• Clinical Research •

Changes of diabetic macular edema post vitrectomy in patients with proliferative diabetic retinopathy

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Abstract

● **AIM:** To investigate the change of diabetic macular edema (DME) post vitrectomy and its risk factors.

● **METHODS:** This retrospective study included 365 eyes of 330 patients who underwent vitrectomy for proliferative diabetic retinopathy (PDR) with gradable optical coherence tomography (OCT) imaging from January 2018 to March 2022. The incidence of post vitrectomy DME (PV-DME) was defined as patients with a central retinal thickness (CRT) >300 μm by OCT among patients without preoperative DME.

● **RESULTS:** The cumulative incidence of PV-DME at 3mo was 40.1% (89/222), with its majority subtype of single diffused retinal thickening (66.2%) followed by single cystoid macular edema (27.0%). Multivariate Cox regression analysis indicated that a thicker preoperative CRT [hazard ratio (HR)=1.01, 95% confidence interval (CI) 1.00-1.02] and intraoperative internal limiting membrane peeling (HR=3.18, 95%CI 1.85-5.47) were associated with the presence of PV-DME, while intraoperative intravitreal injection of triamcinolone acetonide (HR=0.28, 95%CI 0.13-0.57) was protective against PV-DME. In eyes with preoperative DME (n=143), the CRT decreased gradually from 468.3±177.7 μm preoperatively to 409.5±151.0 μm (P=0.027), 377.4±141.9 μm (P<0.001), and 368.0±157.6 μm (P<0.001) at 7d, 1 and 3mo postoperatively, respectively. Multivariate linear regression analysis indicated that only a thicker preoperative CRT (β=0.77, 95%CI 0.63-0.92) was associated with a decreasing postoperative CRT.

● **CONCLUSION:** PV-DME is a very common postoperative complication in patients with PDR. Triamcinolone acetonide could prevent its formation. Attention should be paid to patients with a thicker preoperative CRT and internal limiting membrane peeling.

● **KEYWORDS:** diabetic macular edema; proliferative diabetic retinopathy; vitrectomy

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INTRODUCTION

Diabetic retinopathy (DR) is a major and specific microvascular complication of diabetic mellitus (DM), which remains a leading cause of vision loss and preventable blindness in working-aged adults[1]. The most common cause of vision loss in patients with DR is proliferative diabetic retinopathy (PDR) and diabetic macular edema (DME), with a high prevalence of 4.3%[2] and 15.4%[3] in a Chinese cohort, respectively. Optimal control of blood glucose, blood pressure, and possibly blood lipids remain the foundation for the reduction of the risk of retinopathy development and progression. Current treatment strategies for DR aim at managing microvascular complications, including intravitreal pharmacologic agents and laser photocoagulation[4]. However, when DR has progressed to PDR, pars plana vitrectomy (PPV) is needed to offer relief from retinal traction, clearing of media opacities, and stabilization of the proliferation process[4-5]. Although advances in modern PPV for PDR have improved visual outcomes, post vitrectomy DME (PV-DME) occurs commonly.

Macular edema (ME) consists of intraretinal or subretinal fluid accumulation in the macular region, a common postoperative complication that can cause severe impairment of central vision[6-7]. A better understanding of PV-DME, particularly its incidence and predisposing risk factors, is necessary to estimate the clinical burden and develop a preventative strategy for this complication. However, there is little information in the current literature regarding PV-DME. Yoshida *et al*[8] showed that the elevated monocyte chemoattractant protein-1 (MCP-1)

and interleukin (IL)-6 levels after PPV may indicate prolonged inflammation, which can cause postoperative DME. A recent study reported that insulin treatment may reduce the risk of postoperative DME[9]. However, PV-DME incidence and onset time were not accessed among these studies. Moreover, because of the preoperative media opacification, preoperative DME was unable to be evaluated.

With respect to the above, the purpose of this study was to investigate the incidence of newly developed PV-DME and the factors affecting its development. We also evaluated the effect of PPV on patients with preoperative DME.

PARTICIPANTS AND METHODS

Ethical Approval This is a retrospective study on patients with PDR who underwent PPV from January 2018 to March 2022 at a tertiary medical center. The research protocol complies with the ethical guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Eye Hospital of Wenzhou Medical University (approval number: 2022-J-117). The informed consent was waived. The patients' clinical information was obtained from archived electronic medical records.

The inclusion criteria were: 1) patients who underwent PPV for PDR from January 2018 to March 2022; 2) a 3-month or longer follow-up after surgery; 3) gradable optical coherence tomography (OCT) imaging before surgery. The exclusion criteria were: 1) silicone oil tamponade; 2) a history of PPV; 3) any intraocular surgery within 3mo prior to and after this PPV; 4) other ocular conditions that may be responsible for the ME, such as uveitis, retinal vein occlusion, and ocular trauma; 5) patients with a serious postoperative complication, such as neovascular glaucoma and retinal artery occlusion; 6) a history of penetrating ocular trauma.

The 23- or 25-gauge PPVs were performed under retrobulbar (50% mixture of 2% lidocaine and 0.75% bupivacaine) or general anesthesia using two different vitrectomy machines (Stellaris PC, Bausch & Lomb, Bridgewater Township, NJ; Constellation Vision System, Alcon Laboratories, USA). The indication for PPV include neovascularization of the retina, vitreous hemorrhage, preretinal hemorrhage, fibrovascular membranes, and tractional retinal detachment. Additional internal limiting membrane (ILM) peeling, epiretinal membrane (ERM) peeling, or other procedures (panretinal photocoagulation, gas injection, combined cataract surgery, intraocular lens implantation, *etc*.) were performed according to the surgeon's experience.

We used spectral-domain OCT (Spectralis SD-OCT; Heidelberg Engineering, Heidelberg, Germany) with a 30° scanning angle (9×9 mm) at the central macula for image acquisition and the analysis protocol. Central retinal thickness (CRT) was measured at the central 1-mm region of the standard Early Treatment Diabetic Retinopathy Study (ETDRS) subfield. The diagnosis of PV-DME was confirmed if the OCT imaging of the macular showed typical findings of retinal thickening (CRT≥300 μm)[10-11] among patients without preoperative DME. There were three OCT patterns of DME, which was diffused retinal thickening (DRT) as a sponge-like retinal swelling of the macula with reduced intraretinal reflectivity, cystoid macular edema (CME) as intraretinal cystoid spaces of low reflectivity and highly reflective septa separating cystoid-like cavities in the macular area, and serous retinal detachment (SRD) as a shallow elevation of the retina and an optically clear space between the neurosensory retina and retinal pigment epithelium[12]. The OCT images of mixed DME patterns, defined as the mixture of two of these OCT patterns, were also included in our study. The presence of ERM, tractional retinal detachment, and posterior hyaloidal traction were also determined.

Statistical Analysis Statistical analysis was performed using SPSS (IBM, Armonk, NY, version 25.0, USA). A Kaplan-Meier survival curve was constructed to show the cumulative incidence of newly developed postoperative DME. Multiple comparisons were performed with repeated measures analysis of variance, followed by Bonferroni multiple comparison test to compare the CRT between pre-operation, 7d, 1 and 3mo after surgery. Univariate analysis of categorical variables was performed by the Chi-square test or Fisher exact test. Independent *t*-test was used to compare the mean values of normally distributed variables. All variables with a $P<0.1$ in univariate Cox regression analysis or variables considered clinically meaningful were entered into multivariate Cox regression analysis to determine the risk factors for PV-DME. All variables with a $P<0.1$ in univariate liner regression analysis or variables considered clinically meaningful were entered into multivariate liner regression analysis to determine the risk factors for the change of CRT from pre-operation to 3mo postoperatively. Statistical significance was determined using a threshold of $P<0.05$.

RESULTS

A total of 365 eyes from 330 patients (male 196, 59.3%) who underwent PPV for PDR were enrolled in this study. The mean age of the patients was 57.3±10.3y. All patients were divided into two groups according to the presence of DME before surgery. Group A (n=222) were the patients without preoperative DME; Group B (n=143) were the patients with preoperative DME.

In Group A, patients with postoperative DME were younger (P=0.02), had a greater preoperative CRT (P<0.001), higher proportion of males (P=0.01), higher proportion of preoperative intravitreal injection of anti-vascular endothelial growth factor (VEGF; P=0.03), higher proportion of

Table 1 Demographic and clinical characteristics of patients with and without preoperative diabetic macular edema *n* (%)

Parameters	Group A: preop. ME(-), *n*=222			Group B: preop. ME(+), *n*=143		
	Postop. ME(-), *n*=133	Postop. ME(+), *n*=89	*P*	Postop. ME(-), *n*=31	Postop. ME(+), *n*=112	*P*
Age (y)	57.1±9.8	54.00±9.1	0.02	61.6±8.6	59.9±11.1	0.45
Male	66 (49.6)	59 (66.3)	0.01	19 (61.3)	65 (58.0)	0.75
Indication for PPV			0.75			0.95
Neovascularization, and/or VH, and/or preretinal hemorrhage	49 (36.8)	30 (33.7)		11 (35.5)	37 (33.0)	
Fibrovascular membranes	50 (37.6)	38 (42.7)		14 (45.2)	51 (45.5)	
TRD	34 (25.6)	21 (23.6)		6 (19.4)	24 (21.4)	
Duration of DM			0.11			0.50
<10y	32 (24.1)	31 (34.8)		7 (22.6)	35 (31.3)	
10–20y	62 (46.6)	41 (46.1)		18 (58.1)	52 (46.4)	
≥20y	39 (29.3)	17 (19.1)		6 (19.4)	25 (22.3)	
Insulin treatment	65 (48.9)	34 (38.2)	0.12	13 (41.9)	43 (38.4)	0.72
FPG (mmol/L)	8.3±3.2	8.1±2.6	0.54	8.0±1.9	8.8±3.2	0.21
HbA1c (%)	8.0±1.4	8.1±1.4	0.69	7.9±1.2	8.0±1.6	0.80
Preoperative CRT (μm)	201.7±43.6	228.0±36.5	<0.001	436.3±171.3	475.7±179.1	0.30
Pattern of preoperative ME						0.41
CME	-	-	-	16 (25.4)	47 (74.6)	
DRT	-	-	-	13 (21.3)	48 (78.7)	
CME+SRD	-	-	-	2 (12.5)	14 (87.5)	
DRT+SRD	-	-	-	0	3 (100)	
Preoperative ERM	15 (11.3)	11 (12.4)	0.81	18 (58.1)	52 (46.4)	0.25
Preoperative intravitreal injection of anti-VEGF	53 (39.8)	49 (55.1)	0.03	10 (32.3)	49 (53.7)	0.25
Intraoperative ERM peeling	10 (7.5)	9 (10.1)	0.50	18 (58.1)	46 (41.1)	0.09
Intraoperative ILM peeling	61 (45.9)	69 (77.5)	<0.001	24 (77.4)	92 (82.1)	0.55
Intraoperative combined cataract surgery	112 (84.2)	78 (87.6)	0.48	25 (80.6)	97 (86.6)	0.59
Intraoperative PRP	127 (95.5)	88 (98.9)	0.16	28 (90.3)	104 (92.9)	0.93
Intraoperative intravitreal injection			0.004			0.34
No	77 (57.9)	74 (83.1)		19 (61.3)	71 (63.4)	
Anti-VEGF	7 (5.3)	6 (6.7)		1 (3.2)	11 (9.8)	
TA	49 (36.8)	9 (10.1)		11 (35.5)	30 (26.8)	
Postoperative pattern of ME						
CME		24 (27)			35 (31.3)	
DRT		59 (66.3)			63 (56.3)	
CME+SRD		3 (3.4)			11 (9.8)	
DRT+SRD		3 (3.4)			3 (2.7)	

Continual variables are presented as mean±standard deviation; classified variables are presented as number and percentage. ME: Macular edema; CME: Cystoid macular edema; PPV: Pars plana vitrectomy; VH: Vitreous hemorrhage; TRD: Tractional retinal detachment; DM: Diabetes mellitus; FPG: Fasting plasma glucose; CRT: Central retinal thickness; CME: Cystoid macular edema; DRT: Diffused retinal thickening; SRD: Serous retinal detachment; ERM: Epiretinal membrane; ILM: Internal limiting membrane; PRP: Panretinal photocoagulation; VEGF: Vascular endothelial growth factor; TA: Triamcinolone acetonide.

intraoperative ILM peeling (P<0.001), and higher proportion of intraoperative intravitreal injection (P=0.004). By contrast, no statistical significance was found in Group B (Table 1).

In Group A, the cumulative incidence of PV-DME within a 3-month follow-up period was presented in Figure 1. The cumulative incidence at 3mo was 40.1% (89/222). Of the 89 eyes with postoperative DME, 24 eyes (27.0%) displayed CME alone, 59 eyes (66.2%) showed DRT alone, 3 (3.4%) displayed CME and SRD, and 3 (3.4%) showed DRT and SRD. Figure 2 presented the preoperative appearance and PV-DME in 2 different cases.

In Group B, before PPV, 63 eyes (44.0%) displayed CME alone, 61 eyes (42.7%) showed DRT alone, 16 (11.2%) displayed CME and SRD, and 3 (2.1%) showed DRT and

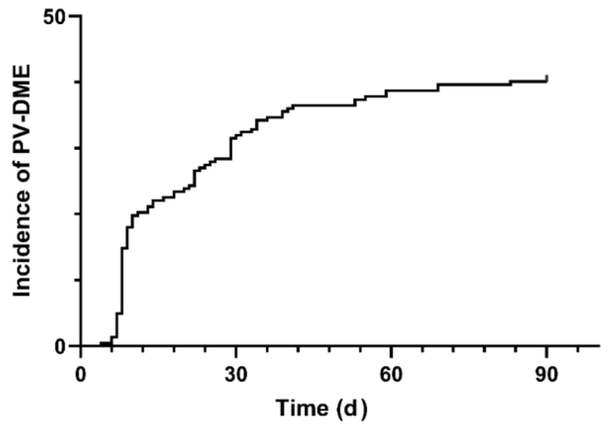

Figure 1 Cumulative incidence of post vitrectomy diabetic macular edema (PV-DME) within a 3-month follow-up.

SRD preoperatively. After PPV, 112 eyes (78.3%) retained ME within the 3-month follow-up period. Of these 112 eyes, the numbers of CME alone, DRT alone, CME and SRD, and DRT and SRD were 35 (31.3%), 63 (56.3%), 11 (9.8%), and 3 (2.7%), respectively.

Table 2 presented the incidence of PV-DME in Group A. Male patients (P=0.01) and patients with a thicker preoperative CRT (P<0.001), with preoperative intravitreal injection of anti-VEGF (P=0.03), with intraoperative ILM peeling (P<0.001), or without intraoperative intravitreal injection of triamcinolone acetonide (TA; P<0.001) had a higher incidence of PV-DME.

Table 3 presented the changes of CRT in Group B. Patients with a thicker preoperative CRT displayed a significant association with the greater changes in CRT (P<0.001).

Figure 3 presented the changes of CRT over time in Group B during the 3-month follow-up period. CRT decreased gradually from 468.3±177.7 μm preoperatively to 409.5±151.0 μm (P=0.03), 377.4±141.9 μm (P<0.001), and 368.0±157.6 μm (P<0.001) at 7d, 1 and 3mo postoperatively, respectively.

Multivariate Cox regression analysis was performed to determine the risk factors for PV-DME, and found that a thicker preoperative CRT [hazard ratio (HR)=1.01, 95% confidence interval (CI): 1.00 to 1.02], intraoperative ILM peeling (HR=3.19, 95%CI: 1.85 to 5.49), and intraoperative intravitreal TA injection (HR=0.28, 95%CI: 0.13 to 0.57) were associated with PV-DME (Table 4).

To determine the risk factors influencing the amount of postoperative CRT change in Group B, multivariate linear regression analysis was performed. Only a thicker preoperative CRT (β=0.77, 95%CI: 0.63 to 0.92) was found to be associated with a decreasing postoperative CRT (Table 5).

Table 2 Incidence of post vitrectomy diabetic macular edema in patients without preoperative diabetic macular edema *n* (%)

Parameters	Incidence of PV-DME	*P*
Age		0.10
<55y	95 (46.3)	
≥55y	127 (35.4)	
Gender		0.01
Male	125 (47.2)	
Female	97 (30.9)	
Indication for PPV		0.75
Neovascularization, and/or VH, and/or preretinal hemorrhage	79 (38.0)	
Fibrovascular membranes	88 (43.2)	
TRD	55 (38.2)	
Duration of DM		0.11
<10y	63 (49.2)	
10–20y	103 (39.8)	
≥20y	56 (30.3)	
Insulin treatment	99 (34.3)	0.12
FPG		0.76
≤6.1 mmol/L	51 (41.2)	
>6.1 mmol/L	165 (38.8)	
HbA1c		0.42
<6.5%	20 (30.0)	
≥6.5%	192 (39.1)	
Preoperative CRT		<0.001
<212.50 μm	110 (26.4)	
≥212.50 μm	112 (53.6)	
Preoperative ERM	26 (42.3)	0.80
Preoperative intravitreal injection of anti-VEGF	102 (48.0)	0.03
Intraoperative ERM peeling	19 (47.4)	0.50
Intraoperative ILM peeling	130 (53.1)	<0.001
Intraoperative combined cataract surgery	190 (41.1)	0.48
Intraoperative PRP	215 (40.9)	0.16
Intraoperative intravitreal injection		<0.001
No	151 (49.0)	
Anti-VEGF	13 (46.2)	
TA	58 (15.5)	

PV-DME: Post vitrectomy diabetic macular edema; PPV: Pars plana vitrectomy; VH: Vitreous hemorrhage; TRD: Tractional retinal detachment; DM: Diabetes mellitus; FPG: Fasting plasma glucose; CRT: Central retinal thickness; ERM: Epiretinal membrane; ILM: Internal limiting membrane; PRP: Panretinal photocoagulation; VEGF: Vascular endothelial growth factor; TA: Triamcinolone acetonide.

DISCUSSION

When using the criterion of a CRT≥300 μm, the present study found a very high incidence of PV-DME of 40.1%, with the majority subtype being DRT alone (66.2%), followed by CME alone (27.0%). This high incidence indicated that 40% of PDR patients may need further treatment, such as intravitreal drug injection, to regain visual function even after PPV. Although a direct comparison was difficult, the current reported incidence was higher than in other studies. A retrospective cohort study showed that of the 124 eyes that underwent PPV for PDR, 10 eyes (8.06%) presented postoperative ME[9]. Sun *et al*[13]

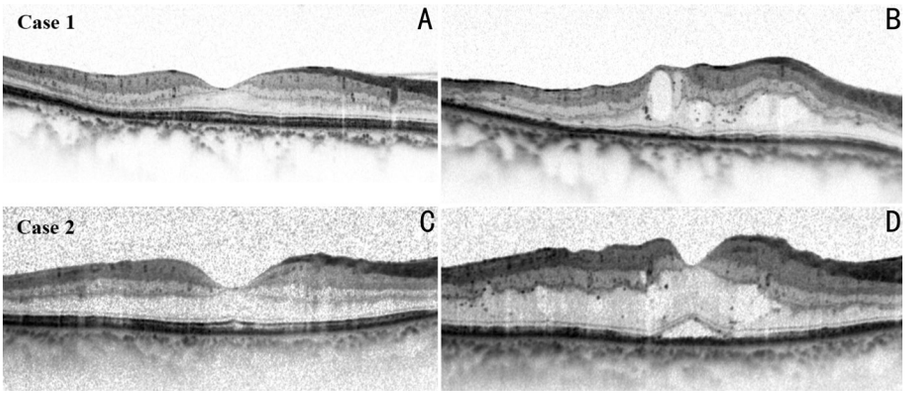

Figure 2 Post vitrectomy diabetic macular edema in 2 different cases A, B: Case 1: preoperative (A), cystoid macular edema occurred 43d postoperatively (B). C, D: Case 2: preoperative (C), cystoid macular edema and serous retinal detachment occurred 26d postoperatively (D).

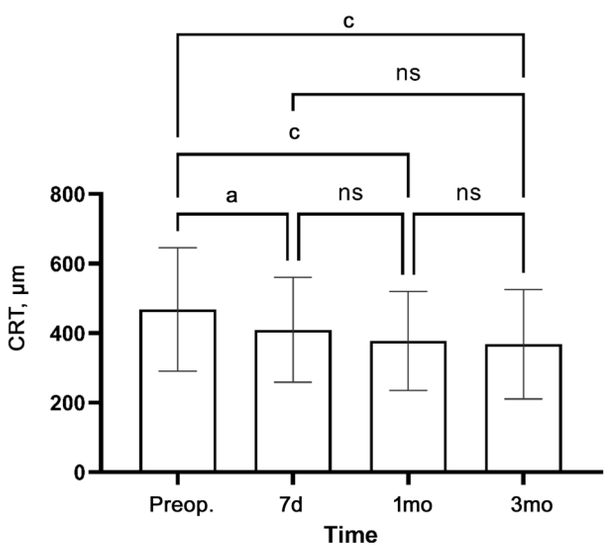

Figure 3 Changes of CRT over time in group B during the 3-month follow-up period CRT: Central retinal thickness. $^{a}P<0.05$, $^{c}P<0.001$.

conducted a study focused on the effect of preoperative injection on vitreous inflammatory cytokines and chemokines and showed that 20 eyes (33.90%) presented ME. In contrast with previous studies, we excluded patients with an unreadable preoperative OCT image and postoperative silicone oil tamponade to focus on the incidence of PV-DME. Patients frequently required the removal of the silicone oil within the 3-month follow-up, and the silicone oil frequently led to decreased macular thickness and microstructural changes[14-15]. Moreover, the definition of ME was different among studies. For example, Sun *et al*[13] determined the presence of ME only by the macular structure (such as DRT, SRD, and CME), but not CRT measurement.

In the present study, the preoperative CRT and intraoperative ILM peeling were independent risk factors for newly developed PV-DME, while intraoperative TA injection prevented PV-DME. Doncel-Fernández *et al*[16] reported that patients without known risk factors for developing CME and major surgical complication presented 9.08 times more probability to develop pseudophakic ME when with a preoperative central macular thickness >260.5 μm. In the present study, a thicker preoperative CRT was also found to be associated with PV-DME.

Whether ILM peeling improves anatomical and functional outcomes has been extensively studied. It has been reported that additional removal of the ILM at the time of PPV may be helpful by removing all tractional forces, inhibiting the proliferation of fibrous astrocytes[17], and preventing postoperative ERM formation[18]. Additionally, the mean thickness of the ILM was significantly higher in diabetic patients, which may disturb the outflow of fluids accumulating into the retina and limit the diffusion of oxygen from the vitreous[19-20]. ILM removal improves exchanges with the oxygen-rich vitreous and promotes the discharge of liquid from the retina. A recent randomized clinical trial showed that the patients who underwent ILM peeling had a better best-corrected visual acuity and a lower incidence of ERM at 6mo than patients without ILM peeling[21]. There was also a trend towards lower central macular thickness on OCT and a lower incidence of DME treatment postoperatively[21]. Hu *et al*[22] indicated that compared with vitrectomy alone, vitrectomy with ILM peeling had higher rate of CRT reduction in patients with DME. However, the result of our study showed that the patients who underwent ILM peeling during PPV were more likely to present PV-DME. Given the close proximity of the ILM to the inner retina and its interdigitation with Müller cell footplates, ILM peeling would unavoidably cause damage to Müller cells[23]. Müller cells release factors that induce tight junction formation in retinal vessels. Abnormalities in Müller cells caused by ILM peeling probably affect this barrier property in the retinal vessels[24]. In addition, the role of Müller cells in controlling the movement of water and ions allows them to buffer intraretinal increases of potassium ions. Ischemia and inflammation can alter the potassium channels of Müller cells and cause them to accumulate intracellular fluid[25].

Table 3 Changes in central retinal thickness in patients with preoperative diabetic macular edema mean±SD, μm

Parameters	Changes of CRT	*P*
Age		0.58
<55y	114.5±192.3	
≥55y	93.7±203.1	
Gender		0.10
Male	76.3±196.2	
Female	132.6±201.7	
Indication for PPV		0.53
Neovascularization, and/or VH, and/or preretinal hemorrhage	73.8±173.0	
Fibrovascular membranes	116.4±199.0	
TRD	104.0±240.6	
Duration of DM		0.97
<10y	104.0±174.9	
10–20y	100.0±213.3	
≥20y	92.48±205.5	
Insulin treatment		0.78
No	95.7±208.1	
Yes	105.5±187.6	
FPG		0.35
≤6.1 mmol/L	53.4±148.4	
>6.1 mmol/L	108.4±207.4	
HbA1c		0.09
<6.5%	175.5±195.4	
≥6.5%	91.6±199.3	
Preoperative CRT		<0.001
<450 μm	25.1±125.1	
≥450 μm	222.3±237.1	
Preoperative ERM		0.48
No	88.0±233.0	
Yes	111.6±159.1	
Preoperative intravitreal injection of anti-VEGF		0.10
No	122.5±216.2	
Yes	66.9±170.1	
Intraoperative ERM peeling		0.26
No	82.7±227.3	
Yes	120.4±158.5	
Intraoperative ILM peeling		0.72
No	87.6±263.5	
Yes	102.3±183.0	
Intraoperative combined cataract surgery		0.98
No	100.4±142.7	
Yes	99.4±208.4	
Intraoperative PRP		0.89
No	91.18±87.3	
Yes	100.2±206.5	
Intraoperative intravitreal injection		0.28
No	81.93±187.5	
Anti-VEGF	170.2±176.7	
TA	117.5±228.6	

SD: Standard deviation; PPV: Pars plana vitrectomy; VH: Vitreous hemorrhage; TRD: Tractional retinal detachment; DM: Diabetes mellitus; FPG: Fasting plasma glucose; CRT: Central retinal thickness; ERM: Epiretinal membrane; ILM: Internal limiting membrane; PRP: Panretinal photocoagulation; VEGF: Vascular endothelial growth factor; TA: Triamcinolone acetonide.

Table 4 Multivariate Cox regression analysis of risk factors for post vitrectomy diabetic macular edema in patients without preoperative diabetic macular edema

Category	Multi-factor analysis	
	HR (95%CI)	*P*
Age	0.98 (0.96 to 1.00)	0.11
Gender	0.79 (0.50 to 1.26)	0.32
Duration of DM	0.82 (0.60 to 1.12)	0.21
Preoperative CRT	1.01 (1.00 to 1.02)	<0.001
Preoperative intravitreal injection of anti-VEGF	0.85 (0.52 to 1.38)	0.50
Intraoperative ILM peeling	3.19 (1.85 to 5.49)	<0.001
Intraoperative intravitreal injection		
Anti-VEGF	0.92 (0.38 to 2.21)	0.84
TA	0.28 (0.13 to 0.57)	<0.001

DM: Diabetes mellitus; CRT: Central retinal thickness; VEGF: Vascular endothelial growth factor; ILM: Internal limiting membrane; TA: Triamcinolone acetonide; HR: Hazard ratio; CI: Confidence interval.

Table 5 Multivariate linear regression analysis of risk factors influencing the amount of CRT change from pre-operation to 3mo postoperatively in patients with preoperative diabetic macular edema

Category	Multi-factor analysis	
	β (95%CI)	*P*
Age	-1.30 (-3.87 to 1.26)	0.32
Gender	34.76 (-16.87 to 86.39)	0.19
Indication for PPV	-12.06 (-49.16 to 25.03)	0.58
HbA1c	4.08 (-14.41 to 22.58)	0.59
FPG	-4.41 (-13.77 to 4.95)	0.40
Preoperative CRT	0.77 (0.63 to 0.92)	<0.001
Preoperative intravitreal injection of anti-VEGF	-13.67 (-73.38 to 46.04)	0.65
Intraoperative ILM peeling	39.02 (-28.63 to 106.68)	0.26
Intraoperative combined cataract surgery	-14.53 (-85.77 to 56.71)	0.69
Intraoperative PRP	-16.59 (-120.94 to 87.76)	0.75
Intraoperative intravitreal injection		
Anti-VEGF	-24.06 (-127.86 to 79.75)	0.65
TA	-24.36 (-85.65 to 36.93)	0.43

PPV: Pars plana vitrectomy; FPG: Fasting plasma glucose; CRT: Central retinal thickness; ILM: Internal limiting membrane; PRP: Panretinal photocoagulation; VEGF: Vascular endothelial growth factor; TA: Triamcinolone acetonide; CI: Confidence interval.

Moreover, we considered that during the procedure of ILM peeling, additional traction was applied to the retina, causing PV-DME. Chromophore toxicity, inflammation, and ganglion cell damage caused by ILM peeling, and the vulnerable vascular bed, lower integrity of the endothelium, and the loss of pericytes of patients with diabetes also contribute to PV-DME development. It is worth mentioning that we focus on the immediate postoperative period. Therefore, a long-term follow-up study is needed to evaluate the effect of ILM peeling in patients with PDR.

The current first-line treatment for DME is the intravitreal injection of anti-VEGF agent, because of its apparent effect in reducing the VEGF level, and a certain effect on the decrease in the levels of downstream inflammatory cytokines[26-27]. However, unexpectedly, neither preoperative nor intraoperative intravitreal anti-VEGF injection was found to prevent PV-DME in the present study. It has been reported that after preoperative intravitreal anti-VEGF injection, the VEGF level dramatically decreased, whereas the influence on the vitreous inflammatory cytokines and chemokines in PDR was limited[13]. Moreover, the decreased half-lives and increased clearance of anti-VEGF drugs in vitrectomies eyes probably also contribute[28]. Despite the preoperative intravitreal injection of anti-VEGF agent, a series of cytokines, including IL-1β, TNF-α, CXCL9, G-CSF, MCP-1, and RANTES, remained at a high level and may lead to PV-DME[13]. Yoshida *et al*[8] reported that elevated MCP-1 and IL-6 levels may indicate prolonged inflammation even after successful vitrectomy, which was significantly associated with PV-DME. Rather than with an anti-VEGF agent, we found an intraoperative intravitreal TA injection effectively prevented PV-DME development in this study. Takamura *et al*[29] reported that intravitreal TA injection at the end of vitrectomy may inhibit postoperative inflammation and ME, which was consistent with our study. Intraoperative intravitreal TA injection can effectively inhibit inflammatory cytokine production, leukocytosis, and the phosphorylation of cell-junction proteins[24].

For patients with preoperative DME, 78.3% of them retained DME during the 3mo after PPV in the present study. Fortunately, the mean CRT displayed a stable trend for reduction after PPV. A greater reduction of CRT in these patients was associated with a thicker preoperative CRT, which may be due to a greater potential for CRT reduction in these patients after surgery. However, intraoperative ILM peeling and intravitreal anti-VEGF or TA injection were not found to be associated with CRT reduction. Patients with DME frequently display retinal structural abnormalities, including ellipsoid zone disruption, external limiting membrane disruption, and blood-retinal barrier breakdown, compared with patients without DME[26,30-31]. Therefore, ILM peeling appears insignificant for exacerbating the macular microstructure. Patients with preoperative DME frequently require a long time and multiple anti-VEGF treatments. Therefore, a single operative injection may not be sufficient.

Our study has some strengths. First, we reported the incidence of PV-DME and DME progression after PPV in a large sample size of PDR patients. Second, preoperative and postoperative macular morphology and CRT were precisely evaluated by OCT. This study also has several limitations. First, due to the retrospective design, there were considerable discrepancies in surgical methods and the follow-up time. Second, the incidence of PV-DME may be overestimated. Patients excluded from this study tended to have poor follow-up. These patients probably had a good visual outcome and less severe DME.

In conclusion, PV-DME is a very common postoperative complication in patients with PDR. TA could prevent its formation. Particular attention should be paid to patients with a thicker preoperative CRT and ILM peeling.

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