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ORIGINAL PAPER

Perfluoro-*n*-octane-assisted autologous internal limiting membrane plug for refractory macular hole surgery

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Abstract

Purpose To evaluate a surgical technique using a perfluoro-*n*-octane (PFO)-assisted autologous internal limiting membrane (ILM) plug for refractory macular holes (MHs).

Methods This study was a retrospective, consecutive, interventional case series. Patients with refractory MHs following PFO-assisted autologous ILM plugs were reviewed between October 1, 2017, and February 28, 2018. The anatomical results of MH preoperatively and postoperatively were evaluated by fundus examination and optical coherence tomography (OCT). The best-corrected visual acuities (BCVAs) before and after surgery were compared as the functional outcome.

Results Six eyes of six consecutive patients with refractory MH were enrolled in this study. Successful MH closure and BCVA improvement after the surgeries were obtained in all eyes. There were four male and two female patients, and the mean age was 63.7 ± 11.1 years. Intraoperatively, the average number of autologous ILM grafts we harvested was 2.2 ± 0.4. The mean follow-up was 6.0 ± 1.7 months. The averaged BCVA before and after the surgery at the last visit improved from 20/356 to 20/153. The ILM graft tissue was still visible, as shown by OCT, in all 6 of 6 (100%) eyes during the follow-up period.

Conclusions This surgical technique using PFO-assisted autologous ILM plug may provide an option for the treatment of refractory MH.

Keywords Refractory macular hole · Internal limiting membrane · Autologous blood clot · Perfluoro-*n*-octane

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Introduction

Macular holes (MHs) can cause threats to central vision with significant reductions in visual acuity. Surgical management via pars plana vitrectomy and internal limiting membrane (ILM) peeling is widely used to relieve the anteroposterior tractions and tangential tractions exerted on the vitreoretinal interface [1]. The closure rate after primary vitrectomy and ILM peeling could reach more than 90% [2]. Unfortunately, some holes failed to close or reopened after the primary surgery.

Fluid–gas exchange is an effective treatment option for eyes with open holes following vitrectomy [3]. However, a portion of the MH may still remain open even after multiple procedures. For refractory MH, a secondary vitrectomy with an autologous ILM graft could be considered as an alternative [4–6]. Although this technique improves the success rate, it can be significantly stressful for the surgeon because of the technical challenges. In this study, we develop and present another alternative surgical technique for autologous ILM graft transplantation.

Subjects and methods

All eyes underwent a 23-gauge pars plana vitrectomy (Constellation; Alcon) with retrobulbar anesthesia. All of the surgeries were performed by the same surgeon (C.-C.L.). After checking for the adequate removal of the vitreous in the previous surgery, a small perfluoro-*n*-octane (PFO) bubble sufficient to cover the hole surface was introduced into the eye, followed by an injection of ICG (concentration: 1 mg/ml in 5% glucose water) dye over the macular area to visualize the extent and the edges of the previous ILM removal. Excessive ICG was immediately removed by suction. Next, PFO was further instilled (approximately 1 ml) to cover the macular area within the arcade vessels. We then peeled off a piece of the ILM close to the vascular arcades, where the edge of the previous peeling was located, to create a graft using 23-gauge disposable forceps (Alcon Laboratories, Inc., Fort Worth, TX, USA). This graft was subsequently simply dragged and placed inside the MH under the PFO tamponade. If the first piece of the graft was not large enough to fill in the MH, a second piece of the ILM graft may be harvested using a similar technique. If any defects of the retinal tissue still existed after the second attempt, then a third piece of the ILM graft was peeled and engaged to fill it. After the MH defect was deliberately packed with ILM graft, the hole margin was gently massaged toward the center with a Tano's diamond-dusted membrane scraper (DDMS) (Synergetics, O'Fallon, MO, USA). Then, we rotated the eyeball to roll the PFO bubble adjacent to MH, and fresh blood obtained from the patient's antecubital vein was then injected gently to cover the MH. The fresh blood soon became a clot on the surface of the macula, forming multiple ILM grafts with a blood clot as a macular plug that sealed the hole in a few minutes. Finally, the PFO was completely removed and further fluid–air exchange was performed. (see the video in Online Resource 1) At the end of the operation, the air was replaced with 20% sulfur hexafluoride gas. Patients were asked to remain face down for 1 day after surgery. The key steps of this technique are outlined in Fig. 1.

Patients who had refractory MHs and who underwent pars plana vitrectomy with autologous transplantation of the multiple ILM grafts and blood clot technique were recruited into the study between October 1, 2017, and February 28, 2018. All patients received comprehensive ophthalmologic examinations before and after the surgery, including measurement of best-corrected visual acuity (BCVA) and optical coherence tomography (OCT) imaging. BCVA using a Snellen chart was converted to the logarithm of minimum angle of resolution (logMAR) for analysis purposes.

Results

A total of six eyes of six consecutive patients were enrolled in this study. Successful macular hole closure and visual acuity improvement were obtained in all 6 (100%) eyes. The demographic data are listed in Table 1. The average age was 63.7 ± 11.1 years (range 44–78 years), and the duration from the primary surgeries ranging from 3 to 20 months (mean 9.7 ± 6.2 months). The mean basal MH size before autologous ILM graft surgery was 1322.0 ± 363.7 μm, and the mean minimum opening of the MH was 658.8 ± 94.4 μm. Intraoperatively, the average number of autologous ILM grafts we harvested was 2.2 ± 0.4 (range 2–3). The mean follow-

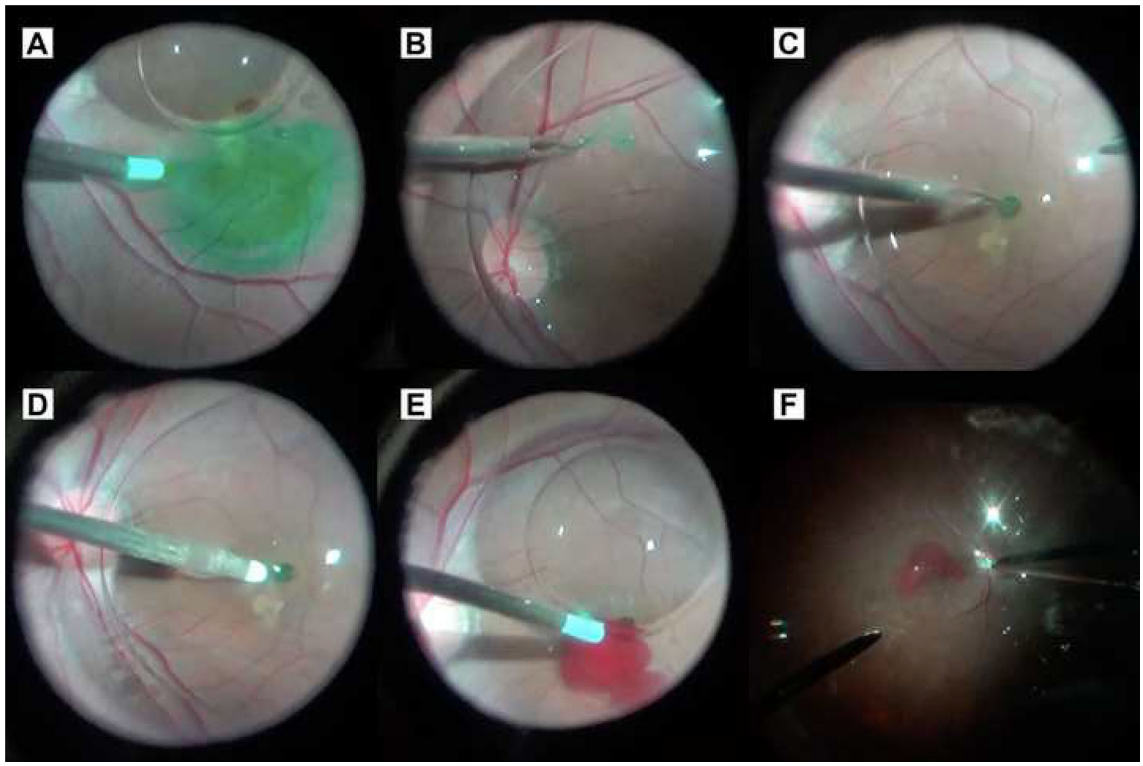

Fig. 1 Key steps of the perfluoro-*n*-octane (PFO)-assisted autologous internal limiting membrane (ILM) plug technique in treating refractory macular hole (MH). **a** A small PFO bubble was introduced into the eye to protect the fovea, followed by an injection of ICG dye. **b** The first piece of the ILM graft was harvested along the edge of the previous peeling area and dragged into the MH under PFO tamponade. **c** Since the first piece of the graft is not large enough to fill in the MH, the second piece of the ILM graft was peeled and placed inside the hole. **d** The hole's margin was gently massaged toward the center with a Tano's diamond-dusted membrane scraper. **e** Autologous blood was used to form a macular plug with multiple ILM grafts. **f** The PFO was completely removed and further fluid–air exchange was performed with 20% sulfur hexafluoride

up was 6.0 ± 1.7 months (range 4–8 months). The averaged preoperative BCVA in logMAR and postoperative BCVA in logMAR at the last visit was 20/356 (1.25 ± 0.39 logMAR) and 20/153 (0.88 ± 0.34 logMAR), respectively. The ILM graft tissue was still visible as shown by OCT in all 6 of 6 (100%) eyes during the follow-up period. None of the eyes exhibited intraoperative or postoperative complications.

Representative fundus photograph and OCT images taken preoperatively and postoperatively show a closed MH and an improvement in visual acuity 8 months after the operation (Fig. 2). OCT showed MH closure with visualized multiple folded layers of ILM plugging the MH. ILM graft tissue could remain with restoration of the foveal contour (Fig. 3).

Discussion

To the best of our knowledge, this is the first report of the successful closure of a refractory MH using the multiple autologous ILM grafts and blood clot technique. However, despite the high success rates achieved with a standard approach for treating MH in patients with failed primary vitrectomy with the ILM removal and repeated fluid–gas exchange procedure, persistent MH remains a problem.

Conventional autologous ILM grafts [4–6], which have been described with success for refractory MHs, are technically challenging because of the fragile nature of the ILM near the arcade area, inappropriate graft sizes, and the loss of the flap with fluid current or during the fluid–air exchange phase. The most difficult part of the ILM transplantation technique is the transferring procedure from the harvest site to precise

Table 1 Clinical characteristics and surgical outcome

Patient no.	Age (years)	Sex	Eye	Duration of failed MH (months)	Minimal diameter of MH (μm)	Basal MH size (μm)	Number of auto-ILM grafts	MH status after auto-ILM transplant	Final lens status	Preoperative BCVA	Final BCVA	Follow-up
1	66	M	OS	20	652	1420	2	Closed	Pseudophakic	20/250	20/125	8
2	78	M	OS	3	601	974	2	Closed	Pseudophakic	20/250	20/100	8
3	44	F	OS	10	584	1024	2	Closed	Phakic	20/100	20/50	6
4	67	M	OS	6	737	1978	3	Closed	Pseudophakic	20/1000	20/200	5
5	62	M	OD	13	807	1321	2	Closed	Pseudophakic	20/1000	20/500	5
6	65	F	OD	6	572	1215	2	Closed	Pseudophakic	20/400	20/100	4

auto-ILM autologous internal limiting membrane, *BCVA* best-corrected visual acuity, *logMAR* logarithm of the minimum angle of resolution, *MH* macular hole

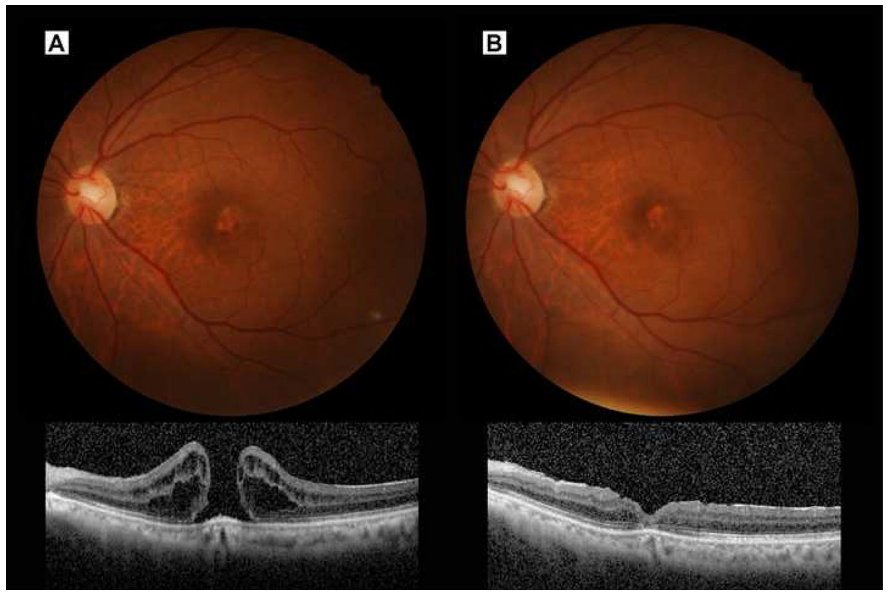

Fig. 2 Results of using perfluoro-*n*-octane-assisted autologous internal limiting membrane (ILM) plug in Patient 1, a 66-year-old man with a refractory macular hole who underwent surgery 20 months after the initial failed vitrectomy and ILM peeling. **a** Preoperative fundus photograph and optical coherence tomography (OCT) image obtained after initial vitrectomy showing an open macular hole with visual acuity of 20/250. **b** Fundus photograph and OCT imaging obtained at 6 months postoperatively, the closed hole remained and the foveal contour was restored with partial restoration of the ellipsoid zone, while visual acuity improved to 20/125

insertion inside the macular hole. The graft may get stuck to the forceps, causing difficulty in releasing it, subsequently becoming a potential risk for retinal injury. Herein, we moved and adjusted the flap under PFO to help the positioning of the ILM graft. Case series of PFO-assisted ILM transplantation have been reported before [7–9]; however, the differences between their procedure and ours are in considering the timing of PFO injection and the design of the ILM graft. In our surgical procedure, a single small PFO bubble is injected right at the beginning of the surgery before ILM staining. Only a very small amount of PFO, is needed, enough to cover the hole, to prevent any toxicity from the staining material. Additionally, multiple pieces of ILM graft tissue were used in attempts to repair large MH defects, instead of using a single graft, because we considered that recalcitrant MH could be closed more promptly when graft tissue becomes a filler, which may serve as a stronger scaffold for Müller cell proliferation and migration. Furthermore, a sufficient ILM graft placed in the MH may supply the hole with more neurotrophic factors to bridge the healing process [10]. Taken together with the stability of the ILM grafts under PFO, multiple pieces of graft could be obtained, which would be enough to fill the whole MH.

During the operation involving the "massage" technique, our attempt to release the traction of epiretinal glial tissue and bring the borders of the MH together mechanically may promote adhered cellular remnants of glia and Müller cells re-approximate both macular hole edges. In addition to this technique, we applied autologous blood to turn the ILM graft and blood clot mixture into a macular plug to stabilize the multiple ILM grafts in place [11], which prevents instant intraoperative failure. Accordingly, it is not necessary to have an additional fluid aspiration after a 5 to 10 min wait after the fluid–air exchange to maximize vitreous cavity dehydration [12]. Moreover, the plug could also act as a glue to decrease the risk of dislocation of the ILM grafts postoperatively. Therefore, the patients were requested to remain in a prone position for only 1 day.

There are also a few potential disadvantages to the procedure. Firstly, the macular toxicity of PFO has been ascribed to a combination of chemical and mechanical toxicities [13]. However, the toxicity concerns from PFO are decreased because the small

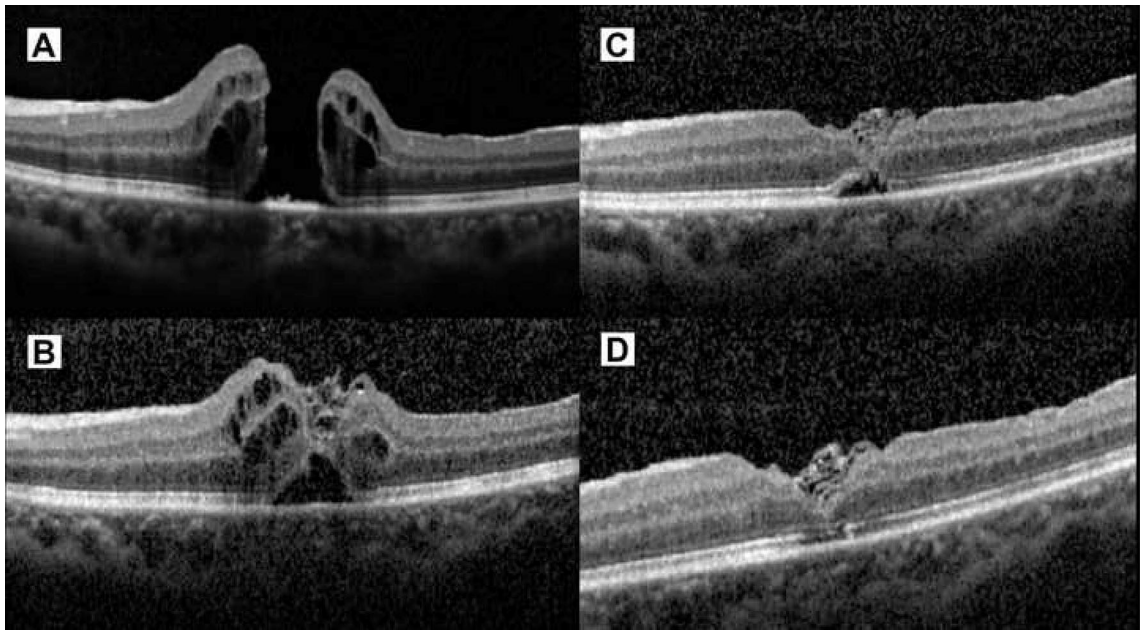

Fig. 3 Results of using perfluoro-*n*-octane-assisted autologous internal limiting membrane (ILM) plug in Patient 3, a 44-year-old female patient with a refractory macular hole. **a** The preoperative optical coherence tomography (OCT) image showed a refractory macular hole. **b** OCT showed the hole was closed 4 weeks after the surgery using two ILM grafts transplantation with autologous blood clot as a macular plug. **c**, **d** She had elevated and cystoid edges with foveal detachment initially, but it was further reattached with restoration of fovea contour. Multilayered ILM grafts tissue plugging in the fovea is readily visible postoperatively and in folding in inner layers. Best-corrected visual acuity improved from 20/100 before surgery to 20/50 at the final visit

amount use and short-time exposure. Secondly, there is a risk of concomitant suction out of the ILM grafts while performing PFO aspiration. So, when removing PFO, we place the tip of the aspirating instrument just within the edge of the PFO bubble and rotate the eyeball to roll the PFO bubble away from the fovea to avoid the potential risk. Moreover, risk of incomplete PFO removal in the vitreous cavity can be responsible for the postoperative inflammation and the symptoms of floaters. Lastly, although the toxicity issues due to blood products and fibrin degradation products used in this technique should not be ignored, the safety concerns are reduced because the multiple ILM grafts tissue barrier serves as filler at the hole.

The limitations of this technique include limited follow-ups to date and a limited number of cases. Although the multiple autologous ILM grafts technique has reached anatomical success and improved short-term functional outcome, the long-term visual function results or microstructure regeneration outcomes are unknown. The fullness of the ILM tissue plugging in the fovea renders it effectively in closing MH, but entails the risk of excessive gliosis, which would require further monitoring. Although the adequate amount of autologous ILM tissue to be used needs to be further studied and determined for this procedure, we believe this technique avoids a potential challenging maneuver and may be a new option for refractory MHs.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the ethics committee of Chang Gung Memorial Hospital and adhered with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

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