

CONVENTIONAL INTERNAL LIMITING MEMBRANE PEELING VERSUS INVERTED FLAP FOR SMALL-TO-MEDIUM IDIOPATHIC MACULAR HOLE

A Randomized Trial

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Purpose: To compare conventional internal limiting membrane (ILM) peeling versus inverted flap technique in small-to-medium idiopathic macular hole.

Methods: Eyes with ≤ 400 μm idiopathic macular holes were randomized into the conventional ILM peeling group (25 eyes) and inverted flap group (25 eyes). A 12-month follow-up was considered. Macular sensitivity (MS) change detected with MP-1 microperimetry was the primary outcome. Secondary outcomes included best-corrected visual acuity change, closure rate, anatomical findings on optical coherence tomography such as U-shape foveal contour, restoration of external limiting membrane, and ellipsoid zone.

Results: In both groups, MS improved throughout the follow-up. Final MS was greater in the conventional ILM peeling group compared with the inverted flap group, being 16.6 ± 2.3 dB versus 14.9 ± 2.9 dB, respectively ($P = 0.026$). In both groups best-corrected visual acuity improved throughout the follow-up, with a final best-corrected visual acuity of 0.19 ± 0.14 logMar (20/31 Snellen) in the conventional ILM group and 0.22 ± 0.11 logMar (20/33 Snellen) in the inverted flap group ($P = 0.398$). Anatomical hole closure was achieved in all cases. No difference in optical coherence tomography findings was shown between the two groups.

Conclusion: A better final MS was found in eyes undergoing conventional ILM peeling. Inverted flap technique has disadvantages compared with conventional peeling for the treatment of small-to-medium idiopathic macular holes.

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First introduced in 1999, internal limiting membrane (ILM) peeling has become a mainstay step in full-thickness macular hole (FTMH) surgery, allowing a higher closure rate and less chance of postoperative hole reopening.¹

About 10 years later, a modified ILM peeling technique was proposed by Michalewska et al² for the treatment of large macular holes. A trimmed flap of peeled ILM was left attached to the hole edges and inverted onto the hole surface. The inverted flap technique was shown to improve anatomic success in closure rate and foveal anatomy.²

Since then, several studies have confirmed better anatomic outcomes of the inverted flap technique in

large macular holes.^{3–5} The effect of this technique on functional outcomes is less clear.⁵ Some authors showed functional benefits compared with conventional ILM peeling,^{3,4} whereas others found no functional improvement or, in some cases, poor results.^{6,7} However, the assessment of functional outcomes may well prove challenging in large macular holes because of the limited visual recovery in such eyes.

Conversely, small macular holes have a far greater chance of good functional recovery, with excellent visual outcomes in about one third of cases.⁸ This higher likelihood of good postoperative visual function would make the assessment of functional outcomes more reliable and accurate. In turn, this could

help to better understand the effect of the inverted flap technique on visual function and shed light on possible differences compared with conventional ILM peeling.

The purpose of this randomized trial was to compare functional and anatomical outcomes of the inverted flap technique versus conventional ILM peeling in small and medium idiopathic FTMHs, primarily looking at microperimetry results.

Methods

The present prospective, randomized clinical trial was conducted at the Eye Clinic of the University of Turin. The study protocol conformed to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board. The study was registered at ClinicalTrials.gov (Identifier: NCT04498624). Written informed consent for participation was obtained from each subject before enrollment. Subject recruitment was between January 2020 and November 2020. The last enrolled patient completed the 1-year follow-up in November 2021.

All consecutive patients diagnosed with idiopathic full-thickness macular hole and scheduled for vitrectomy were assessed for eligibility. Only patients older than 18 years and with idiopathic FTMHs $\leq 400 \mu\text{m}$ were included. The following exclusion criteria were considered: any concomitant ocular or retinal disease that could affect visual function; amblyopia; posterior staphyloma; glaucoma; uveitis; any retinopathy; history of any intraocular surgery apart from uncomplicated cataract surgery; traumatic macular hole; high myopia (>25.5 mm axial length and/or $>6\text{D}$ diopters); media opacity, and/or poor compliance precluding a good-quality level of spectral domain optical coherence tomography (SD-OCT) and microperimetry; FTMH with a diameter larger than $400 \mu\text{m}$; FTMH associated with retinal detachment.

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At baseline, medical history and demographic information were collected from each participant and they underwent a complete eye assessment including best-corrected visual acuity (BCVA) measurement, slit-lamp examination, Goldmann applanation tonometry, IOL master examination (IOL Master, Carl Zeiss Meditec, Jena, Germany), and dilated fundus examination. Early Treatment Diabetic Retinopathy Study (ETDRS) charts were used for BCVA measurement, which was converted into logarithm of the minimum angle of resolution (logMar). Spectral domain-OCT imaging (Spectralis HRA-OCT; Heidelberg Engineering, Heidelberg, Germany) and microperimetry (MP-1, Nidek Technologies, Padova, Italy) were performed in each participant at baseline. Optical coherence tomography imaging was based on a raster horizontal scan protocol covering $30 \times 20^\circ$ with a spacing of $60 \mu\text{m}$ in the high-resolution mode; an additional vertical scan of fovea center was obtained. Baseline scans were set as reference and the inbuilt “follow-up” function was used during the follow-up visits. Measurements were performed manually. Macular hole size was based on minimum linear diameter (MLD), measured at the narrowest point between the hole edges through the center of the fovea.⁹ Microperimetry was performed in a dimly lit room once pupils had been dilated (tropicamide 1%). The instrument provides a 45° fundus view with an automated eye tracking system. Background luminance was set at 1.27 cd/m^2 . White Goldmann III stimuli with 200 millisecond duration were used. Stimulus intensity ranged from 0 to 20 dB, varying by 1-dB steps, starting with 10 dB intensity. A 45-point grid projected onto the central 8° was tested using a 4-2 staircase strategy. The “follow-up” function was used during the follow-up visits. Mean sensitivity of the 45-point tested area was defined as mean macular sensitivity (MS). All participants received a training session and baseline microperimetry test was carried out twice within one week to reduce learning effects. Microperimetry and OCT imaging were performed by two independent blinded investigators (P.M., G.P.).

Randomization and Treatment

Block randomization was performed two weeks after the baseline visit. Participants were randomized to the inverted flap group or the conventional ILM peeling group, according to preallocated codes contained in sealed envelopes. Participants and outcome assessors were masked to the treatment group assignment. Each participant underwent a standard 25-gauge pars plana vitrectomy (Constellation), under peribulbar anesthesia. Combined phacoemulsification with intraocular lens implantation was conducted in all phakic participants.

All surgeries were performed by the same vitreoretinal consultant (M.R.). After a core vitrectomy, a posterior vitreous detachment was induced, if not present. Membraneblue-Dual (DORC, Zuidland, The Netherlands) staining was performed (to stain the ILM). In cases where an epiretinal membrane was present, this was peeled. In the conventional ILM peeling group, the ILM was peeled off in an area of two-disk diameters centered on the fovea, with no ILM remaining around the hole. In the inverted flap group, a two-disk diameters ILM flap was peeled in a circumferential way and left attached to the macular hole edges. This flap was trimmed using a vitreous cutter, inverted and left to cover the macular hole, with no attempt to insert it inside the hole. In all cases, end grip forceps were used to grasp and peel the ILM, without scraper assistance. In both groups, a fluid-air exchange was performed, with subsequent 20% sulfur hexafluoride gas filling. Face-down position was recommended for 5 days postoperatively.

Follow-up Visits

Participants were examined on day one and day 14 postoperatively to assess postoperative eye condition. A complete eye examination and OCT imaging were performed at 1-month, 3-month, 6-month, and 12-month follow-ups. The microperimetry test was performed at the 6-month and 12-month follow-ups.

Outcome Measures

In both groups, a change in microperimetry macular sensitivity between baseline and follow-up visits was considered as a primary outcome measure. Best-corrected visual acuity change, rate of macular hole closure, anatomical findings on SD-OCT imaging, and postoperative complications were considered as secondary outcome measures. Anatomical findings on SD-OCT imaging included rate of normal foveal morphology with a U-shape contour,¹⁰ and restoration of external limiting membrane (ELM) and ellipsoid zone (EZ) in the foveal region.¹¹ Retinal layers were considered as restored when they were visible as continuous hyperreflective lines without discontinuities on OCT images. The latter grading was performed by two masked investigators (G.P., P.M.) who analyzed OCT scans independently. Cases of disagreement were resolved by a third investigator (M.F.).

Statistical Analysis

Sample size calculation was based on the results of our preliminary data. To obtain a 90% power with a 0.05 alpha (two-sided), 44 patients (22 per group) needed to be recruited. Allowing for a 10% drop-out rate, 50

patients (25 per group) were finally calculated to be the number to be enrolled. Comparisons between the two groups were based on unpaired *t*-test and chi-square test for continuous and categorical variables, respectively. In each group, values of a continuous variable detected at different time-points were compared using analysis of variance test. If significant, multiple comparisons were fitted by using the Tukey HSD (honestly significant difference) test. In each group, values of a categorical variable detected at different time-points were compared by using the Q Cochran test. If significant, multiple pairwise comparisons were fitted. A *P* value < 0.05 was considered significant. Analyses were conducted on SPSS Statistics software version 21 (IBM Corp, Armonk, NY).

Results

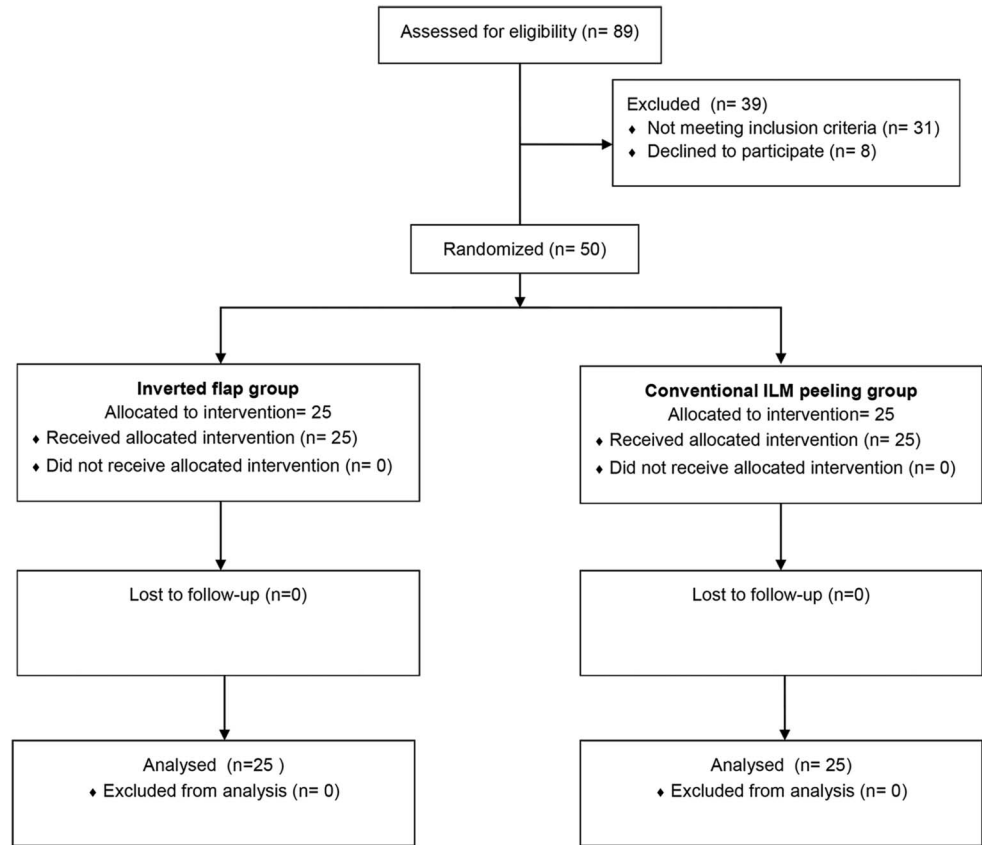
A total of 89 patients were assessed for eligibility, of whom 39 were excluded (Figure 1). Fifty eyes of 50 patients were randomized into the two study groups: 25 eyes in the inverted flap group and 25 eyes into the conventional ILM peeling group. All patients completed the 12-month study period, with no drop outs.

Baseline demographic and clinical characteristics of enrolled patients are shown in Table 1. Mean macular hole diameter was $269 \pm 52 \mu\text{m}$ in the inverted flap group and $254 \pm 70 \mu\text{m}$ in the conventional ILM group. There were 13 phakic eyes in the inverted flap group and 16 phakic eyes in the conventional ILM group. A combined phaco-vitrectomy was performed in all phakic eyes. An epiretinal membrane was found in five and seven eyes in the inverted flap group and conventional ILM peeling group, respectively.

Baseline MS was $11.9 \pm 2.1 \text{ dB}$ in the inverted flap group and $12.2 \pm 2.5 \text{ dB}$ in the conventional ILM peeling group ($P = 0.738$). The analysis of variance analysis showed that macular sensitivity had improved in both groups throughout the 12-month follow-up ($P < 0.001$). However, eyes treated with conventional ILM peeling had a higher MS compared with those treated with the inverted flap technique at the 6-month and 12-month follow-ups (Figure 2). Final MS was $14.9 \pm 2.9 \text{ dB}$ and $16.6 \pm 2.3 \text{ dB}$ in the inverted flap group and conventional ILM peeling group, respectively ($P = 0.026$).

Baseline BCVA was $0.76 \pm 0.22 \text{ logMar}$ (20/115 Snellen) in the inverted flap group and $0.72 \pm 0.21 \text{ logMar}$ (20/105 Snellen) in the conventional ILM peeling group ($P = 0.607$). In both groups, a significant visual improvement was demonstrated throughout the follow-up: the analysis of variance analysis revealed that mean BCVA progressively increased at each follow-up visit in both groups ($P < 0.001$). Mean

Fig. 1. Flow-diagram showing the progression through the study phases.



BCVA was comparable between the two groups at all follow-up visits (Figure 3), with a final BCVA of 0.22 ± 0.11 logMar (20/33 Snellen) and 0.19 ± 0.14 logMar (20/31 Snellen) in the inverted flap group and conventional ILM group, respectively ($P = 0.398$).

Anatomical closure of the hole was achieved in all enrolled patients after surgery, with no case of hole recurrence at the 12-month follow-up.

Table 2 illustrates postoperative anatomical findings on SD-OCT imaging. The proportion of eyes with ELM restoration increased throughout the follow-up in both groups. At 12 months, ELM restoration was found in 76% and 96% of eyes of the inverted flap

group and conventional ILM peeling group, respectively (inverted flap group vs. conventional ILM peeling group, $P = 0.247$). Similarly, the proportion of eyes with EZ restoration increased during the follow-ups in both groups. At 12 months, EZ recovery was shown in 52% and 72% of eyes of the inverted flap group and conventional ILM peeling group, respectively (inverted flap group vs. conventional ILM peeling group, $P = 0.244$). At 12 months, a U-shape foveal contour was found in 76% of eyes in the inverted flap group and 96% of eyes in the conventional ILM peeling group (inverted flap group vs. conventional ILM peeling group, $P = 0.098$; Figure 4).

Table 1. Baseline Characteristics of Included Patients

	IFT (n = 25)	ILMP (n = 25)	P
Age, years	62 ± 5	64 ± 5	0.145
Male/female, n	14/11	13/12	1.000
BCVA, logMar	0.76 ± 0.22 (20/115 Snellen)	0.72 ± 0.21 (20/105 Snellen)	0.607
Macular sensitivity, dB	11.9 ± 2.1	12.2 ± 2.5	0.738
MH diameter, μm	269 ± 52	254 ± 70	0.405
Axial length, mm	23.90 ± 0.59	24.06 ± 0.53	0.304
Combined surgery, n (%)	13 (52%)	16 (64%)	0.567
Presence of ERM, n (%)	5 (20%)	7 (28%)	0.742

dB, decibel; ERM, epiretinal membrane; IFT, inverted flap technique; ILMP, internal limiting membrane peeling; MH, macular hole; n, number.

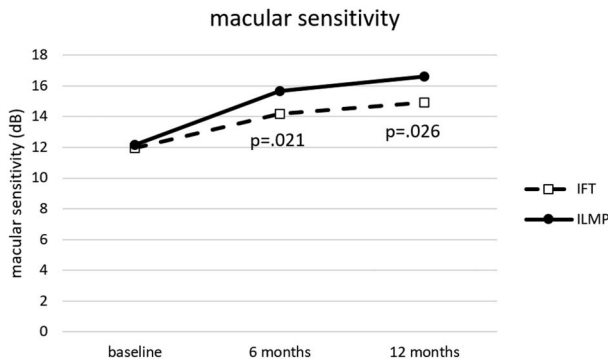


Fig. 2. Macular sensitivity change in the inverted flap group (IFT) and conventional internal limiting membrane peeling group (ILMP) throughout the follow-up.

Discussion

The present randomized trial compared the inverted flap technique versus conventional ILM peeling in eyes with a small-to-medium idiopathic macular hole. Importantly, this study assessed the functional and anatomical outcomes after these two procedures. Our results showed better microperimetry outcomes in eyes treated with conventional ILM peeling, although no differences in visual gain were found.

The inverted flap technique was introduced by Michalewska et al² in 2010 for the management of large FTMHs. The rationale of this technique relies on the assumption that the ILM flap promotes tissue proliferation acting as a scaffold for Muller cells, contained within the ILM, with subsequent gliosis and hole closure. The authors reported a closure rate as high as 98%, which was impressive compared with the 88% closure rate of conventional ILM peeling.² Since then, the inverted flap technique has become commonly used for the treatment of large FTMHs, showing better anatomical and visual outcomes compared with conventional ILM peeling.¹²

Improvement in microperimetric parameters have also been demonstrated in large macular holes treated with the inverted flap technique.¹³ However, microperimetry reliability may be questioned in cases affected by large macular holes given the nonexcellent visual outcome.

The original inverted flap technique introduced by Michalewska et al² has been revised and modified over the years. Original Michalewska's technique involved the creation of an ILM flap attached to macular hole edges. This flap was trimmed and gently massaged over the hole to become inverted.² Some authors commented that this original technique was similar to a packing rather than a simple covering of the hole.¹⁴ Thus, a modification of the original technique involved the creation of a single-layered inverted flap that is left to cover

the hole.^{14,15} This latter technique has been defined by some authors as the "true" flap technique.¹⁴ Perfluorocarbon liquids and viscoelastic devices have been also used to stabilize and flatten this single-layered flap.^{14,16,17}

Evidence on the use of the inverted flap technique for the treatment of small- and medium-size FTMHs is quite limited,^{16,18} with no randomized trials comparing this technique with conventional ILM peeling.

We decided to primarily focus on microperimetry because this would provide a better functional assessment after the two different peeling techniques. In addition, reliability of microperimetry in small-to-medium macular holes is likely to be more reliable and accurate than in large macular holes given that smaller holes have more chance to obtain an excellent visual outcome after surgery.⁸

The inverted flap technique performed in our trial is similar to the original inverted flap described by Michalewska et al.² Our technique involved the creation of an ILM flap that was left attached to the macular hole edges; this flap was trimmed, inverted, and left to cover the macular hole. However, our technique did not involve an insertion of the flap inside the hole; no attempt was made to place the flap inside the hole by the use of forceps.

Our findings showed a higher macular sensitivity at 6 and 12 months in eyes treated with conventional ILM peeling. Visual outcome was comparable between the two groups at each follow-up visit, even if a trend of better visual gain was demonstrated in eyes treated with conventional ILM peeling.

Very recently, Baumann et al¹⁸ and Chou et al¹⁶ published the results of their retrospective studies that compared conventional ILM peeling versus inverted flap technique in eyes with a $\leq 400 \mu\text{m}$ FTMH.

Baumann et al¹⁸ included 36 eyes treated with conventional ILM peeling and 24 eyes treated with the inverted flap technique, considering a 12-month follow-up. Baumann's inverted flap technique seems very similar to the one we performed in our trial. A flap of ILM was left attached to hole margin and inverted to cover the hole. Their study failed to demonstrate a difference in visual outcome between conventional ILM peeling and the inverted flap technique at each follow-up visit (3, 6 and 12 months).¹⁸ This is in agreement with our results.

Chou et al¹⁶ included 55 eyes in the conventional ILM peeling group and 62 eyes in the inverted flap group. A 12-month follow-up was considered. The authors performed a single-layered inverted flap technique. The flap was stabilized and flattened using a subperfluorocarbon liquid and a viscoelastic device. The former one was then removed, whereas the viscoelastic one was left in place at the end for the surgery.

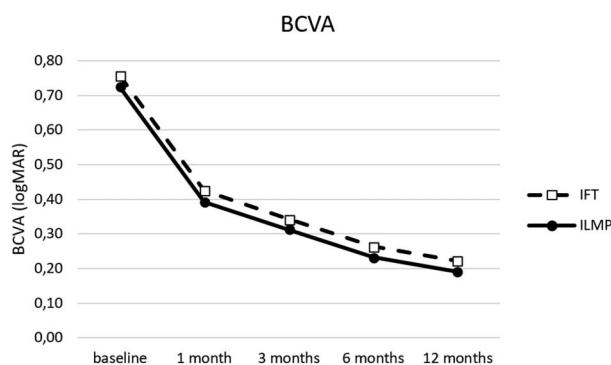


Fig. 3. Best-corrected visual acuity (BCVA) change in the inverted flap group (IFT) and conventional internal limiting membrane peeling group (ILMP) throughout the follow-up.

The authors found a similar closure rate between the conventional ILM peeling group and the inverted flap group (97% vs. 98%, respectively). Interestingly, Chou et al¹⁶ found a greater visual gain in eyes treated with the inverted flap technique at 1, 3, and 6 months postoperatively, whereas at 12 months visual gain was comparable with conventional ILM peeling. The authors speculated that the inverted flap technique allowed a faster functional recovery.

Regarding OCT parameters, our trial showed that final rates of ELM and EZ recovery and U-shape foveal contour were slightly higher in the conventional ILM peeling group. However, these findings did not reach statistical significance. Baumann et al¹⁸ did not find any difference in EZ and ELM recovery between conventional ILM peeling and the inverted flap technique. Chou et al¹⁶ reported an earlier restoration of ELM in the inverted flap group compared with conventional ILM peeling: the rate of ELM restoration was higher in the inverted flap group at 1 and 3 months, whereas this was comparable between the two groups at 12 months.

A possible explanation why functional and anatomical findings of Chou et al¹⁶ are not in line with those reported in the present trial and in Baumann's study,¹⁸ could be related to the surgical technique of inverted flap. The inverted flap technique adopted by us and by Baumann et al¹⁸ involved the creation of an ILM flap

attached to hole margins that was trimmed and inverted to cover the hole, but not to fill it. However, it is possible to speculate that because the flap consists of multiple layers, some parts of the flap might have moved, in some cases, below the minimum aperture of the hole. This could be comparable to a sort of insertion of the flap inside the hole, even if no specific attempt was made to insert the flap inside the hole. A true insertion technique involves the filling of the hole with an ILM flap that is placed inside the hole using intraocular forceps.¹⁹ The ILM insertion technique has been shown to provide worse functional outcomes in large macular hole compared with single-layered ILM flap.^{7,19} Park et al¹⁹ demonstrated a worse visual outcome in eyes treated with ILM insertion compared with single-layered inverted flap. In addition, no case of postoperative recovery of ELM and EZ was observed in the inserting flap group.¹⁹ Iwasaki et al⁷ compared conventional ILM peeling with inverted flap technique in large macular hole. Their inverted flap technique included a covering technique or a true inserting technique. A better ELM and EZ recovery was shown in the conventional ILM peeling group. In the inverted flap group, a 50% rate of ELM recovery was found in eyes treated with a covering technique, whereas no case of ELM recovery was observed in eyes treated with a filling technique.⁷

On this basis, it could be supposed that a migration of some parts of the flap below the minimum aperture of the hole may affect negatively, functional outcomes resembling an insertion technique.

The following limitations affected the present study. First, this trial was conducted in a single institution and all surgeries were performed by the same vitreoretinal consultant. On the one hand, broad conclusions cannot be drawn. However, a possible bias related to the involvement of multiple surgeons and assessors has been avoided. Second, the sample size calculation was based on microperimetry outcomes. Consequently, this study could not be powered enough to show a difference in visual outcome and/or in structural OCT findings between the two surgical techniques. It cannot

Table 2. Optical Coherence Tomography Findings Following Inverted Flap Technique and Conventional Peeling

		1 month	3 months	6 months	12 months	Q Cochran	IFT Versus ILMP
							P (Fisher's Exact Test)
ELM recovery	IFT (n = 25)	14 (56%)	16 (64%)	18 (72%)	19 (76%) ^a	0.015	1 month: 0.773;
	ILMP (n = 25)	16 (64%)	20 (80%)	22 (88%) ^b	23 (92%) ^c	0.002	12 months: 0.247
EZ recovery	IFT (n = 25)	8 (32%)	10 (40%)	11 (44%)	13 (52%) ^b	0.021	1 month: 1.000;
	ILMP (n = 25)	9 (36%)	12 (48%)	16 (64%) ^d	18 (72%) ^e	<0.001	12 months: 0.244
U-shape contour	IFT (n = 25)	17 (68%)	17 (68%)	18 (72%)	19 (76%)	0.194	1 month: 0.520;
	ILMP (n = 25)	20 (80%)	20 (80%)	22 (88%)	24 (96%)	0.053	12 months: 0.098

Pairwise comparison versus baseline; ^aP = 0.018, ^bP = 0.013, ^cP = 0.002, ^dP = 0.012, ^eP < 0.001.

EZ, ellipsoid zone; IFT, inverted flap technique; ILMP, internal limiting membrane peeling.

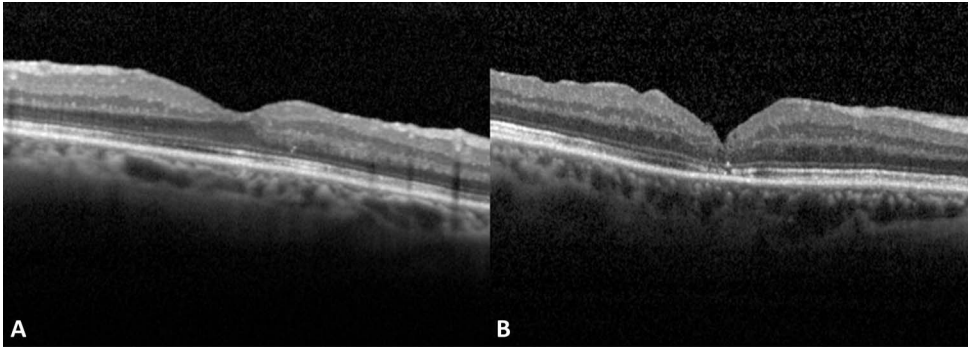


Fig. 4. A. An OCT scan showing a case with a U-shape foveal contour at 12 months in the conventional internal limiting membrane peeling group; **(B)** an OCT scan showing a case with a non-U-shape foveal contour at 12 months in the inverted flap technique group.

be excluded that a larger sample size could have shown a difference between the two techniques regarding visual outcome and/or OCT findings. Larger randomized trials aimed at investigating visual outcome and structural OCT parameters are needed.

In conclusion, conventional ILM peeling provided better functional outcomes in macular sensitivity compared with the inverted flap technique, with no difference in visual gain. These findings support the choice of conventional ILM peeling for the treatment of small-to-medium idiopathic macular holes rather than traditional inverted flap technique. Further randomized trials are needed to investigate whether a single-layered inverted flap technique may provide better outcomes in small-to-medium idiopathic macular holes.

Key words: idiopathic macular hole, internal limiting membrane peeling, inverted flap technique, microperimetry, vitrectomy.

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