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Intraoperative fibrin formation during Descemet membrane endothelial keratoplasty

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ABSTRACT

Purpose: To describe Descemet membrane endothelial keratoplasty (DMEK) cases complicated by spontaneous intraoperative fibrin formation.

Methods: DMEK surgeries performed at two centers using a standardized technique were reviewed retrospectively for the occurrence of intraoperative fibrin formation. Cases were assessed for recipient medical history, donor age, best spectacle-corrected visual acuity (BSCVA), intraoperative unscrolling time, 6-month endothelial cell loss (ECL), and the course of the mate donor cornea.

Results: In this review of 868 cases of standardized DMEK surgery with surgical peripheral iridotomy, 32 eyes of 29 patients (3.7%) were complicated by the formation of intraoperative fibrin formation, including 3 patients that developed fibrin in both eyes. Three of the 32 grafts failed (9.4%). None of the mate corneas transplanted (n = 27) developed complications related to fibrin. The donor age ranged from 51 to 75 years and recipient age ranged from 49 to 82 years (median, 66 years). Unscrolling time ranged from 1 to 105 min (median, 15 min). Nine eyes required one rebubble procedure. No eyes had vision-limiting comorbidities, and the 6-month BSCVA was ≥20/40 in all eyes. Six-month ECL ranged from 19% to 73% (median, 44%).

Conclusions: We conclude that fibrin formation during DMEK surgery is an uncommon but important complication that can make graft manipulation more difficult, and may have deleterious effects on endothelial cell density and graft survival.

1. Introduction

Endothelial keratoplasty has become the primary surgical approach for treating disorders of the corneal endothelium, and Descemet membrane endothelial keratoplasty (DMEK) is gaining popularity as the preferred technique over Descemet stripping automated endothelial keratoplasty (DSAEK) because of its rapid visual recovery, superior visual outcomes, and lower risk of rejection.[1] Challenges of DMEK include graft insertion and positioning due to the thinness and scrolling properties of the donor tissue. Various techniques have been described for inserting, unfolding, and positioning the graft tissue in a controlled and reproducible manner,[2–4] and these steps can be made even more challenging when complicated by the unexpected formation of fibrin in the anterior chamber.

Intraoperative fibrin formation has been reported infrequently *during* intraocular surgery,[5,6] but it has been described widely in the literature as a *postoperative* complication. Most commonly, fibrin reactions have been associated with pediatric cataract surgery, intraocular surgery in patients with pseudoexfoliation syndrome or uveitis, and procedures complicated by intraocular hemorrhage.[7–12]

We conducted a retrospective review of DMEK cases performed at two institutions using a standardized technique to investigate the incidence, etiology, and clinical outcomes of intraoperative fibrin formation.

2. Materials and methods

A retrospective review was conducted of all DMEK surgeries

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performed at the Devers Eye Institute between February 1, 2013 and November 1, 2016 and the University of Iowa between October 1, 2012 and November 1, 2016 using the standardized technique described by Terry et al.[1,4,13] Cases were excluded if the standardized technique was not used or if postoperative follow-up was less than 6 months. Cases described from the Devers Eye Institute were part of an ongoing Institutional Review Board (IRB) approved, HIPAA compliant study of endothelial keratoplasty in which all participants signed an IRB approved, HIPAA compliant clinical research consent form. Cases described from the University of Iowa were collected as part of an IRB approved retrospective review. Written consent to publish these cases was not obtained. This report does not obtain any personal identifying information. This research adhered to the tenets of the Declaration of Helsinki.

2.1. Case definition and records review

Specific notations of intraoperative events are made in the operative records at both institutions regarding deviations from the expected operative procedure and unexpected intraoperative findings, including fibrin formation during surgery. Cases of intraoperative fibrin formation were defined as DMEK surgeries in which strands of fibrin were visible in the anterior chamber and/or interfered with positioning of the graft. The operating surgeon noted the presence of fibrin in the operative report when it occurred; since the point at which fibrin first became visible during the case was not accurately documented, this parameter was not included in the analysis.

Operative records were reviewed for the occurrence of intraoperative fibrin formation. All identified cases underwent further review of recipient and donor records for the following parameters: recipient medical history, recipient anticoagulation status at the time of surgery, indication for surgery, donor age, pre-preparation donor endothelial cell density, intraoperative unscrolling time, best spectacle-corrected visual acuity (BSCVA), 6-month central corneal thickness by ultrasound pachymetry, 6-month endothelial cell density, and the course of the mate donor cornea. Fellowship trained cornea surgeons reviewed each case to identify possible comorbidities or variables associated with fibrin formation. Six-month endothelial cell loss (ECL) was calculated for each case. Postoperative cases requiring a rebubble procedure for progressive and/or visually significant graft detachment were recorded. Cases in which the recipient cornea failed to clear were recorded as primary graft failures.

2.2. Statistical analysis

All statistical analyses were performed using SPSS Version 21 (SPSS Inc., Chicago, IL). Descriptive statistics were calculated and are expressed as median values and percentages.

3. Results

Of the 868 cases included in the analysis, 32 eyes of 29 patients (3.7%) developed intraoperative fibrin (Tables 1 and 2). Three patients developed fibrin during DMEK surgery in both eyes. In two of these patients, the second eye was treated with preoperative topical steroids for 1 week prior to surgery with four times a day dosing. In the cohort of 32 eyes, the recipient age ranged from 49 to 82 years (median, 66 years), and 22 patients (76%) were female. The incidence of fibrin formation was greater at the University of Iowa (25 eyes, 7.1%) than the Devers Eye Institute (7 eyes, 1.3%) despite using the same standardized surgical technique and comparable unscrolling times. In 24 cases (75%), the patient was taking an anticoagulant prior to surgery (nonsteroidal anti-inflammatory drugs, aspirin, clopidogrel, or mesalamine). In at least 12 cases, the patient had not stopped taking anticoagulant medications prior to surgery. Additionally, 7 patients (8 eyes) had a history of diabetes. Within the cohort of 32 eyes, fibrin was noted to have occurred prior to graft manipulation in 15 cases, and was associated with intraoperative hemorrhage in 3 cases. Of the 3 noted occurrences of fibrin associated with intraocular hemorrhage, bleeding occurred during peripheral iridotomy creation in 2 cases and during graft unfolding in 1 case where blood was noted to emanate from the angle.

Table 1
Summary of DMEK cases with intraoperative fibrin.

	Devers	Iowa	Total
Fibrin Cases	7	25	32
Total Cases	519	349	868
Incidence (%)	1.3	7.1	3.7
Median Age	66	66	66
Female	7	8	25
Preoperative Anticoag Medications	3	21	24
Triple	6	2	8
Average Unscroll (min)	27.1	20.5	22.1
Rebubble	3	6	9
Graft Failure	0	3	3

Cornea donor ages ranged from 51 to 75 years (Supplementary Table 1). No donor had a past medical history of diabetes. Thirteen cases (41%) prepared DMEK grafts had an S-stamp. All mate corneas that were transplanted (n = 27) did not have complications reported to the eye bank. Twenty-two mate corneas were used for DMEK surgery and did not have reports of fibrin occurrence.

All eyes received a surgical peripheral iridotomy or iridectomy. Unscrolling time ranged from 1 to 105 min (median, 15 min). Nine eyes required one rebubble procedure for graft edge lifts. Three eyes had graft failure and underwent subsequent endothelial keratoplasty. One eye did not have the graft inserted due to dense fibrin formation and a different graft was inserted at a second surgery on postoperative day 69. Mean 6-month BSCVA was 20/25 in the 28 successful surgical cases. Six-month ECL ranged from 19% to 73% (median, 44%).

4. Discussion

This case series describes several cases of intraoperative fibrin formation during DMEK surgery across two centers and investigates its associations. To our knowledge, fibrin formation during DMEK surgery has only been described in 1 case report up to this point. Here, we report on 32 cases of fibrin during DMEK surgery in 29 patients from a larger series and describe the impact of this relatively uncommon but important surgical complication.

Fibrin in the anterior chamber can increase the difficulty of unscrolling and positioning the donor tissue. In our case series, the average unscrolling time was 15 min; however, some cases required more than an hour to unfold the tissue and additional maneuvers to break adherent fibrin strands to the graft, iris, or angle. In some cases, direct manipulation was needed to break fibrin strands adherent to the graft tissue (in contradistinction to the indirect 'no touch' corneal tapping used in routine cases), which can be traumatic to the tissue and other intraocular structures. The incidence of fibrin at the University of Iowa was 5.5 times higher than at Devers, although there was a shorter unscrolling time at the University of Iowa. Given the participation of residents during DMEK cases at the University of Iowa, these findings may represent learner effects for both operating residents and supervising faculty responding to intraocular fibrin occurrence. While all successfully completed cases achieved better than or equal to 20/40 vision, in light of such maneuvers it is unsurprising that this series reports increased rebubble procedure rates endothelial cell losses in the subset of cases complicated by intraoperative fibrin formation compared to other published series of DMEK outcomes.[1,13,14] Of note, our data suggest a possible correlation between unfolding time and endothelial cell loss (analysis not shown) in DMEK cases complicated by

Table 2
Six month outcomes for DMEK recipients with intraoperative fibrin.

Eye	Surgical indication	First Eye or Second Eye	Unscroll Time (min)	Rebubble	Graft Failure	6 mo ECD	6 mo ECL (%)	6 mo BSCVA	6 mo CCT
1	Fuchs	First	1	N	N	2404	20.2	20/20	526
2	Fuchs	Second	32	Y	N	863	70.5	20/20	473
3	Fuchs	First	27	N	N	1538	40.8	20/40	511
4	Fuchs	First	49	N	N	691	72.3	20/40	582
5	Fuchs	First	19	Y	N	774	72.8	20/30	452
6	Fuchs	Second	19	N	N	1795	19.2	20/20	567
7	Fuchs	First	42	Y	N	1866	36.6	20/25	540
8	Fuchs	Second	105	Y	N	*	*	20/25	555
9	Fuchs	First	Φ	*	*	*	*	20/20	*
10	Fuchs	Second	15	N	N	2052	26.1	20/20	601
11	Fuchs	Second	5	Y	N	*	*	20/40	558
12	Fuchs	First	12	N	N	1539	39.7	20/25	538
13	Fuchs	First	α	N	N	728	68.8	20/30	560
14	Fuchs	Second	49	N	Y	*	*	20/25	*
15	Fuchs	First	€	N	N	732	68.7	20/20	540
16	Fuchs	First	21	N	N	1466	46.3	20/25	590
17	Fuchs	Second	20	N	N	*	*	20/20	545
18	Fuchs	First	5	N	N	*	*	20/30	486
19	Fuchs	First	10	N	N	1698	35.9	20/20	521
20	Fuchs	Second	2	N	N	1720	46.8	20/20	517
21	Fuchs	First	15	Y	N	*	*	20/20	528
22	Fuchs	First	6	N	N	1306	53.9	20/20	476
23	Fuchs	First	14	N	N	1283	52.9	20/25	584
24	Failed PK	First	36	N	Y	*	*	20/25	*
25	ICE (Chandler)	First	4	Y	N	2031	21.0	20/30	496
26	Fuchs	First	2	N	N	1900	34.8	20/30	497
27	Fuchs	Second	11	N	N	1936	24.7	20/25	498
28	Fuchs	Second	10	N	N	1951	32.3	20/20	518
29	Failed PK**	First	39	Y	Y	*	*	20/30	*
30	HSV endotheliitis	First	36	N	N	1865	30.3	20/20	404
31	Fuchs	Second	20	Y	N	*	*	20/30	553
32	Fuchs	First	14	N	N	1183	61.0	20/25	502
Median			15			1618.5	40.2	20/25	527
Minimum			1			691	19.2	20/20	404
Maximum			105			2404	72.8	20/40	601
Average			22.1			1514.6	44.3	20/25	525.6
Sum				9	3				
Percentage				28.1	9.7				

Φ Surgical case was aborted after fibrin identification and prior to tissue insertion.
α Complex case requiring donor tissue be removed, re-stained, and re-inserted.
€ Complex case with a significant amount of donor tissue exiting through the main wound with the injector.
* Data is unavailable or not applicable due to surgical complication.
** Initial PK performed for scarring due to HSV.

fibrin; this association may be useful to track in future studies.

In our review, we did not find a singular common demographic or associated condition for all cases. The most common association in this cohort was the use of anticoagulation therapy prior to surgery. Of 27 mate corneas, none had any report of any complication, including 22 that were used for DMEK. This finding indicates that the origin of intraoperative fibrin is not intrinsic to the donor tissue or eye bank processes. Fibrin occurred in 15 of 32 cases prior to graft manipulation. The presence of fibrin prior to unfolding in these 15 cases suggests that fibrin may form independently of graft unscrolling maneuvers at least in certain cases.

A logical and important consideration raised by our data is that bleeding in the anterior chamber, noted in our series to have occurred during peripheral iridotomy creation (2 cases) and from the angle during graft unscrolling (1 case), constitutes a risk factor for fibrin occurrence. We propose two potential mechanisms for fibrin formation during DMEK surgery: 1. Gross or microscopic hemorrhaging during creation of the surgical peripheral iridotomy/iridectomy, and 2. reflux of serum with or without red blood cells through the trabecular meshwork during periods of intraoperative hypotony. It is noteworthy that our surgical technique employs temporary shallowing of the anterior chamber associated with hypotony to achieve graft unscrolling.[4] Among documented fibrin occurrences reported in this series, the patient was prescribed a systemic anticoagulant medication preoperatively in 24 cases, and was documented to have been taking an anticoagulant to the day of surgery in 12 cases. Although it is possible that anticoagulant use is a risk factor for fibrin formation, a dedicated prospective analysis of fibrin occurrence and recipient and operative factors is needed to determine the relative risk of anticoagulant use during DMEK surgery, particularly given the implications for perioperative patient care and management of systemic comorbidities.

Taking measures to reduce the risk of both intraoperative bleeding and hypotony may reduce the risk of intraoperative fibrin formation. One may consider performing the iridotomy preoperatively with *both* an argon laser to cauterize the iris vessels and a Nd:YAG laser, and completing the procedure at least 1 week prior to the DMEK procedure may be of further value. If the iridotomy or iridectomy is performed intraoperatively, performing it early enough in the procedure to allow sufficient time for viscoelastic tamponade of a bleeding vessel may be prudent. Attempts should be made to ensure that the eye is normotensive after the removal of viscoelastic and during the moments immediately leading up to tissue injection such as during graft preparation. Utilizing preloaded DMEK tissue, or preparing the tissue before preparing the recipient, may also be beneficial in this regard.

Minimizing the duration of hypotony during tissue unscrolling may also deter fibrin formation and can be achieved by repressurizing the eye after withdrawal of the injector (while maintaining a chamber that is sufficiently shallow to employ the corneal tapping technique) and by centering and unscrolling the tissue expediently.

Options for management when fibrin becomes manifest are limited at this time. Expeditious and atraumatic positioning of the graft, if possible, is paramount to minimize endothelial cell loss. If fibrin is impeding graft unscrolling, sweeping the anterior chamber with a cyclodialysis spatula or cannula may be helpful to clear fibrin away from the affected graft surfaces. The use of intracameral fibrinolytics is a consideration and has been described in the postoperative setting of pediatric cataract surgery with a robust postsurgical fibrin reaction.[9] However, fibrinolytic agents may cause further hemorrhaging and worsen the problem if it is secondary to hemorrhage.

This study is limited by its retrospective design. A large prospective study is needed to carefully identify potential risk factors and a specific etiology. Since all cases in this series had a surgical iridotomy or iridectomy, a prospective study examining the difference in incidence between a surgical iridotomy/iridectomy and a preoperative laser peripheral iridotomy may help further characterize this complication. Although histopathologic analysis was not performed, the behavior of the substance encountered during DMEK surgery suggests that it is fibrin and not lens material, depigmented iris tissue, dehemoglobinized erythrocytes, or vitreous because of its intraoperative transience and quick postoperative resolution.

In conclusion, intraoperative fibrin formation during DMEK surgery is an uncommon but important complication that can make graft unscrolling and positioning more difficult and potentially more damaging to the tissue. This reaction may have deleterious effects on endothelial cell loss and graft survival that are likely related to additional graft manipulation. Attention to intraoperative minimization of hypotony may be important in limiting fibrin occurrence during DMEK surgery.

Patient consent

The accumulation of data was carried out with approval from our Institutional Review Board (IRB). Written consent to publish these cases was not obtained. This report does not obtain any personal identifying information.

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Authorship

All authors attest they meet the current ICMJE criteria for authorship.

CRediT authorship contribution statement

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Declaration of competing interest

No conflicting relationship exists for any author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajoc.2020.100686.

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