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Long-Term Outcome After Bilateral Descemet Membrane Endothelial Keratoplasty for Fuchs Endothelial Corneal Dystrophy

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Purpose: The aim of this study was to assess the long-term clinical outcome, complications, and graft survival of bilateral Descemet membrane endothelial keratoplasty (DMEK) in patients with Fuchs endothelial corneal dystrophy.

Methods: This was a retrospective cohort study of 181 patients (362 eyes) with sequential bilateral DMEK for Fuchs endothelial corneal dystrophy. Clinical outcomes were assessed up to 5 years postoperatively. Outcome measures were best-corrected visual acuity, pachymetry, endothelial cell density, graft survival, and complication rates.

Results: Contralateral DMEK was performed on average 15 ± 11 months (range: 2–60 months) after the first eye. From 1 until 5 years after DMEK, best-corrected visual acuity, pachymetry, endothelial cell density, and graft survival did not differ between the first and second eyes (all $P > 0.05$). Graft detachment occurred in 67 eyes (19% [18% first eyes, 19% second eyes], 6% bilateral), graft rejection in 9 eyes (3% [3% first eyes, 2% second eyes], 1% bilateral), glaucoma in 25 eyes (7% [8% first eyes, 6% second eyes], 2% bilateral), and graft failure in 22 eyes (6% [4% first eye, 8% second eye], 2% bilateral). All differences were not significant (all $P > 0.05$). Five-year graft survival rates were comparable for first and second eyes (0.95 and 0.92, respectively; $P = 0.15$).

Conclusions: Clinical outcomes after bilateral DMEK are similar in both eyes and sustainable in the longer term. Within the first 5 years, the same complication may rarely occur in the contralateral eye.

Key Words: eye, DMEK, bilateral, cornea, keratoplasty, visual acuity, endothelial cell density, allograft rejection, graft failure, complications, graft survival, Fuchs endothelial corneal dystrophy

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Descemet membrane endothelial keratoplasty (DMEK) has become the gold standard in the treatment of eyes with Fuchs endothelial corneal dystrophy (FECD).^{1–7} By solely replacing the diseased corneal layers, this selective endothelial keratoplasty technique results in better globe integrity, quick visual recovery, outstanding clinical outcomes, low complications, and allograft rejection rates, providing graft longevity, especially in eyes with FECD.^{3,8–11} These results encourage a sequential (early) bilateral treatment in many patients with FECD as known from cataract surgery.^{12,13}

However, there are conflicting reports on an increased incidence of allograft rejection after bilateral keratoplasty because the immune system may have been sensitized by the allograft of the first-operated eye, potentially leading to allograft rejection in the second eye, and at the same time increasing the risk of an immune response against the graft in the first eye.^{14–21} This has been described as being dependent on the time interval between the surgeries, the graft diameter, or presence of vascularizations in penetrating grafts.^{14,19,20} For bilateral DMEK, such a correlation within the early postoperative phase has so far not been observed and clinical outcomes seem to be equally good in the first and second eyes.^{12,13} To date, it is not known whether these observations are sustainable and may also apply in the longer term for both eyes.

Besides a possible increased risk of allograft rejection after bilateral keratoplasty, there is also evidence that surgery or inflammation in 1 eye may induce ocular inflammation in the fellow eye,^{22–25} whereas increased (subclinical) inflammation or allograft rejection has been associated with a drop in endothelial cell density (ECD).²⁶

The current study evaluated the intraoperative and postoperative complications, long-term results, and 5-year graft survival in a large cohort after bilateral DMEK. Furthermore, we assessed whether ECD in the first-operated eye decreases at an increased rate after DMEK in the second eye, compared with patients who had received DMEK in only 1 eye.

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MATERIALS AND METHODS

From a consecutive series of 900 DMEK surgeries, 362 eyes of 181 patients (98 female and 83 male) who had received bilateral standard DMEK (as an isolated surgery not combined with cataract surgery) for FECD and had potentially reached the 5-year follow-up in both eyes were included in this retrospective study (Fig. 1, Table 1). The mean recipient age at the time of surgery was 66 (± 10) years (range: 40–89 years; Table 1). Regarding lens status, 96 eyes were phakic and 266 eyes pseudophakic; 44 patients were phakic and 129 patients were pseudophakic bilaterally and 8 patients were either phakic or pseudophakic in 1 eye (Table 1).

To detect an association between the surgery of the second-operated eye and a subsequent increase of the ECD decrease in the first-operated eye, a subgroup analysis was performed. From the 181 patients, only those patients were included in the subgroup analysis who had a time span of at least 12 months between the surgery of the first and second eye, and who had sufficient consecutive ECD counts available for the first eye after the surgery of the second eye (at least 2). Consequently, 59 patients could be included in the analysis, and the timepoint of the DMEK of the second eye served as “timepoint zero” for all 59 patients (Fig. 1). To analyze the ECD decrease of the first eyes, the ECDs *before* and *after* “timepoint zero” were calculated between the different timepoints -1 , $+1$, $+2$, etc., where “timepoint -1 ” was the last follow-up of the first-operated eye before, and “timepoint $+1$ ” was the first follow-up after “timepoint zero,” that is, the timepoint of surgery of the second eye. The generated ECD decreases were compared with the ECD decrease of a control group of 140 eyes (140 patients, 81 female, 59 male) selected from the same DMEK database that had received DMEK in only 1 eye with a follow-up of at least 5 years (Fig. 1, Table 1).

All patients had signed an informed consent document for research participation before surgery. The study adhered to the Declaration of Helsinki. According to the Dutch legislation, no institutional review board or ethics committee approval was required because of the retrospective nature of the study.

DMEK Graft Preparation and DMEK Surgery

DMEK graft preparation and surgery were performed as previously described.^{27,28} DMEK grafts were prepared at Amnitrans EyeBank Rotterdam, The Netherlands, and stored free floating in organ culture medium (CorneaMax; Eurobio, Courtaboeuf, France) until transplantation.

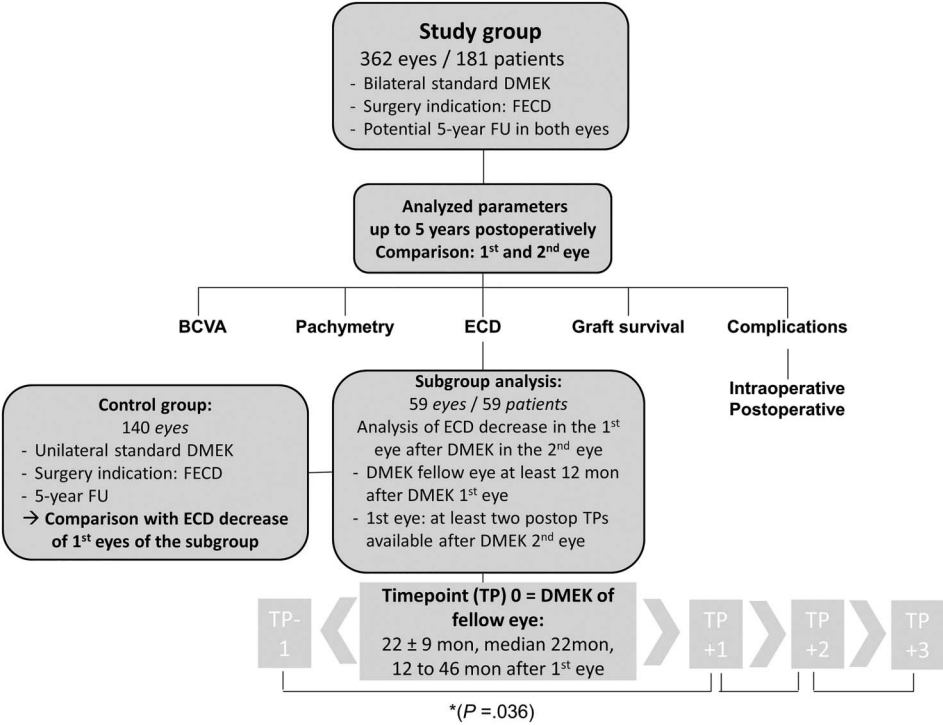
Before DMEK, laser YAG-iridotomy was performed a couple of weeks in advance to reduce the risk of a pupillary block. During DMEK, a circular “descemetorhexis” was performed under air, by scoring and stripping off Descemet membrane (DM) from the posterior stroma with a reversed Sinskey hook (DORC International, Zuidland, The Netherlands). The stained DMEK roll (0.06% trypan blue solution, VisionBlue, DORC International) was then sucked into an injector (DMEK-inserter, DORC International) and injected through a limbal tunnel incision into the recipient anterior chamber. After ensuring correct orientation, the DMEK graft was unfolded and positioned against the recipient stroma by injecting an air bubble underneath it, which was left for 45 to 60 minutes in a completely filled anterior chamber before partial air/balanced salt solution exchange was performed to leave the eye with 30% to 50% air fill. Postoperative medication included chloramphenicol 0.5% 6 times daily during the first week and 2 times daily during the second week each and ketorolac tromethamine 0.4% and dexamethasone 0.1% 4 times daily for 4 weeks. After 1 month,

TABLE 1. Demographics of Patients With FECD Receiving Bilateral DMEK and of a Control Group With Unilateral DMEK for FECD

Parameter	Study Group Bilateral DMEK	First Eyes	Second Eyes	Subgroup First Eyes for ECD Analysis	Control Group Unilateral DMEK
Number of eyes (patients)	362 (181)	181	181	59 (59)	140 (140)
Mean time interval first versus second DMEK eye $\pm$ SD, in months (median, range)	15 $\pm$ 11 (11, 2–60)	—	—	23 $\pm$ 9 (23, 12–46)	—
Patient sex, n (%)					
Male	83 (45.9)	—	—	37 (62.7)	59 (42.1)
Female	98 (54.1)	—	—	22 (37.3)	81 (57.9)
Mean recipient age $\pm$ SD, in years (median, range)	66 $\pm$ 10 (67, 40–89)	66 $\pm$ 10 (66, 40–88)	67 $\pm$ 10 (68, 41–89)	68 $\pm$ 8 (69, 45–82)	67 $\pm$ 9 (68, 42–80)
Lens status, n (%)					
Pseudophakic	266 (73.5)	132 (72.9)	134 (74.0)	44 (74.6)	101 (72.1)
Phakic	96 (26.5)	49 (27.1)	47 (26.0)	15 (25.4)	39 (27.9)
Patients with different bilateral lens status, n (%)	8 (4)	—	—	—	—
Mean donor age $\pm$ SD, in years, (median, range)	65 $\pm$ 10 (65, 38–85)	64 $\pm$ 10 (64, 38–84)	66 $\pm$ 10* (66, 44–85)	n.a.	n.a.
Mean participation time $\pm$ SD, in months (median)	52 $\pm$ 16 (60)	55 $\pm$ 13 (60)	49 $\pm$ 18† (60)	54 $\pm$ 14 (60)	59 $\pm$ 4 (60)

No significant difference between first and second eyes, except for donor age: * $P = .028$ and mean participation time: † $P = .001$.
ECD, endothelial cell density; n, number; n.a., not assessed.

FIGURE 1. Study group and sub-group overview. Diagram displaying the study group characteristics after bilateral DMEK, exclusion criteria, and outcome parameters. Furthermore, the diagram provides an overview of the subgroup characteristics of the first eyes for ECD decrease analysis at different time-points (TP–1: last ECD count before DMEK in the second eye; T0: at least 12 months after DMEK in the first eye; TP+1: first ECD after DMEK in the second eye, etc). The ECD difference between the time intervals were compared with the ECD in control eyes after unilateral DMEK.



dexamethasone was switched to fluorometholone 0.1% 4 times daily, followed by a routine tapering regimen. After 1 year, patients were advised to continue using fluorometholone once a day or every other day indefinitely.

Data
Patients’ charts and surgery reports were reviewed for intraoperative and postoperative complications. Patients’ data were collected before surgery, at 6 months, 1 year,

TABLE 2. Clinical Outcomes After DMEK in First and Second Eyes of Patients Undergoing Bilateral DMEK

Follow-Up Post DMEK	Preoperative	6 mo	1 yr	2 yrs	3 yrs	4 yrs	5 yrs
Mean ECD (±SD), in cells/mm ² [ECL compared with previous FU§]							
First eyes	2556 (±197) (n = 180)	1577 (±537) (n = 177)	1512 (±527) [–5%] (n = 174)	1384 (±511) [–7%] (n = 167)	1278 (±513) [–6%]* (n = 162)	1179 (±489) [–7%] (n = 154)	1127 (±473) [–6%] (n = 142)
Second eyes	2553 (±189) (n = 180)	1596 (±455) (n = 165)	1513 (±472) [–5%] (n = 162)	1437 (±483) [–8%] (n = 152)	1371 (±469) [–9%]* (n = 139)	1278 (±484) [–8%] (n = 131)	1213 (±471) [–7%] (n = 119)
Mean pachymetry (CCT), (±SD) in µm							
First eyes	672 (±97) (n = 172)	524 (±55)† (n = 172)	526 (±38) (n = 173)	533 (±39) (n = 169)	535 (±38) (n = 162)	537 (±44) (n = 155)	538 (±40) (n = 142)
Second eyes	662 (±90) (n = 178)	540 (±93)† (n = 171)	529 (±44) (n = 165)	534 (±48) (n = 154)	537 (±38) (n = 143)	536 (±37) (n = 132)	537 (±43) (n = 120)
Mean BCVA (±SD), in logMAR							
First eyes	0.48 (±0.32) (n = 169)	0.05 (±0.15)‡ (n = 159)	0.05 (±0.11) (n = 165)	0.04 (±0.10) (n = 157)	0.02 (±0.08) (n = 150)	0.05 (±0.18) (n = 144)	0.06 (±0.12) (n = 142)
Second eyes	0.43 (±0.33) (n = 167)	0.11 (±0.23)‡ (n = 155)	0.07 (±0.17) (n = 156)	0.06 (±0.15) (n = 144)	0.05 (±0.14) (n = 134)	0.05 (±0.15) (n = 122)	0.05 (±0.11) (n = 120)

*P = 0.035, ECD decrease between second and third year after DMEK comparing first and second eyes.
†P = 0.052, pachymetry values at 6 months FU comparing first and fellow eyes.
‡P = 0.024, BCVA values at 6 months FU comparing first and fellow eyes.
§ECL was determined individually for each eye at each follow-up and was then averaged for all eyes.
||Excluding n = 37 low visual potential eyes.
FU, follow-up; n, number of eyes.

TABLE 3. Endothelial Cell Density in a Subgroup of First Eyes Before and After Descemet Membrane Endothelial Keratoplasty in the Second Eye

Timepoint	Subgroup: First Eyes of Bilateral DMEK Eyes (n = 59)	Control Group: Unilateral DMEK Eyes (n = 140)	P
Timepoint -1: before DMEK in the second eye			
Mean ECD $\pm$ SD, in cells/mm ²	1353 $\pm$ 553 (n = 59)	1514 $\pm$ 471 (n = 130)	
Timepoint +1: up to 1 yr after DMEK in the second eye			
Mean ECD $\pm$ SD, in cells/mm ²	1228 $\pm$ 544 (n = 59)	1394 $\pm$ 463 (n = 130)	0.16
Mean ECD decrease $\pm$ SD, in %*†	-10 $\pm$ 11 (n = 59)	-8 $\pm$ 9 (n = 129)	
Timepoint +2: up to 2 yrs after DMEK in the second eye			
Mean ECD $\pm$ SD, in cells/mm ²	1123 $\pm$ 538 (n = 58)	1291 $\pm$ 446 (n = 130)	0.67
Mean ECD decrease $\pm$ SD, in %*†	-7 $\pm$ 18 (n = 58)	-6 $\pm$ 15 (n = 128)	
Timepoint +3: up to 3 yrs after DMEK in the second eye			
Mean ECD $\pm$ SD, in cells/mm ²	1112 $\pm$ 560 (n = 48)	1212 $\pm$ 434 (n = 131)	0.13
Mean ECD decrease $\pm$ SD, in %*†	-9 $\pm$ 10 (n = 47)	-6 $\pm$ 10 (n = 129)	
Timepoint +4: up to 4 yrs after DMEK in the second eye			
Mean ECD $\pm$ SD, in cells/mm ²	1125 $\pm$ 588 (n = 28)	1109 $\pm$ 430 (n = 116)	0.62
Mean ECD decrease $\pm$ SD, in %*†	-7 $\pm$ 10 (n = 28)	-8 $\pm$ 12 (n = 115)	

*ECD decrease was calculated based on ECD at the previous follow-up timepoint.

†ECD decrease was compared with the ECD decrease the control group.

n, number.

and yearly up to 5 years after DMEK. Outcome measures included ECD, central corneal thickness (CCT), best-corrected visual acuity (BCVA) converted to the logarithm of the minimum angle of resolution (logMAR), graft survival, and intraoperative and postoperative complications. ECD, CCT, and BCVA (excluding eyes with visual comorbidities [n = 37]) were measured using noncontact autofocus specular microscopy (Topcon SP3000p; Topcon Medical Europe BV, Capelle a/d IJssel, The Netherlands), Scheimpflug imaging (Pentacam HR; Oculus Optikgeräte GmbH, Wetzlar, Germany), and Snellen visual acuity chart, respectively. ECD outcomes were presented as absolute ECD values and as an endothelial cell loss when compared

with preoperative ECD values or the previous follow-up values. Survival time was calculated as the time between DMEK surgery and the last available follow-up timepoint or the time between surgery and graft failure.

Graft detachment was assessed by using anterior segment optical coherence tomography (Heidelberg Engineering GmbH, Heidelberg, Germany) and Scheimpflug imaging. Graft detachment was defined as minor ($\leq 1/3$ of the graft surface area) or major detachment ($> 1/3$ of the graft surface area). Allograft rejection was defined as the presence of an endothelial rejection line or keratic precipitates (with or without an increase in corneal thickness), anterior uveitis, and/or ciliary injection on slit-lamp biomicroscopy. Graft failure could result from “endothelial failure” with or without an event of allograft rejection or from “technical failure,” as a result of persistent DMEK graft detachment.

Statistical Analysis

The comparison of first and second eyes, as well as subgroup analysis was performed by using the independent *t* test. The chi-square test was used to analyze the dependencies of surgical and postoperative complications. Kaplan–Meier survival analysis was performed to estimate graft survival distributions in the first and second eyes by using log-rank tests. All analyses were performed using IBM SPSS Statistics software, version 27. *P* values of < 0.05 were considered statistically significant.

RESULTS

Contralateral DMEK was performed on average 15 (± 11) months (range: 2–60 months, median: 11 months) after DMEK in the first eye. The mean participation time was 52 (± 16) months after DMEK. Patient age and lens status did not differ between the first and second eyes (both *P* > 0.05 ; Table 1).

Clinical Outcomes and Graft Survival

First/second eyes improved from a preoperative mean logMAR BCVA of 0.48 (± 0.32)/0.43 (± 0.33) to postoperative 0.05 (± 0.15)/0.11 (± 0.23) (177 eyes/165 eyes) and 0.06 (± 0.12)/0.05 (± 0.11) (142 eyes/120 eyes) at 6 months and 5 years, respectively (Table 2). First eyes had a significantly better BCVA at 6 months than the second eyes (*P* = 0.024); this difference diminished at the later timepoints until 5 years postoperatively (*P* > 0.05).

Mean preoperative ECD in the first/second eye of the study group decreased from preoperatively 2556 (± 197)/2553 (± 189) cells/mm² to 1577 (± 537)/1596 (± 455) cells/mm² at 6 months (177 eyes/165 eyes) and to 1127 (± 473)/1213 (± 471) cells/mm² at 5 years (142 eyes/119 eyes), respectively; the values were similar in both eyes for all timepoints (*P* > 0.05). In addition, the decrease in ECD was similar in both eyes (all *P* > 0.05), except for the annual ECD decrease between the second and third year after DMEK that was higher in the first-eye group (*P* = 0.035; Table 2).

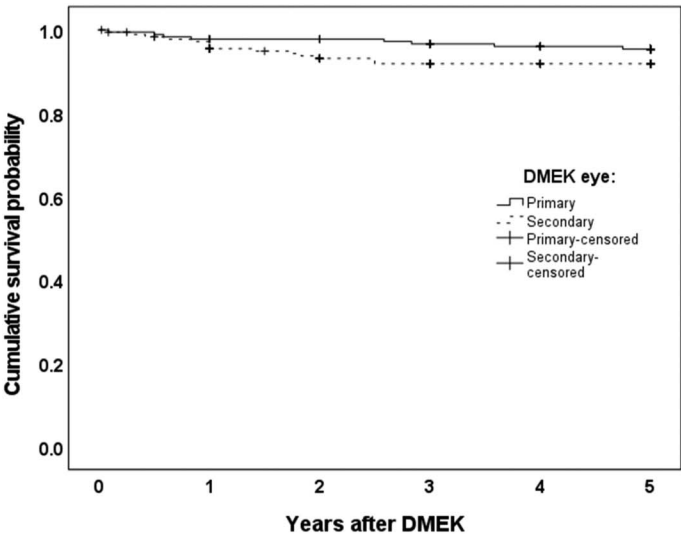


FIGURE 2. Kaplan–Meier curve of cumulative graft survival probabilities after bilateral DMEK. Survival probabilities and number of eyes at risk per follow-up moments are presented in the table next to the graph. Survival probabilities for the first and second eye were similar at the yearly follow-ups up to 5 years after DMEK ($P = 0.15$).

		Years after DMEK					
Primary eye	Cumulative survival probability at FU	Estimate	0.98	0.98	0.97	0.96	0.95
		SE	0.01	0.01	0.01	0.02	0.02
	Cumulative events		4	4	6	7	8
	Remaining cases		176	172	167	160	148
Secondary eye	Cumulative survival probability at FU	Estimate	0.97	0.93	0.92	0.92	0.92
		SE	0.01	0.02	0.02	0.02	0.02
	Cumulative events		6	12	14	14	14
	Remaining cases		171	158	144	135	124

We next assessed whether DMEK surgery of the second eye had an impact on the ECD decrease in the first eye, that is, whether the ECD decreased in a higher rate after DMEK was performed in the second eye. As such, we analyzed a subgroup of 59 eyes of 59 patients (time span between DMEK in the first and second eye at least 12 months, average 22 (± 9) months, range: 12 to 46 months; Fig. 1, Table 3) and compared the ECD decrease of their first eyes with those of a control group of unilateral DMEK eyes; no significant differences were found in the ECD decrease at all timepoints (all $P > 0.05$; Table 3).

Pachymetry values (Table 2) at 6-month follow-up seemed higher in the second eyes compared with the first-operated eyes, but did not differ significantly between both eyes throughout the entire study period (all $P > 0.05$). Graft survival probability in the first and second eyes 5 years after DMEK was 0.95 and 0.92 ($P > 0.15$), respectively (Fig. 2).

Intraoperative and Postoperative Complications

Surgical difficulties (Table 4) were related to 1 of the following: (1) the descemetorhexis (16% [$n = 57$ eyes], 4% ($n = 7$ patients) bilateral), (2) the anterior chamber instability (16% [$n = 58$ eyes], 2% ($n = 4$ patients) bilateral), or (3) other challenges, such as an upside-down graft orientation or iris bleeding (22% [$n = 81$ eyes], 6% [10 patients] bilateral). Intraoperative complications were evenly distributed between the first and second eye except for difficulties during the descemetorhexis which were reported more frequently in the second eye compared with the initially operated eye ($n = 21$ vs. $n = 36$, $P = 0.03$). Postoperative complications were equally distributed among both eyes (all $P > 0.05$; Table 4).

Graft detachment was noted in 19% ($n = 67$ eyes, 6% [$n = 10$ patients] bilateral) and required rebubbling in 20 eyes (6%, 1% [$n = 2$ patients] bilateral). Elevation of the

intraocular pressure occurred in 25 eyes (7%, 2% ($n = 4$ patients) bilateral) due to (1) mechanical angle closure with or without an air-bubble dislocation in 7 eyes (2%, 5 phakic, 2 pseudophakic), occurred only unilaterally; (2) steroid-induced intraocular pressure elevation (4%, $n = 14$) that was bilateral in 3 patients (2%); and (3) exacerbation of preexisting glaucoma (1%, $n = 4$) that was bilateral in 1 patient (1%).

Allograft rejection was detected in 9 eyes (3%) of 8 patients (3% = first eye, 2% = second eye, 1% bilateral [1 patient]), of which only 1 patient had discontinued topical steroids. In 6 eyes (6 patients), rejection could be reversed successfully with intensified topical steroids. In all 9 eyes, DMEK of the second eye was performed 7 to 30 months after the first surgery. Rejection occurred 1 to 59 months after DMEK: for the first eyes ($n = 6$), in 4 eyes, this was 6 to 49 months after the second surgery while 2 eyes had rejection about 6 months before the surgery of the second eye. Among the rejections in the second eyes ($n = 3$), 1 experienced rejection 1 month after DMEK when switching to a lower potent steroidal eye drop and the other 2 eyes had rejection 10 and 27 months after DMEK. The patient with bilateral rejection had a medically managed glaucoma before DMEK that was also well controlled after DMEK.

Graft failure was noted in 10 eyes of 9 patients of which most had an endothelial failure without allograft rejection ($n = 7$, bilateral: none) or with allograft rejection ($n = 3$, 1 bilateral). In 12 eyes, resurgery was performed for technical graft failure, which was required in 2 patients bilaterally.

DISCUSSION

The current study shows that the good early clinical outcomes in a large group of patients with FECD with bilateral DMEK are sustainable until at least 5 years after the second surgery and that the same DMEK complications may rarely occur in both eyes. Because DMEK is known to show an

TABLE 4. Intraoperative and Postoperative Complications After DMEK in Both Eyes

Complications	Entire Cohort (n = 362 Eyes)	First Eyes (n = 181 Eyes)	Second Eyes (n = 181 Eyes)	Complication in Both Eyes (n = 181 Patients)	P
Intraoperative difficulties, n (%)					
Descemetorhexis difficulties	57 (16)	21 (12)	36 (20)	7 (4)	0.03
DM double layer	30	12	18	5	
Difficult rhexis (sticky/fragile/thin DM/stroma)	22*	8 (3 double layers)	14 (1 double layer)	2	
Remnants	9	4	5	0	
AC pressure difficulties	58 (16)†	29 (16)	29 (16)	4 (2)	>0.99
Backward pressure	42	22	20	4	
Air escaping/AC collapsing/shallow AC	28‡	13 (6 backward pressure)	15 (6 backward pressure)	0	
Other difficulties	81 (23)	42 (23)	39 (22)	10 (6)	0.71
Iris bleeding/air behind iris/floppy iris	10	7	3	0	
Upside-down graft orientation	72§	36 (1 floppy iris)	36	10	
Postoperative complications, n (%)					
Graft detachment	67 (19)	32 (18)	35 (19)	10 (6)	0.06
≤1/3 (minor)	34	21	13		
>1/3 (major)	33	11	22		
Rebubbling	20 (6)	7 (4)	13 (7)	2 (1)	0.17
Glaucoma	25 (7)	14 (8)	11 (6)	4 (2)	0.43
Mechanical angle closure, possible air-bubble dislocation	7	3	4	0	
Steroid-induced ocular hypertension	14	9	5	3	
Exacerbation of preexisting glaucoma	4	2	2	1	
Allograft rejection	9 (3)	6 (3)	3 (2)	1 (1)	0.31
Graft failure	22 (6)	8 (4)	14 (8)	3 (2)	0.19
Secondary graft failure (endothelial failure without rejection)	7	3	4	0	
Secondary graft failure after rejection	3	1	2	1	
Technical failure (graft detachment)	12	4	8	2	
Secondary transplant	19 (5)	6 (2)	13 (4)	3 (2)	0.10
Repeat DMEK	14	4	10	1	
DSEK	4	2	2	2	
DMET	1	—	1	—	

Statistically significant differences are displayed in bold.

*Complication occurred with "double layer in 4 eyes".

†17 eyes were phakic.

‡Complication occurred with backward pressure in 12 eyes.

§Complication occurred with floppy iris in 1 eye.

||Including 2 eyes with failure in the presence of a graft detachment.

AC, anterior chamber; DMET, Descemet membrane endothelial transfer; DSEK, Descemet stripping endothelial keratoplasty; n, number.

excellent early outcome with fast and near-complete visual recovery, especially in eyes with FECD,^{3,8} in the past years, the threshold to perform DMEK in the second eye soon after the first eye has become relatively low, for both surgeons and patients (similar as after cataract surgery). As early sequential DMEK would require clinical stability of the first eye, the Melles Cornea Clinic did not usually perform the second DMEK before 3 months after DMEK of the first eye. After this time, possible graft detachment has usually been managed (within the first postoperative month)^{29,30} and refractive stability is achieved (within 3 postoperative months).³¹ Another reason not to quickly perform consecutive DMEK is the uncertainty about inducing an allograft rejection in any of the eyes because a higher graft rejection incidence has been reported in bilateral penetrating grafts.^{15–21} Longer time

intervals (eg, 18 or 34 months) between the 2 surgeries have been described to be beneficial in avoiding rejection.^{16,18} In the current cohort, except for 2 patients who received sequential DMEK within 2 months, all second eyes were operated beyond the 3-month follow-up, that is, on average 15 months (median: 11 months) after the first eye.

Clinical Outcomes

Despite isolated differences in clinical outcomes in first and second eyes concerning the 6-month follow-up for BCVA (worse in the second eye), and ECD decrease between the second and third postoperative year after DMEK (decrease significantly higher in the fellow eye, 6% vs. 9%), these differences disappeared toward the 5-year

postoperative mark. Concerning BCVA at 6 months, the higher frequency of major graft detachments in the second eyes (22 eyes vs. 11 eyes), and more time allowed for spontaneous graft attachment without surgical treatment before the 6-month follow-up, could explain the inferior BCVA and trend of the higher pachymetry values in the second eyes. Graft survival probability was over 90% for both eyes, which is comparable to 5-year DMEK outcome studies.^{9,32,33}

Surgical interventions in first eyes have been shown to induce ocular inflammation in fellow eyes. In addition, nonsurgical ocular inflammation in 1 eye (eg, chronic herpes) may be associated with signs of inflammation in the other eye.^{22–25} Given that ocular inflammation and rejection have been associated with an ECD decrease,²⁶ we investigated whether the ECD decline increased in the first eye subgroup after DMEK of the second eye; however, this association could not be detected. Further studies including targeted diagnostics (eg, laser flare photometry, confocal microscopy, and aqueous humor analysis) would be needed to directly assess the ocular inflammatory status in bilateral surgery and its possible association with an ECD decrease.³⁴

Intraoperative and Postoperative Complications

The advantage of the possibility to perform any surgery bilaterally is that one can learn from the results of the first surgery and hereby anticipate and ideally prevent certain difficulties and complications in the surgery of the second eye. Concerning intraoperative complications, one would therefore expect less complications in the second eye. In our cohort, however, complications during a descemetorhexis happened significantly more often in the second eye, probably because with increasing surgical experience so-called “double layers,” namely, splitting of Descemet membrane, were recognized more easily than in the earlier surgeries of first eyes. Complications, such as remnants and iris bleeding, occurred randomly, lacking a bilateral trend possibly because the surgeon may be alerted to avoid this complication in the second eye. Interestingly, intraoperative backward pressure was perceived during DMEK not only in phakic eyes and occurred in 2% bilaterally. Because this may complicate graft unfolding, one may consider measures for the second eye to lower the pressure intraoperatively by administering acetazolamide or other agents to facilitate the surgery. It was striking that an upside-down graft positioning in the anterior chamber was observed in almost 20% of eyes, although bilaterally in only 5%. This could be avoided by carefully monitoring how the graft is injected into the anterior chamber.

Graft detachment was the most frequent postoperative complication that may occur bilaterally in about 5% of cases. Unlike the Cologne group, which found a higher risk of rebubbling in the second eye, when the first eye already had received a rebubbling, in our series bilateral reinjection of air was required in only 1%.³⁵ This difference may be due to the individual treatment strategies of graft detachment. Our group has been rather conservative, because some grafts and graft configurations, in our experience, often show spontaneous reattachment.

An increased tendency for graft failure as observed for patients whose other eye had received penetrating keratoplasty³⁶ could not be observed within 5 years after DMEK which may be due to the observed low incidence of endothelial failures (<3%) after DMEK. DMEK graft rejection remains a rare complication with 3% in first eyes and 2% in second eyes, and 1% bilaterally. No concrete trend or association could be observed between surgery and rejection timepoint until 5 years postoperatively. Hence, it seems to be safe to perform early sequential bilateral DMEK. Future investigations of bilateral complications or adjustment of treatment would benefit from a prospective/multicenter study designed to assess risk factors concerning graft rejection and other possible DMEK complications.

CONCLUDING REMARKS

Clinical outcomes after bilateral DMEK are sustainable in the longer term in both eyes. Bilateral intraoperative difficulties are rare, as are bilateral postoperative complications up to 5 years. It seems safe to perform DMEK in the second eye shortly after the first eye. However, it may be reasonable to only proceed early with the fellow surgery when there is a medical/subjective need, as in advanced corneal edema or younger patients who, for example, require a fast reintegration into their job.

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