• Clinical Research •

Corneal epithelial defects following vitreoretinal surgery: incidence and outcomes from the DISCOVER study

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Received: 2021-01-12 Accepted: 2021-08-12

Abstract

● **AIM:** To investigate the incidence, risk factors, clinical course, and outcomes of corneal epithelial defects (CED) following vitreoretinal surgery in a prospective study setting.

● **METHODS:** This was a post-hoc analysis of all participants in DISCOVER intraoperative optical coherence tomography study. Subjects with CED 1d after surgery without intraoperative corneal debridement was defined as the postoperative CED group. Subjects who underwent intraoperative debridement were defined as intraoperative debridement group. Eyes were matched 2:1 with controls (eyes without postoperative CED) for comparative assessment. The primary outcomes were the incidence of CED on postoperative day one and the incidence of required intraoperative debridement. Secondary outcomes included time to defect closure, delayed healing (>2wk), visual acuity (VA) and presence of scarring at one year and cornea consult.

● **RESULTS:** This study included 856 eyes that underwent vitreoretinal surgery. Intraoperative corneal debridement was performed to 61 (7.1%) subjects and postoperative CED developed spontaneously in 94 (11.0%) subjects. Significant factors associated with postoperative CED included prolonged surgical duration (P=0.003), diabetes mellitus (P=0.04), postoperative ocular hypotension (P<0.001). Prolonged surgical duration was associated with intraoperative debridement. Delayed defect closure time (>2wk) was associated with corneal scar formation at the end of the 1y in all epithelial defect subjects (P<0.001). The overall rate of corneal scarring for all eyes undergoing vitrectomy was 1.8%.

● **CONCLUSION:** Prolonged duration of surgery is the strongest factor associated with both intraoperative debridement and spontaneous postoperative CED. Delayed defect closure is associated with a greater risk of corneal scarring at one year. The overall rate of corneal scarring following vitrectomy is low at <2%.

● **KEYWORDS:** corneal epithelial defect; vitreoretinal surgery; intraoperative optical coherence tomography

DOI:10.18240/ijo.2022.01.13

Citation: Sarici K, Petkovsek D, Martin A, Yuan A, Goshe JM, Srivastava SK, Reese JL, Ehlers JP. Corneal epithelial defects following vitreoretinal surgery: incidence and outcomes from the DISCOVER study. *Int J Ophthalmol* 2022;15(1):83-88

INTRODUCTION

Corneal epithelial defects (CED) following vitreoretinal surgery may result spontaneously or from intraoperative debridement due to the lack of corneal clarity that impairs fundus visibility during the operation. CED may increase discomfort postoperatively, impair visualization of the posterior segment, increase frequency/number of postoperative visits, and potentially result in corneal scarring. Although most post-surgical CEDs heal quickly without sequelae, these patients require close follow-up and treatments. There have been limited studies on the preoperative and intraoperative risk factors of postoperative CEDs or intraoperative debridement to avoid late period complications.

Various risk factors have been associated with postoperative CEDs, including: diabetes mellitus (DM), par plana vitrectomy (PPV) combined with lensectomy, tamponade usage, prolonged surgical duration, and postoperative ocular hypertension (HTN)[1-3]. In addition to its association with spontaneous postoperative CEDs, prolonged surgical duration has been linked to the need for intraoperative corneal debridement[4]. DM, HTN, tamponade usage are factors associated with delayed closure[1,5]. Epithelial defects with delayed healing are at risk for corneal scarring, neovascularization, infectious keratitis, corneal melting, and perforation.

The main goal of this study to investigate the incidence and risk factors associated with intraoperative debridement and postoperative CEDs following PPV. This study is unique given its large sample size and long-term follow-up (*i.e.*, 1y). Previous studies evaluated the postoperative cases by excluding subjects who underwent intraoperative epithelial debridement[6-7]. In this study, we evaluated subjects with either intraoperative debridement or postoperative CEDs in terms of late-stage corneal complications.

SUBJECTS AND METHODS

Ethical Approval The Institutional Review Board approved the study adhered ethical principles of the Helsinki Declaration and written informed consent was given by all subjects.

The primary inclusion criterion of this study is all subjects in the DISCOVER study database who underwent vitreoretinal surgery. The DISCOVER (Determination of Feasibility of Intraoperative Spectral Domain Microscope Combined/ Integrated OCT Visualization during En Face Retinal and Ophthalmic Surgery) study is a prospective, ophthalmic surgery study evaluating the role of intraoperative OCT in ophthalmic surgery. The methods of the DISCOVER study have been previously described[8-9].

All the subjects underwent small gauge PPV for various diagnoses by surgeons at the Cole Eye Institute, Cleveland Clinic, Ohio, USA. In select cases, phacoemulsification and intraocular lens implantation were performed simultaneously. Corneal debridement was performed when corneal epithelial edema significantly decreased fundus visualization quality or pre-existing corneal pathology (*e.g.*, irregular epithelium) prevented required posterior pole visualization. In some subjects who underwent corneal debridement, a bandage contact lens was placed intraoperatively, according to the surgeon's preference and/or an occlusive pressure patch was applied at the conclusion of surgery. Combined surgery, duration of surgery, gauge of surgery, and tamponade type were all recorded.

As part of the prospective data collection within the DISCOVER study, CED presence, intraocular pressure (IOP) and visual acuity (VA) were collected on postoperative day 1. Subjects who underwent intraoperative debridement were defined as the intraoperative debridement group. Subjects who presented with a spontaneous epithelial defect on postoperative day one (*i.e.*, without intraoperative corneal debridement) were defined as the postoperative CED group. Eyes with IOP >21 mm Hg or <7 mm Hg within 1wk postoperatively were defined having ocular hypertension or ocular hypotension, respectively. Eyes requiring greater than 2wk to achieve corneal epithelial closure were defined as having delayed epithelial healing. All CED subjects received an ophthalmic ointment in addition to their postoperative topical treatments (topical antibiotic and steroid).

The clinical charts of all patients for both the intraoperative debridement and postoperative CED groups were reviewed retrospectively. In addition, control eyes were matched 2:1 by age/gender from those eyes not requiring without postoperative CED within the DISCOVER study for comparative assessment. Subjects with a follow-up period of less than 6mo were excluded from the study. Preoperative demographic features, systemic and ophthalmic clinical histories, ocular co-morbidities, previous surgical or non-surgical treatments, VA, IOP, anterior and posterior segment slit lamp biomicroscopic findings were recorded.

The primary outcome was the presence of postoperative CED on postoperative day one and the incidence of required intraoperative debridement. Secondary outcomes included: total time to resolution of epithelial defect, frequency of delayed epithelial healing (>2wk), frequency of patients requiring consultation with a cornea specialist, presence of new (*i.e.*, postoperative) corneal scarring at one year. Based on slit-lamp biomicroscopy examination, corneal opacification or corneal irregularities that caused by marked treatment resistant corneal edema at the end of 1y was defined as corneal scar. Assessment of the visual significance of the corneal scar was unable to be assessed given the retrospective nature of the review and complexities of the underlying retinal disease.

Statistical Analysis All data was analyzed with SPSS version 18. Continuous variables are expressed as mean±standard deviation for demographic data. The Mann-Whitney *U* test and Student's *t*-test were used to compare nonparametric and parametric values, respectively, between the two groups. The Chi-squared test with Fisher's exact test was used for categorical data analyses. The percentage of patients with CED at the different time points were represented using a Kaplan-Meier curve. Regression analysis was used to identify predictive risk factors of CED and for primary and secondary outcomes. Statistical significance was defined as a P value <0.05.

RESULTS

This study included 856 eyes undergoing vitrectomy surgery. Intraoperative corneal debridement was required in 61 (7.1%) subjects and spontaneous postoperative CED developed in 94 (11.0%) subjects. Of the 574 subjects without postoperative CED, 188 were selected as control group with matching the age (±3y) and gender in a 2:1 ratio. The demographic and clinical characteristics of the subjects are indicated in Table 1.

In the postoperative CED group, the length of the surgery time (P<0.01), ocular hypotension (P<0.01), and DM (P=0.04) were found as associated risk factors (Table 2). The mean surgical times in the intraoperative debridement and postoperative CED group were 130±58 and 100±67min, respectively; while in the control group it was 88±38min (P=0.003). Operation

Table 1 Demographic and clinical data summary *n* (%)

Parameters	Eyes with spontaneous postop. CED	Eyes requiring intraoperative corneal debridement	Matched control eyes without postop. CED
No.	94	61	188
Age (mean±SD), y	60.7±16.5	55.4±17.7	60.4±17.8
Gender			
Male	48 (51.1)	24 (39.3)	96 (51)
Female	46 (48.9)	37 (60.6)	92 (48.9)
Diabetes mellitus	26 (27.6)	12 (19.7)	17 (9.0)
Lens status			
Pseudophakic	41 (43.6)	25 (40.9)	98 (52.1)
Phakic	49 (52.1)	29 (47.5)	84 (44.7)
Aphakic	4 (4.3)	6 (9.8)	6 (3.2)
Dry eye syndrome	11 (11.7)	7 (11.5)	24 (12.8)
Uveitis	14 (14.9)	15 (24.6)	24 (12.8)
Glaucoma	22 (23.4)	10 (16.4)	53 (28.2)
HSV keratitis	1 (1.1)		
Preop. glaucoma surgery	8 (8.5)	2 (3.3)	20 (10.6)
Other cornea (LASIK, dystrophy, trauma, transplant)	5 (5.3)	11 (18.0)	25 (13.3)
Duration of follow-up (mean±SD), mo	11.4±3.0	10.6±2.7	11.0±3.2

LASIK: Laser-assisted *in situ* keratomileusis.

Table 2 Factors associated with postoperative corneal epithelial defect *n* (%)

Parameters	Eyes with spontaneous postop. CED	Matched control eyes without postop. CED	*P*	Odd ratio
No.	94	188		
Age (mean±SD), y	60.7±16.5	60.3±17.8	0.70	-
Gender (M/F)	48/46	96/92	0.55	-
Diabetes mellitus	26 (27.6)	17 (9.0)	0.04	2.01
Dry eye syndrome	11 (11.7)	24 (12.8)	1.00	-
Uveitis	14 (14.9)	24 (12.8)	0.80	-
Glaucoma	22 (23.4)	53 (28.2)	0.50	-
Prior glaucoma surgery	8 (8.5)	20 (10.6)	0.77	-
Other corneal pathology (LASIK, dystrophy, trauma, transplant)	18 (19.1)	25 (13.3)	0.90	-
Gauge of surgery				
23	45 (47.9)	89 (47.3)	0.81	-
25	47 (50.0)	95 (50.5)	0.93	-
Tamponade				
SF_6	25 (26.6)	33 (17.6)	0.60	-
C_3F_8	16 (17.0)	38 (20.2)	0.50	-
Air	21 (22.3)	47 (25.0)	0.61	-
Silicone	11 (11.7)	29 (15.4)	0.79	-
Combined phacoemulsification surgery	33 (35.1)	50 (26.6)	0.13	-
Duration of surgery (min)	100±67	88±38	0.003	1.01
Postop. ocular hypotension (IOP<7 mm Hg)	25 (26.6)	39 (20.7)	<0.001	2.72

LASIK: Laser-assisted *in situ* keratomileusis.

length was significantly greater in the intraoperative CED group compared to the postoperative CED group (*P*=0.01). There was no statistically significant association with gauge of surgery (*P*=0.98), combined phacoemulsification surgery (*P*=0.13), tamponade usage (*P*=0.37), prior glaucoma surgery (*P*=0.50) and other corneal features (laser-assisted *in situ* keratomileusis, dystrophy, trauma, transplant; *P*=0.90). The median time of documentation of resolution epithelial defects in the postoperative CED group and the intraoperative debridement group was 1wk (range: 1-24wk; Figure 1). It is important to note that the 1wk visit was usually the first returning postoperative visit after the postoperative day 1 visit

Table 3 Results and comparision of postop. CED group and intraoperative corneal debredment group *n* (%)

Parameters	Eyes with spontaneous postop. CED	Eyes requiring intraoperative corneal debridement	*P*
No.	94	61	
Duration of surgery (min)	100±67	130±58	0.01
Delayed epithelial healing (>2wk)	25 (26.6)	11 (18.0)	0.07
Cornea consult 2	16 (17.0)	14 (23.0)	0.36

Table 4 Predictive factors for corneal scarring at 1y *n* (%)

Parameters	CED with scarring	CED without scarring	*P*	Odd ratio
No.	16 (10.3)	139 (89.6)		
Defect closure time (wk)	5.13±7.8	2.07±2.3	0.00006	0.729/wk
Prior glaucoma surgery	3 (18.7)	7 (5.0)	0.04211	11.059

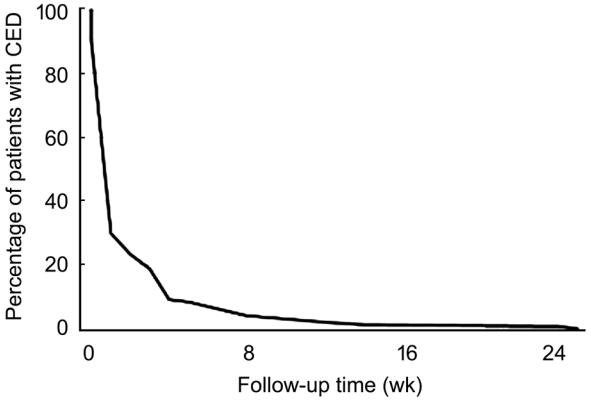

Figure 1 Kaplan-Meier curve of presence of corneal epithelial defects.

and may overestimate time to closure since these eyes were not typically followed daily. Comparative assessment between the intraoperative debridement group and postoperative CED's group was performed in regard to surgical time, delayed epithelial healing, requirement cornea specialist consult (Table 3).

Cornea specialist consultation was requested in 16 (17.0%) subjects in the postoperative CED group and in 14 (23.0%) subjects in intraoperative debridement group. No occurrences of infectious ulceration, corneal melting or perforation were observed in either group. Postoperative herpes simplex virus (HSV) epithelial keratitis developed in one subject with a history of preoperative HSV keratitis. This subject had epithelial keratitis resistant to topical and systemic antiviral therapy resulted in the development of corneal scar.

Delayed epithelial healing occurred in 25 eyes (26.6%) in the postoperative CED group (mean 6.8wk) and in 11 eyes (18.0%) of the intraoperative debridement group (mean 6.3wk). When the risk factors for delayed healing were analyzed in 155 subjects with all epithelial defect subjects, tamponade usage was found to be statistically significant and postoperative hypotony trended towards significance (P=0.02 and P=0.05, respectively). DM, duration of surgery, and ocular hypertension were not found to be predictive risk factors for delayed epithelial healing.

Corneal scarring developed in 16 (10.3%) of 155 subjects with epithelial defects and 1.8% overall. In eyes that developed corneal scarring, epithelial defect resolution time was a mean of 5±8wk, while eyes that did not develop corneal scarring had defect resolution in 2±2wk. There was a statistically significant relationship between corneal scar development and defect closure time (P=0.00006, odd ratio=0.729/wk), as well as prior glaucoma surgery (P=0.042, odd ratio=11.1; Table 4).

DISCUSSION

Corneal complications may be encountered by surgeons following vitreoretinal surgery. The incidence of post vitrectomy CEDs ranges from 6.1% to 28.1% in the literature[6-7,10-11]. In our study, postoperative epithelial defects developed in 94 of 795 (11.8%) subjects who underwent vitrectomy. Prolonged duration of surgery, HTN and hypotension, and DM were found to be risk factors for postoperative CED formation. In previous studies, prolonged duration of surgery is associated with increased postoperative CED formation and intraoperative debridement rate[4,7,12]. In our study, while the duration of surgery was significantly higher in both groups compared to the group without CEDs, the operation length in the intraoperative debridement group (130±58min) was significantly higher than the postoperative CED group (100±67min) likely contributing in these cases to the need for intraoperative intervention due to loss of visualization. Chen *et al*[6] did not identify surgery duration as a factor for persistent corneal epithelial defect formation in their study. While Hiraoka *et al*[12] created a risk scale predictive of postoperative CEDs that included surgical time, intraoperative lensectomy, tamponade.

Intraocular pressure changes are common issues following vitrectomy. In studies conducted in the literature on the formation of post vitrectomy CED, ocular hypertension has been predominantly evaluated with minimal attention to hypotony. Chiang *et al*[7] found that ocular hypertension was not associated with post vitrectomy CED's, while Chen *et al*[6] found it to be a contributing factor. In our study, we demonstrated that postoperative ocular hypotension was found

to be associated with the development of post vitrectomy CEDs. Ocular hypotony can disrupt intraocular fluid dynamics, causing endothelial dysfunction and consequently corneal epithelial complications[13-14].

We demonstrated that, like other studies in the literature, the presence of DM is associated in the formation of postoperative CEDs[4,7,10,12,15-16]. DM causes structural changes and functional impairment in corneal epithelium, stroma and endothelium[17-20]. There are studies showing that DM contributes to delays in healing of corneal epithelial defect[6,12,17,21]. Interestingly, we did not find a relationship between DM and delayed epithelial healing and corneal scar at the end of the first year. However, this may be related to a high prevalence of DM in less complex cases and the pathology complexity (a possible surrogate for tamponade requirement) may be a more a significant factor.

While the tamponade usage was not associated with the incidence of postoperative CED, we found that the use of tamponade among all epithelial defects was associated delayed epithelial healing. Previous studies have demonstrated that tamponade use is associated in CED development and delayed corneal recovery. Both gas tamponade and silicone tamponade have been linked to endothelial cell loss and CED[1,6-7,22-24]. In the literature, there is no consensus on the impact of specific tamponade type. We did not find a statistically significant difference in the sub-analysis of tamponade type in cases with delayed epithelial healing.

Published reports have identified the intraoperative debridement rates during vitrectomy to be between 8% and 24%[4,19,25-26]. In our study, the intraoperative debridement rate was 7.1%. The operation time in the intraoperative debridement group was longer than the postoperative CED group. This result is consistent with the study in which Virata *et al*[4] stated that the duration of surgery was higher in subjects undergoing intraoperative debridement. Interestingly, extended exposure to microscope light may result in long-term dysfunction in the corneal epithelium and corneal film layer[27-28]. Finally, the potential high complexity of these cases and overall disease burden in these eyes may be a major factor for poorer prognosis, including long-term hypotony, severe ocular ischemia, and long-term tamponade requirements.

There are important limitations in this study that should be recognized. Defect diagnosis and closure times can only be determined based on the frequency of clinical visits. The study may not be adequately powered to detect true differences in the risk factors for postoperative CED compared to intraoperative debridement. A binary distinction for DM may not provide maximum differentiation for defining risk, such as HbA1c or duration of DM. Variable thresholds for epithelial debridement by different surgeons creates unique challenges for standardized risk assessment. It is also difficult to estimate the clinical significance of corneal scarring given the underlying retinal disease and retrospective nature of the chart review. The retrospective assessment limits characterization by objective parameters such as depth, degree of opacity, or topographic irregularity

This study demonstrated that longer duration of surgery is the most strongly associated factor with development of spontaneous CED and intraoperative corneal debridement. Further research is needed to better identify the critical factors involved in reducing risk of corneal scar formation and delayed healing. Using the results from this study, a potential future prospective trial could be considered in high-risk individuals for earlier more aggressive corneal intervention, including topical therapeutics, corneal specialist consultation and possible use of other healing-promoting modalities (*e.g.*, amniotic membrane, bandage contact lens).

ACKNOWLEDGEMENTS

Foundation: Supported by National Institutes of Health/ National Eye Institute, Bethesda, Maryland, USA (K23-EY022947-01A1).

Conflicts of Interest: Sarici K, None; **Petkovsek D,** None; **Martin A,** None; **Yuan A,** None; **Goshe JM,** served a speaker for Zeiss and Dompe; **Srivastava SK,** a consultant for Bausch and Lomb, Novartis, Carl Zeiss Meditec; a researcher for Allergan and Bausch and Lomb; and has a patent licensed to Leica; **Reese JL,** None; **Ehlers JP,** a consultant for Alcon, Allergan, Leica, Santen, Thrombogenics, Genentech, Novartis, Aerpio, Allegro, Regeneron, Roche, Stealth, Adverum and Zeiss; has intellectual property licensed to Leica; and receives research support from Alcon, Adverum, Genentech, Regeneron, Boehringer-Ingelheim, Novartis, Aerpio, and Thrombogenics.

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