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CLINICAL STUDY

Pars plana vitrectomy for diabetic fibrovascular proliferation with and without internal limiting membrane peeling

P-Y Chang[1], C-M Yang[2], C-H Yang[2], M-S Chen[2] and J-Y Wang[3]

Abstract

Objective **To evaluate the anatomical and functional results of internal limiting membrane (ILM) peeling during pars plana vitrectomy for fibrovascular proliferation (FVP) in diabetic retinopathy.**

Methods **The study was a prospective comparative case series in design. Patients undergoing pars plana vitrectomy for mild to moderate diabetic FVP were divided into either Group 1: vitrectomy only, or Group 2: further ILM peeling in the macular area. Best-corrected visual acuity, fundus examination, and optical coherence tomography (OCT) were conducted at 3 and 6 months postoperatively.**

Results **There were 26 eyes of 25 patients in Group 1 (non-ILM peeling) and 23 eyes of 22 patients in Group 2 (ILM peeling). At 6 months postoperatively, OCT-identifiable epiretinal membrane (ERM) was found in 10 of 26 eyes (38.5%) in Group 1and 0 of 23 eyes in Group 2 ($P=0.001$) and six eyes (23.1%) in Group 1 developed biomicroscopic ERM, whereas no patients in Group 2 had ERM ($P=0.02$) at 6 months. OCT identifiable ERM correlated significantly with central macular thickness ($r=-0.58$, $P<0.001$), the presence of intraretinal cystic space ($r=0.60$, $P<0.001$), and fovea depression reappearance ($r=0.36$, $P=0.008$). Factors associated with poor visual outcome were macular detachment ($P<0.001$) and non-ILM peeling ($P=0.004$).**

Conclusions **This pilot study suggests that ILM peeling during vitrectomy for diabetic fibrovascular proliferative membranes may minimize postoperative ERM formation and improve visual prognosis.**

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Keywords: diabetic retinopathy; internal membrane peeling; epiretinal membrane; fibrovascular proliferation

[1]Department of Ophthalmology, Far Eastern Memorial Hospital, Pan-Chiao, Taipei, Taiwan

[2]Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan

[3]Department of Healthcare Administration, Asia University, Taipei, Taiwan

Correspondence: C-M, Yang Department of Ophthalmology, National Taiwan University Hospital, College of medicine, National Taiwan University, 7, Chung-Shan S. Rd., Taipei, Taiwan
Tel: +886 2 23123456 ext 5187;
Fax: +886 2 23412875.
E-mail: chungmay@ntu.edu.tw

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Introduction

Progressive fibrovascular proliferation (FVP) is the major cause of recurrent or persistent vitreous haemorrhage, macular or disc traction, and traction retinal detachment in proliferative diabetic retinopathy (PDR).[1,2] Timely surgical treatment may release traction and improve vision, but recurrent epiretinal membrane (ERM) may limit the anatomical and functional results.[1,3]

The retinal internal limiting membrane (ILM) is a basement membrane that has been thought to support glial proliferation.[4] This basement membrane scaffolding may play a role in the development of persistent macular oedema and in the proliferation, or reproliferation of ERM.[5] Earlier studies have suggested ILM peeling as an adjunct to macular surgery may improve surgical outcomes in certain macular diseases, such as macular holes,[6–8] epiretinal membranes,[9,10] and diabetic macular oedema;[11–13] however, the effect of ILM peeling in the prevention of postoperative ERM remains unknown in diabetic active FVP, which is characterized by a strong proproliferative biological environment.[14,15] To answer this

question, we conducted a prospective, comparative case series study to evaluate
the visual and functional outcomes of vitrectomy, with or without ILM removal, in eyes with progressive FVP.

Materials and methods

From 1 April 2007 to 15 September 2007, patients with PDR and requiring surgical treatment were selected for the study. The inclusion criteria were (1) biomicroscopic evidence of active progressive FVP on the disc and adjacent to the arcades with or without macular detachment and (2) complete panretinal photocoagulation at least 1 month before planned surgery. Active FVP was defined as visible neovascularization within the proliferative tissue with evidence of fresh vitreous or preretinal haemorrhage. Exclusion criteria were (1) presence of systemic blood diseases or bleeding tendency; (2) presence of iris or angle neovascularization; (3) previous vitreoretinal surgery; (4) severe traction detachment with FVP extending to or beyond the equator; and (5) a combination of tractional and rhaegmatogenous detachment. Forty-nine consecutive cases (47 patients) were selected and underwent surgery by one surgeon (CMY). A sample size of 11 in each group would be required to achieve an 80% testing power based on the results from our retrospective clinical and OCT study after diabetic vitrectomy for FVP (unpublished data), and the results from the earlier studies on diabetic macular oedema after ILM peeling.[11–12] The sample size in this study was decided by doubling the calculated number to assure a reliable result. Group 1 cases had surgery without concomitant ILM peeling. Group 2 had ILM peeling after the removal of FVP. All patients signed a written informed consent before surgery. Study approval was obtained from the institutional review board of National Taiwan University Hospital (NTUH-REC No.:200704053M). All patients completed a 6-month follow-up. Baseline information included demographic data, best-corrected visual acuity (BCVA), slit-lamp examination, and stereoscopic biomicroscopy of the fundus.

Surgical techniques

All patients underwent standard three-port pars plana vitrectomy (PPV). The procedures involved the removal of anterior–posterior traction, fibrovascular tissues, as well as old or fresh blood as completely as could be safely performed. Small amount of triamcinolone acetonide (TA) was used to identify residual posterior hyaloid and preretinal membranes when their complete removal was uncertain. Haemostasis was obtained by raising the infusion bottle or endodiathermy. Supplementary photocoagulation was then performed. Patients were assigned into the two groups at this point determined by coin flipping. Group 1 patients received peripheral cryotherapy, air–fluid exchange, and intravitreal infusion of 10% C3F8 to reduce postoperative recurrent vitreous haemorrhage.[16,17] Group 2 patients had further ILM peeling before cryotherapy and air–fluid exchange was performed.

ILM peeling techniques

Balance salt solution (BSS)-resuspended TA in a concentration of 20 mg/ml and 0.20%. ICG in 5% G/W were prepared as described previously.[18,19] About 0.05 ml of TA suspension was injected to coat the disc and the posterior pole followed by the injection of a small amount of ICG solution onto the predesignated site chosen for initiating ILM break (temporal and adjacent to the margin of TA containing area). After excessive TA and ICG were washed out, Tano's diamond-dusted membrane scraper was used to create an ILM break within the ICG stained area. Laminorhexis with a vertical end-gripping forceps (St Louis, MO, USA) was performed in a circular manner up to the arcade across the macula, with the torn ILM flap constantly highlighted by the coated TA particles. The area of ILM peeling was extended about 6-disc diameters horizontally and from the upper arcade to the lower arcade vertically centering on the fovea. Once ILM delamination was complete, the remaining TA was removed with passive aspiration.

Complete ophthalmic examinations were performed at 1 day, 1 week, and every month thereafter. Optical coherence tomography (OCT) and fundus photography were used to obtain the assessment of postoperative macular detail and thickness by a masked observer (CPY). A standard 6 mm, 6-line OCT (Stratus OCT™, Carl Zeiss Meditec, Inc., Dublin, CA, USA) study was carried out to determine the fovea configuration and central retinal thickness at 3 and 6 months postoperatively. The appearance of a membrane tuft or edge (with higher reflectivity) contiguous with the retinal surface was defined as OCT-identifiable ERM. Fluorescein angiography was only performed for worsening macular oedema.

For statistical calculations, Snellen VA was converted to logarithm of minimal angle of resolution (logMAR) equivalents.[20] Preoperative and postoperative VA were compared using Wilcoxon-matched pairs signed-rank test. Statistical analysis was performed using SPSS v.10.0 (SPSS, Chicago, IL, USA). Categorical variables were compared using the χ^2-test. The non-parametric Mann–Whitney *U*-test and the Wilcoxon signed-rank test were used to assess the other outcomes. Linear regression was used to analyse the association of two or more independent variables in predicting a dependent

variable. All statistical analyses were based on two-sided tests and $P \leqslant 0.05$ was considered statistically significant.

Results

There were 26 eyes of 25 patients in Group 1 (non-ILM peeling) and 23 eyes of 22 patients in Group 2 (ILM peeling). The baseline clinical characteristics of the 47 patients are summarized in Table 1. Age, gender, and haemoglobin A1c (HbA1c) were not significantly different between the two groups. Ten eyes (38.5%) in Group 1 and 7 eyes (30.4%) in Group 2 had macular detachment. The extent of FVP was further divided into two grades: Grade 1 was focal adhesions only; Grade 2 was broad adhesion $\geqslant 1$ sites. Statistical analysis showed no significant difference in the extent of FVP and in the lens status between the two groups.

Median preoperative BCVA was 20/2000 (range: hand motion, 20/200; mean logMAR, 2.18 ± 0.68) in Group 1 and 20/2000 (range: hand motion, 20/100; mean logMAR, 1.94 ± 0.60) in Group 2 ($P = 0.28$.) Postoperatively, median BCVA was 20/200 (range: 20/2000–20/50; mean logMAR, 1.17 ± 0.39) in Group 1 and 20/200 (range: 20/400–20/50; mean logMAR, 0.96 ± 0.3) in Group 2 at 3 months ($P = 0.09$); median BCVA was 20/200 (range: finger counting, 20/50; mean logMAR, 1.38 ± 0.49) in Group 1 and 20/125 (range: 20/2000–20/40; mean logMAR, 1.07 ± 0.46) in Group 2 at 6 months ($P = 0.04$). There were significant improvements in the final logMAR BCVA at 6 months compared with the preoperative status for both groups (Wilcoxon sign-rank test, $P < 0.005$ and $P < 0.005$, respectively; Figure 1).

Retinal attachment was achieved in all eyes. Seven of twenty-three (30.4%) preoperative phakic eyes in Groups 1 and 5 of 16 (31.3%) in Group 2 developed cataract progression ($P = 0.61$) during the first 3 months. Five patients in Group 1 and three patients in Group 2 had cataract surgery during follow-up. Clinically evident ERM was defined as biomicroscopic appearances of semitransparent opaque premacular tissue along with stretching and distortion of retinal vessels or surface wrinkling. Six eyes (23.1%) in Group 1 developed ERM, whereas no patients in Group 2 had ERM ($P = 0.02$) at 6 months. Surgical results for the two groups are summarized in Table 2. No ICG-related toxicity was detected on clinical examination or with postoperative

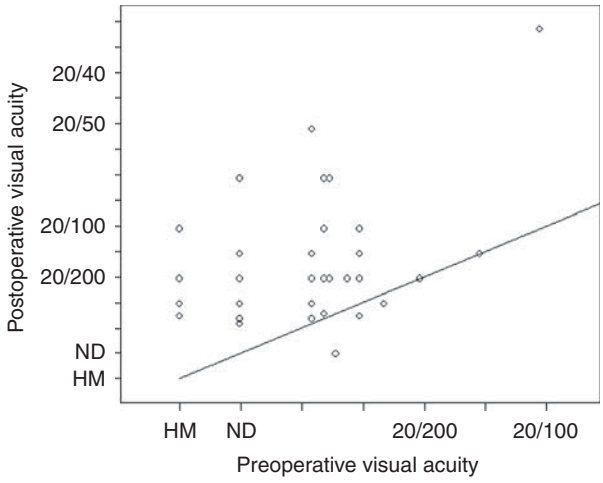

Figure 1 Scatter gram of visual acuity before and after surgery. Points above and below the diagonal line represent eyes with improved and worsened vision, respectively.

Table 1 Baseline demographics and clinical data of the patients

	Group 1 (non-ILM peeling)	*Group 2 (ILM peeling)*	P-*value*
Gender (n)			0.86
Male	12	10	
Female	13	12	
Age (years) (mean ± SD)	57.4 ± 7.5	56.0 ± 8.9	0.56
Haemoglobin A1c (%; mean ± SD)	7.9 ± 0.8	8.1 ± 0.8	0.59
Eyes (n)			0.22
Right	9	12	
Left	17	11	
Lens status (n)			0.16
Phakic eyes	23	16	
Pseudophakic eyes	3	7	
Fibrovascular proliferation involing quadrant (mean ± SD)	2.6 ± 0.9	2.3 ± 1.0	0.22
Extent of fibrovascular proliferation[a] (n/n) (Grade 1/2)	10/16	10/13	0.72
Macular detachment rate (*n*; %))	10 (38.5%)	7 (30.4%)	0.56
Preoperative visual acuity, logMAR units (mean ± SD)	2.18 ± 0.68	1.94 ± 0.60	0.28

[a]Grading of the extent of fibrovascular proliferation was defined as follows: Grade 1 = focal adhesions only; Grade 2 = broad adhesion $\geqslant 1$ sites.

Table 2 Surgical results of vitrectomy with or without internal membrane peeling of the patients at 3 and 6 months postoperatively

		Group 1 (non-ILM peeling)	*Group 2 (ILM peeling)*	P-*value*
Attachment rate (*n*; %)	3 months	26 (100%)	26 (100%)	
	6 months	26 (100%)	26(100%)	
Progression of lens opacity (*n*; %)	3 months	7 (30.4%)	5 (31.3%)	0.61
	6 months	2 (11.1%)	2 (15.4%)	0.57
Transient vitreous haemorrhage (*n*; %)	3 months	5 (16.7%)	5 (21.7%)	0.83
	6 months	0 (0%)	0 (0%)	
Biomicroscopic evidence of epiretinal membrane (*n*; %)	3 months	3 (11.5%)	0 (0%)	0.25
	6 months	6 (23.1%)	0 (0%)	0.02
Postoperative visual acuity, logMAR units (mean ± SD)	3 months	1.17 ± 0.39	0.96 ± 0.30	0.09
	6 months	1.38 ± 0.49	1.07 ± 0.46	0.04

Table 3 Optical coherence tomography (OCT) measurements of the patients after surgery at 3 and 6 months postoperatively

		Group 1 (non-ILM peeling)	*Group 2 (ILM peeling)*	P-*value*
OCT evidence of epiretinal membrane (*n*; %)	3 months	4 (15.4%)	0 (0%)	0.11
	6 months	10 (38.5%)	0 (0%)	0.001
Central macular thickness (mean ± SD)	3 months	287.8 ± 91.1	227.9 ± 57.9	0.04
	6 months	263.0 ± 76.9	185.9 ± 43.9	0.001
Intraretinal cystic change (*n*; %)	3 months	10 (38.5%)	3 (13.0%)	0.04
	6 months	7 (26.9%)	1 (4.3%)	0.03
Presence of foveal depression (*n*; %)	3 months	8 (30.8%)	11 (47.8%)	0.25
	6 months	11 (42.3%)	17 (73.9%)	0.03

fluorescein angiography. Only one patient in Group 1 required ocular antihypertensive agents for temporary pressure elevation that resolved within 3 months.

Results of OCT measurements are shown in Table 3. At both 3 and 6 months postoperatively, central macular thickness in Group 1 was significantly thicker than that in Group 2 ($P=0.04$ and $P=0.001$, respectively). Foveal depression reappeared in 11 eyes (42.3%) in Group 1 and in 17 eyes (73.9%) in Group 2 ($P=0.03$) at 6 months. Intraretinal cystic space occurred in 10 eyes (38.5%) in Groups 1 and 3 (13%) in group 2 ($P=0.04$) at 3 months; the change was noted in seven eyes (26.9%) in Group1 and one eye (4.3%) in Group 2 ($P=0.03$) at 6 months. No eyes in Group 2 had OCT-identifiable ERM, whereas 10 eyes (38.5%) in Group 1 had this finding ($P=0.001$). In the 10 eyes with OCT-identifiable ERM, partial separation of the membrane from the macular surface was noted in six eyes; membrane tufts or complete attachment of the membrane to the retina was noted in four eyes. (Figure 2) At 6 months, OCT-identifiable ERM correlated significantly with central macular thickness ($r=-0.58$, $P<0.001$), the presence of intraretinal cystic space ($r=0.60$, $P<0.001$), and the reappearance of the fovea depression ($r=0.36$, $P=0.008$).

In the linear regression model, predictors of poor visual outcome were macular detachment ($P<0.001$) and non-ILM peeling ($P=0.04$). Age ($P=0.11$) and the number of quadrants of FVP involvement ($P=0.22$) were not found to be associated with visual outcome.

Discussion

ILM peeling has become an integral part of surgical management of certain vitreoretinal diseases, such as idiopathic macular hole; it has also been advocated as an important adjunct in treating other conditions, such as idiopathic ERM[6] or diabetic macular oedema.[8–10] Although evidence suggests that ERM formation may be inhibited after ILM removal, the results obtained from cases with idiopathic ERM or diabetic macular oedema may not be readily applied to diabetic eyes with active FVP because of certain unique features in the latter condition. First, a complex vitreoretinal relationship exists in diabetic FVP. In other conditions, either posterior vitreous detachment or a transparent avascular hyaloid on the retina is present; in FVP, thick, vascularized, and highly adherent hyaloid–fibrovascular membranes usually remain fully or partially attached to the posterior retina even if peripheral PVD has developed. In addition, there may be additional ERM formed between the hyaloid and the retina. Second, the proinflammatory and proangiogenic environment in eyes with active diabetic FVP provides stronger stimulation for tissue proliferation compared with other disease entities.[14,15,21] Third, the recurrent ERM in eyes with active diabetic FVP may cause greater structural alteration of the macula, thus affecting visual prognosis more than recurrent ERM in other diseases. On the basis of the above considerations, we conducted this study to evaluate the effect of ILM peeling in eyes with active

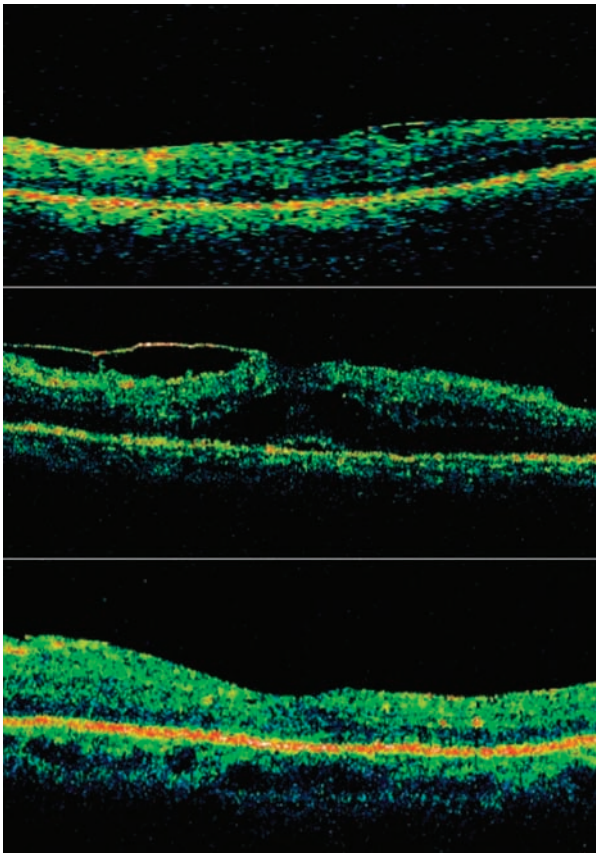

Figure 2 Macular tomograms of postoperative epiretinal membranes in patients underwent pars plana vitrectomy with (bottom) or without (top and middle) internal membrane peeling (ILM). Optical coherence tomogram (OCT; top) shows partially non-adherent epiretinal membrane with intraretinal fluid attributed to macular oedema. There are focal points of adhesions. OCT (middle) shows epiretinal membrane with the schisis-like cavity as large separation of the neural retinal layers with noticeable areas of remaining backscatter anterior to the retinal pigment epithelium. OCT (bottom) shows smooth retinal surface after pars plana vitrectomy with IL M peeling.

diabetic FVP. Eyes with extensive proliferation and complicated detachment are not good candidates for further ILM peeling because they require laborious surgery with possible significant intraoperative bleeding or creation of retinal breaks. Therefore only patients with mild-to-moderate proliferation localized in the posterior retina were enrolled. Our study suggests ILM peeling may significantly reduce postoperative ERM formation in eyes with mild to moderate active diabetic proliferation.

In this study, the 6-disc diameters ILM peeling area was wider than usually created for a macular hole or idiopathic ERM.[9] Removal of the ILM may prevent later ERM formation by removing a scaffold for proliferating astrocytes and myofibroblasts.[12,22] Furthermore, removal of the ILM guarantees complete separation of the posterior hyaloid from the macular surface. One study has shown that even after triamcinolone-assisted PPV, residual posterior hyaloid can still be found on the ILM by transmission electron microscopy.[23] These residual hyaloid fragments may be the source of new ERMs. Whether the ILM peeling *per se* or the complete removal of the posterior hyaloid contribute more to the reduction of postoperative ERM in this study remains unknown.

Our study showed the central macular thickness in the ILM peeling group ($185.8 \pm 43.9\,\mu m$) was significantly thinner than in the non-ILM peeling group ($263.0 \pm 76.9\,\mu m$) at 6 months. This could be the direct effect of an ERM-free condition in the ILM-peeling group, or as other investigators theorized, that removal of basal lamina of Muller cells may lead to changes in the protoplasmatic skeleton of the retina and thereby enable more rapid resolution of diffuse macular oedema (DME).[11] Recchia and colleagues[12] showed the reduction in macular thickness by OCT in 8 of 11 eyes with persistent DME after ILM removal. On the other hand, in their DME case series, Yamamoto *et al*[13] were able to achieve significant reduction of mean foveal thickness ($224.9\,\mu m$) without ILM removal. Whether ILM peeling facilitates reabsorption of macular oedema remains controversial.

In an earlier study reporting the results of vitrectomy specifically for massive central fibrovascular membranes with traction macular detachment, the investigators found that 9 of 28 eyes developed postoperative ERM.[1] ILM peeling had not been performed in that series. In this study, 10 of 26 eyes in the non-ILM peeling group had ERM identified by OCT at 6 months postoperatively; however, only 6 of these 10 eyes were detected by indirect fundus examination ($P = 0.02$). The diagnosis of ERM based solely on slit-lamp biomicroscopy examination may underestimate the frequency of postoperative ERM formation. OCT may be a better method to evaluate the effect of ILM peeling. The examination helps identify fine ERM and assesses retinal thickness, intraretinal oedema, and residual posterior hyaloid. Although multiple factors may affect postoperative visual potential in diabetic eyes, such as cataract, macular perfusion, or preexisting macular photoreceptor dysfunction secondary to macular detachment or oedema, the significant difference in postoperative VA between the two groups in our study suggests that ERM play an important role in affecting the visual outcome.

In this study, TA and ICG were used to assist ILM peeling. In PDR, where adherent posterior hyaloid fragment or ERM are present, proper ILM staining may greatly facilitate identification and peeling of true ILM. Although ICG has good staining property, it has potential toxicity to the RPE and ganglion cells.[7,24,25] Alternative

staining materials including trypan blue or TA particles have their limitations as well. To take the advantage of both ICG and TA while minimizing the side effects, we employed TA suspension to cover and protect the posterior retina and only stained a limited area of ILM with ICG. As only very small and localized temporal macula was in contact with ICG just for initiating the flap, the toxicity of ICG was negligible. The crucial initial ILM flap creation was easily performed in the stained area and the flap was readily visible. A small amount of TA was left to coat the macular area for highlighting the ILM flap and its edge during subsequent ILM peeling.[5] Both TA suspension and 5% G/W-diluted ICG solution are all slightly greater in density than BSS. This property ensures that when these substances are injected, they will slowly descend into the desired place instead of floating up in the vitreous cavity, thus allowing more controlled application of these substances to designated areas.

This pilot study provides data suggesting that ILM peeling during PPV for diabetic fibrovascular proliferative membranes may not have deleterious effects and may minimize postoperative ERM formation. Macular detachment and non-ILM peeling were two factors associated with poor visual outcome. A larger series may be needed to more definitively address the role of ILM peeling in diabetic patients.

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