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Risk Factors for Cystoid Macular Edema After Descemet Membrane Endothelial Keratoplasty

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Purpose: To investigate factors associated with cystoid macular edema (CME) after Descemet membrane endothelial keratoplasty (DMEK) in Asian eyes.

Methods: In this retrospective, interventional, consecutive case series, 77 eyes of 65 patients who underwent DMEK were evaluated; in 53 eyes, cataract surgery was performed 1 month before DMEK (staged DMEK), and 24 eyes underwent DMEK alone (simple DMEK). Central retinal thickness, incidence of CME, postoperative best-corrected visual acuity, central corneal thickness, and corneal endothelial cell density were assessed at 1, 3, and 6 months after surgery. Multiple regression analysis and stepwise variable selection were performed for parameters such as type of surgery, iris damage scores, age, sex, axial length, preoperative visual acuity, rebubbling, air volume in the anterior chamber on postoperative day 1, history of diabetes, and endothelial cell density loss rates at 6 months after surgery.

Results: CME occurred in 12 (15.6%) of 77 eyes. There was no significant difference in best-corrected visual acuity between eyes with and without CME ($P = 0.27$). Multivariable analysis revealed that the difference in iris damage scores between before and after DMEK ($P < 0.001$), air volume in the anterior chamber ($P = 0.012$), simple DMEK ($P = 0.020$), and rebubbling ($P = 0.036$) were significantly associated with CME. Stepwise variable selection indicated that iris damage ($P < 0.001$) was the most important risk factor for CME.

Conclusions: Iris damage due to DMEK might be a possible risk and aggravating factor for the development of CME after DMEK. Surgeons should attempt to minimize damage to the iris.

Key Words: Descemet membrane endothelial keratoplasty, endothelial keratoplasty, cystoid macular edema, iris abnormality, bullous keratopathy

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Descemet membrane endothelial keratoplasty (DMEK) results in rapid and good improvement in postoperative visual acuity. It is used to treat corneal disorders, such as Fuchs endothelial corneal dystrophy (FECD), bullous keratopathy, and corneal endothelial decompensation. Nevertheless, there are some factors that may negatively affect the outcome. Among these, cystoid macular edema (CME) is a well-known disorder that occurs after cataract surgery, when it is also known as Irvine–Gass syndrome.[1,2] This complication can be observed after different ocular surgeries, including DMEK.[3–7] Recent studies using spectral domain optical coherence tomography (SD-OCT) have shown that the incidence of CME after DMEK is 7% to 13.8%.[4–7] Therefore, Heinzelmann et al[4] recommended regular SD-OCT monitoring during the first 6 months after DMEK. Conversely, Hoerster et al[5] reported that hourly early postoperative topical steroid therapy was very effective in reducing the incidence of CME after DMEK.

Nevertheless, some important questions regarding CME after DMEK remain. Because all previous reports involved patients from Western countries, the difference in the incidence of CME after DMEK between Asian eyes and Caucasian eyes remains unknown, as to the factors triggering CME after DMEK. In our previous report, we showed that iris damage may contribute to the development of iris posterior synechia after DMEK, likely as a result of "subclinical pathological inflammation."[8] Therefore, we hypothesized that CME after DMEK may also be associated with postoperative inflammation.

In the present study, to test this hypothesis, we investigated the risk factors for the development of CME after DMEK in Asian eyes, as well as the onset probability of this sight-threatening condition.

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MATERIALS AND METHODS

Study Design

This retrospective multi-center study was approved by the Institutional Review Board at Jichi Medical University and adhered to the tenets of the Declaration of Helsinki (JICHI18–110). The study procedures followed all institutional guidelines, and all patients provided informed consent before the procedures were performed.

Patients

This retrospective multi-center study included 77 eyes of 65 patients with corneal endothelial dysfunction at Yokohama Minami Kyosai Hospital, Kanazawa University, and Heart Life Hospital in Japan, between 2015 and 2017. All patients underwent DMEK; 53 eyes underwent staged DMEK [phacoemulsification and intraocular lens (IOL) implantation surgery was performed 1 month before DMEK], and 24 eyes underwent simple DMEK (phacoemulsification and IOL implantation surgery was performed more than 6 months before DMEK) for pseudophakic eyes. All patients exhibited corneal edema, regardless of cataract surgeries. Because CME most often occurs within 6 months after cataract surgery, the cutoff point was set at 6 months postoperatively.[4,9] The inclusion criteria were the same as those used for DMEK and a follow-up period >6 months. Exclusion criteria were previous corneal surgery or a history of previous CME. All patients were of Asian descent (Japanese).

Surgical Techniques and Postoperative Treatment

In the staged group, patients were administered 1.5% levofloxacin (Cravit; Santen, Osaka, Japan) and betamethasone (Sanbetason; Santen) 4 times daily and bromfenac (Bronuck; Senju Pharmaceutical Co, Osaka, Japan) 2 times daily between cataract surgery and the DMEK procedure.

Standardized DMEK was performed as previously reported.[10,11] After surgery, 0.4 mg of betamethasone (Rinderon; Shionogi, Osaka, Japan) was injected subconjunctivally and 1.5% levofloxacin eye drops (Cravit; Santen) were instilled. Two hours after completing surgery, slit-lamp examination was conducted and intraocular pressure was checked. All patients were instructed to remain supine for several days until the air in the anterior chamber (AC) had disappeared. Postoperative medications included 1.5% levofloxacin (Cravit; Santen) and betamethasone (Sanbetason; Santen) 4 times daily for 3 months and tapered thereafter. Topical tropicamide was not included in the postoperative regimen.

When CME was diagnosed postoperatively, topical bromfenac (Bronuck; Senju Pharmaceutical Co) and a sub-Tenon injection of triamcinolone acetonide (MaQaid; Wakamoto Pharmaceutical Co, Tokyo, Japan) were immediately applied and administered, respectively. After cataract surgery, postoperative medications included topical bromfenac as well as 1.5% levofloxacin and betamethasone.

Ophthalmic Examinations

All patients attended follow-up visits as per standard protocols. The evaluated parameters included the postoperative (1, 3, and 6 months after surgery) best-corrected visual acuity [BCVA; logarithm of the minimum angle of resolution (logMAR)], central corneal thickness (CCT), corneal endothelial cell density (ECD), and central retinal thickness (CRT), as well as the air volume in the AC and axial length (AXL) on postoperative day 1.

In addition, iris damage scores, age, sex, preoperative visual acuity (Pre-VA), rebubbling, a history of diabetes, and the ECD loss rates at 6 months after surgery, were recorded. The presence or absence of CME was examined at 1 and 3 weeks after cataract surgery by SD-OCT. BCVA was measured as decimal VA and converted to logMAR units for statistical analysis.

The iris damage score was defined as an area of iris damage and classified by means of 5 grades, as previously reported.[12,13] Briefly, grade 0 involved no damage, grade 1 involved iris damage limited to a single quadrant. Grades 2, 3, and 4, involved notable damage in 2, 3, and 4 quadrants. The iris damage score was evaluated before and after DMEK.

CRT was measured by OCT (OCT, RS3000; Nidek, Hiroishi, Japan) and evaluated by a retinal specialist (H.T.). CCT was measured using corneal tomography (SS1000; Tomey Corporation, Aichi, Japan). ECD was evaluated with a specular microscope (FA3509; Konan Medical Hyogo, Japan). AXL was measured using optical biometry (IOL Master 500; Carl Zeiss Meditec, Oberkochen, Germany). CRT was measured manually during OCT, between the inner membrane and Bruch membrane, using an OCT measurement function (RS3000, Nidek).

Statistics

Statistical analysis was performed using JMP Pro software version 13.2.0 (SAS Institute, Cary, NC).

The incidence of CME was compared between staged DMEK and simple DMEK cases by Pearson χ^2 test. Ordinal multivariable logistic regression analysis was used to estimate the effect of potential CME risk factors (BCVA, CCT, ECD, CRT, air volume in the AC, AXL on postoperative day 1, the difference of iris damage scores between before and after DMEK, age, sex, Pre-VA, rebubbling, history of diabetes, and ECD loss rates at 6 months postoperatively). Associations between preexisting characteristics and CRT (μm) were examined using the regression line and multivariable regression analysis after stepwise variable selection (using the minimum Bayesian information criterion and increasing the number of variables). Stepwise variable selection and multivariate analysis were performed using CME and CRT (μm) at 1 month after DMEK, sex, age, AXL (mm), Pre-VA, postoperative air in AC, rebubbling, history of diabetes, ECD loss rates at 6 months after DMEK, simple or staged DMEK, iris damage scores before DMEK, iris damage scores after DMEK, and differences in iris damage scores between before and after DMEK as explanatory variables.

Statistical significance was defined as $P < 0.05$.

RESULTS

Characteristics of the Patients

Table 1 summarizes the characteristics of patients who underwent DMEK in the current study. The mean age of the

TABLE 1. Characteristics of Patients Who Underwent DMEK

	CME	n-CME	All Eyes	*P*
N	12	65	77	
Age	70.6	72.8	72.4	0.40
Sex				
Male (eyes)	6	20	26 (34%)	0.20
Female (eyes)	6	45	51 (66%)	
Preoperative BCVA (LogMAR)	0.76	0.82	0.81	0.68
Postoperative BCVA (LogMAR)	0.12	0.072	0.08	0.28
AXL (mm)	23.4	23	23.0	0.40
AC depth (mm)*	2.98	2.91	2.93	0.75
Rebubbling				
+	4	9	13 (17%)	0.098
−	8	56	64 (83%)	
Etiology				
FECD	4	21	25 (32%)	0.72
	16%			
ALI	3	25	28 (36%)	
	11%			
PBK	1	8	9 (12%)	
	11%			
PEX	2	6	8 (10%)	
	25%			
Others	2	5	7 (9%)	
	29%			
CRT (μm)	542	245	291	<0.001
Iris damage due to DMEK	0.92	0.32	0.42	<0.001
ECD loss rate	41.0%	45.0%	44.6%	0.37
DMEK				
Staged	6	47	53 (68%)	0.13
Simple	6	18	24 (32%)	

"Others" includes failed penetrating keratoplasty (2 eyes), posterior polymorphous dystrophy (1 eye), corneal endotheliitis (2 eyes), iridocorneal endothelial syndrome (1 eye), and unknown (1 eye).

Staged DMEK, phacoemulsification, and IOL implantation surgeries were performed 1 month before DMEK. Simple DMEK, DMEK for pseudophakic eyes.

Iris damage score due to DMEK was "iris damage score before DMEK" minus "iris damage score after DMEK."

*There were some missing data; these data were from 6 eyes with CME and 36 eyes without CME.

ALI, bullous keratopathy by argon laser iridotomy; n-CME, non-CME occurrence; PBK, pseudophakic bullous keratopathy; PEX, pseudoexfoliation corneal endotheliopathy.

patients was 72.4 years (range, 48–85 years); 22 of 65 cases (30.1%) were male. Mean AXL was 23.0 ± 1.61 mm. BCVA improved significantly from 0.81 ± 0.53 logMAR preoperatively to 0.080 ± 0.15 logMAR at 6 months postoperatively ($P < 0.001$). Postoperative corneal ECD was 1493 ± 492 cells/mm^2 at 6 months (ECD loss rates at 6 months: 44.6% ± 17.1%). No eyes showed signs of pupillary block, microbial infection, or endothelial rejection. Partial detachment of the graft, requiring rebubbling into the AC, was observed in 13 eyes within 7 days after surgery, and the graft showed complete attachment immediately after rebubbling in all eyes. There was no primary graft failure. Mean postoperative air volume in the AC was 75.8% (range: 40%–100%).

The reasons for surgery were FECD (25 eyes, 32%), bullous keratopathy from argon laser iridotomy (28 eyes, 36%), pseudophakic bullous keratopathy (9 eyes, 12%), pseudoexfoliation syndrome (8 eyes, 10%), and others (including failed penetrating keratoplasty, 2 eyes; posterior polymorphous dystrophy, 1 eye; corneal endotheliitis, 2 eyes; iridocorneal endothelial syndrome, 1 eye; unknown, 1 eye). All data are shown in Supplemental Digital Content 1 (see data set, http://links.lww.com/ICO/A776).

CME

Twelve eyes showed CME (incidence: 15.6%). All CME appeared within 1 month. Subjects in the simple DMEK group had a CME incidence of 25% (6 of 24 eyes), whereas those in the staged DMEK group had an incidence of 11.3% (6 of 53 eyes) ($P = 0.13$). The median CRT in the CME group was 542.40 ± 23.1 μm, and in the non-CME group, it was 244.7 ± 9.90 μm ($P < 0.001$). In the staged DMEK group, none of the eyes exhibited CME during the period between cataract surgery and DMEK. As a first-line medical therapy, sub-Tenon injections of triamcinolone acetonide were administered and comprised sufficient treatment of CME. None of the subjects had CME recurrence. A representative case with CME is shown in Figure 1.

Table 1 also shows the patient profiles of 2 groups and the CME occurrence rates by etiology. There was no

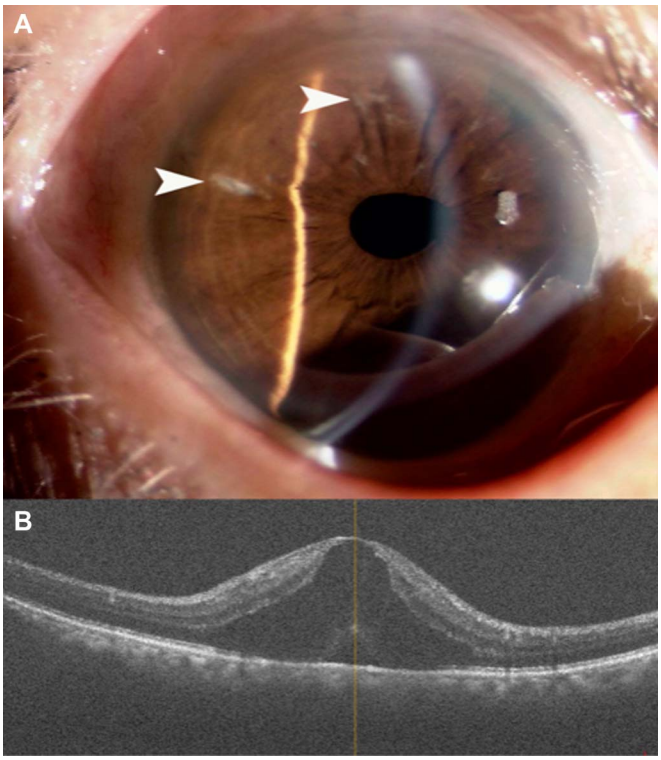

FIGURE 1. A representative case of cystoid macula edema after DMEK. A, In this representative case, mild iris damage is limited to 2 quadrants. The arrows indicate iris damage; in this case, the iris damage score was 2. B, One-month follow-up visit: CME was observed and administration of a NSAID was added to the routine postoperative treatment. By the following month, the CME had been cured.

correlation between the etiology and the occurrence of CME ($P = 0.72$). The iris damage scores before and after DMEK, as well as the differences between these scores, are shown in Supplemental Table 1 (see Supplemental Digital Content 2, http://links.lww.com/ICO/A777).

Table 2 shows the factors associated with the occurrence of CME. Multivariable analysis revealed that the differences in iris damage scores between before and after DMEK [$P < 0.001$, odds ratio (OR) = 16], air volume in the AC ($P = 0.012$, OR = 2.3×10^{-4}), simple DMEK [$P = 0.020$, OR = 14, CME+; 6 eyes (25%), CME−; 18 eyes (75%)], and rebubbling [$P = 0.036$, OR = 18, CME+; 4 eyes (31%), CME−; 9 eyes (69%)] were significantly associated with the occurrence of CME. Although the difference in iris damage scores between before and after DMEK was neither associated with rebubbling ($P = 0.72$) nor with simple DMEK ($P = 0.16$), it was weakly associated with air in the AC ($P = 0.041$). Moreover, stepwise variable selection demonstrated that the difference in iris damage score between before and after DMEK ($P < 0.001$) was the most important risk factor for the occurrence of CME. Multiple linear regression analysis and stepwise selection also showed that the difference in iris damage score between before and after DMEK (multiple linear regression: $P < 0.001$; stepwise variable selection: $P < 0.001$) was significantly associated with greater CRT.

TABLE 2. Factors Associated With CME After DMEK by Multivariable Analysis

Clinical Factors	OR	95% CI	*P*
Age	0.97	0.85–1.1	0.62
AXL	1.4	0.74–2.8	0.27
Air in the AC	2.3×10^{-4}	1.5×10^{-7}–0.34	0.012
Preoperative BCVA (LogMAR)	0.39	0.051–3.0	0.34
Iris damage due to DMEK	16	2.4–110	<0.001
Loss rates of ECD	0.30	1.9×10^{-3}–44	0.63
Male			
Yes	3.1	0.35–27	0.29
Simple DMEK			
Yes	14	1.0–200	0.020
Rebubbling			
Yes	18	0.91–360	0.036
History of diabetes			
Yes	0.35	0.031–3.8	0.38

Iris damage score due to DMEK was "iris damage score after DMEK" minus "iris damage score before DMEK."

CI, confidence interval; Simple DMEK, DMEK for pseudophakic eyes.

DISCUSSION

The current study found that the incidence of CME after DMEK in Asian eyes was 15.6%. Multivariable analysis demonstrated that the incidence of CME correlated with the difference in iris damage between before and after DMEK, air in the AC, simple DMEK, and rebubbling. Although air in the AC was identified as a contributing factor, we suspected that it may have been a confounding factor, and thus performed stepwise variable selection. Regardless of confounding factors, stepwise variable selection showed that the difference in iris damage scores between before and after DMEK alone was the primary risk and aggravation factor for CME development.

The incidence of CME reported here was higher than that previously reported in Caucasian eyes (7%–13.8%).[4–7] The increase in CME incidence might be attributed to the difference in etiology. As we previously reported,[8] bullous keratopathy from argon laser iridotomy, pseudoexfoliation syndrome, or pseudophakic bullous keratopathy are leading etiologies of DMEK in Japan, whereas the proportion of FECD is relatively lower than that in Western countries. Indeed, Kitazawa et al[14] reported a strong association between CME and primary angle-closure glaucoma patients after Descemet stripping automated endothelial keratoplasty; they attributed this association to the presence of iris damage in those patients. Furthermore, Yamaguchi et al[15] showed elevated cytokine levels in Japanese patients with bullous keratopathy. Taken together, higher inflammation levels in Japanese patients with bullous keratopathy might explain the high incidence of CME after DMEK, compared with patients in Western countries where the primary etiology is FECD.

In this study, we found that iris damage due to DMEK was the primary risk and aggravating factor for CME; moreover, air in the AC, rebubbling, and simple DMEK were risk factors for CME. Rebubbling, as a source of mechanical stress to the eye, might trigger inflammation; this might then increase the risk of CME development. Hoerster

et al previously predicted the inflammatory nature of CME that develops after DMEK.[16,17] Although evidence regarding the role of inhibiting postoperative inflammatory response after DMEK is scarce, Hoerster et al[5] provided good evidence of the effect of regulating postoperative CME after DMEK. They compared 2 groups of 75 eyes each, who received prednisolone acetate eye drops 1% 5 times daily or hourly for the first week after triple-DMEK. Surprisingly, none of the patients in the hourly steroid group developed CME, but 9% of those receiving topical steroid therapy 5 times per day developed subsequent CME.

Another important finding of the current study incidentally revealed a strategy for preventing postoperative CME. We found that simple DMEK, rather than staged DMEK, was correlated with a higher incidence of CME. Patients in the staged DMEK group were administered nonsteroidal antiinflammatory drugs (NSAIDs) before the DMEK procedure. The use of NSAIDs might inhibit cyclooxygenase enzyme, and thereby the synthesis of all downstream proinflammatory prostaglandins.[18,19] A 2014 meta-analysis on cataract surgery reported that topical NSAIDs might be more effective than topical corticosteroids in preventing CME and advocated their use after routine surgery.[20] The application of NSAIDs might thus have inhibited the inflammation that aggravates CME when CME developed in our study. Our results are also consistent with a previous report from Japan about the impact of NSAIDs after Descemet stripping automated endothelial keratoplasty.[21]

The strength of the study is the disclosure of the risk factors for CME development after DMEK in Asian eyes. Multivariate analysis and stepwise variable analysis showed that the difference in iris damage scores between before and after DMEK alone was significantly associated with CME development after DMEK. We used a strict, routine OCT-based checkup, including CRT measurement and checking on CME, and our sample size of 77 eyes was the largest and first Asian DMEK case series on CME thus far.

Our study had some limitations, that is, the retrospective design and the lack of evaluation of the cytokine profile in the aqueous humor. The retrospective design could not eliminate eyes that had received NSAIDs from the staged DMEK group. Strict protocols, including fluorescein angiography, might be useful for excluding other retinal diseases that could cause CME.

In conclusion, the current study of 77 eyes identified a post-DMEK CME incidence of 15.8%, and iris damage was identified as the main risk factor for CME development. Surgeons should attempt to cause as little damage to the iris as possible. In addition, early application of antiinflammatory drugs could facilitate good outcomes after surgery. Furthermore, we recommend that SD-OCT be used frequently in the first 6 months after DMEK as a check-up. With an appropriate treatment regimen, such as topical application of NSAIDs, CME should not have a negative impact on the final DMEK visual outcomes.

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