

REVIEW ARTICLE



Secondary macular holes – A review of current management strategies

Tal Corina Sela¹, Amir Hadayer^{2,3}, Alon Zahavi^{2,3}

¹Medical Corps, Israel Defense Forces, Israel, ²Department of Ophthalmology, Rabin Medical Center, Petah Tikva, Israel, ³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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Address for correspondence:

Alon Zahavi, Department of Ophthalmology, Rabin Medical Center, Petah Tikva, Israel; Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. Tel.: +972-3-9376101. E-mail: alonzahavi@gmail.com

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Introduction

Macular holes (MHs) are full thickness retinal defects involving the anatomical fovea.^[1] The first staging system for MHs was described by Gass in 1988.^[1,2] The use of optical coherence tomography (OCT) led to the development of newer staging systems.^[1,3,4] At present, the international vitreomacular traction (VMT) study classification system is generally accepted and used:^[4] (1) Vitreomacular adhesion (VMA) – an incomplete perifoveal vitreous detachment with preserved foveal contour. This is a part of the natural course of posterior vitreous detachment (PVD), in which the vitreous remains strongly attached to the retina at a certain perifoveal area and is usually asymptomatic. VMA is considered focal if ≤1500 µm or broad if >1500 µm. (2) VMT - progression of PVD may result in tractional forces on the macula. This may be accompanied by foveal surface contour change, intraretinal pseudocyst formation, and/or foveal elevation from the retinal pigmented epithelium (RPE). Symptoms include decreased visual acuity (VA) and metamorphopsia. As in VMA, this condition is subclassified to focal or broad according to the vitreous attachment's width. (3) Full thickness MH (FMTH) - An anatomical foveal defect

Abstract

Secondary macular holes (MHs), most commonly caused by ocular trauma and high myopia, often pose a therapeutic challenge. The development of modern imaging modalities as well as advanced surgical techniques enables a better pre-operative evaluation, diverse treatments, and improved prognosis. This review presents and discusses the treatment options for each of these conditions, to provide the necessary up to date knowledge for decision-making in these cases.

involving all the neural retinal layers, from the internal limiting membrane (ILM) to the RPE. FTMH can be subclassified by size as small (\leq 250), medium (>250 and \leq 400), and large (>400); by VMT status; and by cause as primary or secondary.

Most MHs are idiopathic, but some are secondary to trauma, severe myopia, or other conditions.^[1,5,6] This review focuses on the most common etiologies for secondary MHs, treatment modalities, and relevant considerations.

Traumatic MHs (TMHs)

TMHs constitute 5–9% of all MHs.^[7:10] TMHs develop in approximately 1.4% of blunt trauma cases and 0.15% of open globe injuries,^[11] and occur predominantly among male children and adolescents.^[7,12] Other potential causes of TMHs include laser injury, surgical trauma, lightning strikes, and electrical shock.^[13] TMHs can result in severe central visual field loss.^[7,13] Other ocular pathologies may develop concurrently with TMH, such as commotio retinae, hyphema, vitreous or subretinal hemorrhage, retinal detachment, uveal tears, and choroidal rupture.^[7,14] These may further complicate the clinical course, and result in a poorer prognosis.^[7,13] In some cases, the MH can present immediately following the trauma, while in others it may occur only few weeks later.^[13] The pathogenesis of TMHs is not fully understood and treatment protocol is not well established.^[7,12,13,15,16] It has been suggested that while idiopathic MH (IMH) formation is related to chronic traction, TMHs are the result of acute traction forces on the macula.^[1,12,13] However, in contrast to IMHs, a significant portion of TMH cases (10–67% according to different reports) may resolve spontaneously.^[7,17] Therefore, observation before any intervention is a reasonable option for many patients. Vitrectomy surgery which is the mainstay of surgical treatment for IMHs,^[5,18,19] was adopted for the treatment of TMHs and is currently the main treatment modality.^[7,13,15,16,19]

Spontaneous closure

Spontaneous closure of TMHs is not uncommon and may result in a significant improvement in VA.^[20-24] Kusaka et al. and Yamada et al. each reported on three cases of spontaneous hole closure within up to 6 months.^[23,25] Mitamura et al. followed patients with TMHs for 4 months before performing surgery.^[24] They reported that five of 11 eyes (45%) achieved closure during that period. Two additional eyes of two patients who refused surgery achieved closure within 12 months. In 2002, Yamashita et al. reported spontaneous closure in eight of 18 eyes (44%).^[20] Mean follow-up was 8.4 months and all eight eyes achieved closure within 4 months. In 2015, Chen et al. and Miller et al. reported spontaneous closure rates of ten out of 27 eyes (37%) and 11 out of 28 eyes (39%), respectively.^[21,22] Interestingly, spontaneous closure rates were similar, despite remarkable difference in mean follow-up duration in the two series, as the former was 0.74 years and the latter was 2.2 years. Bor'i et al. recently reported a less promising spontaneous closure rate of seven of 33 eyes with TMHs (21%) within a follow-up of 6 months.^[12] If spontaneous closure did not occur, surgery was performed.

Predictive factors for potential spontaneous closure

Chen et al. found that smaller holes and the absence of intraretinal cysts are predictive of spontaneous closure.^[21] Specifically, mean minimum diameter of holes that spontaneously closed among their series of 27 eyes was 244.9 µm compared to 523.9 µm in those that did not close spontaneously (P = 0.007). The absence of intraretinal cysts surrounding the MH was also predictive of hole closure, observed in 10% of holes that ultimately achieved closure compared to 76.5% of holes that did not close (P = 0.001). In Miller's report,^[22] the 11 holes (39%) that closed spontaneously, did so within 1.7-67.3 weeks from presentation (median 5.6 weeks). Eleven patients underwent vitrectomy surgery, of which five patients achieved closure. The authors noted that the persistent holes increased in size on sequential OCT scans during follow-up. Yamashita et al. also investigated predictive signs for spontaneous closure.^[20] In addition to their series of 18 patients with TMHs, of which eight achieved spontaneous closure (which was described earlier), they also conducted a literature review documenting 12 additional eyes for which spontaneous closure was documented. All together they reported the characteristics of 20 cases of TMH spontaneous closure. They found that these MHs were rather small and that the presence of subretinal fluid or complete PVD at presentation of the MH was uncommon: 15 cases were 0.1–0.2 disk-diameter and the rest up to 0.4 disk-diameter. The presence or absence of subretinal fluid was recorded in 18 of the 20 eyes. Among these 18 eyes, a subretinal fluid cuff was observed only in two cases. There were no cases associated with PVD.

Pars plana vitrectomy

In 1999, Amari et al. published the results of 23 eyes with TMHs which underwent vitrectomy surgery, gas tamponade, and prone positioning.^[26] Mean follow-up duration was 27 months. Hole closure was achieved in 16 eyes (70%). Six of the seven eyes with persistent MH achieved closure after a second vitrectomy surgery reaching an overall closure rate of 96%. Mean BCVA improved from 20/160 to 20/60 at the end of the follow-up. Johnson et al. reported a series of 25 eyes with different stages of TMHs treated with vitrectomy, gas tamponade, and prone positioning.^[15] Three eyes underwent ILM peeling during surgery. In 12 eyes, serum was used as surgical adjuvant. Hole closure was achieved in 96% of patients and VA improvement of two or more lines was observed in 84% of patients. Serum use during surgery was not associated with statistically better results. In their literature review, Liu and Grzybowski also addressed the effect of vitrectomy on TMHs.^[17] They reported an anatomical success rate of 45-100% (median 92.5%), and functional success rate of 27-100% (median 84%), defined as improvement of two or more Snellen lines BCVA. In a single arm meta-analysis comparing surgical treatment versus observation for TMHs, the pooled hole closure and VA improvement rates were 91.9% and 74.8% for vitrectomy treatment compared with 36.8% and 43.8% for observation.^[7] It is worth noting that studies included in this meta-analysis differed from one another in the treatment protocol, as they used different tamponading materials and adjuvant treatments. In patients who underwent surgery, visual outcomes were significantly better with early intervention. Younger age (<24 years) and smaller MH (median hole size = 0.2 decimal degrees) were predictive of spontaneous closure.

Timing of vitrectomy

In Yamashita's report of 20 cases with spontaneous closure, 35% achieved closure within 1 month, 70% within 3 months, and 100% within 9 months.^[20] In the case series by Miller *et al.* described earlier, among the 11 patients who were treated by vitrectomy, hole closure rate was 45.5%.^[22] Median logMAR VA of the vitrectomy group improved from 1.2 to 0.8 (P = 0.016), and from 1.6 to 0.6 (P = 0.043) after excluding the six eyes (54.5%) that failed to achieve closure. Among the patients who underwent surgery, mean time to surgery was shorter in those who ultimately achieved closure than in those who did not (11.0 and 56.3 weeks, respectively, P = 0.017). Hence, while watchful waiting seems a reasonable approach in cases of TMHs, one should carefully consider when a surgical intervention is required

as it seems that longer waiting might result in lower success rates. Moreover, in young children, delayed treatment can lead to deprivation amblyopia.^[17]

Enzymatic vitreolysis during vitrectomy surgery

Unlike idiopathic MHs, where the vitreous body gradually separates from the retina over the years,^[4] in TMHs which occurs mainly in children and youngsters, the vitreous body usually remains strongly attached to retina.^[27] During vitrectomy, the cortical vitreous has to be separated from the retina,^[28] a part of surgery which might be more challenging in TMHs and thus cause more iatrogenic trauma.^[29-31] Margherio et al. performed autologous plasmin assisted vitrectomy in four cases of pediatric TMHs.^[30] They reported a simple and atraumatic PVD creation with successful hole closure and VA improvement. Later on, Chow et al. reported a series of 16 eyes with TMHs treated by vitrectomy, of which ten underwent autologous plasmin injection 15 min before surgery.^[8] Of these ten eyes, four were the eyes from the previous report by Margherio et al.^[30] According to their report, plasmin was used according to surgeon discretion to facilitate the detachment of the posterior hyaloid.^[8] They noticed that this was more common with younger patients, and attributed it to the surgeon's clinical impression that the vitreous is firmly attached to the retina in this age group. However, the use of plasmin did not show any significant effect on anatomical or functional results. Wu et al. evaluated the effect of plasminassisted vitrectomy in the treatment of TMHs in 13 eyes.^[29] Closure rate was 92% and VA improvement of two or more lines was observed in 92% of cases. Compared to recorded anatomical and functional success rates, as in Johnson et al., [15] Liu and Grzybowski,^[17] and Gao *et al.*,^[7] these results are satisfying.

In 2012, Stalmans et al. published the results of two large randomized placebo-controlled trials examining the use of Ocriplasmin (Jetrea, ThromboGenics, Inc., NJ,USA) for the treatment of VMA.^[32] Ocriplasmin is a recombinant truncated form of human plasmin which has proteolytic effect on the vitreoretinal interface. Overall, 464 patients were treated with ocriplasmin and 188 received placebo. Following treatment 26.5% of patients in the ocriplasmin group reached resolution of VMA within 28 days from treatment, compared to 10.1% in the placebo group (P < 0.001). Since TMHs often occur in a young age group with a firmly attached vitreous base, the use of ocriplasmin which was shown to be beneficial in PVD induction can be considered during surgical treatments in these cases. Drenser et al. randomized 24 eyes of 22 pediatric patients who were scheduled for vitrectomy due to varying indications to receive ocriplasmin (16 eyes) or placebo (8 eyes), 30-60 min prior to surgery.^[33] The use of ocriplasmin did not achieve an advantage in terms of PVD induction, neither after injection and before surgery nor after vitrectomy.

ILM peeling and ILM flap for TMHs

Kuhn *et al.* reported 100% closure rate of 17 eyes with stages 2–3 TMHs following vitrectomy with ILM peeling.^[11] VA

improvement of ≥ 2 Snellen lines was observed in 94% of eyes and mean VA improvement was six Snellen lines. No ILM peelingrelated complications were observed. Abou Shousha published his experience with 12 eyes with large TMHs (1300–2800 μ m),^[34] treated by vitrectomy, brilliant blue G assisted ILM peeling, creation of an ILM flap, and gas tamponade. Time from trauma to treatment was between 3 and 6 months. Post-surgery, OCT examination revealed hole closure in all cases, and an improvement in VA was observed. An example of TMH following vitrectomy and inverted ILM flap can be seen in Figure 1.

Choice of tamponade material

Hammouda et al. conducted a retrospective study comparing the use of 14% C3F8 gas versus silicone oil for tamponade after vitrectomy with ILM peeling for TMH.[35] Silicone oil was used in children, in large MHs and in patients who were unable or unwilling to position. Patients treated with C3F8 (13 patients) were instructed to position for 2 weeks or until 50% of the gas was absorbed, while those treated with silicone (nine patients) were instructed to position for as long as possible, and at least 12 h a day for 2 weeks. Closure rates were 92.3% and 66.67% for the gas and silicone groups, respectively. Pre-operative VA was similar between groups. Post-operative VA was significantly better in the C3F8 treated groups 1, 6, and 12 months postsurgery, when the latter was 0.433 for the C3F8 group and 0.245 for the silicone oil group (P < 0.05). These results indicate superiority of C3F8 over silicone oil, though this may be partially related to patient selection. Bor'i et al. conducted a retrospective study comparing 14% C3F8 (16 patients) against silicone oil



Figure 1: Traumatic macular hole (TMH). Pre-operative (a) and post-operative (b) macular optical coherence tomography sections through a TMH following vitrectomy and inverted internal limiting membrane (ILM) flap. Hole closure with a disruption at the ellipsoid zone can be seen following the procedure. Note the rolled ILM attached to the hole margin

(ten patients) for tamponade after vitrectomy with ILM peeling for TMHs which did not resolve spontaneously after 6 months of observation.^[12] Six months after operation, anatomical closure was achieved in 94% and 90% of C3F8 and silicone oil treated patients, respectively (no statistically significant difference). Although pre-operative logMAR BCVA was worse in the C3F8 group (1.1 compared to 0.8 in the silicone oil), post-operative mean BCVA was significantly better in this group, with a logMAR VA of 0.2 and 0.3 for C3F8 and silicone oil at 6 months, respectively (P = 0.04). The authors suggested that this may be due to patient selection and silicone oil preference over gas in more complicated cases, or due to toxicity of silicone oil to the photoreceptors and RPE.

Treatment of TMHs-summary

A considerable proportion of TMHs may resolve spontaneously, with the majority closing 3–6 months after the trauma. There is some evidence that small hole diameter, absence of intraretinal cysts, and younger age are predictive factors for spontaneous closure. On the other hand, surgical intervention results in high closure rates and VA improvement, and it has been shown that delayed surgery might be associated with less favorite anatomical and functional outcome and may result in amblyopia in children. Therefore, it is important to consider if and when to operate, and when to prefer careful observation, to achieve optimal results.

Myopic MHs (MMHs)

High myopia over -6.0 diopters can be complicated with a secondary MH [Figure 2].^[36,37] The pathophysiology is not fully understood. It has been suggested that the pathologic growth of the eyeball in myopic eyes may lead to posterior staphyloma, manifesting as a posterior scleral protrusion.^[38] As the staphyloma grows the retina which is tightly attached to the sclera stretches and things.^[39,40] Concurrently, VMT causes tractional forces on the posterior retina.^[41] The growing anteroposterior axial length together with the VMT can lead to foveoschisis and the formation of a FMTH.^[37,41,42] Retinal detachment is a rare complication of idiopathic MH, but it is relatively more frequent

200 µm

Figure 2: Myopic macular hole (MMH). A macular optical coherence tomography section through a MMH. Note the rolled-up retina at the hole margins, and the bare retinal pigment epithelium at the base

in cases of MMHs.^[39,43] The reported incidence of foveoschisis in high myopia is 9–34%, and approximately 50% of patients with foveoschisis will subsequently develop either a MH or retinal detachment within 2 years.^[44] Mean age for MMH formation is 55 years.^[43] In a study evaluating the severity of myopia as a risk factor for MH development, longer axial length and higher myopia were found to correlate with younger age of MH onset (*P* < 0.0001 for both).^[36] Mean age of MH onset was 52.1, 64.5, and 69.8 years for patients with axial lengths of ≥26.0, 23.0– 25.99, or <23.0 mm, respectively. No significant correlation was found between myopia severity and MH dimensions. The MMH is occasionally difficult to diagnose clinically, and OCT should be used liberally in such cases.^[37] Vitrectomy and macular buckling (MB) are the two main surgical approaches for this condition.^[39]

Pars plana vitrectomy

In 2001, Patel et al. published a retrospective case-series of 20 eyes with MMH treated with vitrectomy.^[21] Different adjuvant agents such as TGF β 2 or platelet extract were used in some cases. Primary MH closure was observed in 55% of eyes 3 months post-surgery and in 60% to the end of the follow-up (mean 19.9 months). Seven eyes were re-operated and final MH closure rate was 85%. Mean VA improved by two Snellen lines. The use of adjuvants did not improve anatomical or functional outcomes. Another retrospective study reported the results of 24 highly myopic patients (higher than -8.0 diopters) treated by vitrectomy with autologous platelet concentrate as adjuvant, SF6 tamponade and face-down positioning.^[40] In some patients, ILM peeling was also performed. One-month post-surgery, closure rate was 87.5% (21 of 24 eyes). The three eyes that did not achieve primary closure were re-operated and the final closure rate was 100%. The authors reported one case of peripheral retinal detachment 4 months post-operation. Mean VA was improved from 20/200 to 20/70. A recent large multicentered study evaluated retrospectively the outcome of vitrectomy surgery in 110 eyes with MMH related retinal detachment.^[41] The ILM was peeled in almost all eyes (104 patients). Tamponade material differed, with overall 77 eyes treated with gas tamponade and 33 with silicone oil. Reattachment rate was 85% and was higher for eyes treated with gas tamponade than in eyes treated with silicone oil (91% vs. 73%, respectively, P < 0.05). MH closure was achieved in 52% of eyes and mean logMAR BCVA improved from 1.38 to 1.09.

ILM peeling, inverted ILM flap and foveolar sparing ILM peeling

Song *et al.* conducted a prospective interventional study to evaluate the Viscoat (Alcon Laboratories, TX, USA) assisted inverted ILM flap technique for the treatment of large MMH.^[38] Fifteen eyes with mean axial length of 28.83 mm and mean baseline minimal MH diameter of 597.6 μ m underwent surgery. Hole closure was achieved in 100% of the eyes. Mean logMAR BCVA was improved from 1.28 before surgery to 1.07 6 months post-surgery (*P* = 0.019). The authors reported that no retroversion of the inverted ILM flap occurred during fluidair exchange. The authors suggest that the limited functional results may be explained by the severe myopia and the large baseline size of the MH. Another prospective comparative study evaluated the results of vitrectomy with ILM peeling versus the inverted ILM technique for MMH (aided by perfluorocarbon for flap placement).^[37] Sixteen and 12 eyes were included in each group, respectively. Gas tamponade was performed in all patients who were instructed to maintain prone positioning after surgery. Closure rates were 81.2% and 91.7%, respectively, with no statistically significant difference between groups. Postsurgery, median BCVA was better in the ILM peeling group, with logMAR BCVA of 0.25 compared to 0.4 in the inverted ILM flap group (P = 0.027). BCVA improvement rate was also higher in the in ILM peeling group, 93.7% compared to only 50% in the ILM flap group (P = 0.011). Foveolar sparing ILM peeling is a technique designed to allow preservation of Mullercells function by conservation of foveolar ILM, which is intact in myopic traction maculopathy.^[42] Ho et al. reported the results of a retrospective study examining the long-term (>36 months of follow-up) results of this procedure versus traditional peeling (12 and 7 eyes, respectively) for the treatment of myopia related macular traction. Progression to a FTMH occurred in 28.6% of patients in the total ILM peeling group and in 0% of the foveolar sparing peeling group (statistical significance of this finding was not indicated). Before operation, all eyes lacked the inner segment/outer segment (IS/OS) junction lines. After the operation, the IS/OS was recovered in 75% of the foveolar non ILM peeling group as opposed to 14.3% in the total ILM peeling group. The mean post-operative improvement in BCVA was more remarkable in the foveolar sparing ILM peeling group (P < 0.05). Moreover, in the foveolar non-peeling group, long-term BCVA was stable, while in the total peeling group a deterioration of BCVA was observed (P = 0.013). Another recent retrospective study also compared ILM peeling with foveolar sparing ILM peeling during vitrectomy surgery with gas tamponade for myopic foveoschisis without MH.[44] Twenty eyes underwent traditional ILM peeing and 13 eyes underwent foveolar sparing ILM peeling. Full regression of foveoschisis was observed in 75% and 77% of eyes in traditional ILM peeling and foveal sparing groups, respectively. Partial regression was observed in 15% and 23% eyes of each group, respectively. BCVA and central foveal thickness improved significantly after surgery in both groups, and no statistically significant difference was found between groups. Two eyes in the total peeling group developed MHs, while no similar complication was observed in the foveolar non-peeling group. No other complications were observed and no statistically significant differences in complications were found between groups. An example of ILM peeling during vitrectomy can be seen in Figure 3.

Macular buckling (MB)

In the modern version of MB, a silicone band is placed posteriorly to the sclera, beneath or in between the extraocular muscles, and sutured to the sclera.^[39,45-47] There are a few designs of macular



Figure 3: Internal limiting membrane (ILM) peeling during vitrectomy. A color image of ILM peeling in a myopic macular hole following ILM dying with Trypan blue and brilliant blue G. Note the retina and denuded from the ILM negatively stained

buckles in use, which slightly differ from each other in shape and insertion technique.^[45] Posterior buckling supports the posterior staphyloma, enables reshaping of the scleral wall and retina, and counteracts against the tractional forces caused by VMT.^[39]

In a retrospective case series of 21 cases with MMH treated by posterior MB either with concurrent vitrectomy or after a previously failed vitrectomy,^[39] hole closure was achieved in 19 eyes (90.5%). Retinal reattachment was observed in all eyes, in which a MH-related retinal detachment was found (n = 11). It was noted that 71.4% of patients enjoyed improvement in BCVA following surgery and mean BCVA was improved from 0.054 to 0.176. One patient developed diplopia after the operation, but it spontaneously resolved 2 months later. No other complications were observed. In 2018, Alkabes and Mateo published a literature review regarding the anatomical and functional outcomes of MB versus PPV in the treatment of MMH related retinal detachment, myopic foveoschisis, and MMH with foveoschisis.^[48] They found a total of 272 eyes with MH-related retinal detachment which were treated by MB alone or combined with vitrectomy. Retinal reattachment rates ranged between 81.8% and 100% and MH closure between 40% and 93.3%. A second surgery due to persistent retinal detachment was performed in 2.9% of eyes. Rate of BCVA improvement varied between 27.3% and 100%. Data for 178 eyes with myopic foveoschisis which were treated by MB revealed a highly varying rate of resolution ranging between 25-100%. It should be noted that a 100% resolution rate was reported in 5 of the 11 included studies. Concurrent vitrectomy was performed in thre of the studies. As to MMHs with foveoschisis, 39 eyes treated by MB (either combined with PPV or not) were described in the review. Hole closure with foveoschisis resolution was achieved in 100% of eyes. BCVA improvement rate was between 80% and 100%. Information from all the included studies revealed that the most common complications of MB included RPE changes (2.4% of eyes),

the need for subsequent MB removal (2%), MB malpositioning (1.8%), and choroidal effusion (1.8%). Few studies compared the results of vitrectomy and MB for the treatment of MMH. A recent randomized controlled trial compared MB and PPV for the treatment of macular schisis related retinal detachment due to high myopia, but without MH.^[47] Eighty-five patients were randomly assigned to either MB with C3F8 gas injection and face down positioning, or PPV with ILM peeling, gas tamponade, and face down positioning. Seventy-eight of the patients completed the study, 40 and 38 in the MB and PPV groups, respectively. Surgical failure, defined as the presence of post-operative FTMH with concurrent macular detachment necessitating a second surgery, was more prevalent in the vitrectomy group (18.4%) vs. 2.5%, P = 0.021). Post-operative mean BCVA improved in both groups, but significantly more in the MB group (mean improvement of 21.7 vs. 4.5, *P* = 0.002).

Posterior scleral reinforcement (PSR)

Zhu *et al.* recently reported their results of 19 eyes with MH retinal detachment secondary to high myopia who were treated with PSR.^[49] They used human sclera from deceased donors, which was cross-linked by 0.1% genipin. The cross-linked sclera was placed underneath the inferior oblique, external rectus, and inferior rectus muscles, and sutured to sclera. To support the staphyloma, the reinforcement flap was stretched into a U shape to surround the posterior pole. Retinal reattachment and hole closure rates were 100% and 73.7%, respectively. Mean logMAR BCVA improved from 1.27 to 0.88.

Treatment of MMHs – Summary

Vitrectomy, macular buckling, or both are valid treatment options for MMHs. A few small cohort studies compared the results of MB to vitrectomy. Several possible modifications to vitrectomy surgery have been described such as ILM peeling (total vs. foveal sparing), various tamponade material, and duration of positioning. The foveolar sparing technique is noninferior to the more common total ILM peeling, and could serve as a reasonable alternative which allows preservation of Mullercells. The paucity of large comparative studies and numerous surgical variations create a challenge in comparing treatment modalities and further research is necessary to determine the treatment of choice.

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