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Article

Fluid Gas Exchange for Flap Closure of Idiopathic Macular Hole

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Abstract: Purpose: We evaluated the outcomes of fluid-gas exchange (FGE) for long-term flap closure of idiopathic macular hole (MH) after the inverted internal limiting (ILM) flap technique.**Methods:** We included eyes showed flap closure without complete MH closure, connection of the apart macular tissue, 1 month postoperatively after the inverted ILM flap technique. The eyes stayed at flap closure at 2 months postoperatively further underwent in-office FGE with 16% C_3F_8. **Results:** Among 10 eyes, 5 eyes (50%) showed flap closure at 2 months postoperatively further underwent FGE for complete MH closure while the remaining 5 eyes (50%) progressed directly at 2 months postoperatively. The improvement in vision of all flap closure from baseline was significant (p=0.015), with the mean baseline vision was 1.19 [Snellen equivalent (SE), 20/307] ± 0.52 logMAR and the mean final vision being 0.63 (SE, 20/85) ± 0.38 logMAR. The group that underwent FGE showed a better final vision of 0.45 (SE, 20/75) ± 0.23 logMAR than the group that didn't undergo FGE (0.81 [SE, 20/128] ±0.44 logMAR). All eyes achieved complete MH closure, including the eyes that underwent FGE in a mean period of 5.60 months (range 3-10 months) after the inverted ILM flap technique. The eyes that underwent FGE achieved higher rate of foveal restoration [complete external limiting membrane (ELM): 80%; complete ellipsoid zone (EZ): 60%] than those that didn't receive FGE (complete ELM: 40%; complete EZ: 10%). **Conclusions:** Eyes that underwent FGE accelerated complete MH closure and showed better final vision and fovea l restoration.

Keywords: Fluid gas exchange; flap closure; idiopathic macular hole; vitrectomy; inverted internal limiting membrane flap technique

1. Introduction

Michalewska et al. first described the inverted internal limiting membrane (ILM) flap technique for an idiopathic full-thickness macular hole (MH) in 2009.[1] This technique was widely used and useful in specific conditions such as large a MH, myopic MH, retinal detachment secondary to MH, and uveitis.[2-5] A modified version of the classic ILM flap technique, the temporal ILM flap technique, was introduced by Michalewska et al., in which the ILM was peeled only temporal side of the fovea and this temporal ILM flap was inverted to cover the MH.[6]

Flap closure,[6, 7] just a thin ILM flap covering the MH, was a specific and crucial transition period for complete MH closure, two-end reconnection of macular structures, and foveal restoration, especially after the inverted ILM flap technique for MH. The inverted ILM flap that completely covers the MH in place acts as a bridge between the edges of the MH to allow Müller cells migration and gliosis.[8] Shiode et al. further reported that Müller cell migration and gliosis are induced in a "dry" environment, where the ILM plays the role of a scaffold for separation from the vitreous fluid under an absolute dry period after fluid-gas exchange (FGE).[9]

Moreover, Boninska et al. reported that flap closure occurred in 14% to 16% of cases and even a thin ILM flap covering the MH after surgery would allow macular reconnection and foveal restoration to continue from the external limiting membrane (ELM), followed by the ellipsoid zone (EZ).[10] However, the intervals between the phases of flap closure varied across previous studies, ranging from several months to even more than one year without vision improvement after the inverted ILM flap.[6, 7, 11] No further treatment has been proposed until complete healing of all layers of macular structures themselves for vision recovery. In view of the findings of Shiod et al., our study used simple

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in-office fluid-gas exchange (FGE) for long-term flap closure to complete MH closure, reconnection of the two ends of the macular structures, in a prolonged dry environment.

2. Materials and methods

This study followed the tenets of the Declaration of Helsinki tenets and was approved by the hospital's institutional review board (IRB). We retrospectively reviewed the medical records and consecutively recruited patients who underwent pars plana vitrectomy and ILM peeling with superior inverted ILM flap covering the MHs for idiopathic MH between June 2015 and November 2018. The inclusion criteria were eyes of idiopathic MH kept at the status of ILM flap closure at 1 month after inverted ILM flap techniques. The exclusion criteria were eyes with an axil length (AL) of ≥ 26 mm or a refraction error > -6 diopters (D), retinal detachment (RD); macular epiretinal membrane with a lamellar hole or pseudohole; or MH secondary to causes such as diabetic retinopathy, trauma, and uveitis; or a history of previous vitreoretinal surgery.

Three hundred and four eyes with MHs of various causes underwent surgeries by one retinal surgeon from June 2015 to November 2018. Among them, two hundred twenty-seven eyes underwent the inverted ILM flap techniques. We further excluded eyes with high myopia (AL>26mm; 43 eyes) and MH secondary to causes such as diabetic retinopathy (11 eyes), branch retinal vein occlusion (3 eyes), trauma (3 eyes), rhegmatogenous RD (8 eyes), and a history of previous vitreoretinal surgery (14 eyes). Thus, one hundred forty-three eyes left with idiopathic MH that underwent the inverted ILM flap technique were assessed. At last, ten (6.99%) eyes showed ILM flap closure on the OCT images at 1 month after inverted ILM flap techniques and included in our study.

The presence of the ILM flap covering the MH was defined as flap closure, a type of MH closure.[6,7] Reconnection of the two ends of the macular structures was defined as a complete MH closure, and complete restoration of the layers of the external limiting membrane (ELM) and ellipsoid zone (EZ) was referred to as foveal restoration. These ten eyes kept at the status of ILM flap closure on the OCT images at 1 month postoperatively were then grouped depending on whether they showed complete MH closures on OCT images obtained 2 months postoperatively. The eyes just flap closure without below tissue connection at 2 months postoperatively further underwent additional in-office fluid gas exchange (FGE) with 16% C_3F_8 gas. All ten patients underwent a detailed ophthalmologic examination before and after inverted ILM flap techniques as baseline and post-operation data and additional in-office FGE as pre-FGE and post-FGE information, including measurement of best-corrected visual acuity (BCVA) using the Snellen chart, AL or refraction measurement, slit-lamp biomicroscopy, indirect ophthalmoscopy, and fundus photography after dilation of the pupils with 10% phenylephrine and 1 % tropicamide. The microstructure of the MHs was evaluated using spectral-domain OCT (RTVue scanner; Optovue, Inc. Fremont, CA). Multiple scans were centered on the fovea, and the scan length was 6.0 mm or 9.0 mm. The size of the MHs was measured parallel to the retinal pigment epithelium at the nearest point of retinal apposition. The medical records contained data related to sex, age, refractive errors, lens status, size of the original MHs including minimal and base diameters, OCT findings including central foveal thickness (CFT), MH closure type, foveal restoration, and complications before and after inverted ILM flap techniques and additional in-office FGE.

Surgical techniques

For all patients with idiopathic MH, a standard 23-gauge pars plana vitrectomy was performed. The epiretinal membranes were peeled if present, followed by ILM peeling and tamponade with 16% perfluoropropane (C_3F_8) gas. As brilliant blue G is not available in Taiwan, we used 0.05% indocyanine green to stain the ILM and informed the patients of possible toxicities. With ILM inverted flap technique, the ILM was not completely peeled but was left in place with a superior flap around the MH and attached to the MH edges. The superior ILM flap with the appropriate size to cover MH was then inverted and gently covered the MH with ILM forceps. All patients were instructed to maintain a facedown posture for 2 weeks postoperatively. No patients in the study did concurrent cataract surgery with the ILM flap technique.

The in-office FGE was performed at clinic with the patient in lateral decubitus position, the face positioned at the lateral margin of the surgical bed with highly elevation. The 30-gauge needle with a 10c.c. syringe full of 16% C_3F_8 gas is inserted through 3-4 mm posterior to the temporal limbus. First step, push some gas into vitreous cavity and observe the gas-fluid level through the cornea and lens. Then check the intraocular pressure by finger touching eyeball to feel the eyeball is too hard or not. Third, pull the syringe to aspirate the vitreous fluid out. These three procedures

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repeated to let the eyeball full of 16% C_3F_8 gas. The patients maintained a facedown posture for 2 weeks after in-office FGE.

Statistical analysis

For data analysis, visual acuity values were converted into the logarithm of the minimum angle of resolution values for calculation. The baseline and postoperative visual acuities were compared using the Wilcoxon signed-rank test. We used the Mann –Whitney U test to compare continuous variables, such as age, refraction error, visual acuity, and follow-up duration between the groups. For categorical variables, we compared differences between groups using a chi-square test or Fisher's exact test in terms of sex, lens status, and restoration of ELM and EZ. Data were analyzed using IBM SPSS statistical software version 20.0 (Armonk, NY, USA)). A *P*-value of <0.05 was considered significant.

Results

Among the 143 patients with idiopathic MH, 10 eyes (6.99%) showed ILM flap closure on OCT images at 1 month postoperatively after the inverted ILM flap technique. The patients' mean age was 60.60± 3.69 years. Women accounted for 70% (7/10). Among these 10 eyes, five (50%) eyes still showed only the ILM flap covering the MHs without complete MH closure and foveal restoration at 2 months postoperatively. They further underwent FGE, while the other 5 (50%) eyes directly progressed to complete MH closure at 2 months postoperatively. Table 1 summarizes the characteristics of the overall patient population and the two flap closure groups. The general data of the two flap closure groups showed that the final visual outcomes were not significantly different with respect to sex, lens status, age, refraction error, MH size, baseline visions, complete MH closure time and baseline and postoperative CFT. The two groups showed no significant difference in sex, lens status, age, refraction error, MH size, baseline and final visual acuity, and baseline and postoperative CFT.

Table 1. General data of f two groups of flap closure.

	Total, n= 10	***P***	**underwent FGE, n=5**	**didn't undergo FGE, n=5**	***P***
Male, n (%)	3 (30)	0.833[b]	1 (20)	2 (40)	0.490[a]
OD, n (%)	6 (60)	1.000 [b]	4 (80)	2 (40)	0.524[a]
Phakic, n (%)	9 (90)	1.000 [b]	5 (100)	4(80)	0.292 [a]
Age (mean SD), y	60.60 (3.69)	0.149[c]	58.40 (3.36)	62.80 (2.68)	0.056[b]
Snellen equivalent (mean SD),d	0.65 (1.19)	0.778 [c]	0.85 (0.60)	0.45 (1.64)	0.841[b]
Epiretinal membrane, n (%)	2 (20)	0.089[b]	0 (0)	2 (40)	0.114 [b]
Preoperative CFT (mean SD), µm	408.60 (56.03)	0.210 [c]	412.00 (64.32)	405.20 (53.82)	0.861 [b]
Size of original MH					
Minimal diameter (mean SD), µm	250.89(67.99)	0.620 [c]	243.32 (52.53)	258.46 (86.59)	1.000 [b]
Base diameter (mean SD), µm	495.34 (179.55)	0.842 [c]	504.07 (237.95)	486.62(125.39)	0.841 [b]
Baseline BCVA, logMAR (mean SD)	1.19 (0.52)	0.709 [c]	1.06 (0.57)	1.32 (0.48)	0.310 [b]
Final BCVA, logMAR (mean SD)	0.63 (0.38)		0.45 (0.23)	0.81 (0.44)	0.222 [b]
MH closure time (mean SD), months	3.60 (3.20)	0.052 [c]	5.60 (3.58)	1.60 (0.55)	0.007 [b]*
Final CFT, (mean SD), µm	246.20 (32.88)	0.920 [c]	260.40 (27.19)	232.00 (34.48)	0.222 [b]
Follow-up time (mean SD), months	14.30 (9.01)	0.017 [c*]	14.40 (4.83)	14.20 (12.64)	0.690 [b]

*P<0.05, [a] chi-square or fisher exact test; [b] Mann-Whitney U test, [c] Pearson correlation

FGE, fluid gas exchange; n, number; %, percentage; y, years; d, days; SD, standard deviation; CFT, central foveal thickness; MH, macular hole; BCVA: best-corrected visual acuity; logMAR, logarithm of minimum angle of resolution

Functional outcomes

The mean final BCVA in the group that received additional FGE was 0.45 [snellen equivalent (SE), 20/75] ± 0.23 logMAR and that in the group without FGE was 0.81 (SE, 20/238) ± 0.44 logMAR. Although the final vision was not significantly different between the two groups, the mean final vision in the FGE group was superior to that in the group that did not undergo FGE. Follow-up evaluations showed no complications noted in these 10 cases.

Figure 1 shows that 8 (80%) patients had better final vision than baseline vision. Among them, all the eyes that underwent FGE showed better final vision than baseline vision. However, two eyes (20%) that did not undergo FGE showed similar or worse final vision and their cataract persisted at the final visit. One patient had a baseline vision of

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0.7 logMAR (SE, 4/20) and showed the best vision at 1 month postoperatively (0.52 logMAR; SE, 6/20), which was much better than the final vision of 0.7 logMAR (SE, 4/20). The other patient had a baseline vision of 1.1 logMAR (SE, 16/200) and showed the best vision at 1 month postoperatively (1.1 logMAR; SE, 16/200), which was relatively better than the final vision of 1.3 logMAR (SE, 10/200). The vision in these two eyes may improve further after cataract surgeries.

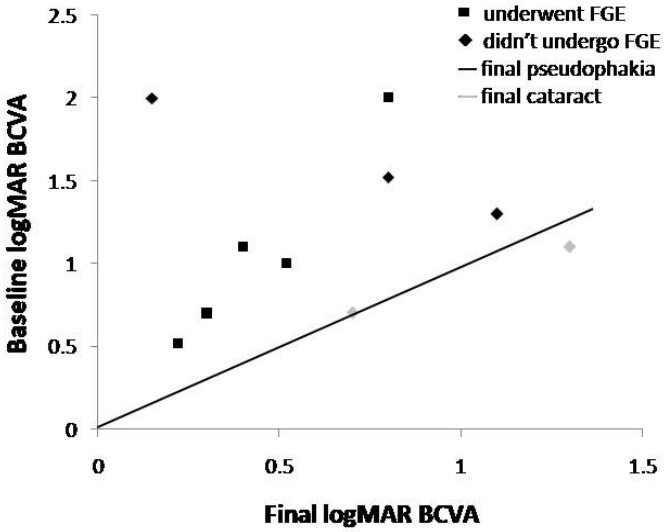

Figure 1. Distribution of baseline and final logMAR BCVA of all patients. The slanting line indicates that the patient's baseline and final logMAR BCVA were equal. The spots in the slanting line's left zone indicate that the patient had poor baseline logMAR BCVA but showed better final logMAR BCVA. A Total of 8 patients showed spots in the left zone of the slanting line. One patient who showed a spot on the slanting line and one patient who showed a post in the right zone of the slanting line had persistent cataract at the final visits.

Table 2 presents the baseline and postoperative vision data of all patients and the different groups. Significant improvements were observed in the final vision from baseline in the flap closure (P=0.013) and the FGE group (P=0.043). The mean postoperative vision gradually improved from 1.19 (SE, 20/307) ± 0.52 logMAR at baseline to 0.92 (SE, 0.92) ± 0.21 logMAR at 3 months postoperatively and mildly worsened to 0.96 (SE, 20/181) ± 0.28 logMAR at 12 months postoperatively but obviously improved to 0.63 (SE, 20/85) ± 0.38 logMAR at the final visit. The mean postoperative vision in the group with FGE slowly improved from 1.06 (SE, 20/230) ± 0.57 logMAR at baseline to 0.90 (SE, 20/158) ± 0.57 logMAR at 3 months postoperatively, and gradually kept improving to 0.80 (SE, 20/125) ±0.14 logMAR at 12 months postoperatively but improved to 0.45 (SE, 20/56) ± 0.23 logMAR at the final follow-up. However, the mean postoperative vision in the group without FGE gradually improved from 1.32 (SE 20/414) ± 0.48 logMAR at baseline to 0.94 (SE, 20/174) ± 0.18 logMAR at 3 months postoperatively. It then gradually worsened to 1.30 (SE, 20/395) ± 0.00 logMAR at 12 months postoperatively but subsequently improved to 0.81 (SE, 20/128) ± 0.44 logMAR at final visit. The difference in vision between two groups was significant at 12 months postoperatively (P=0.009), with 4 patients (80%) in the group that did not receive FGE still showing cataract and presenting with poor vision at 6 and 12 months postoperatively.

Table 2. The preoperative and postoperative visions of total patients and two groups.

BCVA logMAR	Total (Mean SD)/*P* SE	underwent FGE (Mean SD)/*P* SE	didn't undergo FGE (Mean SD)/*P* SE	*P*
Pre-operation	1.19 (0.52) 20/307	1.06 (0.57) 20/230	1.32(0.48) 20/414	0.310 [b]
Postoperative 1 months	1.00 (0.35)/0.173 [d] 20/200	0.88 (0.31)/0.655 [d] 20/150	1.15(0.38)/0.109 [d] 20/280	0.310[b]
Postoperative 3 months (post-FGE 1 months)	0.92 (0.21)/0.176 [d] 20/165	0.90 (0.57)/0.715 [d] 20/158	0.94 (0.18)/0.109 [d] 20/174	0.690 [b]
Postoperative 6 months (post-FGE 4 months)	0.96 (0.23)/0.237 [d] 20/181	0.86 (0.13)/0.715 [d] 20/143	1.08 (0.29)/0.285 [d] 20/238	0.286 [b]

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Postoperative 12 months (Post-FGE 10 months)	0.96 (0.28)/0.138 [d] 20/181	0.80 (0.14)/0.593 [d] 20/125	1.30 (0.00)/0.180 [d] 20/395	0.009[b]*
Final	0.63 (0.38)/0.013 [d]* 20/85	0.45 (0.23)/0.043 [d]* 20/56	0.81 (0.44)/0.197 [d] 20/128	0.222 [b]

*P<0.05, [b] Mann-Whitney U test, [d] Wilcoxon signed rank test

FGE: fluid gas exchange; BCVA: best-corrected visual acuity; logMAR, logarithm of minimum angle of resolution; SD, standard deviation; SE, Snellen equivalent

Anatomical outcomes

The time of complete MH closure different significantly (*P*=0.007) between the two groups. In both groups, all MHs were eventually reconnected and closed. The mean time of complete MH closure in the FGE group was 5.60 ± 3.58 months (all listed: 3, 3, 3, 9, 10 months), and that in the group that did not undergo FGE was 1.60 ± 0.55 months (range, 1-2 months) after the inverted ILM flap technique. At 2 months postoperatively, the overall MH closure rate in the eyes that showed flap closure was 50% (5/10). For the group that underwent FGE, the mean interval for complete MH closure after FGE was 3.60± 3.58 months (all listed: 1, 1, 1, 7, 8 months) and complete MH closure occurred 1 month after FGE was 60% (3/5).

Figure 2 presents the findings for the presence of a complete ELM and EZ at a different time points in eyes with flap closure at 1 month postoperatively. A complete ELM was observed in 50% of the eyes at 6 months postoperatively, 60 % at 12 months postoperatively, and 60% at the mean follow-up period of 14.30 ± 9.01 months. However, a complete EZ was observed in 10% of the cases at 6 and 12 months postoperatively and 40% of the cases at the final visit with a mean follow-up period of 14.30 ± 9.01 months.

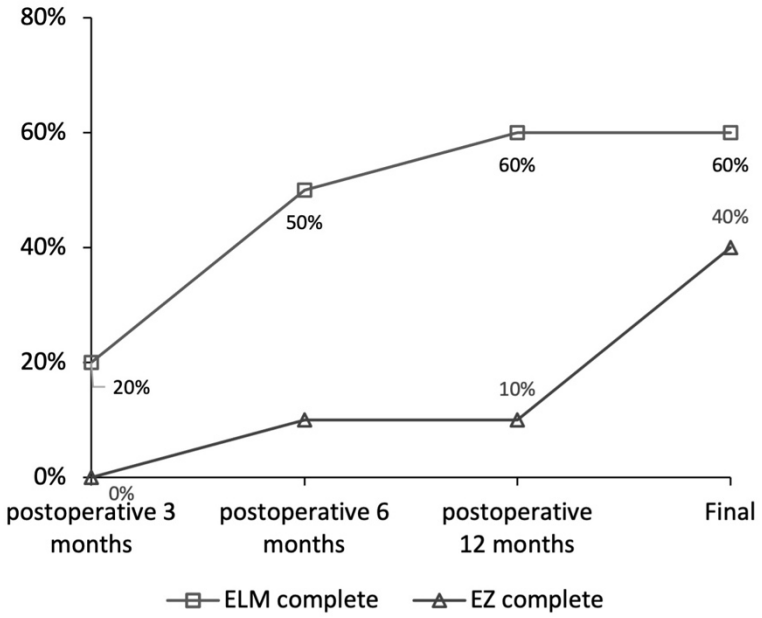

Figure 2. Complete ELM and EZ achieved at different time points in patients showing flap closure at 1 month postoperatively. Complete ELM was achieved in 50% of the cases at 6 months postoperatively, 60 % of the cases at 12 months postoperatively and at the final follow-up. However, restoration of the complete EZ was achieved in 10% of the cases at 6 months postoperatively and in 40% of the cases at the final follow-up.

Table 3 summarizes the data for the presence of complete ELM and EZ in different flap closure groups. Although the two groups showed no significant differences for the presence of a complete ELM and EZ, the group that received FGE showed a relatively higher rate of 80% (4/5) for a complete ELM and 60% (3/5) for a complete EZ that did not receive FGE (complete ELM, 40% [2/5]; complete EZ, 10% [1/5]) over a mean follow-up period of 14.30 ± 9.01 months.

Table 3 The eyes with complete ELM and EZ in two groups of flap closure.

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	Total n=10	underwent FGE n=5	didn't undergo FGE, n=5	*P*
ELM complete, n (%)	6 (60)	4 (80)	2(40)	0.197
EZ complete, n (%)	4 (40)	3 (60)	1 (10)	0.197

*P<0.05, Chi-square or Fisher exact test

ELM, external limiting membrane; EZ, ellipsoid zone; FGE: fluid gas exchange

Figure 3 shows the findings of a 54-year-old female patient who showed ILM flap closure at 1 month postoperatively (Fig. 3C) and 2 months (Fig.3D) in her right eye after the inverted ILM flap technique for idiopathic MH with a vision of 4/20 (Fig.3A and B). The minimum diameter of the MH was 166.67 μm while the base diameter was 305.56 μm. Without complete MH closure and foveal restoration, her right eye further underwent FGE at 2 months postoperatively. The inner retina was reconnected between the edges of the MH at 3 months postoperatively (Fig. 3E). She underwent cataract surgery of the right eye at 9 months postoperatively. At 12 months postoperatively, complete ELM and EZ with a CFT 271 μm were noted on horizontal views of OCT images and her vision improved to 8/20 (Fig. 3F). Her final vision improved to 10/20 at 24 months postoperatively.

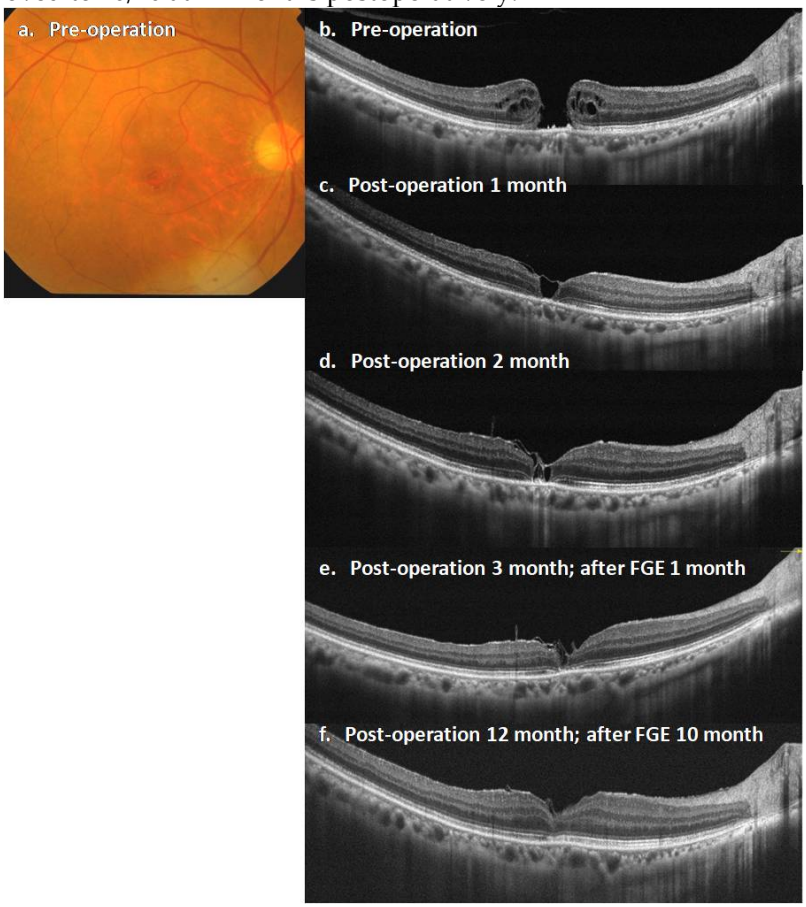

Figure 3. A 54-year-old female patient presented with idiopathic MH on fundus photography and OCT (Fig. a and b). A thin ILM flap covered the MH from in fundus pictures and OCT images obtained at 1 and 2 months postoperatively (Fig. c and d). The patient then underwent further FGE. A thin ILM flap with reconnection of the apart macular tissue was found at 3 months postoperatively (Fig. e). Horizontal views of OCT images showed a good foveal contour and complete ELM and EZ with CFT of 271 μm at 12 months postoperatively (Fig. f).

3. Discussion

Casini et al. compared the classic inverted ILM technique proposed by Michalewska et al. and modified method described by Casini et al. and found the rates of flap closure at 3 months postoperatively were 7.5% and 10.26%, respectively, for large MH,[7] but both methods did not yield significantly different flap closure at 6 months postoperatively. In a study by Michalewska et al., the rate of flap closure at 6 months postoperatively after the temporal

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inverted ILM flap techniques was 6%, and the rate 12 months postoperatively after the classic inverted ILM flap techniques was 3%[6] with flap closure maintained without complete MH closure. In the study of Tsui et al., the incidence of flap closure after temporal flap of the inverted ILM flap technique for non-high myopia group of MH reported 31.25% (5/16), higher than previous studies and all the cases at the status of flap closure remained within 4 months.[11] In our study, 6.99% of the eyes showed ILM flap closure at 1 month postoperatively after the superior inverted ILM flap technique for idiopathic MHs. However, all flap closures, including those performed in-office FGE progressed to complete MH closure within 12 months postoperatively. We further found that the mean time required to connect the two ends of macular structures and achieve complete MH closure was 3.60 (range, 1-8 months) months after FGE in the group that underwent FGE. Thus, all eyes in the group that receive FGE required a mean time of 5.60 months (range, 3-10 months) after the inverted ILM flap technique to achieve complete MH closure, a little longer than 4 months but less than 12 months, reported by Tsui et al. with temporal flap of inverted ILM flap technique and Michalewska et al. with classic inverted ILM flap technique. In fact, 60% (3/5) of the eyes at the status of flap closure which performed in-office FGE progressed to complete MH closure 1 month after FGE, 3 months after the inverted ILM flap technique. Therefore, the use of in office FGE in our study did accelerate connection of two ends of macular tissue and shorten the interval of the flap closure.

The percentage of ILM flap closure in our study was less than those reported by Casini et al. and Michalewska et al., while the mean minimum diameter and base diameter of MH in our study were 250.89 / 495.34 (36.00/179.57) μm, smaller than those reported by Casini et al.[7] (561 / 836 and 603 /884μm), Michalewska et al.[6] (544/894μm) and Tsui et al.[11] (non-high myopia group, 738/1582μm). An MH with a larger minimal diameter may show a higher rate of flap closure after inverted ILM flap techniques. However, the shape of MH showed exaggerated differences between the minimum and base diameters in these studies.

Faria et al. proposed that one of the following situations may occur after inverted ILM flap techniques as follow: (1) The ILM flap flips back, resulting in surgical failure (2) The ILM flap dips into the hole, which contacts the inner lining of the hole (3) The ILM flap stays over the hole in the intended position. They further suggested that the third situation is ideal because the hole will close, with better visual outcomes and outer retinal layer realignment.[12] Some studies have reported that the final visual acuity is lower in eyes with flap closure than in eyes that initially develop complete MH closure,[10] including U type, V type or irregular closure.[13, 14] However, the cases in our study all showed the third situation at 1 month postoperatively. All of them were confirmed to show complete MH closure and foveal restoration on OCT during follow-up assessments. Although the vision was not significantly different between the preoperative and 1-, 3-, 6- and 12- postoperative intervals overall or in each group, it was significantly different between the groups with and without FGE at 12 months postoperatively (P=0.009) because more patients who did not receive FGE also did not undergo cataract surgeries. Moreover, the baseline and final vision in eyes showing flap closure were significantly different (P=0.013), especially the eyes with FGE (P=0.043).

Regarding foveal restoration after the temporal inverted ILM flap technique, Michalewska et al. reported that at 12 months postoperatively, ELM defect was still present in 25% of the cases and EZ defect were present in 57% of the cases.[6] Casini et al. compared the classic and modified types of inverted ILM flap techniques and reported ELM defects rates of 20% / 28.21% and EZ defect rates of 45% / 51.28% at 12 months postoperatively.[7] Boninska et al. compared flap closure with initially developed MH closure and reported that reconnection of ELM and EZ did not differ between the two groups, while reconstruction of the ELM preceded restoration of the EZ.[10] However, for all flap closure in our study, 60% of the patients showed a complete ELM and 10% showed a complete EZ at 12 months postoperatively while 60% showed a complete ELM and 40% showed a complete EZ at the mean follow-up of 14.30 ± 9.07 months, which were relatively slower than the foveal restoration rates reported in previous studies using different methods of inverted ILM flap technique, not specifically for the flap closure. The eyes that underwent FGE showed late-onset of complete MH closure, whereas eyes that did not undergo FGE showed early-onset of complete MH closure. For foveal restoration, we further found that eyes underwent FGE showed higher completion rates of the ELM (80%) and EZ (60%) than those that did not undergo FGE at the mean follow-up period of 14.30 ± 9.01 months. The completion rates of ELM and EZ in the eyes underwent FGE approached to those findings in the studies using different methods of inverted ILM flap technique, not specifically for the flap closure. Moreover, the group that underwent FGE showed late onset of complete MH closure but a better final vision and a higher rate of foveal restoration. Additional in-office FGE did create a prolonged period of dry space for the long-term flap closure to accelerate Müller cell migration and gliosis along the inverted ILM flap and reconnect the entire layers of both ends of the separated macular structures including enhancing foveal restoration of ELM and EZ.

This study had some limitations including the retrospective design, a small sample size, variable and short follow-up period in the group that did not receive FGE.

In conclusion, we performed additional in-office FGE for eyes that sill kept at the stage of flap closure at 2 months postoperatively. Both flap closure groups achieved complete MH closure within 10 months postoperatively. Although the eyes

that received FGE showed later onset of complete MH closure, the final vision in these eyes was significantly better and their foveal restoration was higher. Thus, FGE enhances and accelerates complete MH closure of the flap closure.

Abbreviations: MH: macular hole; ILM: inverted internal limiting; ELM: external limiting membrane; EZ: ellipsoid zone; FGE: fluid-gas exchange; AL: axial length; D: diopters; RD: retinal detachment; BCVA: best-corrected visual acuity; OCT: optical coherence tomography; CFT: central foveal thickness

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Availability of data and materials: All data supporting our study will be shared upon request, although most of the data has been provided in the manuscript.

Contributors: K-L P collected clinical data and images and edited the images. K-L P and T-T W wrote the statistical analysis plan, cleaned and analyzed the data and drafted and revised the paper. T-T W was responsible for clinical treatment of the patients, initiated the study, designed data collection tools, implemented the study and revised the drafted paper. All authors have read and approved the final manuscript.

Ethics approval: The study was approved by the Institutional Review Board of Kaohsiung Veteran General Hospital with a number of 20-CT6-08.

Consent for publication: Written informed consent was obtained from the patients for publication of this study and accompanying images. All copies of the written consents are available for review by the Editor of this journal.

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