• Clinical Research •

Efficacy of internal limiting membrane peeling for diabetic macular edema after preoperative anti-vascular endothelial growth factor injection

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Received: 2020-05-22 Accepted: 2020-08-26

Abstract

• **AIM:** To explore the efficacy of minimally invasive vitrectomy (MIV) with or without internal limiting membrane (ILM) peeling on the treatment of diabetic macular edema (DME) in proliferative diabetic retinopathy (PDR) combining with preoperative anti-vascular endothelial growth factor (anti-VEGF) injection.

• **METHODS:** Totally 132 eyes (132 patients) diagnosed PDR with DME were included between June 2015 and June 2018 in Tianjin Eye Hospital. The single MIV treatment group included 68 eyes and the MIV combined with ILM peeling group included 64 eyes. Anti-VEGF drugs were injected intravitreally 1wk before the operation and the period of follow-up was 1 to 3y. Best-corrected visual acuity (BCVA), central retinal thickness (CRT), total macular volume (TMV), macular edema (ME) severity, intraocular pressure (IOP), and complications were recorded. Prognostic factors of visual acuity following ILM peeling were analyzed.

• **RESULTS:** The BCVA was higher than preoperative values at 1, 3, 6, and 12mo after surgery in both groups (all $P<0.05$). At 6 and 12mo, the BCVA of the combined group was significantly higher than that of the MIV only group (0.52±0.23 *vs* 0.64±0.29 logMAR, $P=0.011$ in 6mo; 0.41±0.25 *vs* 0.52±0.25 logMAR, $P=0.008$ in 12mo). Mean CRT values postoperative were significantly lower than preoperative values in both groups from the 1st month (1mo 397.65±106.18 *vs* 451.94±118.88 μm in MIV only group; 388.88±108.68 *vs* 464.36±111.53 μm in combined group; both $P<0.05$) and decreased gradually. The differences between the two groups were statistically significant at 3, 6, and 12mo ($P=0.004$, 0.003, 0.00 respectively). The TMV was decreased from the 3rd month in the single treatment group (3mo 11.14±1.66 *vs* 12.20±2.09 mm^3, $P<0.05$). At 12mo, the proportion of eyes with edema that had CRT more than 350 μm was significantly lower than before surgery (13.24% *vs* 77.94% in MIV only group; 1.56% *vs* 81.25% in combined group; both $P<0.05$). There was no significant difference in the recurrence incidence of macular epiretinal membrane, ME, transient IOP increase, vitreous rebleeding, or traction retinal detachment between the two groups. BCVA after ILM excision was positively correlated with the CRT and ME degree before and after surgery ($r=0.430$, 0.485, respectively; $P<0.05$).

• **CONCLUSION:** MIV combined with ILM peeling accelerates the absorption of ME, improves vision, reduces the postoperative CRT and TMV, and reduces the recurrence rate of postoperative ME.

• **KEYWORDS:** proliferative diabetic retinopathy; macular edema; vitreous macular traction; internal limiting membrane; minimally invasive vitrectomy; anti-vascular endothelial growth factor

DOI:10.18240/ijo.2020.11.12

Citation: Guo J, Bi X, Chen SN, Chen S, He GH, Wu B, Zhang W, Wang J. Efficacy of internal limiting membrane peeling for diabetic macular edema after preoperative anti-vascular endothelial growth factor injection. *Int J Ophthalmol* 2020;13(11):1758-1764

INTRODUCTION

Diabetic retinopathy (DR) is a common chronic microvascular complication that causes vision loss in

diabetic patients. When DR progresses to proliferative diabetic retinopathy (PDR), vision is gradually impaired. During a DR epidemiological study, diabetic macular edema (DME) was present in 51% of the cases with non-proliferative diabetic retinopathy (NPDR), while PDR was present in 49% of the cases[1]. DME is also one of the leading causes of central vision loss, and even blindness, in DR patients[2]. Therefore, when PDR is combined with DME, it is particularly important to be intervened effectively and to explore safe and effective treatment methods to save the vision.

At present, the main treatment approaches for DME are laser photocoagulation therapy[3], glucocorticoids[4-5], anti-vascular endothelial growth factor (anti-VEGF)[6] vitreous injection therapy, and vitrectomy. When DME occurs in advanced PDR, early vitrectomy is most effective[7]. In recent years, vitrectomy has moved toward a minimally invasive, 23G vitrectomy surgery system[8]. This approach can effectively reduce macular edema (ME) and retinal edema[9] and relieve the mechanical pulling of the retina, which is the most effective way to prevent further deterioration.

Vitrectomy combined with internal limiting membrane (ILM) peeling has since become the standard procedure for macular hole surgery and improved techniques, such as inner boundary membrane flap flipping and retaining macular fovea ILM peeling, have been gradually applied in clinical practice, which achieved better results[10-11]. However, the use of combined ILM peeling in DME patients with vitrectomy is controversial. Gandorfer *et al*[12] observed the effect of vitrectomy combined with ILM peeling in 12 cases of diffuse DME, and concluded that combined ILM peeling treatment was better than simple vitrectomy in reducing ME and improving vision. Kim *et al*[8] compared 29 cases of vitrectomy with ILM peeling or vitreous injection of triamcinolone acetonide (TA) in the treatment of ME and found a significantly greater benefit in the combined surgical treatment group compared with the injection group. Some scholars have also reported that, for diffuse non-stretching DME with ineffective laser treatment, vitrectomy, with or without ILM peeling, does not improve the visual acuity of patients[13]. VEGF plays an important role in the development of DME, but not all patients are affected, and about two-thirds of patients have sustained DME[14]. Therefore, there is a lack of research on the combination of minimally invasive vitrectomy (MIV) and ILM peeling for the treatment of DME after a preoperative anti-VEGF injection, especially for refractory DME with PDR where there is no clear and effective treatment. Further clinical studies are required to determine whether there is a greater advantage of MIV combined with ILM peeling versus MIV without ILM peeling in the treatment of refractory DME.

In this study, according to DR staging and DME diagnostic criteria, DME cases diagnosed with stage V PDR were selected for inclusion and treated using 23G MIV, with or without ILM peeling, after a preoperative anti-VEGF injection. Clinical effects and complications of the two treatment approaches were compared to explore the advantages and disadvantages of ILM peeling. Providing the relative prognostic factors for vision will help clinicians choose the appropriate procedure in PDR ME and to evaluate prognoses.

SUBJECTS AND METHODS

Ethical Approval The protocol for this study was approved by the Ethics Committee of Tianjin Eye Hospital. The written informed consent was received from all participants.

Subjects PDR patients with DME and intraoperative retinal edema in the macular area were enrolled from June 2015 to June 2018 in Tianjin Eye Hospital. Many patients have poor blood glucose control. During hospitalization and observation, the patients were asked to control and maintain fasting blood glucose ≤8.0 mmol/L and postprandial blood glucose ≤10.0 mmol/L. Patients with hypertension were controlled below 160/90 mm Hg (1 mm Hg=0.133 kPa). Exclusion criteria were cataracts that prevented observation of the fundus, trauma, glaucoma, fundus laser treatment, and previous anti-VEGF injection. Clinical data were collected from 132 patients undergoing MIV, with (combined group, 64 eyes) or without ILM peeling (MIV only group, 68 eyes). The mean time since the diagnosis of diabetes was 9.72±3.88y. All patients were informed of the surgical risk prior to surgery and signed an informed consent form.

Inspection Criteria Best-corrected visual acuity (BCVA) measurements before and after the operation were obtained with the international standard visual acuity chart and the standard optometry step examination. The results were converted to the logarithm of minimum resolution angle (logMAR) visual form and recorded for statistical analysis. Epiretinal membranes (ERMs) and macular traction were observed in most patients. B-ultrasonic instrument and fundus camera were used to evaluate the location and proportion of an ERM. Central retinal thickness (CRT) and total macular volume (TMV) values were measured by optical coherence tomography (OCT). CRT is the vertical distance between the inner surface of the retina under the macular fovea and the upper retinal pigment epithelium. High edema of the retina in the macular area makes it impossible to accurately distinguish the position of the macular fovea. Therefore, the highest point of edema near the macular fovea was used as the measuring point for the patient for review of OCT. Generally, DME is classified by fluorescence fundus angiography (FFA). In this study, the degree of DME was graded with CRT. CRT less than 250 μm was recorded as “1,” 250 μm to 350 μm as “2,” and more than 350 μm as “3.”

Methods Used in the Operation Anti-VEGF drugs were injected intravitreally 1wk before the operation. All patients were given 0.5% levofloxacin eye drops for 3d and 0.5% compound tropicamide eye drops for 2h before surgery. A standard 23G three-channel vitrectomy through the pars plana was performed by the same surgeon. According to our clinical practice over the years, these patients are prone to recurrent bleeding. Therefore, all eyes were treated with panretinal photocoagulation (PRP) and filled with silicone oil. Moreover, if ILM peeling was required, the peeling range was about 2 discs diameter (DD).

Postoperative Management After surgery, levofloxacin, pranoprofen, and compound tropicamide eye drops were given. Patients with high intraocular pressure (IOP≥21 mm Hg) were treated with local or systemic treatment for lowering IOP. After discharge, patients remained in a prone position for 3-4wk and the fundus were examined regularly. A fundus laser was usually performed at 1mo after the surgery. Stable patients underwent silicone oil extraction at 3 to 6mo after surgery. The majority of patients with lens opacification progressed faster when the silicone oil was taken out and cataract phacoemulsification was combined with intraocular lens implantation. A small number of young patients underwent silicone oil extraction with mild lens opacity. However, lens opacification often affects visual acuity within 2y after an operation and requires cataract surgery. The operation will be difficult. Patients with good compliance were followed up for 2 to 3y. BCVA, IOP, fundus photography, and OCT were reviewed at 1, 3, 6, and 12mo. BCVA, IOP, and fundus examinations were performed at longer follow-up visits.

Statistical Analysis All data in this study were processed using SPSS25.0 statistical software for statistical analysis, and BCVA was converted to logMAR. The measurement data are all expressed as the mean±standard deviation (SD), and analyzed by single factor analysis of variance (ANOVA) and Students *t*-test. Counting data are expressed by frequency and rate and were analyzed using χ^2 test and Fisher's exact probability test. The correlation between each factor and postoperative logMAR BCVA was analyzed using the Spearman correlation test. With α=0.05 as the test level, $P<0.05$ was considered statistically significant.

RESULTS

Baseline and Demographic Data This study included 132 eyes (132 patients, including 76 men and 56 women). The mean age of the patients was 56.36±8.55y. Sixty-eight eyes were included in the MIV only group and 64 eyes were included in the combined group. Gender, age, course of diabetes, and history of hypertension did not differ significantly between the two groups ($P>0.05$). There was no significant difference in ocular conditions, including IOP, mean logMAR BCVA, CRT, TMV, or ME degree ($P>0.05$). Baseline and demographic data of patients prior to surgery are summarized in Table 1.

Table 1 Comparison of preoperative general data of the two groups

Parameters	MIV only group (*n*=68)	Combined group (*n*=64)	*P*
Sex (male/female)	41/27	35/29	0.317
Age (y)	57.60±6.73	55.11±10.37	0.107
Course of diabetes (y)	9.51±3.39	9.93±4.37	0.534
History of hypertension (*n*)	38	31	0.248
IOP (mm Hg)	14.53±3.07	15.35±3.37	0.149
BCVA, logMAR	1.13±0.29	1.14±0.35	0.883
CRT (μm)	451.94±118.88	464.36±111.53	0.538
TMV (mm^3)	12.16±2.13	12.18±2.33	0.966
Moderate and severe edema (*n*)	56	52	0.524

MIV: Minimally invasive vitrectomy; IOP: Intraocular pressure; BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; TMV: Total macular volume.

Table 2 Comparison of the BCVA between the two groups before and after surgery mean±SD, logMAR

Time	MIV only group	Combined group	*t*	*P*
Preop.	1.13±0.29	1.14±0.35	-0.147	0.883
Postop. 1mo	1.02±0.28[a]	0.98±0.24[a]	0.886	0.388
Postop. 3mo	0.88±0.31[a]	0.81±0.28[a]	1.381	0.170
Postop. 6mo	0.64±0.29[a]	0.52±0.23[a]	2.579	0.011
Postop. 12mo	0.52±0.25[a]	0.41±0.25[a]	2.678	0.008

MIV: Minimally invasive vitrectomy; BCVA: Best-corrected visual acuity. [a]$P<0.05$ compared with preoperative.

Best-corrected Visual Acuity Changes in the two Groups BCVA of MIV only group and combined group postoperative 1, 3, 6, and 12mo were higher than before surgery (Table 2). There was no difference in the BCVA before surgery between the two groups (t=-0.147, P=0.883). The BCVA of the combined group was better than that of the MIV only group at 6 and 12mo after surgery (P=0.011, 0.008, respectively; Table 2).

Central Retinal Thickness Changes in the two Groups The CRT of the two groups at 1, 3, 6, and 12mo were statistically significantly lower than before surgery (Table 3). There was no significant difference in preoperative mean CRT between the two groups (t=-0.618, P=0.538). The mean CRT of the combined group was significantly lower than that of the MIV only group at 3, 6, and 12mo (P=0.004, 0.003, 0.00, respectively, Figures 1 and 2; Table 3).

Total Macular Volume Changes in the two Groups In the MIV only group, TMV at 3, 6, and 12mo were statistically significant lower compared with that before surgery. TMV at 1, 3, 6, and 12mo in the combined group were lower compared with that before surgery (Table 4). There was no significant difference in the average TMV before and after surgery between the two groups (Table 4).

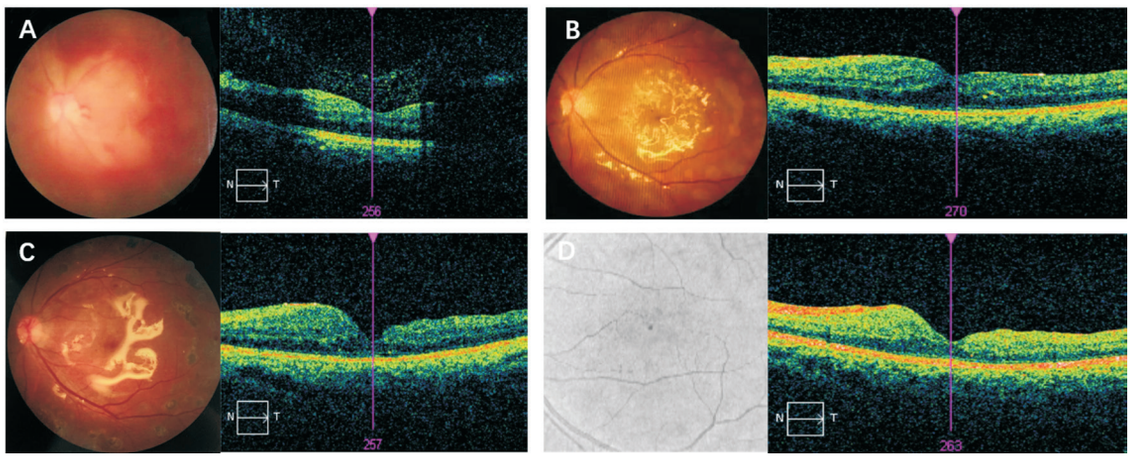

Figure 1 Fundus and macular OCT changes of one case in the combined group A: Preoperative, CRT: 470 μm; B: 1mo after surgery, CRT: 430 μm; C: 6mo after surgery, CRT: 331 μm; D: 12mo after surgery, CRT: 325 μm.

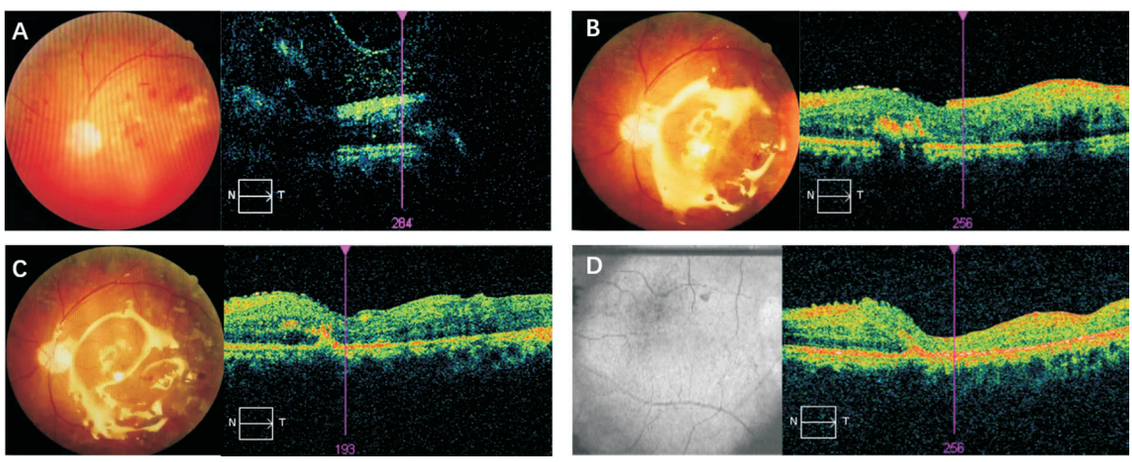

Figure 2 Fundus and macular OCT changes of one case in the MIV only group A: Preoperative, CRT: 112 μm; B: 1mo after surgery, CRT: 432 μm; C: 6mo after surgery, CRT: 345 μm; D: 12mo after surgery, CRT: 285 μm.

Table 3 Comparison of CRT between the two groups before and after surgery mean±SD, μm

Time	MIV only group	Combined group	*t*	*P*
Preop.	451.94±118.88	464.36±111.53	-0.618	0.538
Postop. 1mo	397.65±106.18[a]	388.88±108.68[a]	0.469	0.640
Postop. 3mo	338.75±85.22[a]	297.28±76.14[a]	2.294	0.004
Postop. 6mo	304.69±61.43[a]	274.56±50.76[a]	3.061	0.003
Postop. 12mo	290.29±52.93[a]	255.07±44.3[6]a	4.130	0.000

MIV: Minimally invasive vitrectomy; CRT: Central retinal thickness. [a]*P*<0.05 compared with preoperative.

Table 4 Comparison of TMV between the two groups before and after surgery mean±SD, mm^3

Time	MIV only group	Combined group	*t*	*P*
Preop.	12.20±2.09	12.18±2.33	0.056	0.955
Postop. 1mo	11.74±1.93	11.69±2.18[a]	0.154	0.878
Postop. 3mo	11.14±1.66[a]	11.08±2.11[a]	0.177	0.860
Postop. 6mo	11.03±1.56[a]	11.00±1.72[a]	0.114	0.909
Postop. 12mo	10.99±1.53[a]	10.92±1.46[a]	0.289	0.773

MIV: Minimally invasive vitrectomy; TMV: Total macular volume. [a]*P*<0.05 compared with preoperative.

Macular Edema Severity Changes At 12mo, the CRTs of 13 eyes were less than 250 μm after surgery in the MIV only group, which was significantly more than before surgery (χ^2=10.757, *P*=0.029). Nearly half of the eye CRTs were less than 250 μm after surgery in the combined group, which was significantly more than before surgery (χ^2=7.226, *P*=0.027). There was no significant difference in the proportion of CRT between the two groups before surgery (χ^2=1.932, *P*=0.381). In terms of the proportion of CRT at 12mo, the combined group was significantly better than the MIV only group (χ^2=16.170, *P*=0.000; Table 5).

Correlation Analysis Between Visual Acuity and Observed Indexes The related factors of BCVA after ILM peeling were analyzed, including patient age, course of diabetes, BCVA, degree of ME, CRT, and TMV before surgery, and CRT, and TMV at 12mo after surgery.

The results showed a moderate positive correlation between preoperative CRT and postoperative degree of edema with postoperative BCVA (*r*=0.430, 0.485, respectively; *P*<0.05). The positive correlation between preoperative degree of

edema and postoperative CRT with postoperative BCVA was relatively weak (r=0.279, 0.313, respectively; P<0.05). The thicker the preoperative and postoperative CRT, were associated with worse postoperative visual recovery (Table 6).

Postoperative Complications and Adverse Reactions During the follow-up period, there were no significant differences in the incidence of macular membrane, ME recurrence, transient IOP increase, vitreous rebleeding, or tractional retinal detachment (TRD) after surgery between the two groups (all P>0.05). There were no other serious complications or adverse reactions, such as retinal tear or endophthalmitis in either group (Table 7).

Postoperative Complications Management All eyes with ME after surgery were treated with membrane peeling *via* silicone oil extraction. In the next few years, the fundus was more stable. Patients with higher IOP were given ocular hypotensive agents after surgery, and those who still had higher IOP were given an anterior chamber puncture. None of the patients underwent glaucoma surgery because of higher IOP. Patients with vitreous rebleeding of the eyes, due to less bleeding, were advised to rest, and were given Yunnan Baiyao orally to promote the complete absorption of blood accumulation.

Table 5 ME level changes before and at final follow-up eyes (%)

CRT	MIV only group		Combined group	
	Preoperative	Postoperative	Preoperative	Postoperative
>350 μm	53 (77.9)	9 (13.2)	52 (81.2)	1 (1.6)
250-350 μm	13 (19.1)	46 (67.6)	12 (18.8)	32 (50)
<250 μm	2 (2.9)	13 (19.1)	0	31 (48.4)

MIV: Minimally invasive vitrectomy; CRT: Central retinal thickness.

Table 6 Analysis of prognostic factors of visual acuity

Observed indexes	Spearman correlation coefficient (r)	P
Age (y)	0.189	0.136
Course of diabetes (y)	-0.094	0.459
Preoperative BCVA	0.084	0.510
Preoperative CRT	0.430	0.000
Preoperative TMV	0.196	0.120
Preoperative degree of edema	0.279	0.025
Postoperative CRT	0.313	0.012
Postoperative TMV	-0.029	0.820
Postoperative degree of edema	0.485	0.000

BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; TMV: Total macular volume. Linear correlation analysis with postoperative BCVA by Spearman correlation analysis.

DISCUSSION

Significance of Vitrectomy Combined with ILM Peeling in the Treatment of DME Lewis *et al*[9] first proposed in 1992 that the use of vitrectomy for the treatment of ME is effective. The proposed mechanism is that surgery relieves retraction of the posterior vitreous cortex (PVC) on the macula, promotes fluid flow, reduces the blood flow rates of both the choroidal and retinal vessels, increases oxygenation on the inner retinal surface, and reduces the VEGF concentration in the vitreous cavity[15]. Previous studies[16] have shown that the PVC remains on the surface of the inner boundary membrane in the macular region, whether the posterior vitreous detachment (PVD) existed before surgery or was induced by vitrectomy. Vitrectomy combined with ILM peeling to treat DME not only completely removes the inducing factors of mechanical traction in the retinal macular, but also reduces the production of vasoactive factors associated with DME and inhibits the proliferation of retinal cells and ME recurrence[17]. Other scholars have found that abnormal thickening of the ILM can hinder the diffusion of various cytokines, while ILM peeling can avoid further blood-retinal barrier (BRB) destruction caused by local accumulation of VEGF in the retina[18]. Bonnin *et al*[17] suggested that exfoliation of the ILM is beneficial to the osmotic effect of water-soluble oxygen in the vitreous cavity in the retina, thus improving retinal edema in the macular region.

Effect of ILM Peeling on DME

Best-corrected visual acuity The results of this study showed that BCVA at each time point after surgery in the MIV only group and the combined group was significantly higher than before surgery, and that the improvement was most apparent at 6mo after the operation. MIV with or without ILM peeling has a benefit in improving the visual acuity of patients with severe PDR and ME, which is consistent with previous literature reports[19]. We believe that peeling the ILM completely relieves vitreoretinal traction, reduces vasoactive factor sources, such as VEGF, and removes the residual PVC, effectively inhibiting macular membrane growth and ME recurrence. Nevertheless, some scholars[13] believe that, after a follow-up of 12mo, combined surgery does not show superiority in improving visual function. This may be because the BCVA of DME patients is ultimately affected by factors such as a prolonged course of the disease, postoperative medication, systemic condition control, cataract progression, or small sample size. In this study, the number of cases was moderate and patients were followed up for two to three years. Patients were educated to control and maintain blood glucose levels. All patients underwent cataract surgery. Therefore, the conclusion of this study is more accurate than conclusions of some previous studies.

Central Retinal Thickness and Total Macular Volume In this study, the average CRT and TMV of the affected eyes at each time point after surgery in the two groups were decreased to varying degrees compared with before surgery. The decrease in CRT was most obvious at 1 and 3mo after the

Table 7 Comparison of postoperative complications between the two groups at final follow-up eyes (%)

Group	Macular membrane	Recurrent ME	Transient IOP increase	Vitreous rebleeding	TRD
MIV only group	6 (8.82)	4 (5.88)	9 (13.24)	2 (2.94)	2 (2.94)
Combined group	0	0	6 (9.38)	4 (6.25)	0

MIV: Minimally invasive vitrectomy; IOP: Intraocular pressure; ME: Macular edema; TRD: Tractional retinal detachment.

operation, and then it decreased gradually, and the changing trend was consistent with the BCVA after surgery. We believe that the restoration of vision depends on the restoration of the anatomical structure. When comparing the average CRT at different times after surgery in the two groups, it was found that the CRT of the combined group was significantly lower than that of the MIV only group at all timepoints except at 1mo after surgery. We believe that combined surgery is more effective in alleviating ME. The lack of a significant difference in CRT at 1mo after surgery may be due to the early postoperative inflammatory response caused by mechanical stimulation of the retina which was caused by exfoliation of the ILM, resulting in a transient aggravation of the swelling of the retinal nerve fiber layer[20-21]. However, this does not rule out the suggestion that the mean CRT before surgery in the MIV only group was thinner than that in the combined group.

After surgery, there was no significant difference in TMV between the two groups. The TMV level of the combined group was lower than that of the MIV only group, and the TMV trend of the two groups was consistent with that of CRT and BCVA. The results showed that the combined group still has a greater advantage in restoring the anatomical structure of the macular area and alleviating retinal edema than the MIV only group, which is similar to previous results of Hu *et al*[22].

Macular Edema Severity Several studies have shown[23] that there is a clear correlation between hard exudation under the fovea of macula and vision in DME patients. Therefore, the severity of ME as assessed by the range of hard exudation of the posterior pole and thickening of the retina is an important index with which to objectively evaluate the improvement and prognosis of DME after surgery.

From the fundus condition of patients after surgery in this study, we can see that the hard exudation gradually decreased with time. At 12mo, the proportion of edema with CRT more than 350 μm in both groups decreased significantly compared with that before surgery, and the proportion of edema with CRT less than 250 μm was higher than before surgery, especially in the combined group (48.4%). The proportion of ME with CRT more than 350 μm was also significantly lower than that in the MIV only group, but there was no significant difference in ME severity between the two groups before the operation. These results showed that 23G MIV with or without combined ILM peeling can effectively improve ME. However, the ME of the combined group decreased rapidly, and the hard exudation decreased rapidly. This further suggests that ILM excision is of great significance in the treatment of PDR merging refractory ME with assisted vitrectomy after preoperative anti-VEGF injection.

In summary, DME patients who have complications of vitreous hemorrhage and a large amount of preretinal proliferative membrane before surgery may choose MIV combined with ILM peeling treatment. The combined operation is an effective method for the treatment of PDR with ME, and is helpful for the recovery of anatomical structure and function in the macular area and a reduction in the recurrence rate. There is an absolute correlation between visual function after ILM excision and CRT before and after surgery in DME patients. It is essential before and after the operation to fully assess the patient's condition, as reasonable selection of cases and appropriate operation times can achieve a better curative effect in the surgical treatment of DME.

This study has a few of shortcomings. First, it is difficult to peel the membrane, and the operator therefore needs excellent surgical techniques. Second, it remains controversial whether the toxic effect of dye on the retina is an important factor affecting postoperative BCVA recovery. Along with our long-term follow-up and continuous improvement of surgical protocols, combined therapy has become a routine treatment for PDR patients. Intravitreal injection of anti-VEGF drugs within 1wk before operation can better repel neovascularization and reduce bleeding caused by exfoliation during the operation, can shorten the operation time, and will produce a better postoperative effect.

ACKNOWLEDGEMENTS

Foundation: Supported by the Hospital Project of Tianjin Eye Hospital (No.YKZD1901).

Conflicts of Interest: Guo J, None; **Bi X,** None; **Chen SN,** None; **Chen S,** None; **He GH,** None; **Wu B,** None; **Zhang W,** None; **Wang J,** None.

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