VITRECTOMY GUIDED BY STAINING OF THE INTERNAL LIMITING MEMBRANE WITH INDOCYANINE GREEN

Thesis
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By
Ahmed Mohamed Reda Awadein
M.B.,B.Ch., M.Sc Degree in Ophthalmology

Supervisors
Prof. Dr. Effat Aly Abd El-Naby
Professor of Ophthalmology
Cairo University

Prof. Dr. Omar Mohamed El-Zawahry
Professor of Ophthalmology
Cairo University

Dr. Ahmed Mostafa Abd El-Rahman
Lecturer of Ophthalmology
Cairo University

Cairo University
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KEYWORDS

Indocyanine green (ICG) - Vitrectomy – Macular hole – Internal limiting membrane (ILM) – Fluorescein angiography – Visual Field – Electroretinography (ERG) - Transmission electron microscopy (TEM)

ABSTRACT

Title: Vitrectomy guided by staining of the internal limiting membrane with indocyanine green

Aim: To study the value of staining of ILM with ICG in macular hole surgery and to study the possible complications related to both peeling of ILM and to ICG

Subject and Methods: The study was performed on 10 patients with idiopathic macular hole (group A) and 10 patients with traumatic macular hole (group B). All patients were subjected to pars plana vitrectomy followed by ICG-assisted peeling of the ILM. Anatomical success was assessed based on clinical examination and OCT. Visual improvement was measured in both groups. Possible complications related to ICG were studied by fluorescein angiography, visual field analysis and ERG. The removed ILM was examined by transmission electron microscopy

Results: Closure of the macular hole was achieved in 80% of patients of group A and in 90% of patients of group B. Statistically significant improvement in visual acuity was obtained in patients of group A. Visual improvement in group B was nil. Fluorescein angiography showed perimacular hyperfluorescence in only 2 patients. Visual field showed improvement in macular sensitivity which correlated with both the anatomical success rate and the
visual improvement. ERG showed improvement in 30-Hz flicker amplitude. The removed ILM showed proliferation of glial cells on the inner surface with no histopathological evidence of other retinal elements.

**Conclusion:** ICG-assisted peeling of the ILM has given encouraging results in macular hole surgery, particularly in idiopathic macular hole.
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<tr>
<td>AC</td>
<td>Anterior chamber</td>
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<tr>
<td>BCVA</td>
<td>Best corrected visual acuity</td>
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<td>BL</td>
<td>Basal lamina</td>
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<td>cc</td>
<td>Cubic centimeter</td>
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<td>CF</td>
<td>Collagen fibrils</td>
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<td>ELM</td>
<td>External limiting membrane</td>
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<td>ERG</td>
<td>Electroretinography</td>
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<td>ICG</td>
<td>Indocyanine green</td>
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<td>ILM</td>
<td>Internal limiting membrane</td>
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<td>IMH</td>
<td>Idiopathic macular hole</td>
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<tr>
<td>KV</td>
<td>Kilovolt</td>
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<tr>
<td>mm</td>
<td>Millimeter</td>
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<tr>
<td>mm²</td>
<td>Square millimeter</td>
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<tr>
<td>MERG</td>
<td>Multifocal electroretinography</td>
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<tr>
<td>MC</td>
<td>Müller cells</td>
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<tr>
<td>MVR</td>
<td>Microvitreoretinal blade</td>
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<tr>
<td>nm</td>
<td>Nanometer</td>
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<tr>
<td>OCT</td>
<td>Optical coherence tomography</td>
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<tr>
<td>PAM</td>
<td>Potential acuity meter</td>
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<tr>
<td>PFCL</td>
<td>Perfluorocarbon liquid</td>
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<tr>
<td>PVD</td>
<td>Posterior vitreous detachment</td>
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<tr>
<td>RPE</td>
<td>Retinal pigment epithelium</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SLO</td>
<td>Scanning laser ophthalmoscope</td>
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<tr>
<td>TEM</td>
<td>Transmission Electron Microscopy</td>
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<tr>
<td>TGF-β2</td>
<td>Transforming growth factor beta-2</td>
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<td>μm</td>
<td>Micrometer</td>
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<td>VEP</td>
<td>Visual evoked potential</td>
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INTRODUCTION
AND AIM OF WORK
Introduction

Pars plana vitrectomy was originally designed by Machemer and associates as a mean to remove non-clearing vitreous haemorrhage, and to allow retinal reattachment by release of vitreous traction. With increased clinical experience and technical developments in vitreous surgery, indications for vitrectomy have expanded to include a wide variety of retinal and vitreous pathologies (Smiddy, 2000).

The retinal internal limiting membrane (ILM) forms the structural boundary between the retina and vitreous. It is derived mostly from the basement membrane elaborated by the footplates of Muller cells, with vitreous fibrils contributing to the inner portion of the ILM (Heegard, 1994). The retinal ILM provides a basement membrane scaffold that can support cellular proliferation (Madreperla et al., 1995). In 1996, Yoon and colleagues observed cellular proliferation on the ILM and hypothesized that forces generated by contraction of these cells may enlarge macular holes. Similarly, it may be involved in disorders that affect the vitreoretinal interface, including epiretinal membranes, macular pucker and vitreoretinal traction.
Surgical removal or peeling of ILM has been described as a potentially useful adjunct to vitreoretinal surgery, particularly in select macular hole cases. However, the removal of ILM may be difficult to perform because of its poor visibility. Inappropriate removal of the ILM risks damage to the retina, e.g. retinal edema or retinal pigment epithelium alterations (Park et al., 1999).

An experimental study in cadaveric eyes described a technique for staining the internal limiting membrane using indocyanine green (ICG) injected intravitreally. The study demonstrated that staining of the ILM renders the nearly invisible ILM clearly visible and greatly facilitates its peeling, which thus offers better visualization and protection to the retina. This could be attributed to the better contrast between the stained ILM and the underlying unstained retina. There was no evidence for retinal or retinal pigment epithelial cellular toxicity attributable to ICG (Burk et al., 2000).

In corroboration with this experimental study, few studies were performed to evaluate the value of staining of the ILM with indocyanine green during macular hole surgery. The studies confirmed that staining of the ILM allows better visualization and ensures satisfactory and atraumatic removal of the ILM (Kwok et al., 2001).
Introduction and Aim of Work

Removal of ILM in traumatic macular holes has been suggested as a surgical option in improving vision. The majority of eyes benefit from ILM removal, even when additional traumatic macular pathology is present (Kuhn et al., 2001)

Aim of work:

This study is designed to:

1- Study the value of staining of ILM with ICG in macular hole surgery (idiopathic and traumatic types), particularly in assisting peeling of ILM and identification of epiretinal membranes

2- Study the possible complications related to both peeling of ILM and to ICG

3- Study the efficiency of this technique as regards anatomical and functional outcome of the patient
REVIEW OF LITERATURE
Anatomy of internal limiting membrane

The internal limiting membrane (ILM) forms the innermost layer of the retina and the outer boundary of the vitreous. It gives the posterior retina a characteristic sheen when observed with the ophthalmoscope (Anthony et al., 1997).

**Thickness and continuity:**
The thickness of the ILM varies between 20-100 nanometer (nm) in the anterior retina. Posteriorly, the ILM attains a thickness of 0.5-2.0 micrometer (μm). It continues uninterrupted at the fovea where it is thickest. It is absent at the edge of the optic disc.

At the periphery of the retina, the membrane is continuous with the basal lamina of the ciliary epithelium. The basal lamina shows breaks at the pars plana and at the ciliary processes. At these points, vitreous fibrils are in direct contact with the cell membranes of the epithelial cells. These breaks in the basal lamina increase with age, and basal laminar fragments may be found in the cortical vitreous in the adult eye.

With ageing, the ILM becomes thicker and interrupted at the ora serrata (Heegaard, 1994).
Anatomy

**Structure:**

Both the retina and the vitreous contribute to the formation of this membrane, which consists of four elements: (1) collagen fibrils, (2) proteoglycans (mostly hyaluronic acid) of the vitreous, (3) the basement membrane (basal lamina) and (4) the plasma membrane of the Müller cells and other glial cells of the retina (*Fig. 1*).

By electron microscopy, the collagen fibrils of the vitreous are seen enmeshed in the vitreal proteoglycans and finally insert into the basement membrane of the glial cells.

*Fig. (1)*: Transmission electron micrograph of the internal limiting membrane (ILM), showing the insertion of collagen fibrils (CF) of the vitreous into the basal lamina (BL) of the Müller cells (MC) (*Anthony et al., 1997*).
The basement membrane stains positively with periodic acid-Schiff and red with Mallory trichrome. However, the vitreal contribution to the ILM stains blue with Mallory trichrome, which is indicative of its collagenous nature. The external portion of the ILM exhibits a mosaic pattern that depicts the irregularities of the foot processes of the Müller cells (Fig. 2). The irregularities form pockets which are filled by the overlying basement membrane. These pockets are called basement membrane facets.

Fig. (2): Photomicrography showing the mosaic pattern of the retina as revealed by a flat preparation stained with silver, which outlines the footplates of the Müller cells that attach to the ILM (Anthony et al., 1997).
Anatomy

The vitreous portion of the ILM appears smooth in flat sections of the retina, except at the retinal periphery where it may be irregular (Sebag et al., 1984).
Vitreous cortex and vitreoretinal junction

The term vitreous cortex is applied to the dense broad zone, 0.2-0.3 millimeters (mm) in width, adjoining the retina. Microscopically, it is formed by a condensation of fibrils, cells and glycosaminoglycans. Its fibrils are 12 nm wide (Fig. 3). These fibrils insert into the ILM of the retina posteriorly, blending with the basal lamina of the Müller cells, or with the basal lamina of the ciliary body epithelium anteriorly (Smiddy et al., 1989).

Fig. (3): Appearance of indigenous vitreous with collagen fibrils (Smiddy et al., 1989).
The vitreous cortex is divided into the vitreous base, anterior hyaloid, posterior hyaloid, peripapillary and perimacular cortex (*Tripathi et al., 1984*).

1- **Vitreous base:**

The vitreous base is a broad band of vitreous condensation and attachment which runs circumferentially from a point 2 mm anterior to the ora serrata to a point 2-4 mm behind it (*Faulborn and Bowald, 1982*).

Collagen fibrils are densely packed at the vitreous base and are firmly inserted throughout its width. Collagen fibrils at the vitreous base are wider than elsewhere in the cortex, about 45 nm wide. They are organized as groups of tapering bundles which pass out at right angles to the retinal surface (*Smiddy et al., 1989*).

In old age, small crypts may be found between the Müller’s cell foot plates at the vitreous base. Vitreal fibres may perforate the ILM to fill these crypts (*Fig. 4*). Thus, traction on the vitreous base may create a retinal tear, the forerunner of a retinal detachment (*Sebag et al., 1984*).

With age, the vitreous base broadens anteriorly and posteriorly, having a relatively straight course temporally and a more wandering course nasally. There are also racial differences, with the vitreous base lying more posteriorly in the African and Chinese (*Daicker, 1972*).
Fig. (4): Photomicrograph of the peripheral retina and ora serrata showing:

a- Paraffin embedded section demonstrates the presence of glycosaminoglycans within the cystic spaces
b- Cystic spaces (CS) extending from the internal limiting membrane (ILM) to external limiting membrane (ELM)
c- Cystic spaces (CS) in communication with the ILM (Tripathi, et al., 1984).
2- **Anterior hyaloid:**

The anterior hyaloid is the portion of the vitreous surface that stretches forwards from the anterior margin of the vitreous base at the ora serrata. The collagen fibrils of the anterior cortex are arranged in compact lamellae, parallel with the plane of the pars plana. These collagen fibrils are woven into a mesh-like structure (*Faulborn and Bowald, 1982*).

3- **Posterior hyaloid:**

Just posterior to the vitreous base, the fibrils of the vitreous cortex curve backwards along the inner retina and pass towards the central vitreous. Posterior to the equator the fibrils blend with the ILM of the retina (*Sebag et al., 1984*).

4- **Peripapillary and perimacular cortex:**

The peripapillary cortex is firmly united to a narrow zone of marginal retina 10 μm wide at the edge of the disc. This is where the Müller’s fibres and associated ILM end. A similar but less dense attachment to perimacular retina occurs. Both attachments are more developed in young eyes (*Sebag et al., 1984*).
Anatomy

Vitreoretinal junction:

The strength of attachment between the vitreous and retina varies according to the anatomical region and to age.

- **Anatomical region (Fig. 5):**

  In young eyes the vitreous face is adherent to the posterior lens capsule in the region of hyaloidocapsular ligament. The vitreous body is firmly attached to the retina in the following regions:

  1- Vitreous base: the vitreous body is firmly attached to about 2 mm zone of the pars plana and continues posteriorly to about 4 mm width of the peripheral retina
  2- Margins of optic disc
  3- Margins of macular region forming an annular attachment 3-4 mm in diameter
  4- Overlying retinal blood vessels.

Elsewhere, the attachment between the retina and vitreous is loose *(Faulborn and Bowald, 1982).*
Fig. (5): Schematic view of the vitreous attachments. The vitreous is firmly attached (solid line) to about 2 mm zone of the pars plana (1) and continues posteriorly to about 4 mm width of the peripheral retina (2). The dotted line anteriorly represents the anterior vitreous face. Posterily the vitreous face is attached to the edge of the optic disc (3). A similar annular attachment is seen at the macular region (4). AC= anterior chamber, CC = Cloquet’s canal (Tripathi, 1984).

- **Age:**
  In young eyes, the attachment between Müller’s cell membranes and cortical collagen fibrils strong. If the vitreous is pulled away from the retina, the cell membrane of the Müller’s cell breaks. This attachment loosens with age (Sebag et al., 1984).
Macular hole

Full-thickness macular holes are defects involving all layers of the retina, from the internal limiting membrane through the outer segment of the retinal photoreceptors. Lamellar holes involve only a portion of retinal layers (Aaberg et al, 1970).

Causes of full-thickness macular holes:

1- Idiopathic macular hole: This is the most common type (Gass, 1988).
2- Traumatic macular hole (Madreperla and Benetz, 1997).
3- Pathologic myopia (Curtin, 1983).
4- Laser-induced (Lim et al., 1991).
5- Electric current (Campo and Lewis, 1984).
6- Solar retinopathy (Gass, 1988)
7- Other causes e.g. pilocarpine use (Garlikov and Chenoweth, 1975), Best’s disease (Mehta et al., 1991), adult vitelliform macular degeneration (Noble and Chang, 1991) and traction from epiretinal membranes (Aaberg et al, 1970).
Idiopathic macular hole (IMH)

Idiopathic macular hole (Fig. 6) affects emmetropic patients in the sixth or seventh decade. It affects women more often than men (Aaberg et al., 1970).

Fig. (6): Idiopathic macular hole, stage 4 (Smiddy, 2000).

**Histopathology:**

The edges of IMH are typically rounded with some cystic changes in the outer plexiform and inner nuclear layers (Fig. 7) Nodular proliferations of retinal pigment epithelium (RPE) may cause yellowish deposits on the base
of macular holes. Variable photoreceptor degeneration around the hole may occur, suggesting the inability to support good vision. *(Guyer et al., 1990).*

![Histopathology of idiopathic macular hole. Note the intact retinal pigment epithelium (Frangieh et al., 1981).](image)

**Fig. (7):** Histopathology of idiopathic macular hole. Note the intact retinal pigment epithelium *(Frangieh et al., 1981).*

Cellular proliferation on the ILM and fibroglial membrane formation is noted in long-standing macular hole *(Fig. 8).* Contractile cells have also been identified in the vitreous of patients undergoing surgery for impending macular holes *(Yoon et al., 1996).* Eyes with IMH were thought to lose vision secondary to tissue loss (operculum), cystic retinal changes and retinal cuff formation with photoreceptor degeneration *(Madreperla et al., 1995).*
Fig. (8): Margins of a macular hole with a fibroglial membrane distorting the ILM (*Wendel et al.*, 1999).

After surgery for macular hole, proliferation of glial cells (*Fig. 9*) or hole closure and near-normal return of retinal anatomy may occur (*Funata et al.*, 1992).

Fig. (9): Healed macular scar examined at autopsy showing a glial scar occupying the entire foveola. The photoreceptors are discontinuous in a 0.05 mm wide zone (A) (*Funata et al.*, 1992).
In a histopathological study on an eye with successfully closed macular hole, there was complete resolution of the cystic changes and return of xanthophylls to the center of the macula. The photoreceptors returned to their normal appearance. The authors concluded that the mechanism of hole closure following macular hole surgery is therefore sealing of the hole rather than chorioretinal adhesion (Madreperla et al., 1994).

Theories of the pathogenesis of IMH include:

1- **Tangential vitreoretinal traction:**

Gass in 1988 proposed that tangential traction caused by shrinkage of premacular vitreous cortex is responsible for IMH formation. The process typically begins in eyes with liquefied pockets of premacular vitreous and no posterior vitreous detachment (PVD). This suggests that IMH begins as a foveolar cystic change with an "unroofing" of the hole. Scanning electron microscopic studies have shown that even after apparent spontaneous PVD, there are remnants of posterior vitreous in membrane in the foveal area. These glial cells can create tangential traction leading to formation of IMH.
Gass described four stages of macular hole (Fig. 10):

a- **Stage 1A (impending macular hole):**

It is caused by localized shrinkage of perifoveal vitreous cortex, causing tractional shallow detachment of the foveola.

It is characterized clinically by foveolar detachment resulting in yellow spot or perifoveal ring with loss of foveolar depression. The yellow spot measure about 100-300 μm in diameter and has been attributed to increased visibility of xanthophyll resulting from a shallow foveolar detachment.

It may be asymptomatic or the patient may notice sudden onset of metamorphopsia, especially if the other eye has impaired vision.

b- **Stage 1B (occult macular hole):**

It is caused by further vitreous contraction leading to tiny breaks in the photoreceptors in the center of the foveola but with intact ILM.

It is characterized by yellow ring with a bridging interface.
Fate of stage 1 lesions:

- Stage 1 lesions are transient. They may resolve within a few weeks owing to spontaneous vitreofoveal separation. Resolution may be accompanied by improvement of vision and metamorphopsia. A semitranslucent premacular opacity may be visible biomicroscopically, representing contracted vitreous cortex.

- Approximately 40% of impending macular holes progress to full-thickness macular holes. The yellow ring enlarges progressively because of continued traction. Contracted prefoveal vitreous usually remains tightly adherent to the retinal surface. The contracted prefoveal vitreous appears as a semitransparent opacity, or may become transparent and invisible.

_Gass_ believes that most cases of enlargement of the yellow ring result from the formation of an occult tear in the foveolar umbo, which is the weakest part of the fovea. This is followed by progressive centrifugal displacement of retinal receptors. Loss of retinal receptors does not occur in the majority of eyes.
c- Stage 2 macular hole:

It is caused by condensation of prefoveal cortical vitreous and separation of the later from the retinal surface to form a pseudo-operculum. Thus, this break is in the contracted prefoveal vitreous bridging around the retinal hole, and not in the retinal tissue itself.

It is characterized by a visible full-thickness break that is first seen usually at the inner edge of the yellow ring. Yellow pigmentation fades in this area because of possible diffusion of xanthophylls out of the retina.

Fate of stage 2 macular hole:

- The macular hole enlarges over a period of days to weeks to stage 3 or 4.
- Eyes with eccentric holes and those with pericentral hyperfluorescence in fundus fluorescein angiography are more likely to progress than those with central holes.
Fig. (10): Stages of development of idiopathic macular hole (Gass, 1995).

d- Stage 3 macular hole:
It is characterized by separation of the pseudo-operculum from the edge of the hole without PVD. The underlying retinal hole continues to enlarge, presumably because of centrifugal retraction of retinal tissue. The underlying RPE within the area of retinal hole shows thinning and depigmentation. This contributes to the hyperfluorescence seen on fluorescein angiography. Multiple yellow opacities are seen at the level of the RPE within most holes. These opacities change in number and distribution over time. The retina near the margin of the hole may show microcystic changes. Wrinkling of the inner retinal surface caused by an epiretinal membrane may be seen in 10-20% of cases.

**e- Stage 4 macular hole:**
It is characterized by complete separation of the vitreous from the entire macular surface and optic disc with presence of Weiss ring in front of the optic nerve head.

**Fate of stage 3 and 4 macular hole:**
- Visual acuity stabilizes at about 6/60
Spontaneous closure is rare but may be caused by growth of an epiretinal membrane.

2- Degenerative hypothesis:

*Lipham and Smiddy* in 1997 postulated that an atrophic process is the primary cause of the full-thickness macular hole. The pathogenesis of macular hole passes through the following stages:

1- Foveal perforation:
A central tiny foveal perforation occurs, possibly as a consequence of atrophic disorder, akin to atrophic peripheral retinal breaks (*Fig. 11*). The cystic changes seen with full-thickness macular holes may mediate this process or may be a secondary effect.
2- **Healing process:**

A healing response consisting of proliferation of the now-exposed glial elements occurs. The proliferation of these glial elements may take one of two courses:

- Glial cells may grow around the edges of the macular hole onto the surface of the retina. Subsequent contraction of these glial cells leads to progressive enlargement of the hole (**Fig. 12**).
Fig. (12): Proliferation of glial cells around the edge of the macular hole onto the surface of the retina (dark arrows) (*Lipham and Smiddy, 1997*).

b- Glial cells may grow along the posterior surface of the hyaloid, which act as a template. The glial cells cross-link and reapproximate the edges of the macular hole (*Fig. 13*). This may be the same mechanism by which macular hole surgery is successful. However, with surgery the template is the fluid-gas interface and the proliferation stimulus is surgical trauma or adjuvant. If the hole cross-link and spontaneously seals, it may even escape clinical detection.
3- Posterior vitreous detachment:
If posterior vitreous detachment occurs, one of the possible scenarios may result:

a- If the vitreous separates without pulling the fibroglial plug with it, near normal macular morphology is preserved. A relatively good vision is maintained. The patient and the clinician may be unaware of the presence of full-thickness hole (Fig. 14)
Fig. (14): Posterior vitreous detachment without pulling the fibroglial plug (Lipham and Smiddy, 1997).

b- If the separating vitreous drags the glial plug with it, an apparent operculum with a reexposed full-thickness hole may occur. This sequence represents a delayed manifestation of a previously formed, but arrested, occult macular hole. Moreover, the vitreous is no longer in a position to serve as a healing template. This may cause glial cell proliferation, which may lead to further enlargement of this reopened macular hole. (Fig. 15).
c- A portion of the glial plug may separate yielding a pseudo-operculum, but the remaining portion keeps the hole closed. Perhaps this is what has been referred to as a lamellar macular hole.

Fig. (15): Posterior vitreous detachment dragging the operculum of fibroglial tissue (*Lipham and Smiddy, 1997*).

**3- Involutional macular thinning:**

This may be initiated by compromised choroidal circulation (*Morgan and Schatz, 1985*).
**Macular Hole**

### Traumatic macular hole

The mechanism of macular hole formation after trauma include:

1- Concussion and residual vitreomacular traction following incomplete vitreous detachment.
2- Traumatic vitreal displacement and vitreoretinal traction.
3- Prolonged macular edema in the resolution phases after macular trauma (*Garcia-Arumi et al., 1997*).

### Myopic macular hole

The mechanisms of macular hole formation in myopia include:

1- Progressive thinning and stretching of the posterior pole.
2- Staphyloma formation with accentuated stretching of the posterior pole causes thinning of the retina.
3- Relative ischaemia of the sensory retina due to decreased retinal and choroidal blood flow.
4- Cystic degeneration and atrophy of the macula.
5- Vitreous degeneration and PVD which occurs in younger age in pathologic myopia.

6- Abrupt dehiscence of macular tissue due to anteroposterior vitreoretinal traction.

7- Focal contraction of the prefoveal vitreous cortex may also occur as in IMH *(Curtin, 1983).*
Role of Internal Limiting Membrane in the Pathogenesis of Idiopathic Macular Hole

In 1989, Smiddy and associates examined the histopathological nature of the preretinal sheet of vitreous overlying the macula in 29 patients with IMH. Fragments of internal limiting membrane with fibrous astrocytes were present in some of the specimens (Fig. 16).

Fig. (16): Preretinal tissue containing fragments of ILM (asterisk) and fibrous astrocytes with intracytoplasmic filaments (brackets and inset) and basement membrane formation (arrowheads) (Smiddy et al., 1989)
Smiddy and associates suggested that this fibrous tissue may represent an epipapillary membrane that was removed with the posterior hyaloid layer.

In 1995, Madreperla and associates studied the opercula associated with IMH. The inner surface of the opercula was covered by processes of Müller cells (Fig. 17) with numerous sections of smooth endoplasmic reticulum and prominent intercellular junctions. Fibrous astrocytes with densely packed 10-nm intermediate filaments and surrounding basement membrane were also present (Fig. 18). Fragments of ILM were present in some areas.

Fig. (17): Photomicrograph of a macular hole operculum with a thin layer of cortical vitreous (arrow) on the inner surface. The nucleus (N) and cell processes of Müller cells are present (Madreperla et al., 1995).
**Fig. (18):** Macular hole operculum consisting of Müller cell process (top) with numerous sections of smooth endoplasmic reticulum (arrows) and intercellular junctions (arrowheads). Fibrous astrocytes (bottom) are present with 10-nm filaments (F) and basement membrane (arrowheads) (Madreperla et al., 1995).

*Madreperla and associates* postulated that the opercula associated with macular hole represent part of the reparative process. They highlighted the role of Müller cells and fibrous astrocytes in the pathogenesis of macular hole, perhaps in an attempt to seal the macular hole.
In 1996, Yoon and colleagues conducted a study on twelve patients with unilateral IMH. They performed vitrectomy for these patients with intentional removal of the internal limiting membrane and the adherent epiretinal tissue overlying and surrounding the hole. They excised specimens were examined with transmission electron microscopy and the findings were compared with the preoperative stage of the macular hole.

In stage 2 macular hole, fibrocytes embedded in collagen fibrils were present (Fig. 19).

Fig. (19): Surgical specimen from stage 2 macular hole showing fibrocytes (fib) enmeshed in a collagenous matrix. Inset show individual collagen fibril, 10 nm in diameter (arrow) (Yoon et al., 1986).
In stage 3 and 4 macular holes, there was proliferation of glial cells on the inner surface of the ILM. The cellular proliferation was more marked in stage 4 than stage 3 macular holes (*Fig. 20 and 21*).

*Fig. (20)*: Surgical specimen from stage 4 macular hole showing proliferation of myofibroblasts on ILM with microvilli (arrow), intercellular junctions (upper inset) and subplasmalemmal filaments (*Yoon et al., 1986*).

_Yoon and colleagues_ concluded that tangential vitreous traction and possible cellular proliferation in the layer of vitreous overlying the fovea causes the formation of macular hole (stage 1) and pseudo-operculum (stage 2) as proposed by _Gass_. The cells in this fibrocellular
proliferation may represent fibroblastic differentiation of facultative hyalocytes.

**Fig. (22):** Surgical specimen from stage 4 macular hole showing proliferation of fibrous astrocytes on ILM with abundant intracytoplasmic intermediate filaments (inset) (*Yoon et al., 1996*).

The pseudo-operculum shrinks in stage 3 holes. The incomplete PVD in stage 3 allows the proliferation of cells from the RPE onto the retinal surface over the ILM. These proliferative cells undergo myofibroblastic differentiation, causing retraction of the edges and widening of the hole. There is a continuum between stages 3 and 4 macular holes. The more extensive proliferation of myofibroblasts in stage 4 than stage 3 macular hole is due to loss of the tamponading effect of or biochemical property of the vitreous when a complete PVD occurs. Another factor is
the longer duration of stage 4 than 3 holes, thus allowing more time for cellular proliferation (*Fig. 22*).

**Fig. (22):** Schematic diagram depicting the mechanism of macular hole formation (*Yoon et al., 1996*).

The study hypothesized that IMH enlarge, in part, because of myofibroblastic contraction on the ILM. They suggested removal of the ILM and the adherent contractile cells as a reasonable surgical approach to both relieve the tangential
traction on the prefoveal vitreous and remove the scaffold for the proliferation of glial cells (*Yoon et al., 1996*).

Another study by *Ezra and associates* in 1997 on the histological characteristics on the opercula associated with IMH confirmed these findings. The opercula were composed primarily of Müller cells and fibrous astrocytes. Fragments of ILM were demonstrated in 61% of specimens. Neurites and synaptic complexes resembling those of photoreceptors were present in 39% of cases. The presence of these neurites was correlated with poor surgical anatomical success rate and these opercula were considered to be true opercula resulting from a full-thickness foveal tear.
Assessment of macular holes

1- Slit-lamp biomicroscopic examination:

The accuracy of clinical diagnosis of full-thickness macular holes depends mainly on slit-lamp biomicroscopic examination (*Smiddy et al., 2000*).

During examination, the patient may note a total discontinuity in the slit-lamp beam as it passes over the hole (Watzke-Allen test). If the beam appears only to narrow or thicken slightly, the lesion may represent only a cystic change. Alternatively, a 50-µm spot laser aiming beam pointed directly in the center of the hole will not be seen (*Martinez et al. 1994*).

A translucent operculum suspended posteriorly, in front of the hole, is seen in 25% of patients (*Gass, 1987*).

The RPE at the base of the hole is intact but can show hyperplastic or atrophic response (*Judson and Yannuzzi, 1994*).

Epiretinal membrane formation surrounding the hole may distort its contour in 20%. A halo of subretinal fluid may encircle the hole, creating a limited sensory retinal detachment in over 50% of cases seen (*Gass, 1987*).
Assessment of macular holes

2- Visual acuity:

The mean preoperative visual acuity is 6/60 Snellen equivalent with a range from 3/60 to 6/18.

After vitrectomy, improvement of visual acuity by 2 lines or more is expected in 66% (Scott et al., 2000).

3- Ultrasonographic evaluation:

The spectrum of identifiable echographic features in IMH include (1) a thin, smooth, membrane-like surface minimally elevated over the macula (limited PVD); (2) macular thickening; (3) an operculum; and (4) a complete posterior vitreous face separation (Fig. 23). Echographic features correlate accurately with clinical features (Dugel et al., 1994).

Fig. (23): Posterior vitreous detachment in a patient with macular hole (Dugel et al., 1994).
4- **Optical coherence tomography (OCT):**

OCT is similar to ultrasound B-scan except that light, rather than sound, is used which enables high resolution. It is a non-invasive non-contact imaging modality with high longitudinal resolution (10-micron). It is based on the principle of low coherence interferometry. Light is split by a fiber coupler with half sent to a reference arm and half sent to the sample arm. One fiber directs light to the tissue being imaged and another fiber directs light to a moving reference mirror. By using a low-coherence light source and measuring the interference between light backscattered from the tissue and from the reference mirror, the distance and magnitude of optical scattering within the tissue can be measured (*Puliafito et al., 1996*) (*Fig. 24*).

Tomographic image is achieved by performing successive axial measurements at different transverse points. To enhance differentiation of structures a false color scheme is employed, with red and yellow colours for areas with low reflection and blue and black colours for areas with low reflection (*Imai et al., 1999*) (*Fig. 25*).
Assessment of macular holes

Fig. (24): Schematic diagram depicting the optical principles of optical coherence tomography (Puliafito et al., 1996).

Fig. (25): Diagram demonstrating the axial scanning to obtain a tomographic image (Puliafito et al., 1996)
Preoperative evaluation:

1. The cross-sectional view produced by OCT can distinguish full-thickness macular holes (Fig. 26), pseudoholes, and cysts (Hee et al., 1995).
2. OCT can be used in staging macular holes (Fig. 27) and quantitative measurement of hole diameter and the surrounding macular edema (Hee et al., 1995).
3. OCT is useful in evaluation of the vitreoretinal interface at the site of the macular hole; including evaluation of the presence of PVD, macular hole operculum and areas of vitreoretinal adhesion (Wilkins et al., 1996).
4. OCT is useful in assessment of the extent and adherence of the epiretinal membranes surrounding macular holes (Wilkins et al., 1996).
5. OCT can be used to evaluate the presence of any secondary retinal thickening around the macular hole (Hee et al., 1995).
6. OCT can be used to evaluate the vitreoretinal interface in patients’ fellow eyes to detect early PVD (Wilkins et al., 1996).
Assessment of macular holes

Fig. (26): Horizontal OCT scan through centre of a fovea with stage 2 macular hole. OCT examination confirms an IMH with a perifoveal PVD and a small prefoveal opacity. The edges of the macular hole are elevated because of a combination of intraretinal cyst formation and a small cuff of subretinal fluid. HF = hyaloid face, NFL = nerve fibre layer, RPE-Ch = retinal pigment epithelium and choriocapillaris, Ph-OPL = photoreceptors and outer plexiform layer (Hee et al., 1995).

Fig. (27): OCT of different stages of macular hole (Puliafito et al., 1996).
**Assessment of macular holes**

**OCT picture of successfully repaired macular holes:**
Postoperative OCT images of repaired macular holes can be categorized into three patterns (*Fig 28*):

1. **U-type** (normal foveal contour): The RPE is covered with mildly to moderately backscattering layers with a smooth circular surface.
2. **V-type** (steep foveal contour): The RPE is covered with moderately backscattering layers with a notch.
3. **W-type** (foveal defect of neurosensory retina): There is abrupt or gradual termination of sensory retinal layers with exposure of the surface of the RPE.

Postoperative visual acuity correlates with these patterns of OCT images with the best visual acuity in the U-type and the worst visual acuity in W-type (*Imai et al., 1999*).
Assessment of macular holes

Fig. (28): U-type (1), V-type (2) and W-type (3) OCT images after closure of IMH (Imai et al., 1999)

Takahashi in 2000 classified the patterns of closure of IMH in OCT into simple closure (normal foveal configuration) and bridge formation mimicking a foveal retinal detachment. The bridge formation appears to reflect an early fragile phase in the anatomic closure of macular holes. It takes an average of 2 months for the bridge tissue to attach to the RPE. Visual improvement starts after the fovea assumes a normal configuration.

5- Scanning laser ophthalmoscope (SLO):

Scanning laser ophthalmoscope is a non-invasive technique which permits an objective, topographic measurement of the fundus. It employs a confocal optical system to enable high resolution along the optical axis (Akiba et al., 1996).

Preoperative evaluation:

1- Assessment of the topography of the ILM in the macular area: The confocal arrangement of the laser tomographic scanner permits examination of retinal topography in the axis perpendicular to the retinal surface (Bartsch et al.,
2- Evaluation of thickness and extent of epiretinal membranes by confocal imaging of the fundus with argon blue or green illumination (Akiba et al., 1996).

3- SLO dark-field mode with a diode laser may be useful for clear observation of fine retinal features around macular holes. The retinal folds around IMH indicate the presence of traction on the macula and hence may be good markers for macular repair after surgery (Yoshida et al., 1998).

4- Differentiation of pseudoholes from full-thickness macular holes: Irregular rippling undulations are frequently observed around pseudoholes, whereas elevated cuffs are observed around full-thickness holes (Akiba et al, 1999).

5- Quantitative and reproducible three-dimensional analysis for macular holes (Fig. 29): It allows measurement of area, depth and volume parameters of both macular hole and its rim (Hudson et al., 1996).

6- Prediction of the visual outcome after surgery by correlation with area, depth and volume of the macular hole and its rim (Hudson et al., 1996).
Assessment of macular holes

Fig. (29): SLO intensity image of a full-thickness macular hole preoperatively (a) and 3 months postoperatively (b). Topographic difference image (c) and significance marker (d) 3 months postoperatively relative to baseline (red represents significant reduction of retinal height, while green represents significant elevation) (Hudson et al., 1996).
**SLO picture of successfully repaired IMH:**
SLO after successful macular hole surgery show closure of the holes and flattening of the cuff and retinal striae. Postoperative small depressions corresponding to the healed macular holes is caused by gliosis. Large concave depressions may result from postoperative changes of the retina; including swelling of ganglion cells and loss of outer and inner segments of photoreceptor cells in the region of preoperative cuff (*Kobayashi et al., 2000*).

**6- Visual field and scanning laser ophthalmoscope perimetry (SLO perimetry):**

**Preoperative values: (Fig. 30)**
1- Assist in the diagnosis of full-thickness macular holes: SLO microperimetry shows an absolute scotoma within the macular break and a relative scotoma on the cuff (*Kakehashi et al., 1996*).

2- Differentiation of full-thickness macular holes from impending macular holes and macular pseudoholes: Deep scotomas are seen in eyes with full-thickness macular holes but not in pseudoholes (*Tsujikawa,
Assessment of macular holes

1997).

Fig. (30): SLO microperimetry showing absolute scotomas within the macular break (black spots) and relative scotomas on the surrounding fluid cuff (white spots) (Tsujikawa, 1997).

3- Prediction of visual outcome after surgery: Visual outcome following surgery correlates with the maximum parahole sensitivity (highest intensity of stimulus to which the patient did not respond to any
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of the stimuli around the hole (Amari et al., 2001).
SLO microperimetry eliminates some of the classical problems involved in transformation techniques in perimetry such as: optical distortions, unsteady fixation and alignment (Anderson, 1996).

Visual field changes after successful IMH surgery:

- In case of complete closure absolute scotoma disappears or is replaced by relative scotoma.
- In atrophic closure absolute scotoma persists.
- Postoperative paracentral scotomas may be detected in areas that were tested normally before surgery especially after vitrectomy combined with peeling of the ILM. Scotomas are located temporally and/or inferiorly and often appear like nerve fibre bundle defects. They may be caused by trauma to the nerve fibre layer during surgery (Haritoglou et al., 2001).

7- Multifocal electroretinography (MERG):

Preoperative values:
1- Evaluation of macular function: Focal macular electroretinogram using a 4-degree stimulus spot show a
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decrease in b-wave amplitude and prolonged implicit time of the b-wave (Terasaki et al., 1998).

2- ERG can be used to evaluate the foveal ERG in patients’ fellow eyes to detect eyes at risk for macular hole formation. (Birch et al., 1988).

3- Prediction of visual outcome after surgery: Qualitative change (implicit time) is more important than qualitative change (amplitude) in electroretinograms for predicting postoperative corrected visual acuity (Terasaki et al., 1998).

**ERG changes after successful IMH surgery:**
After successful macular hole closure, the b-wave amplitude increases and the b-wave implicit time decreases significantly (Terasaki et al., 1998).

8- **Visual evoked potential:**

VEP in macular hole show prolongation of P100 latency and reduction in the steady-state VEP amplitude in 93% of cases (Johnson et al., 1987).
Surgical treatment of full-thickness macular holes

The surgical options for treatment of full-thickness macular hole include:

1- Laser photocoagulation
2- Pneumatic induction of PVD and pneumatic retinopexy
3- Posterior scleral buckling
4- Vitrectomy and intravitreal injection of tamponade
5- Vitrectomy with injection of adjuvants for closure of the macular hole
6- Vitrectomy with peeling of the internal limiting membrane around the macular hole

Laser photocoagulation

Laser photocoagulation applied to the rim of the hole in order to decrease the surrounding halo of subretinal fluid has been suggested. Both argon and krypton laser were used to place a circumferential row of laser spots surrounding the outer edge of the hole (Schocket et al., 1988).
Surgical treatment of macular holes

Investigators have reported limited visual improvement in eyes treated with laser photocoagulation. Intuitively, laser treatment to the cuff may actually impair visual function, and this form of treatment has gained little acceptance (Wendel et al., 1999).

Pneumatic induction of PVD and pneumatic retinopexy

A gas bubble introduced into the vitreous cavity might serve to relieve vitreoretinal tractional forces creating and holding macular holes open as well as tamponade the hole (Rashed and Sheta, 1989).

A single gas bubble of a long-acting gas e.g. sulfur hexafluoride, perfluoroethane or perfluoropropane is injected using a 27-gauge needle through the pars plana into the midvitreous. The patient is positioned face-down to tamponade the macular hole and the intraocular pressure is monitored for pressure spikes (Chan et al., 1995).

The results of pneumatic retinopexy in IMH are still questionable. In his study, Chan and his associates reported successful closure of the hole in 50% of patients of stage 2. In the remaining 50%, the hole progressed from stage 2 to 4. In stage 3, none of the patients had closure of the hole.
Surgical treatment of macular holes

**Posterior scleral buckling**

A special episcleral explant is sutured to the sclera at the site of the macular hole to support the break (Fig. 31). The technique is technically difficult because of the posteriorly situated sutures (Sasou et al., 2000).

![Diagram of posterior buckling procedure](image)

**Fig. (31):** Posterior buckling procedure (Sasou et al., 2000)

**Vitrectomy with intravitreal injection of tamponade**

In 1991, *Kelly and Wendel* published the first report of successful closure of IMH with pars plana vitrectomy. Several authors have since reported results with closure of IMH ranging from 58-94% (*Kishore and Wendel, 2001*).
Surgical treatment of macular holes

Technique (Kishore and Wendel, 2001):

- A standard 3-port vitrectomy is performed and the anterior and mid vitreous are removed.
- Induction of posterior vitreous detachment:

Posterior vitreous detachment is induced or completed using one of many techniques:

1- Suction: This is done using a silicone-tipped suction cannula connected to active suction (150-250 mmHg) or a vitreous cutter on suction only.

The suction cannula or the vitreous cutter is gently swept over the retinal surface around the optic nerve or temporal to the macula (Fig. 32). The silicone tip is noticed to flex (Fig. 33) once the vitreous is engaged (fish-strike sign).

![Fig. (32): Engagement of the vitreous cortex with the vitreous cutter nasal to the disc (Kishore and Wendel, 2001).](image)
Fig. (33): Fish strike sign: Bending of silicone-tipped extrusion needle on engaging adherent vitreous cortex (*Kelly and Wendel, 1991*).

This suction maneuver is safe as long as the vitreous cortex is still present, since the vitreous plugs the port and prevents retinal incarceration. Once engaged, PVD is created by continued suction with anterior traction, while moving the tip over the retinal surface (*Wendel et al., 1999*).

2- Sharp dissection with a membrane pick or barbed microvitreoretinal (MVR) blade to create an opening in the posterior hyaloid near the disc margin. A blunt 90º pick is inserted through this opening and the posterior hyaloid is peeled by a combination of anterior, centrifugal and circumpapillary movements (*Han et al., 1988*).
3- Bimanual technique: using an extrusion needle in one hand and an illuminated spatula in the other hand. Once the posterior hyaloid is engaged, continued suction is applied while an illuminated spatula is introduced beneath the posterior hyaloid to facilitate its separation (Mein and Flynn, 1991). Alternatively, an illuminated spatula may be passed through the engaged posterior hyaloid (Fig. 34). This allows fluid to go through these holes to facilitate detachment of posterior hyaloid (Ruiz-Moreno and Pérez-Santonja, 1998).

Fig. (34): Flexible cannula with posterior hyaloid impaled in the tip. The illuminated spatula goes just beneath the tip of the silicone cannula (Ruiz-Moreno and Pérez-Santonja, 1998).
Surgical treatment of macular holes

4- Autologous plasmin injected into the vitreous cavity 15 minutes prior to vitrectomy. This induces rapid and atraumatic separation of posterior hyaloid (Margherio et al., 1998).

- Peeling of epiretinal membranes (Fig. 35):
  Significant epiretinal membranes are seen clinically in only 10-20% of eyes; however, they are found histologically in 75% of eyes with IMH. Meticulous dissection of all visible epiretinal membranes is currently recommended. These membranes may be removed with standard techniques using a barbed MVR blade, pick or vitreous forceps. A diamond-dusted silicone cannula (Tano’s brush) may facilitate removal of epiretinal membranes (Lewis et al., 1997).

Fig. (35): Peeling of epiretinal membrane with microforceps (Kishore and Wendel, 2001)

- Fluid-air exchange (Fig. 36):
Surgical treatment of macular holes

The peripheral retina should be examined carefully for any tears before air-fluid exchange. Fluid is removed just anterior or nasal to the optic nerve with a flute needle or extrusion cannula Subretinal fluid surrounding the macular hole may be removed; however, its removal may be complicated by enlargement of the hole and usually is not necessary. To ensure maximal dehydration, some surgeons advocate waiting for 10-15 minutes, so that residual fluid can be removed from the posterior pole. *(Rubin et al., 1995).*

**Fig. (36):** Fluid-air exchange, suctioning fluid from the surface of the optic disc *(Glaser et al., 1992).*

- Internal tamponade:
Surgical treatment of macular holes

1- Long-acting gas e.g. sulfur hexafluoride, perfluoroethane or perfluoropropane (Thompson et al., 1996)

2- Silicone (Goldbaum et al., 1998)
   - Postoperative face-down positioning for 1-2 weeks (Tornambe et al., 1997)

Adjuvants for closure of macular hole:


2- Human autologous serum: Autologous serum is capable of inciting fibrocellular proliferation. It has been tried as an adjuvant for closure of macular hole with a high rate of success (Liggett et al., 1995).

3- Autologous platelet concentrate: In 1995, Gaudric and colleagues reported a statistically significant higher rate of closure of macular hole with autologous platelet concentrate.

4- Tissue glue prepared from pooled human plasma: The biologically active components of this substance are fibrinogen, fibrinectin, factor VIII, plasminogen and
Surgical treatment of macular holes

thrombin. Anatomical closure of the hole was achieved in 87% (Tilanus and Deutman, 1995).

5- Bovine thrombin:
Bovine thrombin was used as a biological adjuvant for closure of macular hole and was associated with a high rate of success. However, a high rate of postoperative inflammatory reaction was reported (Vine and Johnson, 1996).

6- Partially cross-linked gelatin:
An absorbable plug made of partially cross-linked gelatin is inserted into the macular hole after vitrectomy and peeling of epiretinal membranes (Peyman et al., 1997).

7- Cyanoacrylate:
It acts by induction of chorioretinal scarring rather than simple adhesiveness (Sheta et al., 1990).

Most retina surgeons do not use adjuvants for macular hole surgery at this time. Excellent surgical results have been obtained without the use of adjuvants; however they may have a role in the management of chronic macular holes and in patients with a prior failed surgery (Kishore and Wendel, 2001).

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Complications of macular hole surgery:

They include:

A- General complications associated with vitreous surgery such as the progression of cataract, retinal detachment, suprachoroidal hemorrhage, high intraocular pressure, vascular occlusion, epiretinal membrane formation, cystoid macular edema and endophthalmitis (Smiddy et al., 2000).

B- Specific complications more common in macular hole surgery

1- Changes in RPE:
The Vitrectomy for Macular Hole Study described alterations in RPE in 33% of eyes following macular hole surgery.

Three types of RPE alterations were described:

a- Facet lesions in 65%: They are well-defined localized areas of RPE hyper- or hypopigmentation measuring 500 μm. They are associated with hyper- or hypofluorescence or late staining on fluorescein angiogram.
Surgical treatment of macular holes

b- Phototoxicity lesions in 23%: They are larger and have a round or oval shape. They are characterized by diffuse stippling throughout the macula. They show wide hyperfluorescence and late staining on angiography.

c- Scattered hyperfluorescent lesions in 7%
Visual acuity as measured by potential acuity meter (PAM) was significantly worse in eyes with RPE alteration than those without. Eyes with phototoxicity lesions had significantly worse visual acuity than those with facet lesions. Facets may have been caused by mechanical trauma during removal of the hyaloid or subretinal fluid or by compromised choriocapillaries perfusion from prolonged postoperative gas tamponade (Poliner and Tornambe, 1992).

2- Visual field defects:
Peripheral visual field loss have been reported in 16% of patients undergoing vitrectomy for macular hole. Field defects are seen mostly as absolute and/or scotomas in the inferior or temporal field (Melberg and Thomas, 1995). The theories proposed for the cause of visual field loss include:
Surgical treatment of macular holes

a- Direct mechanical trauma to the optic nerve with the tip of suction cannula (Melberg and Thomas, 1995).

b- Retinal ischaemia from elevated postoperative pressure or prolonged face-down positioning (Pendergast and McCuen, 1996).

c- Damage to the peripapillary inner retina during stripping of adherent vitreous cortex (Hutton et al., 1996).

3- **Failure of closure**

Failure of macular to close may lead to extreme enlargement and distortion of remaining macular tissues. Usually, however, if the hole enlarges, this is only minimal, and the visual acuity decreases by less than one line. The reported rate for failure of closure varies between 3% (Thompson et al., 1994) and 53% (Ryan and Gilbert, 1994).

4- **Late reopening of macular hole:**

Reopening of successfully treated macular hole occurs in 4.8%. Reopening may occur from 2 to 22 months after
Surgical treatment of macular holes

initial surgery. 38% of eyes with reopening of macular hole have significant epiretinal membrane formation at the time of reopening. Epiretinal membrane formation may lead to a reinstatement of tangential tractional forces, serving to reopen the hole (Duker et al., 1994).
Vitrectomy with peeling of the internal limiting membrane

In 1996, Yoon and colleagues observed cellular proliferation on the ILM in IMH and hypothesized that forces generated by contraction of these cells may enlarge macular holes. They suggested removal of the ILM and the adherent contractile cells as a reasonable surgical approach to both relieve the tangential traction on the prefoveal vitreous and remove the scaffold for the proliferation of glial cells.

Various studies have shown that ILM peeling significantly improves visual and anatomic success in all stages of recent, chronic, holes, reopened and failed macular holes, while eliminating reopening for holes greater than 300 μm (Brooks, 2000). Removal of ILM and the overlying epiretinal membrane in myopic macular holes can result in complete relief of macular traction. Primary removal of the ILM may contribute to a high initial success rate for retinal reattachment and be an important adjuvant to the treatment of retinal detachment resulting from myopic macular hole (Kadonosono et al., 2001).
Removal of ILM in traumatic macular holes has been suggested as a surgical option in improving vision. The majority of eyes benefit from ILM removal, even when additional traumatic macular pathology is present (Kuhn et al., 2001).

**Technique of peeling ILM:**
1- Creation of a flap:
   A barbed MVR blade or a bent 22-gauge needle is used to create an initial ILM tear (Burk et al., 2000)
2- Elevation of flap and removal of the ILM:
   An end-gripping forceps (Fig. 37-39) is used to peel the ILM in a continuous circular motion, similar to capsulorhexis in cataract surgery (Eckardt et al., 1997).

**Fig. (37):** Eckardt end-gripping forceps (Eckardt et al., 1997).
Fig. (38): 2 models of end-gripping forceps (Kwok et al., 2001).

Fig. (39): Dorc end-gripping forceps (Kuhn et al., 2001).

**Difficulties in peeling the ILM:**

1- Difficulty in stripping the ILM over extensively detached retina:
Surgical treatment of macular holes

Flattening of the detached retina with perfluorocarbon liquid (PFCL) is useful to provide counter traction during peeling (Nishimura et al., 2002).

2- Difficulty in identifying the ILM:
Staining of the ILM with ICG renders the nearly invisible ILM clearly visible and greatly facilitates its peeling, which thus offers better visualization and protection to the retina (Kwok et al., 2001).
Indocyanine Green Dye

Indocyanine green (Fig. 40) is a sterile water soluble carbocyanine dye that absorbs and emits light in the infrared spectrum. It has a molecular weight 775 dalton. Chemically, it is an N-hydro (3,3,3,3) tetramethyl (1,1) di 4-sulfabutyl 4,5,4,5, dibenzo, indotricarbocyanine hydroxide sodium salt (Hope-Ross et al., 1994).

![Structural formula of indocyanine green](image)

Fig. (40): Structural formula of indocyanine green (Hope-Ross et al., 1994).

It was manufactured primarily in the United States and sold under the name of cardiogreen.
Surgical treatment of macular holes

It is available in 25 and 50 mg vials in the crystallized form. In preparation for intravenous injection, it is dissolved in the accompanying aqueous solvent that contains sodium iodide by an amount never exceeding 5% in order to prevent crystallization. When dissolved, its pH is 5.5-6.5 (Brekow et al, 1997).

Under direct exposure to bright light (47 foot candle), the aqueous form decays approximately 10% in 10 hours. So it should be used within 10 hours after reconstitution. Yet, once bound to protein, it becomes stable (Brekow et al, 1997).

Its physical and chemical properties were first described by Fox and Wood in 1960. Its first application in fundus angiography was by Kogure et al in 1970 when it was used to visualize the fundus of owl monkeys. The studies areas of non perfusion in the retina by angiography that was performed by injecting the dye into the carotid circulation (Kogure et al., 1970).

After injection, it is rapidly and highly bound to plasma proteins (98%), 80% of which is bound to globulins probably alpha 1-lipoprotein. So it does not leak from the fenestrated walls of choriocapillaries. Being strongly bound to protein, dye excretion by the kidney does not occur. It is not detected in the spinal fluid (Flower, 1992).
Surgical treatment of macular holes

The dye has a high affinity for the vascular endothelium that may account for its persistence in the large choroidal vessels especially veins long after injection (Flower, 1992). The dye exhibits concentration fluorescence quenching. Normally increased dye concentration in the blood vessels results in increased fluorescence. However, after a peak fluorescence is obtained, further increase in the dye concentration results in decreased fluorescence. This phenomenon is thought to be due to dimer formation when the dye concentration is very high. This can be observed after dye bolus transit images (Flower, 1993).

The dye absorbs light in the 790-805 nm and emits light in 830-835 nm i.e. in the infrared spectrum. Melanin in the retinal pigment epithelium as well as hemoglobin block visible light but transmit infrared light (Flower, 1992).
Staining of internal limiting membrane

Values of staining of ILM with ICG:

1- Removal of ILM:

Removal of ILM may be difficult to perform because of its poor visibility. Inappropriate removal of the ILM risks damage to the retina, e.g. retinal edema or retinal pigment epithelium alterations (Park et al., 1999). An experimental study in cadaveric eyes described a technique for staining the internal limiting membrane using indocyanine green (ICG) injected intravitreally. The study demonstrated that staining of the ILM renders the nearly invisible ILM clearly visible and greatly facilitates its peeling, which thus offers better visualization and protection to the retina. This could be attributed to the better contrast between the stained ILM and the underlying unstained retina (Fig. 41). There was no evidence for retinal or retinal pigment epithelial cellular toxicity attributable to ICG (Burk et al., 2000).

In corroboration with this experimental study, various studies were performed to evaluate the value of staining of
the ILM with indocyanine green during macular hole surgery. The studies confirmed that staining of the ILM allows better visualization and ensures satisfactory and atraumatic removal of the ILM (Kwok et al., 2001).

Da Mata and associates in 2001 conducted an interventional prospective case series study on 24 eyes with stage 3 or 4 macular holes. All eyes underwent a pars plana vitrectomy, including peeling of the posterior cortical hyaloid when necessary. Indocyanine green dye (0.5%) was instilled into the posterior vitreous cavity over the macula and left in place for 3-5 minutes. After removal of the ICG, the retinal ILM was peeled. Medium-to-long acting gas tamponade was used in all cases, and all patients were asked to position face down for 1 to 2 weeks. The study found that ICG stained the retinal ILM, but did not stain the underlying retina. Indocyanine green staining greatly facilitated the surgeon’s ability to visualize and peel the ILM in each case. Peeled tissue was sent for both light and electron microscopic studies, which confirmed that the ICG-stained tissue was truly retinal ILM. Anatomical closure of the macular hole was achieved in 88% of eyes with a single surgery. Visual acuity improved in 96% of patients after surgery. They found no intraoperative or postoperative complications related to ICG use, and there
Indocyanine Green

was not clinical or fluorescein angiographic evidence of ICG toxicity.

_Foulquier et al_ in 2002 conducted a retrospective case series study to compare the anatomical and visual results of patients undergoing macular hole surgery without ILM peeling and those with ILM peeling assisted by ICG staining. They compared 21 patients with ILM peeling assisted by ICG staining to 17 patients without ILM peeling. The anatomical success rate of closure of the macular hole was 90% in those with ILM peeling and 22% in those without ILM peeling. Visual acuity improved by 2 lines in 62% of patients with ILM peeling compared to only 44% in those without ILM peeling. The improvement in macular threshold was statistically significant.

_Kwok and associates_ conducted another study in 2003 to study the effect of ICG-assisted ILM removal in patients with stage 3 and 4 macular hole. 41 eyes were included in the study with a mean follow-up period of 15 months. Standard pars plana vitrectomy was performed with removal of ILM for an area of 3-4 disc diameters around the macular hole assisted by ICG 0.5%. This was followed by injection of 12% perfluoropropane and face down positioning for 2 weeks. The anatomical rate of closure of the macular hole in this study was 87.8% with a higher rate
in those with recent holes compared to chronic holes. The median preoperative BCVA was 20/200 and the median postoperative BCVA was 20/100. No patient suffered from a diminution in BCVA. The improvement in BCVA was highly significant statistically.

In 2002, Weinberger and associates conducted a study to demonstrate the beneficial effect of ICG-assisted ILM peeling when combined with autologous platelet concentrate. The study was performed on 18 eyes with IMH. Standard pars plana vitrectomy was performed with removal of ILM assisted by ICG. This was followed by injection of autologous platelet concentrate. The eyes were tamponaded with 20% sulfur hexafluoride. The patients were followed by scanning laser ophthalmoscope and automated visual field. Visual acuity improved in 14 of the 18 patients. No negative effect on retinal structure and function was observed by SLO nor by the automated visual field analyzer.

In India, studies of the effect of ICG-enhanced ILM peeling on macular hole surgery have also shown promising results. In a study on 18 eyes with ICG-assisted peeling of the ILM, the anatomical success rate of closure of the macular hole was 83%. 50% of patients have improvement in visual acuity by 2 lines. The visual
Indocyanine Green

improvement was better in holes smaller than 400 μm (Kumar et al., 2002).

Fig. (41): Removal of ILM after staining with ICG (Burk et al., 2000).
2- Identification of epiretinal membranes:

A possible role of ICG could be in identifying epiretinal membranes. It was shown that the ILM was stained bright green, but the epiretinal membranes were unstained. Because the epiretinal membranes are clearly identified, they could be completely and safely removed (Kusaka et al., 2001).

3- Delineation of residual posterior vitreous cortex:

Staining of ILM could prove useful during vitrectomy for diabetic macular edema with adherent cortical vitreous. Staining of vitreoretinal interface using indocyanine green could help the surgeon to distinguish between the residual vitreous cortex and the internal limiting membrane (Gandorfer et al., 2001).

Technique of injection of ICG:

Various techniques have been described in the literature for dilution and injection of indocyanine green

1- Dilution with viscoelastic material:
Indocyanine Green

Twenty-five milligrams of ICG are dissolved in 10 ml of distilled water. 0.2 ml of this solution is then mixed with 0.6 ml of viscoelastic material with low molecular weight, to get a final concentration of 0.06%.

Standard 3-port pars plana vitrectomy is performed followed by surgical separation of the posterior cortical vitreous from the optic nerve head and posterior retina. A small amount of viscoelastic material containing ICG is placed on the retina for 30 seconds (Kadonosono et al., 2000).

2- Dilution with balanced salt solution:

Twenty-five milligrams of ICG are dissolved in 0.5 ml of sterile aqueous solvent. The mixture is shaken for approximately 5 minutes until there is a homogenous green solution without any visible particles. Next, 4.5 ml of sterile balanced salt solution is added to produce a solution with a final ICG concentration of 0.5% and osmolarity of 270 mOsm.

Standard 3-port pars plana vitrectomy is performed followed by fluid-air exchange. ICG is injected under the air bubble over the retinal surface and left for approximately 5 minutes (Burk et al., 2000).
Complications of peeling ILM and indocyanine green:

Various complications have been reported with peeling of the ILM and the use of indocyanine green:

1- Retinal pigment epithelial changes:
Brief exposure of cultured human retinal pigment epithelial cells to indocyanine green results in decreased mitochondrial enzyme activity but does not appear to influence cellular morphology or ultrastructure (Sippy et al., 2001).
Atrophic changes in RPE at the site of the previous macular hole, or in areas where the indocyanine green solution would have had direct access the bare RPE cells have been reported (Engelbrecht et al., 2002).

2- Damage to inner retinal layers:
Peeling of the ILM carries the risk of damage to the inner retinal layers, if the cleavage plane did not coincide exactly with the inner undulating aspect of the ILM.
Dilutions of indocyanine green as recommended in the literature may alter the structure of the retina to some degree. Possible factors responsible for this inadvertent
action may include (1) concentration, (2) osmolarity pH, (3) time of tissue contact, and (4) mechanical factors from more forceful traction during peeling (*Gandorfer et al.*, 2001).

*Haritoglou et al* in 2002 observed cellular elements resembling the plasma membrane of Muller cells and other retinal structures adherent to the retinal side of the removed ICG-stained ILM. Moreover, none of the patients in his study had improvement in his BCVA. Postoperative visual field defects developed in 7 of 20 eyes. He postulated that intravitreal injection of ICG may also cause retinal damage by altering the cleavage plane to the innermost layers.

3- **Subretinal hemorrhage:**
Subretinal and vitreous hemorrhage can occur during peeling of the ILM due to injury of blood vessels. This usually can be stopped by elevating intraocular pressure during the time of hemorrhage. The hemorrhage usually resolves completely, with no consequences on visual outcome (*Nakata et al.*, 2003).

4- **Iatrogenic punctuate chorioretinopathy:**
Small punctuate choroidal lesions are observed in the macular region after peeling of ILM. These punctuate
lesions correspond to the area where ILM was grasped with forceps. The size of these lesions range from 100-400 μm. Their number range from 8-15. In fluorescein angiography, they appear as hypofluorescent lesions with late staining of their margins. They appear to have an innocent nature with no effect on visual outcome (Karacorlu et al., 2003)

5- Paracentral scotoma:
Paracentral scotomas may be detected in areas that were tested normally before surgery. They are located temporally and/or inferiorly and often appear like nerve fibre bundle defects. They may be caused by trauma to the nerve fibre during surgery (Haritoglou et al., 2001).

6- Persistence of fundus fluorescence:
Normally, by the first postoperative day, all traces of residual ICG disappear clinically and could no longer be detected. However, persistent fundus fluorescence of the optic disc and macular center as detected by infrared photography occurs in all patients following the use of ICG and can persist up to 6 months. This is attributed to the accumulation of ICG in the macular RPE and in the optic nerve. Although this persistent fluorescence is not associated with functional compromise of visual outcome,
it signifies that ICG is concentrated in the retinal tissues. This may carry a later risk of phototoxic damage to the macular photoreceptors and RPE (Tadayoni et al., 2003).

7- **Focal macular ERG changes:**
It is believed that the ILM plays an important role in retinal function, because it is the basal lamina of the Müller cells that are involved in the generation of the electroretinogram b-wave. There is selective delay of recovery of ERG b-wave after peeling of ILM in comparison to conventional vitrectomy without peeling of the ILM (Terasaki et al., 2001).
MATERIAL AND METHODS
Material and methods

Inclusion criteria:

The study was performed on 20 patients with macular hole. The study included 10 patients with idiopathic macular hole (Group A) and 10 patients with traumatic macular hole (Group B). Patients with myopic macular hole were excluded from the study. Group A included 4 patients with stage 3 and 6 patients with stage 4 macular hole.

Preoperative evaluation:

All 20 patients were subjected to the following:

A- History and demographic data:

The demographic data of both groups were analyzed and compared as regards age, sex and mean duration of symptoms. The data of both groups were compared using pooled t-test for independent samples.
B- Clinical evaluation:

1- Measurement of best corrected visual acuity (BCVA): Visual acuity was converted to Snellen’s decimal fraction for statistical analysis.

2- Detailed slit lamp examination and assessment for the presence of any cataractous changes.

3- Measurement of intraocular pressure using Goldmann applanation tonometer.

4- Complete fundus examination using both binocular indirect ophthalmoscope and slit lamp biomicroscopy with Volk® 90 diopters lens and assessment of the following:

   a- Size of macular hole in relation to the optic disc

   b- Presence and extent of any subretinal fluid around the macular hole

   c- Any visible epiretinal membrane. They were plotted on a diagram for correlation with intraoperative findings.

   d- Any evidence of posterior segment trauma such as choroidal rupture or retinal pigment epithelium alteration particularly in traumatic cases.
**Material and Methods**

e- Continuity of the beam across the hole and instruction of the patient to report any slit lamp abnormalities; such as distortion, bending or breaking of the beam

f- Presence of vitreous liquefaction spaces and examination for the presence of incomplete of complete PVD

C- **Optical coherence tomography**

This was done using *OCT 2000*, *software version A 4.0, Humphrey*. Optical coherence tomographic images were obtained through a dilated pupil. The macula was scanned in both the vertical and horizontal directions through the center of the fovea with a scan length of 5 mm. An infrared video camera demonstrated the location and direction of the optical coherence tomographic scan in the macular area. To ensure scanning through the very center of the fovea, the examination was repeated several times and the images that showed the thinnest sensory retina at the center of the foveal depression was adopted. The size of the macular hole and the height of retinal elevation were calculated.
**Material and Methods**

**D- Automated visual field:**

This was done using *Humphrey’s visual field analyzer 740-1774*. Both central 30-2 threshold and macular threshold programs were used sequentially to plot any nerve bundle defect and the extent of central scotoma. The central 30-2 threshold program tests points every 6° in the central 30°, while the macular threshold program tests 16 points within 4° of fixation. The patient’s error of refraction was corrected for near and a corresponding trial lens with thin rim was placed in front of the tested eye. The patient was given clear instructions about the test and monitoring of fixation was done. The stimulus used was a Goldmann size I equivalent and was white in colour. Standard background illumination of 31.5 apostilb was used. The results of the test were printed in numeric, grey scale and depth defect format. The reliability of the patient was interpreted according to the fixation losses, and to the number of false positive and false negative errors. In test results with low reliability, the test was repeated at another time. The density and size of scotomas were recorded. *FASTPAC strategy*
was used to determine the statistical significance of any visual field defect.

Fig. (42): Central 30-2 program test points

Fig. (43): Macular threshold program test points
Material and Methods

E- **Fluorescein angiography:**

This was done using *Topcon TRC-50IA* fundus camera.
- A colour photograph and a red-free photograph were taken before injection.
- Fluorescein 10% 5 ml were injected rapidly into the antecubital vein.
- Photographs were taken at approximately 1-second interval between 5 and 25 seconds after injection.
- Pictures were then taken at approximately 5-seconds interval till the end of 4 minutes.
- Pictures were captured and computer processed via *Topcon Imagenet program*.

The size of the macular hole and the presence of any retinal pigment window defect elsewhere were recorded for correlation later with postoperative findings

F- **Electroretinogram:**

This was done using *UTAS-2000 model, LKC-technology*. Pupils were dilated with 10% phenylephrine and 1% tropaicamide before examination. The patient was placed for 45
Material and Methods

minutes in a dark room for dark adaptation. Full-field ERG was then recorded by Ganzfeld system, which incorporates full field stimulus and full field background. A gold foil electrode was placed on the eyelid and a reference electrode was placed on the patient’s forehead. ERG was done under both photopic and scotopic conditions using single flashes of dim short and long wavelength stimuli then single flashes of dim white light. 30 Hertz flicker amplitude and implicit time were also recorded.

Operative technique:

All twenty patients were subjected to the same technique for comparison.

- A standard 3-port vitrectomy was performed. Using a 19-gauge microvitreoretinal blade (Alcon®), three sclerotomies were made 4 mm from the limbus. A Geuder G-32180® 4 mm length infusion cannula was fixed in the lower temporal quadrant using a preplaced Vicryl® 6/0 suture. The upper temporal and upper nasal ports were used for both the vitrectomy cutter (Geuder vitrectomy cutter G-
Material and Methods

28164®) and the endoilluminator (Geuder endoilluminator G-26070®) and the anterior and mid vitreous were removed. Vitrectomy was performed under standard Ocular® vitrectomy lenses for visualization. The procedure was performed using Geuder® Megatron 1-Plus vitrectomy machine for both cutting and illumination. The parameters were set at 250 mmHg vacuum pressure and a cutting rate of 300 per minute.

- Induction of posterior vitreous detachment:
  Posterior vitreous detachment was induced or completed using a silicone-tipped suction cannula connected to active suction (250 mmHg).
  The suction cannula or the vitreous cutter was gently swept over the retinal surface around the optic nerve. Once engaged, PVD was created by continued suction with anterior traction, while moving the tip over the retinal surface.

- Peeling of epiretinal membranes (Fig. 30):
  Significant epiretinal membranes were removed using vitreous forceps. A diamond-dusted silicone cannula (Geuder G-29061®) was used to facilitate removal of epiretinal membranes whenever needed.
Material and Methods

- Preparation of indocyanine green:
  Indocyanine green was freshly prepared at the time of surgery. Twenty-five milligrams of ICG (*Indocyanine green, Akon Incorporation*) were dissolved in 10 ml of distilled water. 0.2 ml of this solution was then mixed with 0.6 ml of methyl cellulose (*Ocuvis®, Cima Incorporation*) 1%, to get a final concentration of 0.06%.

- Application of indocyanine green:
  A small amount of methyl cellulose containing ICG is placed on the macular area using a flute needle. The infusion cannula was clamped during injection of indocyanine green to allow the dye to settle on the macular area. The dye was left on the retina for 30 seconds then the infusion cannula was unclamped and the residual dye was removed using active suction. The effectiveness of staining of the ILM was recorded.

- Peeling of internal limiting membrane:
  1- Creation of a flap:
  A barbed MVR blade was used to create an initial ILM tear.
2- Elevation of flap and removal of the ILM:

A Dorc® end-gripping forceps was used to peel the ILM in a continuous circular motion. The ILM was peeled for an area extending between the temporal arcades vertically and between the temporal edge of the disc to one disc diameter from the edge of the macular area horizontally. The simplicity and the completeness of removal of the planned area to be peeled were reported. Any iatrogenic breaks during the procedure were recorded and treated using endolaser during the procedure or postoperative argon laser thereafter.

- Fluid-air exchange:

  The peripheral retina was examined carefully for any tears before air-fluid exchange. Fluid was removed just anterior or nasal to the optic nerve with a flute needle. Subretinal fluid surrounding the macular hole was not removed.

- Internal tamponade:

  Internal tamponade with silicone oil was done whenever needed, particularly in cases complicated with iatrogenic breaks.

- Postoperative face-down positioning for 1-2 weeks
Preparation of the removed ILM specimen:

- The peeled specimens were put in a buffered glutaraldehyde solution for 6 hours. The specimens were then transferred to a phosphate buffer glutaraldehyde solution overnight.

- They are then double fixed in buffered osmium tetroxide for one hour.

- This was followed by three washes in distilled water each for ten minutes. Serial dehydration in ascending grades of alcohol 50%, 70%, 90%, 96% and three changes in absolute alcohol, each for ten minutes, was then performed.

- The specimens were then transferred to a transitional solvent propylene oxide, to replace the ethanol and were kept for five minutes.

- Embedding was carried out by passing the specimen in a propylene oxide/araldite mixture as follow:

  Propylene oxide : Araldite
  3 : 1 for one hour
  1 : 1 for three hours
  1 : 3 for six hours
Material and Methods

- The specimens were left in a pure araldite mixture for overnight. The specimens were then transferred to a flat embedding mould containing fresh araldite mixture and left in the oven to polymerize at 45°C for 24 hours. The temperature was then raised to 60°C for another 48 hours or until the specimen is totally polymerized.

- Trimming was done to remove the excess araldite around the specimens.

- Ultrathin sections were prepared with the aid of diamond knife (Brunel Rocking Microtome Ltd) and double stained with uranyl acetate and lead citrate. The sections were examined using transmission electron microscope Joel-JSM-5200, at 100 KV.

- The removed tissue is examined to document its nature. The presence of any proliferating glial cells on the ILM were recorded. The presence of any other neural or retinal elements is recorded.
Material and Methods

Postoperative evaluation:

All 20 patients were subjected to the following:

A- Clinical evaluation:

1- Measurement of best corrected visual acuity:
   BCVA was measured at one, three and six months. Visual acuity was converted to Snellen’s decimal fraction for statistical analysis. Comparison of preoperative and postoperative BCVA was done using paired t-test for statistical analysis. The visual outcome of patients with complete closure of the macular hole was compared to those with incomplete or failure of closure of the macular hole in both groups. Visual outcome of both groups was also compared using pooled t-test for independent samples.

2- Assessment of the development of cataractous changes at one, three and six months postoperatively.

3- Measurement of intraocular pressure using Goldmann applanation tonometer during the first week postoperatively and after one, three and six months postoperatively.
Material and Methods

4- Complete fundus examination using both binocular indirect ophthalmoscope and slit lamp biomicroscopy during the first week postoperatively and after one, three and six months postoperatively and assessment of the following:

a. Size of macular hole. Patients were subsequently categorized according to the results into:
   1- Patients with successful complete closure of the hole.
   2- Patients with incomplete complete of the hole.
   3- Patients with no change in size of the hole.
   4- Patients with enlargement of the hole.

   Accordingly, the success rate of anatomical closure was calculated. The success rate of both groups was then compared using pooled t-test for independent samples.

b. The time of closure of the macular hole was reported. The mean time of closure of the macular hole was calculated and compared in both groups.

c. Presence of any retinal pigment alteration in the macular area.
Material and Methods

d. Any iatrogenic break. They were treated with argon laser if not done intraoperatively.
e. Any retinal detachment occurring as a complication of vitrectomy.

B- Optical coherence tomography:

It was done along both horizontal and vertical meridian after one month and six months postoperatively. The size of the macular hole and the height of retinal elevation were calculated.

C- Automated visual field:

This was done using after six months. Both central 30-2 threshold and macular threshold programs were used sequentially to plot any nerve bundle defect and the extent of central scotoma. Results were compared to preoperative findings using paired t-test. The improvement in retinal sensitivity in both groups was compared using pooled t-test for independent samples. Correlation of the degree of improvement in retinal sensitivity and both the degree of visual improvement and the anatomical success rate of closure was done using bivariate correlation procedure.
Material and Methods

D- Fluorescein angiography:

This was done after six months. The size of the macular hole and the presence of any retinal pigment window defect elsewhere were recorded and correlated with preoperative findings. The presence of any other angiographic changes were recorded.

G- Electroretinogram:

This was done under both photopic and scotopic conditions after six months. 30 Hertz flicker amplitude and implicit time was also recorded. Data were compared to preoperative findings.
RESULTS
**RESULTS**

The results will be discussed under the following headlines:

A- Demographic and preoperative data
B- Intraoperative findings
C- Success rate as regards closure of macular hole and improvement of BCVA
D- Possible complications related to ICG
E- Histopathological studies
F- Possible complications related to vitrectomy

**A- Demographic and preoperative data**

The study was performed on 10 patients with idiopathic macular hole (group A) (*Fig. 44*) and 10 patients with traumatic macular hole (group B) (*Fig. 45*).

1- **Age:** The mean age was 58.7 years with a standard deviation of 3.71 years in group A and 21.8 years with a standard deviation of 3.94 years in group B. The difference was statistically significant (p-value = 0.0001).
2- **Sex:** In group A, 7 patients were females (70%) with three male patients (30%). In group B, 9 patients were males (90%) with a single female patient (10%). The difference was statistically significant (p-value = 0.024).

3- **Mean duration of symptoms:** In group A, the mean duration of symptoms was 6.9 months with a standard deviation of 2.3 months. In group B, the mean duration of symptoms was 3 months with a standard deviation of 1.49 months. The difference was statistically significant (p-value = 0.003).

4- **Mean size of macular hole:** The mean size of macular hole measured by optical coherence tomography was 409.1 μm with a standard deviation of 89.54 μm in group A and 425.3 μm with a standard deviation of 72.21 μm in group B. The difference was statistically insignificant (p-value = 0.667).

5- **Presence of retinal detachment:** A small and shallow cuff of subretinal fluid was present around the macular hole in all 20 patients.
Results

Fig. (44): Idiopathic macular hole in a patient of group A

Fig. (45): Traumatic macular hole in a patient of group B showing an adjacent choroidal rupture


**B- Intraoperative findings**

1- **Effectiveness of staining:**

Satisfactory staining of ILM was obtained in all 20 patients (100%). Satisfactory staining was defined by staining that allows identification of ILM from underlying nerve fiber layer once a flap was created.

2- **Extent of removal of ILM:**

Complete removal of ILM for an area of 2 disc diameters around the macular hole was achieved in 19 patients (95% success rate). Patchy removal of ILM was obtained in only one patient with traumatic macular hole.

3- **Delineation of epiretinal membranes:**

Epiretinal membranes were observed intraoperatively in only one patient with idiopathic macular hole. The use of ICG did not allow identification of any further epiretinal membranes that could not be identified clinically.
4- Iatrogenic breaks:

Iatrogenic breaks during trial of elevation of the flap were observed in three patients (30%) with idiopathic macular hole (Table 1). One patient with iatrogenic break was treated intraoperatively with argon endolaser and internal silicone tamponade. The remaining 2 patients were tamponaded intraoperatively with silicone and were treated postoperatively with argon laser (Fig. 46). No iatrogenic breaks were observed in patients with traumatic macular hole.

<table>
<thead>
<tr>
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<th>Group A</th>
<th>Group B</th>
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<tr>
<td>Single break</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2 breaks</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Multiple breaks</td>
<td>1</td>
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</table>

Table (1): Number of patients with iatrogenic breaks in both groups
Results

Fig. (46): Patient with iatrogenic breaks treated by postoperative argon laser
A- Appearance of laser burns immediately following treatment
B- Appearance after 2 weeks showing complete closure of the macular hole
Results

5- Use of silicone tamponade:

Silicone oil tamponade was used in 3 patients (30%) of group A with iatrogenic breaks. No patient in group B needed silicone oil.

C- Success rates

1- Closure of the macular hole:

Closure of macular hole was documented by clinical examination and optical coherence tomography at one and six months postoperatively.

A- Group A:

In group A, complete closure of the macular hole was achieved in 8 of 10 patients (80%) (Fig. 47 and 48). In the remaining 2 patients, one patient showed a reduction of size with failure of complete closure (Fig. 49 and 50), while in the other patient, the size of the macular hole increased (Fig. 51 and 52).

The mean time of closure of macular hole was 3.3 days with a standard deviation 1.82 days.
Fig. (47): Patient with idiopathic macular hole
A- Preoperative fundus picture
B- Postoperative appearance after 2 weeks showing complete closure of the macular hole with reflections of silicone oil
Results

Fig. (48): Optical coherence tomography in the same patient with idiopathic macular hole
A- Preoperative appearance
B- Postoperative appearance after 2 weeks showing complete closure of the macular hole with restoration of the normal foveal depression.
Fig. (49): Patient with idiopathic macular hole

A- Preoperative appearance

B- Postoperative appearance after 2 weeks showing incomplete closure of the macular hole
Fig. (50): Optical coherence tomography in the same patient with idiopathic macular hole

A- Preoperative fundus picture

B- Postoperative appearance after 2 weeks showing incomplete closure of the macular hole
**Fig. (51):** Patient with idiopathic macular hole

A- Preoperative fundus picture

B- Postoperative appearance after 2 weeks showing enlargement of the macular hole with reflections of silicone oil.
Results

**Fig. (52):** Optical coherence tomography in the same patient with idiopathic macular hole

A- Preoperative fundus picture
B- Postoperative appearance after 2 weeks showing enlargement of the macular hole

**B- Group B:**

In group B, complete closure of the macular hole was achieved in 9 of 10 patients *(Fig. 53 and 54)* with reduction in size but failure of complete closure in the remaining patient *(Fig. 55 and 56).*

The mean time of closure of macular hole was $2.3 \pm 1.63$ days for group B.
Results

Fig. (53): Patient with traumatic macular hole
A-Preoperative fundus picture
B-Postoperative appearance after 2 weeks showing complete closure of the macular hole.
Fig. (54): Optical coherence tomography in the patient with traumatic macular hole
A- Preoperative appearance
B- Postoperative appearance after 2 weeks showing complete closure of the macular hole with restoration of the normal foveal depression.
**Results**

*Fig. (55):* Patient with traumatic macular hole

A- Preoperative fundus picture

B- Postoperative appearance after 2 weeks showing incomplete closure of the macular hole.
**Results**

**C- Difference between group A and B:**

The difference between success rate of closure of group A and B was statistically insignificant (p-value = 0.47)

The difference between the time of closure of the macular hole of group A and B was statistically insignificant (p-value = 0.591).

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**Fig. (56):** Optical coherence tomography in the same patient with traumatic macular hole

A- Preoperative fundus picture

B- Postoperative appearance after 2 weeks showing incomplete closure of the macular hole
2- Best corrected visual acuity:

Best corrected visual acuity was measured and then converted to Snellen’s decimal fraction preoperatively and at one, 3 and 6 months postoperatively. For statistical analysis, the BCVA at 6 months postoperatively was used.

A- Group A:

In group A, the mean preoperative BCVA was 0.091 with a standard deviation of 0.007. The mean postoperative BCVA was 0.21 with standard deviation of 0.008. The difference between preoperative and postoperative BCVA was statistically significant in group A (p-value = 0.019). Moreover, no patient suffered from a decrease in BCVA.

In patients with successful closure of the macular hole, the mean preoperative BCVA was 0.089 with a standard deviation of 0.007. The mean postoperative BCVA was 0.24 with standard deviation of 0.008. The difference between preoperative and postoperative BCVA in patients with successful closure of macular hole was statistically significant (p-value = 0.005).

In the patient with reduction in size but failure of complete closure of macular hole, the mean preoperative BCVA was 0.1, while the mean postoperative visual acuity was 0.2.
Results

In the patient with enlargement in size of macular hole, the mean preoperative BCVA was 0.05. There was no postoperative improvement or reduction in BCVA.

The visual outcome in group A was much better in patients with successful closure of the macular hole, compared to those with no or incomplete closure of the macular hole (Fig. 57). However, the presence of only 2 patients with no or incomplete closure limited the attainment of a visually significant difference between those with and those without complete closure.

Fig. (57): Histogram showing difference in preoperative and postoperative BCVA in patients of group A
Results

B- Group B:

In group B, the mean preoperative BCVA was 0.088 with a standard deviation of 0.004. The mean postoperative BCVA was 0.095 with a standard deviation of 0.004. This difference between preoperative and postoperative BCVA in group B was statistically insignificant (p-value = 0.815). No patient suffered from a decrease in BCVA.

In patients with successful closure of the macular hole, the mean preoperative BCVA was 0.095 with standard deviation of 0.004. The mean postoperative BCVA was 0.101 with a standard deviation of 0.004. The difference between preoperative and postoperative BCVA in patients with successful closure of macular hole was statistically insignificant (p-value = 0.817).

In the patient with reduction in size but failure of complete closure of macular hole, the mean preoperative BCVA was 0.05. There was no postoperative improvement or reduction in BCVA.

The visual improvement in group B was trivial regardless of whether the hole has closed or not (Fig. 58). However, the presence of only one patient with incomplete closure limited the attainment of a visually significant difference between complete and incomplete closure.
Results

![Histogram showing difference in preoperative and postoperative BCVA in patients of group B.](image)

**Fig. (58):** Histogram showing difference in preoperative and postoperative BCVA in patients of group B.

C- Comparison of postoperative visual outcome in group A and group B:

In group A, the mean improvement in BCVA was 0.119 which corresponds to about one line improvement in Snellen’s chart and ranging up to 0.23 which corresponds to approximately 2 lines improvement in Snellen’s chart.

In group B, the mean improvement in BCVA was less than 0.01. The improvement of BCVA was much more in group A than group B (Fig. 59). This difference between the improvement of BCVA in group A and group B was statistically significant (p-value = 0.003).
**Results**

![Histogram showing difference in preoperative and postoperative BCVA in patients of group A and B](image)

**Fig. (59):** Histogram showing difference in preoperative and postoperative BCVA in patients of group A and B

**D- Possible complications related to ICG**

They were assessed by the following:

1- **Persistence of indocyanine green staining of macular area postoperatively:**

In 18 of the 20 patients, the ICG staining of the macular area disappeared completely on the first postoperative day. In only two patients, green staining of the peripapillary area and the macular area persisted for 4


Results

days postoperatively, and then disappeared completely with no hazardous changes or phototoxic changes in fluorescein angiography (Fig. 60).

![Fundus picture on the second postoperative day showing persistence of ICG staining of the peripapillary and macular area](image)

Fig. (60): Fundus picture on the second postoperative day showing persistence of ICG staining of the peripapillary and macular area

2- Fluorescein angiography:

A- Preoperative findings:

In both group A and B, there were transmission hyperfluorescence in the macular area corresponding to the size of the macular hole (Fig. 61). In addition, two patients in group B
showed other manifestations of trauma in the form of choroidal rupture (Fig. 62).

**Fig. (61):** Fluorescein angiography of a patient of group A showing transmission window defect corresponding to the macular hole
**Results**

![Fig. (62): Fluorescein angiography of a patient of group B showing transmission window defect corresponding to the macular hole with a peripapillary choroidal rupture](image)

**B- Postoperative findings:**

1. **Change in size of the macular hole:**

a. **Group A:**

   In the 8 patients in which the macular hole closed clinically, the transmission fluorescence caused by the macular hole disappeared completely at the same time coinciding with the closure of the macular hole (*Fig. 63*). In the remaining 2 patients, the size of the transmission hyperfluorescence decreased in one patient and increased in one patient.
Results

Fig. (63): Fluorescein angiography of a patient of group A showing complete closure of macular hole with perimacular laser marks for iatrogenic breaks.

**b- Group B:**

The angiographic findings were similar to group A with complete disappearance of the transmission hyperfluorescence in 9 patients with complete closure of the macular hole (*Fig. 64*) and reduction in size of the transmission hyperfluorescence in the tenth patient.
Results

Fig. (64): Fluorescein angiography of a patient of group B:

A- Preoperative appearance showing a transmission window defect corresponding to the macular hole

B- Postoperative appearance after 6 months showing complete closure of macular hole with disappearance of central hyperfluorescence

2- Appearance of perimacular transmission hyperfluorescence:

In addition to changes in the size of the macular hole, transmission fluorescence around the macular area occurred in 2 patients. One of these 2 patients was of group B and showed incomplete closure of the macular hole (Fig. 65), while the other
patient was of group A and has a closed macular hole (Fig. 66).

Fig. (65): Fluorescein angiography of a patient of group B:

A- Preoperative appearance
B- Postoperative appearance after 6 months showing incomplete closure of macular hole together with perimacular transmission hyperfluorescence.
Results

Fig. (66): Fluorescein angiography of a patient of group A: Postoperative appearance after 6 months showing complete closure of macular hole together with appearance of perimacular transmission hyperfluorescence.

3- Visual field:

A- Preoperative findings:

Preoperative automated visual field using the macular threshold program showed either an absolute or very dense central scotoma surrounded by an area of relative scotoma in all 20 patients.

B- Postoperative findings:

1- Macular threshold:

A- Group A:

Postoperatively, the density of the central scotoma decreased to a variable extent in the 10 patients (Fig. 67 and 68). The degree of improvement of the retinal sensitivity in the macular area correlated positively with the improvement of visual acuity. The correlation was statistically significant.
Results

at the 0.01 level with Pearson’s correlation value of 0.805 (Fig. 59).

Fig. (67): Macular threshold of a patient with group A: Preoperative appearance after 6 months showing dense central scotoma surrounded by relative scotoma
Fig. (67 cont’d): Macular threshold of a patient with group A: Postoperative appearance after 6 months in a patient with successful closure of the macular hole showing improvement in retinal sensitivity.
Fig. (68): Macular threshold of a patient with group A: Preoperative appearance showing dense central scotoma surrounded by relative scotoma.
Fig. (68 cont’d): Macular threshold of a patient with group A: Postoperative appearance after 6 months in a patient with incomplete closure of the macular hole showing little improvement in retinal sensitivity.
**Results**

*Fig. (69):* Scatter diagram showing positive correlation between improvement in BCVA and improvement in macular sensitivity in group A.

**B- Group B:**

Postoperatively, the macular threshold program showed little improvement of retinal sensitivity (*Fig. 70*). The degree of improvement of the retinal sensitivity in the macular area correlated positively with the improvement of visual acuity (*Fig. 71*). The correlation was statistically significant at the 0.05 level with a Pearson’s correlation value of 0.678.
**Fig. (70):** Macular threshold of a patient with group B: Preoperative appearance showing absolute central scotoma surrounded by relative scotoma
Fig. (70 cont’d): Macular threshold of a patient with group B: Postoperative appearance after 6 months in a patient with complete closure of the macular hole showing little improvement in retinal sensitivity.
Results

![Graph showing correlation between BCVA and macular sensitivity](image)

**Fig. (71):** Scatter diagram showing positive correlation between improvement in BCVA and improvement in macular sensitivity in group B

**2- Central 30º field:**

Postoperative visual field using 30-2 program showed no decrease in retinal sensitivity in the central 30º field *(Fig. 62).*
Results

Fig. (72): Central 30° field of a patient with group A: Preoperative appearance.
Results

Fig. (72 cont’d): Central 30º field of a patient with group A: Postoperative appearance showing no significant change in retinal sensitivity.
**Results**

4- Electroretinogram:

**A- Preoperative findings:**

Preoperative ERG of all 20 patients showed diminution in 30 Hz flicker amplitude denoting affection of macular function with nearly normal b-wave amplitude and implicit time. There was no difference between electroretinographic findings in group A and group B.

**B- Postoperative findings:**

Following surgical repair, the 30 Hz flicker amplitude increased to reach normal value in all 20 patients (Fig. 73). The increase in the amplitude was more marked in patients with successful closure of the macular hole than those with incomplete closure. There was little change in b-wave value amplitude and implicit time (Fig. 74)
Results

**Fig. (73):** Preoperative ERG in a patient of group A showing diminution in 30 Hz flicker amplitude

**Fig. (73 cont’d):** Postoperative ERG in the same patient showing increase in 30 Hz flicker amplitude
Results

Fig. (74): Postoperative ERG in a patient of group B showing normal b-wave amplitude and implicit time

**E- Histopathological studies**

The peeled specimens were examined using transmission electron microscopy. Due to the small size and the difficult preparation of the specimens, it was possible to examine only 10 samples. These specimens were obtained from 6 patients with idiopathic macular hole and 4 patients with traumatic macular hole.

**Group A:**

The specimens examined showed fragments of ILM composed of collagen fibrils (*Fig. 75*). These fragments were covered in some areas by glial cells in all specimens
Results

(Fig. 76). No neural or retinal elements were identified in the six specimens examined.

Fig. (75): Fragments of ILM from a patient in group A

Fig. (76): Fragments of ILM covered by glial cells (G)
Results

Group B:

The 4 specimens examined showed fragments of ILM. These fragments were covered by glial cells which were less numerous than group A (Fig. 77). No other retinal tissue were identified in the specimens examined.

Fig. (77): Fragments of ILM covered by glial cells (G) in a patient with group B

F- Possible complications related to vitrectomy

1- Cataractous changes in the lens:

Cataractous changes developed in all 3 patients who received silicone oil injection at the end of the 6 months
Results

period. However, the cataractous changes were faint in the first 6 months and no patient suffered a diminution of BCVA that warranted surgery. No other patient developed cataractous changes in the lens during the first 6 months.

2- Increased intraocular pressure:

No elevation of intraocular pressure occurred during the follow up period of the study in all 20 patients.

3- Intraocular inflammation:

Intraocular inflammation and infection were not reported in all 20 patients during the 6-months follow-up period.

4- Other complications related to vitrectomy such as corneal edema or retinal detachment were not reported during the follow up period.
DISCUSSION
Discussion

The introduction of pars plana vitrectomy for macular hole in an attempt to relieve vitreoretinal traction by *Kelly and Wendel* in 1991 has been the cornerstone for macular hole surgery. Since then, enduring research kept going on in an attempt to improve the anatomical and functional success rate of pars plana vitrectomy.

The use of biological and chemical adjuvants to enhance closure of the macular hole has bestowed a flourishing field for macular hole surgery for a while. However, success rate is still not satisfactory and they are not free of complications.

Removal of ILM in macular hole surgery as an adjuvant for vitrectomy was first proposed by *Yoon and colleagues* in 1996. They suggested removal of the ILM and the adherent contractile cells as a reasonable surgical approach to both relieve the tangential traction on the prefoveal vitreous and to remove the scaffold for proliferation of the glial cells.

Ever since, numerous studies are being performed to study the efficiency of this technique as regards anatomical and visual success. Removal of the ILM is yet difficult to
Discussion

perform because of its poor visibility. Inappropriate removal of ILM risks damage the retina e.g. retinal edema, haemorrhages, iatrogenic breaks or retinal pigment epithelium alteration.

Introduction of ICG for staining the ILM has afforded a great help in identifying and rendering the nearing invisible ILM clearly visible with better visualization and protection to the retina.

Nevertheless, ICG itself has its own hazards. Use of ICG carries risk of retinal pigment epithelium alteration, paracentral visual field changes, focal ERG changes as well as phototoxic hazards to the retina.

This study was performed in an attempt to evaluate the value of staining of ILM with ICG in macular hole surgery (idiopathic and traumatic types), particularly in assisting peeling of ILM and identification of epiretinal membranes. The possible complications related to both peeling the ILM and to ICG were searched for. The overall efficacy of this technique as regards anatomical and functional outcome was investigated.

This study was performed on 10 patients with IMH (group A) and 10 patients with traumatic macular hole (group B). Group A included 6 patients with stage 3 and 4 patients with stage 4 holes. Patients with myopic macular
Discussion

hole were excluded from the study because of the little evidence of the role of ILM in the pathogenesis of myopic macular hole. In addition, myopic patients have thinned retina with a surrounding relatively large cuff of retinal detachment which renders peeling of the ILM technically difficult and risky.

Patients with IMH were mostly females (70%), while patients with traumatic macular hole were mostly males (90%). The mean age of the patients in this study was 58.7 years in group A and 21.8 years in group B. This incidence compares to the known demographic distribution of macular holes.

Patients were subjected to a standard 3-port vitrectomy followed by induction or completion of PVD using a silicone-tipped suction cannula connected to active suction.

ICG was freshly prepared at the time of surgery to avoid any light or chemical decomposition. ICG was prepared in a technique similar to the method used in Burk et al. (2000). ICG was dissolved in distilled water then mixed with methyl cellulose 1% to get a final concentration of 0.06%.

In contrast to our study, Da Mata et al. (2001) and Kwok et al. (2003) used ICG prepared by simple dilution
Discussion

with distilled water only to get a final concentration of 0.5%. They used this relatively higher concentration for staining the ILM. The fluid nature of this ICG solution necessitated application of ICG under air to allow satisfactory contact of ICG with the ILM for staining; therefore, fluid-air exchange was performed before application of the ICG. ICG was left on the retinal surface for 2-3 minutes.

The method of dilution used in our study offered a relatively lower concentration of ICG (0.06%), which would decrease any possible toxicity. Moreover, the further dilution of ICG with methyl cellulose provided a higher viscosity solution that allows better contact of ICG with the ILM for staining. This helped to decrease the time required for contact with the retina to only 30 seconds. Furthermore, the methyl cellulose-diluted ICG was applied directly to the retinal surface without the need of fluid-air exchange.

Satisfactory staining of ILM was obtained in all 20 patients, with complete removal of ILM in 19 patients. This demonstrates the high efficiency of ICG in both highlighting and enabling removal of the ILM.

ICG was peeled for an area of approximately 2 disc diameters around the hole. The area removed was intermediate between the area of 1-2 disc diameters
**Discussion**

removed in *Foulquier et al (2002)* and the 3-5 disc diameters-area removed in *Kwok et al (2003)*. Up till now there is no universe consensus of the exact area of the ILM that need to be removed to remove the scaffold for glial cell proliferation and reduce the tangential traction of the prefoveal vitreous. Further controlled studies to evaluate the exact extent of the glial cells proliferation on the ILM and to compare the final outcome for different areas of ILM peeled are needed. This will help to establish an agreement about the area of the ILM that has be removed.

Although *Kusaka et al.* in 2001 have reported use of ICG to delineate epiretinal membranes, particularly invisible ones, in our study the use of ICG didn’t offer help in identification of any epiretinal membrane. This can be ascribed to the relatively low incidence of epiretinal membranes met with in our study.

Nonetheless, removal of ILM was not a completely safe procedure. It was complicated by iatrogenic breaks during elevation of the flap in 3 of the patients with IMH. These breaks were treated with laser photocoagulation and silicone oil tamponade. These iatrogenic breaks did not result in late complications such as retinal detachment. Patients with traumatic macular hole did not develop iatrogenic breaks. This was attributed to the easier
**Discussion**

dissection in younger age in the patients with traumatic macular hole. Although the depth of these iatrogenic breaks cannot be accurately determined, they are believed to be partial thickness retinal breaks based on clinical examination and slit lamp biomicroscopy.

Subretinal fluid surrounding the macular hole was not removed for fear of widening of the hole or damage to the surrounding retinal tissue and to allow a more precise evaluation of the efficiency of the technique by its own. Similarly, no biological or chemical adjuvants were used in the study to allow a more controlled study design.

Patients were tamponaded with air only. In the three patients with iatrogenic breaks, silicone oil was used instead. The use of silicone oil was associated with some cataractous changes during the follow-up period. However, these cataractous changes did not lead to a visual impairment during the follow-up period that necessitated cataract extraction. No other complications related to silicone oil was reported in our study.

In most patients in our study, the ICG disappeared completely on the first postoperative day with no clinical evidence of retinal staining. In 2 patients persistent ICG staining of the peripapillary and macular areas remained for 4 days, and then disappeared completely with no hazardous
changes or phototoxic changes in fluorescein angiography. This postoperative green staining can be either due to persistent retinal staining or due to ICG than gained access to the subretinal space through the macular hole.

Although there was no clinical evidence of residual ICG by the first postoperative day in most patients, residual subclinical ICG may be present that needs most sophisticated investigation to be detected. Tadayoni et al. in 2003 have reported persistent fundus fluorescence of the optic disc and macular center by infrared photography in all patients following the use of ICG that persist up to 6 months.

In patients with IMH, the anatomical rate of closure of the hole was 80% (8 of 10 patients). In the remaining 2 patients, the size of the macular hole decreased in one patient and increased in the other patient. Although loss of the retinal vertical anchoring effect of ILM with cigarette paper-like rolling of the edge of the macular hole has been proposed as a mechanism of enlargement of the hole, this was not documented by OCT in our study.

The anatomical success rate in our study compares to the success rates in other studies. Da Mata et al. in 2001 reported a success rate of 88% in a series of 24 eyes with stage 3 and 4 macular hole using ICG-assisted peeling of
the ILM and long-acting gas for tamponade. Foulquier et al. (2002) reported a success rate of 90% in a retrospective study on 21 patients. Lastly, Kwok et al. (2003) reported a success rate of 87.8% in a series of 41 eyes with stage 3 and 4 macular holes using ICG-assisted peeling of the ILM and 12% perfluoropropane.

In patients with traumatic macular hole, the anatomical rate of closure of the hole was similar to those with IMH with a success rate 90% (9 of 10 patients). The size of the macular hole decreased but did not close in the remaining patient.

The anatomical success rate in our study on patients with traumatic macular hole match up to the success rate in Kuhn et al (2001). Kuhn et al. reported a success rate of 90% in a series of 14 eyes with traumatic macular hole using vitrectomy, peeling of the ILM and injection of long acting gas.

The postoperative visual improvement in patients with IMH was statistically significant with a mean preoperative and postoperative BCVA of 0.091 and 0.21 respectively. This corresponds to an average of 1-2 Snellen’s lines improvement in BCVA. The improvement in BCVA was slightly lower than previous studies (Da Mata et al., 2001 and Kwok et al., 2003), where visual
outcome ranged from 2-3 lines improvement in BCVA. This could be attributed to the lower preoperative BCVA in our studied patients and the relatively longer duration of macular hole. The visual outcome was better in patients with successful closure of the macular hole than those with no or incomplete closure of the hole.

In contrast to patients with IMH, the visual outcome in patients with traumatic macular hole was trivial with a mean preoperative and postoperative BCVA of 0.088 and 0.095 respectively. The improvement in BCVA is far less than one Snellen’s line improvement in BCVA. Most of the patients couldn’t attain a postoperative BCVA more than 0.1 and only one patient attained a postoperative BCVA of 0.2. The visual improvement was trivial regardless of whether the hole has closed or not.

The marked difference in visual outcome between patients with IMH and traumatic macular hole can be attributed to damage of the macular photoreceptors or papillomacular bundle directly by the trauma, toxic effect of products of resolving macular hemorrhage following trauma or secondary damage by gliosis.

The possible hazardous complications of ICG were evaluated using fluorescein angiography, automated visual field and electroretinography.
**Discussion**

A perimacular transmission hyperfluorescence appeared in 2 patients in the study. The size and the intensity of the hyperfluorescence remained constant throughout the angiogram. These changes were attributed to either a direct effect of ICG on the RPE or phototoxic reaction from the endoilluminator mediated either directly or assisted by indocyanine as a photosensitizer. Compared to other patients who did not develop these hyperfluorescent changes, there was no difference in visual outcome and no changes in visual field, which implicates the innocent nature of these changes in our cases. These RPE changes were similar to those reported in *Engelbrecht et al.* in 2002. Nevertheless, *Engelbrecht et al.* reported atrophic changes in RPE at the site of the macular hole, which we did not encounter with in this study.

The automated visual field showed a decrease in the density of central scotoma. This was more evident in patients with IMH than those with traumatic macular hole. The degree of improvement of retinal sensitivity correlated positively with the improvement in visual acuity. No new central or paracentral scotomas developed in all 20 patients, even in patients with no or incomplete closure of the hole. These results are similar to those of *Kwok et al.* in 2003 who reported no side effects with the use ICG in macular
Discussion

hole surgery. Nevertheless, they contradict with the much higher incidence of paracentral scotomas reported with Haritolou et al. in 2002 who reported new scotomas in 70% of his cases.

The ERG showed improvement of 30-Hz flicker amplitude following surgical repair. There was little change in b-wave amplitude and implicit time. This again contradicts with the results of Terasaki et al. in 2001 who reported selective delay in recovery of ERG b-wave after peeling of ILM in his study.

ICG may alter the structure of the retina to some degree. Possible factors responsible for this inadvertent action may include (1) concentration, (2) osmolarity (3) time of tissue contact, and (4) mechanical factors from more forceful traction during peeling (Gandorfer et al., 2001).

In this study, we tried to decrease the possible toxic effects of ICG, by dilution with viscoelastic to a final concentration of 0.06% to decrease concentration and by decreasing the time of contact to less than 30 seconds.

Other studies recommended the use of glucose 5% diluent instead of distilled water to avoid the toxic effect of the hypo-osmotic solvent. This solution is called infracyanine green and has been evaluated in the use of
staining of ILM and was found to equally effective to ICG with a presumed less toxic effect (*Ullern et al., 2002*).

Still further, other dyes as trypan blue has been recently evaluated for staining the ILM. Trypan blue offers the advantages of being cheaper than ICG and that it has been experienced with its intraocular use in staining of the anterior lens capsule and proved to have a large safety margin. Studies have demonstrated the efficiency of trypan blue for staining of ILM during vitrectomy for macular hole and epiretinal membranes (*Li et al., 2003*).

A controlled prospective study to compare these dyes as regards toxic effect is warranted.

Examination of the histopathological specimens removed documented that removed membrane is the internal limiting membrane. Moreover, glial cells were seen in some specimens. These results were similar to those observed by *Yoon and colleagues* in 1996 and confirmed the role of the ILM as a scaffold for proliferation of the glial cells.

There was no evidence of other retinal structures on the membrane. This disapproved with the results of *Haritoglou et al* in 2002, which found cellular elements resembling plasma membrane of Muller cells adherent to the retinal side of the ILM and postulated that intravitreal
injection of ICG may cause retinal damage by altering the cleavage plane to the innermost retinal layers. Moreover, 

*Haritoglou et al* reported no improvement of BCVA in all patients and postoperative visual field defects in 7 patients. This present study revealed a much better functional outcome, which correlated well with the histological results.

The present study found an excellent anatomical success rate of closure of both IMH and traumatic macular hole. The functional outcome was much better in IMH than traumatic macular hole. The complications related to ICG were minimal in the form of hyperfluorescent perimacular lesion with no effect on BCVA. However, further controlled studies are wanted to confirm these results and a longer term follow up period could help in delineating any late complications.
SUMMARY

This study was performed to determine the value of ICG-assisted peeling of the ILM in macular hole surgery and to outline any possible risks associated with this procedure.

The study was performed on 10 patients with idiopathic macular hole and 10 patients with traumatic macular hole. Standard pars plana vitrectomy was performed followed by staining of the ILM with ICG and peeling of the ILM around the macular hole for an area of 2 disc diameters. This was followed by intraocular injection of tamponading material (air or silicone) and face down positioning.

Satisfactory staining of ILM was obtained in all 20 patients and the ILM was removed completely in 19 patients. However, the value of ICG to delineate an invisible epiretinal membranes in this study was limited.

Iatrogenic breaks during peeling of the ILM occurred in 3 patients with idiopathic macular hole. They were treated with argon laser photocoagulation and silicone oil tamponade was used.

Closure of the macular hole in this study was documented by clinical evaluation and by OCT. Successful
anatomical closure of the macular hole was achieved in 80% of patients with IMH and in 90% of patients with traumatic macular hole. The difference in the success rate between both groups was statistically insignificant.

The functional visual outcome in both groups was measured in Snellen’s decimal fraction. The mean preoperative and postoperative visual acuity in both groups was compared using paired t-test. The visual outcome in both groups was compared using pooled t-test for independent samples.

The postoperative visual improvement in patients with IMH was statistically significant with a mean preoperative and postoperative BCVA of 0.091 and 0.21 respectively. This corresponds to an average of 1-2 Snellen’s line improvement in BCVA. The visual outcome was better in patients with successful closure of the macular hole than those with no or incomplete closure of the hole.

In contrast, the visual outcome in patients with traumatic macular hole was trivial with a mean preoperative and postoperative BCVA of 0.088 and 0.095 respectively. This is far less than one Snellen’s line improvement in BCVA. Most of the patients could not achieve a postoperative BCVA more than 0.1 and only one
Summary

patient achieved a BCVA of 0.2. The visual improvement in patients with traumatic macular hole was negligible regardless of whether the hole has closed or not.

The possible complications of the technique were evaluated using fluorescein angiography, automated visual field and ERG.

Postoperative transmission hyperfluorescence appeared in 2 patients in this study. Compared to other patients who did not develop these hyperfluorescent changes, there was no difference in visual outcome and no changes in visual field, which implies the innocent nature of these changes.

The automated visual field showed a decrease in the density of central scotoma. The improvement in macular sensitivity was more in patients with IMH than in patients with traumatic macular hole. The degree of improvement of retinal sensitivity correlated positively with the visual improvement. No new central or paracentral scotomas developed in all 20 patients even in patients with no or incomplete closure of the hole.

The ERG showed improvement of 30-Hz flicker amplitude following surgical repair. There was little change in b-wave amplitude and implicit time. There was no
Summary

electroretinographic evidence of functional damage to the photoreceptors or to the RPE.

The removed ILM was examined histopathologically using TEM. Glial cells were seen on the inner surface of the ILM. There was no histological evidence of other retinal structures in the removed ILM, which implied a relatively atraumatic technique to the remaining retinal layers.

The anatomical success rate in this study was excellent with a high success rate of closure of the macular hole in both groups and little evidence of iatrogenic damage to the retinal structures. The functional outcome was much better in patients with IMH than in patients with traumatic macular hole. The complications related to ICG were minimal in both groups.
CONCLUSION
Conclusion

The use of 0.06% ICG for staining and assisting peeling of the ILM has given encouraging results as regards anatomical success and functional improvement particularly in idiopathic macular hole. This concentration has proven to cause minimal effects on the retinal photoreceptors and retinal pigment epithelium.

Nevertheless, further double-blinded controlled studies are warranted to confirm the anatomical and functional results between patients undergoing macular hole surgery without peeling of the ILM and those with peeling of the ILM as well as to compare the results between those without and those with the use of ICG for staining.

Moreover, residual subclinical ICG that needs most sophisticated investigation to be detected such as infrared photography may persist after surgery. A longer term follow up period could help in delineating any late complications.
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الملخص باللغة العربية

استئصال الجسم الزجاجى بمساعدة صبغ الغشاء الداخلى المحدد للشبكة

بمادة الاندوسيانين الأخضر في حالات ثقب الماقولة

إن إزالة الغشاء الداخلى المحدد للشبكة يعتبر من الوسائل الجراحية الحديثة التي تحسن من النتائج التشريحيّة والوظيفية بعد الجراحة.

وقد ساعد استخدام مادة الاندوسيانين الأخضر في صبغ الغشاء الداخلى المحدد للشبكة في تسهيل إزالة الغشاء الداخلى المحدد للشبكة مع التقليل من احتمال حدوث مضاعفات ناجمة عن نتخذ الشبكة.

في هذا البحث تم دراسة اثار استخدام مادة الاندوسانيين الأخضر 0.06% لصبغ الغشاء الداخلى المحدد للشبكة في حالات ثقب الماقولة الأولى والتصادمي.

في هذه الدراسة تم استخدام مادة الاندوسانيين الأخضر 0.06% لصبغ و إزالة الغشاء الداخلى المحدد للشبكة لعدد عشر حالات ثقب ماقولة أولى و عدد عشر حالات ثقب ماقولة تصادمي.

وقد أظهرت الدراسة غلق ثقب الماقولة في 0% من حالات ثقب الماقولة الأولى و 90% من حالات ثقب الماقولة التصادمي. كما أظهرت الرسالة تحسن النظر بعد الجراحة في حالات ثقب الماقولة الأولى. بينما لم يتحسن النظر لدرجة مذكورة في حالات ثقب الماقولة التصادمي.

و قد تم دراسة المضاعفات المحتملة لمادة الاندوسانيين الأخضر

باستخدام تصوير قاع العين بصبغة الفلوريسين، وكذلك بعض مجالات إبصار ورسم كهرباء للشبكة. وقد أظهرت الرسالة حدوث زيادة بصبغة الفلوريسين حول مركز الابصار في حالتين، و أن لم تؤثر هذه الزيادة على حادة النظر بعد الجراحة. بينما لم تثبت وجود اثار ضارة سواء في مجال الابصار أو رسم كهرباء الشبكة.

كما تم دراسة الغشاة المزالة باستخدام الميكروسكوب الإلكتروني الناقل. ووجد عدم وجود مكونات شبكية أخرى في الغشاء المزالة.

وقد أفرزت الدراسة نتائج مطمنة تشجع على استخدام مادة الاندوسانيين الأخضر في صبغ الغشاء الداخلى المحدد للشبكة للتسهيل إزالة الغشاء الداخلى المحدد للشبكة مع التقليل من احتمال حدوث مضاعفات ناجمة عن نتخذ الشبكة.
استئصال الجسم الزجاجي بمساعدة صبغ الغشاء الداخلي المحدد للشبكية بمادة الإندوسيايين الأخضر

رسالة مقدمة من
أحمد محمد رضا عوضين
توطئة للحصول على درجة الدكتوراة
في طب و جراحة العيون

تحت إشراف

ابن. عفت على عبد النبى
أستاذ طب و جراحة العيون
كلية الطب – جامعة القاهرة

ابن. عمر محمد الظواهرى
أستاذ طب و جراحة العيون
كلية الطب – جامعة القاهرة

د. أحمد مصطفى عبد الرحمن
مدرس طب و جراحة العيون
كلية الطب – جامعة القاهرة

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