황반원공 환자에서 상측 역위 내경계막절편술과 내경계막박리술의 장기간 비교

Long-term Comparison of Superior Inverted Internal Limiting Membrane Flap Creation and Internal Limiting Membrane Peeling for Macular Hole Closure

김희원, 김양재, 문다루치, 김시열

Hee Weon Kim, Yang Jae Kim, Daruchi Moon, Si Yeol Kim

대구누네안과병원

Nune Eye Hospital, Daegu, Korea

Purpose: To compare the long-term surgical results of the superior inverted internal limiting membrane (ILM) flap creation and ILM peeling for the treatment of macular hole (MH).

Methods: In this retrospective, comparative study, 36 eyes of 36 patients with macular holes were treated by pars plana vitrectomy with the superior inverted ILM flap technique (FLAP group), while 37 eyes of 37 patients were treated with the ILM peeling technique (PEEL group). Pre- and postoperative best-corrected visual acuity (BCVA), central foveal thickness (CFT), and recurrence rates were analyzed.

Results: At two years after surgery, BCVAs (logarithm of the minimal angle of resolution) were 0.13 ± 0.19 and 0.17 ± 0.30 ($p = 0.368$) and the CFT measured $181.22 \pm 59.24 \mu\text{m}$ and $174.44 \pm 65.92 \mu\text{m}$ in the FLAP group and PEEL group, respectively ($p = 0.715$). Recurrence of MH was observed in three cases in the FLAP group and one case in the PEEL group ($p = 0.615$). No statistically significant risk factors associated with recurrence were found.

Conclusions: The superior inverted ILM flap technique and ILM peeling technique both ensured good anatomical and functional outcomes at two years after surgery. The superior inverted ILM flap technique led to a higher recurrence rate than the ILM peeling technique at two years after surgery, but without statistical significance.

Keywords: Inverted internal limiting membrane flap; Internal limiting membrane peeling; Macular hole; Superior inverted internal limiting membrane flap

Introduction

Since Kelly and Wendel [1] first reported the successful clo-

sure of idiopathic macular holes (MH) by vitrectomy with gas tamponade, the surgical success rate has improved with further modifications such as internal limiting membrane (ILM) peeling introduced during subsequent procedures [2-4].

Address reprint requests to Si Yeol Kim, MD, PhD

Nune Eye Hospital, #2179 Dalgubeol-daero, Jung-gu, Daegu 41940, Korea
Tel: 82-53-715-3300, Fax: 82-53-715-3443
E-mail: kimsy49@gmail.com

Received: 2020. 10. 14.

Revised: 2021. 1. 21.

Accepted: 2021. 2. 15.

An important factor influencing postoperative functional and anatomic results is the MH diameter. Although advances in surgical techniques and diagnostic tools have improved the anatomical outcomes of MH surgery, postoperative visual recovery is usually limited, especially in patients with large MHs. Studies of conventional vitrectomy with ILM peeling noted that the best postoperative functional outcomes were associated with a U-shaped closure approach, which is similar to the normal foveal shape and present in 45% of cases on postoperative optical coherence tomography (OCT). Flat MH margins with bare retinal pigment epithelium, which are generally associated with worse functional results than other closure types, were observed postoperatively in 19% to 39% of stage 3 and 4 full-thickness MHs [5-7].

Recently, various surgical strategies, such as the inverted ILM flap technique, have been introduced to improve postoperative outcomes for patients with large MHs [8-11]. In a prospective randomized study, a closure rate of 98% was achieved when the inverted ILM flap technique was performed as compared with the 88% closure rate attained with conventional vitrectomy and ILM peeling [8]. Also, the results of temporal inverted ILM flap creation were as effective as those of classic inverted ILM flap creation for the repair of large stage 4 MHs with a less dissociated optic nerve fiber layer [11].

Many variations of the ILM technique have been reported over the years, and the superior inverted ILM flap technique has also been introduced [12], which ensures that the possibility of ILM flap slippage due to gravity is reduced relative to with the temporal inverted ILM flap technique. Later, several reports comparing the superior ILM flap technique and ILM peeling technique were published [13,14], but these were only short-term comparison studies of 6 to 12 months in duration. The aim of this study is therefore to compare long-term surgical results of more than two years between patients undergoing superior ILM flap creation or ILM peeling.

Materials and Methods

This retrospective and comparative study followed the principles of the Declaration of Helsinki and was approved by the Institutional Review Board of the participating hospital (IRB no. N-200515-02). We reviewed the medical records of consecutive patients who had MH and who were treated

by 23-gauge pars plana vitrectomy (PPV) with the superior inverted ILM flap technique or ILM peeling technique between March 1, 2015 and March 31, 2020. The surgery of choice was performed by one of four surgeons in each case, and the operation method was chosen according to each individual's preference. C3F8 gas tamponade was used in all cases. As is the clinical standard, all patients underwent a complete ophthalmic evaluation preoperatively, which included best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, intraocular pressure measurement, slit-lamp examination, fundus examination with fundus photography, and spectral-domain OCT (Spectralis HRA+OCT; Heidelberg Engineering, Heidelberg, Germany). MH closure was defined as the absence of a neurosensory defect over the fovea.

The information collected retrospectively from each of the patient medical records included age, sex, axial length, preoperative lens status, preoperative and postoperative BCVAs, the base diameter of the MH, central foveal thickness, successful MH closure rate, recurrence rate, and any intraoperative and postoperative complications.

The study inclusion criteria were as follows: 1) clinical presentation of full-thickness MH with or without retinal detachment, 2) treatment with conventional 23-gauge three-port PPV with superior inverted ILM flap creation or ILM peeling, and 3) follow-up data for at least two years from the date of surgery. Conversely, the study exclusion criteria were as follows: 1) preexisting ocular diseases or a history of ocular surgery, except for cataract surgery and 2) use of air tamponade, sulfur hexafluoride (SF₆) gas tamponade, or silicone oil tamponade in the primary surgery. The study group included 36 eyes of 36 patients treated with the superior inverted flap technique (FLAP group) and 37 eyes of 37 patients treated using the conventional ILM peeling technique (PEEL group).

All eyes included in this study were treated with a 23-gauge vitrectomy system, a wide-angle viewing system, and a binocular indirect ophthalmomicroscope. A posterior vitreous detachment was first created, followed by the removal of the residual thin premacular posterior cortex. The peripheral vitreous was also excised. Then, triamcinolone acetonide was deployed intraoperatively to facilitate visualization of the vitreous and posterior hyaloids in all eyes. If an epiretinal membrane (ERM) was present, it was peeled. The ILM was stained by an injection of 0.05% indocyanine

green (ICG) into the vitreous cavity over the macula area, followed by an immediate lavage. In the FLAP group, ILM forceps were used to grasp and peel the ILM off at the superior side of the MH. During this peeling action, the ILM was not removed completely from the retina but instead was left attached to the superior edge of the MH, then inverted and gently coaxed over the MH until adequate coverage was achieved. The size of the ILM flap was created to be threefold the diameter of the optic disc in width and twofold the diameter of the optic disc in length (Fig. 1). In the PEEL group, the whole ILM was peeled within the vascular arcade. Following fluid-air exchange, the air was replaced with 14% C3F8 gas. Patients were instructed to spend seven days in the prone position.

During follow-up visits at two years postoperatively, all patients underwent visual acuity measurement, slit-lamp examination, indirect ophthalmoscopy, and OCT imaging. The BCVA was recorded in decimal acuity and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses.

For statistical analysis, the Statistical Package for the Social Sciences version 23.0 for Windows (IBM Corp., Armonk, NY, USA) was used. An independent *t*-test was used for comparisons between the two groups, while a paired *t*-test was used to assess the visual and structural changes in MH within groups. Binary logistic regression analysis was used to analyze the prognostic factors affecting the recurrence rate. A *p*-value of less than 0.05 was judged to be statistically significant.

Results

In this study, 36 eyes of 36 patients subjected to superior inverted ILM flap creation and 37 eyes of 37 patients subjected to ILM peeling were enrolled. In total, the mean age of the patients ($n = 30$ men and $n = 43$ women) was 61.63 ± 5.71 years (range: 52-78 years), the mean axial length was 24.57 ± 9.16 mm (range: 21.51-30.56 mm), and the mean preoperative BCVA (logMAR) was 0.79 ± 0.28 (range: 0.40-2.00). Eleven eyes were pseudophakic and 62 eyes were phakic. Phacoemulsification was performed on 62 phakic eyes prior to PPV, including 30 eyes of the FLAP group and 32 eyes of the PEEL group, with all of these eyes undergoing intraocular lens implantation. The mean value of the base MH di-

Figure 1. The intraoperative view and schematic drawing of the creation of a superior inverted limiting membrane internal limiting membrane (ILM) flap. (A) The ILM was peeled by more than a two-fold diameter distance from the superior edge of the macular hole (MH). (B) The ILM flap was inverted in the inferior direction to fully cover the MH. (C) Overall diagrammatic representation of the superior inverted ILM flap technique.

ameter was 658.84 ± 251.62 μm (range: 204-1,301 μm). Four cases in the FLAP group and four cases in the PEEL group had MHs with diameters of less than 400 μm , while seven cases in the FLAP group and 11 cases in the PEEL group had MHs with diameters of greater than 800 μm . No intraoperative or postoperative complications related to the surgery were noted in both groups. Detailed patient characteristics are presented in Table 1; the general characteristics of study participants exhibited no statistically significant differences between the two groups.

At two years after surgery, the BCVAs were 0.13 ± 0.19 in the FLAP group and 0.17 ± 0.30 in the PEEL group, respectively, and the mean BCVA improvement was statistically significant in both groups ($p < 0.001$ and $p < 0.001$, respectively, paired *t*-test) (Table 2). The CFT at two years showed no statistically significant difference between these two groups. Fig. 2 and 3 demonstrate anatomical changes that may occur in the MH following surgery with the superior

Table 1. General characteristics of study participants

	Superior inverted ILM flap technique group (n = 36 eyes)	ILM peeling technique group (n = 37 eyes)	p-value*
Age (years)	61.76 ± 6.26	61.50 ± 5.17	0.239
Sex (male:female)	15:21	15:22	0.848
Axial length (mm)	24.53 ± 8.85	24.98 ± 11.40	0.258
Cataract co-operation	30 (83)	32 (86)	0.063
BCVA (logMAR)	0.74 ± 0.26	0.83 ± 0.29	0.231
Base diameter of the MH (μm)	628.03 ± 235.92	690.50 ± 266.39	0.230

Values are presented as mean ± standard deviation or number (%).

ILM = internal limiting membrane; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution; MH = macular hole.

*Independent-samples *t*-test.

Table 2. Comparison of postoperative anatomical and functional outcomes between the superior ILM flap creation group and ILM peeling group at two years

	Superior inverted ILM flap technique group (n = 36 eyes)	ILM peeling technique group (n = 37 eyes)	p-value
BCVA (logMAR)			
Preoperative	0.74 ± 0.26	0.83 ± 0.29	0.231*
Postoperative	0.13 ± 0.19	0.17 ± 0.30	0.368*
p-value†	< 0.001	< 0.001	
Central foveal thickness (μm)	181.22 ± 59.24	174.44 ± 65.92	0.715*
Recurrence	3 (8.33)	1 (2.70)	0.615‡

Values are presented as mean ± standard deviation or number (%).

ILM = internal limiting membrane; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution.

*Independent-samples *t*-test; †Paired *t*-test; ‡Fisher's exact test.

inverted ILM flap technique and the ILM peeling technique, respectively.

The recurrence rate was 8.33% (n = 3/36) and 2.70% (n = 1/37) in eyes in the FLAP group and the PEEL group, respectively (*p* = 0.615) (Table 2). The mean MH diameters among recurred cases in the FLAP group and PEEL group were 1,022 μm and 973.00 ± 107.36 μm, respectively. The mean period of recurrence was 10.33 ± 7.23 months (range: 2-15 months) in the FLAP group and two months in the PEEL group. In all cases of recurrence, PPV with ILM peeling was performed. Anatomical MH closure was achieved in all three recurrent cases of the FLAP group; however, an open hole persistent in the one recurrent case in the PEEL group remained.

A binary logistic regression analysis was performed for the prognostic factors correlated with the recurrence of the MH. The surgical technique, sex, age, axial length, presence

of cataract co-operation, preoperative BCVA, and preoperative base MH diameter were set as independent variables and analyzed. As a result, there were no statistically significant factors associated with the recurrence rate (Table 3).

Discussion

Since the initial success rate of MH surgery by vitrectomy was reported as 68% [1], closure rates of MH have improved to 90% to 98% when using the ILM staining technique [15,16]. For the repair of full-thickness MH, ILM peeling can be a method of choice but has also been linked to a dissociated optic nerve fiber layer [17-20]. Recently, Michalewska et al. [8] reported that the inverted ILM flap technique successfully improved the closure rate (98%) and visual acuity relative to outcomes attained using the conventional ILM peel-

Figure 2. Anatomical changes in the macular hole (MH) after surgery using the superior inverted internal limiting membrane flap technique in a 65-year-old woman (axial length = 23.42 mm). (A) Preoperative fundus photograph and spectral-domain optical coherence tomography show the MH, which had a base diameter of 892 μm . (B) At two years after surgery, the MH had recovered well and the measured central foveal thickness was 256 μm . Also, the best-corrected visual acuity (logMAR) had improved from 0.52 to 0.10.

Figure 3. The anatomical changes in the macular hole (MH) after surgery using the internal limiting membrane peeling technique in a 71-year-old man (axial length = 24.82 mm). (A) Preoperative fundus photograph and spectral-domain optical coherence tomography show the MH, which had a base diameter of 776 μm . (B) At two years after surgery, the MH had recovered well, and the measured central foveal thickness was 224 μm . Also, the best-corrected visual acuity (logMAR) had improved from 0.40 to 0.15.

Table 3. Association of recurrence rate with demographic and clinical variables by binary logistic regression analysis

Variable	OR	95% CI	<i>p</i> -value*
Surgical technique	0.526	0.012-23.757	0.741
Sex	0.419	0.013-13.724	0.625
Age	0.539	0.050-5.839	0.611
Axial length	1.352	0.764-2.390	0.300
Cataract co-operation	61.683	0.256-14837.085	0.141
BCVA (logMAR)	1.164	0.641-2.113	0.619
Base diameter of the MH (μm)	2.378	0.233-24.229	0.464

OR = odds ratio; CI = confidence interval; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimal angle of resolution; MH = macular hole.

*Binary logistic regression analysis.

ing procedure. Moreover, after Choi et al. [12] first reported on the superior inverted ILM flap technique for the treatment of MH, Ghassemi et al. [14] found that the superior inverted

ILM flap technique also showed good surgical results similar to those of the temporal inverted ILM flap technique, although the surgical success rate was higher (100%).

The hypothesis of the closure of an MH the inverted ILM flap technique is that the ILM may act as a scaffold for glial cells to proliferate, thus enhancing closure of the MH. Another explanation might be that ILM provides a barrier to disable the entrance of fluid from the vitreous cavity to the MH. In addition, once a vacuum is created inside the MH closed by the flap, the retinal pigment epithelium outflow is changed [11].

In this study, the superior inverted ILM flap technique and the ILM peeling technique both achieved good postoperative visual outcomes at two years after surgery and no statistical difference was found between these two techniques. Moreover, although the superior inverted ILM flap technique led to a higher MH recurrence rate at two years after surgery, there was no statistically significant difference between the techniques.

We consider the causes of the higher recurrence rate in the

superior inverted ILM flap technique group to be as follows: 1) the horizontal traction remaining at the edge of the flap may trigger a recurrence of the MH and 2) ERM remaining around the macula may cause greater tractional force, relative to ILM peeling, which can completely remove the ERM together with the ILM.

There are some limitations in this study. The enrolled number of patients was small, so detailed analysis focusing on such parameters as the size of MH and the presence of high myopia was difficult. In addition, since the cases with and without co-occurring cataract surgery were mixed, the evaluation of changes in visual acuity between the two techniques is limited. However, the percentage of cataract surgery cases was not statistically different between the technique groups, so the findings seem to be reliable to some extent. Also, as there were four surgeons involved in this research and the choice of the surgical method was based on their individual judgment, a bias may exist. Accordingly, there could be a difference in the average MH diameter between the two groups, although there was no statistical significance observed. When analyzing only cases with an MH diameter of more than 800 μm , the recurrence rates were 9.09% (1/11 cases) in the PEEL group and 43.86% (3/7 cases) in the FLAP group and, thus, not statistically significant ($p = 0.245$, Fisher's exact test).

Although there was no statistical significance between the technique groups in the surgical outcomes, it is important to keep in mind that, per our study, the superior inverted ILM flap technique may lead to more complications, such as MH recurrence, during long-term follow-up. Therefore, it is expected that valuable results can be derived if large-scale, long-term studies involving more cases were to be conducted in the future. In addition, it is also expected that a study on the size of the ILM flap, which dictates postoperative safety, is also necessary.

In conclusion, MHs were successfully closed using both the superior inverted ILM flap technique and the ILM peeling technique. The anatomical and functional results of those techniques are promising, even though each technique has its unique pros and cons. It is important to select the appropriate technique according to the characteristics of individual surgical cases. In this respect, it will be beneficial to conduct a well-controlled large-scale study to establish guidelines for which technique is most appropriate according to the surgical case.

Conflicts of Interest

The authors declare no conflicts of interest relevant to this article.

References

1. Kelly NE, Wendel RT. Vitreous surgery for idiopathic macular holes. Results of a pilot study. *Arch Ophthalmol* 1991;109:654-9.
2. Christensen UC, Krøyer K, Sander B, et al. Value of internal limiting membrane peeling in surgery for idiopathic macular hole stage 2 and 3: a randomised clinical trial. *Br J Ophthalmol* 2009;93:1005-15.
3. Ternent L, Vale L, Boachie C, et al. Cost-effectiveness of internal limiting membrane peeling versus no peeling for patients with an idiopathic full-thickness macular hole: results from a randomised controlled trial. *Br J Ophthalmol* 2012;96:438-43.
4. Spiteri Cornish K, Lois N, Scott NW, et al. Vitrectomy with internal limiting membrane peeling versus no peeling for idiopathic full-thickness macular hole. *Ophthalmology* 2014;121:649-55.
5. Imai M, Iijima H, Gotoh T, Tsukahara S. Optical coherence tomography of successfully repaired idiopathic macular holes. *Am J Ophthalmol* 1999;128:621-7.
6. Michalewska Z, Michalewski J, Nawrocki J. Diagnosis and evaluation of macular hole with the HRT 2 retina module. *Ophthalmology* 2007;114:881-8.
7. Michalewska Z, Michalewski J, Cisiecki S, et al. Correlation between foveal structure and visual outcome following macular hole surgery: a spectral optical coherence tomography study. *Graefes Arch Clin Exp Ophthalmol* 2008;246:823-30.
8. Michalewska Z, Michalewski J, Adelman RA, Nawrocki J. Inverted internal limiting membrane flap technique for large macular holes. *Ophthalmology* 2010;117:2018-25.
9. Mahalingam P, Sambhav K. Surgical outcomes of inverted internal limiting membrane flap technique for large macular hole. *Indian J Ophthalmol* 2013;61:601-3.
10. Kuriyama S, Hayashi H, Jingami Y, et al. Efficacy of inverted internal limiting membrane flap technique for the treatment of macular hole in high myopia. *Am J Ophthalmol* 2013;156:125-31. e1.
11. Michalewska Z, Michalewski J, Dulczewska-Cichecka K, et al. Temporal inverted internal limiting membrane flap technique versus classic inverted internal limiting membrane flap technique: a comparative study. *Retina* 2015;35:1844-50.
12. Choi SR, Kang JW, Jeon JH, et al. The efficacy of superior invert-

- ed internal limiting membrane flap technique for the treatment of full-thickness macular hole. *Retina* 2018;38:192-7.
13. Kannan NB, Kohli P, Parida H, et al. Comparative study of inverted internal limiting membrane (ILM) flap and ILM peeling technique in large macular holes: a randomized-control trial. *BMC Ophthalmol* 2018;18:177.
14. Ghassemi F, Khojasteh H, Khodabande A, et al. Comparison of three different techniques of inverted internal limiting membrane flap in treatment of large idiopathic full-thickness macular hole. *Clin Ophthalmol* 2019;13:2599-606.
15. Ando F, Sasano K, Ohba N, et al. Anatomic and visual outcomes after indocyanine green-assisted peeling of the retinal internal limiting membrane in idiopathic macular hole surgery. *Am J Ophthalmol* 2004;137:609-14.
16. Beutel J, Dahmen G, Ziegler A, Hoerauf H. Internal limiting membrane peeling with indocyanine green or trypan blue in macular hole surgery: a randomized trial. *Arch Ophthalmol* 2007;125:326-32.
17. Tadayoni R, Paques M, Massin P, et al. Dissociated optic nerve fiber layer appearance of the fundus after idiopathic epiretinal membrane removal. *Ophthalmology* 2001;108:2279-83.
18. Ito Y, Terasaki H, Takahashi A, et al. Dissociated optic nerve fiber layer appearance after internal limiting membrane peeling for idiopathic macular holes. *Ophthalmology* 2005;112:1415-20.
19. Mitamura Y, Ohtsuka K. Relationship of dissociated optic nerve fiber layer appearance to internal limiting membrane peeling. *Ophthalmology* 2005;112:1766-70.
20. Spaide RF. "Dissociated optic nerve fiber layer appearance" after internal limiting membrane removal is inner retinal dimpling. *Retina* 2012;32:1719-26.