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· Editorial ·

How internal limiting membrane peeling revolutionized macular surgery in the last three decades

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INTRODUCTION

The Italian anatomist Filippo Pacini discovered the internal limiting membrane (ILM) in 1844[1]. The ILM is the basement membrane of the retinal Müller cells representing the structural interface between the retina and the vitreous. The macular ILM is thickest, measuring 2.5 μm and progressively thins to 0.5 μm at the vitreous base[2]. The ILM is important for the early development of the retina and the optic nerve, but it can cause problems when it becomes thicker with age or when cells grow on it and exert tractional forces on the retina.

Removing the ILM from the retina (ILM peeling) is a common surgical procedure for various diseases affecting the vitreomacular interface (VMI). These pathologic conditions include macular holes, macular puckers (postoperative) epiretinal membranes (ERM), diabetic macular edema, retinal detachment, retinal vein occlusions, vitreomacular traction, optic pit maculopathy, and Terson's syndrome.

It was in the late 1980s that the possibility of ILM peeling was considered a surgical option in treating vitreoretinal disorders. Morris *et al*[3] presented the first case of ILM peeling in 1990 in patients with Terson's syndrome and sub-ILM macular hemorrhage. They postulated that ILM removal could be used for other tractional types of maculopathies. Kelly and Wendel[4] performed a vitrectomy and removed the posterior cortical vitreous to relieve traction over the macula, shedding light on ILM peeling as a possible therapy in treating full-thickness macular holes (FTMH). Closure rates of up to 95% with significant improvement in visual acuity have been reported in primary macular hole surgery, especially after introducing ILM peeling[5]. In 2010, the "inverted ILM flap" technique increased closure rates[6]. Meanwhile, the method has evolved from total peeling to inverted flap to just temporal peeling and temporal flap to mitigate its adverse effects and improve surgical outcomes. Using dyes to stain the ILM, also known as "chromovitrectomy", has made the retinal surface peeling more precise, complete, and probably less traumatic[7]. Unified and evolving classification systems are necessary to compare surgical techniques and outcomes[8].

WHAT IS THE RATIONALE FOR PEELING THE INTERNAL LIMITING MEMBRANE?

ILM peeling is believed to improve FTMH closure by various mechanisms. Despite the ILM being only a few microns thick, it contributes significantly to retinal rigidity, and its removal increases retinal compliance, aiding hole closure. It may improve the oxygen supply to the inner retina. Surgical peeling of ILM removes the remaining macular cortical vitreous, which could exert residual tangential traction and inhibits the formation of postoperative ERM and secondary tangential traction. Finally, ILM removal, with its trauma to the Müller cell end feet, may lead to a retinal glial cell proliferative response, which could enhance macular hole repair[9].

We have proposed that Müller cell-mediated tissue movements, which create the fovea during ontogenetic development, may also play a role in the closure of macular holes[10-11]. We suggested that the regular regeneration of the foveal morphology proceeds by Müller cell-mediated tissue movements without cell proliferation. In contrast, the irregular foveal regeneration partially proceeds by the proliferation of Müller and retinal pigment epithelium (RPE) cells[12]. Healing changes after macular hole surgery include outward migration of the inner retinal layers and inward migration of photoreceptors. These changes result in an appearance of the healed fovea that approached the normally expected configuration of the fovea and is associated with improved acuity. The foveation process, photoreceptors' inward migration, and inner retina's outward migration may not necessarily occur fully in every postsurgical eye[13].

TECHNICAL ASPECTS AND INDICATIONS OF INTERNAL LIMITING MEMBRANE PEELING

25-gauge (25G) instruments allow minimal invasiveness and faster recovery after ILM peeling. After removing the vitreous and posterior hyaloid, gas tamponade is applied to close the macular hole and promote healing. The outcomes of this procedure are satisfactory in terms of morphology and function. Still, some factors negatively affect the initial closure rate, such as extended axial length, the large diameter of the macular hole, and the long duration of symptoms. In persistent holes, a second surgery may achieve closure. To facilitate ILM peeling, adjuvant dyes are used to make the ILM more visible. The ILM can be grasped directly with forceps, or a flap can be created with a membrane scraper and then peeled in a circular motion parallel to the retina. The ILM is removed from the eye or used to fill the hole. A variation is foveal-sparing ILM peeling, which preserves the ILM at the fovea to reduce the risk of complications and preserve visual function[14-15].

Studies have shown that ILM peeling can improve visual acuity and macular hole closure rates, reduce foveal thickness, and improve foveal morphology. Although the technique requires additional intraoperative agents, instruments, and surgical time, the question to peel or not to peel is no longer there. This technique is now widely adopted as a standard of practice. The exact modification of the method depends on several factors, such as surgeon preference, patient characteristics, and clinical scenarios. It is difficult to say which way is best as each has advantages and disadvantages.

1) The need for ILM peeling is more controversial for smaller macular holes, especially those less than 250 μm[16]. The surgical repair of small FMTH with ILM peeling with inverted flap delays the foveal structural repair and gains a low foveal sensitivity compared to the standard technique[17].

2) The inverted ILM flap covering technique resulted in superior reconstitution of outer layers of the retina, and more improvement in postoperative best-corrected visual acuity (BCVA) than the ILM flap filling technique[18].

3) The use of an inverted or pedicle flap appears better suited to primary FTMHs, whereas a free flap benefits refractory FTMHs[19].

4) Specific types of FTMHs have well-established lower closure rates with surgery. Large (>400 μm), chronic (>6–12mo), and traumatic FTMH have lower rates of closure, and most surgeons would always peel the ILM in these cases.

5) Large (400–550 μm) and X-large (550–800 μm) holes can be successfully treated with ILM peel and flap techniques, respectively[8].

6) Peeling is undoubtedly indicated in large, chronic, myopic, and traumatic macular holes. Inverted ILM flap surgery may have an expanding role in some of these cases. Small and recent onset macular holes may not require ILM peeling in all cases, and small and medium-sized macular holes may benefit from an evolving number of alternative ILM-peeling options.

7) All cases of refractory persistent holes responded to macular hole edge manipulation with high closure rates[20].

8) Myopic macular retinoschisis is a traction-induced condition. It can lead to retinal thickening, cystoid spaces, detachment of the fovea (called myopic foveoschisis), and lamellar or FTMH[21]. These conditions benefit from ILM peeling. Surgeons increasingly opt to perform ILM peeling with ILM flap creation. An inverted flap is probably the best method. Fovea-sparing peeling may contribute to better visual acuity outcome and lower risk of postoperative FTMH development in eyes with myopic foveoschisis[22].

9) ERM are characterized by cellular proliferation on the inner retinal surface, and ILM peeling is the only measure proven to be preventative.

INTERNAL LIMITING MEMBRANE PEELING SIZE

There are currently no agreed parameters for the optimum extent of ILM to be peeled during surgery for macular holes. Most surgeons aim to peel an approximately one-disk diameter radius of ILM around the foveal center, but reports vary hugely from 0.5-disk diameters to 3 or more. Enlarging the ILM peel area can result in hole closure in failed cases undergoing revision surgery, and some authors have argued for large ILM peel areas in all cases. A prospective study of patients undergoing surgery with 3-mm and 5-mm peel showed no significant difference in hole closure rates but better visual results in the smaller peel group with less retinal nerve fiber layer thinning, particularly temporally[23]. Conversely, another randomized controlled study with ILM-peeling radii of 0.75 and 1.5 disk diameters found no difference in visual outcomes but did find a benefit of larger peels regarding an improvement in metamorphopsia[24]. The extent of the area of ILM removed is strongly associated with the degree of several postoperative changes, including the shortening of the disk foveal distance, the extent of a dissociated optic nerve fiber layer (DONFL) appearance, and, notably, the postoperative visual acuity. Thus, it is still being determined how much ILM should be optimally peeled during surgery for macular holes. Hypothetically, there may be a minimum ILM-peel area for a set size of the macular hole to allow for enough reduced retinal compliance to permit closure. This area may vary with hole chronicity and other factors. Larger ILM peels would ensure this threshold was passed at the expense of more significant inner retinal changes and potentially reduced visual function.

ADVERSE OUTCOMES OF INTERNAL LIMITING MEMBRANE PEELING

Peeling the ILM can enhance the success of macular hole surgery. Therefore, a common practice in macular hole surgery is to peel the ILM for all cases. However, even the most perfectly performed ILM peel has consequences on retinal structure and function, which may be detrimental in some patients. The specific technique and instrument of ILM peeling, the surgeon's skill, and any staining dye used may add to the risks[25]. Some studies have documented postoperative changes that may affect visual function[26].

1) Müller cells are essential for maintaining the integrity and function of the retina. They span the entire retina thickness and interact with various retinal cells, including photoreceptors and ganglion cells. ILM peeling inevitably causes damage to the Müller cell footplates and may result in the loss of some inner retinal tissue[27]. The extent and consequences of this damage are still unclear and controversial. Some studies have reported changes in retinal morphology, electrophysiology, and metabolism after ILM peeling, while others have found no significant or beneficial effects.

2) DONFL is observed localized to the peeled ILM region. No visual dysfunction (visual acuity, field testing, and scanning laser ophthalmoscope microperimetry) is seen. DONFL appearance may be due to a rearrangement of the optic nerve fibers rather than a loss or damage.

3) Other morphological changes of the macula may occur after ILM peeling, such as temporal thinning, arcuate retinal nerve fiber layer thickening, and a decrease in papillofoveal distance; these anatomical changes do not affect the visual function[28].

4) Dyes that stain the ILM facilitate removal. One of the potential complications of chromodissection is dye toxicity, which can affect the retinal function and structure. Some chromophores, such as indocyanine green (ICG), may cause retinal toxicity due to their photooxidative properties, high osmolarity, or high concentration. Retinal toxicity can manifest as visual field defects, reduced nerve fiber layer thickness, RPE, or ganglion cell damage. Therefore, ICG should be used cautiously and only at low concentrations and short exposure times. A safer alternative is brilliant blue, which has a selective affinity for the ILM and provides good staining in an iso-osmolar solution. It is currently the gold standard dye for ILM peeling.

5) Another potential complication of chromovitrectomy is phototoxic damage, which can occur due to intense light exposure during the surgery. Phototoxic damage can affect the photoreceptors and RPE cells and lead to vision loss.

SURGERY FOR REFRACTIVE MACULAR HOLES

With the advent of modern imaging modalities, the pioneering initiative of Kelly and Wendel has been modified into more sophisticated techniques to treat refractory macular holes, including ILM peeling, inverted ILM (i-ILM), i-ILM flap, pedicle ILM flap, retracting ILM door, autologous free ILM flap, non-ILM grafts, human amniotic membrane (hAM), hAM graft, adjuvant chorioretinal adhesives, and experimental mesenchymal stem cells (MSCs). Other methods studied included relaxing arcuate retinotomy, subretinal infusion, and hydrodissection[24].

Frisina *et al*[29] evaluate the efficacy of different surgical techniques for FTMHs that do not respond to pars plana vitrectomy and ILM peeling. The main outcomes measured were the closure rate of refractory FTMH and the improvement of BCVA. Ten surgical technique subgroups were identified: autologous platelet concentrate (APC); lens capsular flap transplantation (LCFT); autologous free ILM flap transplantation (free ILM flap); ILM peeling enlargement, macular hole hydrodissection (MHH), autologous retinal graft (ARG), silicone oil (SO), hAM, perifoveal relaxing retinotomy, arcuate temporal retinotomy. The closure rate of refractory FTMH was comparable among subgroups; no significant heterogeneity was detected. BCVA improvement is strongly associated with surgical technique and significant heterogeneity among subgroups was observed. Three groups of surgical technique subgroups with similar BCVA improvement were established: high BCVA improvement (hAM); intermediate BCVA improvement (APC, ARG, LCFT, MHH, SO); low BCVA improvement (free ILM flap, enlargement of peeling, arcuate temporal retinotomy). The most effective techniques for treating refractory FTMH in terms of visual recovery are hAM, lens capsular flap, and APC, which achieve better functional results than free ILM flap. MHH, ARG, perifoveal relaxing, and arcuate temporal retinotomy involve complex and unnecessary surgical steps considering the surgical alternatives with equivalent anatomical and functional results. Different prognostic parameters for APC have been described[30].

CONCLUSION

In the last 30y, ILM peeling, with its various modifications, has become a standard method of macular surgery. The rationale for ILM peeling is to remove the rigid basement membrane of Müller cells. This increases the elasticity of the denuded macula; then, a hole can close as the retinal tissue goes through the various steps of foveogenesis again[31].

The optimal surgical approach for recurrent or persistent macular holes is still being investigated. Adjuncts like APC and hAM offer a valid therapeutic option for persistent holes. All options should be evaluated in randomized trials, and if this is not possible in close international cooperation[8,20,32].

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