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REVIEW ARTICLE

Idiopathic macular holes – A review of current management strategies

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Abstract

Macular holes (MHs) cause considerable ocular morbidity, reducing visual acuity, and distorting central vision. Idiopathic MHs (IMHs) are the most common subtype of this pathology. Modern treatment options for IMHs include pneumatic vitreolysis, vitrectomy, and chemical vitreolysis. Extensive laboratory and clinical research have led to the development of unique surgical approaches and techniques for each treatment modality offered, thus enabling tailored treatment for individual patients depending on the specific clinical scenario. This review summarized what is known about MHs physiologically and clinically and highlights the experience gained with different treatment modalities. Better understanding of this unique pathology may offer our patients better care and better visual outcomes.

Description of the Condition

Macular holes (MHs) are retinal defects which involve the center of the anatomical fovea.[1,2] Severity may range from asymptomatic incidentally discovered MHs, to advanced vision-threatening ones.[2,3] MHs are often described according to the extent of retinal layers involvement. Full-thickness MHs (FTMHs) encompass all the layers of the retina from the internal limiting membrane (ILM) to the retinal pigmented epithelium (RPE) [Figure 1].[2] Partial-thickness MHs, also termed lamellar holes, involve only the inner retinal layers, while the photoreceptors layer may remain intact [Figure 2].[2,3] Although the majority of cases are idiopathic (>85%), MHs may also be secondary to various conditions, among the most common of which are high myopia and ocular trauma.[2,4,5] Kumawat *et al.* described in detail other infrequent causes of secondary MHs.[5]

Epidemiology

The reported prevalence of idiopathic MHs (IMHs) in the general population ranges between 0.02% and 0.33%.[1,4] IMHs are more common in women (approximately 70% of cases) and usually appear in the 6th and 7th decades of life.[1,4,6] For patients with an idiopathic FTMH in one eye, the risk for developing an MH in the fellow eye is 10–20%.[1,7]

Pathophysiology

IMHs are the sequelae of vitreomacular adhesion (VMA) and traction (VMT).[2] The vitreous is a clear gel-like structure enveloped by a hyaloid membrane (the vitreous cortex), the posterior part of which is attached to the ILM of the retina. With aging, the vitreous body liquefies, shrinks, and gradually detaches from the retina, starting at the posterior pole. Physiologically, the vitreous will continue to detach from the retina and eventually remain firmly attached to the retina only at the vitreous base, straddling the ora serrata. In most cases, this process results in no retinal damage.[2,8,9] However, incomplete or abnormal detachment may result in pathologic VMA and VMT, which can distort the foveal contour and result in MH formation [Figure 3].[8] The traction forces affect the foveola and might impair central vision, causing distorted vision or decreased visual acuity (VA).[2,5,10]

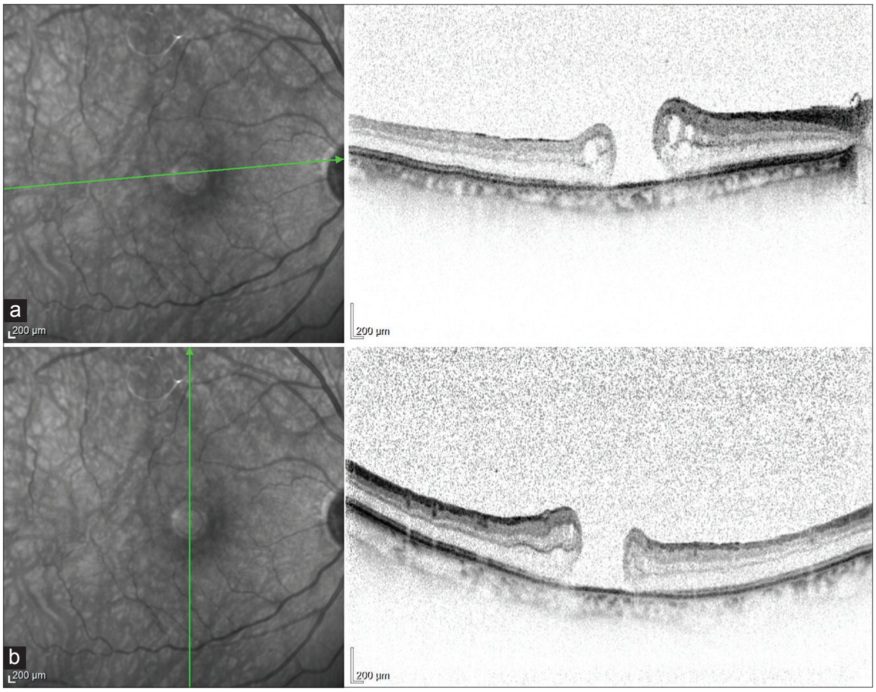

Figure 1: Full-thickness macular hole (FTMH). A horizontal (a) and vertical (b) macular optical coherence tomography section through an FTMH. Note the edematous and rolled up retina around the hole, and the bare retinal pigment epithelium at the base of the hole

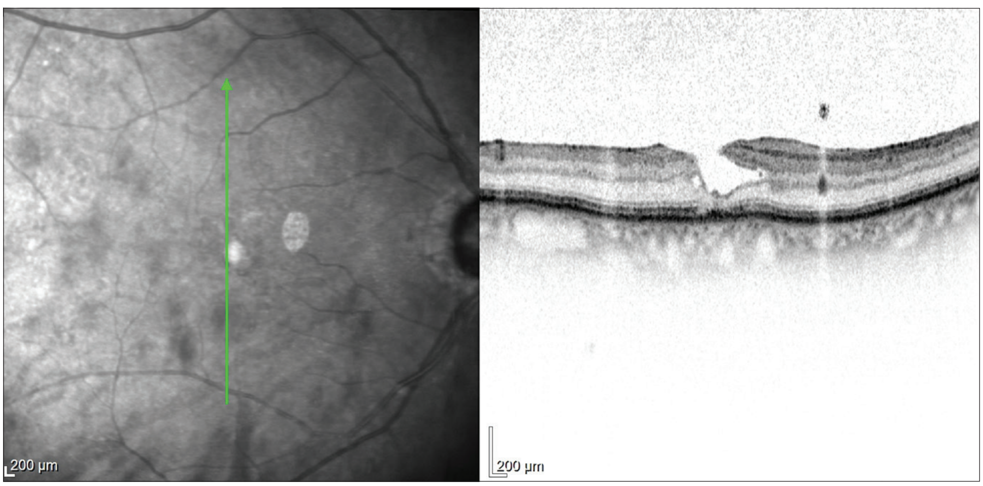

Figure 2: Lamellar macular hole. A vertical macular optical coherence tomography section through a lamellar macular hole. Note that the pathology involves mostly the internal retinal layers. The retinal pigment epithelium and the outer retina is also affected but to a lesser extent

Staging

In 1988, Johnson and Gass described a staging system based on slit-lamp biomicroscopy findings for IMHs, that is, still commonly accepted and used.[2,6,11] Later on, the use of optical coherence tomography (OCT) enabled better understanding of the condition, and updated staging systems were described.[2,10,12,13] Table 1 summarizes the main characteristics and differences of the commonly used staging systems.

Treatment Modalities for MHs

Vitrectomy

Pars plana vitrectomy is a surgical technique during which the vitreous gel is removed from the eye through cannulas in the sclera.[14] Vitrectomy was first reported as a treatment for MHs by Kelly and Wendel, in 1991.[15] In their series, 52 patients were treated with pars plana vitrectomy, removal of adherent

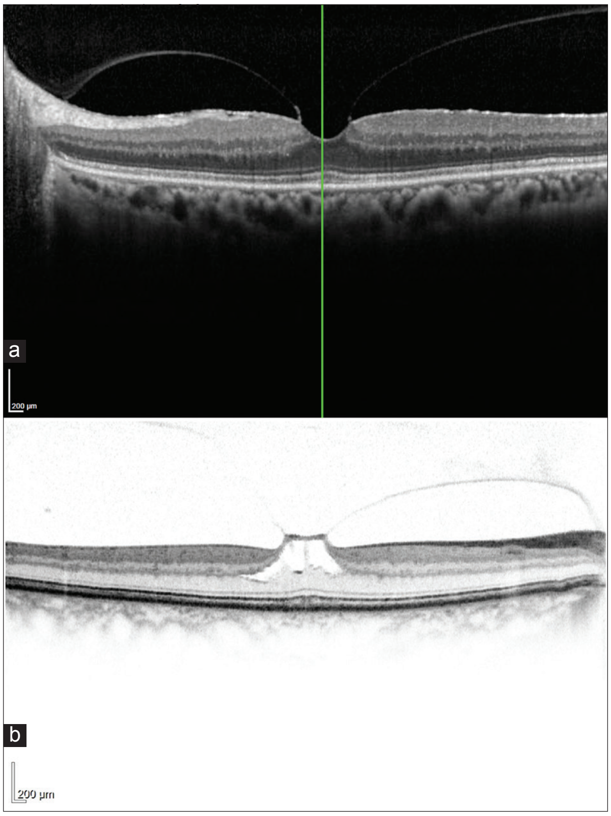

Figure 3: Vitreomacular adhesion (VMA) and vitreomacular traction (VMT). (a) A macular optical coherence tomography cross-section demonstrating VMA. The posterior vitreous is attached to the perifoveolar area with minimal distortion of the foveal contour. (b) VMT is demonstrated as the posterior vitreous exerts traction on the retina, elevating the foveolar depression and separating the inner retina from the outer retina creating a schisis-like appearance

cortical vitreous, stripping of epiretinal membranes, total gas-fluid exchange with injection of non-expansible concentration of sulfur hexafluoride (SF_6) and face-down positioning for a week post-operative. Of the 52 patients, reattachment of the macula was achieved in 58% of patients, and 73% of them enjoyed improvement in VA. Since then, surgical adjustments and improvements have been made, and treatment is more case dependent.[16,17] It has been shown that vitrectomy with posterior hyaloid detachment is effective in alleviating VMT.[14,15] Treatment success is measured mostly by improvement in best-corrected VA (BCVA) and anatomical hole closure. VA improvement largely depends on pre-operative VA, MH size, and symptoms duration.[1,16,18]

In 2001, the American Academy of Ophthalmology published an ophthalmic technology assessment report investigating and reporting the accumulated knowledge regarding the treatment of MHs.[7] This report was based on a broad literature review that included three multicentered randomized controlled trials (RCTs) comparing surgery versus observation for MHs. Level 1 quality evidence from these studies showed that vitrectomy surgery is superior to the observation for MHs Stages 3 and 4. According to this report, only one randomized study evaluated the benefits of surgery over observation for Stage 2 MHs, and although it did not show an advantage in terms of VA, it revealed a statistically significant lower rate of progression for the surgery group. In another RCT comparing surgery with observation for Stage 1 MHs, surgery failed to show superiority.

Banker *et al.* reported the 12-month follow-up results of their multicentered RCT, comparing vitrectomy surgery (95 eyes) with observation (92 eyes).[19] Complications in the vitrectomy group included RPE alterations, retinal detachment, reopening of the hole, choroidal neovascular membrane, cystoid macular edema, and endophthalmitis. All these complications occurred in the post-operative short term (up to 15 weeks). No complications occurred in the observation group. Complications reported in other studies included infection, retinal tears, intraocular pressure elevation, hypotony, choroidal detachment, endophthalmitis, and vitreous hemorrhage.[7,20,21] In the long term, nuclear sclerotic cataract formation is very common, and retinal detachment may occur.[7,20,21]

ILM Peeling

Rationale

Being a relatively rigid membrane, removal of the ILM aids hole closure by improving retinal compliance.[16] ILM peeling further helps healing by removing vitreous cortex residues which can exert traction after surgery, eliminating the bed for fibrocellular proliferation surrounding the hole, and promoting glial cell proliferation which was found to improve hole contraction [16,18,22]

ILM dyeing

The ILM is a colorless membrane located at the interface between the retina and the vitreous. Its thickness varies across the retinal surface, reaching 0.4–1.4 μm at the macula.[23] ILM peeling is challenging and carries additional risks including increased surgery time, use of intraocular dyes, retinal toxicity, increased retinal inflammation and edema, and mechanical retinal damage.[18,23] Vital dyes are used to enhance the ILM visualization and improve safety during surgery. In addition to increasing ILM visibility, vital dyes may make the ILM more rigid and fragile.[18]

The first dye in use was indocyanine green (ICG).[18] It allows good visualization of the ILM but shortly after its introduction, it became clear that ICG causes dose-dependent retinal toxicity. ICG has photosensitizing properties, leading to increased toxicity with longer application time, higher ICG concentration, and extended light exposure.[18,23] Trypan blue (TB) has a better safety profile, but it is not ILM specific and also stains epiretinal membranes. Brilliant blue G (BBG), despite showing reduced contrast in comparison to ICG, is ILM specific and safer.[18] Shukla *et al.* reported similar rates of anatomical closure for all three dyes, but visual outcomes were better with TB and BBG compared to ICG.[22] A meta-analysis conducted by Azuma *et al.*

showed better functional results with BBG compared to other dyes, with no significant difference in anatomical results.[24]

Triamcinolone acetonide is a glucocorticoid which is also used as vital dye.[23] It is not ILM selective and it tends to deposit inside the MH during surgery [Figure 4].[23,25] Although its use has been associated with intraocular pressure elevation, cataract formation, and acute endophthalmitis,[23,26] the previous studies did not reveal inferior anatomical or functional results with its use.[25,26] More recently, acid violet 17 was introduced. It is an ILM-specific dye, allowing satisfying contrast with acceptable safety profile,[23,27] but it is not yet commercially available until toxicity information is further investigated.[18] Heavier than water dyes are prepared by mixing the above compounds with either deuterium oxide, polyethylene glycol, or mannitol. Their use spares the need for fluid-air exchange.[16]

Efficacy of ILM peeling in MH surgery

A recent Cochrane review evaluated the benefits of ILM peeling compared to no ILM peeling in MHs [Figure 5].[14] The reviewers concluded favorable results for ILM peeling in Stages 2, 3, and 4 MH. According to their results, which are based on four RCTs, distance VA was better in the ILM peeling Group 3 months after surgery but was similar at 6 and 12 months post-surgery. The rate of primary hole closure, i.e., complete apposition of the hole's margins after a single operation, was higher in the ILM peeling group with greater odds ratio for closure at advanced stages. For MH Stages 3 and 4, ILM peeling also resulted in higher rates of final hole closure. Moreover, for holes Stages 2 and 3, patients of the ILM peeling group also required less reoperations. Intraoperative and post-operative complication rates and quality of life were similar between the two groups. The authors postulated that the lack of difference in distance VA at 6 and 12 months was related to reoperations in the no peeling group; since their 3-month distance VA and primary closure rates were inferior, they had a higher rate of reoperations, during which ILM peeling was very frequent and VA improved as a result [Figure 6].[14]

ILM peeling for chronic MHs

MHs are regarded as chronic 12 months after the onset of symptoms [Figure 7].[28] The literature is relatively sparse regarding this type of IMHs, and it is controversial whether surgical treatment is indicated in these cases as several studies reported relatively low success rates.[28-30]

Stec *et al*. reported 57% primary anatomical success rate in their retrospective series of 23 eyes with chronic MHs (mean duration 4.2 years) Stages 2–4 treated by vitrectomy, gas tamponade, and posturing with or without ILM peeling.[29] All eyes in which primary closure was observed underwent ILM peeling during surgery. Seven eyes which did not undergo ILM peeling and did not achieve hole closure underwent a second operation with ILM peeling, and all but one showed subsequent hole closure. Final closure rate allowing for multiple procedures was 83%. The authors reported that ILM peeling is correlated with primary surgical success ($P = 0.0005$). Pre-

Table 1: Macular holes classification

Biomicroscopic staging (Gass classification)[6,11,13]	Common clinical adaptation of Gass classification[2,10]	The international vitreomacular traction study classification system[2]
	Stage 0: Asymptomatic normal appearing macula with VMA, in an eye contralateral to an eye with full-thickness MH	VMA* to central macula. Normal foveal contour
Stage 1A: Foveolar detachment characterized by loss of the foveal depression, with no posterior separation of the vitreous. Yellow spot measuring 250–300 μm Stage 1B: Foveal detachment characterized by an additional loss of the foveal depression, enlargement of the yellow spot to a yellow halo or ring, no vitreofoveal separation	Stage 1: Impending or occult MH	VMT*, no full dehiscence of the vitreous from the inner retinal layers. Distortion of the foveal contour. Intraretinal structural changes or elevation of the fovea above the RPE are present
Stage 2: Early FTMH. The yellow halo becomes a gray-white halo	Stage 2: Small MH <400 μm	Small (≤250 μm) FTMH, with VMT Medium (≥250 μm and ≤400 μm) FTMH, with vitreomacular traction
Stage 3: FTMH with posterior hyaloid detachment with or without an overlying operculum. retinal defect ≥400 μm	Stage 3: Large MH ≥400 μm	Large (≥400 μm) FTMH, with vitreomacular traction
Stage 4: FTMH with complete PVD and Weiss ring	Stage 4: FTMH with PVD	Small, medium, or large FTMH with complete vitreous dehiscence and no traction

*According to the International Vitreomacular Traction Study Classification System, VMA and VMT can be subdivided: (1) By size of attachment area: Focal ≤1500 μm and broad >1500 μm; (2) by the presence of concurrent retinal conditions: Isolated or concurrent. FTMH: Full-thickness macular hole; MH: Macular hole; VMA: Vitreomacular adhesion; RPE: Retinal pigment epithelium; PVD: Posterior vitreous detachment

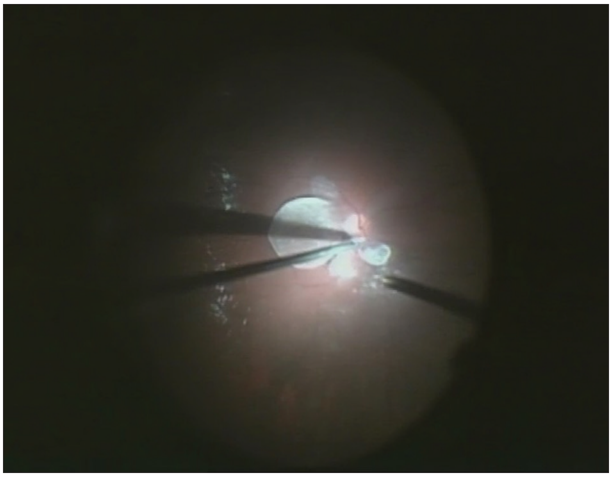

Figure 4: Triamcinolone acetonide (TA) injection. An intraoperative color image of TA injection. TA can be used as a vital dye during macular hole surgery, as shown

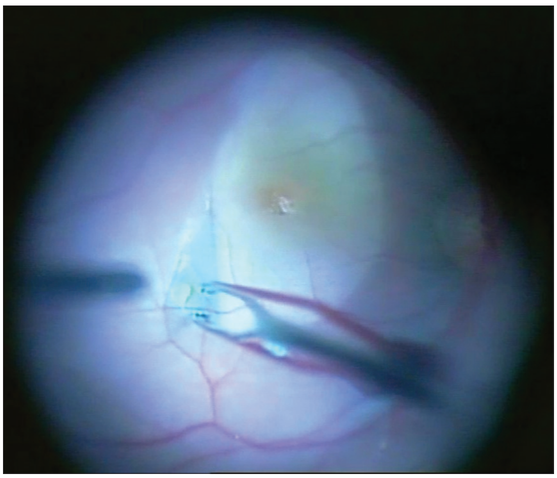

Figure 5: Internal limiting membrane (ILM) peeling. A color image of ILM peeling following ILM dying with Trypan blue and brilliant blue G. Note the ILM flap being grasped with intraocular forceps, and retina denuded from the ILM negatively stained

operative and post-operative mean logarithm of the minimum angle of resolution (logMAR) VAs were 1.14 and 0.74, respectively.

Shukla *et al*. reported the results of vitrectomy with ILM peeling, gas tamponade, and prone positioning for 26 eyes with Stages 3–4 chronic MHs.[28] The mean duration of symptoms was 4.75 years. Eighty-one percentage of eyes achieved anatomical hole closure. Pre-operative and post-operative mean logMAR VAs were 1.12 and 0.76, respectively ($P < 0.005$).

Alternatives for Traditional ILM Peeling

Inverted ILM flap

OCT evaluation of closed MHs reveals that 19–39% remain with bare RPE, despite having flat borders on imaging.[31] These are called "flat open" MHs and are associated with worse VA results as compared to fully covered MHs. Inverted ILM flap technique, first described by Michalewska *et al*., is a modification of the traditional ILM peeling technique, where the ILM is not completely removed.[31] A circular piece of the ILM around the edges of the hole is trimmed to 0.5–1 mm length and then inverted onto the hole. The rationale for this maneuver is to promote hole closure by creating a scaffold for cell proliferation, with the aid of Muller cells from the ILM which stimulate glial cell proliferation. This procedure has been shown to increase hole closure rates for large MHs, but being a non-neural tissue, its benefits regarding VA remain unclear.[18] In their study from 2010, Michalewska *et al*. investigated the benefits of this technique for IMHs larger than 400 μm.[31] They conducted a prospective randomized comparison between two groups, the first included 51 eyes undergoing vitrectomy, TB staining, ILM peeling, and gas tamponade while the second included 50 eyes undergoing the same procedure with the modification of performing an inverted ILM flap. Hole closure rates after one operation were 88% and 98%, respectively. The authors did not report the statistical significance of these findings.

Gu and Qiu conducted a literature review and single-arm meta-analyses investigating the anatomical and functional results of inverted ILM flap technique for large (>400 μm) MHs.[32] They found a closure rate of 95% and VA improvement rate of 75%. Seven of the eight studies included in the analysis lacked a control group. Thus, the authors reviewed additional studies which published the results of vitrectomy with ICG-assisted ILM peeling for MHs larger than 400 μm for comparison with the inverted ILM pooled results. The ILM standard peeling MH closure rate was 87% and VA improvement rate was 57%. This study provided additional evidence that the inverted ILM flap technique achieves better anatomical and functional results for large MH.

A recent prospective RCT by Kannan *et al*. compared the results of standard ILM peeling versus inverted ILM flap for the treatment of very large IMH over 600 μm.[33] Each group consisted of 30 eyes. Closure rate was relatively better in the inverted ILM flap group (90% compared to 76.7%), but this trend was not statistically significant. Mean BCVA 1-month post-surgery was better in the inverted ILM flap group (20/69 as opposed to 20/96 in the ILM peeling group, $P = 0.016$), but 6 months after the operation, there was no significant difference in BCVA between groups. Their results may indicate better probability for anatomical closure with inverted flap technique. The major limitation of this study was its small sample size, and this could have been the main reason for not reaching statistical significance.

Specific complications of inverted ILM flap include spontaneous detachment of the flap during fluid-air exchange or expansion of the RPE atrophy.[31,32] Furthermore, since a part of the stained ILM remains on the retina, any associated retinal toxicity may persist.[34] This may explain the lack of significant difference in long-term BCVA, despite the favorable anatomical results with inverted ILM flap compared with traditional ILM peeling.

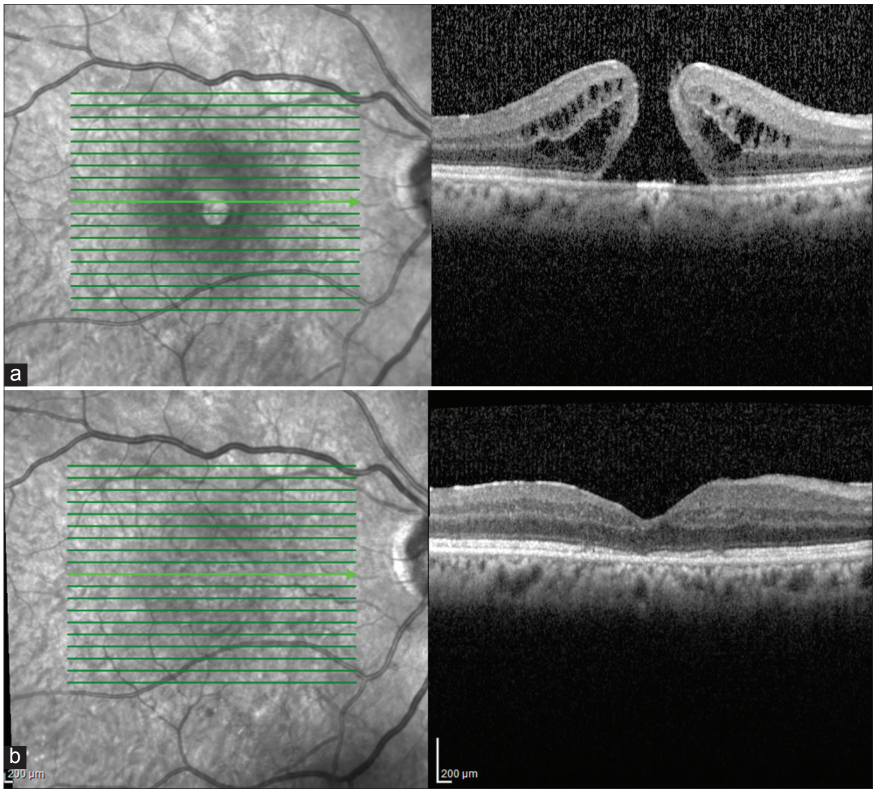

Figure 6: Full-thickness macular hole (FTMH) surgical anatomical results. Pre-operative (a) and 4-month post-operative (b) macular optical coherence tomography sections of an FTMH following vitrectomy and ILM peeling. Complete hole closure can be seen the following procedure. There is minimal distortion of the inner retinal interface. Also note the mild disruption around the ellipsoid zone

Shin *et al.* proposed the use of a heavy fluid, perfluoro-n-octane (PFO), over the inverted ILM flap to keep it in position during the fluid-air exchange.[35] The PFO was then removed and a gas tamponade was performed. In addition to preventing displacement, this technique aims to enable covering of the hole with a single-layered membrane rather than to fold it with multilayered ILM, as was observed on OCT after the original ILM flap technique. They reported the results of this technique in 12 eyes with MHs. Overall closure rate was 83%. Mean logMAR VA was improved from 0.9 before operation to 0.48 6-month post-surgery ($P = 0.004$). Another retrospective study compared the efficacy of PFO-assisted inverted ILM flap (41 eyes) with traditional ILM peeling (51 eyes) in large IMHs (≥400 μm).[36] Closure rate was better in the ILM flap group, reaching 100% as opposed to 88.2% in the ILM peeling group ($P = 0.032$). BCVA improved in both groups and was significantly better in the ILM flap group 1 and 3 months post-surgery, but at 6-month post-surgery, there was no significant difference. It is worth noting that the tamponade material differed between the groups: Air was mostly used in the ILM flap group while SF_6 was commonly used in the traditional peeling group ($P < 0.001$).

Foveolar sparing ILM peeling

Foveolar sparing ILM peeling is a less invasive modification of the original ILM peeling technique, which is designed for the treatment of early MHs where the foveal ILM is usually uninvolved.[37] In this procedure, a central piece of ILM of around 400 μm is preserved over the foveola, to reduce foveolar damage and preserve Muller cells. In a small retrospective study comparing traditional ILM peeling with foveolar sparing ILM peeling for early full-thickness IMH (Stage 2), VA improvement and final VA were better in the foveolar sparing group.[37]

ILM abrasion

ILM abrasion is an alternative to ILM peeling, in which the ILM is gently rubbed around the MH by a diamond-dusted membrane scraper.[38] This technique is designed to eliminate the tractional forces on the retina without the complete removal of the ILM. Possible advantages included sparing the use of ILM dyeing and diminished retinal toxicity and reduced loss of foveal tissue. In a retrospective series of 100 patients with IMH Stages 2–4 treated with ILM abrasion, 94% of patients achieved MH closure.[38] Median pre-operative VA was 20/100 and median 3-month post-operative VA was 20/60.

Gas Tamponade and Post-operative Posturing

Following vitrectomy and ILM peeling, fluid-isovolumetric gas exchange is performed.[15] The first gas used in vitrectomy surgery for MH was SF_6. The rationale for gas tamponade relays

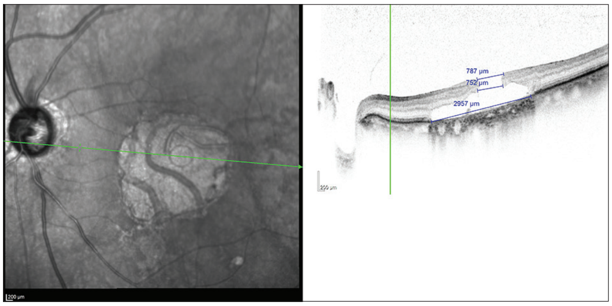

Figure 7: Chronic full-thickness macular hole (FTMH). A large FTMH with atrophic retinal pigment epithelium and atrophic inner retina can be seen in the infrared (left) and optical coherence tomography cross-section (right) images

on the high surface tension between gas and liquid.[20] The surface tension between the gas bubble and the retina aids in pulling the edges of the hole toward each other.[16,20] The gas bubble also acts as scaffold for glial cell migration and proliferation promoting hole closure.[39] Furthermore, it prevents fluid from the vitreous cavity to percolate into the MH, while the RPE pump removes subretinal fluid.[20]

To maximize the contact time of the gas bubble with the MH, patients are usually instructed to maintain a face-down positioning for about a week.[39] Air travel and traveling to high altitudes are forbidden after gas injection as decrease in the atmospheric pressure can result in intraocular gas expansion and subsequent increase in intraocular pressure. Nitrous oxide use for general anesthesia is contraindicated in these patients as it diffuses from the bloodstream into the gas-filled vitreous cavity and increases intraocular pressure.[20] Common complications of gas tamponade include rise in intraocular pressure, subretinal gas, subconjunctival gas, anterior chamber gas, and gas-induced cataract.[20,40]

The common gases used in retinal surgery are SF_6, C_2F_6, C_3F_8, and air when all but the latter are expansile gases in their pure form.[20] They are all inert, odorless, and colorless. For them to be non-expansile, SF_6, C_2F_6, and C_3F_8 should be used in concentrations of 20%, 16%, and 12%, respectively. The duration of gas presence in the vitreous cavity until complete absorption is around 2 weeks for SF_6, 5 weeks for C_2F_6, and 8 weeks for C_3F_8.[20] Silicone oil has also been described as an alternative for long-acting gas, as it remains in the vitreous cavity until removal in a secondary procedure.[41] It has been suggested to spare the need for posturing, thus allowing treatment for patients who cannot posture or must travel by air.[1,7,41] However, silicone oil shows inferior results in terms of anatomical closure and VA in comparison to gas tamponade, most probably due to lesser surface tension as compared to gas and higher photoreceptor toxicity.[20,40,41]

The goal of post-operative face-down posturing is to maximize the contact area and contact time between the gas and the MH.[39] Posturing also helps reduce gas-induced cataract in phakic patients as it reduces contact between the gas and the lens.[20] Unfortunately, posturing is difficult for many patients and unfeasible for some.[39] It may cause backache, sinusitis, and ulnar nerve palsy due to local pressure during posturing.[17,39] Several studies have shown that MHs tend to close early after surgery, suggesting that prolonged positioning may not be mandatory in all cases.[20,39] However, it is important to mention that late reopening of the hole may occur, mostly in larger MHs.[12] Solebo *et al.* conducted a Cochrane review which included three RCTs investigating the impact of posturing on the outcome of surgery for MHs.[39] These study results showed favorable anatomic results for posturing in large (>400 µm) MHs, while no significant advantage was shown for small ones.

The choice of gas type and period of posturing are interdependent. Several studies have been conducted to evaluate the comparative safety and effectiveness of the different gases commonly used in retinal surgery. In their paper from 2016, Madi *et al.* reviewed and described the main results of studies comparing the use of different gases for MH surgery.[16] These studies reported similar anatomical and functional results for different gas types. The authors recommended the use of long-acting gas for patients who cannot posture and in cases of large MHs (>400 µm). They also postulated that posturing may be more beneficial when using short-acting gas. It is worth noting that most studies investigating the choice of gas and duration of posturing were small and retrospective, and methodology differed remarkably between them.[16,40] One recently published large (177 eyes) retrospective study compared the use of SF_6 and C_3F_8 for MHs of all sizes and also for long-lasting MHs (>6 months).[40] The authors found no significant difference between groups in the rate of anatomical closure or in VA improvement. Rise in mean ocular pressure was significantly higher in the C_3F_8 group ($P < 0.05$). The authors concluded that SF_6 achieves comparable results in primary surgery for MHs, with decreased complication rate and shorter recovery.

Autologous ILM Transplantation (ILM Free Flap)

The ILM free flap was originally designed as a secondary surgery for the treatment of persistent MHs after failed vitrectomy with ILM peeling.[42] During this procedure, after ILM staining, a residual peripheral patch of ILM is peeled free and positioned to cover the MH. To keep the flap in place, a low-molecular-weight viscoelastic material is then placed over the flap to stabilize it.[42] This is followed by fluid-air exchange, gas tamponade, and post-operative posturing. The rationale for this procedure is that the ILM patch may promote foveal healing by Muller cell proliferation within the hole and subsequent repositioning of photoreceptors. In a small series of 10 patients with MHs after the previous vitrectomy, MH closure was achieved in 90% of patients.[42] Mean logMAR BCVA was improved from 0.99 before surgery to 0.57 at the end of the follow-up ($P = 0.007$). Velez-Montoya *et al.* conducted a multicentered RCT comparing vitrectomy surgery with conventional ILM peeling, ILM peeling with inverted ILM flap, and the free ILM flap techniques as the first treatment for large MHs >400 µm (12, 12, and 14 patients in each group, respectively).[34] Baseline BCVA was similar between groups. Although a trend of improvement in BCVA was observed in all groups, this trend was statistically significant only in the inverted ILM flap group.

Observation and Spontaneous Closure

It is generally accepted that for IMHs Stages 2–4, surgical treatment is warranted. Yet, some VMT cases or early FTMHs may spontaneously resolve.[43] Among eyes with VMT, about 60–70% will progress to FTMHs, while the remaining fraction will resolve spontaneously.[44] According to a recent literature review of 58 spontaneously resolved IMHs, the incidence of spontaneous closure is 4–11.5%.[43] MH closure was observed for all stages, though it was less frequent with more advanced stages. Hole diameter was documented in 50 cases. The mean diameter of spontaneously closed holes was 178.6 μm. Thirty-four of MH cases were smaller than 250 μm, four were 250 μm, 13 were between 250 μm and 400 μm, and one was >400 μm. The mean closure time was 100.9 days. Mean BCVA before and after closures were 0.36 and 0.7, respectively.

Ocriplasmin

Ocriplasmin intravitreal injection was developed as a biologic non-surgical alternative to treat VMA.[9] It is a recombinant protease which liquefies the vitreous body, thereby promoting the separation of the vitreous from the retina [Figure 8].[21] According to the combined results of two parallel RCTs comparing one injection of ocriplasmin with placebo (saline) injection for the treatment of VMA with or without an FTMH, VMA resolution rates were 26.5% compared with 10.1%, respectively ($P < 0.001$).[9] Among cases with documented presence of MH before treatment (153 eyes), MH closure was observed in 40.6% and 10.6% of patients in the ocriplasmin and placebo groups, respectively ($P < 0.001$). Subsequent vitrectomy due to progression was required in 17.7% and 26.6% of patients in the ocriplasmin and placebo groups, respectively ($P = 0.02$). Six months after the intervention, VA improvement of three or more lines on the eye chart was observed in 12.3% of the ocriplasmin group as opposed to 6.4% of patients in the placebo group ($P = 0.02$). After excluding patients who had undergone vitrectomy from the calculation, VA improvement rates were 9.7% and 3.7%, respectively ($P = 0.008$). The incidence of ocular adverse events was higher in the ocriplasmin group (68.4% vs. 53.5%, $P < 0.001$), but the authors mentioned that these were mostly transient and mild. In another retrospective report of 35 eyes with symptomatic VMA or VMT treated with ocriplasmin injection, VMA resolution was observed in 42.9% of eyes and complete posterior vitreous detachment (PVD) was observed in 34.3% of eyes.[45] Closure of FMTHs was observed in one of six eyes (16.7%), despite the persistence of VMA in this case. Juncal *et al.* reported the results of a retrospective series of 22 eyes of 11 patients with bilateral MH.[46] Each patient was treated with vitrectomy with ILM peeling in one eye and ocriplasmin in the contralateral eye. Ocriplasmin was used only in eyes with VMT due to the drug's mechanism of action. There was no significant difference in baseline mean base diameter and VA between the two groups. Closure was observed in 36.4% and 90.9% of the

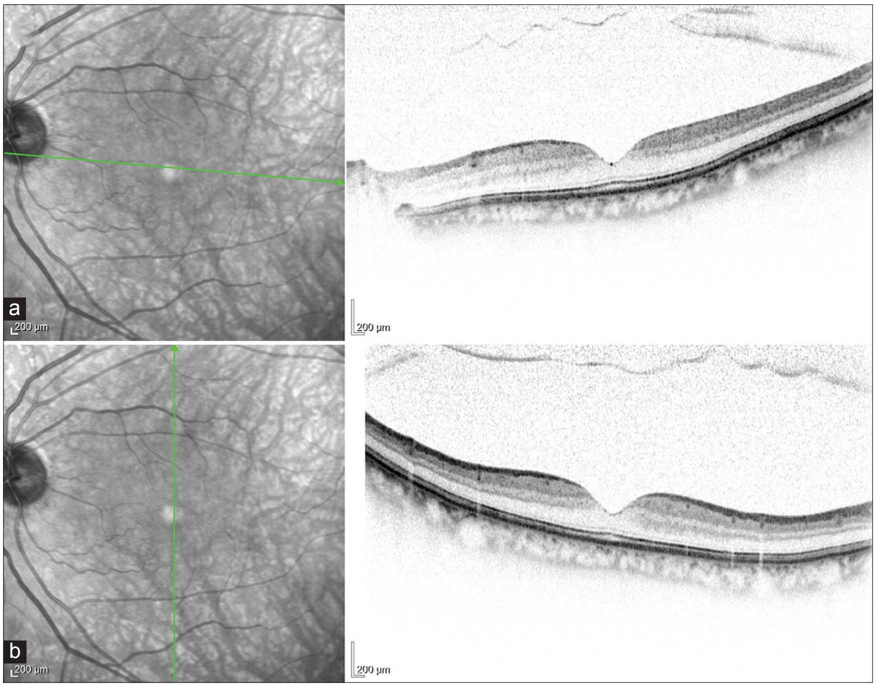

Figure 8: Posterior vitreous detachment (PVD). A horizontal (a) and vertical (b) macular optical coherence tomography section demonstrating the posterior vitreous having completely detached from the retina

ocriplasmin and vitrectomy eyes, respectively ($P = 0.031$). Three additional ocriplasmin-treated eyes (27.2%) showed VMT release without hole closure. Subsequent vitrectomy was performed in all of the ocriplasmin-treated eyes which did not achieve closure, with final closure rate of 100% in the ocriplasmin group. There was no significant difference in final BCVA between groups (at the end of the follow-up and after complementary surgery if was performed).

Adverse effects of ocriplasmin include photopsias, blurred vision, reduced VA, vitreous floaters, eye pain, tearing, eye redness, foreign body sensation, dryness, photophobia, and eye discharge.[21] OCT examination demonstrated a transient loss of the OS ellipsoid zone, worsening of subretinal fluid, and transient outer retinal layers disruption.[21,45] These findings may indicate photoreceptor damage secondary to ocriplasmin retinal toxicity. Cases of retinal detachment and development of MH were also reported with ocriplasmin.[8,9,21]

Pneumatic Vitreolysis (PVL)

PVL is a minimally invasive office-based technique that was developed for small MHs and VMTs.[44] During PVL, intraocular gas is injected intravitreally to induce PVD and release traction, enabling closure of small Stage 2 MH. Chan *et al.* conducted a retrospective study of 50 eyes with symptomatic VMT (35 eyes) or Stage 2 MH ≤300 μm (15 eyes) treated with intraocular C_3F_8 PVL.[44] In cases of MHs, patients were guided to maintain face-down position for 3–4 days. Other patients were instructed only to avoid a supine position. PVD was achieved in 86% of all eyes, 80% of eyes with VMT only, and 100% of eyes with MHs. MH closure rate after one gas injection was 53.3%. One eye received two injections and another eye received three injections to achieve closure. Final closure rate was 66.7%. Mean logMAR VA improved from 0.4022 before treatment to 0.2783 at the end of the follow-up ($P < 0.001$). Regarding complications, the authors described one eye with VMT that progressed to Stage 2 MH after PVL and PVD and another eye that developed retinal detachment.

Another retrospective study described the results of different treatment modalities for symptomatic VMA, VMT, and MHs: Ocriplasmin injection (7 eyes); PVL with C_3F_8 (8 eyes); pars plana vitrectomy (10 eyes); and controls (10 eyes).[8] The vitrectomy group underwent vitrectomy including ILM dyeing with ICG and ILM peeling and, in the case, MH also SF_6 tamponade and face-down positioning. Control eyes were those with concurrent eye diseases which warrant treatment with an anti-vascular endothelial growth factor injection, and these eyes received only this treatment which was used as placebo. After 28 days, VMT resolution was achieved in 0% of controls and in 42.9%, 87.5%, and 100% of eyes treated with ocriplasmin, PVL, and vitrectomy, respectively. Compared to controls, resolution rates were significantly higher for the vitrectomy ($P < 0.0001$) and PVL ($P = 0.0005$) groups, but not for the ocriplasmin group ($P = 0.1$). The authors of this study also conducted a literature review which included 1042 eyes diagnosed with VMA or VMT. Of these, 253 were controls, 726 treated with ocriplasmin, and 63 treated with PVL. VMT resolution rates were 9%, 26%, and 84%, respectively. FTMH was found in 62, 209, and 15 of eyes in the control, ocriplasmin, and PVL groups, respectively, and MH closure was observed in 7%, 36%, and 59% of these eyes, respectively.

Adjuvant Treatments

Additional treatments developed for MH management include the use of autologous serum, an absorbable partially cross-linked gelatin plug, transforming growth factor beta-2 (TGFβ2), thrombin-activated fibrinogen, thrombin, plasmin, and autologous blood or platelet concentrate.[7,47] TGFβ2 seemed promising initially, hypothesized to promote glial cell proliferation and MH closure. This notion was refuted by an RCT, in which it did not show superiority to placebo.[48] Autologous platelet concentrate was also thought to stimulate glial wound healing and hole closure by growth factors available in platelets' granules.[7] In a multicentered double-blinded RCT examining platelets versus placebo, a higher percentage of eyes achieved hole closure in the platelets group, but there was no significant difference in final VA between groups.[7] Similarly, autologous blood was also proposed as an adjuvant therapy, but no beneficial effect was proven.[47] These alternatives were concluded to be non-superior to placebo, while incurring more complications including endophthalmitis, proliferative vitreoretinopathy, and retinal hemorrhage.[47] Ultimately, their use was abandoned.

Summary of Findings and Practical Recommendations for the Management of IMHs

Treatment options for MH vary and are summarized in Table 2. Vitrectomy is the treatment of choice for Stages 2–4 MHs. ILM peeling during vitrectomy has greatly improved surgical results and is beneficial for MHs Stages 3 and 4 and seemingly also for Stage 2 MHs. ILM peeling leads to higher rates of hole closure, reduces the need for repeated surgery, and apparently improves VA (as stated before, this result was observed at 3-month post-surgery but not at 6 and 12 months post-surgery, most probably due to repeated surgery in the non-peeling groups). Modifications of the traditional ILM peeling technique may be suitable for specific clinical scenarios:

- Foveolar sparing ILM peeling can be considered in small Stage 2 MHs
- Inverted ILM peeling has favorable results in large MHs >400 μm
- The use of PFO increases flap stability and may result in better anatomical and functional results
- ILM abrasion has been presented as a possible technique, however, this approach is not supported by sufficient data
- ILM dying is widely used in MH surgery. BBG and TB appear safer than ICG and result in better post-operative VA
- Gas tamponade and posturing are beneficial for large MH over 400 μm. According to the findings of the research by Modi *et al.*,[40] it is possible that the use of SF_6 and posturing should be

Table 2: Treatment options for VMA, VMT, and MHs

Pathology	Treatment options
VMA	Intraocular ocriplasmin injection/ observation
VMT	PVL/vitrectomy/ocriplasmin/observation
Small Stage 2 MH	PVL/vitrectomy with or without ILM peeling. If ILM peeling is done, consider foveolar sparing technique
	Consider gas tamponade and posturing
Stage 2 MH	Vitrectomy with or without ILM peeling
	Consider gas tamponade and posturing
Stage 3 MH	Vitrectomy with ILM peeling
	Consider gas tamponade and posturing
Stage 4 MH	Vitrectomy with ILM peeling
	Consider gas tamponade and posturing
Large Stage 4 MH >400 μm	Vitrectomy with ILM peeling – consider using inverted ILM peeling technique Gas tamponade and posturing

VMA: Vitreomacular adhesion; VMT: Vitreomacular traction; PVL: Pneumatic vitreolysis; MH: Macular hole; ILM: Internal limiting membrane

preferred in most cases after vitrectomy, while in patients who cannot posture longer-acting gases should be used.

Chronic MHs have worse prognosis than acute ones, but surgical treatment, preferably with ILM peeling, could lead to anatomical and functional improvement in a considerable portion of patients. Additional research in this subset of MHs is warranted.

VMT and small MHs may benefit from minimally invasive procedures such as PVL – a relatively simple intervention with promising results. Ocriplasmin may be used for the treatment of early symptomatic VMA or VMT, while observation and waiting for spontaneous resolution for about 3 months is also a reasonable option. Although treatment with ocriplasmin for MHs could lead to primary hole closure and spare the need of a more invasive procedure, its results seem inferior to PVL or vitrectomy; thus, it should be used in carefully selected cases and in a joint decision with the patient.

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Conclusion

Modern treatment options for idiopathic macular holes are numerous. Ophthalmologists should be aware of the different modalities and offer tailored treatment for individual patients depending on the specific clinical scenario. Such personalised treatment is warranted for better patient care and better visual outcomes.

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