· Brief Report ·

Corneal stromal lenticule transplantation for covering macular hole during vitrectomy

Wen-Ting Ding[1], Yi-Le Xu[1], Di Li[1], Xiao-Xiao Qian[1], Jian Li[1], Hong-Wei Ge[2], Xiao-Hua Zhang[1], Ren-Jian Hu[1], Yong-Ping Hu[1]

[1]Department of Ophthalmology, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou 310006, Zhejiang Province, China
[2]Department of Urology, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou 310006, Zhejiang Province, China
Correspondence to: Yong-Ping Hu. Department of Ophthalmology, Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Huansha Road, No.261, Hangzhou 310006, Zhejiang Province, China. huyongping@hospital.westlake.edu.cn
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Abstract
● **AIM:** To describe an innovative surgical technique for pathologic myopia and macular holes accompanied by retinal detachment using allogeneic corneal stromal lenticule transplantation combined with pars plana vitrectomy.
● **METHODS:** The allogeneic corneal stromal lenticule was harvested through small incision lenticule extraction (SMILE) and stored at -30°C in advance. After pars plana vitrectomy, an allogeneic corneal stromal lenticule was thawed, trimmed into approximately 60 μm thick and 100 μm larger than the macular hole and transferred to cover the macular hole through the trocar. Autologous whole blood was dripped to seal the corneal stromal lenticule. The vitreous cavity was then filled with perfluoropropane (C_3F_8) or sterile air.
● **RESULTS:** The technique was performed on three eyes of three patients. The mean postoperative follow-up period was 77.3±50.0d. Postoperatively, the macular hole of all eyes was restored. All patients' visual acuities also improved. No complications occurred during the follow-up period.
● **CONCLUSION:** The innovative corneal stromal lenticule transplantation technique provides convenient operations, less surgical invasion, effective results, and reliable safety for macular hole repair during follow-up time.
● **KEYWORDS:** corneal stromal lenticule transplantation; femtosecond laser small incision lenticule extraction; macular hole; surgical technique

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INTRODUCTION

A macular hole is a vitreoretinal interface disease that leads to severe impairment of central vision, characterized by partial- or full-thickness neurosensory retinal defects in the macula. Most commonly idiopathic or related to vitreomacular traction syndrome, macular holes can also be associated with a variety of macular pathologies[1-2]. Notably, the progressive elongation of the eye axis in pathologic myopia can lead to posterior scleral staphyloma and the development of secondary macular holes, which in turn may progress to retinal detachment[3].

Various methods have been employed to repair macular holes, with the primary treatment being pars plana vitrectomy, often combined with techniques involving the manipulation of the internal limiting membrane (ILM)[4-7]. Advanced surgical techniques, such as lens capsular flap transplantation[8], amniotic membrane transplantation[9-10], and autologous neurosensory retinal transplantation[11-13], have been developed to enhance the success rates of these procedures. These tissue grafts serve as scaffolds that promote cell proliferation and facilitate the regeneration of retinal layers. Specifically, autologous neurosensory retinal transplantation may stimulate functional recovery through contact with the retinal pigment epithelium (RPE) or the edges of the macular hole. While the closure rates for refractory macular holes are comparable across these techniques, amniotic membrane transplantation has been found to be the most efficient for visual recovery, and lens capsular flap transplantation tends to yield better functional outcomes than the free ILM flap technique[14].

Despite these advancements, complications can arise from ILM peeling, such as the formation of corrugations or irregularities on the retinal surface, known as the dissociated optic nerve fibre layer (DONFL)[15]. This condition can lead to damage of the ganglion cells and subsequent microperimetric changes[16-17]. The absence of ILM in recurrent macular holes presents a challenge, as does the scarcity of materials for lens capsular flap transplants. Post-cataract surgery, particularly when involving neodymium:yttrium-aluminum-garnet (Nd:YAG) laser posterior capsulotomy and a transparent lens, may leave no capsular flap available for macular hole repair. Additionally, parafoveal atrophy has been observed in patients who received human amniotic membrane grafts[18]. Current research suggests that autologous neurosensory retinal transplantation may involve complex and often unnecessary surgical procedures, especially when simpler alternatives with similar anatomical and functional outcomes are available[14]. Furthermore, it carries the risk of postoperative complications, including choroidal neovascularization, retinal detachment, cystoid macular edema, and reactive pigment epithelial hyperplasia[11,19].

In response to these challenges, we have recently introduced an innovative surgical technique for macular hole closure that combines pars plana vitrectomy with corneal stromal lenticule implantation.

PARTICIPANTS AND METHODS

Ethical Approval Adhering to the Declaration of Helsinki, we secured ethics approval from the Institutional Review Board of the Affiliated Hangzhou First People's Hospital, School of Medicine, Westlake University, Hangzhou, China (approval number 2022-025, dated 24/08/2022). Prior to the surgery, informed consent was obtained from all patients, and the study was registered in ClinicalTrials.gov (ID NCT05875909, registered on 19/04/2023).

The surgeries for macular hole repair were conducted by the corresponding author (Hu YP), under local anesthesia. A video (Video 1, online supplementary) and Figure 1 illustrate the corneal stromal lenticule transplantation procedures. All the corneal stromal donors underwent screening for hepatitis, syphilis and human immunodeficiency virus to exclude infection.

Patients underwent a 25-gauge, 3-port pars plana vitrectomy using the Constellation Vision System by Alcon Laboratories, Inc. Essential steps included triamcinolone acetonide staining and achieving a thorough posterior vitreous detachment. For patients with pathologic myopia and macular holes accompanied by retinal detachment, a fluid-air exchange was performed. We utilized a flute needle to remove subretinal fluid. The corneal allogeneic stromal lenticule, approximately 60 μm thick, was harvested through small incision lenticule extraction (SMILE) and stored in sterile normal saline at -30°C using a Panasonic MDF-539 device from China. Permission was obtained for the use of each corneal stromal lenticule. After thawing at room temperature and staining with 0.25% indocyanine green, the corneal stromal lenticule was trimmed to be approximately 100 μm larger than the macular hole. Stripping pliers were used to secure the corneal stromal lenticule through the trocar, and it was carefully spread over the hole, ensuring close contact through gentle massage. A drop of fresh autologous whole blood was applied to stabilize the

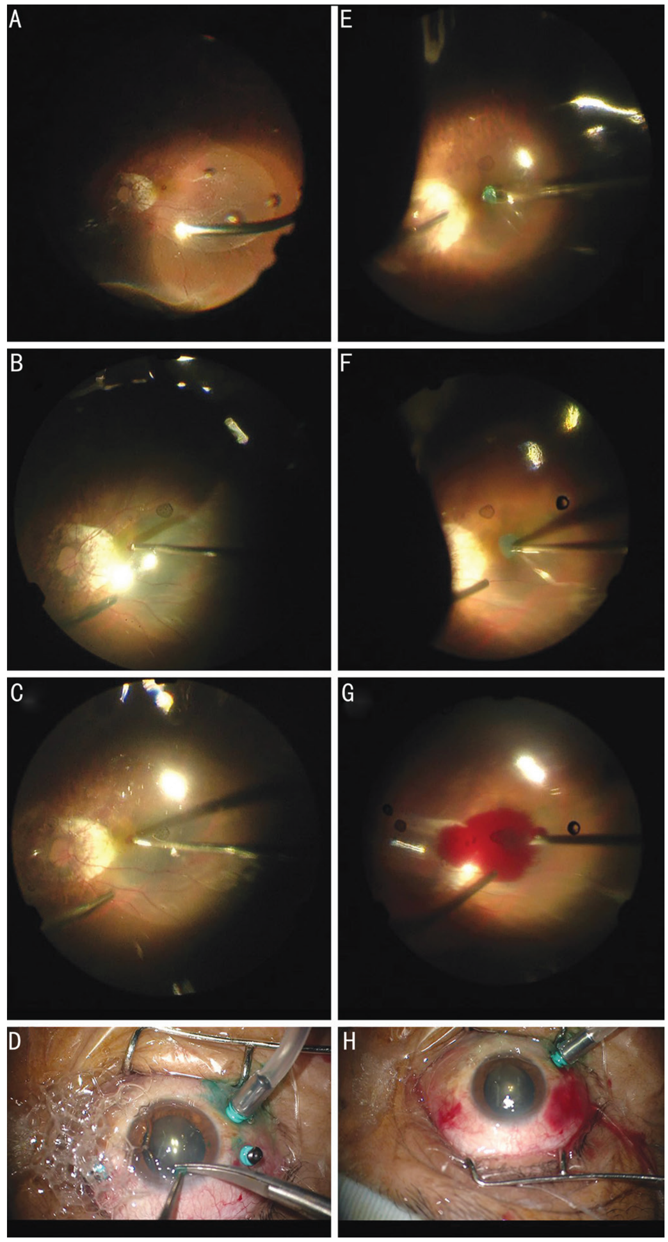

Figure 1 The corneal stromal lenticule transplantation procedures for macular hole repair A: Patients underwent a 25-gauge, 3-port pars plana vitrectomy; B: Fluid-air exchange was performed subsequently; C: The subretinal fluid was drained by a flute needle. D: The corneal stromal lenticule was stained with indocyanine green and trimmed; E: Spread of the corneal stromal lenticule over macular hole with stripping pliers; F: A close contact of the corneal stromal lenticule with macular hole was confirmed; G: To immobilise the corneal stromal lenticule, a drop of fresh autologous whole blood was dripped over the corneal stromal lenticule; H: The vitreous cavity was filled with 14% perfluoropropane (C_3F_8). Surgical incision was self-closed.

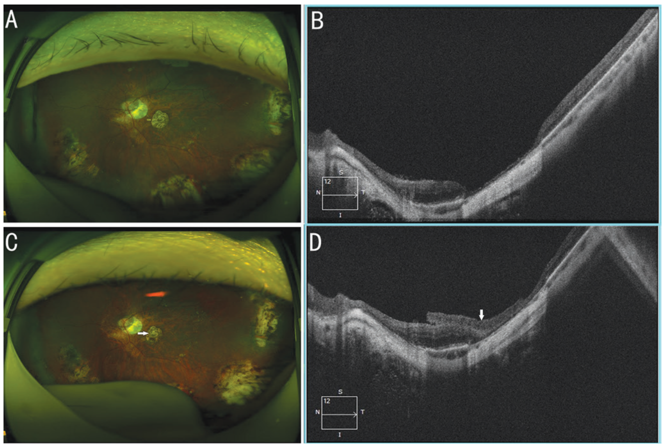

Figure 2 Preoperative (A and B) and postoperative (C and D) fundus images by panoramic ophthalmoscope (Daytona, P200T, Optos®; Dunfermline, UK) and optical coherence tomography (OCT, by Carl Zeiss Meditec, Inc., Germany) scans taken from Patient 1 The macular hole was closed with a corneal stromal lenticule (arrow).

corneal stromal lenticule. The vitreous cavity was filled with 14% perfluoropropane (C_3F_8) for cases with retinal detachment or sterile air for idiopathic macular holes. The surgical incision closed naturally or was sutured with a 6-0 polyglactin 910 suture (ETHICON®). Postoperatively, patients were advised to maintain a prone position for two weeks.

RESULTS

The technique was applied in three eyes of three patients, comprising two women and one man, with one case of macular hole after pars plana vitrectomy and silicone oil injection, and two cases of macular hole retinal detachment due to pathologic myopia. The patients' mean age was 55y, range from 52 to 57y. Throughout the surgery and the postoperative period, no complications were observed.

In all cases, the macular holes were successfully closed, and the retina was reattached after a mean follow-up time of 77.3±50.0d (range, 32–131d), as shown in Figures 2–4. Optical coherence tomography (Carl Zeiss Meditec, Inc., Germany) was used to observed the corneal stromal lenticule structure at the final follow-up. However, in Figure 2C and Figure 3C, the corneal stromal lenticule was less distinct due to atrophied choroid.

The preoperative best-corrected visual acuity (BCVA) for the patients was 20/1000, hand motion (HM)/10 cm, and HM/50 cm, respectively. At the final follow-up, the BCVA improved to 20/200, 20/333, and 20/250.

During the follow-up period, no adverse events such as inflammation, infection, rejection reaction, ocular hypertension, ocular hypotension, recrudescent macular hole, parafoveal atrophy, corrugations or irregularities, choroidal neovascularization, retinal detachment, cystoid macular edema, graft changes, reactive pigment epithelial hyperplasia, displacement, or opacification of the corneal stromal lenticule

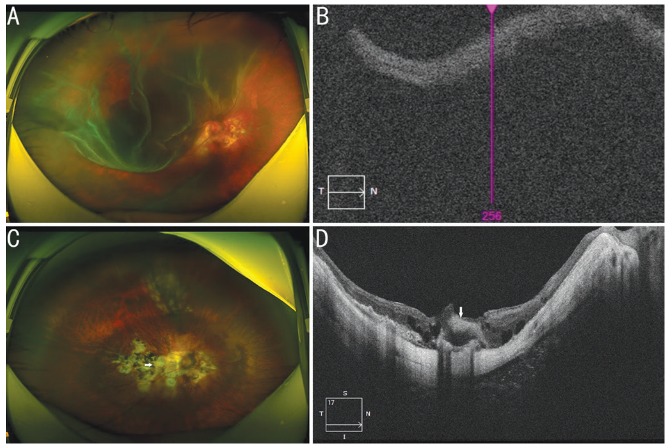

Figure 3 Preoperative (A and B) and postoperative (C and D) fundus images by panoramic ophthalmoscope (Daytona, P200T, Optos®; Dunfermline, UK) and optical coherence tomography (OCT, by Carl Zeiss Meditec, Inc., Germany) scans taken from Patient 2 The macular hole was closed with a corneal stromal lenticule (arrow), and the retina was reattached (C and D).

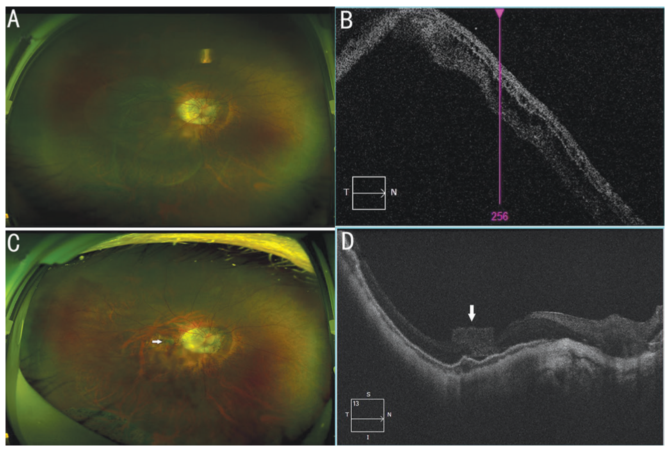

Figure 4 Preoperative (A and B) and postoperative (C and D) fundus images by panoramic ophthalmoscope (Daytona, P200T, Optos®; Dunfermline, UK) and optical coherence tomography (OCT, by Carl Zeiss Meditec, Inc., Germany) scans taken from Patient 3 The macular hole was closed with a corneal stromal lenticule (arrow), and the retina was reattached (C and D).

were noted. The clinical data of the patients is summarized in Table 1.

DISCUSSION

Macular holes are a common oculopathy causing severe visual impairment, particularly in pathological myopia where they can lead to macular hole retinal detachment and a subsequent decline in visual quality.

Surgeons have employed various techniques to restore the macular hole and reattach the retina, such as peeling, inverting, inserting ILM[4-6], lens capsular flap transplantation[8], amniotic membrane transplantation[9-10], and autologous neurosensory retinal transplantation[11-13]. However, these techniques have been found to have drawbacks as previously described[11-12,15,18-19].

Table 1 Clinical data of the patients received corneal stromal lenticule transplantation

Patient	Age (y)	Gender	MH size (μm)	Follow-up time (d)	Preop. BCVA	Postop. BCVA	MH closed	Retina reattached	Complications
1	57	Female	1955	32	20/1000	20/200	Yes	Yes	None
2	57	Female	Not measured	131	Hand motion/10 cm	20/333	Yes	Yes	None
3	52	Male	Not measured	69	Hand motion/50 cm	20/250	Yes	Yes	None

The macular hole sizes of patient 2 and patient 3 were not measured due to large amounts of subretinal fluid. MH: Macular hole; BCVA: Best-corrected visual acuity.

Historically, pars plana vitrectomy combined with ILM peeling and silicone oil tamponade was the standard treatment for macular hole retinal detachment. The procedure is challenging due to the thinness of the ILM in these patients and the floatation of the retina in the vitreous cavity upon detachment, which complicates the peeling process. Essential steps for reattaching the retina in macular hole retinal detachment include fluid-air exchange and subretinal fluid drainage, during which the ILM may be removed or translocated, potentially leading to macular hole relapse[20].

Post fluid-air exchange, surgeons may experience blurry vision, increasing the operational difficulty in a gas medium. The ILM can roll up after fluid-air exchange, making it difficult to spread over the macular hole. Consequently, this technique can sometimes result in an unclosed macular hole and recurrent retinal detachment[21]. To address this, some surgeons have adopted intraoperative perfluorocarbon liquid tamponade after fluid-air exchange to peel the ILM[22]. This method requires rapid ILM peeling and is prone to complications such as unclosed macular hole, recurrent retinal detachment, and proliferative vitreoretinopathy upon C_3F_8 absorption.

Amniotic membrane transplantation is known to support the growth of RPE cells and promote their proliferation and differentiation. However, a study observed parafoveal atrophy around the amniotic membrane graft in 40% of eyes within the first month post-surgery, with dislocation occurring in an additional 20%. Preexisting maculopathy, surgical trauma, and contraction of the amniotic membrane graft are potential contributing factors. The sticky stromal side of the contracted graft, when in contact with the RPE, may drag the fragile RPE, leading to parafoveal atrophy[18]. In contrast, corneal stromal lenticules are thicker and less sticky, making them less likely to induce RPE changes. In our study, no parafoveal atrophy has been observed to date. Optical coherence tomography of the three patients indicates that corneal stromal lenticule may serve as scaffolds for the regeneration of retinal layers and have the potential to induce cell proliferation.

While lens capsular flap transplants are limited by material availability, corneal stromal lenticules are more readily available and thicker, offering surgeons an easier grip and coverage for macular holes. Autologous neurosensory retinal transplantation is an alternative for treating refractory macular holes, acting as a scaffold and forming a macular plug to seal the hole[23-24]. Müller cells in the peripheral retina, with their progenitor properties, may migrate to the outer nuclear layer, proliferate, and replace lost photoreceptor cell[25]. Choroidal neovascularization has been observed, possibly due to vascular endothelial growth factor (VEGF) secretion from ischemic transplanted retinal tissue[12]. As corneal stromal lenticules are non-ischemic, they secrete less VEGF, reducing the likelihood of choroidal neovascularization.

Our research confirms the success of corneal stromal lenticule transplantation in treating macular holes and macular hole retinal detachment, showing promising results in improving BCVA, closing the macular hole, and reattaching the retina.

What are the suitable indications of corneal stromal lenticule transplantation? Although no local scars caused by corneal stroma after macular hole healing is observed during the follow-up period, the possibility of scars may reduce visual functions. We suggest recurrent giant macular hole or macular hole retinal detachment with pathological myopia might be the suitable indications, and using peeling, inverting, inserting ILM in other common macular hole cases.

Corneal stromal lenticule transplantation is a suitable technique for managing macular holes and macular hole retinal detachment in highly myopic patients. This technique is advantageous due to the selectable and appropriate thickness of the corneal stromal lenticule. Typically, the thickness of a corneal stromal lenticule after femtosecond laser small incision lenticule extraction ranges from 60 to 100 μm. We prefer a thickness of approximately 60 μm, as it is thicker than the ILM and human amniotic membrane, yet not too thick to be manipulated with stripping pliers to cover the macular hole. Our experience indicates that the thickness of the corneal stromal lenticule does not significantly vary between patients or holes, and we have found it easy to spread, move, and cover the macular hole repair following fluid-air exchange. This innovative technique helps avoid ganglion cell damage and microperimetric changes. The ready availability of suitable and abundant corneal stromal lenticules, due to the widespread use of femtosecond laser small incision lenticule extraction, has facilitated our surgery. To date, we have not observed parafoveal atrophy, choroidal neovascularization, retinal detachment, or cystoid macular edema in our patients.

However, our study is limited by a small number of patients and a short follow-up period. Future studies with larger caseloads and longer follow-up periods are necessary to confirm the safety and effectiveness of corneal stromal lenticule transplantation.

The lack of a control group may affect the generalizability of our findings. Potential long-term risks, such as corneal stromal lenticule rejection, displacement, or resorption, require attention. Corneal stromal lenticules, primarily composed of collagenous fibers, rarely cause graft rejection, and the presence of Langerhans cells and dendritic cells in the corneal stromal lenticule is associated with immune privilege. The highest incidence of graft rejection occurs within the first 18mo following keratoplasty[26]. No uveitis has been observed in our study according to optical coherence tomography, but further follow-up is needed. We use fresh autologous whole blood to immobilize the corneal stromal lenticule and instruct patients to maintain a prone position for two weeks postoperatively. However, elderly patients may have difficulty maintaining this position, increasing the risk of corneal stromal lenticule displacement. We have observed fusion of the corneal stromal lenticule and retina in one patient (Figure 3D), but not in the others. Future follow-ups will measure the corneal stromal lenticule to assess for resorption.

In conclusion, while corneal stromal lenticule transplantation for macular hole repair has shown preliminary success with encouraging clinical outcomes, these results are based on a very limited dataset. More randomized controlled clinical trials are needed to validate these findings.

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