ORIGINAL ARTICLE

THE OUTCOME OF THE INVERTED INTERNAL LIMITING MEMBRANE FLAP TECHNIQUE FOR THE REPAIR OF LARGE IDIOPATHIC MACULAR HOLES

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Background: Full-thickness macular hole is defined as an anatomical defect in the fovea that spans from the internal limiting membrane to the retinal pigment epithelium, assessed by spectral-domain optical coherence tomography. The Objectives of the study are to determine the anatomical and visual outcome in patients undergoing pars plana vitrectomy along with inverted internal limiting flap closure in large idiopathic full-thickness macular holes (>400 µm). **Methods:** A prospective interventional study was conducted at a tertiary teaching eye hospital in Karachi, where patients of either gender and having macular holes greater than >400 µm were recruited. The study was conducted From January 9 to July 8, 2022, and all patients underwent pre-operative fundus examination and pars plana vitrectomy with inverted ILM flap closure. Data was entered and analyzed using SPSS 23. Follow-ups were conducted at 1 and 3 months. **Results:** A total of 94 patients were enrolled with a mean age of 49.17±13.8 years. The mean duration of symptoms was 3.1±1.4 months. The mean pre-operative macular hole diameter was 854.31±08.36 µm and Stage 3 and 4 MH was present in 36.2% and 63.8% of patients, respectively. Anatomical closure was achieved in 93.6% of eyes (n=88/94). Pre-operative mean BCVA was LogMAR 0.90±0.24, which improved to LogMAR mean 0.70±0.27 at the final follow-up. As of the last follow-up, 92.6% of patients showed improved visual outcomes, with a mean three-line improvement in Snellen lines. After data stratification, no statistically significant result was obtained. **Conclusion:** The use of the inverted ILM flap technique resulted in improved anatomical and visual outcomes, in cases of large idiopathic macular holes.

Keywords: Macular hole; Vitrectomy; Internal limiting flap

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INTRODUCTION

Full-thickness macular hole (FTMH) is defined as an anatomical defect in the fovea that spans from the internal limiting membrane (ILM) to the retinal pigment epithelium (RPE), assessed by spectral-domain optical coherence tomography (SD-OCT).[1] The pathophysiology of idiopathic full-thickness macular holes is unknown, however, it is thought to include anteroposterior and/or tangential tension applied by the posterior vitreous cortex at the fovea, with involutional macular thinning being a risk factor.[2] It is estimated to be present in 33 out of every 10,000 individuals older than 55 years.[3,4]

Anatomical outcomes after the treatment of macular holes (MH) with vitrectomy have been widely successful, with the success rate of MH closure close to roughly 95%.[5–9] When a hole is larger than 400 µm, it is more likely to suffer surgical failures, such as failure to close, reopen, flat-open closures, or bare retinal pigment epithelium on the MH margins.[10] The inverted internal limiting membrane (ILM) flap approach, introduced by Michalewska *et al* in 2010, demonstrated an impressive 98% MH closure rate for treating big idiopathic MH and myopic FTMH, compared to just 88% utilizing standard vitrectomy and ILM peeling.[11] Several studies in recent years have indicated that the inverted ILM flap method (IFT) may be preferable for the treatment of large MHs, even for holes wider than 1000 µm, suggesting the inverted ILM flap as the sole viable procedure.[12–15]

A prospective interventional study was performed to assess the anatomical and visual outcome in patients undergoing pars plana vitrectomy along with inverted internal limiting membrane (ILM) flap closure in idiopathic large macular holes with MD >400 µm, in a low to middle-income country with limited resources available.

MATERIAL AND METHODS

From January 9 to July 8, 2022, this was a prospective interventional study undertaken at LRBT Tertiary Teaching Eye Hospital Korangi in Karachi, Pakistan, with approval from the hospital ethics council. Consecutive sampling was done to recruit patients with idiopathic full-thickness macular holes (FTMH) with a diameter greater than 400 µm. Patients with a macular diameter (MD) >1500 µm, traumatic MHs, myopic MHs, pseudo-macular/ lamellar holes, presence of co-existing ocular pathologies like glaucoma, uveitis & optic atrophy affecting vision, MH associated with retinal detachment, MH duration of greater than 6 months, significant dioptric media opacity, previous retinal surgery, diabetic and vascular retinopathy, and patients with high myopia >6D were excluded from the study.

Patients were recruited from the hospital's outpatient department. The nature and objective of the research were explained to the patients, and prior to surgery, all 94 patients gave written consent for participation. Before the surgery, a detailed anterior segment and fundus examination was performed, and the procedure was performed by a single experienced vitreoretinal surgeon. Best corrected visual acuity (BCVA) was measured using Snellen's chart (converted into a logarithm of the minimum angle of resolution, i.e., LogMAR for data analysis), while FTMH parameters and indices were measured using Heidelberg Spectralis SD-OCT. This was done before and after the procedure at follow-ups 30- and 90-days following surgery. All the information was recorded in a pre-designed form.

The surgical procedure utilized included core vitrectomy. All procedures were carried out under general or local anaesthesia. Micro-incision vitrectomy using a 25-gauge vitrectomy system (Constellation Vision System, Alcon® surgical) was performed under tight aseptic conditions, followed by surgical induction of posterior vitreous detachment (PVD), if already not induced. The ILM was then dyed with a 0.05% solution of Heavy Brilliant Blue G dye (HBBG), followed by peeling it, using the Finesse Flex loop and end grasping forceps, in a concentric fashion for roughly 2-disc diameters with margins left in the shape of a hinge to be tucked into the hole with an end. Following the air-fluid exchange, 20% sulphur hexafluoride (SF6) gas was introduced to cause internal tamponade.

The collected data were processed using SPSS version 23. Age, duration of symptom, preoperative MD, and preoperative VA were reported as mean and standard deviation. Gender, eye involvement, occupation, anterior segment pathology, comorbidities, stage of MH, anatomical results, and improvement in visual outcomes were recorded qualitatively as frequency and percentage. Stratification was used to adjust for effect modifiers such as age, gender, eye involvement, comorbidities, stage of MH, duration of symptom, preoperative MD, and preoperative VA. Post-stratification, chi-square, or Fischer exact tests were used, with a *p*-value of ≤0.05 considered significant.

RESULTS

A total of 94 participants were included in the study, the mean age of whom was 49.17 years (30–75 years). Table-1 summarizes the baseline characteristics of the sample population. The mean duration of symptoms was 3.1±1.4 months. The mean pre-operative MD was 854.31±108.36 µm and the mean BCVA was LogMAR 0.90±0.24 (Snellen equivalent 20/160). Median visual acuity was 20/145. Stage 3 MH was present in 36.2% of patients and Stage 4 MH was present in 63.8% of patients.

Anatomical closure was achieved in 93.6% of eyes (n = 88/94). The mean BCVA at the final follow-up at 3 months was LogMAR 0.70±0.27 (Snellen equivalent 20/100). As of the last follow-up, 92.6% of patients showed improved visual outcomes, with a mean three-line improvement in Snellen lines.

Data stratification was performed to determine the effect modifiers such as age group, gender, eye involved, anterior segment pathology, comorbidities, stage of macular disease, length of symptoms, preoperative MD, and preoperative BCVA (Table-2). No statistically significant difference was found (*p*>0.05).

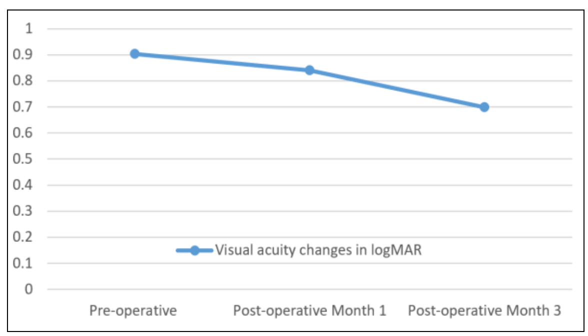

Figure-1: Mean Visual Acuity Changes in LogMAR

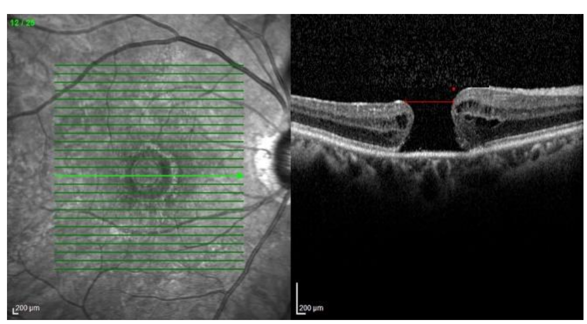

Figure-2: Pre-operative optical coherence tomography of one patient

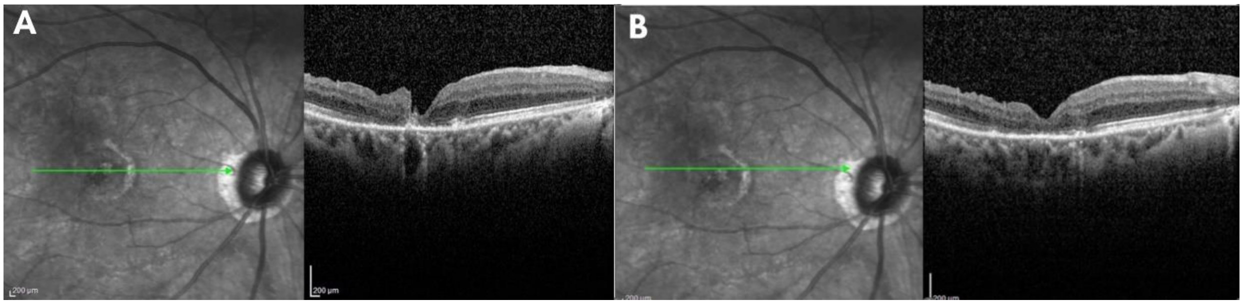

Figure-3: A and B shows post-operative optical coherence tomography of one patient at weeks 4 and 12

Table-1: Baseline characteristics

		N= 94
Age in years, mean (± SD)		49.17 (±13.85)
Gender		
	Male, n (%)	52 (55.3)
	Female, n (%)	42 (44.7)
Duration of symptoms in months, mean (± SD)		3.1 (±1.41)
Eye involved		
	Left eye, n (%)	48 (51.1)
	Right eye, n (%)	46 (48.9)
Anterior segment pathology present, n (%)		32 (34.0)
Comorbidities		
	Diabetes, n (%)	22 (23.4)
	Hypertension, n (%)	25 (26.6)
	Ischemic heart disease, n (%)	16 (17.0)
Pre-operative BCVA LogMAR, mean (± SD), Snellen equivalent		0.903 (±0.38), 20/160
Pre-operative macular hole diameter in µm, mean (± SD)		854.31 (±108.36)
Stage of macular hole		
	Stage 3, n (%)	34 (36.2)
	Stage 4, n (%)	60 (63.8)

Table-2: Anatomical outcomes after data stratification

		Anatomical outcome		***p*-value**
		Closed	**Not closed**	
Age, n (%)				
	30–50 years	40 (90.9)	4 (9.1)	0.314
	51–75 years	48 (96.0)	2 (4.0)	
Gender, n (%)				
	Male	50 (96.2)	2 (3.8)	0.263
	Female	38 (90.5)	4 (9.5)	
Eye involved, n (%)				
	Left eye	46 (95.8)	2 (4.2)	0.478
	Right eye	42 (91.3)	4 (8.7)	
Anterior segment pathology, n (%)				
	Present	29 (90.6)	3 (9.4)	0.394
	Absent	59 (95.2)	3 (4.8)	
Duration of symptoms, n (%)				
	1–3 months	36 (97.3)	1 (2.7)	0.240
	4–6 months	52 (91.2)	5 (8.8)	
Pre-operative visual acuity, n (%)				
	Equal to or less than 20/200	48 (98.0)	1 (2.0)	0.072
	More than 20/200	40 (88.9)	5 (11.1)	
Stage of Macular hole, n (%)				
	Stage 3	33 (97.1)	1 (2.9)	0.304
	Stage 4	55 (91.7)	5 (8.3)	
Pre-operative Macular hole diameter in µm, n (%)				
	Equal to or less than 800 µm	60 (96.8)	2 (3.2)	0.081
	More than 800 µm	28 (87.5)	4 (12.5)	

DISCUSSION

Full-thickness macular holes (FTMH) are a common cause of significant visual deterioration. Individuals with macular holes (MH) suffer from poor visual acuity due to a lack of retinal tissue in the fovea, however, clinically visual impairment can present out of proportion to the diameter of the MH.[16] It may also be linked to the existence of a cuff of subretinal fluid with accompanying photoreceptors.[16]

Various surgical approaches have been described for treating MHs. In 1991, Kelly and Wendel demonstrated that vitrectomy with strict face-down gas tamponade could successfully treat FTMHs, with an anatomic success rate of roughly 60% [37]. The use of autologous plasmin for idiopathic and traumatic MHs has also been brought to light. Plasmin-assisted vitrectomy surgery for the treatment of paediatric MHs, successfully closed 12/13 holes (92%)[17], however in another trial closure of MHs didn't occur, but it did make surgery easier[18]. Intravitreal ocriplasmin has also been shown to achieve non-surgical closure of MH in almost 40% of eyes in the ocriplasmin group, compared to 10% in the placebo group, in a randomized, double-blind trial.[19] The resection of ILM is thought to aid in the success of MH procedures. Its resection is also related to a lower chance of the MH reopening in the future [38]. In a meta-analysis, comparing ILM peeling vs no peeling, significant statistical improvement in BCVA was noted favouring peeling at 3 months post-operatively.[20] However, studies examining these various surgical approaches did not include large MHs (>400 m), which are tough to connect with glial tissue. As a result, large MHs are more likely to remain open or heal in a Type 2 fashion.[10,21,22] Chhablani *et al*. observed that the likelihood of Type 1 closure with ILM peeling was 100% only if the hole's diameter was smaller than 300 µm.[21]

In this study, 94 eyes with holes greater than 400 µm were evaluated and showed an anatomical closure rate of 95.7% (90/94 eyes), indicating a greater anatomical success rate and a superior functional result with an inverted ILM flap technique. The technique involves reflecting inverted ILM tissue within the hole to cover it.[11] The closure is likely caused by the migration of glial cells and photoreceptors to the fovea through the IFT, which provides a natural and smooth framework without gaps.[11,23] According to Shiode *et al*, the neurotrophic and growth factors retained on the surface of the ILM flap stimulate Muller cell proliferation and migration. Muller cells then secrete growth factors and neurotrophic factors that may promote retinal neuronal survival.[24] The technique has even been found to be superior in achieving anatomical success in the case of retinal detachment associated with FTMH.[25]

Numerous additional studies and trials have shown similar findings to the current study in literature, demonstrating that the inverted internal limiting membrane (I-ILM) flap approach is preferable for treating large idiopathic MH. The work by Khodani M. *et al*. showed excellent anatomical and visual results in closing holes larger than 1000 µm.[15] Mahalingam's study likewise showed high closure with 100% of the eyes achieving visual improvement.[12] This approach can successfully seal MHs with a minimum diameter larger than 550 µm, however, vision recovery may be restricted for super large MH with a diameter >700 µm, according to a multicenter study conducted in Japan.[26] All 25 eyes of 25 patients with large FTMH underwent anatomic closure in retrospective research by Maier *et al*. and at six months after surgery, the mean BCVA improved from 0.7 LogMAR (Snellen equivalent of 6/30) to 0.2 LogMAR (Snellen equivalent of 6/9.5).[27] The results of a systematic review and single-arm meta-analysis indicated that 95 percent of FTMH with MD >400 µm would close anatomically and 75 percent would improve visually following IFT.[28] The inverted internal limiting membrane flap approach was reported to have a 100% closure rate in all 55 eyes in a recent study published in 2020 with a 12-month follow-up. At the last follow-up, there was significant improvement ($p<0.001$) in BCVA from mean 0.98 LogMAR (Snellen equivalent of 20/190) to mean 0.42 LogMAR (Snellen equivalent of 20/53).[29]

Concerns have been raised about the I-ILM flap method. Since the ILM only needs to be excised partially, it remains linked to the MH margins, meaning the surgical approach has a high learning curve. One major source of concern is the possibility of ILM flap displacement, particularly during the fluid-air exchange.[11] There might be other complications as well, such as Müller cell damage, development of paracentral retinal holes, and thinning or atrophy of the RPE.[30–32] None of these issues were observed in this study.

This study's anatomical and visual success rate is comparable to that seen in the literature, demonstrating outstanding results of pars plana vitrectomy with an inverted ILM flap. Patients with large MHs, who would otherwise have a decreased chance of hole closure, are more likely to benefit from the surgical approach provided in this study, which increases the quality of life, particularly for patients with good visual acuity in the opposite eye.

The first limitation of the present study is a lack of a randomized model. Since large macular holes are uncommon, it is difficult to take a large sample size by a single surgeon within a limited timeframe. However, we were still able to assess 94 eyes. Moreover, patients in tertiary healthcare settings frequently fall through the cracks when it comes to follow-ups, so the short follow-up period made it impossible to confidently assess the procedure's safety and efficacy. Additionally, all retinal surgeries were performed by the same vitreoretinal consultant in a single institution in this trial. While broad conclusions cannot be drawn from the study, a possible bias caused by the participation of multiple surgeons and assessors has been avoided. It is necessary to conduct larger randomized trials in multiple institutions in order to evaluate the rate of success, both anatomically and functionally, of this surgical technique.

CONCLUSION

It was found that the inverted ILM flap technique resulted in improved anatomical and visual outcomes in cases of large MHs, even with limited resources available. Despite promising results, this study has a limited number of patients and follow-up duration. Due to the rarity of large MHs, it is difficult, however, to obtain a large sample size in a limited time frame by a single surgeon operating on an MH. For a comprehensive assessment of the long-term effects of this procedure, larger comparative studies and a longer follow-up will be required.

AUTHORS' CONTRIBUTIONS

MU and SF conceived the idea and designed the study outline. SF performed data collection. MU processed the experimental data and performed the analytic calculations. MU and AM did a literature review and drafted the manuscript. MU, SF and AM prepared figures and tables of the manuscript. SF supervised the project and did the final proofreading. All authors contributed to the final version of the manuscript. All authors approved the submitted version.

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