and 36 months, respectively.

Regarding the astigmatism, the mean ± SD refractive cylinder at registration was −3.9 ± 2.2 dpt (n = 25). Postoperatively, following values were measured: −4.7 ± 2.7 dpt (n = 17), −3.6 ± 2.7 dpt (n = 15), −3.5 ± 2.5 dpt (n = 10) and −4.4 ± 3.1 dpt (n = 7) at 3, 6, 12 and 24 months after DMEK surgery, respectively. The change in astigmatism before and after surgery was not significant at any time-point (p = 0.619).

Immune reactions and graft survival

Seven out of 52 eyes (13.5%) presented with an immune reaction after surgery. Eighteen out of 52 eyes (34.6%) needed a regraft due to graft failure achieving a mean graft survival time of 24 ± 12.3 months. The overall graft survival was 65.4% at 30.6 ± 10.3 months.

Comparison between oversized and undersized DMEK graft

In our cohort, one surgeon (CC; n = 32) used slightly oversized DMEK grafts whereas the other surgeon (BB; n = 20) used same-sized or slightly undersized DMEK graft. When comparing the outcome between these different-sized grafts, there was no

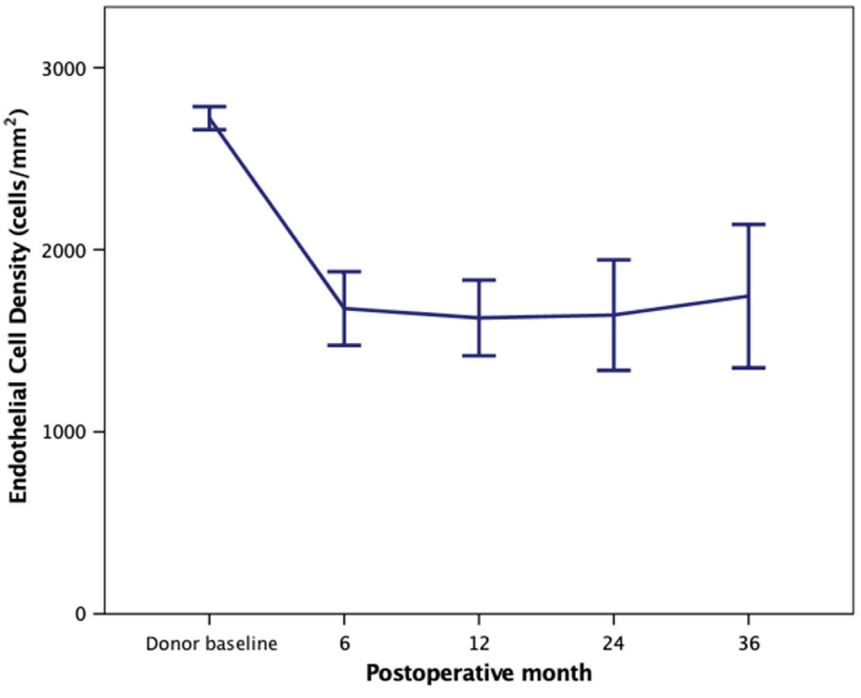

Fig. 3. Mean ± SD of the endothelial cell density (ECD) after DMEK for failed PK of the donor was 2723 ± 226 cells/mm^2. Six- and 12-month ECD was 1676 ± 394 cells/mm^2 (n = 17) and 1625 ± 404 cells/mm^2 (n = 17). Two- and 3-year ECD was 1641 ± 363 cells/mm^2 (n = 8) and 1745 ± 44 cells/mm^2 (n = 2), respectively. There was no significant difference between the postoperative values (p = 0.965).

significant difference in any of the outcome parameters (rebubbling rate p = 0.822; 3-month BCVA p = 0.247; 6-month BCVA p = 0.084; 12-month BCVA p = 0.268; 2-year BCVA p = 0.586; 3-year BCVA p = 0.782; 6-month ECD-decrease p = 0.411; 12-month ECD-decrease p = 0.241; 2-year ECD-decrease p = 0.701).

Discussion

Our study shows that DMEK after failed PK achieves good long-term outcomes up to three years after surgery. Compared to a regraft by PK, DMEK allows for more rapid recovery and represents a less invasive procedure. The visual outcome is comparable to other reported studies. Pasari et al. (2019) reported that 74% of their cohort consisting of 69 eyes achieved an improved VA at 12 months postoperatively. In our cohort, 87.5% of the documented 12-month BCVA values were better when comparing to the VA before surgery. Heinzelmann et al. (2017) reported an improvement of VA in 17 out of 19 patients at 15 months after surgery.

Many of the eyes included in this analysis had additional extracorneal eye diseases such as age-related macular degeneration, amblyopia or advanced stage of glaucoma. Since we did not exclude these patients from VA analysis, this explains the lower visual outcome found in eyes after failed PK compared to eyes receiving DMEK as a first corneal transplantation. Furthermore, the original PK transplant and its astigmatism may also represent a reason for the lower visual outcome.

Also, we could show in our study that the visual outcome can increase up to 6 months after surgery and then remain stable. In comparison with the classic DMEK-procedure in eyes without previous surgeries, where the visual outcome recovers very fast, in such complex eyes with previous failed PK the visual recovery can take longer (Fig. 1). This observation was also made by other authors (Gundlach et al. 2015; Einan-Lifshitz et al. 2018; Pierne et al. 2019).

In our cohort, we did not notice a complete dislocation of the DMEK graft. However, the interlocking of the two transplants can result in dislocation of the new posterior lamellar graft. This occurs mostly when using a DSAEK graft and is reported in the literature in about 6% (Price & Price 2006). Ang et al. (2014) reported in a Asian population of 113 eyes better graft survival rates after DSAEK using mostly oversized grafts without descemetorhexis of the recipient cornea when comparing to repeat PK; the dislocation rate was 6%.

In our cohort, the endothelial cell loss was comparable to that reported by others. Anshu et al. reported 2013 in a small cohort (n = 6) a ECD loss of 33% at 6 months. Pasari et al. (2019) reported 2019 in a larger cohort (n = 93) ECD loss rates of 31% at 6 months, 44% at one year and 47% at two years. Einan-Lifshitz et al. reported a ECD loss of 41% at 6 months and 48% at one year (n = 28) (Einan-Lifshitz et al. 2018). As previously described in other studies, the increased endothelial cell loss compared to DMEK transplantation in healthy eyes may be explained through the additional manipulation for centring the graft due to irregular wound margins (Pasari et al. 2019).

Also, the higher rebubbling rate leads to a higher ECD loss rate (Gerber-Hollbach et al. 2017). Interface gaps may be a reason for the higher rebubbling rate. Hereby, performing an anterior segment OCT prior to surgery may be helpful.

The descemetorhexis in eyes with previous PK is challenging and remains controversial in several studies. Some surgeons prefer performing an endothelial keratoplasty (DSAEK) after failed PK without performing a descemetorhexis and Descemet's stripping (Nottage & Nirankari 2012). In this case, it is conceivable that due to the thicker graft the inner interface is even larger having potentially more additional interfaces and can represent an even bigger problem for the intraoperative gas tamponade (Nottage & Nirankari 2012). In our cohort, we performed in all eyes a descemetorhexis. An adjuvant intraoperative help in correctly positioning the graft can be the intraoperative OCT (iOCT) device if available (Steven et al. 2013).

Regarding the size of the DMEK graft, different approaches exist. Some surgeons prefer undersized DMEK grafts in relation to the failed PK graft while others prefer oversized grafts. Price pleads for using same size or oversize graft without descemetorhexis (Price et al. 2011; Anshu et al. 2013). Melles et al. recommends not to oversized grafts (Lavy et al. 2017). Alio Del

Barrio et al. (2019) used undersized DMEK grafts for failed PK without host descemetorhexis and reported restoration of corneal clarity in all cases ($n = 8$); however, an increased ECD loss of approximately 50% at 6 months occurred.

Compared to other studies, we report an acceptable survival rate of 65.4% after two and a half years. Einan-Lifshitz et al. (2018) reported a survival rate of 57% after 3 years, Pasari et al. (2019) 80% after 3 years and 76% after 4 years. Possible explanations for the low graft survival rate in our cohort may include (i) the complex initial situation in most eyes (e.g. glaucoma tubes), (ii) the probably compromised immune status of the recipient and (iii) a disrupted balance of aqueous humour, thus all leading to a persistent risk of a latent graft failure with subtle clinical signs.

In conclusion, DMEK is a feasible long-term option after failed PK. However, patients should be adequately counselled about the risks and success rates of the procedure. Patient selection should be performed carefully; a PK graft without stromal scars and an initial subjective contentment of the patient with the original PK before graft failure may increase the success of the DMEK-procedure.

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