• Review Article •

Internal limiting membrane flap technique in macular hole surgery

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Abstract

● Vitrectomy combined with internal limiting membrane (ILM) peeling is popular for the treatment of macular hole (MH). However, the improvements of MH closure rate and postoperative visual acuity are not satisfactory especially in large and refractory MHs. Currently, the ILM flap technique has gradually been applied for the treatment of MH and achieved high MH closure rate. The ILM flap technique has many variations, including the difference of the size, shape, number, and manner in which the flaps put on the MHs. The ILM flap technique also has some auxiliary means including perfluoro-n-octane (PFO), dye, autologous blood and adhesive viscoelastics. There is controversy about the effects between several technique variations of ILM flap, and it needs to be explored in the future.

● **KEYWORDS:** internal limiting membrane flap; macular hole; internal limiting membrane peeling

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INTRODUCTION

Macular hole (MH) refers to localized or full-thickness defect of macular neuroepithelial layer. According to the cause of the disease, it is divided into secondary and idiopathic MHs. Secondary MHs occur after ocular trauma, high myopia and so on[1]. The incidence of MH in high myopia might be result of the combination of factors[2-4]. Most researchers believe that the anterior and posterior traction between vitreous and retina in macular area, and the tangential traction between epiretinal membrane and internal limiting membrane (ILM) are main reasons for the formation and expansion of MH. High myopia is often accompanied by the extension of the axis of the eye, which causes the posterior part of the sclera expand to form the posterior scleral staphyloma. However, the extension of the retina is much smaller than that of the sclera, forming a reverse vertical pull on the retina. In addition, high myopia is often along with retinal atrophy, choroidal atrophy, and decreased adhesion of the retinal neuroepithelium and pigment epithelium, which increase the risk of MH and retinal detachment[2-4].

Idiopathic MH refers to MH without other induced eye diseases and the cause is unclear[1]. At present, most researchers believe that it is due to the pathological vitreoretinal traction at the fovea[5]. Gass[6-7] divided MHs into four stages. For patients with stage 1 MHs, conservative treatment could be taken, because they often remain stable or even improve[8]. Most patients with stage 2 to 4 MHs have a poor prognosis without treatment, so surgery is recommended[9-10].

Currently, vitrectomy combined with ILM peeling has been widely used for the treatment of MH. Peeling the ILM can relieve anteroposterior and tangential traction on the surface of retina and achieved 93% to 98% of MH closure[11-12]. However, large MH might increase the risk of surgery failure and the MH closure rate was 40% to 80% using ILM peeling technique[13-15]. In addition, it was reported that after ILM was removed, the following retinal structure abnormalities could be observed including defects of retinal pigment epithelium (RPE), photoreceptor cell layer as well as nerve fiber layer[16-18]. Also, the fovea might displace to the optic nerve and the distance of them was changed. The temporal retina became thinner and the nasal retina became thicker. Therefore, the methods of treating MH should be improved especially large MH[13-15].

The inverted ILM flap technology was first applied by Michalewska *et al*[19] in 2010 in order to treat MH larger than 400 μm. It achieved anatomical and functional improvements. Subsequently, more and more studies begin to report research on ILM flap technology, and various surgical changes occur. The ILM is defined as the innermost layer of the retina. An experimental model study of monkeys with MH[20] showed that constituent proteins of ILM could promote Müller cells

to proliferate and migrate. Migrating Müller cells expressed greater neurotrophic factors and b-FGF than stable Müller cells. These factors might contribute to MH closure and photoreceptors recovery. Additionally, ILM flap would form a compartment that avoid fluid from vitreous cavity into MH and provide a beneficial environment for glial proliferation and functional recovery[19,21-22].

SURGICAL TECHNIQUES

Classical Inverted Internal Limiting Membrane Flap The inverted ILM flap technique was first applied by Michalewska *et al*[19] in 2010 in order to treat MH larger than 400 μm. It achieved a 98% MH closure rate in 50 eyes of the study (Figure 1). Then this technique was used in MH with high myopia in 2014[23]. After the surgery, all patients achieved MH closure and visual improvement (P=0.02).

However, this technique seemed like using folded ILM to pack the MH rather than a true flap to cover it. The ILM was peeled for about two-disc diameters and remained was massaged over the MH from all sides until it became inverted[19]. Instead of a true flap, it was more like 'ILM plug' or 'ILM insertion'. And after the surgery, a multilayered membrane was observed which might not be beneficial for recovery[24].

Then, Shin *et al*[24] first introduced a true flap technique (single-layered flap of the ILM) for covering MH (larger than 400 μm) with the assistance of perfluoro-n-octane (PFO) in 2014. It was difficult maintaining the ILM flap in the proper position until fluid-air exchange with single-layered ILM flap technique. Then PFO was used to cover macula and keep the flap position. After the surgery, 10 (83%) eyes acquired MH closure. The postoperative visual acuity improved significantly.

Modified Inverted Internal Limiting Membrane Flap

The temporal inverted internal limiting membrane flap Michalewska *et al*[22] in 2015 reported a modified temporal inverted ILM flap surgery for treating large stage IV MH (87 eyes; Figure 2). The nasal ILM was remained in place and not peeled off which helped to protect the area from surgical trauma and reduce the occurrence of dissociated optic nerve fiber layer (DONFL). DONFL was a result of ILM removal while there was no report or evidence that development of DONFL was associated with poor functional outcomes[16]. No obvious difference in anatomical and functional results were detected in the modified temporal technique compared with the classical inverted ILM flap technique. This suggested that the ILM flap might not be necessarily the same size as the classical inverted ILM flap. Because the aim of the treatment was to obtain MH closure with minimal iatrogenic injury. However, the displacement of flap in fluid-air exchange was still a problem to solve and occurred in two eyes. It caused surgical failure and reoperations were required to keep flap on the MH[22,25].

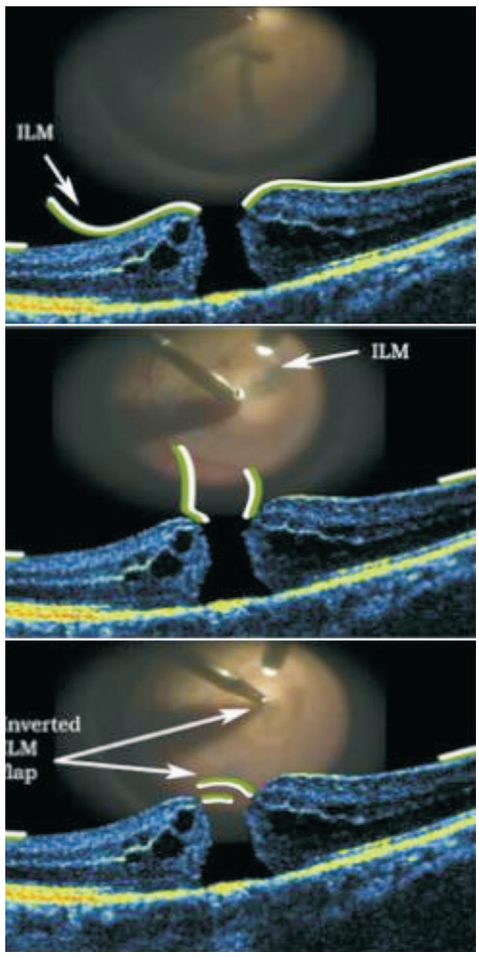

Figure 1 Classical inverted ILM flap technique ILM was peeled in circular fashion for about two disc diameters and remained was massaged over the MH from all sides until it became inverted (image comes from Michalewska *et al*[19]).

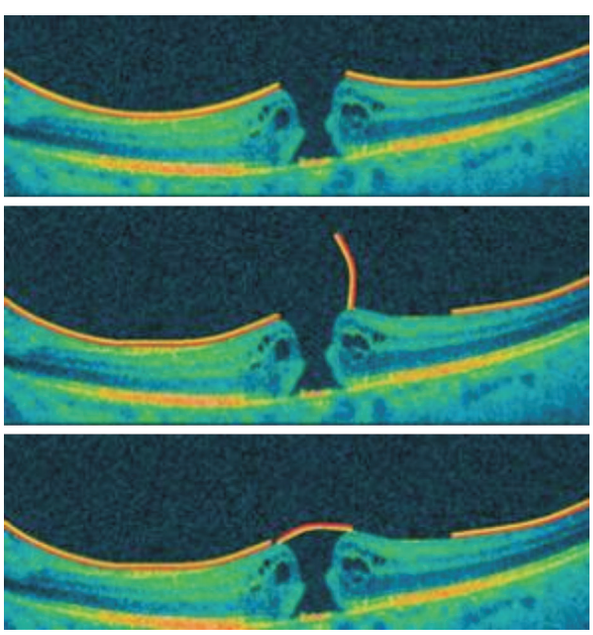

Figure 2 Modified temporal inverted ILM flap technique The temporal ILM was peeled off for about two diameters of the optic nerve and inverted to cover MH completely. The nasal ILM was left in place (image comes from Michalewska *et al*[22]).

The large semicircular inverted internal limiting membrane flap Flap unfolding was a potential problem in inverted ILM flap technology. To solve this problem, Chen[26] proposed a modified technique in 2017. A large semicircular flap (4 disc diameter) was used to cover the MH in high myopia MH patients (Figure 3). The MHs of all patients (17 eyes) in the study were successfully closed and the vision improved after the surgery (P=0.01). The ILM flap covered a large area on the hole reducing the possibility of flap flipping. If the flap had a slight displacement, the possibility of not covering the MH was decreased. In addition, when patients took sitting postures after the surgery, due to the effect of gravity, the flap was easier to maintain the downward position to cover the MH. However, this technique had some limitations. The production of the large flap was more technically demanding, especially in patients with high myopia. In addition, the large ILM flap was not available in each eye, because some of ILM might be peeled off before.

The C-shaped temporal inverted internal limiting membrane flap Another modified method called the C-shaped temporal inverted ILM flap for treating highly myopic eyes with MH retinal detachment referred by Ho *et al*[27] in 2018 (Figure 4). MH closure rate was 100% (18 eyes) and retinal attachment rate was 95% after the treatment. Also, vision obtained significant improvement (P<0.001). The modified method adopted a smaller ILM flap (1.5 disc diameter) than the classic ILM flap (2 disc diameter). The size of the flap had been modified to avoid the diameter of the flap being larger than necessary. Moreover, the C-shaped ILM flap surgery introduced 270-degree ILM flap instead of 180-degree flap which could reduce more traction and facilitate the closure of MH.

The Pedicle Internal Limiting Membrane Transposition Flap For refractory MHs with no ILM found around the MH, then the above surgical procedure could not be performed. In this condition, the pedicle ILM transposition flap technique could be considered. It was introduced by Gekka *et al*[28] in 2015. The residual ILM was peeled into strips starting at the hole and kept one end of the strip connected to the retina above MH. Then Gekka *et al*[28] stretched the stripped ILM from its attachment point and covered the MH. MHs were closed successfully (two eyes) without adverse events. In addition, the possibility of the flap loss was decreased since one end of the stripped ILM flap had been attached to the retina. However, number of eyes studied was not enough (two eyes), and a larger sample size study was needed in the future to prove the efficacy.

Cabbage Leaf Inverted Internal Limiting Membrane Flap Aurora *et al*[29] described cabbage leaf inverted ILM flap surgery for treating chronic, large and full-thickness MH. Three inverted ILM flaps sealed the hole which seemed like cabbage leaves. The bases of these flaps were connected to the edge of MH. Then the flaps were trimmed and flipped over the MH, one above the other, like the cabbage leaves. After

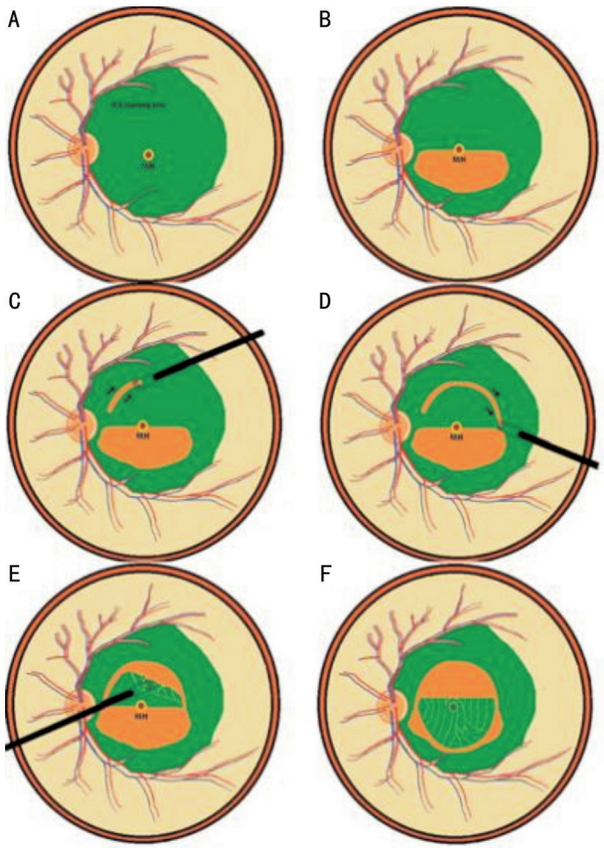

Figure 3 Large semicircular inverted ILM flap technique ILM at the lower 180° around MH was peeled while the ILM at the upper 180° was produced as a 4-disc diameter semicircular flap to cover the area of hole (image comes from Chen[26]).

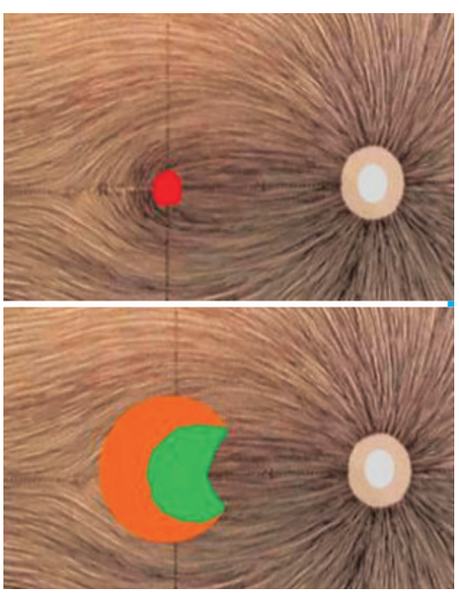

Figure 4 C-shaped temporal inverted ILM flap technology The temporal ILM flap was peeled around MH in 270-degree (C-shaped) and trimmed to retain about 1.5-disc diameter ILM flap to flip over MH (image comes from Ho *et al*[27]).

the surgery, the best-corrected visual acuity (BCVA) improved with type 1 MH closure. In the cabbage leaf technique, the retina surface of the flap was interlocked with the vitreous surface of the overlapping flap. It better stuck the flaps together and prevented the displacement of flaps in the process of fluid-gas exchange. Also, multilayered ILM flaps could cover MH better and more completely. It formed the compartment between the retinal nerve sensory layer, RPE and ILM, which was beneficial to the recovery of foveal tissue.

Floating Internal Limiting Membrane Flap In the study of Yamashiro *et al*[30] in 2018, the floating ILM flap technique was introduced for highly myopic patients. All eyes included achieved MH closure and retinal reattachment. And no additional manipulation of flap was performed to cover the MH (Figure 5). After the surgery, the free ILM flap floating in the vitreous cavity would adhere to the RPE in MH region once patients changed the positions. When the floating ILM flap was attached to the retina, it would promote the gliacyte to proliferate, then filling the hole and facilitating the closure of the MH without any additional manipulation of flap. However, the number of the eyes included in this surgery was small (nine eyes) and it was the retrospective research. Then larger sample size with prospective method are required to prove the surgical effect.

Free Internal Limiting Membrane Flap

A free internal limiting membrane flap Free flap technique could be considered for refractory MHs after initial surgical failure, and the surrounding tissue in the macula is not sufficient to perform inverted flap techniques. Studies comparing free flap technology with inverted flap technology suggested that they both could achieve favorable anatomical and functional recovery in treating large MH[31-32]. Also, retinal microstructural regeneration and ellipsoid zone defects reduced were observed after one year of follow-up in a study of 11 eyes by Vieregge *et al*[33]. In the study of Morizane *et al*[34] (Figure 6), free flap technology could be used in patients with refractory MH including idiopathic large MH lasting more than 1y (4 eyes), MH secondary to trauma (1 eye), pit-macular syndrome (2 eyes), foveoschisis with myopia (2 eyes), and proliferative diabetic retinopathy (1 eye). Regular surgery failed to achieve MH closure in these eyes. After autologous transplantation of the ILM, 9 eyes (90%) obtained successful MH closure and the postoperative BCVAs improved significantly (P=0.007). However, there are some limitations in the study introduced by Morizane *et al*[34]. The number of the eyes was small and the follow-up time was not long enough (the follow-up time was about 12±5mo). Further studies with larger sample size and longer observation time were needed to prove the efficiency of the free flap technique on the management of refractory MHs.

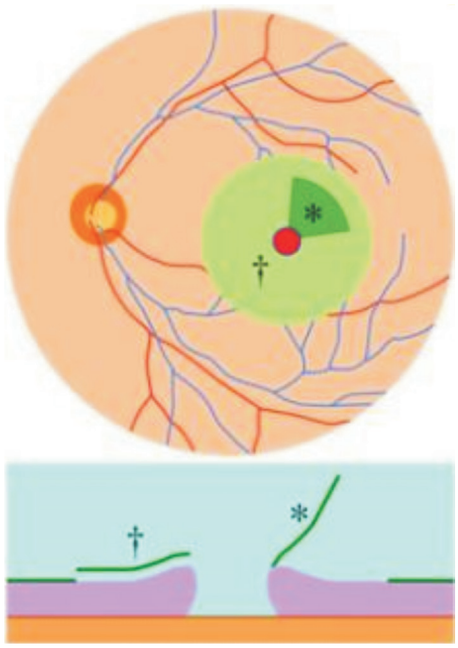

Figure 5 Floating ILM flap technique †The ILM was removed for about 2 disc diameters from the hole. *Remained flap was connected to the edge of MH (about 1-2 disc area; image comes from Yamashiro *et al*[30]).

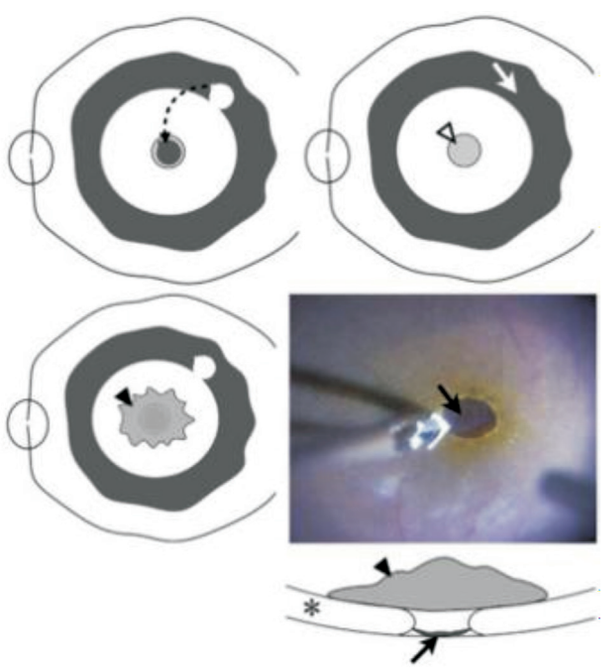

Figure 6 Free ILM flap technique A free ILM flap was peeled off (about the same size as the MH) and put inside the MH, stabilizing the flap with viscoat on the surface (image comes from Morizane *et al*[34]).

Multiple free internal limiting membrane flap A free ILM flap within the MH had the concern of floating up or escaping to the subretinal space. Chen *et al*[35] in 2018 applied the multiple free ILM flap insertion technique and it was used in patients with small-to-medium sized MH or shallow retinal detachment in high myopia. The ILM was removed to made free ILM flaps. Viscoelastics was introduced on the MH

before the first free flap prepared to be nudged into the hole. Viscoelastics was adopted to hold the first inserted flap on the MH, preventing the flap from floating up or sinking down to the subretinal space. Repeat the process to insert the following four free flaps into MH. In order to prevent the second and the third flaps from displacing the preceding flap, the initial flap used to insert into MH would usually be selected larger. When multiple free flaps were packed successfully, they would keep in specific positions more stably and support each other, acting as a bridge connecting different edges of the MH. This technique decreased the possibility of the flap loss. Also, it was suitable for MHs with shallow retinal detachment, since there was no need to use the instrument to insert the flap deeply into the MH. Multiple free ILM flap insertion surgery acquired 100% MH closure rate (13 eyes), compared with ILM peeling technique (42.9% MH closure rate; 14 eyes; $P<0.001$)[35]. And retina reattachment rate was 100% in both groups. Although the multiple free flap insertion technique closed MHs effectively, the visual recovery of this technology was unsatisfactory. The visual improvement showed no significant difference in the multiple free ILM flap group ($P=0.078$). The manipulation of multiple flaps might cause potential complications including mechanical damage to the RPE layer during repeated insertion and retinal toxicity of remained indocyanine green (ICG) on multiple flaps. Additionally, flaps occupied the space between the separated outer layers of the retina which might prevent the recovery of photoreceptor cells. The unfavorable visual outcome resulted from this effect remained to be proved.

Double Internal Limiting Membrane Insertion Free ILM flap technique had been introduced for the treatment of patients with large MHs or refractory MHs after primary operation. However, the free ILM flap had no supporting structure and the free flap might float up or sink down so it was not applicable for MH patients with retinal detachment. In the inverted flap technique, flap tends to flip back and then the insertion process would be prolonged. The repeated operations near the hole might result in damage of retina structure and impair the recovery of vision. Thus, double ILM insertion technique was introduced by Chen and Yang[36] for treating high myopia with MH retinal detachment. Both the free ILM flap and inverted flap were inserted together to MH. A small amount of viscoat was used before peeling the ILM. It prevented ICG from entering into the MH and reduced the retinal toxicity of the dyes. After inserting the inverted flap, viscoat was again applied to cover on the surface of the flap. It decreased the possibility of inverted flap folding back and the loss of free ILM flap. Also, since the inverted ILM flap was kept in the MH, the free ILM flap could not sink down to subretinal cavity; due to the presence of the free ILM flap, the inverted flap could not flip back. They supported and locked each other to keep the inserted flap issue steady. After the surgery, all eyes (9 eyes) acquired MH closed and retina reattached. This technique greatly stabilized the ILM at the specific location especially when perifoveal ILM was insufficient. However, further studies with a large case number were needed to confirm the observation. ILM flap could be covered on or inserted into the MH. In the studies of Park *et al*[37] and Rossi *et al*[38], the inverted ILM flap cover technique might get better vision recovery while ILM insertion surgery was more beneficial for treating large MHs. Among them, U-shaped closure was common (insertion group 63.6%, inverted ILM flap cover group 76.9%)[37-38]. The ILM tissue inserted into holes might obstruct photoreceptor cells regenerations. Also, when ILM was inserted into MH, it might cause mechanical damage of RPE and long-term direct contact between the residual ILM of the stain and RPE might cause chemical damage of RPE. These might be the reason why the recovery of vision in inverted flap cover surgery was better than that in insertion surgery.

Auxiliary Means

Assisted with perfluoro-n-octane PFO could be applied on the MH to stabilize the free or inverted ILM flap at proper place till the end of fluid-air exchange[21,24,39-40]. Additionally, PFO could help flatten the retina and the ILM flap is easily made with the posterior counter traction of PFO[41]. Due to its vapor pressure, a small bubble of residual PFO was removed by evaporation instead of using lavage, thus reducing the risk of flap displacement. Therefore, PFO was selected among various heavy liquids[24].

Assisted with dye Peeling the ILM completely was a technical operation because it was difficult to distinguish the ILM from other retinal issue. Additionally, incomplete removal of ILM might result in the hole failing to close. Also, mechanical damage of the retinal structure during the process of ILM peeling might cause paracentral scotomata. Intraocular stains were applied to visualize the retina to completely remove the ILM and reduce the risk of surgical trauma. Available stains were usually ICG, brilliant blue G (BBG), tryptan blue (TB), and triamcinolone acetonide (TA). However, some studies had shown that ICG might have toxic effects on the retina. Compared with ICG, TB was safer without toxicity to RPE cells[42]. Previous studies showed that it was non-toxic to rabbit retina when it was rapidly removed[43-44]. Also, TB was cheaper and easier to remove because of its high water-solubility. While TB was required to remain for a longer time in contact with ILM compared with ICG[45-46]. Compared with ICG or TA, BBG was a preferable adjuvant contributing to better visual outcomes of ILM peeling in patients with MH while it showed no significantly difference in the closure rate[47-48].

Assisted with autologous blood Macular plug includes inverted ILM flap with autologous blood clumps (ABC) or autologous gluconated blood clumps (AGBC).

Lai *et al*[49] introduced inverted ILM flap with ABC operation in highly myopic patients with MHRD in 2015. Fresh blood was drawn from anterior elbow vein of patients and injected into the eye to cover MH. Then blood quickly turned into the blood clot. The ABC and flap mixed to form the macular plug which could seal MH in minutes. Patients only needed to keep the prone posture for one day after initial surgery assisted with gas tamponade. It reduced the time for patients to stay prone. This technique achieved retina attached in all eyes and obvious BCVA improvement (P=0.001). Also, 26 eyes (96%) obtained MH closure.

Another research referred by Chakrabarti *et al*[50] used macular plug formed of AGBC and inverted ILM flap to treat large stage 3, stage 4 MHs in 2017. It also achieved satisfactory MH closure and significant functional improvement. Preparation of AGBC before the surgery: 1 mL of 5% glucose was added to autologous blood (2 mL). Then the ILM flap and AGBC formed the macular plug. This technique allowed the patients to adopt any comfortable position without gas tamponade, especially suitable for those patients with poor cooperation.

Inverted ILM flap might act as a bridge which could be beneficial for glial cells to proliferate. Moreover, the formed blood clot could seal the MH, also the constituents and growth factors in the blood would promote recovery. Additionally, ILM flap technique associated with AGBC or ABC might decrease the risk of flap loss or displacement. However, there is a risk of infection from autologous blood products.

Assisted with viscoelastics We conclude that viscoelastics supplies three main auxiliary functions. First, viscoelastics used before peeling ILM reduces the toxicity of the dye to the retina. Second, viscoelastics applied over the ILM flap could act as a ballast to reduce the displacement of the flap and keep it in the correct position. Third, it acts as a binder to stabilize the flap.

For example, these functions of adhesive viscoelastics (Viscoat, Alcon) were applied in the study of Song *et al*[51]. Viscoelastics was injected into the MH and then ILM was stained with ICG. The ILM below the hole was completely removed but the above ILM was retained to the MH. Viscoelastics was injected to inferior half of the MH and applied as a binder. Flipped the ILM flap over the entire hole and flattened the flap. Supplemental viscoelastics was then injected to the surface of the inverted ILM flap like the ballast. This technique could acquire anatomical and functional recovery in highly myopic patients with large MH[51]. Also, it was simple and cost-effective and viscoelastics showed no toxic impact on the retina and it could be remained in the position[52].

OUTCOMES

Both functional and anatomical recoveries of MH are affected by the MH type. For idiopathic MH, studies indicated MH closure rate was 89% to 100% using inverted ILM flap technique and 70% to 92% using the ILM peeling technique[32,53-55]. Different from idiopathic MH, high myopia is often accompanied by the extension of the axis of the eye, posterior scleral staphyloma, retinal atrophy and choroidal atrophy. It was difficult for treating MH in highly myopic eyes[56-57]. Studies reported that the inverted ILM flap operation could obtain 75%-100% MH closure rate compared with ILM peeling operation (25%-88.9%) in highly myopic eyes[17-18,56,58]. Also, a Meta-analysis supported that higher MH closure rate was achieved in ILM flap surgery than in ILM peeling surgery for treating patients with high myopia[59].

Though postoperative visual acuity has improved for both highly myopic MH and idiopathic MH, there is no significantly statistical superiority in ILM flap technique compared with ILM peeling technique[17,53-54,57,60-65]. A retrospective, multi-center study in Japan showed the recovery of vision was also correlated with the preoperative vision and MH size[53]. Additionally, there is no uniformed criteria in selecting ILM dye and various dye might have different effects. Dye especially ICG might have toxic effect on retina and BBG could be the superior option[42-44,47-48]. Moreover, the ILM flap technique has several technique variations, including classical inverted ILM flap, modified inverted ILM flap, floating ILM flap, free ILM flap and double ILM insertion technique. And a series of auxiliary means has been applied in this technique, assisting with PFO, dye, autologous blood and adhesive viscoelastics. There is controversy about the effects between several technique variations of ILM flap, and it needs to be explored in the future.

ADVERSE EVENT

One problem of the ILM flap technology in the treatment for MH is that gliosis by Müller cells could not be controlled, and there is a risk of hyperproliferation of the glial. The proliferation of glial cell is efficient for closing MH. However, excessive proliferation may bring toxic influence on retinal issue which will cause poor visual prognosis[66]. The foveal highly reflective lesion could be observed after the operation of ILM flap. Glial hyperproliferation was reported to be associated with ILM insertion or classical ILM flap surgery, as they put folded ILM into the MH without a guideline of a proper amount. The technique of a single layer had lower risk[19,23-24]. It suggested a hyperplasia of the fovea and sustained activation of glial cells might result in tissue damage. If scar formation was caused, it might obstruct the ellipsoid recovery[19,67]. Another problem of using the ILM flap technology for treating MH is the possibility of flap unfolding,

displacement or even loss[68]. In addition, not all ILM could be produced into suitable flaps for the treatment of MH. This technique requires sufficient perifoveal ILM remained and careful operation to avoid iatrogenic damage. Also, the remained dyes on the ILM (especially ICG) might cause toxic effects and RPE atrophy in contact with retina[69-70].

CONCLUSION

In general, ILM flap operation could be considered for patients with refractory MHs, such as, full thickness MHs[68], very large MHs (even greater than 2000 μm)[58,71-72], high myopia with or without retinal detachment, failure of initial MH surgery[73-74], and accompanied with other problems: best vitelliform dystrophy (BVD)[75], large traumatic MHs with choroidal rupture and subretinal hemorrhage[76-77], large MHs secondary to uveitis[78] and so on. This new technology could help achieving high MH closure rates. However, an important problem is that the flap might be unfolded, lost, or displaced. Therefore, methods including enlarging the flap area, multiple flaps, auxiliary PFO, adhesive viscoelastics, and autologous blood are proposed to stabilize the flap. Although this technique has increased the overall MH closure rate, the improvement of vision is not as good as expected. This might be because the unintentional mechanical damage to RPE during operation, the residual dye of the flap on the toxicity of RPE, excessive gliosis and proliferation obstructed the recovery of photoreceptor. Therefore, further follow-up researches are required to identify the long-time complications of the flap technology. Further animal experiments are needed to study expression regulation to prevent hyperproliferation of the glial. A greater number of surgical procedures are needed, increasing the proficiency of the surgeon and improving the technique step by step. ILM flap technique has many variations, including the difference of the size, shape, number, and manner in which the flaps put on the MHs. There is controversy about the effects and the choice of several technique variations of ILM flap, and it needs to be explored in the future.

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