AUTOLOGOUS NEUROSENSORY RETINAL TRANSPLANTATION: Bridging the Gap.

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Review

AUTOLOGOUS NEUROSENSORY RETINAL TRANSPLANTATION

Bridging the Gap

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Purpose: To review the autologous retinal transplantation surgical technique, indications, rationale, and current outcomes of data published to date.

Methods: Review of surgical technique, preoperative and postoperative best-corrected visual acuity, and macular hole (MH) closure rate in studies with at least five eyes.

Results: The weighted average macular hole closure rate is 88%, with a MH closure rate ranging from 66.7% to 100%. The weighted average best-corrected visual acuity improved from mean logarithm of the minimum angle of resolution 1.35 (Snellen equivalent of 20/450) preoperatively to mean logarithm of the minimum angle of resolution 1.02 (Snellen equivalent of 20/210) postoperatively. From the largest autologous retinal transplantation case series, 37% of patients gained 3 or more lines of visual acuity after autologous retinal transplantation for primary or refractory MHs and 74% gained 3 or more lines of visual acuity after autologous retinal transplantation for MH–retinal detachments. Functional improvement including negative Watzke–Allen sign and conversion from positive to negative scotoma was reported in large case series.

Conclusion: Autologous retinal transplantation is a promising technique for closure of large and refractory MHs otherwise difficult to repair with conventional techniques. This technique may allow for replacement of neural tissue in the macula through cell rehabilitation and regeneration through presumed ectopic synaptogenesis, retinal progenitor cell differentiation and integration, and/or retinal progenitor cell material transfer to host neurons.

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Before the 1990s, macular holes (MHs) were believed unfixable until Kelly and Wendel[1] published the first series of MH repair demonstrating a 58% closure rate with pars plana vitrectomy alone. A significant advancement in MH closure (rates > 90%) was achieved with internal limiting membrane (ILM) peeling and development of chromovitrectomy to improve surgical visualization.[2,3] Nevertheless, despite these advances, large (>400 μm) and refractory MHs remain difficult to repair with traditional surgical approaches.[4,5] Numerous techniques aiming to address traction, alter tamponade agents, promote closure with adjuvant agents and/or growth factors, or use of scaffolds were developed to repair these challenging MHs.[3,6] Despite this, visual prognosis for these cases remains guarded compared with standard MH surgery.

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Autologous retinal transplantation (ART) was first performed for refractory myopic MH repair in a pseudophakic patient who underwent previous vitrectomy with ILM peeling.[7] In ART, a peripheral retinal graft is harvested and placed in the MH followed by gas or silicone oil tamponade. This technique promotes neural tissue integration and rehabilitation of damaged retina. Surgeons worldwide have used this technique for challenging MH repairs.

Rationale and Biological Basis

Although the mechanisms underlying MH pathogenesis are not fully understood, an abnormal vitreomacular interface resulting in both anteroposterior and tangential traction likely plays a role in MH pathogenesis.[8] Macular hole surgery addresses anteroposterior traction with vitrectomy and posterior vitreous detachment induction, and tangential traction with epiretinal membrane and/or ILM peeling. Although this is sufficient for most MH, tissue replacement may be necessary to achieve successful MH closure and visual improvement in certain cases.

After ART, optical coherence tomography (OCT) images demonstrate flattening of the MH edges with centripetal migration of surrounding retina and eventual graft integration.[7,9] The graft creates a barrier between the vitreous cavity and previously exposed subretinal space, allowing subretinal fluid to be removed by the retinal pigment epithelium (RPE) promoting MH closure.[7,9,10] Autologous retinal transplantation enables cellular rehabilitation in addition to tissue replacement. Animal models have demonstrated a degree of synaptic plasticity after dissociation of photoreceptors from their corresponding bipolar cells and vice-versa.[11–13] It is hypothesized that transplanted retinal photoreceptors could directly synapse with bipolar cells in the host area through ectopic synaptogenesis. Transplanted healthy photoreceptors may also promote cell–cell communication that rehabilitates damaged photoreceptors at the host site. Retinitis pigmentosa models demonstrated reactivation of dormant cones after healthy rod photoreceptor transplantation by re-establishing glucose transport that promoted synthesis of cone outer segments.[14]

The retinal graft may also contain retinal progenitor cells (RPCs). Fish and amphibians demonstrate significant regenerative capabilities from RPCs at the ciliary margin zone of the anterior retina.[15] A subset of Müller cells harvested from cadaveric human retina samples were shown to demonstrate immortality and pluripotency in vitro with expression of neural stem cell markers.[16,17] These cells differentiate into rod photoreceptors and retinal ganglion cells in vitro and integrate into outer and inner nuclear retinal layers when transplanted into animal models.[18,19] Integrated precursor cells demonstrate functional improvement in pupillary reflex and scotopic tasks in rod degenerative mice models.[20] Models of retinal injury or developing retinas demonstrate more effective incorporation of RPCs as compared to normal retina models, suggesting that extracellular matrix, relative hypoxia, and other developmental factors affect these cells' pluripotency.[18,21] In addition, RPCs rehabilitate surrounding tissue through material transfer. Pearson et al[22] demonstrated extensive material transfer of protein and RNA to photoreceptors outside of the localized RPC subretinal injection site, replacing previously lost cellular functions in retinal degeneration models. In summary, ART replaces tissue and integrates healthy photoreceptors and potential RPCs, which may allow for structural and functional rehabilitation of surrounding retina.

Indications for Autologous Retinal Transplantation

Autologous retinal transplantation was initially performed for closure of refractory myopic MH that did not resolve with peeling of ILM and when lens capsule (or other scaffold) was not available to harvest.[7] Today, the indications for ART have expanded to include use in any large MH refractory to conventional techniques,[23] combined large MH-associated retinal detachments (with or without proliferative vitreoretinopathy),[24] large primary MH that would not close with traditional surgical approaches (e.g., high myopia–associated MH),[25] and large MH associated with other ocular (e.g., macular telangiectasia Type 2) or systemic conditions (e.g., Alport syndrome).[9] This technique was modified for use in patients without MH, in cases of end-stage exudative age-related macular degeneration and one patient with a chronic retinal detachment without MH, to improve vision after graft integration.[26,27]

Surgical Technique

Preoperative estimation of MH dimensions using spectral-domain OCT is essential to prepare an adequately sized graft. Additional direct measurements may be performed intraoperatively with instruments such as the FINESSE Flex loop (Alcon, Fort Worth, TX). The retinal graft is oversized by about 1.2 to 1.5× the original defect because of shrinkage of the retinal graft as the tissue integrates into the defect.[7,9,28]

If the eye was not previously vitrectomized, a standard three-port pars plana vitrectomy is performed. A fourth port may be placed for chandelier illumination and bimanual maneuvers. Additional ILM peeling is often not helpful, particularly in eyes that have previously undergone ILM peeling. The retinal autograft site is then retinopexied using multiple rows of barrier endolaser. Light endodiathermy is applied to blood vessels at the edge of the graft to control intraoperative bleeding and to delineate the graft. The graft can be excised directly using vertical scissors or excised after induction of a focal retinal detachment with balanced salt solution infusion through a 41-gauge subretinal cannula. End-grasping forceps and curved or vertical scissors are helpful to excise the graft, leaving a graft hinge attached to prevent its migration into the vitreous cavity before instillation of perfluorocarbon liquid (PFCL). Perfluorocarbon liquid is instilled to cover both the MH and donor site. After PFCL instillation, the graft hinge is severed, and the graft is transferred to the recipient site using end-grasping forceps or a FINESSE Flex loop (Alcon). Unimanual technique under PFCL is sufficient for MH without retinal detachment. However, graft manipulation and transfer to the MH is easier with a bimanual technique, especially in cases associated with retinal detachment, to maintain graft orientation, prevent graft slippage or loss, and prevent subretinal migration of PFCL.

Some surgeons tuck the graft subretinal (when the macula is already detached as in MH-associated retinal detachment) or leave the graft preretinal.[26,28] In the latter, the graft edge is apposed to the temporal edge of the MH and the nasal edge slightly "overhangs" the defect in anticipation of the postoperative retinal shift. The surgeon's choice of tamponade agent is then instilled into the eye. Some surgeons keep PFCL for short-term tamponade with staged PFCL removal about two weeks later, perform direct PFCL to silicone oil exchange, or perform a fluid–gas exchange with gas endotamponade. Choice of tamponade agent does not significantly affect postoperative visual outcomes.[28] The authors prefer short-term PFCL tamponade with staged removal of PFCL because fluid–gas exchange or silicone oil exchange increase the risk of graft slippage or loss. This approach also allows the surgeon to verify the graft position with a postoperative OCT, and the graft can be further micro-adjusted at the time of PFCL removal.

The most common graft harvest sites were superior (45%), inferonasal (17%), and superotemporal (11%), with 84% of grafts harvested posterior to the equator in the largest published case series.[28] Reported intraoperative complications include intraoperative graft slippage (2.3%), undersized graft (1.5%), subfoveal RPE damage (0.8%), and intraoperative bleeding (3.1%).[28] Infrequent postoperative complications include graft dislocation, postoperative proliferative vitreoretinopathy, postoperative retinal detachment, endophthalmitis, subfoveal RPE damage, choroidal neovascularization, and subretinal or vitreous hemorrhage.[28,29] Adjunct autologous blood clot or dispersive ophthalmic viscoelastic devices have been used to prevent graft dislocation but require further study.[10,30]

Anatomic, Visual, and Functional Outcomes

When analyzing ART series of at least five eyes, the weighted mean closure rate was 88% (range: 66.7%–100%) for a variety of MH repairs (Table 1).[9,10,25,28–34] Patients with larger MH diameters demonstrated lower rates of successful closure.[9,34] Cases without successful closure usually did not achieve graft integration into the surrounding tissue. It was postulated that some degree of RPE loss or dysfunction led to accumulation of persistent subretinal fluid that prevented graft integration.[34]

Anatomic success was achieved in most ART cases; however, visual acuity improvement was less frequently reported.[11] At minimum, patients with successful MH closure demonstrated a negative Watzke–Allen sign with improved binocular function by transforming a noticeable positive scotoma into a negative scotoma.[9] Many patients gained several lines of visual acuity (Table 2).[9,10,25,28–34] In the largest ART series, 12% of patients attained a postoperative visual acuity of 20/50 or better after ART for primary or refractory MH; none of these patients underwent ART for combined MH–retinal detachment.[28] Anatomic features associated with significant visual acuity improvement included ellipsoid zone reconstitution and alignment of neurosensory layers (ANLs) (graft inner plexiform layer to host inner plexiform layer, graft outer plexiform layer to host outer plexiform layer, etc.).[28] For MH–retinal detachment cases, a 79% single-surgery retinal reattachment rate was reported with a 95% MH closure rate.[28] The weighted mean preoperative best-corrected visual acuity improved from 1.35 logarithm of the minimum angle of resolution (logMAR) (Snellen equivalent of 20/450) to 1.02 logMAR (Snellen equivalent of 20/210) for ART studies with at least 5 eyes (Table 1).[9,10,25,28–34] Refinement of this technique would improve MH closure rate and functional outcomes for our patients.

Challenges and Future Directions

Autologous retinal grafts expand the surgical repertoire and offer vitreoretinal surgeons an additional tool

Table 1. Outcomes of ART for MH in Studies With at Least Five Eyes

Author(s)	Publication Year	No. of Eyes	Mean Minimal Diameter Macular Hole, μm (Range)	Mean Basal Diameter Macular Hole, μm (Range)	Closure Rate, %	Mean Preoperative BCVA, logMAR	Mean Postoperative BCVA, logMAR	Mean Follow-up, months (Range)
Wu et al[30]	2018	6	538 (219–785)	978.5 (576–1820)	66.70%	1.47	1.09	25.2 (12–51)
Grewal et al[9]	2019	41	825 (336–1,649)	1,468.1 (621–2,600)	87.80%	1.11	1.03	11.1 (6–36)
Ding et al[31]	2019	5	—	—	100.00%	2.38	1.46	6 (6)
Chang et al[10]	2020	10	—	1,404 (811–2,250)*	90.00%	1.65	0.88	12 (12)
Rojas-Juárez et al[32]	2020	13	964.1 (512–3,193)	1,615.38 (889–2,943)	76.92%	0.92	0.75	12 (12)
Tanaka et al[25]	2020	7	661.4 (601–890)	1,214 (1,020–1,459)	100.00%	1.1	0.68	12 (12)
Takeuchi et al[29]	2020	5	1,175 (798–1,688)	1,504 (856–2,501)	100.00%	0.84	0.76	13.6 (6–24)
Moysidis et al[28]	2020	130	837 (743–931)†	1,470 (1,305–1,635)†	89.00%	1.37	1.05	8.6 (7.8–9.4)†
Li et al[33]	2020	10	—	1,192.6 (576–1814)*	80.00%	2.01	1.32	- (3–6)
Sonmez[34]	2021	7	788.9 (644–1,100)	1,146.7 (653–1768)	100.00%	1.53	0.89	18.8 (12–38)

*measurements were reported as mean diameter of MH without specification of location of measurement within the MH.
†SD was reported in this study instead of range.
BCVA, best-corrected visual acuity.

Table 2. Percent Gain in Snellen Visual Acuity for ART Case Series of At Least five Eyes

Author(s)	Publication Year	No. of Eyes	Type of MH	Gain of at Least 3 Lines of VA (%)	Gain of at Least 5 Lines of VA (%)
Wu et al[30]	2018	6	Refractory MH	67	33
Grewal et al[9]	2019	41	Refractory MH	37	—
Ding et al[31]	2019	5	MH–retinal detachment	80*	80*
Chang et al[10]	2020	10	Refractory MH	90	70
Rojas-Juárez et al[32]	2020	13	Refractory MH	—	—
Tanaka et al[25]	2020	7	Primary MH	57	57
Takeuchi et al[29]	2020	5	Refractory MH	20	0
Moysidis et al[28]	2020	35	Primary MH	37	17
		76	Refractory MH	37	25
		19	MH–retinal detachment	74	68
Li et al[33]	2020	10	MH–retinal detachment	100*	60*
Sonmez[34]	2021	7	Refractory MH	100*	71*

*In series where logMAR was reported, improvement in 0.3 logMAR was deemed equivalent to a gain of at least 3 lines of visual acuity and improvement in 0.5 logMAR was deemed equivalent to a gain of at least 5 lines of visual acuity.

to treat previously inoperable MHs. We have learned a significant amount from large ART case series; yet, there is considerably more work to be conducted.

Moysidis et al[28] found no difference in postoperative visual acuity with location of retinal harvest site. Superior graft harvest sites may theoretically minimize the risk of proliferative vitreoretinopathy from surgically induced retinal breaks and allow for prolonged tamponade (particularly with gas) when compared to inferior graft harvest sites. RPCs have been isolated from several locations;[16–19,35] however, the optimal source of RPCs has yet to be identified. As we learn more about RPCs, their distribution, and methods to image them preoperatively, we may target preferential graft sites. Furthermore, optimal methods to harvest retinal grafts warrant further investigation. It is unclear whether shearing forces during induction of a focal retinal detachment lead to more graft photoreceptor damage versus direct graft excision and whether this affects visual outcomes. In addition, it is uncertain whether a retina–choroidal graft would produce better outcomes or improves graft integration as compared to a retina graft alone. In cases with RPE or choroidal compromise, a combined retina–choroidal graft would likely be more beneficial compared to a retina graft alone.[27] Furthermore, the choroid and retina could be harvested in separate locations depending on the robustness of donor sites.

Although Moysidis et al[28] did not demonstrate any difference in visual acuity with choice of endotamponade agent, PFCLs have higher oxygen diffusion coefficients and would provide optimal oxygen tension for survival of the retinal graft in the earliest stages of an avascular transplant. Optical coherence tomography angiography has shown evidence of vascularization of the graft superficial plexus in the first two to three weeks and partial vascularization of the deep plexus at 3 months.[36] During the first few weeks of graft transplantation, the graft presumably relies on oxygen diffusion from the choroid and the vitrectomized vitreous cavity.[28] This likely leads to upregulation of vascular endothelial growth factors and other growth factors that re-establishes the partial blood supply as demonstrated on OCT angiography.[28,36] Relative early hypoxia of the graft may also contribute to RPC expansion and pluripotency as demonstrated in vitro.[21] Further investigation regarding graft vascularization and its effects on graft viability would help us understand the success rate of the surgery and visual outcomes.

Patients with optimal integration of the retinal graft demonstrate alignment of neurosensory layers with preservation of the ellipsoid zone leading to improved visual outcomes.[28] The optimal placement of the retinal graft likely plays a significant role for successful ANLs. Optical coherence tomography evidence of ANLs can be first noted at postoperative week one with complete integration at one to two months.[28] Factors that affect ANLs still require study. It is unclear whether MH morphology or chronicity affects ANLs. Several patients with ANLs had intact ILM in the Global Consortium Study.[28] It is postulated that Müller cells help achieve ANLs. In addition, ILM peeling outside of the macula is more challenging and may cause mechanical trauma to the graft. Therefore, the authors do not advocate for routine ILM peeling over the graft, if not previously peeled. The effect of retained graft ILM and its influence on anatomic and visual outcomes requires further exploration. Histopathological studies may help answer these questions in the future.

No studies have directly compared this technique with other grafting techniques. Caporossi et al demonstrated a 100% closure rate for recalcitrant MH with the use of human amniotic membrane as a graft in 36 eyes, arguing that their technique was more approachable for other surgeons compared with other techniques (ART, lens capsule scaffold, and ILM scaffold) with similar visual outcomes.[37] A prospective trial comparing various grafting techniques to determine efficacy would be clinically useful. True neurosensory tissue replacement with the potential therapeutic benefits of ectopic synaptogenesis, material transfer, and RPCs could only be achieved with ART. Other scaffolding techniques may impair synapse reformation by acting as a barrier between neuronal cells and potentially lyse previous photoreceptor–RPE connections,[38] interrupting the visual cycle and contributing to photoreceptor and RPE degeneration. These trials would allow surgeons to develop a personalized approach of different techniques to repair larger and refractory MH for individual patients. Further study would guide patient selection for primary or early ART (e.g., myopic MH) to achieve optimal functional and visual outcomes and obviate unnecessary surgical procedures.[25,28]

Finally, ART for large MH-associated retinal detachments, pediatric patients, and patients with pathologic myopia warrants more attention. There are limited case series (largest n = 19) concerning outcomes of ART for MH–retinal detachments.[28] It is unclear whether a staged procedure, primary retinal detachment repair followed by surgery to close the MH, improves visual outcomes. Larger cohorts studying MH–retinal detachments are needed. Few cases have been published for ART in patients younger than 50 years, with the youngest patient being 7 years.[39] Safety and efficacy for pediatric cohorts requires further study, especially because ART goes against the established dogma of avoiding iatrogenic retinal breaks at all costs in pediatric retinal surgery. Pathologic myopes present another unique challenge. It is much more difficult to harvest thinner retina in these patients. The MH is also difficult to visualize intraoperatively. Readily available fundus photographs, OCT images, retinal drawings, or intraoperative OCT helps surgeons identify landmarks for intraoperative graft placement.[40] Optimal graft placement is also difficult in cases with posterior staphyloma. During transfer of the graft, one should follow the contour of associated staphylomas without lifting the graft to prevent the graft from wrapping around the instrument. If the graft wraps around an intraocular instrument and is unable to flatten, return to the original graft location, slowly release the graft, and reattempt placement into the MH.

In summary, ART is a promising technique for difficult MH cases and may be a useful technique to use for patients with outer retinal layer loss. Further research is needed to understand the potential visual improvement to be gained with this technique and its implications for similar therapies that aim to restore degenerated retinal tissue.

Key words: autologous retinal transplant, macular hole, myopia, retinal transplantation, stem cells, surgical technique.

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