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Macular holes: vitreoretinal relationships and surgical approaches

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Abstract

Idiopathic full-thickness macular holes develop as a result of anteroposterior and tangential traction exerted by the posterior vitreous cortex at the fovea. Vitreoretinal relationships during the development of macular holes can be demonstrated in detail by ocular coherence tomography, facilitating an improved understanding of their pathogenesis and guiding clinical management. Surgical strategies for the repair of macular holes are designed to relieve vitreofoveal traction and to promote flattening and reapposition of the macular hole edges by intraocular gas tamponade. A period of face-down positioning postoperatively is conventionally advised. However, the evidence to support this recommendation is weak and practice varies considerably. Surgical removal of the inner limiting membrane (ILM) is advocated to ensure thorough removal of any tangential tractional components including any residual cortical vitreous. Current evidence suggests that ILM peeling can improve anatomical outcomes but the effect on visual function is less predictable; unsuccessful attempts to peel the ILM can be associated with poor visual outcome. The use of vital dyes can facilitate visualisation of the ILM and help achieve complete, atraumatic peeling. Indocyanine green dye can enable high rates of macular hole closure but has been associated with poorer visual outcomes suggesting a dose-dependent toxicity. Trypan blue dye offers an alternative that may have a more favourable risk profile. An improved understanding of vitreoretinal relationships may facilitate a tailored approach to surgery in individuals with macular holes. Vitrectomy to relieve anteroposterior traction is central in the management of all full-thickness holes. The use of long-acting gases, prolonged face-down positioning, and ILM peeling may be more valuable for larger holes, longstanding holes, and those that have failed to close following conventional surgery.
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Introduction

Idiopathic full-thickness macular holes are an important cause of central visual loss and are particularly common in women over the age of 65 years.[1,2] An understanding of anatomical changes occurring at the vitreomacular interface has led to the development of surgical techniques resulting in high success rates. Anatomical closure and stabilisation of visual acuity can be achieved in over 90% of cases, and visual improvement in over 70% of eyes.[3–7] Outcomes are expected to improve further as a result of modifications to the conventional surgical technique, including peeling of the inner limiting membrane (ILM), with or without vital staining. Variations in the use of intraocular gas tamponade agents and postoperative positioning regimens may enable more individuals to benefit, accelerate visual rehabilitation, and reduce complications.

Pathogenesis of macular holes

The pathogenesis of idiopathic full-thickness macular holes is not clearly understood but is believed to involve anteroposterior traction and/or tangential traction exerted by the posterior vitreous cortex at the fovea. It has been suggested that involutional macular thinning is a predisposing factor.[8] There is no consensus on the exact mechanism of vitreofoveal traction.

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Anteroposterior traction may be a result of dynamic tractional forces on an abnormally persistent vitreofoveal attachment following perifoveal vitreous separation.[9–11] Tangential traction may result from contraction of prefoveal vitreous cortex following invasion and proliferation of Müller cells.[12] Evidence for the role of posterior vitreous attachment in the development of macular holes includes its association with an increased risk of macular hole development in the fellow eyes of individuals with unilateral macular holes and with the subsequent enlargement of established holes.[13,14] A cone-shaped zone of Müller cells, the 'Müller cell cone', forms the central and inner part of the fovea centralis and appears to confer structural support, serving as a plug to bind together the foveolar photoreceptor cells.[15] Vitreofoveal traction may result in disinsertion of the Müller cell cone from the underlying foveolar photoreceptor cells, resulting in the formation of a foveal schisis or 'cyst'.[9–11] A dehiscence in the roof of the foveal cyst extends by centric expansion or in a peri-centric manner to form a crescentic hole that progresses to a horseshoe tear.[9] Subsequently, complete avulsion of the cyst roof results in a fully detached operculum that is suspended on the posterior vitreous cortex in the prefoveal plane.[9,11,16] Opercula appear to be comprised primarily of vitreous cortex and glial elements[17,18] with a variable amount of foveal tissue, including photoreceptor cell bodies in 40% of cases.[19] The photoreceptor layer, which is no longer anchored by the Müller cell cone at the foveola, undergoes passive centrifugal retraction to form a full-thickness retinal dehiscence with centrifugal displacement of xanthophyll.[15,20] The edge of the hole becomes progressively elevated by a cuff of subretinal fluid, often accompanied by thickening of the neurosensory retina, which may be due to retinal hydration by recruitment of vitreous fluid via the hole, causing further elevation of the hole edges.[21]

In the event of vitreofoveal separation during the development of macular hole, the relief of traction can result in regression of a cyst, but spontaneous closure of an established full-thickness macular hole is relatively uncommon.[22] In a minority of cases, the roof of the foveal cyst opens without disruption of the photoreceptor layer, resulting in a partial-thickness or 'lamellar' hole that may or may not progress to a full-thickness defect.[23]

While the majority of age-related macular holes are idiopathic in aetiology, full-thickness macular holes may also occur in association with high myopia, following posterior segment surgery such as scleral buckling and pneumatic retinopexy, and following ocular trauma.[24] Traumatic macular holes typically result from blunt injury but have also been reported following laser injury and lightning strike. Spontaneous resolution of small full-thickness macular holes following trauma in young patients is not uncommon and can be associated with good visual recovery.[25]

Optical coherence tomography (OCT) is a powerful non-invasive, non-contact imaging technique capable of producing cross-sectional images of ocular tissue *in vivo* of high longitudinal resolution (10 μm). OCT has yielded important insights into the pathogenesis of macular hole development and the mechanism of surgical repair. OCT can be invaluable in the clinical diagnosis of full-thickness macular hole in instances where there is uncertainty when using biomicroscopy, as the appearance on OCT can distinguish full-thickness macular holes from partial-thickness holes, macular pseudoholes, and cysts. OCT is also useful for defining the stage of macular hole development and providing a quantitative measure of hole size and associated macular oedema. OCT has been used to evaluate the vitreoretinal interface in the fellow eyes of individuals with macular holes and enables the detection of subtle separations of the posterior hyaloid from the retina that are not evident clinically.[26] The configuration of macular holes on OCT can be predictive of postoperative visual outcome.[11,27,28] Ultrahigh-resolution OCT offers enhanced visualisation of retinal architecture providing additional detailed information on the morphology of macular disease.[29] High-speed OCT offers three-dimensional imaging of macular holes that facilitates the understanding of abnormalities in the vitreofoveal interface. It also provides consecutive orthogonal images that allow much more precise and minute observation of three-dimensionally extending intraretinal structural changes associated with a macular hole than conventional OCT imaging, including the involvement of the photoreceptor cells in macular holes.[30] These recent advances in OCT imaging promise to improve the understanding of disease progression and its management.

Surgical approaches for macular holes

The rationale for surgical management of idiopathic macular holes, originally described by Kelly and Wendel in 1991,[31] is to relieve vitreofoveal traction and to promote flattening and reapposition of the macular hole edges by intraocular tamponade. Suggested mechanisms by which the hole edges are approximated include the formation of a fibrin membrane or plug, and the resolution of intraretinal hydration by blocking the recruitment of vitreous fluid through the hole.[21] This is achieved conventionally by pars plana vitrectomy with meticulous removal of posterior cortical vitreous and of any epiretinal membranes at the macula. An air–fluid exchange is performed, usually followed by exchange for long-acting intraocular tamponade and face-down

positioning for up to 14 days postoperatively. Modifications of the original technique include peeling of the ILM, with or without the aid of a vital dye, and alternative posturing regimens.

The Vitrectomy for Prevention of Macular Hole study suggested that any benefit of vitrectomy in preventing progression to full-thickness macular holes is minimal and unlikely to outweigh the risk of surgical complications.[32] Instead, it is proposed that stage 1 holes should be managed conservatively, as many resolve spontaneously and only a minority of patients are likely to progress to full-thickness macular holes.

Vitrectomy and intraocular gas tamponade significantly improve the rate of both anatomical closure and visual function in eyes with full-thickness macular holes. Outcomes are particularly favourable for stage 2 holes and holes of less than 6 months duration. Kelly and Wendel,[31,33] in their original series, reported an anatomical closure rate of 58% and visual improvement in 73% of eyes in which holes were closed. Two large randomised controlled trials have since compared the effects of surgery with the natural history of macular holes.[22,34,35] In the Moorfields Macular Hole Study (MMHS), the overall anatomical closure rate for stage 2, 3, and 4 macular holes was 81% at 24 months following surgery compared to 11% in the observation group, and surgery was associated with a significant reduction in macular hole dimensions.[22] Operated eyes improved in median Snellen acuity from 6/36 to 6/18, compared with a deterioration from 6/36 to 6/60 in the observation group. Median near acuity improved in the operated group from N10 to N5, whereas that in the observation group deteriorated to N14. The number of eyes with Snellen acuity of 6/12 or better increased from 0% at baseline to 44% at 24 months in the operated group *vs* 0% at baseline to 7% in the observation group.

Both the MMHS and the Vitrectomy for Macular Hole Study (VMHS) demonstrated a clear benefit of surgical management for stage 3 and 4 macular holes. In the VMHS, anatomical closure at 6 months was achieved in 69% of eyes randomised to surgery compared to only 4% of eyes randomised to observation alone ($P<0.001$). The surgically treated eyes had significantly better visual acuity at 6 months as measured ETDRS visual acuity (mean acuity 20/115 in operated eyes *vs* 20/166 in observed eyes, $P<0.01$) and higher word reading scores.[35] The MMHS demonstrated a similar effect, with a mean difference of 2 lines Snellen acuity between the two groups.[22] Surgical techniques and outcomes have since improved, and many case series now report primary anatomical closure following conventional surgery in more than 90% of eyes with full-thickness macular holes.[3–6]

Intraocular tamponade agents in macular hole surgery

Intraocular tamponade following vitrectomy for macular holes is believed to facilitate reapposition of the rim of detached neurosensory retina and to provide an interface with the vitreous fluid component that serves as a template for a fibrin membrane and glial migration across the macular hole. It is also suggested that the tamponade agent might address intraretinal hydration by preventing subretinal recruitment of vitreous fluid through the hole.[21]

Favourable anatomical and visual outcomes can be achieved by long-acting gas tamponade with strict face-down posturing as originally advocated.[31] In a comparative study of 52 eyes, use of 16% perfluoropropane gas resulted in anatomical closure in 97% and improvement in visual acuity by a mean of 3.1 lines, whereas use of air resulted in closure in only 53.3% and improved mean acuity by only 1.3 lines.[36] In another comparative series of 149 eyes, tamponade by 16% perfluoropropane and face-down posturing for 2 weeks resulted in an anatomical closure rate of 94%, compared to 65% following tamponade by lower concentrations of perfluoropropane and shorter durations of posturing; visual outcomes paralleled the rates of macular hole closure.[37]

Prolonged face-down posturing presents an arduous challenge and is an unrealistic expectation for many individuals. A number of studies have suggested that the use of short-acting gases or short durations of face-down posturing can result in anatomical and visual outcomes comparable to that of longer tamponade, with rapid visual recovery. In a non-randomised comparative trial of 62 eyes, tamponade by 23% sulphahexafluoride and face-down posturing for 6 days resulted in anatomical closure in 93.5%, compared to 96.7% following tamponade by 16% perfluoropropane and face-down posture for 2–4 weeks. The final visual outcome was similar in both groups.[38] In a series of 58 eyes, macular hole surgery involving ILM peel, intraocular air tamponade, and face-down posturing for only 4 days resulted in a primary anatomical closure of 91% and final closure rate of 95%.[39] Good anatomical and visual outcomes have been reported following gas tamponade without prescribed face-down posturing. In a series of 31 eyes, combined cataract/vitrectomy surgery and 15% perfluoropropane but no face-down posturing resulted in primary anatomic closure in 79% and final closure in 85%. Forty-eight per cent of eyes attained visual acuity of 20/50.[40] In another series that included 20 eyes, combined surgery with tamponade by 20% C2F6 without face-down posturing resulted in anatomical closure in 90% and improvement in visual acuity by at least 0.3 logMAR units in 95%.[41]

An alternative proposal for patients who are unable to perform prolonged face-down posturing is the use of silicone oil tamponade.[42] Macular hole surgery with the use of silicone oil and no posturing (except to avoid face-up position) results in primary anatomical closure rates of 80–97%.[42–44] The rate of primary failure of hole closure may be reduced by ensuring an optimal oil fill.[42] The effect of silicone oil tamponade on visual outcome following macular hole surgery, however, is not clear. In a non-randomised comparative trial of 54 eyes, visual outcome following silicone oil tamponade was significantly better than outcome following the use of short-acting gas; 74% of eyes achieved visual acuity of 6/12 or better following oil *vs* 47% following sulphahexafluoride.[44] Other reports have suggested that the use of silicone oil may be associated with a poorer visual outcome. In a series of 10 patients unable to perform prolonged face-down posturing, macular hole surgery using silicone oil tamponade resulted in an anatomical closure rate of 80% but an improvement in visual acuity in only 38% of these eyes, even after removal of secondary cataract.[43] While this finding may reflect longer durations of macular hole in this selected group of patients, the possibility that silicone oil may have a toxic effect on the exposed outer retina at the fovea suggests that its early removal may be advisable in this situation. The value of face-down positioning will be determined only by an appropriately designed randomised controlled trial. The feasibility and size of such a trial is the subject of an ongoing multicentre pilot study in London.

Peeling of the ILM

Surgical removal of the ILM from the macula is advocated in an attempt to further improve anatomical and visual outcomes of surgery for macular holes. The rationale for peeling the ILM is to ensure thorough removal of any tangential tractional components implicated in the development of macular holes including any residual posterior component of schitic cortical vitreous,[45] or epiretinal membrane and associated glial cells.[46] ILM peeling might also promote glial repair by inducing local expression of growth factors and reduce the possibility of late reopening of surgically closed holes by removal of a potential scaffold for reproliferation of myofibroblasts.

Current evidence suggests that ILM peeling can improve anatomical outcome but the effect on visual function is less well established. A number of non-randomised comparative series suggest that ILM peeling results in a higher rate of hole closure and that this is associated with improved visual outcomes. In one study of 160 eyes, ILM peeling was associated with 100% hole closure rate and no reopenings, compared to 82% closure with 25% reopenings in the non-ILM peeled group.[6] In another comparative study of 39 eyes, ILM peeling resulted in 90% hole closure and improvement of visual acuity by 2 lines or more in 62%, compared to 50% closure and 44% improvement in acuity without ILM peel.[47] In another study, ILM peeling resulted in anatomical closure in 97.7% of 44 eyes *vs* 77.3% of 97 eyes without ILM peeling.[48] Visual acuity after surgery was 6/15 or better in 70.4% eyes *vs* 56.7% eyes, and increased by 2 or more lines in 77.3% eyes compared to 64.9% eyes, respectively; the use of ILM peeling was associated with greater than twofold increased probability of developing 6/15 vision or better.[48] Other studies, however, have not demonstrated any advantage of ILM peeling. In one non-randomised comparative series of 107 eyes, an overall closure rate of 89% was achieved with visual acuity improving by 2 lines or more in 85% of eyes; ILM peel was associated with no statistically significant difference in closure rate or visual outcome.[5]

While ILM peeling may improve the rate of anatomical closure, evidence suggests that it can result in an adverse effect on visual function. In one series, ILM peel resulted in anatomical closure in 100% of 29 eyes compared to 85.1% of 27 eyes without ILM peel. Of eyes with holes successfully closed, however, visual improvement of 3 or more lines at 3 months was achieved in only 44.8% following ILM peeling *vs* 79.2% of 24 eyes without ILM peel ($P = 0.01$).[49] In another series that included 193 eyes with macular holes, ILM peel was attempted in all cases. Although anatomical closure achieved after complete ILM peel was associated with improved visual outcomes, the rate of anatomical closure was inversely correlated with the extent of ILM peel actually achieved. It was suggested that excessive unsuccessful attempts at ILM peeling may enhance anatomical success (possibly through enhanced promotion of glial healing) at the expense of poorer visual outcome, presumably resulting from damage to inner retinal elements.[50] Small paracentral scotomata have been observed on microperimetry in more than 50% of eyes in which ILM peel has been attempted, possibly due to direct trauma resulting in small defects in the nerve fibre layer. The scotomata may be multiple but are generally asymptomatic, non-progressive, and not associated with any significant effect on visual acuity.[51] ILM peeling can also result in a punctate chorioretinopathy[52] and in delayed recovery of the macular focal electroretinogram b-wave, suggesting an alteration of retinal physiology in the macular region.[53]

ILM peeling appears to improve the rate of anatomical closure, but its effect on visual outcome is less predictable and excessive unsuccessful attempts to peel the ILM are associated with poor visual outcome. While

ILM peeling may be performed for full-thickness macular holes of any stage, it is probably most valuable for larger stage 3 or 4 holes,[54] longstanding holes, those that have failed to close, or those that have reopened following conventional surgery.

Peeling of posterior vitreous cortex from the retinal surface can result in iatrogenic retinal tears. In the MMHS, retinal tears occurred in 3.2% of eyes and were effectively treated intraoperatively by retinopexy.[22] Retinal detachments occurred in 5.6% of eyes in the MMHS and in 11% of eyes in the VMHS.[55] Retinal detachments generally occur within the first 6–8 weeks postoperatively and have a high success rate of anatomical reattachment following further surgery.[22] Although retinal detachment does not preclude improved final visual acuity, involvement of the macula and the development of proliferative vitreoretinopathy indicate poorer prognosis.[22]

Staining of the ILM

ILM peeling is a technically challenging manoeuvre, in part because of the difficulty in distinguishing the ILM from the posterior vitreous cortex and the nerve fibre layer of the retina with confidence. Inadvertent injury to the nerve fibre layer can cause paracentral scotomata,[51] and unsuccessfully attempted ILM peel can result in poor visual outcome.[50] To achieve reproducible, complete, atraumatic ILM peeling, the use of a vital dye has been advocated to facilitate its clear identification.

Indocyanine green (ICG) dye selectively stains the ILM to facilitate its identification. Furthermore, the application of ICG induces a cleavage plane that facilitates removal of the ILM. ICG-assisted ILM peeling is associated with high rates of macular hole closure (88–97%) in several reported series.[56–59] However, the use of ICG can be associated with poorer visual outcomes despite these high rates of anatomical closure.[48] Several series have reported high rates of anatomical closure, with no significant improvement in visual acuity[60–63] Moreover, the use of ICG has been associated with the development of irreversible peripheral nasal visual field defects, consistent with retinal nerve fibre damage involving predominantly the temporal retina.[60,61,63]

The reasons for poor visual acuity and unexpected visual field defects associated with the use of ICG are not well understood, but mechanical, toxic, or phototoxic mechanisms may be involved. Analysis of ILM peeled after ICG staining has demonstrated adherence of additional retinal elements including remnants of Müller cell footplates, neuronal cells, and ganglion cells, suggesting that ICG may alter the cleavage plane to involve the innermost retinal layers.[60,64–66] A number of studies have suggested that ICG may be toxic to exposed retinal pigment epithelium at the base of the macular hole. ICG-related retinal hyperfluorescence persists for up to 9 months following intravitreal application, and unusual retinal pigment epithelial changes in the area of the macular hole have been noted postoperatively in a high proportion of eyes.[62] Application of ICG induces degeneration of outer retinal cells and an adverse effect on retinal function in experimental models.[67] ICG can induce phototoxic injury in retinal pigment epithelial cells *in vitro*[68] and evidence suggests that the spectral absorption properties of ICG may result in a phototoxic effect at the vitreoretinal interface.[69]

The inconsistent effects of ICG on visual outcome reported in the literature may reflect the differences in concentrations of dye and durations of exposure.[70] Brief (<30 s) intravitreal application of ICG at low concentration (0.05%) can effectively stain the ILM, resulting in a high rate of anatomical success and significant functional improvements.[7] The application of perfluorocarbon liquid, viscoelastic, or whole blood to the macular hole before ICG staining has been advocated to protect the exposed foveal RPE from possible toxic effects.[71] In view of a possible phototoxic effect, the intensity and duration of endoillumination should also be minimised.

Trypan blue dye (TB) offers an alternative to ICG for ILM staining. TB is reported to facilitate anatomical closure of macular holes in 94–100% of eyes[72–74] with no significant adverse effects reported up to 1 year postoperatively. A small randomised controlled trial comparing TB with ICG 0.05% demonstrated no significant difference in visual outcome between the groups. However, visual recovery was statistically significant only in the TB group and there was a higher rate of persistent central scotomata in the ICG group, suggesting that even low-dose ICG may have a potentially adverse effect on functional results.[75]

Outer macular defect

Visual recovery following surgical closure of macular holes may be gradual. Although substantial improvement in visual acuity occurs soon after cataract extraction, further improvement may be observed for up to 2 years.[76] Delayed recovery of vision can be associated with a slowly resolving subfoveal defect or 'cyst' evident on OCT in the outer retina following successful surgery[77] or spontaneous closure.[78] The nature of the contents of this defect is unknown. To test the hypothesis that the defect might contain viscous fluid or cellular debris that delay foveal reattachment and visual recovery, we drained fluid from the macular hole during surgery in a small series of 12 eyes. Only 2 of the 12 specimens of submacular fluid were eosinophilic, suggesting that most

did not have elevated protein content and high viscosity. Cellular material was identified, however, in fluid from 6 of the 12 macular holes drained, including photoreceptor cells in three cases and macrophages in another three specimens. Whether the photoreceptors found in our specimens were shed spontaneously or dislodged during surgery is not clear. In either scenario, loss of photoreceptors into the submacular fluid may contribute to impairment of retinal function. Outer retinal defects were evident in a significant minority (33%) of closed holes despite drainage of submacular fluid, but were compatible with good visual acuity. In a contemporaneous series of eight control eyes undergoing similar surgery without fluid aspiration, four of the seven closed holes developed persistent outer retinal defects. A larger study would be required to determine whether drainage of submacular fluid has a significant effect on visual outcome.

Prognostic factors

The outcome of macular hole surgery is dependent on the stage of the hole and the duration of symptoms but is not dependent on the age of the patient. Anatomical and visual outcomes are inversely correlated to the stage of the hole and are greatest following surgery for small stage 2 holes.[22] The closure rate in patients undergoing surgery within 1 year of onset is 94.0%, and in those waiting 1 year or more it is 47.4%.[79]

Although the best functional results are obtained if surgery is performed within 6 months of the onset of symptoms, visual improvement may be achieved in patients who have been symptomatic for much longer.[80,81] Surgery for macular holes secondary to trauma can result in closure rates comparable to those of idiopathic holes, but high myopia or the presence of a localised macular detachment is associated with a relatively poor prognosis.[82]

Following failure of primary surgery to close macular holes, further surgery involving rigorous dissection of epiretinal membranes, with or without ILM peel, and long-acting gas tamponade can result in anatomical closure and improvement in visual acuity.[83] Alternatively, in eyes with unclosed macular holes following vitrectomy with ILM peeling, additional gas injection during the early postoperative period can result in successful closure.[84] In the MMHS, eyes in which hole closure was achieved after a second procedure attained slightly poorer logMAR and Snellen acuities than eyes in which closure had been achieved after a single procedure but achieved similar near acuities.[22]

Visual recovery is inversely correlated with vision in the fellow eye, tending to be greater where vision in the fellow eye is subnormal.[85] Bilateral visual function improves in a significant proportion of patients after macular hole surgery, particularly where vision in the fellow eye is subnormal.[3] Successful closure improves stereoacuity[86] and has a beneficial effect on patients' subjective perception of visual function[87] but the effect of macular hole surgery on patients' quality of life has yet to be fully evaluated. Recent advances in functional retinal imaging are expected to facilitate an improved understanding of the pathogenesis of macular holes. Together with progress in surgical technology, this is likely to further improve visual prognosis and quality of life for the many individuals who develop macular holes.

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