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Autologous Retinal Transplant for Refractory Macular Holes: Multicenter International Collaborative Study Group

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Purpose: To report the structural and functional outcomes of autologous neurosensory retinal transplant for closure of refractory large macular holes (MHs).

Design: Multicenter, retrospective, consecutive case series.

Participants: A total of 41 eyes of 41 patients with a full-thickness MH refractory to prior vitrectomy with internal limiting membrane (ILM) peel and tamponade.

Methods: All patients underwent pars plana vitrectomy, autologous neurosensory retinal transplant with gas, silicone oil tamponade, or short-term perfluoro-*n*-octane heavy-liquid tamponade. All patients had at least 6 months' follow-up.

Main Outcome Measures: Anatomic closure of MH, change in ellipsoid zone (EZ) and external limiting membrane (ELM) defect on OCT, visual acuity (VA) recovery, and surgical complications were analyzed.

Results: Mean number of prior surgeries was 1.5±0.94 (range, 1–3), and patients were followed for a mean of 11.1±7.7 months (range, 6–36 months). Complete anatomic closure of MH by OCT was achieved in 36 of 41 eyes (87.8%). Mean corrected VA (logarithm of the minimum angle of resolution [logMAR]) improved ($P = 0.03$) from 1.11±0.66 (range, 0.48–3) to 1.03±0.51 (range, 0.1–2) at the last postoperative visit. The VA improved (≥0.3 logMAR units) in 15 eyes (36.6%), was stable in 17 eyes (41.5%), and worsened in 9 eyes (21.9%). Among eyes with anatomic closure, VA improved in 52.3% and worsened in 13.8%, whereas in those without closure, VA worsened in 20% and improved in none. Mean preoperative largest basal diameter was 1468.1±656.4 μm (range, 621–2600 μm), and mean inner-opening diameter was 825±422.5 μm (range, 336–1649 μm). Mean preoperative EZ defect was 1777.3±513.8 μm (range, 963–2808 μm), which decreased to 1370±556.9 μm (range, 288–2000 μm) at final follow-up ($P = 0.007$). Mean preoperative ELM was 1681.5±429 μm (range, 1172–2606 μm), which decreased to 1408.5±571.2 μm (range, 200–2000 μm) at final follow-up ($P = 0.017$). Major postoperative complications were retinal detachment (n = 1) and vitreous hemorrhage (n = 1). There were no cases of proliferative vitreoretinopathy, endophthalmitis, suprachoroidal hemorrhage, or choroidal neovascularization.

Conclusions: The autologous retinal transplant technique offers a high degree of anatomic success and proved safe in this initial experience for closure of refractory MHs. *Ophthalmology 2019;■:1–10 © 2019 by the American Academy of Ophthalmology*

With modern vitreoretinal surgical techniques typically involving pars plana vitrectomy, internal limiting membrane (ILM) peel with gas tamponade, and face-down positioning, closure rates of macular holes (MHs) after primary surgery exceed 90%.[1–4] However, anatomic and functional success are more difficult to achieve in refractory MHs after a prior ILM peel, and closure rates of reoperation rarely exceed 70%, with relatively poor final visual acuity (VA).[5]

There are limited surgical options available once the posterior hyaloid has been detached and the ILM removed. Several different techniques have been described to attempt closure when reoperating on these patients, such as repeat fluid–gas exchange,[6] endotamponade with silicone oil,[7] radial relaxing retinotomies on the MH margin,[8] perifoveolar laser photocoagulation to form chorioretinal adhesions resulting in permanent photoreceptor loss,[9,10] temporal scleral imbrication,[11] autologous ILM flap,[12] addition of autologous blood to the autologous ILM flap,[13] autologous anterior or posterior lens capsule flap,[14,15] episcleral posterior buckling,[16] adjuvant blood components including platelet-rich plasma,[17,18] suprachoroidal buckling and scleral shortening techniques,[19,20] or the more recently introduced amniotic membrane as a scaffold to plug the MH.[21]

Since our initial report of autologous neurosensory retinal free flap for closure of myopic MH associated with foveoschisis,[22] there has been increased adoption of the technique, and its indications have expanded beyond myopic MH.[23–25]

In this report, we describe the utility of this technique along with long-term outcomes in a large consecutive multicenter series among different surgeons. Surgical

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complications and visual and anatomic postoperative outcomes are discussed.

Methods

The operative reports, surgical logs, and medical records from consecutive patients with refractory MHs after at least 1 prior surgery who underwent surgical repair with an autologous neurosensory retinal free flap from 4 centers were reviewed: Duke University Vitreoretinal Service, Durham, North Carolina; Charles Retina Institute, Memphis, Tennessee; Sant'Anna Institute, Brescia, Italy; and Yokohama City University Medical Center, Yokohama, Japan, from May 2015 to June 2017. The study protocol was approved by the Institutional Review Board for Human Subjects Research at Duke University, Durham, North Carolina, and by each individual institution, and the study adheres to the tenets set forth in the Declaration of Helsinki. Surgical informed consent was obtained from all participants.

All patients had >6 months of postoperative follow-up. Exclusion criteria were patients who had any ocular history of diabetic retinopathy, vascular occlusion, retinal neovascularization, inflammatory disease, or trauma. Inclusion criteria were patients with refractory full-thickness MHs after at least 1 prior surgery with removal of the ILM and an intraocular tamponade.

OCT was performed before and after surgery in all eyes using a commercially available spectral-domain OCT device (Spectralis HRA OCT; Heidelberg Engineering, Heidelberg, Germany; or Topcon SDOCT; Topcon, Tokyo, Japan). Wide-field fundus photography (Optos, Marlborough, MA), and autofluorescence imaging were performed at postoperative visits when possible.

Surgical Technique

Three-port 20-, 23-, or 25-gauge pars plana vitrectomy (Constellation; Alcon, Fort Worth, TX) was performed with retrobulbar or peribulbar anesthesia using monitored anesthesia care or under general anesthesia. A 25-gauge chandelier illuminator (Alcon) was used to facilitate bimanual maneuvers when needed. In all eyes, any residual peripheral vitreous was removed with the assistance of scleral depression. Indocyanine green dye solution (25 mg indocyanine green in 20 ml 5% dextrose-water solution) or Brilliant Blue (Doubledyne, Alfaintes, Italy) was applied around the MH within the arcade to confirm the extent and adequacy of the previous ILM peel. The surgical maneuvers and instrumentation were not standardized and were left to the discretion of the individual surgeon.

As described previously, a neurosensory retina harvest site was selected in the mid-periphery, typically superior to the superotemporal arcade.[22] The size of the harvest was selected to be approximately 2 disc diameters initially and in subsequent cases was calibrated according to the size of the MH. Harvest location was dependent on surgeon preference and included locations superior, temporal, and nasal beyond the arcade. Endolaser barricade was applied in a circular manner around a 2 disc-diameter area of the retina followed by endodiathermy to the blood vessels at the edges of the site.

The edge of the graft was held, if required, using forceps (Alcon 23-g or 25-g Max Grip or ILM forceps) and cut using vertical or curved scissors (Alcon 23-g or 25-g Revolution DSP Vertical or Curved Scissors or 23-g Pneumatic Scissors).

The full-thickness neurosensory retinal free flap harvest was then completed and gently moved toward the MH. The diathermy marks at the edges and the pattern of the retinal vessels served as anatomic markers to maintain the correct orientation of the retinal free flap. Perfluoro-*n*-octane (PFC) heavy liquid (Perfluoron; Alcon) was instilled over the retinal flap after it was placed to cover the MH. The edges of the flap were gently flattened, and it was stretched to lay flat and cover the entirety of the hole. Alternatively, PFC was instilled over the posterior pole to cover the retina beyond the harvest site before the harvest of the retinal flap, and cutting and maneuvering the retinal flap were performed under PFC.

Intraocular tamponade was composed of silicone oil, C_3F_8 gas, or short-term PFC tamponade. When silicone oil was used as tamponade, direct PFC-silicone oil (1000 centistokes) exchange was performed at the end of surgery. By using active aspiration, a few bubbles of PFC were removed from the edges of the flap. The flap was visualized to be covering the MH under silicone oil. All sclerotomies were closed with a single interrupted suture or noted to be self-sealing. The patients were positioned face down postoperatively for 1 week except when PFC was used as tamponade, in which case patients were positioned supine. If silicone oil was used for tamponade, it was usually removed within 1 to 3 months and PFC was removed within 2 weeks.

The primary study outcome evaluated was anatomic MH closure after the retinal free flap, confirmed by OCT. Secondary outcomes were VA improvement and restoration of the outer retinal bands—external limiting membrane (ELM) and ellipsoid zone (EZ) measured using OCT. These were evaluated in a central reading center using the inbuilt caliper tool (Heidelberg Eye Explorer, Heidelberg Engineering) or based on exported images from other platforms with appropriate scale adjustment using ImageJ (National Institutes of Health, Bethesda, MD). Microperimetry was not used as an outcome because it was not consistently performed across all patients.

Statistical Analysis

Analyses were performed using SPSS 21 (SPSS Inc., Chicago, IL). Recorded Early Treatment of Diabetic Retinopathy Study and Snellen VA were converted to logarithm of the minimum angle of resolution (logMAR) VA. Counting fingers and hand movement were defined as 0.01 (20/2000 Snellen, 2.0 logMAR) and 0.001 (20/20000 Snellen 3.0 logMAR), respectively.[26] Visual improvement was defined as an increase of at least 0.3 logMAR units, and decline was defined as a decrease of at least 0.3 logMAR units (equivalent to 15 Early Treatment of Diabetic Retinopathy Study letters change). Descriptive statistics were computed. Nonparametric Wilcoxon rank-sum test was used because the data were not normally distributed. P values <0.05 were considered statistically significant. The 25th and 75th quartiles of the preoperative anatomic characteristics were calculated. All patients underwent examination at postoperative day 1, week 1, month 1, month 3, and month 6. Interim visits were as needed. All eyes had a minimum follow-up duration of 6 months.

Results

Included were 41 eyes of 41 patients who underwent the surgical procedure and met the eligibility criteria. Patients' mean age at the time of surgery was 61±14.9 years; 27 patients were female, and 14 patients were male. Mean follow-up was 11.1±7.7 months. Preoperative demographic and anatomic characteristics of patients are summarized in Table 1.

Mean preoperative corrected VA (logMAR) was 1.11±0.66 (range, 0.48−3; interquartile range [IQR], 0.7−1), which showed an improvement ($P = 0.03$) to 1.03±0.51 (range, 0.1−2; IQR, 0.6−1.3) at the last postoperative visit. As defined by our criteria, vision improved in 15 eyes (36.6%), was stable in 17 eyes (41.5%), and worsened in 9 eyes (21.9%).

Among patients with good-quality OCT images available, mean preoperative largest basal diameter was 1468.1±656.4 μm (range,

Table 1. Preoperative Characteristics of Eyes with Large Refractory Macular Holes Undergoing Autologous Retinal Transplant (n = 41)

Characteristic	Value (SD)
Mean patient age (IQR), yrs	61±14.9 yrs (63−69.3)
Gender, no. (%)	
Men	14 (34.1)
Women	27 (65.9)
Mean logMAR preoperative VA (IQR)	1.11±0.66 (0.7−1)
Inner opening diameter (μm)(IQR)	825±422.5 (1090−1225)
Number of prior surgeries (range)	1.5±0.94 (1−3)
Mean axial length (mm) (IQR)	27.85±3.18 (28.9−29.8)
Lens status baseline	
Phakic, n (%)	11 (26.8%)
Pseudophakic, n (%)	30 (73.2%)
Coexisting ocular comorbidities	
Pathologic myopia	28
Macular telangiectasia type 2	1
Inactive choroidal neovascular membrane	2
Alport syndrome	1

IQR = interquartile range; logMAR = logarithm of the minimum angle of resolution; VA = visual acuity.

621−2600 μm) and mean inner-opening diameter was 825±422.5 μm (range, 336−1649 μm) (Figs 1−3). None of the eyes had an inverted retinal transplant placed as visualized on the postoperative OCT images.

Complete anatomic closure of MH on OCT was achieved in 36 of 41 eyes (87.8%). Mean size of residual MH in the 5 eyes not closed was 1069±556.2 μm.

Mean axial length was 27.85±3.18 mm (range, 22.8−31.36 mm; IQR, 28.9−29.8 mm). Mean choroidal thickness was 75.8±86.24 μm (range, 13−241 μm; IQR, 33.5−84 μm), consistent with the majority of eyes being high myopes.

Among the 36 eyes with complete anatomic closure, 12 (33.3%) had stable VA (logMAR) (as defined by our criteria) from a preoperative mean 1.14±0.56 (range, 0.48−2; IQR, 0.9−1.5) to a postoperative mean 1.17±0.56 (range, 0.6−2; IQR, 1.33−1.5). Nineteen eyes (52.3%) had improved VA from a preoperative mean 1.58±0.82 (range, 0.7−2; IQR, 1−2) to a postoperative mean 0.93±0.47 (range, 0.6−2; IQR, 0.6−1.3). Five eyes (13.8%) had a decline in VA from a preoperative mean 0.94±0.25 (range, 0.7−1.3; IQR, 0.7−1) to a postoperative mean 1.38±0.37 (range, 1−2; IQR, 1.3−1.3).

Among the 5 eyes without anatomic success, 3 had stable VA (unchanged at mean 1.0 (range, 1; IQR, 1-1), and 2 had a decline in VA from a preoperative mean 0.62±0.11 (range, 0.54−0.7; IQR, 0.58−0.66) to a postoperative mean 1 (range, 1; IQR, 1). None of the eyes without anatomic success had improved VA.

Among eyes with coexisting ocular pathology, 28 eyes were high myopes (axial length ≥26.5 mm), 4 of which had an MH-associated retinal detachment (RD), 1 had Alport syndrome, 1 had macular telangiectasia type 2, and 2 had a preexisting inactive choroidal neovascular membrane (Fig 4). Preoperatively, 12 of 41 eyes (29.3%) had a flat open refractory MH configuration with dry and flat edges.

Mean preoperative EZ defect was 1777.3±513.8 μm (range, 963−2808 μm), which decreased to 1370±556.9 μm (range, 288−2000 μm) at final follow-up (P = 0.007). Mean preoperative external limiting defect was 1681.5±429 μm (range, 1172−2606 μm), which decreased to 1408.5±571.2 μm (range, 200−2000 μm) at final follow-up (P = 0.017).

Mean number of prior surgeries was 1.5±0.94 (range, 1−3). All eyes had an ILM peel previously. Four eyes had undergone a RD repair, 2 of which were also associated with proliferative vitreoretinopathy (PVR) repair previously in which the internal limiting had been peeled. Three eyes had a silicone oil tamponade previously.

Two eyes underwent a repeat autologous neurosensory retinal free flap because of an incomplete MH closure with the initial flap. Although 73.2% of eyes were pseudophakic at baseline, all eyes were pseudophakic at final follow-up. Postoperative neurosensory retinal flap dislocation was seen in 2 procedures. Closed MHs demonstrated a negative Watzke-Allen sign.

The patients were followed up for a mean of 11.1±7.7 months (IQR, 6−13 months; range, 6−36 months). Major postoperative complications were RD (n = 1) and vitreous hemorrhage (n = 1). There were no cases of PVR, endophthalmitis, or suprachoroidal hemorrhage. Postoperatively, there were no cases of choroidal neovascularization at the graft site or harvest site. One eye developed an epiretinal membrane over the harvest site, but this did not affect VA (Fig 5). There were no cases with intraocular inflammation. However, cystoid macular edema−like inner retinal cystic changes were seen on OCT in 7 eyes, usually at the 5-month or later visit, but these did not affect vision or receive treatment (Fig 6).

Baseline MH size was smaller (1107±454.3 μm) in those with visual improvement than in those without visual improvement (1866±645.6 μm, P = 0.01). Baseline VA was 1.63±0.81 logMAR (95% confidence interval [CI], 1.19−2.08) in those with visual improvement versus 1.04±0.51 logMAR (95% CI, 0.78−1.30) in those with no change in vision and 0.85±0.24 logMAR (95% CI, 0.67−1.03) in those with worsened vision postoperatively (P = 0.005, 1-way analysis of variance). We did not observe any correlation between anatomic success and the preoperative largest basal diameter or inner opening diameter of the recalcitrant MH.

Discussion

In this large multicenter international series, we obtained an autologous neurosensory retinal transplant and placed it over the refractory MH, resulting in anatomic closure in approximately 90% of cases with improved restoration of EZ and ELM. Overall, the autologous neurosensory retinal flap resulted in visual improvement in more than 36% of eyes.

Surgical options for refractory myopic MH are limited, and although visual results may be poor despite successful anatomic closure in myopic MH due to several factors, including chorioretinal atrophy, anatomic closure reduces the risk of progression to RD. An ILM flap, either an inverted or free flap, has been described to close refractory and myopic MHs.[27−31] Inverted ILM flaps, although successful for primary repair of myopic MH, cannot be applied to MHs that have failed to close despite an initial wide ILM peel. Although improved outcomes have been described with autologous ILM flaps, harvesting ILM tissue for an autologous flap in the peripheral macula is challenging in high myopes because of the often concomitant posterior staphyloma, chorioretinal atrophy, and poor staining of the ILM.[12,13] In addition, the fragile nature of the ILM in such eyes makes repositioning an autologous flap under the base of the MH a challenging maneuver.[13] In cases of MH complicated by RD, it is especially

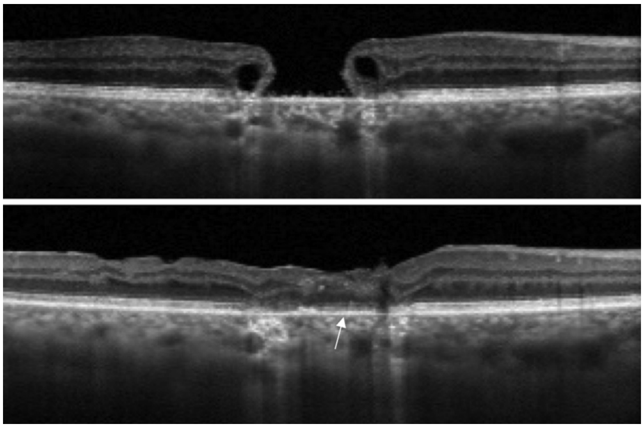

Figure 1. Preoperative (top) and postoperative (bottom) OCT scans after the autologous neurosensory retinal flap for a refractory macular hole. Vision improved from 20/200 preoperatively to 20/60 at 6 months, and there is partial restoration of the external limiting membrane and ellipsoid zone (*white arrow*).

difficult to stabilize the ILM free flap and prevent it from dislodging during the surgery.[27]

Autologous blood has been reported to help seal the ILM over the MH and as an adjunct with the retinal flap.[13,24,32] The use of various adjuvants, such as platelet concentrate,[33] transforming growth factor-β,[34] and autologous serum,[35] has been described with varying success rates. However, the challenge is that any ILM flap-based technique typically is difficult to apply for large refractory MH >1000 μm in size with a prior wide ILM peel such as in our series. The lens capsule, which has been described as an alternative tissue scaffold, cannot be used in pseudophakic eyes with an open posterior capsule.[14] Macular buckling and scleral imbrication techniques to address the posterior staphyloma described in myopic MHs carry the intraoperative risks of perforation and subretinal hemorrhage, and the long-term risks of compression of the macula from the macular buckle, prolapse to fat, extrusion, and strabismus.[36,37] In addition, their effectiveness may be limited in nonmyopic eyes with large refractory MH.[11,16]

Myopic MHs are challenging because they often may be associated with foveoschisis and a posterior RD, which portends a poorer prognosis; such MHs may attain a flat-open configuration even after retinal reattachment, reopening rates are higher, and myopic MH refractory to such interventions are especially challenging to manage.[38,39] Recent case series indicate that first-time surgery with ILM peeling or inverted ILM insertion achieves an MH closure rate ranging from 35% to 100% and a retinal reattachment rate ranging from 69% to 100%.[28,40] In recalcitrant cases, ILM-based techniques cannot be used because the ILM has already been peeled adequately and autologous ILM flaps can be challenging to harvest in such high myopes with a posterior staphyloma and brittle ILM.

In our series, with a heterogeneous population from North America, Southern Europe, and Asia, 28 eyes (68.3%) were highly myopic, and of these 25 achieved anatomic closure (89.3%). In all 4 eyes with a MH associated RD, the MH closed, demonstrating that this technique offers a high

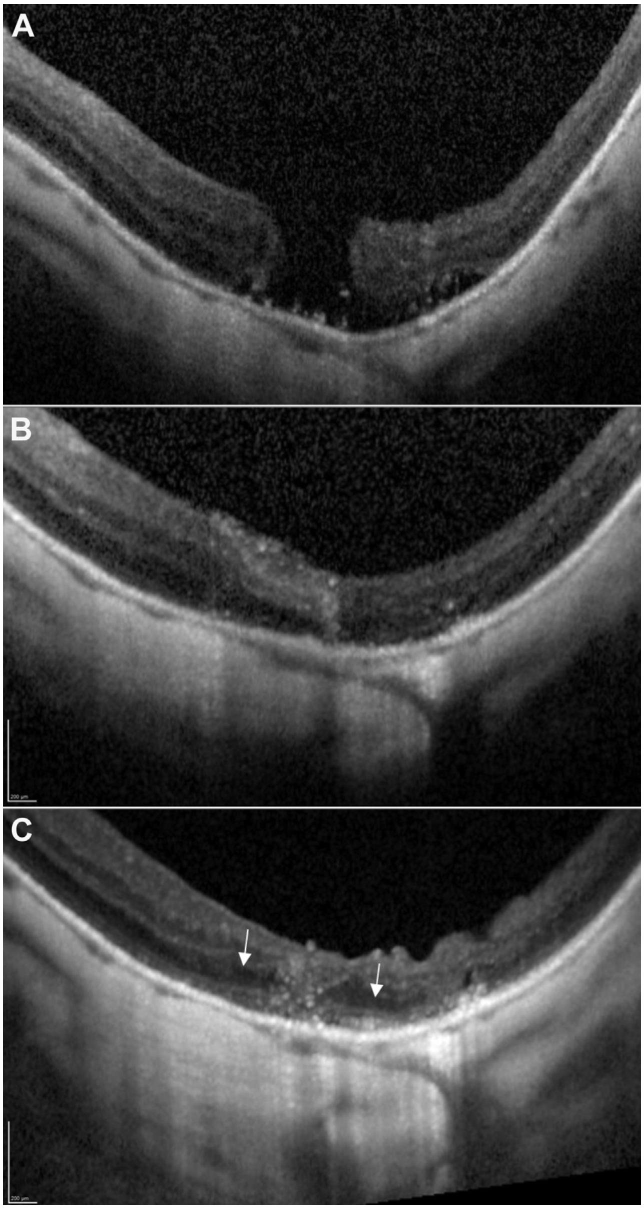

Figure 2. High myope with axial length of 28 mm with a refractory macular hole after 2 prior surgeries with internal limiting membrane flap and gas tamponade and a second procedure with silicone oil tamponade. Preoperative vision was 20/200 **(A)**. After the autologous neurosensory retinal flap, vision improved to 20/160 at month 1 **(B)**. Silicone oil was removed at 5 weeks, and by 6 months there was improved integration of the retinal flap and partial restoration of the external limiting membrane and ellipsoid zone (*white arrows*) with improvement in vision to 20/80 **(C)**.

anatomic closure rate in these challenging refractory cases in which ILM-based techniques are not an option.

Although the exact mechanism remains unknown, inverted and autologous ILM flaps are thought to act as a scaffold for the proliferation of glial cells, thus allowing closure of MH.[22] The mechanism for an autologous retinal transplant seems to be different than just a scaffold. Integration of the transplanted tissue with the host tissue

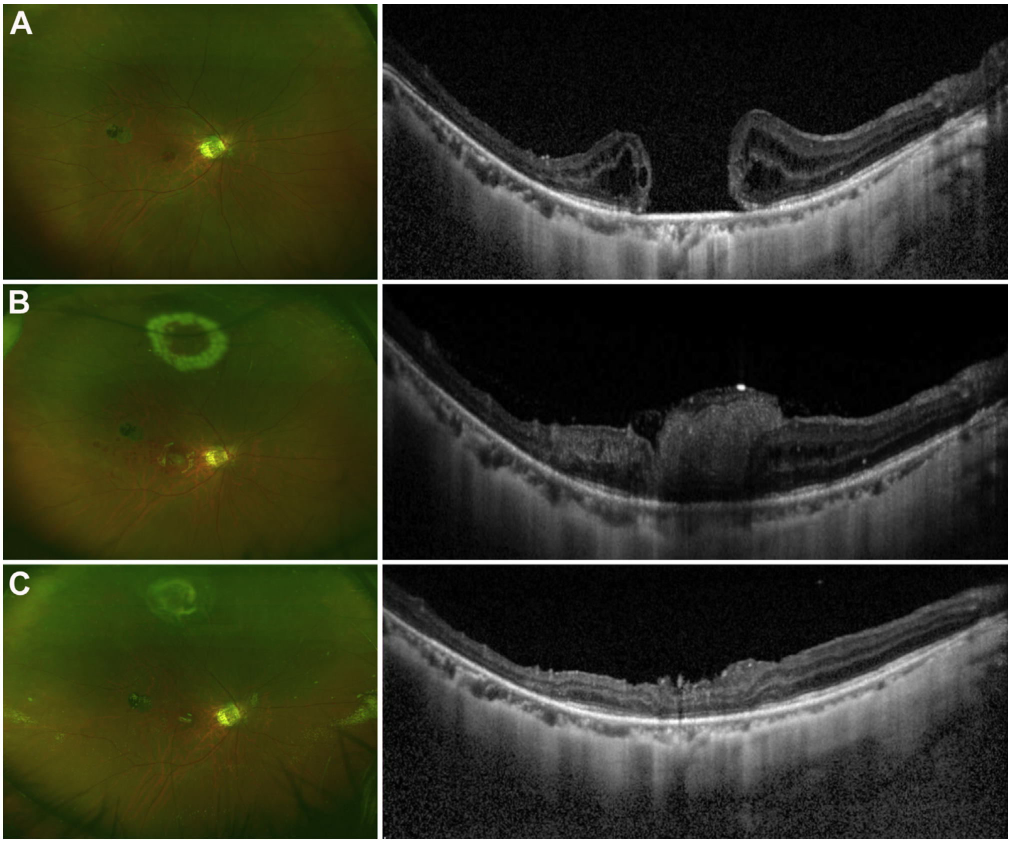

Figure 3. High myope with axial length of 27 mm with a refractory macular hole (MH) after intravitreal ocriplasmin injection and an internal limiting membrane peel with C_3F_8 gas tamponade. Preoperative visual acuity (VA) was 20/100 **(A)**. After the autologous neurosensory retinal flap, vision was 20/200 on day 1 and the hyperreflective retinal flap is visualized in place over the MH **(B)**. At 2 months postoperatively, there was significant integration of the retinal flap with improved architecture of the inner retinal layers **(C)** as well as partial restoration of the external limiting membrane and ellipsoid zone with improvement in VA to 20/160.

as seen on the OCT images indicates an as yet unknown mechanism that allows incorporation of the transplant with some migration of the surrounding retina and with partial restoration of outer layers.

On the basis of our experience with these initial 41 procedures, we believe the size of the retinal free flap should be approximately 0.5 disc diameter larger than the size of the MH to allow for appropriate handling and positioning of the flap, to increase the chances of retaining the flap in the MH after fluid-air exchange (when performed), and to permit adequate coverage of the MH despite some decentration of the flap postoperatively. We think that proper positioning of the transplant in the MH is important for better integration and function. In patients with Alport syndrome, this may be a useful technique because in the genetic defect in collagen type 4, conventional ILM removal techniques may not help close the MH.[41,42] If the MH remains open at the edge, it may stimulate further enlargement into an even more giant hole, and complete closure of the hole is key to aborting the expansion process of those holes.

In contrast to an ILM flap or a lens capsule flap, which often has to be mechanically positioned inside the MH with the potential for iatrogenic trauma, the neurosensory retinal flap is a thicker, sturdier tissue and can be positioned on the surface of the MH, thereby minimizing potential trauma. However, despite the larger and thicker retinal flap, we experienced flap displacement as the most common intraoperative and immediate postoperative complication in our series, under both silicone oil and gas tamponade. Further refinement of surgical techniques will help optimize sustained flap positioning. Based on the experience with initial cases, we advocate the use of PFC liquid before harvest of the flap because it is easier to stabilize the movement and maneuver it into position under PFC. This can then be followed by fluid-air or PFC silicone oil exchange, or PFC can be left as a short-term tamponade. In our recent experience, PFC is now being routinely used for 1 to 2 weeks. This allows secure accurate placement of the transplant in the MH area, avoids any dislocation with exchanges, and seems to help achieve better functional results possibly because of better initial oxygenation to the retinal flap, especially in those chronic cases with underlying retinal pigment epithelium atrophy. We also did not observe any cases of PFC toxicity, elevated intraocular pressure,

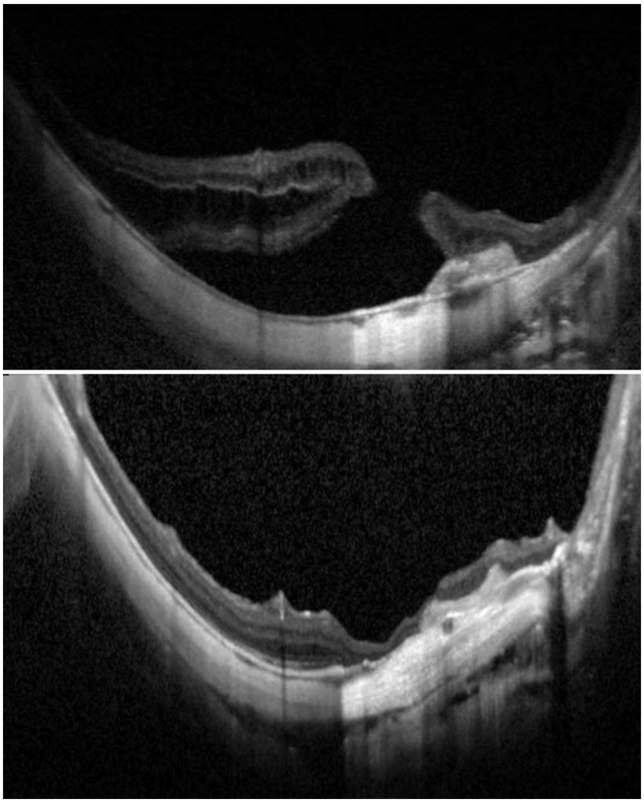

Figure 4. High myope with axial length of 31.7 mm with myopic choroidal neovascular membrane that had regressed after multiple intravitreal bevacizumab injections with a refractory full-thickness macular hole after prior inverted internal limiting membrane flap with C_3F_8 gas tamponade and a visual acuity (VA) of 20/400 (*top*). Sixteen months after the autologous neurosensory retinal flap (and silicone oil removal and cataract extraction in the interim), the VA had improved to 20/160 (*bottom*) and there was partial restoration of the external limiting membrane and ellipsoid zone.

intraocular inflammation (early or delayed), or flap displacement after PFC removal. Short-term use of intraocular PFC has been shown to be relatively safe.[43–47]

We observed late development of cystoid macular edema—like changes in the graft in several cases, usually 4 to 6 months after surgery. These intraretinal cysts were usually limited to the area of the retinal flap and did not affect visual recovery. However, none of the cases in this series required treatment with topical or periocular steroids, and the edema resolved within a few months.

Postoperative OCT scans illustrate bridging tissue in the junctional area of the retinal flaps, indicating integration of the retinal flap tissue. Although the mechanism of this integration, the partial outer retinal layer restoration, and the improved visual function are unclear, several hypotheses can be derived from previous experimental and animal work. Immunohistochemical analysis of the peripheral human retina has shown cells positive for markers present in stem cells of neural origin (Pax6, Sox2, Nestin) and epithelial origin (ABCG2, N-cadherin).[48] Cells with characteristics of neural progenitor or stem cells have been isolated from the neural retina.[49,50] Müller glia isolated from the peripheral retina may be a source of producing cells with properties of rod photoreceptors.[51] Johnsen et al[48] showed that the neuroepithelial stem cells with Müller glia characteristics could respond to retinal injury by targeted migration into the vitreous. By using human enucleated eyes, vitreous samples from eyes with PVR, and a mouse model of PVR, they suggested that neural stem cells present in the Müller glia were quiescent in adult human peripheral retina and activated by retinal injury such as PVR. It could be that the autologous retinal transplant stimulates such processes.

Peng et al[52] suggested that rod bipolar cell dendrites have the capability of ectopic synaptogenesis, alternative connections when the preferred contacts are not available. Horizontal and rod bipolar cell processes have been

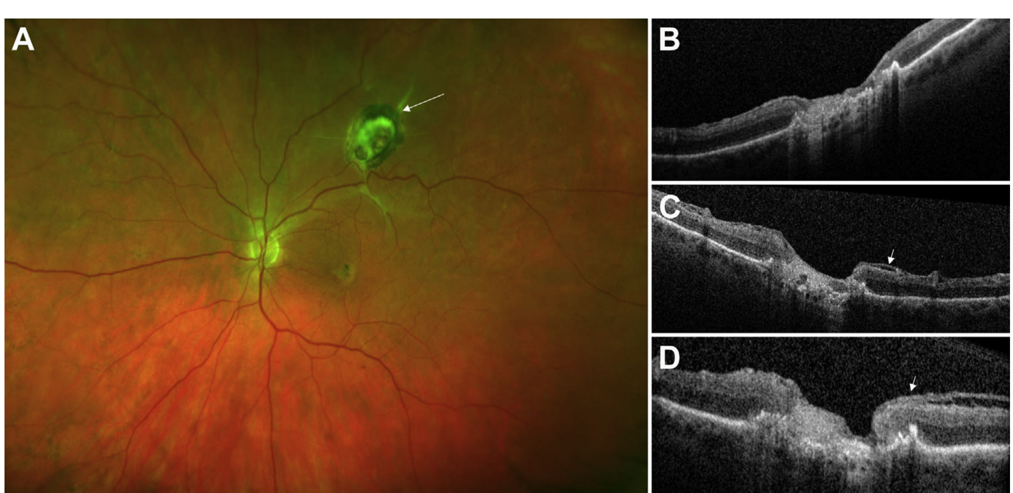

Figure 5. Development of an epiretinal membrane (ERM) over the harvest site in a single case. Photograph showing an ERM over the harvest site (**A**, *white arrow*) and sequential OCT showing no ERM at 3 months (**B**) and development of an ERM at 6 months (**C**, *white arrow*) and 12 months (**D**, *white arrow*).

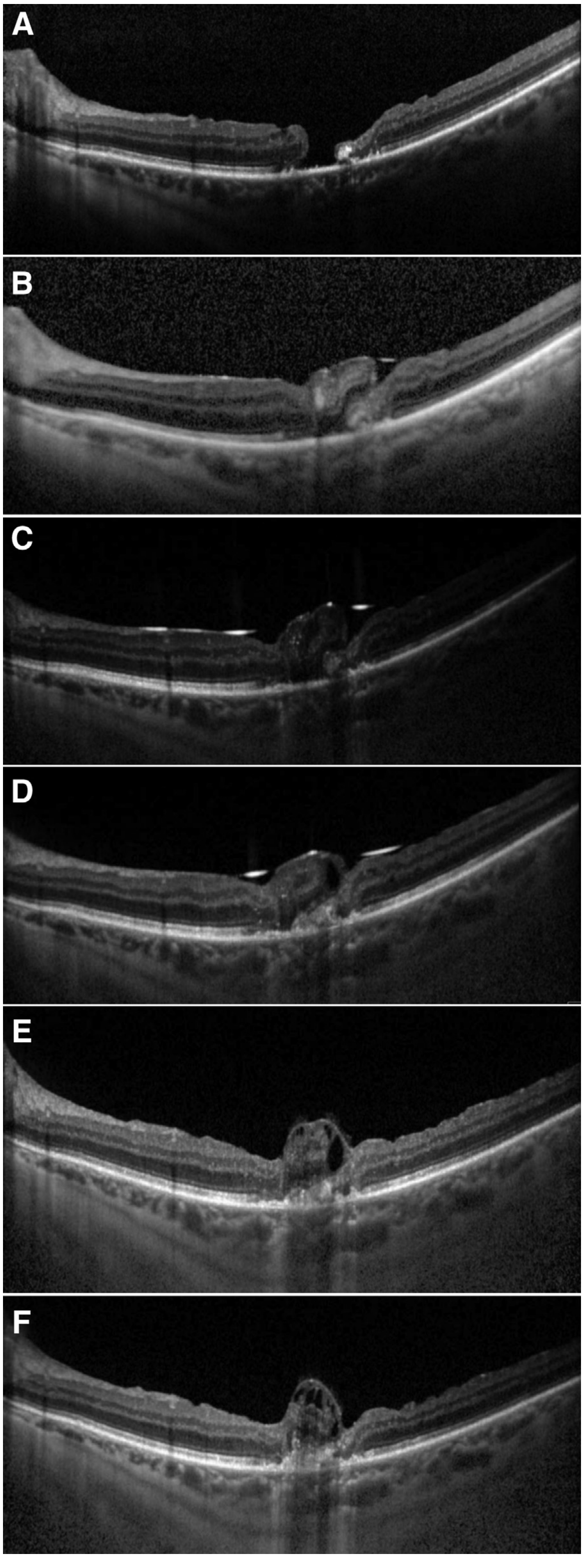

Figure 6. Sequential OCT scans up to 12 months after an autologous retinal flap in a refractory full-thickness macular hole with juxtafoveal telangiectasia after a prior internal limiting membrane peel and gas tamponade. Preoperative visual acuity (VA) was 20/200 **(A)**. At 1 week postsurgery **(B)**, the VA was 20/400 and the retinal flap is visualized as hyperreflective tissue. At 1 month, there is improved integration of the retinal flap **(C)** and VA improved to 20/160 and further to 20/100 at 3 months **(D)**. At 6 months, there is partial restoration of the outer retinal bands and development of cystic spaces in the inner retina, and VA improved to 20/80 **(E)**. At 12 months after surgery, there is slightly increased cystic spaces and VA is 20/100 **(F)**.

shown to grow into the outer nuclear layer and form ectopic synapses with photoreceptors as a result of photoreceptor degeneration such as after RD.[53−55]

Although a study of the functional properties of such ectopic synapses would need physiologic analysis at a cellular level, synaptic rewiring between cone and rod bipolar cell dendrites remains a possibility.[52] Although previous work does provide a framework to possibly explain the partial restoration of outer retinal layers and improved visual function seen with our technique, further analysis, animal and in vitro, clearly is required to better understand the true regenerative potential of this cell population. It is important to recognize that, as yet, all these mechanisms remain hypotheses.

There are patients such as those in our series who have undergone multiple previous surgeries with a wide ILM peel. There is some controversy whether it is worthwhile operating on chronic large MHs in patients with poor baseline vision. Such patients have traditionally not had any surgical options available to them, and such large refractory MHs are often observed without the patients being offered surgical intervention. An open hole in an eye with high myopia poses the risk of recurrent RD in addition to contributing to hindered central vision.[56] However, reoperations involve time, expense, and effort on the part of the patients. It is important to emphasize that the main goal of this procedure is to provide anatomic closure of refractory MH and retinal reattachment in MH RD cases. Although VA improvements were a secondary outcome measure, vision improved in 36.6%, stayed the same in 41.5%, and worsened in 21.9%. The majority of eyes also showed microstructural regeneration of the retina with improved restoration of EZ and ELM.

Patients would want to know whether it is worthwhile to undergo a repeat surgery, the chances of closing the MH, and the level of vision expected. It can be argued, however, that an unoperated MH, whether primary or recalcitrant to previous surgery, is a potential lost opportunity to stabilize or improve vision.[57] To minimize or avoid decline of macular function, there may be benefit to surgery, even if VA is not expected to improve much or at all. Attempting to restore anatomy closer to normal by appropriate surgical intervention may be necessary to preserve vision and optimize functional recovery. However, we would not recommend this procedure in eyes with extensive chorioretinal scarring that would preclude obtaining a viable retinal transplant or those with retinal ischemia, neovascularization, and inflammation. Reduction of central scotomas, which was subjectively described by the majority of the patients, is known to be important in patients with MHs.[58] Even in patients with stable VA, patients described a gradual but significant reduction of the central black spot in their visual field and reported that this reduction of the central scotoma helped them significantly with tasks at both distance and near. The improvement in VA and subjective reduction in the central scotoma with a negative Watzke-Allen sign further corroborate the autologous neurosensory retinal transplant maintaining some degree of retinal function. We are confident that with more recent experience, better functional results may be achieved in large and myopic MHs potentially even as a primary procedure before the development of extensive underlying retinal pigment epithelium atrophy due to chronicity.

Study Strengths and Limitations

Strengths of this study include it being a large series of consecutive cases undergoing the autologous neurosensory retinal flap procedure for MHs with a robust follow-up among different surgeons. However, our study is limited by its retrospective nature, lack of standardized imaging, individual variations in technique and patient selection, different tamponade agents, and lack of controls. Future investigations should include quality of life metrics, such as the Visual Function Questionnaire, because Snellen VA alone may not be the most accurate parameter to assess visual rehabilitation after this procedure.

In conclusion, while acknowledging these limitations, we present a large international series of encouraging long-term surgical outcomes of autologous neurosensory retinal transplant for refractory MHs. Overall, there was a high degree of anatomic success, and the technique proved safe in this initial experience for closure of refractory MHs. Such patients did not previously have viable surgical options available, and this technique may provide the basis of a surgical technique upon which other improvements can be built and serve an important tool in the surgical armamentarium for management of such challenging refractory MHs.

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Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
CI = confidence interval; **ELM** = external limiting membrane; **EZ** = ellipsoid zone; **ILM** = internal limiting membrane; **IQR** = interquartile range; **logMAR** = logarithm of the minimum angle of resolution; **MH** = macular hole; **PFC** = perfluoro-*n*-octane; **PVR** = proliferative vitreoretinopathy; **RD** = retinal detachment; **VA** = visual acuity.

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