Multilayered inverted internal limiting membrane flap technique versus standard internal limiting membrane peeling for large macular holes: A comparative study

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Purpose: To evaluate the outcome of vitrectomy with multilayered inverted internal limiting membrane flap technique (ML-IILM) versus vitrectomy with standard ILM peeling for large macular holes in terms of visual acuity and anatomical closure. Methods: A hospital-based, prospective, randomized, interventional study was conducted during three calendar years with a total 150 eyes (75 in each group) in two groups—vitrectomy with ILM peeling (Group A) and vitrectomy with ML-IILM flap technique (Group B) after informed consent of study participants who met the inclusion criteria. Results: The mean minimum and maximum diameter of macular hole did not differ statistically in both the groups. Macular hole index had no significant difference between both groups. Pre-operative visual acuity was not statistically significantly different between the two groups. During follow-up, best corrected visual acuity (BCVA) at 1 month, 3 months, 6 months, and 12 months was significantly better in Group B (0.12 ± 0.07 at 1 month, 0.14 ± 0.10 at 3 months, 0.18 ± 0.11 at 6 months, and 0.19 ± 0.12 at 12 months) compared to Group A (0.20 ± 0.11 at 1 month, 0.22 ± 0.13 at 3 months, 0.30 ± 0.12 at 6 months, and 0.31 ± 0.14 at 12 months) (P = 0.001 for each). Type 1 anatomical closure (flattening of cuff and opposition of edges of hole) was achieved in 78.66% (59/75) cases in Group A and 93.33% (70/75) cases in Group B (P = 0.0016). Conclusion: Vitrectomy with multilayered inverted ILM flap technique had significantly higher anatomical closure and better visual outcome than vitrectomy with standard ILM peeling.

Key words: Anatomical closure, ILM flap, ILM peeling, large macular hole, vitrectomy, visual acuity

A macular hole is defined as a full thickness defect of foveal retina from internal limiting membrane to outer segment of photoreceptor layer.[3] Though internal limiting membrane (ILM) peeling-assisted pars plana vitrectomy is a widely used safe and reliable surgical technique for macular hole with excellent closure rate, in difficult situations like large macular holes (diameter >600 µm), the surgical outcomes are usually poor.[5,7] In these situations, extensive areas of ILM denudation is done for better outcome.[6,9] This approach results in unfavourable late anatomical changes like progressive dissociation of optic nerve fiber layer, a decrease in the papillomacular distance, asymmetric displacement of the macula, persistent loss of photoreceptor layer, retinal pigment epithelium defects, foveal tissue loss that correlates with poorer visual recovery, and frequent need of re-surgeries.[6,10,11]

To overcome these problems, Michalewska et al.[12,13] described a new surgical technique known as inverted internal limiting membrane (ILM) flap technique (IFT), in which an ILM flap is left on the margin of the macular hole that covers it. This novel technique was found to result in better anatomical and visual outcomes compared to standard ILM peeling (standard macular hole surgery).[14]

Several reports have compared both techniques debating to conclude the preferred one.[6,15,16] The data from Indian subcontinent in this context is also lacking. Various ILM flap-related problems like misplaced flap, loss of flap in cutter probe can occur with the original inverted ILM flap technique. In this article, the authors describe a modified approach of inverted ILM flap in macular hole surgery, which helps to minimise the flap-related complications.[17,18]

Therefore, this study was planned to evaluate the outcome of vitrectomy with multilayered inverted internal limiting membrane (ML-IILM) flap technique versus vitrectomy with ILM peeling (standard macular hole surgery) for large macular hole (diameter >600 µm) in terms of visual acuity and anatomical closure.

Methods

This hospital-based, prospective, randomized, interventional study was conducted during three calendar years among patients referred to a tertiary care eye center after permission of institutional ethics committee. The study was conducted in accordance with the ethical standards of the Institutional Ethical Committee (IEC) and with the Helsinki Declaration of 1975.

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A total of 150 eyes (75 in each group) were included in the study after written informed consent of the study participants. All 150 cases were randomized using sealed envelope method in two groups—vitrectomy with standard ILM peeling (Group A) and vitrectomy with ML-IILM technique (Group B).

All patients were informed about the need and details of the surgical procedure and the possible occurrence of complications related to the surgery.

We included consecutive treatment-naive patients (>50 years), with idiopathic full thickness macular hole (FTMH) with minimum base diameter >600 µm. We excluded patients with past medical history of amblyopia, inflammatory eye diseases, hypertensive retinopathy, diabetic retinopathy, retinal detachment or retinal surgery, glaucoma, high myopia (≥−6 D), and co-existing ocular pathologies affecting vision or patients refusing for consent.

All patients underwent complete history including ocular, medical, and family history. Preoperative parameters were recorded including best corrected visual acuity (BCVA) in Snellen lines (converted into decimal unit for statistical analysis), Intra-ocular pressure (IOP), Slit lamp bio microscopy, Indirect ophthalmoscopy, and Optical coherence tomography (Topcon Corporation, Tokyo; Carl Zeiss, Dublin, California, USA).

From each OCT study, the macular hole parameters were assessed by using the calliper software tool. The measurements made were the minimum diameter (minimal extent of the hole), the maximum diameter (diameter at the level of retinal pigment epithelium), and the height (the maximal distance between the retinal pigment epithelium and the vitreoretinal interface). Stage of macular hole (Gass classification, posterior vitreous detachment (PVD) status, and the macular hole index (MHI, ratio of the macular hole extent to its maximum diameter) was calculated.

This was a blinded study as the operating surgeon and the person collecting study data were different. All surgeries were performed by a single surgeon in this study.

Surgical technique

In both groups, after core vitrectomy (23-Gauge, 25-Gauge), PVD induction was performed. Preservative-free Triamcinolone Acetonide was used to facilitate visualization of the vitreous and posterior hyaloid. Brilliant blue G dye was slowly injected and left for about 20–30 seconds. In group A, after adequate staining, ILM along with any epiretinal membrane present was grasped and peeled off in a circumferential pattern for about 2 disc diameter around the macular hole using ILM peeling forceps [Fig. 1]. In Group B, a small bubble of perfluorocarbon liquid (PFCL) was injected at the posterior pole after staining the macula with Brilliant blue G dye. Multilayered flaps were fashioned toward the macular hole edge and rolled up inside the edge with ILM forceps [Fig. 2]. The flaps turned into a sticky consistency under PFCL and were gently placed over the hole and were not stuffed inside. During fluid air exchange the PFCL bubble was slowly aspirated. The ILM clump formed at the center did not dislodge after PFCL aspiration. At the end of surgery, 20% Sulfur Hexafluoride (SF6) gas was used as tamponade in all cases. Postoperative face down position was instructed for 1 week. In phakic patients, combined phaco-emulsification with implantation of intraocular lens followed by pars plana vitrectomy was carried out.

Follow-up was done at week 1, 1 month, 3 months, 6 months, and 12 months. During follow-up following parameters were recorded: full ophthalmological examination, slit lamp examination, IOP, best corrected visual acuity using Snellen acuity chart converted into decimal unit for statistical analysis, Indirect Ophthalmoscopy and OCT.

The main outcomes measured on OCT were anatomical closure and type of anatomical closure.

Type-1 Anatomical closure: flattening of macular hole with resolution of sub-retinal cuff of fluid and neurosensory retina (NSR) completely covering the fovea [Fig. 3].

Type-2 Anatomical closure: when the whole rim of the NSR around the macular hole was attached to the underlying retinal pigment epithelium (RPE) but NSR was absent at the fovea.

At the end of study, data was collected, documented, and analysis was done statistically.

Sample size calculation

Sample size was calculated as 62 subjects for each of two groups at alpha error 0.05 and power of 80%. Assuming 20% non-response, the sample size was inflated to 75 subjects in each group, which was also enough to estimate all other study variables.

Statistical analysis

Microsoft Excel® and SPSS® 17.0 for Windows® were used for data storage and analysis. Qualitative data was summarized in the form of proportion. Continuous variables were expressed as mean ± standard deviation. Student’s t test and Chi Square test were used to determine statistical difference between variables. Statistical significance was set at P value ≤0.05.

Results

All 150 cases of large macular hole were randomly assigned in 2 groups: vitrectomy with ILM peeling (standard macular hole surgery) – Group A and vitrectomy with ML-IILM technique – Group B.

The mean age of patients in Group A was 64.17 ± 5.95 years and in Group B was 65.39 ± 4.868 years (P > 0.05). The mean duration of macular hole was 3.4 ± 1.3 months in group A and 3.90 ± 1.52 months in group B (P > 0.05). The difference in the mean minimum diameter of macular hole was statistically non-significant among the groups (749.7 ± 167.6 µm in Group A, 765.6 ± 77.01 µm in group B, P > 0.05). Similarly, the mean maximum diameter of macular hole was statistically non-significant in both the groups (1560 ± 417.5 µm in Group A, 1579 ± 358 µm in group B, P > 0.05) [Table 1].

The mean macular hole index had no significant difference between both the groups (0.2769 ± 0.07598 in Group A, 0.2835 ± 0.0743 in group B, P > 0.05). The mean value of pre-operative visual acuity was not statistically significantly different between both groups (0.09449 ± 0.02835 in group A, 0.09264 ± 0.01532 in group B, P > 0.05) [Table 1].

Both the groups were comparable in terms of age, duration of macular hole, diameter of macular hole, macular hole index, and pre-operative visual acuity (P > 0.05) [Table 1].

During follow-up, the mean post-operative BCVA at 1 month, 3 months, 6 months, and 12 months was significantly less compared to the pre-operative BCVA (Table 1). The mean post-operative BCVA was significantly higher in Group B compared to Group A in the follow-up period (P < 0.05). The mean post-operative BCVA was significantly higher at 1 month (P < 0.05), 3 months (P < 0.05), and 12 months (P < 0.05) in Group B compared to Group A (Fig. 4). There was no statistically significant difference in the BCVA between the two groups at 6 months (P > 0.05).

Type-1 closure was seen in 66.7% of Group A and 71.7% of Group B. The difference is statistically non-significant among the groups (P > 0.05). Type-2 closure was seen in 33.3% of Group A and 28.3% of Group B. Type-2 closure was significantly lower in Group A compared to Group B (P < 0.05).

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better in Group B (0.12 ± 0.07 at 1 month, 0.14 ± 0.10 at 3 months, 0.18 ± 0.11 at 6 months, and 0.19 ± 0.12 at 12 months) compared to Group A (0.20 ± 0.11 at 1 month, 0.22 ± 0.13 at 3 months, 0.30 ± 0.12 at 6 months, and 0.31 ± 0.14 at 12 months) (P = 0.001 for each) [Table 2].

Anatomical closure was achieved in 100% (75/75) cases in Group B compared to 93.33% (70/75) cases in Group A [Table 3]. Type I closure (flattening of cuff with filling of neurosensory defect) was better in group B compared to group A and was achieved in 70/75 (93.33%) in Group B compared to 59/75 (78.66%) in Group A. Type II closure (flattening of cuff with persistent foveal neurosensory defect) occurred in 6.66% (5/75) cases in Group B compared to 15.66% (11/75) cases in Group A (P < 0.05). Among Group A 6.67% (5/75) cases failed to achieve any anatomical closure [Table 3]. There were no vitrectomy-related complications like retinal detachment, endophthalmitis or retained PFCL bubbles in the post operative period.

**Discussion**

The most widely used treatment for macular hole is pars plana vitrectomy with ILM peeling with gas injection and postoperative face down position. Internal limiting membrane peeling relieves the tractional forces responsible for causing the hole by removing the template upon which glial tissue proliferates as well as triggers reparative gliosis by injuring the Muller cells, which constitute the framework of ILM. However, large neural defects are difficult to bridge by the glial tissue. Hence, large macular holes have a propensity to remain open with standard ILM peeling.

In the last decade, some studies compared the anatomical and functional outcome of ILM flap technique with conventional ILM peeling in large macular hole and few of them found inverted ILM flap technique [Fig. 2] superior to conventional ILM peeling. Michalowski et al. found anatomical closure rate was higher in inverted ILM flap technique (98%) compared to conventional ILM peeling (88%).

There are few inherent challenges in the technique described by Michalewska et al. particularly while using nonvalved tracer cannula system secondary to fluid turbulence. These include misplaced flap during fluid air exchange, lost flap in the cutter probe and difficulty in repositioning the flap under fluid. The ML-I ILM flap under PFCL for large macular holes described by the authors is a safe and reproducible surgical technique. The internal limiting membrane under PFCL becomes thread-like in texture and does not float freely under the high surface tension of the heavy liquid. This aids in the easy reposition and maneuvering of the flap during surgery.

The stability of the flap is excellent after PFCL aspiration.

Large macular holes (minimum diameter >600 µm) are a surgical challenge with poorer than usual anatomical prognosis. The anatomical closure rate and visual outcome in patients undergoing vitrectomy for macular hole (diameter >600 µm) with either inverted ML-IIILM flap technique or standard macular hole surgery was evaluated in this study.

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**Figure 1:** Standard Macular hole surgery technique. (a) PVD induction, (b) BBG staining macula, (c and d) wide peeling of ILM in an onion peel fashion

**Figure 2:** (a-d) Inverted ILM flap technique (a) ILM peeling toward macular hole, (d) stump of ILM over the hole, (c) trimming of the stump, (d) trimmed stump of ILM overlying the macular hole). (e-h) Multilayered inverted ILM flap technique (ML-ILM) under PFCL (e) small bubble of PFCL injected over BBG stained macula, (f and g) ILM flap inversion under PFCL, (h) gentle tug over macular hole to the bunched up ILM
In the current study, we achieved 100% anatomical closure after vitrectomy with ML-IILM flap technique that was higher compared to 93.33% anatomical closure after vitrectomy with standard ILM peeling.

There is a possibility of flap-related complications in the standard inverted ILM peeling technique like flap loss during fluid air exchange\(^\text{[10]}\) and inadvertent flap loss in vitrectomy cutter probe during its trimming. The modified approach circumvents these difficulties by injecting PFCL. No case of flap loss or flap dislocation was noted under PFCL in the present series. In addition, there is no need to trim the multiple flaps with the cutter as the ILM under PFCL folds back on itself inside the hole. As there is ample scaffold inside the macular hole using the ML-ILM flap technique, there is a very high probability to achieve a type 1 closure. In the current study, the mean post-operative BCVA was better in ML-IILM technique compared to conventional ILM peeling at 3-months', 6-months', and 12-months' follow-up.

In the current study, the anatomical success was better in ML-IIILM flap technique (type 1 closure in 93.33% cases) compared to standard ILM peeling (type 1 closure in 78.66% cases). Manasa et al.\(^\text{[25,26]}\) also found better Type 1 closure rate with the ILM flap (62.8%) than ILM peeling (33.3%). Other authors also reported similar observation of better Type 1 anatomical closure rates with the ILM flap technique (96%) in comparison to ILM peeling (69%).\(^\text{[12]}\) However, some studies did not find significant difference between these two techniques.\(^\text{[27‑29]}\)

The ML-IIILM flap technique under PFCL provides a smooth and gap-free natural scaffold for the migration of glial cells and

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### Table 1: Characteristics of study participants

| Outcome                                      | Group A (Vitrectomy with Internal Limiting Membrane peeling) | Group B (Vitrectomy with Inverted Internal Limiting Membrane flap technique) | \(P\)   |
|-----------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|--------|
| Age (years) (Mean±SD)                        | 64.17±5.953                                                   | 65.39±4.868                                                                 | 0.173  |
| Duration of macular hole (months)             | 3.4±1.3                                                       | 3.90±1.52                                                                   | 0.2    |
| Minimum diameter (μm) of macular hole        | 749.7 μm±167.6                                               | 765.6±77.01                                                                  | 0.458  |
| Maximum diameter (μm) of macular hole        | 1560±417.5                                                   | 1579±358.0                                                                   | 0.761  |
| Macular hole index                           | 0.2769±0.07598                                               | 0.2835±0.0743                                                                | 0.342  |
| Pre-operative visual acuity                  | 0.09449±0.02835                                              | 0.09264±0.01532                                                              | 0.620  |
| Phakic                                        | 18                                                           | 21                                                                          | 0.712  |
| Pseudophakic                                  | 57                                                           | 54                                                                          |        |

### Table 2: Post-operative visual acuity

| Post-operative visual acuity                  | Group A (vitrectomy with Internal Limiting Membrane peeling) | Group B (vitrectomy with Inverted Internal Limiting Membrane flap technique) | \(P\)   |
|-----------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|--------|
| At 1 month                                    | 0.20±0.11                                                     | 0.12±0.07                                                                    | 0.001  |
| At 3 months                                   | 0.22±0.13                                                     | 0.14±0.10                                                                    | 0.001  |
| At 6 months                                   | 0.30±0.12                                                     | 0.18±0.11                                                                    | 0.001  |
| At 12 months                                  | 0.31±0.14                                                     | 0.19±0.12                                                                    | 0.001  |

### Table 3: Anatomical and functional outcome

| Outcome                                      | Group A (vitrectomy with Internal Limiting Membrane peeling) | Group B (vitrectomy with inverted Internal Limiting Membrane flap technique) | \(P\)   |
|-----------------------------------------------|---------------------------------------------------------------|-----------------------------------------------------------------------------|--------|
| Anatomical Closure                           | 70 (93.33%)                                                   | 75 (100%)                                                                   |        |
| Anatomical Closure                           |                                                               |                                                                             |        |
| Type I                                        | 59 (78.66%)                                                   | 70 (93.33%)                                                                  | 0.0001 |
| Type II                                       | 11 (15.66%)                                                   | 05 (06.67%)                                                                  |        |
| No closure                                    | 5 (6.67%)                                                     | 0                                                                           |        |

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**Figure 3:** (a) Preoperative OCT of left eye full thickness macular hole with base diameter of 855 microns. (b) Postoperative 4 weeks OCT showing type 1 closure with ILM flaps visible inside the hole area after ML-ILM flap technique
photoreceptors toward the fovea leading to better anatomical and functional outcome as shown in our study.

As large macular hole is an uncommon condition, it is difficult to take a large sample size operated by a single surgeon in a limited time period. Despite this fact, we have included 150 eyes in our study, which is the largest size in randomized control trials in the available literature.[29] This was a single center study so further studies are needed to evaluate the rate of success, both anatomical and functional, according to the size of large macular hole.

Conclusion
This study concludes that vitrectomy with ML-ILM flap technique had significantly better success rate (anatomical closure) and better visual outcome than the standard macular hole surgery (Vitrectomy with ILM peeling).[30,31] The ML-ILM technique under PFCL is a safe and easily reproducible technique and offers distinct advantages over all the currently described ILM peeling technique in terms of flap-related complications.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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