

Clinical outcomes with large macular holes using the tiled transplantation internal limiting membrane pedicle flap technique

Li-Ping Wang, Wen-Tao Sun, Chun-Ling Lei, Jin Deng

Department of Ophthalmology, Shaanxi Ophthalmic Medical Center, Xi'an Fourth Hospital, Affiliated Guangren Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China

Co-first authors: Li-Ping Wang and Wen-Tao Sun.

Correspondence to: Wen-Tao Sun. Department of Ophthalmology, Shaanxi Ophthalmic Medical Center, Xi'an Fourth Hospital, Affiliated Guangren Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an 710004, Shaanxi Province, China. 245135237@qq.com

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Abstract

• **AIM:** To report the surgical technique and efficacy of the tiled transplantation internal limiting membrane (ILM) pedicle flap technique after vitrectomy for 33 patients with large macular hole (MH).

• **METHODS:** This study was a prospective noncontrolled interventional study. All patients were treated by vitrectomy, the tiled transplantation ILM pedicle flap and gas tamponade. All patients underwent visual acuity measurements and optical coherence tomography (OCT), during preoperative and the follow-up visits postoperative.

• **RESULTS:** Two high-myopic patient had flap dislocation during surgery. The thorough closure of MH following the tiled transplantation ILM pedicle flap technique was ultimately achieved in 31 patients observed by OCT imaging (93.94%) 1wk after surgery. Visual acuity improved from 1.51 ± 0.31 (logMAR) preoperative to 0.92 ± 0.30 6mo after surgery ($P=0.000$). There were no significant changes in OCT finding during the follow-up period from 1mo to 6mo after surgery.

• **CONCLUSION:** The tiled transplantation ILM pedicle flap technique provides bridge for retinal gliosis to achieve successful closures of the large MHs, and the microenvironment of this technique is more similar to the normal physiological conditions.

• **KEYWORDS:** tiled transplantation ILM pedicle flap; macular hole; vitrectomy

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INTRODUCTION

Macular hole (MH) is the full thickness defect of the retinal neuroepithelium in the macular fovea leading to the loss of central vision^[1]. Vitrectomy, internal limiting membrane (ILM) peeling, and gas tamponade is a well-established method for the treatment of idiopathic MHs. Despite ILM removal, surgical closure of large MH remains challenging. There were many methods for treating large MHs have been reported, such as inverted ILM flap technique, using whole blood as an adhesive to aid in the fixation of an autologous neurosensory retinal free flap^[2], the transplantation of lens capsular flap and the autologous serum application^[3], and so on. Michalewska *et al*^[4] first reported the inverted ILM flap technique can improve the postoperative visual acuity and the closure rate (98%) of MHs larger than 400 μm in diameter^[5]. The closure rate of myopic MHs was 80% using this technique was reported by Kuriyama *et al*^[6]. Michalewska *et al*^[4,7] also reported that this technology stimulated the glial cells proliferation, establishing bridges between retinal tissue defects in the holes.

If the inverted ILM flap can play a role as a bridge to promote proliferation of glial cells, then we speculate that the tiled transplantation ILM pedicle flap can play the same role. In our clinical report, we describe the clinical effects of tiled transplantation ILM pedicle flap technique in the treatment of large MHs (diameter greater than 400 μm) including idiopathic, in myopic eyes and traumatic MHs.

SUBJECTS AND METHODS

Ethical Approval This study is a prospective noncontrolled interventional study conducted at the Xi'an No.4 Hospital, Xi'an, China. Institute Ethics Committee approval was obtained. The study followed the principles of the Declaration of Helsinki. Each patient was informed about the risks and benefits of the surgery and their written informed consent was obtained.

We analyzed the medical records of patients using pars plana vitrectomy (PPV) and the tiled transplantation ILM pedicle flap technique for the treatment of large MHs in the Xi'an

No.4 Hospital, between September 2016 and May 2018. The inclusion criteria were as follows: minimum diameter of MH \geq 400 μ m; clinical presentation of MH without retinal detachment (RD); intraocular pressure (IOP) <21 mm Hg. Exclusion criteria were a history of RD or proliferative vitreoretinopathy, any kind of retinal surgery, vitreous hemorrhage, optic atrophy, ocular tumors, and glaucoma.

All patients underwent a comprehensive ophthalmological examination before and after surgery, including determining the best corrected visual acuity (BCVA; recorded in snellen visual acuity ratios and was converted to logMAR units for statistical analysis), axial length (Master), IOP (Auto-tonometer TX-20, Canon, Tokyo, Japan), and the posterior segment biomicroscopy using a 90 diopter (D) lens on a slit lamp. The anatomic status of MH preoperative and postoperative were checked using optical coherence tomography (OCT; Spectralis HRA+OCT, Heidelberg, Germany). At least 6mo follow-up period was required after the surgery.

Surgical Procedure A standard 23-gauge PPV (Constellation Vision System, Alcon Laboratories, Inc., Fort Worth, TX, USA) with the tiled transplantation ILM pedicle flap technique was performed in all patients by a single experienced surgeon. Separate vitrectomy was performed in eyes without cataracts and pseudophakic eyes, and phacoemulsification (PEA) with intraocular lens (IOL) implantation were performed in cataract eyes additionally. After a core vitrectomy, posterior vitreous detachment was created assisted by triamcinolone acetonide, followed by removal of the residual posterior vitreous cortex. In order to more clearly visibility, the ILM was stained with a 0.125% solution of indocyanine green (ICG), as described by Shah *et al*^[8]. After that, the ILM was grasped and peeled off in a circumferential pattern for about 2-3 disk diameter around the MH using ILM forceps, leaving a pedunculated ILM flap. Then, the ILM flap was gently peeled off along the edge of the circle, and the width of flap should be larger than or equal to the MH diameter. Then the ILM pedicle flap was tiled over the MH, and was carefully flattened to make sure it was properly positioned. The sodium chondroitin sulfate-sodium hyaluronate (Alcon corporation, Inc., Fort Worth, TX, USA) was placed on the pedicle flap to stabilize it when needed (Figure 1).

To avoid the ILM flap being washed away, we need gentle operation and the lowest level of perfusion pressure (30 cm H₂O) that the vitrectomy machine allowed during the air-fluid exchange. In all patients, the sterilized air was filled in the vitreous cavity to secure the position of the ILM flap. Each patient was required to remain face down for at least 7d postoperatively. All patients underwent IOP, visual acuity measurements, slit-lamp examinations, OCT and indirect ophthalmoscopy assessments, during the follow-up period at 1d, 1wk and at 1, 3, 6mo postoperatively.

Statistical analysis was performed by SPSS 25.0 for windows (SPSS, Inc., Chicago, IL, USA). Numerical variables were presented as mean \pm standard deviation (SD). BCVAs at different time points (baseline, 1 and 6mo after surgery) were compared pair wisely by post-hoc tests after analysis of repeated measures ANOVA using general linear model. A value of $P<0.05$ was considered to be statistically significant.

RESULTS

In all, 24 women (72.7%) and 9 men (27.3%) were included in our study. The age of patients ranged from 19 to 71y (mean 56.82 \pm 10.72y). This study involved 19 right eyes and 14 left eyes. At least 6mo follow-up period was required after the surgery. All the 33 patients displayed large MHs, including one traumatic MH, nine high-myopic MHs, and twenty-three idiopathic MHs. The preoperative visual acuity in the affected eye ranged from 20/2000 to 20/200. The shape of some holes approximately resemble truncated cone. In these eyes the minor diameter (D) of MHs ranged from 429 to 767 μ m with a mean of 602 μ m. The major D of MHs ranged from 765 to 1573 μ m with a mean of 1189 μ m. The axial length of all patients ranged from 20.97 to 30.15 mm (mean 23.94 \pm 2.75 mm). The axial length of high-myopic patients ranged from 25.95 to 30.15 mm (mean 28.10 \pm 1.42 mm). Fourteen patients received PPV, PEA and IOL implantation, while eight patients previously had pseudophakic eyes preoperative, and eleven patients retained the transparent lens in the surgery. Surgeon stained the ILM with a 0.125% solution of ICG in all patients. Of 31 patients underwent successful tiled transplantation ILM pedicle flap. Two high-myopic patients had flap dislocation during surgery. No surgical complications were found in all patients.

Complete closure (defined as no neurosensory defect at the fovea on OCT) was observed in 21 eyes three days after surgery. The complete closure was observed in 31 eyes three days to seven days after surgery. The complete closure of MH was ultimately brought about in 31 patients examined by OCT imaging (93.94%) by 1wk postoperative. Visual acuity improved from 1.51 \pm 0.31 logMAR (range: 20/2000-20/200; median Snellen acuity: 20/500) preoperatively to 0.99 \pm 0.32 logMAR (range: 20/1000-20/50; median Snellen acuity: 20/160) 1mo after surgery ($P=0.000$), and to 0.92 \pm 0.30 logMAR (range: 20/500-20/40; median Snellen acuity: 20/160) 6mo after surgery ($P=0.000$). There was no significant difference in visual acuity between 1mo after surgery and 6mo after surgery ($P=0.544$; Figure 2).

In our study, there were two closure types of MHs such as U-type (Figure 3B) and V-type (Figure 3D, 3F) in nineteen eyes and fourteen eyes, respectively. Linear configuration analogous to transplanted ILM tissues were detected in ten eyes determined by OCT 1mo after the surgery. There were no significant changes in OCT finding during the follow-up period from 1 to 6mo after surgery.

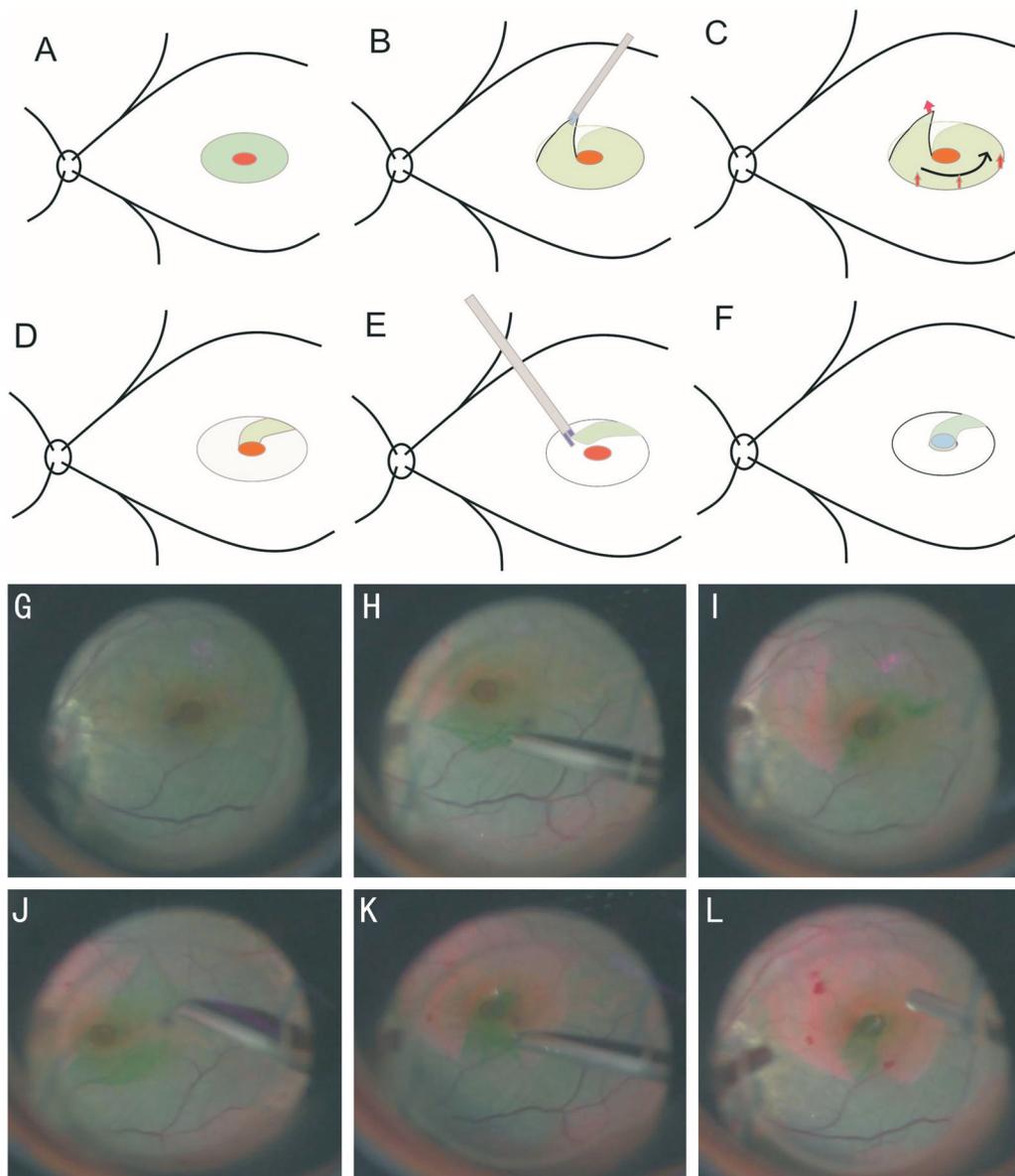


Figure 1 Diagrammatic representation of the tiled transplantation ILM pedicle flap technique and surgical video screenshot of one patient’s left eye A, G: We stained the ILM with a 0.125% solution of ICG; B-D and H-K: The ILM was grasped and peeled off in a circumferential pattern for about 2-3 disk diameter around the MH using ILM forceps, leaving a pedunculated ILM flap; Peel the ILM in the direction of the red arrows; E, L: Then the ILM pedicle flap was tiled over the MH, and was carefully flattened to make sure it was properly positioned; F: Sometimes we placed a sodium chondroitin sulfate-sodium hyaluronate on the ILM flap to stabilize it.

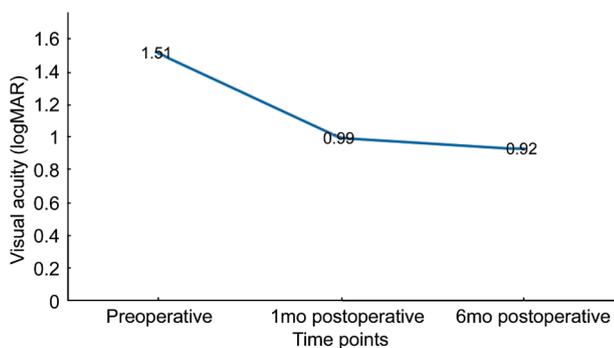


Figure 2 The trend of mean BCVA over time The mean BCVA of patients was significantly improved after surgery, but there was no significant difference between the 1mo postoperative and the 6mo postoperative.

DISCUSSION

Kelly and Wendel^[9] reported that the closure rate of MHs was 58% when ILM peeling assisted PPV was first introduced to manage idiopathic MH, and have improved to 86%-100% assisted by ILM staining technique^[10]. Chuang *et al*^[11] reported that the closure rate of MHs was 87% in patients with high myopia by vitrectomy and ILM peeling. However, the closure rate of MH and improvement of visual acuity were not as good as those in non-high myopia. Longer axial length may increase the risk of anatomic reduction failure^[12]. Large MHs (minimum D >400 μm), however, appeared to be lower closer rate than the idiopathic forms. In addition, about 19%-39% of the anatomically closed large MHs were actually flat-open^[13-15].

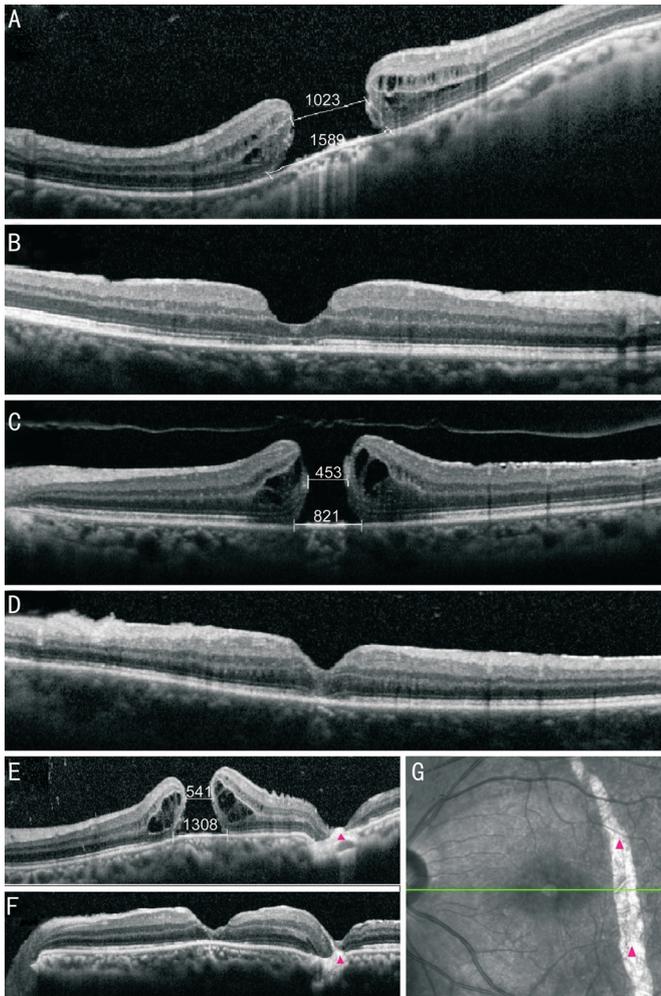


Figure 3 Spectral-domain OCT changes in three representative patients after PPV with the tiled transplantation ILM pedicle flap technique A, C, E: Preoperative OCT images; B, D, F: Seven days postoperative OCT images. Seven days postoperative, the MH had closed. The closure types of first patient was U-type and the other two patients were V-type. The third patient (E-G) is a 19-year-old female patient whose left eye was injured by a beer bottle. G: The fundus photography taken during OCT scanning. The trauma not only caused a large MH but also caused a choroidal rupture (position of the red arrow in the E-G). The MH healed successfully after the PPV with the tiled transplantation ILM pedicle flap technique. Vision increased from 20/500 to 20/40.

The traditional ILM peeling only release the tangential traction, but cannot compensate for tissue shortening in large MHs. The rate of closure for large idiopathic MHs had increased to 98% along the recent advent of the inverted ILM flap technique, and to 100% in a report for high myopic MHs^[4,7]. Michalewska *et al*^[4] hypothesized that the inverted ILM flap technique could improve MHs closure rates and enhance closure by stimulating glial cells proliferation. Müller cells play a key role in supporting the normal function of neurons and are the major glial cells in the retina^[16]. The mechanisms for tissue repair in the MHs by inverted ILM flap technique were as follows: Müller cell fragments in the inverted ILM can proliferate

along the inverted ILM flap and induce glial cell hyperplasia in the retina. The inverted ILM served as basement membrane and scaffolds for tissue proliferation, thus providing an environment to instruct the photoreceptors to assume correct position during the reconstruction process^[4].

We also achieved successful closures of the large MH in our reports, and we did not see any excessive gliosis during the 6mo follow-up period, which displayed as high reflection area in OCT^[17-18]. Although we did not see any excessive gliosis, long-term follow-up will be required to examine excessive gliosis in the retina. We speculate that the mechanisms for tissue repair in the MHs by the tiled transplantation ILM pedicle flap technique are the same as inverted ILM flap technique. It is hypothesized theoretically that the tiled transplantation ILM pedicle flap technique is more advantageous than inverted ILM flap technique, because the microenvironment of former is more similar to the normal physiological conditions, for example, the MHs directly contact the same surface of the ILM the same as normal physiological conditions. The ILM has two sides, one side facing the vitreous and the other side facing the nerve fiber layer of the retina. These two sides are very different. The side facing the vitreous (A side) is completely smooth, and the side facing the nerve fiber layer (B side) is obviously irregular, the reason for the irregularity is that the branching protrusion of the Müller cell is attached to the inner limiting membrane. Our tiled translocation ILM flap technique is obviously not the same as the previously reported various inverted ILM flap techniques. In our technique, the B side of ILM flap is still facing the nerve fiber layer, thus creating a condition that is closest to the normal anatomy for the growth of the MH, which is why the excellent anatomic results with visual improvement are obtained in these cases. However, in the previously reported of inverted ILM flap technique, the B side of ILM is oriented towards the vitreous, which is the significant difference between our technology and their technology. So we speculate that the tiled transplantation ILM pedicle flap technique provides an better environment to instruct the photoreceptors to assume correct position during the reconstruction process, theoretically better than the inverted ILM flap technique. Further comparative and prospective studies involving more patients will be needed to determine the actual efficacy of the technique.

This technique is also an easy-to-use technique that we break down its main process into two parts. The first step is to peel a circular area about 2 papilla disc in size along the edge of the MH, the starting position avoiding the edge of the hole and the vessel. The second step, then to make a pedicled ILM flap, and the width of flap should be larger than the MH diameter. The purpose of the first step is to relax the pull of the ILM on the

MH. The second step is to build a bridge for closing the MH. And the advantage of the pedicled ILM flap compared to the free ILM flap is that the former is not easily detached.

In our report, spontaneous detachment of the flap occurred in two of thirty-three eyes during the air-fluid exchange. The eye axis of the high myopia is significantly longer, and the ILM of high myopia is thinner than the normal eyes. We found that the ILM of high myopia is very tightly bound to the retina and is not easily separated, so it is difficult to get a large and strong enough flap. It may be that the above two reasons why the two high myopia patients had dislocation of the ILM flap during surgery. To address this same problem, Shin *et al*^[19] used perfluoro-n-octane to assist the covering of the MH with a single sheet of ILM flap. In our cases, we did not use perfluoro-n-octane. In our experience, we found that in order to prevent the detachment of the flap during surgery, should pay attention to the following aspects. First, try to peel off a larger ILM flap at the first time, otherwise the usable ILM will become less and less. we gently tiled the flap on the MH, try to make them stick to each other. Second, we found that lowering the perfusion pressure might help to avoid the flap from being washed away during air-fluid exchange. Third, if necessary, low molecular weight hyaluronic acid was used to keep the ILM pedicle flap stable and leave it in place at the end of the procedure.

Imai and Azumi^[20] found an expansion of RPE atrophy happened 1wk after ICG staining, suggesting that ICG-stained ILM flaps may cause RPE injury. However, Hirano *et al*^[21] reported that they observed that the preoperative chorioretinal atrophy did not enlarge up to 6mo postoperative. In our study, we have observed no dilatation of the chorioretinal atrophy up to 6mo postoperative. We need further observations to assess the safety of using ICG staining in the surgery. SF₆, C₃F₈ and sterile air are the most commonly used gas fillers for MH surgery. Intraocular gases can isolate and seal to area of the hole; intraocular gases can produce mechanical tamponade and promote the healing of the hole due to the buoyancy of the gas^[22]. Comparative studies reported that room air had the similar closure rate to SF₆ and C₃F₈^[23-25]. The advantage of filling sterile air is economical and convenient. The patient adhered to face-down for 7d after surgery. In our study, we found that there is also a high anatomic success rate using sterile air. We observed that the macular fovea after the closure of the MH was similar to the letter U, some resembling the letter V. No change in morphology after 6mo of observation. We have not found any difference in prognosis between the two types until now, which require longer observation and further research.

In conclusion, our clinical outcomes suggest that the tiled transplantation ILM pedicle flap technique was beneficial for

the treatment of large MHs, including idiopathic, high myopia and traumatic MHs. Using the tiled transplantation ILM pedicle flap technique provides another option for patients with large MHs.

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