Published in final edited form as:

Cornea. 2020 October ; 39(10): 1243–1246. doi:10.1097/ICO.0000000000002432.

Recipient Factors Associated with Graft Detachment of Subsequent Eye in Sequential Descemet's Membrane Endothelial Keratoplasty

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Abstract

Purpose: To evaluate recipient factors associated with graft detachment in the subsequent eye of patients who underwent sequential Descemet's membrane endothelial keratoplasty (DMEK).

Methods: Retrospective, consecutive case series with 158 eyes of 79 patients who underwent DMEK surgeries in both eyes between Oct 2013 and Apr 2019 for treatment of Fuchs endothelial dystrophy. The main outcome measure was the presence of graft detachment (any amount of detachment) at postoperative 1 week in the subsequent eye. Preoperative, intraoperative and postoperative factors were evaluated for association with graft detachment.

Results: Out of 79 patients (158 eyes) with a mean follow-up of 11.7 ± 8.4 months, 18 patients (36 eyes) developed graft detachment in both eyes 1 week postoperatively. The risk of detachment in the subsequent eye was increased when the first eye had any amount of detachment (odds ratio=2.8; 95% CI= 1.1 to 7.3; $p=0.037$). When the first eye had a clinically significant detachment (>30% detached), the risk of detachment occurring in the subsequent eye was greater (odds ratio=15.7; 95% CI= 1.8 to 134.5; $p=0.012$). This risk of graft detachment in the subsequent eye increased 33% for every 5% increase in the detachment percentage in the first eye (odds ratio=1.3; 95% CI= 1.1 to 1.6; $p=0.008$).

Conclusion: The presence of graft detachment after DMEK increases the risk of graft detachment in subsequent DMEK in the contralateral eye. Modification in perioperative care and surgical technique in the contralateral eye, such as a larger gas bubble, use of SF6 20%, and combining cataract surgery, may be needed when graft detachment occurs after DMEK in the first eye.

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No conflicts of interest reported by authors

Keywords

DMEK; Fuchs; Descemet

INTRODUCTION

Descemet's membrane endothelial keratoplasty (DMEK) is becoming the preferred surgery for Fuchs endothelial corneal dystrophy due to superior visual outcomes, faster visual rehabilitation, and a lower rate of immunologic rejection compared to conventional surgeries including Descemet's stripping automated endothelial keratoplasty.¹⁻³ However, there are still barriers to more widespread DMEK adoption, primarily the higher post-operative graft detachment and re-bubbling rates.⁴ The etiology of or definitive risk factors associated with graft detachment have not been identified in various studies regarding potential roles of recipient or donor factors,⁵⁻⁸ and therefore there is no standardized perioperative management to prevent detachment.⁹

As we occasionally experienced graft detachment in both eyes after sequential DMEK surgery, we hypothesized that recipient factors may have a role in graft detachment. To evaluate this hypothesis, we investigated the (1) association of preoperative, intraoperative, and postoperative factors with graft detachment, and (2) association of the graft detachment between each eye of patients who underwent bilateral DMEK sequentially.

PATIENTS AND METHODS

The University of Michigan Institutional Review Board approved this retrospective study, which was conducted in accordance with the tenets of the Declaration of Helsinki guidelines and all applicable federal and state laws.

Participants

This retrospective, consecutive, interventional case series evaluated 158 eyes of 79 patients who had bilateral DMEK surgeries for Fuchs endothelial dystrophy between October 2013 and April 2019. All medical records were reviewed from patients 18 years or older who underwent bilateral DMEK surgeries, with or without combined cataract surgery.

Surgical Protocol

Routine DMEK surgery was performed by three surgeons (CTH, BLT and SIM) using a standardized technique. Briefly, to decrease the risk of developing post-operative pupillary block, each patient received a YAG laser peripheral iridotomy, placed inferiorly, approximately 1 week prior to surgery. On the surgery date, each patient received a retrobulbar block of 3 cc of 0.5% bupivacaine and 2% lidocaine (50:50 mix) followed by application of a Honan balloon for 10 minutes.

If a patient had a planned concurrent phacoemulsification and lens implantation with DMEK surgery, then the phacoemulsification was performed first; otherwise, DMEK was performed in the following fashion. Using a measuring trephine, an 8.0mm diameter circle was marked

on the epithelial surface. Using a 7515 blade, two paracenteses were created superotemporally and inferotemporally. The anterior chamber was filled with ophthalmic viscosurgical device (OVD; Healon; Johnson & Johnson Vision, Santa Ana, CA), and a reverse Sinsky hook was utilized to strip Descemet's membrane along the epithelial marking. A 2.75 mm temporal clear corneal incision was used to remove Descemet's membrane with Utrata forceps and sent to pathology. Next, OVD was removed using the irrigation-aspiration hand piece of the phacoemulsification machine. The donor tissue was obtained as pre-stripped or preloaded from the eye bank. When the tissue was obtained pre-stripped only, trypan blue was dripped on the Descemet's surface and tissue was partially trephined using a 7.5 mm sized Barron punch. The peripheral Descemet's membrane was removed. The Descemet's membrane was then stripped and placed in a bed of trypan blue for 3 minutes. The membrane was floated in BSS. A modified Straiko-Jones tube injector was used to load the tissue. The donor tissue was injected into the anterior chamber. The temporal incision was closed using one 10-0 nylon suture. The tissue was opened using a variety of described techniques.¹⁰ A small amount of filtered air was injected underneath the unfolded tissue to support it. When required based on the surgeons' discretion or preference, SF₆ 20% or C₃F₈ 12% was placed under the graft to replace the air. Patients were observed during post-op recovery in face-up positioning for approximately 120 minutes and discharged home after the surgeon noted that the graft was still attached using a handheld or portable slit-lamp. Post-operative care consisted of maximizing face-up positioning for the first week along with instillation of prednisolone acetate 1% drops and ofloxacin 0.3% drops four times per day. The timing of face-up positioning and frequency of topical medication use were tapered by surgeon preference. Patients who had an unremarkable post-operative course were evaluated at post-operative day 1, post-operative week 1, and post-operative month 1, 2, and 3. Patients who had a significant graft detachment or required an intervention were evaluated more frequently at intervals based on the discretion of the surgeon. A graft detachment was defined as non-adherence of any portion of the graft on slit lamp exam and/or anterior segment optical coherence tomography; if more than 30% of the graft was detached, this was regarded as clinically significant.

Data Acquisition and Analysis

Data retrospectively retrieved included preoperative factors (age, gender, ethnicity, laterality, history of diabetes mellitus and tobacco use); ocular characteristics measured using the optical biometer (Lenstar®; Hagg-Streit, Bem, Switzerland; central corneal thickness, axial length, anterior chamber depth, average keratometric measurement, keratometric measurement of astigmatism and white to white distance); intraoperative factors (type of surgery, donor tissue preparation, use of intracameral gas, and length of surgery); and postoperative factors (length of face-up time when recovering, post-operative day 1 (POD1) gas bubble size in the anterior chamber (%), presence of POD1 block and presence and amount (%) of graft detachment 1 week postoperatively (POW1)). The primary outcome measure was presence of graft detachment at postoperative 1 week after DMEK in the subsequent eye. Preoperative, intraoperative and postoperative factors were evaluated for association with graft detachment 1 week after the surgery. A graft detachment was defined as non-adherence of any portion of the graft on slit lamp exam and/or anterior segment

optical coherence tomography; if more than 30% of the graft was detached, this was regarded as clinically significant.

Statistical Analysis

Characteristics of the sample were summarized with descriptive statistics, including mean and standard deviations for continuous measures, and frequencies and percentages for categorical measures. Logistic regression analysis was performed in order to measure the odds ratio of detachment of the contralateral based on the first eye detachment. SAS version 9.4 (SAS Institute, Cary, NC) was used for all statistical analyses, and $P < 0.05$ was considered statistically significant.

RESULTS

Demographic factors

The baseline characteristics of enrolled patients are described in Table 1. Out of 79 patients (158 eyes) with a mean follow-up of 11.7 ± 8.4 months, 18 patients (36 eyes; 22.8%) developed graft detachment (any amount of detachment) in both eyes at 1 week postoperatively. Thirty-three patients (66 eyes; 41.8%) had no graft detachment in either eye while 28 patients (28 eyes; 35.4%) had some degree of graft detachment in either the first or the subsequent eye (Table 2). Demographic factors (age, gender, and ethnicity) were not associated with the occurrence of postoperative graft detachment ($p > .05$; univariate logistic regression analysis).

Preoperative factors

Graft detachment 1 week after surgery in the subsequent eye had a statistically significant association with anterior chamber depth (odds ratio=0.3; 95% CI= 0.1 to 0.9; $p=.038$; univariate logistic regression analysis) in the subsequent eye. No significant association was found with other measures including mean keratometric measurements ($p > .05$; univariate logistic regression analysis).

The baseline characteristics and measurements of eyes were not different between both eyes ($p > .05$; McNemar's Chi-squared test and Wilcoxon signed rank test; Table 3), and measurements highly correlated themselves to each other (Pearson coefficient 0.8–1.0; $p < 0.0001$; Pearson's correlation analysis).

Intraoperative factors

The risk of graft detachment in the subsequent eye at postoperative 1 week was significantly decreased when DMEK in that eye was combined with cataract surgery (odds ratio=0.3; 95% CI= 0.1 to 0.9; $p=.034$; univariate logistic regression analysis). Neither type of donor tissue preparation (pre-stripped or pre-loaded), type of intracameral gas (filtered air, 20% SF₆ or 12% C₃F₈), nor length of surgery showed significant association with graft detachment in the subsequent eye ($p > .05$; univariate logistic regression analysis).

Postoperative factors

The risk of detachment in the second eye was increased when the first eye had any amount of detachment (odds ratio=2.8; 95% CI= 1.1 to 7.3; $p=0.037$; multivariate logistic regression analysis; Table 4, Model 1). When the first eye had a clinically significant amount of detachment ($>30\%$), the odds ratio was increased to 15.7 (95% CI= 1.8 to 134.5; $p=0.012$; multivariate logistic regression analysis; Table 4, Model 2). Furthermore, this risk increased 33% for every 5% increase in the detachment percentage in the first eye (odds ratio=1.3; 95% CI= 1.1 to 1.6; $p=0.008$; multivariate logistic regression analysis; Table 4; Model 3). Interestingly, the odds of graft detachment in the subsequent eye were decreased when cataract surgery was combined at the time of DMEK surgery in the subsequent eye in the three logistic regression models (odds ratio=0.3, 0.4, 0.3; $p=0.067$, 0.065, 0.053, respectively; multivariate logistic regression analysis; Table 4).

Other factors, such as length of immediate postoperative face-up time, gas bubble size in the anterior chamber 1 day postoperatively or postoperative pupillary block, did not show significant association with graft detachment ($p>.05$; univariate logistic regression analysis).

DISCUSSION

In this study, we evaluated association of recipient factors with graft detachment of the subsequent eye using data collected on patients who received DMEK sequentially in both eyes. Using a multivariate logistic regression model, we found that if the graft detached during the post-operative course of the 1st eye, then there is a greater probability that the post-operative course of the contralateral eye would have a graft detachment. This risk was further increased when the first eye had a clinically significant graft detachment, defined as more than 30%. This definition was based on the report of resolution of detachment without any intervention in eyes with less than 30% detachment.¹⁰ Our study provides a unique look at factors that influence the risk of subsequent eye graft detachment after DMEK in the first eye. In addition, the results in the current study are clinically important because the postoperative course after DMEK in the first eye can shed light on what might be expected after DMEK in the subsequent eye. Our finding that risk of graft detachment in the subsequent eye increased 33% for every 5% increase in the detachment percentage in the first eye has implications for potential modification of perioperative care and surgical technique in the contralateral eye. Alterations in technique, such as a larger gas bubble, use of SF6 20%, and combining cataract surgery in order to deepen the anterior chamber, may prevent graft detachment and improve the overall prognosis of the subsequent eye's DMEK surgery, and therefore, the current authors incorporated those modifications in clinical practice.

In a univariate logistic regression analysis, preoperative (anterior chamber depth) and intraoperative factors (combination with cataract surgery) were significantly associated with graft detachment in the subsequent eye. Because anterior chamber depth and combined cataract surgery are highly dependent variables, our three multivariable regression models included each variable separately. Although these multivariable logistic regression analysis models showed only marginal significance with these factors, we believe that this further supports our hypothesis that graft detachment is more related to recipient factors as opposed

to donor factors. Furthermore, larger anterior chamber depth can be induced by cataract surgery, and consequently accommodate a higher volume of gas in the anterior chamber. Because we clinically measured the size of the gas bubble in proportion to the size of the cornea by slit-lamp examination, the volume of the gas bubble was not able to be quantified. Therefore, we can only speculate that there was no significant association between the gas bubble size in the anterior chamber 1 day postoperatively and the likelihood of detachment in the current study. Further studies that include objective quantification of gas bubble size would better address this question. The influence of cataract surgery on the postoperative attachment of the graft is not yet fully understood. Leon P et al. recently reported the combination of DMEK with cataract surgery as an independent risk factor for postoperative graft detachment,¹¹ however, other studies showed there was no significant difference between pseudophakic DMEK and DMEK combined with cataract surgery.^{12, 13} In the present study, the risk of detachment in the subsequent eye decreased when DMEK in the subsequent eye was combined with cataract surgery although it was marginally significant. Due to the small number of patients underwent DMEK without cataract surgery in the current study, we could not draw a conclusion in comparison of patients undergoing phakic DMEK, pseudophakic DMEK, and DMEK combined with cataract surgery. Another studies with a larger sample size should be also considered to assess whether cataract surgery have an effect on the graft attachment.

The limitations of this study include its reliance on a retrospective chart review of DMEK cases performed by three surgeons in a single academic center. Though having only three surgeons perform all the surgeries is a limitation, having both eye surgeries performed by the same surgeon not only controls for within-patient factors, but also controls for within-surgeon factors. Moreover, surgeon-level factors such as changes over time of post-operative regimen and patient-level factors such as adherence to postoperative instructions could not be specifically analyzed.

In summary, we found that DMEK graft detachment at postoperative 1 week in the subsequent eye was significantly associated with the occurrence and degree of detachment after DMEK in the first eye, and identified several factors that are associated with the risk of graft detachment after subsequent eye DMEK. These findings should be considered in modifying perioperative care as well as surgical technique in the contralateral eye when initial DMEK is associated with graft detachment.

Acknowledgments

Funding: NIH grants EY007003 (Core Center for Vision Research at the Kellogg Eye Center)

REFERENCES

1. Rodriguez-Calvo-de-Mora M, Quilendrin R, Ham L, et al. Clinical outcome of 500 consecutive cases undergoing Descemet's membrane endothelial keratoplasty. *Ophthalmology*. 2015;122: 464–470. [PubMed: 25439596]
2. Anshu A, Price MO, Price FW. Risk of corneal transplant rejection significantly reduced with Descemet's membrane endothelial keratoplasty. *Ophthalmology*. 2012;119:536–540. [PubMed: 22218143]

3. Guerra FP, Anshu A, Price MO, et al. Endothelial keratoplasty: fellow eyes comparison of Descemet stripping automated endothelial keratoplasty and Descemet membrane endothelial keratoplasty. *Cornea*. 2011;30:1382–1386. [PubMed: 21993468]
4. Zhu L, Zha Y, Cai J, et al. Descemet stripping automated endothelial keratoplasty versus descemet membrane endothelial keratoplasty: a meta-analysis". *Int Ophthalmol*. 2018;38:897–905 [PubMed: 28417337]
5. Pilger D, Wilkemeyer I, Schroeter J, et al. Rebubbling in Descemet Membrane Endothelial Keratoplasty: Influence of Pressure and Duration of the Intracameral Air Tamponade. *Am J Ophthalmol*. 2017;178:122–128. [PubMed: 28342720]
6. Schmeckenbacher N, Frings A, Kruse FE, et al. Role of Initial Intraocular Pressure in Graft Adhesion After Descemet Membrane Endothelial Keratoplasty. *Cornea*. 2017;36:7–10. [PubMed: 27755190]
7. Guell JL, Morral M, Gris O, et al. Comparison of Sulfur Hexafluoride 20% versus Air Tamponade in Descemet Membrane Endothelial Keratoplasty. *Ophthalmology*. 2015;122:1757–1764. [PubMed: 26088620]
8. Cirkovic A, Beck C, Weller JM, et al. Anterior Chamber Air Bubble to Achieve Graft Attachment after DMEK: Is Bigger Always Better? *Cornea*. 2016;35:482–485. [PubMed: 26807901]
9. Rapoport Y, Veldman P. A Comprehensive Review of Postoperative Management of Descemet's Membrane Endothelial Keratoplasty. *Semin Ophthalmol*. 2017;32:104–110. [PubMed: 27780445]
10. Yeh RY, Quilendrino R, Musa FU, et al. Predictive value of optical coherence tomography in graft attachment after Descemet's membrane endothelial keratoplasty. *Ophthalmology*. 2013;120:240–245. [PubMed: 23149125]
11. Leon P, Parekh M, Nahum Y, et al. Factors Associated With Early Graft Detachment in Primary Descemet Membrane Endothelial Keratoplasty. *Am J Ophthalmol*. 2018;187:117–124. [PubMed: 29339064]
12. Chaurasia S, Price FW Jr, Gunderson L, et al. Descemet's membrane endothelial keratoplasty: clinical results of single versus triple procedures (combined with cataract surgery). *Ophthalmology*. 2014;121:454–458 [PubMed: 24252821]
13. Siebelmann S, Ramos SL, Matthaei M, et al. Factors Associated With Early Graft Detachment in Primary Descemet Membrane Endothelial Keratoplasty. *Am J Ophthalmol*. 2018;192:249–250.

Table 1.

Baseline characteristics of enrolled patients

Eyes/Patients (n)	158/79
Ethnicity (Non-hispanic Caucasian, %)	100
Gender (M/F, n)	29/50
Age at surgery (mean $\pm$ SD, years)	68.1 $\pm$ 7.4
Diabetes (%)	18.0
Tobacco use (%; pack-years (mean $\pm$ SD))	61.5 (12.2 $\pm$ 22.4)
Follow-up (mean $\pm$ SD, months)	11.7 $\pm$ 8.4

n = numbers; M = male; F = female; SD = standard deviation.

Table 2.

Degree of graft detachment and associated rebubble rate.

Number of Eyes (rebubble)		
	First eye (n=79)	Second eye (n=79)
No detachment	48 (0)	46 (0)
Detachment		
10%	11 (0)	13 (0)
>10% and 20%	8 (2)	6 (1)
>20% and 30%	4 (2)	4 (3)
>30%	8 (8)	10 (10)

Table 3.

Baseline ocular characteristics of enrolled patients.

	First eye (n=79)	Second eye (n=79)	P
Laterality (OD/OS)	40 / 39	39 / 40	.87 [*]
Lens status (Phakic/Pseudophakic)	53 / 26	60 / 19	.0156 [*]
Central corneal thickness (mean ± SD, μm)	640.0 ± 60.8	628.2 ± 53.6	.0006 [†]
Axial length (mean ± SD, mm)	24.2 ± 1.5	24.2 ± 1.5	.8369 [†]
Anterior chamber depth (mean ± SD, mm)	3.3 ± 0.6	3.2 ± 0.4	.2888 [†]
Mean keratometric readings (mean ± SD, diopter)	43.9 ± 1.8	44.1 ± 1.9	.3503 [†]
Corneal astigmatism (mean ± SD, diopter)	1.3 ± 1.6	1.3 ± 1.6	.8723 [†]
White to white diameter (mean ± SD, mm)	12.1 ± 0.5	12.1 ± 0.5	.8460 [†]

SD = standard deviation; OD = right eye; OS = left eye.

^{*} McNemar's test.[†] Wilcoxon signed rank test.

Table 4.

Logistic regression models for influences of variables of each eye on the graft detachment 1 week postoperatively in the subsequent eye.

Variables	Odds ratio (95% CI)	P
Model 1		
Presence of graft detachment at POW1 of first eye	2.8 (1.1, 7.3)	.0372
Combined cataract surgery of subsequent eye	0.4 (0.1, 1.1)	.0646
Model 2		
Clinically significant detachment at POW1 of first eye	15.7 (1.8, 134.5)	.0119
Combined cataract surgery of subsequent eye	0.3 (0.1, 1.1)	.0666
Model 3		
Amount of graft detachment at POW1 (5% unit) of first eye	1.3 (1.1, 1.6)	.0082
Combined cataract surgery of subsequent eye	0.3 (0.1, 1.0)	.0534

CI = confidence interval; POW1 = postoperative 1 week.