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Idiopathic macular hole surgery in Chinese patients: a randomised study to compare indocyanine green–assisted internal limiting membrane peeling with no internal limiting membrane peeling

比較華籍病人在接受自發性黃斑裂孔手術時進行吲哚菁綠視網膜內界膜剝除術與否的隨機研究

Objective. To compare the anatomical and visual outcomes of primary idiopathic macular hole surgery using indocyanine green–assisted internal limiting membrane peeling versus no internal limiting membrane peeling.

Design. Prospective randomised controlled clinical trial.

Setting. University teaching hospital, Hong Kong.

Patients. Fifty-one eyes of 49 Chinese patients with primary idiopathic macular hole were studied.

Interventions. Patients were randomised to undergo pars plana vitrectomy with indocyanine green–assisted internal limiting membrane peeling (26 eyes) or surgery without internal limiting membrane peeling (25 eyes). Perfluorocarbon gas was used in all cases as internal tamponade.

Main outcome measures. Primary macular hole closure rate and best-corrected visual acuity.

Results. The mean follow-up duration was 12 months (range, 6-23 months). Respectively to the indocyanine green–assisted internal limiting membrane peeling group and non–internal limiting membrane peeling group, the primary anatomical closure rate was 92.3% and 32.0% (P<0.001), whereas improvement in best-corrected visual acuity was 3.7 and 1.5 lines (P=0.002). More eyes in the first group (84.6%) had improvement of 2 or more lines of best-corrected visual acuity after surgery than in the second group (32.0%) [P<0.001]. Multivariate logistic regression showed indocyanine green–assisted internal limiting membrane peeling was the only significant predictor for primary closure of the macular hole (adjusted odds ratio=30.8).

Conclusion. Indocyanine green–assisted internal limiting membrane peeling in idiopathic macular hole surgery results in significantly better anatomical and visual outcomes compared with non–internal limiting membrane peeling in Chinese patients.

目的：比較原發性自發黃斑裂孔手術中使用吲哚菁綠視網膜內界膜剝除術與否對手術後癒合及視力復原的結果。

設計：前瞻性隨機對照臨床試驗。

安排：大學教學醫院，香港。

Key words:
Basement membrane;
Epiretinal membrane;
Indocyanine green;
Retinal perforations;
Vitrectomy

關鍵詞：
基膜；
視網膜前膜；
吲哚菁綠；
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玻璃體切除術

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患者：49 名原發性自發黃斑裂孔病人，共 51 隻眼睛。
療法：病人被隨機分為兩組進行平坦部玻璃體切除術，其中一組共 26 隻眼睛在手術中使用吲哚菁綠視網膜內界膜剝除術，其餘 25 隻眼睛則沒有進行視網膜內界膜剝除術。兩組病人同樣以全氟碳化氣體作為內部填塞物。
主要結果測量：原發性黃斑裂孔的癒合率和視力的最佳矯正率。
結果：病人的隨訪期介乎 6 至 23 個月，平均為 12 個月。使用吲哚菁綠視網膜內界膜剝除術的病人，其原發性黃斑裂孔的癒合率為 92.3%，對照組則為 32.0%（P<0.001）。前者最佳矯正視力的改善情況更為明顯，為史奈侖氏視力表 3.7 行，後者則是 1.5 行（P=0.002）。手術後，前者有較多眼睛（84.6%）的最佳矯正視力改善程度達到兩行或以上，後者則較少（32.0%）[P<0.001]。多元邏輯回歸分析顯示，吲哚菁綠視網膜內界膜剝除術是促使原發性黃斑裂孔癒合的唯一顯著因素（調整比數比 =30.8）。
結論：為華籍病人進行原發性自發黃斑裂孔手術中，使用吲哚菁綠視網膜內界膜剝除術較不使用視網膜內界膜剝除術獲得顯著的癒合效果及視力改善。

Introduction

Pars plana vitrectomy and fluid-gas exchange, first performed more than a decade ago, have shown beneficial effects in the treatment of idiopathic macular holes.[1-3] Adjuncts like growth factors and surgical techniques including internal limiting membrane (ILM) peeling have been advocated to improve macular hole closure rate. We have previously demonstrated that removal of indocyanine green (ICG)–stained ILM around idiopathic and myopic macular holes contributes to closure with a favourable visual outcome.[4-8] Some studies of the role of ILM peeling in macular hole surgery, with or without the use of ICG, have confirmed these findings.[9-19] Other studies have nonetheless documented adverse effects of this surgical approach, such as asymptomatic paracentral scotomata, macular oedema, retinal pigment epithelial changes, and poor visual outcome.[20-22] The role of ILM peeling in macular hole surgery thus remains controversial.[23,24]

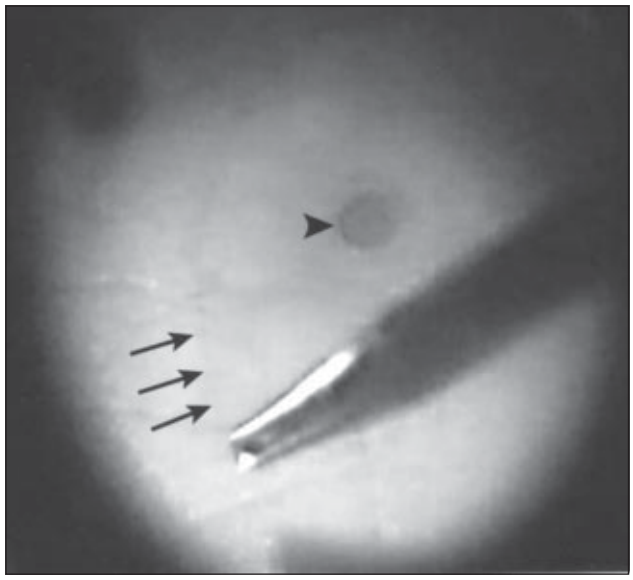

Fig. Intra-operative photograph of the left eye (from surgeon's view)
An intra-ocular forceps holding the indocyanine green–stained internal limiting membrane (arrow) around the pre-existing macular hole (arrow head)

We conducted a randomised controlled trial to evaluate the anatomical and visual outcomes of primary idiopathic macular hole surgery with and without ICG-assisted ILM peeling.

Methods

Patient selection

All patients scheduled for primary idiopathic macular hole surgery by a single surgeon were prospectively recruited from April 2001 to January 2003. Patients were randomly allocated to one of the two groups by drawing sequentially numbered opaque sealed envelopes at the start of surgery. Patients aged less than 18 years, with myopia of 6 or more dioptres, or with traumatic or secondary macular holes were excluded from the study. The protocol was approved by the hospital ethics committee and informed consent was obtained from all patients.

Surgical techniques

The two surgical techniques differed only in the presence or absence of ICG-assisted ILM peeling. No other adjunct, such as growth factor or laser, was used. Three-port pars plana vitrectomy with removal of posterior hyaloid was performed. Fine cellophane epiretinal membrane (ERM) was not removed in the non–ILM peeling group, whereas cellophane ERM was likely to be removed together with the ILM. In the ILM peeling group, 0.2 mL of 1.0 mg/mL ICG solution (Diagnogreen Injection; Daiichi Pharmaceutical, Tokyo, Japan) with osmolality of 299 mOsm was applied while the infusion was temporarily stopped.[4-8] After 30 seconds, infusion was

Table 1. Major baseline characteristics of internal limiting membrane (ILM) peeling vs non–ILM peeling groups

	All eyes, n=51	ILM peeling group, n=26	Non–ILM peeling group, n=25	P value
Mean age (SD) [years]	63.4 (9.3)	63.1 (10.0)	63.6 (8.7)	0.84†
Mean follow-up duration (SD) [months]	12.0 (5.3)	12.7 (5.1)	11.3 (5.5)	0.35†
Macular holes				
Stage 2	7 (13.7%)	4 (15.4%)	3 (12.0%)	1.0‡
Stage 3	23 (45.1%)	9 (34.6%)	14 (56.0%)	0.16§
Stage 4	21 (41.2%)	13 (50.0%)	8 (32.0%)	0.26§
Chronic macular holes with duration >12 months	25 (49.0%)	13 (50.0%)	12 (48.0%)	0.89§
Mean preoperative logMAR BCVA* (SD)	0.93 (0.29)	0.92 (0.29)	0.93 (0.29)	0.95†

* BCVA best-corrected visual acuity
† Two-tailed *t* test
‡ Fisher's exact test
§ Chi squared test

resumed and excessive ICG in the vitreous cavity was removed. Intra-ocular forceps or a myringo-vitreo-retinal blade was used to initiate an ILM flap at the temporal raphe 1.5-2.0 disc-diameter from the macular hole. A 3-4 disc-diameter of ILM was removed in a circular fashion around the macular hole using intra-ocular forceps in a centripetal direction towards the macular hole (Fig). At the end of surgery, fluid-air exchange was performed followed by 12% perfluoropropane (C_3F_8)/air exchange. Patients were asked to maintain a facedown posture for 2 weeks postoperatively.

Data collection

Preoperative data included patients' demographic information, duration, stage and size of macular hole, lens status, and preoperative best-corrected visual acuity (BCVA). The size of the macular hole was assessed by comparison with a peripapillary retinal vein of 125 μm in diameter.[3] Stages of macular holes were confirmed intra-operatively. The anatomical status of a macular hole was categorised by three defined end points (elevated/open, flat/open, flat/closed).[25] Both flat/closed and flat/open holes were considered closed holes. Postoperative data including anatomical status of the macular hole and BCVA were recorded. Best-corrected visual acuity was measured by a certified optometrist who was blinded to the patients' assigned group. Snellen BCVA was converted to the logarithm of the minimum angle of resolution (logMAR) BCVA for analysis. Each 0.1 logMAR unit represents one line of Snellen visual acuity.[26] Fundus photos and fluorescein angiography were performed to assess possible toxicity related to ICG and/or ILM peeling in all patients preoperatively and at 3 months postoperatively. Visual field or multifocal electroretinography to detect retinal dysfunction was not routinely performed.

Main outcome measurements

Primary outcome measures included anatomical closure rates and lines of visual improvement in the two groups. Secondary outcome measures were the proportion of cases with 2 or more lines of visual improvement and the final postoperative logMAR BCVA.

Statistical methods

Sample size was based on our previous study of macular hole surgery with or without ICG-assisted ILM peeling.[8] Using the respective primary closure rate of 90% and 60% for the ILM and the non–ILM peeling groups, and at a significance level of α=0.05 and power of 80%, the calculated sample size was 25 patients in each group. Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 10.0; SPSS Inc, Chicago [IL], US). Analysis was based on intention to treat. Chi squared tests and Fisher's exact tests were performed for comparisons of categorical variables and two-tailed *t* tests were conducted for analyses of continuous variables. Multivariate logistic regression analyses were performed to determine factors independently associated with primary macular hole closure and improvement of 2 or more lines of BCVA.

Results

Patient demographics

A total of 51 eyes in 49 Chinese patients were studied. The numbers of macular holes at various stages were similar between the two groups (Table 1). The median size of macular holes was 500 μm (range, 150-1000 μm). There were 25 (49.0%) chronic macular holes with duration of symptoms of more than 12 months. The mean follow-up duration was 12 months (range, 6-23 months). Twenty-six eyes were randomised to the

Table 2. Anatomical and visual outcomes of internal limiting membrane (ILM) peeling compared with non–ILM peeling

	All eyes, n=51	ILM peeling group, n=26	Non–ILM peeling group, n=25	P value
Primary anatomical success cases after one surgery				
All macular holes	32 (62.7%)	24 (92.3%)	8 (32.0%)	<0.001†
Chronic macular holes	14 (56.0%)	11 (84.6%)	3 (25.0%)	0.003†
Mean postoperative logMAR BCVA* (SD)	0.67 (0.38)	0.56 (0.33)	0.79 (0.39)	0.029‡
Mean improvement of BCVA (lines)	2.6	3.7	1.5	0.002‡
Cases with ≥2 lines of BCVA improvement	31 (60.8%)	22 (84.6%)	9 (36.0%)	<0.001†
Cases with final BCVA of 20/60 or better	23 (45.1%)	16 (61.5%)	7 (28.0%)	0.016†

* BCVA best-corrected visual acuity
† Chi squared test
‡ Two-tailed *t* test

ICG-assisted ILM peeling group whereas 25 eyes were randomised to the non–ILM peeling group.

Preoperative demographics

Baseline characteristics for both groups were similar (Table 1). For all 51 eyes, the mean preoperative logMAR BCVA was 0.93 (standard deviation [SD], 0.29) [Snellen equivalent of 20/170]. The mean preoperative logMAR BCVA for the ILM peeling and non–ILM peeling groups were similar: 0.92 (SD, 0.29) and 0.93 (SD, 0.29), respectively (two-tailed *t* test, P=0.95).

Intra-operative data

Combined macular hole surgery with phacoemulsification and intra-ocular lens implantation was performed in 28 (54.9%) eyes. Phacoemulsification was performed in patients with cataract of nuclear sclerosis 1+ or higher and in patients who preferred to have combined surgery to prevent future cataract development. There was no significant difference between the two groups in the proportion of eyes that underwent combined surgery (Chi squared test, P=0.20). No intra-operative complications were observed in both groups.

Anatomical and visual outcomes

Macular hole closure status of all optical coherence tomographic (OCT) examinations correlated with clinical examinations 3 months postoperatively.[27] Successful primary anatomical closure of the macular hole was achieved in 32 (62.7%) eyes. The primary anatomical success rate was significantly higher in the ILM peeling group compared with the non–ILM peeling group: 24 (92.3%) and eight (32.0%) eyes, respectively (Chi squared test, P<0.001) [Table 2].

Improvement of 2 or more lines at the last follow-up was evident in 31 (60.8%) eyes. More eyes had 2 or more lines improvement in the ILM peeling group than the non–ILM peeling group (Chi squared test, P<0.001). The mean postoperative logMAR BCVA at the last follow-up was 0.67 (SD, 0.38) [Snellen equivalent of 20/94]. The mean final logMAR BCVA was significantly better compared with the mean preoperative logMAR BCVA (two-tailed *t* test, P<0.001) with a mean improvement of 2.6 lines.

The final logMAR BCVA in the ILM peeling group (mean, 0.56; SD, 0.33) was significantly better than the non–ILM peeling group (mean, 0.79; SD, 0.39) [two-tailed *t* test, P=0.029]. The improvement in lines of BCVA was also significantly higher in the ILM peeling group (3.7 lines vs 1.5 lines) [two-tailed *t* test, P=0.002]. Sixteen (61.5%) eyes in the ILM peeling group compared with seven (28.0%) eyes in the non–ILM peeling group had a final BCVA of 20/60 or better (Chi squared test, P=0.016).

After excluding eyes with open macular holes following primary surgery, 24 eyes with closed holes in the ILM peeling group improved by 3.7 lines, whereas eight eyes with closed holes in the non–ILM peeling group improved by 2.7 lines. The difference was not statistically significant (two-tailed *t* test, P=0.30). The mean final logMAR BCVA for closed holes in the two groups was similar: 0.52 (ILM) and 0.50 (non-ILM), respectively (two-tailed *t* test, P=0.89).

The proportions of chronic macular holes were also similar (Chi squared test, P=0.89). Closure rate of chronic macular hole was significantly higher in the ILM peeling group (84.6%) compared with the non–ILM peeling group (25.0%) [Chi squared test,

Table 3. Multivariate logistic regression analysis of factors associated with primary closure of macular hole

Factor	Adjusted odds ratio	95% CI	P value
Internal limiting membrane peeling			
Without	1.0		
With	30.8	5.2-183.7	<0.001
Duration of macular hole			
≤12 months	1.0		
>12 months	0.4	0.7-1.7	0.18
Combined surgery			
No	1.0		
Yes	1.0	0.2-4.7	0.99

Table 4. Multivariate logistic regression analysis of factors associated with an improvement of 2 or more lines in best-corrected visual acuity

Factor	Adjusted odds ratio	95% CI	P value
Internal limiting membrane peeling			
Without	1.0		
With	9.7	1.2-76.4	0.031
Duration of macular hole			
≤12 months	1.0		
>12 months	0.04	0.003-0.500	0.011
Final macular hole status			
Open	1.0		
Closed	1.4	0.05-41.60	0.85
Combined surgery			
No	1.0		
Yes	0.4	0.05-2.40	0.29

P=0.003]. The mean lines of BCVA improvement were significantly higher in non-chronic macular holes compared with chronic macular holes, with 3.4 and 1.8 lines, respectively (two-tailed *t* test, P=0.028). Respectively to the ILM and non–ILM peeling groups, the mean preoperative logMAR BCVA for chronic macular holes was 1.02 and 1.03 (two-tailed *t* test, P=0.95), the mean final logMAR BCVA was 0.76 and 0.94 (two-tailed *t* test, P=0.11), and the improvement for chronic macular holes was 2.6 lines and 0.83 lines (two-tailed *t* test, P=0.045). Nine (69.2%) chronic macular holes in the ILM peeling group had an improvement of 2 or more lines compared with two (16.7%) in the non–ILM peeling group (Chi squared test, P=0.008).

Multivariate logistic regression analysis showed that ILM peeling was the only significant factor associated with primary anatomical closure of the macular hole after adjustment for other covariates (adjusted odds ratio [OR]=30.8) [Table 3]. Logistic regression also showed that ILM peeling was more likely to be associated with an improvement of 2 or more lines in BCVA (adjusted OR=9.7), whereas chronic macular holes were less likely to have an improvement of 2 or more lines in BCVA (adjusted OR=0.04) [Table 4].

Postoperative complications

Complications occurred in five eyes in the ILM peeling group: postoperative retinal detachment (n=2), transient topical steroid-induced ocular hypertension (n=1), transient gas-induced ocular hypertension (n=1), and dislocated intra-ocular lens (n=1). Only one complication—limited inferior retinal detachment—occurred in the non–ILM peeling group. It was successfully managed with barrier laser photocoagulation.

Re-operation was performed in one of the two open macular holes in the ILM peeling group and seven of the 17 open macular holes in the non–ILM peeling group. Indocyanine green–assisted ILM peeling was performed in all cases of re-operation. The re-operated macular hole in the ILM peeling group closed after the second operation. These patients underwent more extensive peeling of any residual ILM after ICG staining, and ILM was removed up to the temporal vascular arcades followed by silicone oil injection. In the non–ILM peeling group, six (85.7%) of the seven macular holes closed after the second operation with ICG-assisted ILM peeling performed.

Eleven (47.8%) of the 23 patients who were phakic due to development of visually significant cataract in the postoperative period required subsequent cataract surgery (seven in ILM peeling group, four in non–ILM peeling group). The difference between the two groups was not statistically significant (Fisher's exact test, P=0.12).

Discussion

The main rationale behind ILM peeling in macular hole surgery is to remove contractile cells on the inner surface of the ILM that may cause enlargement and hinder macular hole closure.[4,28] Scattered or layers of myofibrocytes and microscopic ERM have been observed in surgically removed ICG-stained ILM specimens.[4] A hypothesised benefit of ILM peeling is the associated manipulation during ILM peeling that may promote gliosis and macular hole closure. This remains speculative and further evaluation is warranted.

Previous studies have documented anatomical closure rates between 50% and 81% in conventional macular hole surgery without the use of an adjunct.[3,20,29-31] Anatomical success rates of 81% to 100% have also been reported in various series of macular hole surgery with ILM removal with or without the use of ICG.[4,9-13,15-19] Previous retrospective comparative studies have also shown that the primary anatomical macular hole closure rate is significantly higher in ICG-assisted ILM peeling than non–ILM peeling.[8,18] In this randomised controlled trial, we showed that the primary anatomical success rate for ICG-assisted ILM peeling was significantly better in the ICG-assisted ILM peeling group than the non–ILM peeling group (P<0.001), with rates of 92.3% and 32.0%, respectively. The relatively low (32.0%) anatomical success rate in our non–ILM peeling group compared with previous studies may be attributed to two main factors. First, invisible or fine cellophane ERM was not removed in the non–ILM peeling group, whereas fine cellophane ERM was likely to be removed together with the ILM in the ILM peeling group. Clinically, cellophane ERM is difficult to differentiate from ILM without the help of ICG.[4,21] Additionally, ILM is frequently found following histology of ERM specimens from macular hole surgery.[32] In two studies that reported a high success rate without ILM peeling, the ILM might have been peeled during perifoveal membrane dissection.[32,33] In a randomised controlled trial, Cheng et al[34] reported that ERM removal was significantly associated with higher anatomical hole closure rates. The ERMs in their study were mostly graded as slight cellophane and the 35% anatomical success rate of their ERM non-peeled group was similar to 32% for the non–ILM peeling group in our study. Second, the relatively low anatomical success rate in our non–ILM peeling group may be attributed to the large size and chronicity of macular holes in our study.[3,35-37] Failure of macular hole closure in the ILM peeling group may have been related to patients' unwillingness to maintain a prone position for the required postoperative period. Additionally, the authors suspect that macular holes in the eyes of Chinese subjects are more difficult to close than those of Caucasian subjects although further study is required.

In our study, visual improvement was more marked in the ILM peeling group (P=0.002). The final postoperative logMAR BCVA in the ILM peeling group was also significantly better (P=0.029). There were 2 or more lines of BCVA improvement in 84.6% of the ILM peeling group compared with 36.0% of the non–ILM peeling group (P<0.001). These results were comparable with other studies of ILM peeling.[9,38] Da Mata et al[19] also recently reported a long-term follow-up for patients who underwent ICG-assisted ILM peeling for idiopathic macular hole that 96% of patients had 2 or more lines of visual improvement.

Respectively to the ILM peeling and non–ILM peeling groups, the final BCVA of 20/60 or better was achieved by 61.5% and 28.0% (P=0.016), whereas a final BCVA of 20/50 or better was achieved by 34.6% and 16.0% (P=0.13), which compared less favourably with the two randomised trials that reported 42% and 48% of eyes with BCVA of 20/50 or better, without any adjunct.[29,30] In studies of ILM peeling, with or without ICG staining, the reported proportion of final BCVA of 20/50 or better ranged from 41.7% to 79%.[9,12,13,19,38] The difference between our study and other series is likely to be due to longer duration of symptoms and a higher (49%) rate of chronic macular hole in our series.

The primary anatomical closure rates of chronic macular hole were 84.6% and 25.0% in the ILM and the non–ILM peeling groups, respectively (P=0.003). The rate in the ILM peeling group appeared superior to the reported rates of 62.7% to 81.8% in chronic macular hole surgery with or without other adjuncts.[36-38] Postoperative logMAR BCVA did not differ significantly between groups, nonetheless chronic macular holes in the ILM peeling group had significantly higher lines of BCVA improvement compared with the non–ILM peeling group (P=0.045). More eyes with chronic macular hole in the ILM peeling group also had an improvement of 2 or more lines (P=0.008). Previous studies have also confirmed the superiority of ILM peeling in terms of faster postoperative closure rate of macular holes and greater improvement of BCVA.[36,37]

Multivariate logistic regression analyses showed that ILM peeling was the only independent factor associated with primary closure of the macular hole. Internal limiting membrane peeling and non-chronic macular hole were factors significantly associated with a higher proportion of cases with 2 or more lines improvement in BCVA. The outcome appeared more favourable for macular holes of 12 months' duration or less. Internal limiting membrane peeling is particularly important for Chinese patients who usually present with a more chronic macular hole that is also more advanced (stage 3 or 4).

Previous studies have suggested that the visual outcome for closed macular holes after ICG-assisted

ILM peeling is less favourable than those without ICG staining.[14,17] Our study showed that the final logMAR BCVA for primary closed macular holes was similar, with or without ICG-assisted ILM peeling (P=0.89). Indocyanine green–assisted ILM peeling appeared not to jeopardise the visual outcome. Significantly better postoperative BCVA has been demonstrated following ICG-assisted ILM peeling than non-ILM peeling.[18] These findings have been confirmed in a long-term study in which patients had a mean visual improvement of 6 lines, and 79% had a final BCVA of 20/50 or better.[19] Nonetheless, retinal pigment epithelial changes after ICG-assisted ILM peeling have been reported.[20] Experiments have also demonstrated up-regulation of apoptosis-related genes in retinal pigment epithelial cells treated with ICG and illumination.[39] Potential electrophysiological and functional damage has also been demonstrated in animal studies after intravitreal ICG injection with endoillumination.[40] In view of the possible ICG toxicity, there has been a recent move towards the use of trypan blue for ILM staining. Several studies have demonstrated the beneficial role of trypan blue–assisted ILM peeling in macular hole surgery, although the staining is much lighter and some surgeons find it unhelpful for ILM peeling.[41-43] Application of trypan blue to stain the ILM also requires fluid-air exchange to be performed and may prolong the surgery. Unfortunately, recent experimental studies have reported possible trypan blue toxicity.[44-46] We specifically looked for potential ICG toxicity but none was detected on clinical examination and fluorescein angiography. This may be related to the relatively low ICG concentration with a short intravitreal duration. A recent study showed no side-effects after ICG-assisted ILM peeling with an application of less than 10 seconds of 0.5 mg/mL ICG.[47] Therefore, low concentration with brief exposure appeared useful in ILM peeling. Further research is required to assess the safety and efficacy of ophthalmic dyes in macular hole surgery.

There were several limitations in our study: not all patients received combined surgery with cataract extraction. Patients without combined surgery may develop cataract postoperatively, which causes decreased final vision. The end point of macular hole closure using the definition of flat/closed and flat/open may also affect the quoted surgical success rate. The definition used in this study has been widely used in previous macular hole studies,[6-8] and adopting this end point allows better comparisons between studies. Additionally, not all patients received OCT examination at the end of the study period. We have shown that there is excellent correlation between clinical and OCT examinations and determination of postoperative anatomical end point of macular hole surgery.[27]

The results of this study demonstrate a higher anatomical closure rate and better visual outcome in ICG-assisted ILM peeling compared with non-ILM peeling in primary idiopathic macular hole surgery.

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