

Descemet–membrane endothelial keratoplasty in patients with retinal comorbidity –a prospective cohort study

Kristina Spaniol, Christoph Holtmann, Jan-Hendrik Schwinde, Sophia Deffaa, Rainer Guthoff, Gerd Geerling

University Eye Hospital Düsseldorf, Moorenstraße 5, Düsseldorf 40225, Germany

Correspondence to: Kristina Spaniol. University Eye Hospital Düsseldorf, Moorenstraße 5, Düsseldorf 40225, Germany. kristina.spaniol@med.uni-duesseldorf.de

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Abstract

• **AIM:** To investigate indications, surgical challenges, and outcome of Descemet –membrane endothelial keratoplasty (DMEK) in patients with retinal comorbidities (RC).

• **METHODS:** In a prospective cohort study, 8 eyes of 8 DMEK –patients with known RC were compared to 38 eyes of 38 DMEK –patients without RC. The duration of surgery, the degree of difficulty graded by the surgeon, and the complications through DMEK –surgery were analyzed for each patient. The best –corrected visual acuity (BCVA), the endothelial cell count, the intraocular pressure, and the subjective satisfaction was evaluated after a 6–month follow–up. Data were compared applying the non –parametric Wilcoxon – , Chi –square – and Fisher’s–exact–test with $P \leq 0.05$ as level of significance.

• **RESULTS:** RC –patients had dry age –related macular degeneration ($n=4$) or history of pars–plana vitrectomy ($n=4$). The main indication for DMEK was pain due to bullous keratopathy for the RC–patients ($n=7$, 88%) and visual impairment due to Fuchs endothelial keratoplasty for the non –RC –patients ($n=33$, 87%). The BCVA increased for both groups ($P=0.01$, $P<0.001$) and all corneas cleared. For the RC –patients, the subjective satisfaction improved significantly ($P=0.02$). Oil –filling and missing support of the vitreous body complicated surgery in vitrectomized eyes.

• **CONCLUSION:** DMEK is a favorable technique to treat endothelial disorders even if patients suffer from a retinal comorbidity. By enhancing the corneal clarity, it enables retinal examination or intraocular surgery and increases the patients’ satisfaction. However, in vitrectomized or silicone –oil filled eyes, the duration of surgery and degree of complexity are increased. An experienced surgeon should perform DMEK in these patients. Clinical trial registration number: DRKS00007566.

• **KEYWORDS:** Descemet-membrane endothelial keratoplasty; age-related macular degeneration; pars plana vitrectomy

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INTRODUCTION

Descemet-membrane endothelial keratoplasty (DMEK) is frequently used to treat endothelial disorders. Several authors reported faster visual rehabilitation and reduced risk of graft rejection compared to penetrating keratoplasty (PK) or other lamellar techniques such as Descemet’s stripping automated endothelial keratoplasty (DSAEK)^[1-2].

The incidence of corneal endothelial disorders and retinal comorbidities (RC) increases with age. Age-related macular degeneration (AMD) is a main cause for blindness in the western civilization and affects about 21 million people worldwide^[3]. Pars plana vitrectomy is the standard surgical procedure for the therapy of several retinal pathologies including retinal detachment, pathologic vitreous adhesions, or epiretinal gliosis^[4-5]. Due to the aging population and increasing frequency of intraocular surgery, the number of patients with endothelial disorders and concomitant RC such as AMD or history of vitreoretinal surgery will increase. The indications for DMEK are emerging (*e.g.* phakic DMEK, DMEK with aphakic intraocular lens implantation) but so far the feasibility of DMEK has not been investigated in patients with retinal pathologies^[6-7].

This study analyzed DMEK-patients with coexisting AMD or history of pars plana vitrectomy compared to a cohort without ocular comorbidities to determine the indications for DMEK, the surgical challenges, the outcome, and the subjective satisfaction in this context.

SUBJECTS AND METHODS

All investigations were performed according to the tenets of the Declaration of Helsinki after approval of the local ethical committee. All patients had given written informed consent. The patients did not receive a stipend for participation in the study. We certify that all applicable institutional and governmental regulations concerning the ethical use of

Table 1 Details of the individual patients with retinal comorbidity

Case	Ocular diagnosis	Transplant implantation	Duration of surgery (min)	Donor age (a)	Pre-op BCVA (logMAR)	Post-op BCVA (logMAR)	Pre-op ocular Pain ¹	Post-op ocular pain ¹	Pre-op VA Quality ²	Post-op VA Quality ²
1	Dry AMD, PC-IOL	Simple	48	57	1	0.4	6	0	1	8
2	Dry AMD, PC-IOL, H/O myopia magna	Simple	35	77	0.7	0.5	8	2	3	5
3	Dry AMD, PC-IOL	Simple	15	96	0.5	0.3	4	2	4	6
4	Dry AMD, PC-IOL	Simple	65	71	1	0.2	8	0	0	7
5	H/O PPV, PC-IOL, monocusus	Simple	30	72	1.3	0.2	0	0	1	8
6	H/O PPV, PC-IOL, macular scar	Simple	30	64	1	0.4	7	0	2	6
7	H/O PPV, PC-IOL, oil-filling	Difficult	50	83	2.3	1.5	8	1	1	1
8	H/O PPV, iris-clip IOL, congenital cataract, Irvine-Gass syndrome, epiretinal gliosis	Difficult	154	54	1.3	1	9	1	1	5

AMD: Age-related macular degeneration; H/O: History of; IOL: Intraocular lens; PC: Posterior chamber; PPV: Pars plana vitrectomy. ¹Pre- and post-operative severity of ocular pain graded on an analogue scale from 0-10 with 0=no ocular pain and 10=severe ocular pain; ²Pre- and post-operative quality of visual acuity graded on an analogue scale from 0-10 with 0=very bad visual acuity and 10=perfect visual acuity.

human volunteers were followed during this research. Forty-six eyes of 46 patients who received DMEK at the University Eye Hospital Düsseldorf between 1 July 2012 and 1 July 2014 were included into this prospective cohort study. The same surgeon (Geerling G) performed all surgeries with a standardized "no-touch" technique for graft preparation^[8].

The indication for DMEK, age, sex, lens status of donor and recipient, ocular comorbidities, duration of DMEK surgery, difficulty of graft implantation, remarks by the surgeon in the operation report, the postoperative course including frequency of rebubbling (postoperative injection of air into the anterior chamber in case of transplant detachment), graft rejection/failure, deterioration of AMD, and development of retinal detachments were evaluated. The best-corrected visual acuity (BCVA) using a Snellen visual acuity chart, the preoperative donor- and postoperative recipient endothelial cell density (Nikon Eclipse TE200 and Topcon, Tokyo, Japan), a slit-lamp examination and a funduscopy were documented pre- and 6mo postoperatively. BCVA-results are presented in logarithmic minimum angle of resolution (logMAR).

The surgeon subjectively graded the ease of inserting and attaching the graft as "simple", "moderate", or "difficult" according to the following criteria: "simple": uncomplicated unfolding and attachment of the graft in "no-touch" technique; "moderate": more difficult implantation with more attempts to unfold and attach the graft, but neither risk to damage the graft nor need to switch to a touch-technique (e.g. grasping the transplant with forceps); "difficult": complicated unfolding and/or attachment of the graft with modification of the surgery (e.g. repetitive injection of air into the anterior chamber to induce unfolding of the graft) and/or conversion to touch-technique to enable attachment of the graft to the corneal stroma.

At least 4mo postoperatively, a telephone survey was performed to determine the subjective evaluation of the RC-patients regarding ocular pain and visual acuity. The

patients were asked to grade the pre- and postoperative severity of ocular pain and quality of visual acuity on an analogue scale from 0-10 with 0=no ocular pain/very bad visual acuity and 10=severe ocular pain/perfect visual acuity. The patients were asked: "Would you again decide for DMEK surgery in this eye under the same circumstances? Please answer with 'yes' or 'no'. If the answer is 'no', please give an explanation why".

Statistical analysis was done with SPSS 21.0 (IBM Deutschland GmbH, Köln, Germany). The non-parametric Wilcoxon-test was applied to compare significance of differences between pre- and post-operative measurements, and Chi-square- or Fisher's exact-test to compare patients with and without RC. Differences with $P \leq 0.05$ were considered statistically significant. Data are presented as median (25th/75th quartile).

RESULTS

Patients with Retinal Comorbidity Eight patients [5 women, 3 men, 68 (59/74)y] presented with RC, 4 had dry AMD and 4 had a history of previous vitrectomy. All eyes were pseudophakic prior to DMEK. The individual cases are presented in Table 1. Pars plana vitrectomy had been performed for retinal detachment without macular involvement (3 cases) or macular traction (1 case). Seven eyes (88%) had painful pseudophakic bullous keratopathy (BK) and 1 (12%) had Fuchs endothelial corneal dystrophy (FD). The median donor age was 72 (62/79)y. The pre- and postoperative BCVA-, ECC-, and intraocular pressure (IOP)-values as well as the surgery duration are presented in Figure 1. Six transplant implantations (75%) were considered simple, 2 (25%) difficult. For the difficult implantations (case 7 and 8) the remarks in the operation report: cases 7: very opaque cornea, oil in the anterior chamber; case 8: missing support of the vitreous body, iridolentodonesis, very tight transplant roll, young donor, the transplant needs to be grasped with forceps to be attached to the recipient's stroma.

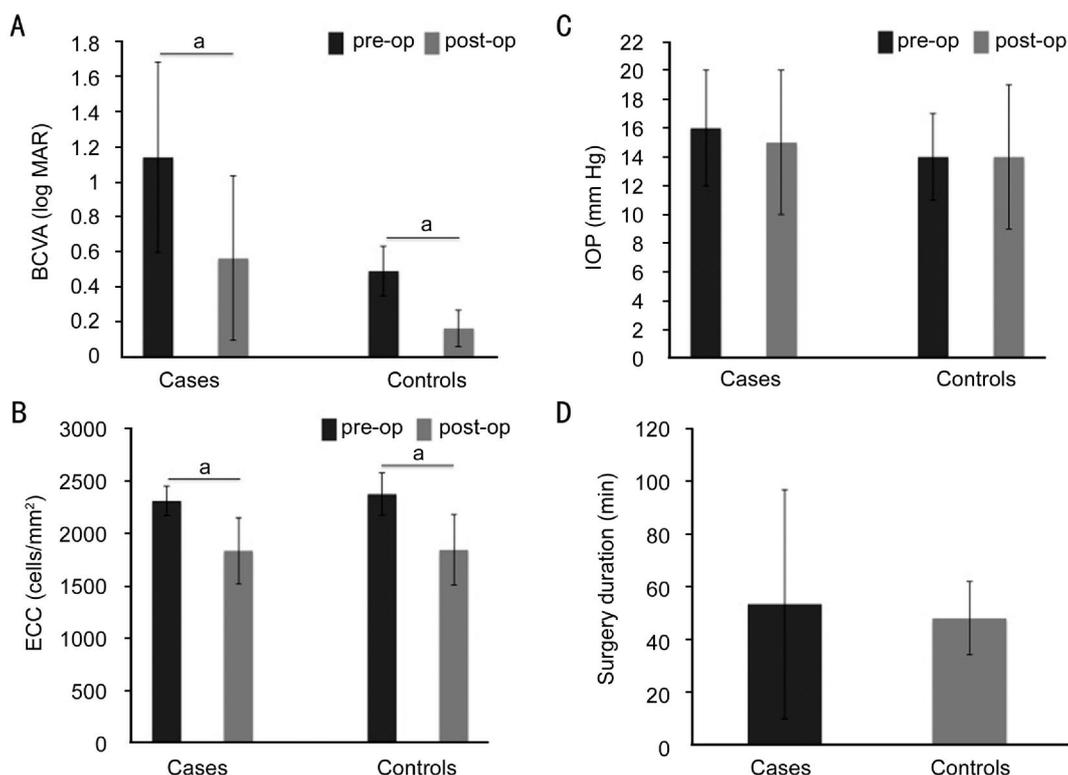


Figure 1 Comparison of pre- and post-operative main outcome measurements and surgery duration between cases and controls For the cases (patients with retinal comorbidity) and controls (patients without ocular comorbidity), BCVA (A) increased, the ECC (B) decreased, and the IOP (C) remained stable after DMEK. The surgery duration (D) and the BCVA (A) showed greater variability for the cases than for the controls. ^a*P*<0.05.

For case 7, the posterior segment remained oil-filled after DMEK, because the patient refused oil removal. Apart from case 8, who required rebubbling twice and had persistent cystoid macular edema (Figure 2), no patient needed rebubbling or had other complications. All corneas became clear. There was no immune rejection or graft failure. No patient developed geographic atrophy, neovascular AMD or a retinal detachment. There was no steroid-induced or angle-closure associated IOP-elevation.

Patients Without Ocular Comorbidities Thirty-eight patients [24 women, 14 men, 73 (67/77)y] presented without retinal or other vision-relevant ocular comorbidities. All had posterior chamber intraocular lenses (IOL) prior to DMEK. Five eyes (13%) had BK, 33 (87%) had FD. The median donor age was 77 (71/85)y. The pre- and postoperative BCVA-, ECC-, and IOP-values as well as the surgery duration are presented in Figure 1. Twenty-seven transplant implantations (71%) were considered simple, 8 (21%) moderate, and 3 (8%) difficult. Reasons for difficult implantations were "a small diameter of the anterior segment and a shallow anterior chamber" in all cases. The surgeon noted a "very opaque cornea" or a "very tight transplant roll" in one case, respectively. The donor of the transplant, which formed a "tight roll", was 42 years old, which was the youngest age of all donors and 25 years old younger than the median donor age.

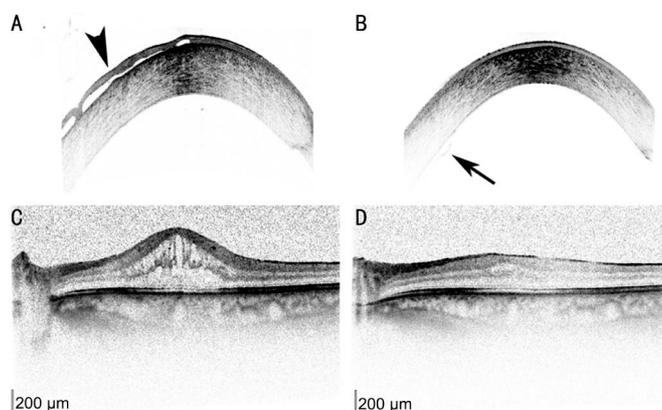


Figure 2 Optical coherence tomography images of case 8 The bullous keratopathy (A, arrowhead) was resolved postoperatively (B). After 2 rebubbings, the transplant showed a minor peripheral detachment (arrow). A persisting cystoid macular decreased from 620 μm (C) to 388 μm (D) after a triamcinolon injection. Scale bar =200 μm.

Nine patients (24%) required rebubbling ones, 3 (8%) required twice. One eye (2.6%) developed graft failure after a prior rebubbling and received successful re-DMEK 6mo later, all other corneas cleared. There was no immune rejection. One patient (2.6%) had a steroid-induced IOP-elevation, there was no angle-closure associated IOP-elevation. No patient developed vision-relevant ocular comorbidities.

Comparison of Patients With and Without Retinal Co-morbidity Comparing both groups, painful BK was significantly more frequent among the patients with RC ($P < 0.0001$). The pre- and postoperative BCVA of the RC-patients was significantly worse ($P < 0.0001$ and $P = 0.001$). ECC, IOP, donor age, duration of surgery, ease of transplant implantation, and frequency of rebubbling and transplant failure did not differ significantly ($P > 0.05$).

Subjective Satisfaction The subjective ocular pain of the RC-patients decreased significantly from 7.5 to 0.5 ($P = 0.02$) and the visual acuity increased from 1 to 6 ($P = 0.02$), equal to "no ocular pain" and "satisfactory visual acuity" after DMEK. Case 7 did not report an increase in visual acuity because the eye was still oil-filled after vitreoretinal surgery. Given the same circumstances, 7 of 8 patients (88%) would again decide for DMEK surgery. One AMD-patient would not repeat DMEK as she had expected a "better visual acuity-outcome".

DISCUSSION

According to our cohort, also patients with known RC benefit from DMEK due to increased visual acuity and decreased ocular pain. However, the indications for DMEK and the surgical challenges differ from the common patient collective.

Indication for Descemet –membrane Endothelial Keratoplasty and Outcome The patients without RC received DMEK for visual rehabilitation and the BCVA-results of our cohort were comparable to the current literature^[9]. In contrast, the RC-patients underwent DMEK to decrease ocular pain, which was achieved successfully and judged to justify DMEK surgery by the patients. Interestingly, the RC-patients were subjectively satisfied with their visual acuity outcome, although the BCVA was significantly lower compared to the patients without RC. Other authors recently showed that DMEK not only improves visual acuity but also contrast sensitivity, which may be a reason for the subjective satisfaction of the RC-patients^[10]. DMEK also increased the corneal clarity, which is an important issue in RC-patients as it facilitates retinal investigations or future vitreoretinal surgery^[11]. If future surgery harms the graft, re-DMEK is still feasible, which is another advantage of DMEK^[12].

Surgical Challenges Delicate steps during the DMEK procedure are graft insertion, unfolding, and adaption to the recipient's stroma and these require good visualization of anterior chamber details^[13]. While eyes without RC did not provide particular surgical challenges, vitrectomized eyes exhibited problems due to silicone oil in the anterior chamber or a missing mechanical support from the vitreous body. Both interfere with the mechanism of shallowing the anterior chamber for unfolding and attaching the graft^[13]. Intravitreal injections with balanced salt solution may compensate the missing support of the vitreous body. However, such

complicated implantations more often require mechanical support with forceps to attach the graft, which may prolong surgery and increase the postoperative ECC loss. If possible, silicone oil should be removed prior to or during DMEK to facilitate graft implantation and prevent silicone oil-induced keratopathy after DMEK^[14].

We also observed difficulties with transplant-specific properties such as low donor age. These grafts show increased elasticity resulting in formation of a "tight roll", which impairs graft unfolding and positioning^[15]. Some surgeons exclude donors younger than 55 years of age and this approach seems to be especially recommendable for complex cases such as vitrectomized or oil-filled eyes^[16].

Postoperative Course DMEK is now performed since 2006 but further studies are needed to evaluate the long-term viability of DMEK transplants especially in eyes with ocular comorbidities. This study monitored patients with RC in a six-month follow up and observed no transplant failure so far although certain patients showed a complicated intraoperative course. As re-DMEK, DSAEK, and PK are still possible after DMEK, it seems to be a reasonable method to enhance corneal clarity and reduce pain from BK in patients with additional ocular comorbidities. DMEK did not induce a progression of AMD or recurrence of retinal detachments in our cohort. This is in accordance with the current literature, which describes only a single case of retinal detachment after DMEK in a highly myopic eye^[17]. In contrast, 2.5% of pseudophakic or aphakic eyes develop a retinal detachment after PK so that minimal invasive procedures as DSAEK or DMEK with less risk of ocular hypotension are preferable in patients with history of retinal detachment^[18]. DMEK requires surgical experience and is less standardized than DSAEK so that some surgeons might favour DSAEK in patients with ocular comorbidities^[16]. However, long-term endothelial cell survival and immune reaction have been found superior for DMEK compared to DSAEK or PK and performing vitrectomy in eyes after DSAEK resulted in an increased loss of ECC^[19] (Ortiz *et al*^[20], $n=3$). Moreover, the incidence of de-novo glaucoma after one year ranges around 35% after DSAEK or PK, but is only 2.7%-4.0% after DMEK which is in accordance with our cohort^[21-22]. These findings underline the relevance of DMEK in patients with pre-existing ocular comorbidities.

Graft detachment, which is a main complication after DMEK with an incidence of 3%-82%, did not occur more often in RC-patients compared to those without RC^[16]. However, vitrectomized eyes are at higher risk of postoperative hypotension, which can enhance detachment rates and may lead to increased rebubbling rates and ECC loss^[17,19]. Although we only observed one case with repetitive graft detachment in a vitrectomized eye this aspect needs to be investigated in larger prospective cohorts.

Subjective Assessment It has been shown that vision related quality of life is significantly impaired in patients with endothelial disorders and improves after endothelial keratoplasty and PK^[23]. This was true for most of our patients, apart from one who did not receive a satisfactory visual acuity. Therefore, especially RC-patients require a detailed preoperative education to clarify the indication for DMEK (increase of visual acuity / relief from ocular pain/increased visibility of the intraocular structures) in order to reduce the risk for postoperative dissatisfaction.

A limitation of this study is the small sample size. However, these data show that DMEK can be successfully performed in patients with RC as it increases the visual acuity to some extent, sufficiently reduces the ocular pain, and improves the patient's quality of life. DMEK in vitrectomized eyes is feasible but the surgery may be more complex and time consuming and should be performed by experienced surgeons. Material from older donors can facilitate graft attachment in such complex cases.

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