Descemet membrane endothelial keratoplasty: graft rejection, failure and survival

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CHAPTER 5

Repeat Descemet Membrane Endothelial Keratoplasty after Complicated Primary Descemet Membrane Endothelial Keratoplasty

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ABSTRACT

Purpose: To describe the clinical outcome and complications of repeat Descemet membrane endothelial keratoplasty (re-DMEK).

Design: Retrospective case series study at a tertiary referral center.

Participants: From a series of 550 consecutive DMEK surgeries with ≥6 months follow-up, 17 eyes underwent re-DMEK for graft detachment after initial DMEK (n = 14) and/or endothelial graft failure (n = 3). The outcomes were compared with an age-matched control group of uncomplicated primary DMEK surgeries.

Methods: The re-DMEK eyes were evaluated for best-corrected visual acuity (BCVA), densitometry, endothelial cell density (ECD), pachymetry, and intraoperative and postoperative complications.

Main Outcome Measures: Feasibility and clinical outcome of re-DMEK.

Results: In all eyes, re-DMEK was uneventful. At 12 months, 12 of 14 eyes (86%) achieved a BCVA of ≥20/40 (≥0.5); 8 of 14 eyes (57%) achieved ≥20/25 (≥0.8), 3 of 14 eyes (21%) achieved ≥20/20 (≥1.0), and 1 eye (7%) achieved 20/17 (1.2); 5 eyes were fitted with a contact lens. Average donor ECD decreased from 2580±173 cells/mm^2 before to 1390±466 cells/mm^2 at 6 months after surgery, and pachymetry from 703±126 mm to 515±39 mm, respectively. No difference in densitometry could be detected between re-DMEK and control eyes (P = 0.99). Complications after re-DMEK included primary graft failure (n = 1), secondary graft failure (n = 2), graft detachment requiring rebubbling (n = 1), secondary glaucoma (n = 2), cataract (n = 1), and corneal ulcer (n = 1). One eye received tertiary DMEK.

Conclusions: In the management of persistent graft detachment and graft failure after primary DMEK, re-DMEK proved a feasible procedure. Acceptable BCVA may be achieved, albeit lower than after DMEK in virgin eyes, and some cases may benefit from contact lens fitting. Complications after re-DMEK may be better anticipated than after primary DMEK because graft detachment and graft failure tended to recur, suggesting that intrinsic properties of the host eye play a role in graft adherence and graft failure.

INTRODUCTION

In recent years, endothelial keratoplasty (EK) techniques such as Descemet stripping EK (DSEK) and Descemet stripping automated EK (DSAEK) have evolved and gained wide acceptance, progressively replacing penetrating keratoplasty (PK) as a primary treatment for endothelial disease. The most recent development in EK is Descemet membrane EK (DMEK), which selectively replaces the Descemet membrane (DM) and the endothelium, providing a near-anatomic restoration of the cornea with fast and unprecedented visual results.[1-4] In addition, DMEK has been shown to give good visual outcome when performed as a secondary procedure after "failed" DSEK/DSAEK.[5,6] In addition, DMEK may be performed for secondary graft failure in PK, as an alternative to repeat PK.[7]

The outcomes of re-keratoplasty have been well documented and include a higher risk of corneal scars and astigmatism and in particular allograft rejection.[8-12] Limited reports or case series are available for repeat EK,[13-17] and in particular for repeat DMEK (re-DMEK).[18,19] With growing numbers of EK surgeries, and with DMEK becoming accepted worldwide, it may be important to determine further treatment options in the event of DMEK transplant failure, the technical feasibility and clinical outcome of re-DMEK, and whether re-DMEK is associated with specific complications.

The aim of our study therefore was to identify causes of unsuccessful primary DMEK, describe the surgical modifications of re-DMEK compared with primary DMEK, and report the clinical outcome of re-DMEK in a series of eyes that previously underwent DMEK compared with DMEK control eyes.

METHODS

From a total of 550 consecutive DMEK cases, 17 eyes of 17 patients (8 male, 9 female; 3 phakic, 14 pseudophakic) with an average age of 69±14 years (range, 47-90 years) underwent re-DMEK after unsuccessful primary DMEK. The initial preoperative diagnoses included Fuchs endothelial dystrophy (n = 15), pseudophakic bullous keratopathy (n = 1), and bullous keratopathy after corneal perforation (n = 1). Primary DMEK grafts were removed and replaced by a secondary DMEK graft in a second operative procedure, and the postoperative course of the re-DMEK was followed for ≤12 months. All re-DMEK surgeries were performed by 2 experienced corneal surgeons (I.D., G.M.; Table 1).

Table 1. Demographics of the Study Group and an Age-matched Control Group of Primary DMEK eyes

Variable	Study Group (Secondary DMEK eyes)	Age-matched control group (Primary DMEK eyes)
Patients / Eyes (n)	17/17	17/17
Age (years), mean ± SD (range)		
Patients	69±14 (47-90)	68±13 (48-88)
Donor 2nd DMEK	66±14 (43-85)	--
Gender (male/female)	8/9	9/8
Pseudophakic/phakic (n)	14/3	14/3
Time (months) between 1st and 2nd DMEK (Mean ± SD, (range))	16±9 (4-33)	--

SD = Standard Deviation; DMEK = Descemet membrane endothelial keratoplasty

All patients signed an institutional review board-approved informed consent; the study was conducted according to the Declaration of Helsinki and registered at www.clinicaltrials.gov (study registration no. NCT00521898).

Donor Tissue Protocol

The procedure for harvesting a DMEK graft has been described previously.[20,21] In short, corneoscleral buttons were excised from donor globes ≤36 hours post-mortem and stored in organ culture at 31°C (CorneaMax; Eurobio, Courtaboeuf, France). After 1 week of culture, endothelial cell morphology and viability were evaluated and the corneoscleral buttons were mounted endothelial side up on a custom-made holder. A 9.5-mm-diameter sheet of DM with its endothelium was removed from the posterior stroma with the corneoscleral rim immersed in balanced salt solution. Owing to the elastic tissue properties, a Descemet roll formed spontaneously, with the endothelium on the outer side. Each Descemet roll was then stored for 5 to 10 days in organ culture medium until the time of transplantation.

Repeat DMEK Operative Procedure

All re-DMEK eyes were operated under local anesthesia (4 ml 1% ropivacain hydrochloride with 1 ml 150 IE Hyason), followed by an ocular massage and a Honan's balloon for 10 minutes; the patient was positioned in the anti-Trendelenburg position. Surgeries were performed as described previously,[22] with a few adjustments (Table 2). Instead of performing a descemetorhexis, the primary DMEK graft was carefully removed from the recipient posterior stroma with a reversed Sinskey hook (D.O.R.C. International, Zuidland, The Netherlands) under air. A 3-mm limbal

Table 2. Surgical Tips for Repeat Descemet Membrane Endothelial Keratoplasty (DMEK)

1.	If possible, identify and remove the cause of graft failure for the initial DMEK graft (control Intraocular pressure, reposition glaucoma tube, remove anterior chamber intraocular lens, etc. before re-DMEK).
2.	If possible, re-open old corneal tunnel incision and side ports, to avoid 'double' entry wounds that may interfere with instrument insertion.
3.	With a reversed Sinskey hook, remove the primary DMEK graft that commonly shows more stickiness to the host stroma than the Descemet Membrane in a virgin eye during descemetorhexis.
4.	Carefully remove 'sticky' graft remnants by additional scraping while monitoring completeness of graft removal 'under air,' but avoid damage to the host posterior stroma. The application of trypan blue into the host anterior chamber may additionally aid to visualize Descemet Membrane remnants.
5.	Particularly when re-DMEK is performed to manage graft detachment with or without extensive corneal edema after initial DMEK, remove all endothelial cells that have migrated over the stroma underneath the detached area, and leave the host anterior chamber filled with air for up to 60-120 minutes, to avoid detachment from recurring in the same quadrant(s).

tunnel incision was made (or reopened) for insertion of the new DMEK graft. After graft removal, the posterior stromal surface was meticulously checked, and any graft remnants were carefully removed with a custom-made scraper (D.O.R.C. International).

The donor Descemet roll was stained with a 0.06% Trypan blue solution (VisionBlue, D.O.R.C. International), configured as a "double roll," and sucked into an injector (DMEK-inserter; D.O.R.C. International) to inject it into the recipient anterior chamber. The graft was oriented endothelial side down (donor DM facing recipient posterior stroma). By indirect manipulation with air and balanced salt solution, the graft was then gently unfolded over the iris and positioned onto the recipient posterior stroma by injecting an air bubble underneath the graft. The anterior chamber was left completely filled with air for ≥60 minutes (average bubble time, 64±8 minutes), followed by an air-liquid exchange to pressurize the eye while leaving a 30% to 50% air bubble in situ. Each operative procedure was recorded on DVD (Pioneer DVR-RT601H-S, Tokyo, Japan). The postoperative medication regime included antibiotics and steroid similar as for primary DMEK.[23]

Data Collection

All eyes were examined before and at 1 week and 1, 3, 6, and up to 12 months after re-DMEK. The clinical outcome was evaluated by comparing the preoperative with postoperative best-corrected visual acuity (BCVA), pachymetry, Pentacam imaging (Oculus, Wetzlar, Germany) and anterior segment optical coherence tomography (Heidelberg Engineering GmbH, Heidelberg, Germany), as well as

slit-lamp biomicroscopy images (Topcon Medical Europe BV, Capelle a/d IJssel, The Netherlands).

For corneal densitometry (backscattered light) analysis (Pentacam; Oculus), 3 different fixed corneal layers - the anterior layer (anterior 120 μm), central layer, and posterior layer (posterior 60 μm) - as well as fixed corneal concentric rings around the apex (central 0-2, 2-6, 6-10, and 10-12 mm) as provided by the software, were examined.[24] Values at 6 months after re-DMEK were compared with those 6 months after uneventful primary DMEK using an age- and lens status-matched control group (Table 1). Corneal density was quantified on a scale from 0 (clear) to 100 (completely opaque).

Donor endothelial cell density (ECD) was evaluated in vitro with light microscopy in the eye bank (Axiovert 40 inverted light microscope; Zeiss, Göttingen, Germany) and photographed (PixeLINK PL-A662; Zeiss). Postoperative ECD was evaluated using a Topcon SP3000p noncontact autofocus specular microscope (Topcon Medical Europe BV).

Eyes with low visual potential (glaucomatous optic neuropathy, age-related macular degeneration) were excluded from BCVA analysis and the eye with primary graft failure after re-DMEK was excluded from BCVA and densitometry analysis.

Statistical Analysis

Intraoperative and postoperative complications, BCVA, and ECD, were recorded in a SQL database. Paired t tests were performed to identify significant differences in outcomes between the study and control group. $P < 0.05$ was considered significant.

RESULTS

Indications for Repeat DMEK

We performed re-DMEK in a series of 17 eyes that showed unsatisfactory visual outcomes after primary DMEK and for which improvement could be expected by a transplant replacement. Low visual outcome after primary DMEK was attributed to clinically significant graft detachment (n = 14) and endothelial graft failure (n = 3; Table 3 [available at www.aaojournal.org]; Figure 1).

In eyes with graft detachment, 3 eyes had a detachment of at least one third and 8 eyes of more than one third of the graft surface area, and 3 eyes had the graft positioned upside down (Figure 2). In these eyes, BCVA ranged from counting fingers (1/60) to 20/25 (0.8). In the 3 eyes with an endothelial graft failure, 1 eye showed a primary graft failure (graft attached, but cornea did not clear after surgery) and 2 eyes had a secondary graft failure (graft attached, cornea initially cleared but decompensated later in the postoperative course) associated with allograft rejection (n = 1) or late endothelial failure without rejection (n = 1; Figure 3).

The average time between the initial and secondary DMEK was 16±9 months (range, 4–33 months; Table 3, available at www.aaojournal.org). The large variation in postoperative time could be attributed to the fact that in some eyes the cornea initially cleared despite graft detachment ("spontaneous corneal clearance") but decompensated later (n = 5; Table 3, available at www.aaojournal.org).

Repeat DMEK Operative Procedure

All re-DMEK surgeries were uneventful and could be performed with minor modification to the standard DMEK protocol (Table 2). In most eyes, the removal of the primary DMEK graft proved more difficult than a descemetorhexis in a virgin eye because of stronger adherence of the graft to the recipient stroma. The DM remnants could best be visualized "under air" using a complete airfill of the recipient anterior chamber. In 6 cases, the posterior corneal stroma was additionally scraped to remove DM remnants.

Visual Acuity

At six months after re-DMEK, 10 of 13 eyes (77%) attained a BCVA of ≥20/40 (≥0.5); 5 of 13 eyes (38%) attained ≥20/25 (≥0.8), and 2 of 13 eyes (15%) attained ≥20/20 (≥1.0). At 12 months, 12 of 14 eyes (86%) attained ≥20/40 (≥0.5); 8 of 14 eyes (57%) attained ≥20/25 (≥0.8), 3 of 14 eyes (21%) attained ≥20/20 (≥1.0) and 1 eye (7%) attained 20/17 (1.2). At both follow-up intervals, 5 eyes had been fitted with a contact lens (Figure 4).

Densitometry

Densitometry values 6 months after re-DMEK were compared with those of control eyes 6 months after uneventful primary DMEK. At 6 months, there was a tendency toward higher densitometry values in the total central concentric ring around the apex (central 0–2 mm) in all layers (P = 0.33), and there was no detectable difference in total densitometry between re-DMEK and control eyes

Table 3: Clinical outcome after initial and repeat Descemet membrane endothelial keratoplasty detailed for the whole study group

No.	STUDY GROUP				PREOP	AFTER INITIAL DMEK							INTER-VAL	AFTER RE-DMEK						
						Last follow-up (months) before re-DMEK								Follow-up 6 months after re-DMEK						
Case/ (DMEK)	Age/ Gender	Indication for initial DMEK	Eye	Lens status	BSCVA	CCT (µm)	Last FU (m)	BSCVA	ECD (cells/mm²)	CCT (µm)	Remarks	Indication for re-DMEK	Time (m) after initial DMEK	BSCVA	BCLVA	Irregular Surface (Pentacam)	ECD (cells/mm²) Preop./ 6m FU	CCT (µm)	Graft status (Pentacam, AS-OCT)	Remarks
1 (26)	74 M	FED	OD	Pseudo-phakic	CF	n.a.	10	20/40 (0.5)	1530	607	Re-bubbling at 3m 'Sponta-neous clearance'	Graft detached >1/3, folds in optical axis	11	20/60 (0.3)	20/23 (0.9)	Yes	2800/ 2020	526	Graft detached ≤1/3, same area as in 1st graft	--
2 (94)	75 M	FED	OD	Pseudo-phakic	20/50 (0.4)	637	6	20/100 (0.2)	n. m.	743	'Sponta-neous clearance'	Graft upside-down	7	20/50 (0.4)	--	No	2500/ 1140	556	Attached	Secondary IOP elevation requiring glaucoma surgery
3 (38)	48 F	FED	OS	Phakic	20/50 (0.4)	678	19	CF*	350 (12m)	650	Re-bubbling at 1m & 6w 'Sponta-neous clearance'	Graft upside-down	20	20/25 (0.8)	--	No	2550/ 1690	566	Attached	Phacoemul-sification at 10m
4 (79)	64 F	FED	OS	Pseudo-phakic	20/60 (0.3)	686	18	20/400 (0.05)	n. m.	834	Re-bubbling at 3m	SGF	21	20/17 (1.2)	--	Mild	2400/ 350	526	Attached	SGF at 12m Tertiary DMEK
5 (36)	71 F	FED	OD	Pseudo-phakic	20/133 (0.15)	643	30	20/60 (0.3)	360 (12m)	663	'Sponta-neous clearance	Graft upside-down	31	20/33 (0.6)	20/28 (0.7)	Yes	2400/ 1110	478	Attached	--

Table 3: Clinical outcome after initial and repeat Descemet membrane endothelial keratoplasty detailed for the whole study group *(continued)*

No.		STUDY GROUP			PREOP		AFTER INITIAL DMEK					INTER-VAL	AFTER RE-DMEK						
							Last follow-up (months) before re-DMEK						Follow-up 6 months after re-DMEK						
Case/ (DMEK)	Age/ Gender	Indication for initial DMEK	Eye	Lens status	BSCVA	CCT (µm)	Last FU (m)	BSCVA	ECD (cells/mm²)	CCT (µm)	Remarks	Indication for re-DMEK	Time (m) after initial DMEK	BSCVA	BCLVA	Irregular Surface (Pentacam)	ECD (cells/mm²) Preop/ 6m FU	CCT (µm)	Graft status (Pentacam, AS-OCT)	Remarks
6 (135)	64 M	FED	OD	Pseudo-phakic	20/60 (0.3)	631	12	20/60 (0.3) 20/40# (0.5)#	940 (6m)	637	Allograft rejection at 10m	SGF	16	20/60 (0.3)	CL induced edema	Mild	2400/ 970	544	Small para-central detach-ment ≤1/3	Paracentral remnant, chronic rejection?
7 (243)	50 M	BK	OD	Phakic	20/80 (0.25)	728	3	20/50 (0.4)	490	719	--	PGF	4	20/17 (1.2) 3m	--	No	2500/ 1500	509	Small peripheral detach-ment ≤1/3, same area as in 1st graft	SGF at 12m
8 (224)	75 F	FED	OS	Pseudo-phakic	20/100 (0.2)	556	9	20/100 (0.2)	n. m.	875	--	Graft detached >1/3, folds in optical axis	10	20/40 (0.5)	--	Yes	2755/ 1410	544	Small peripheral detach-ment ≤1/3	--
9 (225)	86 M	PPBK	OD	Pseudo-phakic	20/50 (0.4)	645	6	20/100 (0.2)	n. m.	735	--	Graft >1/3 detached	11	20/50 (0.4)	--	Yes	2875/ n.m.	446	Attached	--
10 (80)	59 M	FED	OD	Pseudo-phakic	20/40 (0.5)	743	27	20/25 (0.8)	700 (12m)	751	--	Graft ≤1/3 detached	30	20/33 (0.6)	20/20 (1.0)	Yes	2785/ 1360 (12m)	435	Graft detached ≤1/3, same area as in 1st graft	Corneal ulcer at 2.5m

Table 3: Clinical outcome after initial and repeat Descemet membrane endothelial keratoplasty detailed for the whole study group *(continued)*

No.		STUDY GROUP			PREOP	AFTER INITIAL DMEK							INTER-VAL	AFTER RE-DMEK							
						Last follow-up (months) before re-DMEK								Follow-up 6 months after re-DMEK							
Case/ (DMEK)	Age/ Gender	Indication for initial DMEK	Eye	Lens status	BSCVA	CCT (µm)	Last FU (m)	BSCVA	ECD (cells/mm^2)	CCT (µm)	Remarks	Indication for re-DMEK	Time (m) after initial DMEK	BSCVA	BCLVA	Irregular Surface (Pentacam)	ECD (cells/mm^2) Preop/ 6m FU	CCT (µm)	Graft status (Pentacam, AS-OCT)	Remarks
11 (335)	47 F	FED	OS	Phakic	20/28 (0.7)	811	3	20/40 (0.5)	1270	793	Paired donor of case#17	Graft >1/3 detached	4	20/28 (0.7)	--	No	2900/ 2000	563	Attached, folds	--
12 (249)	67 F	FED	OD	Pseudo-phakic	20/50 (0.4)	685	9	20/100 (0.2)	n. m.	809	Central flat ulcer at 8m	Graft >1/3 detached	12	20/50 (0.4)	--	Yes	2500/ 1370	535	Attached	--
13 (107)	85 F	FED	OS	Pseudo-phakic	20/60 (0.3)	680	30	20/133 (0.15)	320 (24m)	680	'Sponta-neous clearance'	Graft >1/3 detached	33	20/23 (0.7)	--	Yes	2600/ 1820	498	Attached	--
14 (329)	87 F	FED	OS	Pseudo-phakic	20/40 (0.5)	614	11	20/80 (0.25)	340	689	--	Graft ≤1/3 detached	12	20/40 (0.5)	--	Yes	2500/ 720	491	Attached	ARMD
15 (319)	90 F	FED	OD	Pseudo-phakic	20/100 (0.2)	724	12	20/133 (0.15)	490 (6m)	564	--	Graft ≤1/3 detached	13	HM	--	Yes	2400/ n.m.	884	Attached	Air-bubble induced IOP elevation PGF
16 (233)	61 M	FED	OD	Pseudo-phakic	20/25 (0.8)	539	15	20/133 (0.15)	n. m.	688	--	Graft >1/3 detached	17	20/33 (0.6)	20/25 (0.8)	No	2500/ 1490	526	Graft detached >1/3, attached after one re-bubbling at 1w	YAG-CT at 4m

Table 3: Clinical outcome after initial and repeat Descemet membrane endothelial keratoplasty detailed for the whole study group *(continued)*

No.	STUDY GROUP			PREOP			AFTER INITIAL DMEK						INTER-VAL	AFTER RE-DMEK							
							Last follow-up (months) before re-DMEK							Follow-up 6 months after re-DMEK							
Case/ (DMEK)	Age/ Gender	Indication for initial DMEK	Eye	Lens status	BSCVA	CCT (µm)	Last FU (m)	BSCVA	ECD (cells/mm²)	CCT (µm)	Remarks	Indication for re-DMEK	Time (m) after initial DMEK	BSCVA	BCLVA	Irregular Surface (Pentacam)	ECD (cells/mm²) Preop/ 6m FU	CCT (µm)	Graft status (Pentacam, AS-OCT)	Remarks
17 (334)	61 M	FED	OD	Pseudo-phakic	20/25 (0.8)	566	14	20/28 (0.7)	n. m.	519	Paired donor of case #11	Graft >1/3 detached	14	20/23 (0.9)	--	Mild	2500/ 1675	490	Attached	--

DM = Descemet membrane
DMEK = Descemet membrane endothelial keratoplasty
FED = Fuchs endothelial dystrophy
BK = Bullous Keratopathy
PPBK = Pseudophakic Bullous Keratopathy
CCT = central corneal thickness
BSCVA = Best spectacle corrected visual acuity
BCLVA = Best contact lens visual acuity
CF = Counting fingers
HM =hand movements
YAG-CT = YAG capsulotomy
ARMD= Age related macular degeneration
n. a. = not available
n. m. = not measurable
w = weeks
m = months
*after YAG laser treatment
#fitted with a contact lens after primary DMEK

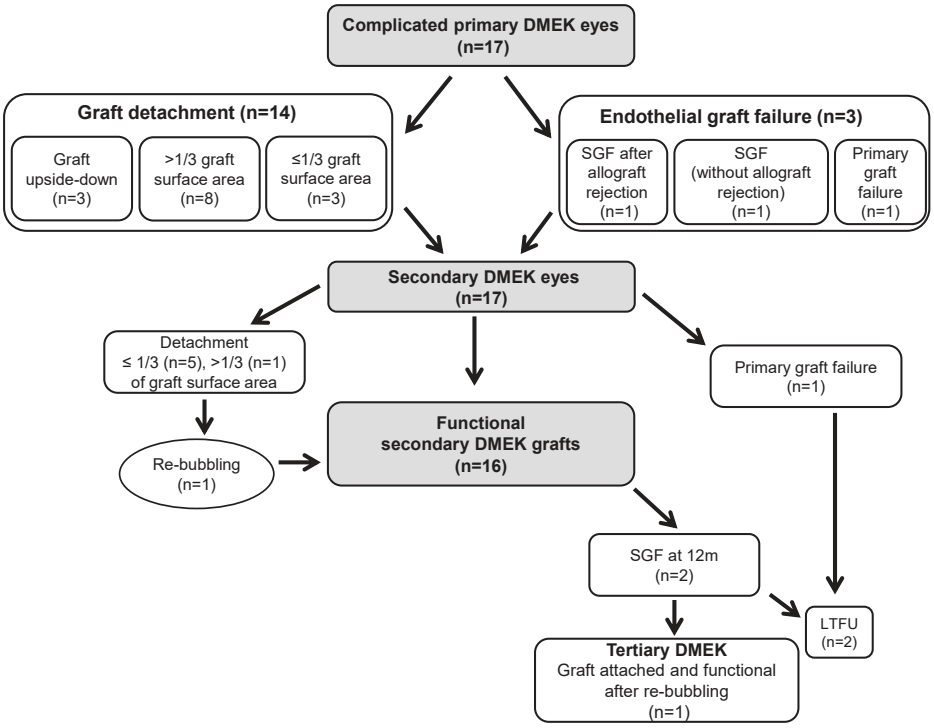

Figure 1. Indications for repeat Descemet Membrane Endothelial Keratoplasty (DMEK) and its postoperative course. LTFU = lost to follow-up; SGF = secondary graft failure.

for any central-to-peripheral optical zone or at any anterior-to-posterior stromal level (P = 0.99; Table 4).

ECD and Pachymetry

Donor ECD (of the second graft) averaged 2580 (±173) cells/mm^2 before (n=17), and 1390 (±466) cells/mm^2 (- 46.1%) at 6 months (n=15) and 1294 (±459) cells/mm^2 (- 49.8%) at 12 months after re-DMEK (n=13). Pachymetry values decreased from 703 (±126) μm before (n=17), to 515 (±39) μm at 6 months after re-DMEK (n=16) (Table 4).

Graft detachment and rebubbling after Repeat DMEK

Significant graft detachment after re-DMEK (more than one third of the graft surface area) was observed in 1 eye (case 16) that was managed with a rebubbling procedure (120-minutes airfill of the host anterior chamber) at 1 week postoperatively. Small peripheral or partial detachments of not more than one third of the graft surface area were detected in 5 eyes (cases 1, 6, 7, 8, and 10) but did

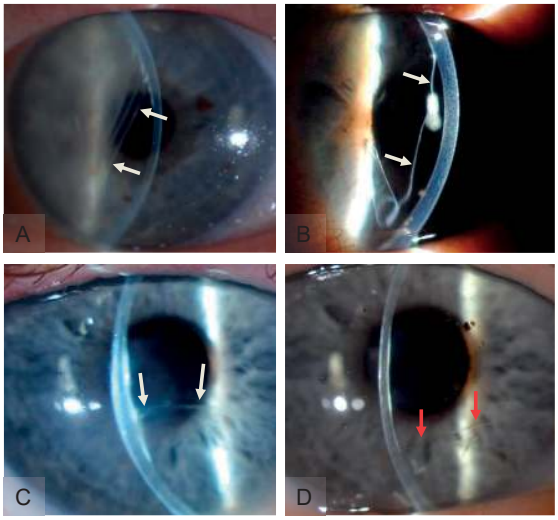

Figure 2. Slit lamp images of graft detachments after primary Descemet Membrane Endothelial Keratoplasty (DMEK), which comprised the main indication for repeat DMEK. (A) Case 8, graft detachment of greater than one third of the graft surface area after primary DMEK (white arrows). (B) Case 3, the graft was positioned upside down and detached (white arrows). (C, D) Case 1, in an eye that had a graft detachment after the initial DMEK (white arrows), the graft detached again in the same area after re-DMEK (red arrows).

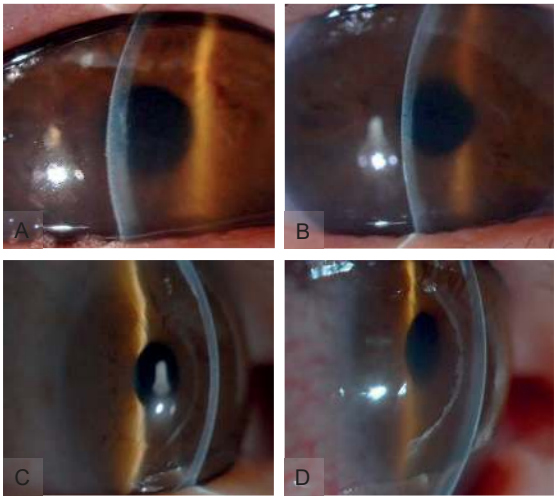

Figure 3. Slit lamp images of an eye that underwent repeat Descemet Membrane Endothelial Keratoplasty (DMEK) for primary graft failure after DMEK that again developed graft failure after repeat DMEK. (A) Case 7, corneal decompensation after traumatic corneal perforation and (B) primary graft failure after initial DMEK. (C) One month after repeat DMEK the cornea cleared, but (D) secondary graft failure was observed at 12 months.

not require further treatment. The remaining 11 re-DMEK eyes showed full graft attachment (Table 3, available at www.aaojournal.org).

In 3 eyes (cases 1, 7, and 10) that developed a partial graft detachment after primary DMEK showed again a detachment in the same corneal quadrant after re-DMEK (Figure 2; Table 3, available at www.aaojournal.org).

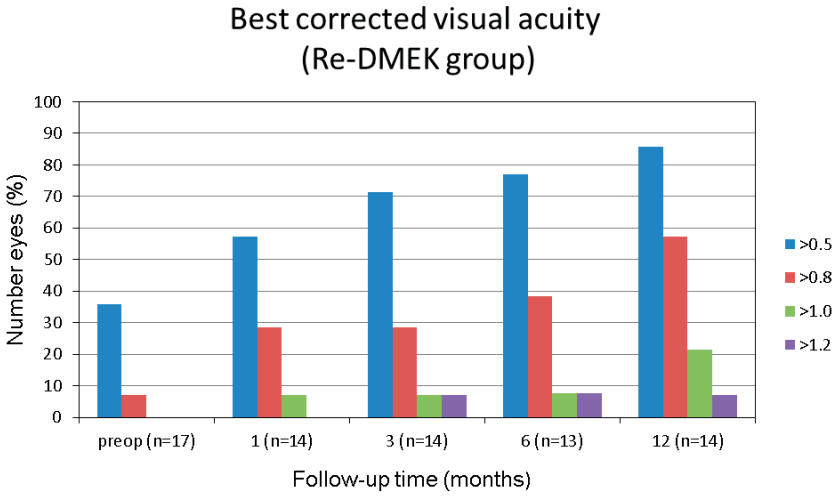

Figure 4. Best-corrected visual acuity ≤12 months after repeat Descemet Membrane Endothelial Keratoplasty. Five eyes were fitted with a contact lens at 6 and 12 months postoperatively. The legend represents the decimal visual acuity levels.

Table 4. Outcome measures Secondary Descemet Membrane Endothelial Keratoplasty (study group) and Primary Descemet Membrane Endothelial Keratoplasty (control group)

Variable	Study group (n=17)	Control group (n=17)	*P*-value
Densitometry*			
Total (ant/central/post & central to peripheral zone)	26.8±3.7 (n=15)	26.1±5.1	*P*=0.99
Total (anterior/central/posterior) 0-2mm zone	25.1±8.7 (n=15)	20.0±3.9	*P*=0.33
Anterior 0-2mm zone	35.3±16.2 (n=15)	28.0±5.4	*P*=0.60
Central 0-2mm zone	19.8±8.1 (n=15)	16.7±3.4	*P*=0.60
Posterior 0-2mm zone	20.3±7.3 (n=15)	15.5±3.5	*P*=0.20
Endothelial Cell Density (cells/mm^2)			
Preoperative	2580±173 (n=17)	2596±244	*P*=0.85
Postoperative 6 months	1390±466 (n=15)	1813±606	*P*=0.04
Postoperative 12 month	1294±459 (n=13)	1728±607	*P*=0.07
Pachymetry (μm)			
Preoperative	703±126 (n=17)	663 (±77)	*P*=0.28
Postoperative at 6 months	515±39 (n=16)	520 (±35)	*P*=0.40

Values are presented as means ± standard deviation unless otherwise noted
*two eyes excluded with a central corneal scar due to an ulcer after DMEK (case 12) and after repeat DMEK (case 10)

Other Postoperative Complications after Repeat DMEK

One eye (case 15) showed primary and 2 eyes (cases 4 and 7; Figure 5) secondary graft failure 12 months after re-DMEK (Table 5). Two of these eyes had also shown secondary graft failure of the initial DMEK graft (Table 3, available at www.aaojournal.org; Figure 3). One eye had a tertiary DMEK that was performed in the same manner as in re-DMEK, and the interface was meticulously scraped to remove all remnants from previous grafts. A postoperative graft detachment was managed by an uneventful rebubbling procedure with 120-minutes airfill of the host anterior chamber. The visual acuity improved from counting fingers (1/60) before surgery to 20/20 (1.0) at 6 months and 20/17 (1.2) at 9 months postoperatively.

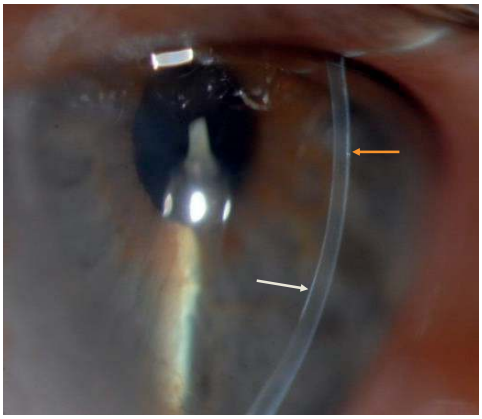

Figure 5. Six months after repeat Descemet Membrane Endothelial Keratoplasty. The eye (case 4) shows typical scarring patterns across the interface between the donor Descemet graft and the host stroma (presumably induced by removal of the first Descemet graft; white arrow) and a subepithelial haze (which may have resulted from prolonged corneal edema; orange arrow).

Table 5. Complications after Repeat Descemet Membrane Endothelial Keratoplasty

Complication	No.
Graft detachment	6
One third or less of graft surface area	5
More than one third of graft surface area	1
Graft failure (primary*/secondary)	3
Suspect of recurrent allograft rejection	1
IOP elevation	2
Air-bubble induced*	1
Secondary glaucoma requiring glaucoma surgery	1
Cataract formation (out of 3 phakic eyes)	1
Corneal ulcer	1
Descemet membrane remnant of primary DMEK graft	1

IOP = intraocular pressure; DMEK = Descemet Membrane Endothelial Keratoplasty;
*This complication occurred in the same eye.

In the 1 eye that underwent re-DMEK for graft failure after allograft rejection (case 6), 2 episodes of suspected recurrent allograft rejection were observed after re-DMEK and were managed by an intensified topical steroid regime.

Two eyes showed postoperative glaucoma (Table 3, available at www.aaojournal.org). In case 15, the intraocular pressure elevation was induced by the air bubble and, although reversed by removal of the air from the host anterior chamber, the cornea of this eye did not clear. The other eye (case 2) had secondary open-angle glaucoma that required filtering surgery.

One of the 3 phakic eyes (cases 3, 7, and 11) developed a cataract for which phacoemulsification was performed 10 months after re-DMEK (case 3).

One eye (case 10) developed a corneal ulcer 2.5 months after re-DMEK that could be managed with systemic and topical antibiotics and steroids.

In 1 eye (case 6), a remnant of the primary DMEK graft was observed at the interface between the secondary graft and the host posterior stroma.

DISCUSSION

Feasibility of Repeat DMEK

Our study showed that re-DMEK was technically feasible in all eyes that showed graft detachment or DMEK transplant failure. Compared with primary DMEK, some modifications in the operative protocol may be considered in re-DMEK to avoid intraoperative and postoperative complications (Table 2). Unlike a virgin DM during descemetorhexis, a DMEK graft was found to show relatively strong adherence to the host posterior stroma, with a higher risk of graft remnants. Performing a "normal" descemetorhexis "under air" to better visualize DM to enable its complete removal in routine DMEK has been advocated, so that in re-DMEK it may be even more critical to monitor previous graft removal "under air." As an additional check, Trypan blue may be applied to stain the primary DMEK graft to identify remnants left in situ.[18] When re-DMEK is performed in eyes that developed a detachment of the initial DMEK graft, it may be especially important to meticulously scrape the recipient posterior stroma in the area of the detachment and remove all (migrated) endothelial cells covering the stromal defect to enable better graft adherence. In these cases, it may also be recommended to increase the air bubble time at termination of the surgery to 90 to 120 minutes

because secondary grafts may show a tendency to detach in the same area as the initial DMEK graft.

Clinical outcome

After repeat PK, visual outcomes have been reported to be worse than in primary PK.[25,26] To manage low visual outcome after primary DSAEK or DSEK, repeat DSAEK or repeat DSEK has been reported to be effective with visual acuity outcomes of ≥20/40 (0.5)[13,16] In our group of re-DMEK eyes, that had reduced visual acuity owing to corneal edema, BCVA improved in all eyes in which re-DMEK was successful. Overall, however, a smaller number of eyes may achieve a final BCVA level that compares to uneventful primary DMEK, with about 40% to 50% of eyes reaching ≥20/25 (≥0.8) after re-DMEK at 6 to 12 months, whereas 80% to 90% may reach this level after primary DMEK.[2,4] In addition, about one third of re-DMEK eyes required contact lens fitting to further improve BCVA.

We recently reported that corneal surface irregularities could result from superficial corneal scarring after long-standing corneal edema.[27] If so, this would be an argument for earlier operative reintervention after failed primary DMEK. Higher paracentral densitometry values in eyes after repeat DSAEK after failed primary DMEK, than after primary DSAEK have been reported,[28] and may relate to diffuse scarring of the interface between the graft and the host posterior stroma and/or subepithelial scarring. However, these findings could not be substantiated in our study because no difference in densitometry values were found between repeat DMEK and control DMEK eyes (Figure 5).

In re-DMEK, ECD decrease seemed to be higher compared with primary DMEK at 6 months (-46% vs. -34%) and at 12 months (-50% vs. -37%).[19,29,30] These results could (in part) be explained by negative selection bias, because eyes with a greater tendency toward lower ECD are more likely to require re-DMEK. Nonetheless, all corneas cleared and pachymetry values returned to normal in all but 1 case that showed primary graft failure, presumably associated with air bubble-induced IOP elevation in the immediate postoperative phase.

Complications

The spectrum of complications after re-DMEK resembled that after primary DMEK. However, some complications may be anticipated when reviewing the postoperative course after the initial DMEK and/or the indication for reintervention. Three eyes (cases 1, 7, and 10) had a graft detachment after initial DMEK and the secondary DMEK graft showed a tendency toward graft detachment in the

same corneal quadrant(s). Two eyes (cases 4 and 7) that showed graft failure of the primary DMEK again developed late graft failure after re-DMEK. Both observations may suggest that host intrinsic properties, like the eye's anatomy and/or comorbidities, may aid or interfere with graft adherence and may influence the risk of graft failure.

Other complications seemed incidental and larger series with longer follow-up may be needed to reveal any difference in complications between primary and secondary DMEK, for example, the risk of allograft rejection, which is known to increase with the number of re-keratoplasty procedures in PK.[12]

Indications for and Timing of Re-DMEK

In a recent case series, the main indication for re-DMEK was upside-down graft positioning.[18] In the current study, re-DMEK was largely performed to manage significant graft detachment (n = 14; of which only 3 grafts were positioned upside down) and primary or secondary graft failure (n = 3).

Compared with other studies that reported reintervention 1 to 6 months after the initial DMEK,[18] in our series re-DMEK was performed at later postoperative time intervals, on average at 16±9 months (range, 4-33 months). Our conservative approach may have resulted from the observation that corneas with partially detached grafts still cleared ("spontaneous corneal clearance").[31,32] As a result, our study may be negatively biased because DMEK eyes with a graft detachment that reached an acceptable BCVA after spontaneous clearance never became eligible for re-DMEK. Also, postponing reintervention may have resulted in longer episodes of corneal edema and secondary superficial and stromal scarring, requiring contact lens fitting to reach the eye's maximal potential.[27] To avoid secondary stromal changes induced by persistent corneal edema owing to a larger graft detachment, it could therefore also be argued to rebubble the graft (or to perform a re-DMEK) in the early postoperative phase.

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