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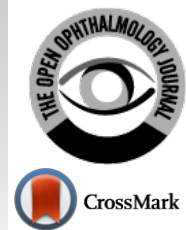
REVIEW ARTICLE

Autologous Retinal Transplant for Macular Hole

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Abstract:

We aim to review scientific literature concerning published studies on autologous retinal transplantation to treat macular hole patients. The following databases were searched: Medline and Medline Non-Indexed Items, Embase (1990–2020), Ovid Medline® (1990 to November 2020), Embase (1990 to November 2020), Ovid Medline® and Epub Ahead of Print, in-Process and Web of Science (all years). Search keywords included "autologous", "retinal transplant", "autologous neurosensory retinal free flap" "transplantation", "macular hole", and "macular hole surgery". Eighteen case series and single case reports were reviewed.

Preoperative and final best-corrected visual acuity, microperimetry and multifocal electroretinogram findings, macular hole closure rate, preoperative and postoperative ellipsoid zone, and external limiting membrane defects were obtained and analyzed. Indications of autologous retinal transplantation for macular hole surgery included refractory macular holes, conventional techniques, and large macular holes. The number of cases included in the different case series ranged from 2 to 130 cases, and prior macular hole surgeries of the patients ranged from 0 to 3. Overall, the published case series of autologous retinal transplants have reported a macular hole closure rate of 66.7 to 100%, as well as a significant improvement in best-corrected visual acuity. The most frequently reported complications included considerable intraoperative bleeding and postoperative dislocation of the graft. The presence of functionality in the graft area has also been documented by microperimetry and multifocal electroretinogram.

In conclusion, the autologous retinal transplantation technique for macular hole patients has emerged as another surgical option, with a high macular hole closure rate and visual improvement.

Keywords: Autologous retinal transplant, Macular surgery, Macular hole, OCT, Microperimetry, Retinal graft.

1. INTRODUCTION

Wendel and Kelly published the first series of cases with idiopathic MH presence successfully treated with vitrectomy [1].

Since MH surgery's original description, multiple variants to the original technique have been described [2 - 10]. Peeling the internal limiting membrane is one of the modifications to the original MH surgery technique that has increased the MH closure rate [2]. However, in up to 10% of the operated cases, the MH closure is not achieved with conventional surgery [5].

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In the last decade, several other techniques have been described for the treatment of MH hole patients. Some of these techniques use transplanted tissue either from the patient's eye or another donor, achieving the MH's closure through various mechanisms [3 - 10].

Autologous internal limiting membrane graft [3], autologous serum [4, 5], blood [6], lens capsule [7, 8], and amniotic membrane [9, 10] are some of the tissues used in MH surgery. One of the most recently described techniques is autologous retinal transplantation (ART). Grewal and Mahmoud described the original ART technique [11]. Since its introduction, several other ART case reports and case series have been published for MH [12 - 29] and other retinal diseases [30 - 32].

This review aims to describe some technical variants, the anatomical and functional results of the case series of ART for MH published to date. The following databases were searched: Embase (1990–2020), MEDLINE and MEDLINE Non-Indexed Items, Ovid MEDLINE® (1990 to November 2020), Embase (1990 to November 2020), Ovid MEDLINE® and Epub Ahead of Print, in-Process and Web of Science (all years). Search keywords included "autologous", "retinal transplant", "autologous neurosensory retinal free flap" "transplantation", "macular hole", and "macular hole surgery". Inclusion criteria for the study/search included ART techniques descriptions for full-thickness MH, MH with/without retinal detachment, naïve MH cases, and MH refractory cases. Nineteen case series and single case reports were reviewed, as they meet the study criteria; two of them were single case reports, and seventeen were case series. The articles included in this review were published between the years 2016 and 2020.

1.1. Surgical Techniques of Autologous Retinal Graft for Macular Hole

In the first description of ART [11], a pars plana vitrectomy was performed using chandelier illumination. Subsequently, a laser barricade was applied around the area chosen for taking the autologous graft, adjacent and superior to the superotemporal vascular arcades, to avoid large retinal vessels to prevent significant bleeding once harvesting was performed.

Harvesting the graft can be accomplished, previously inducing a localized retinal detachment (RD) in the selected area for obtaining the graft, injecting saline solution into the subretinal space with a 41Ga needle [17], although many authors have described harvesting of the graft without inducing an RD [11 - 16, 20 - 24]. Inducing an RD may decrease the risk of traumatizing the choroid vessels with the scissors and subsequent bleeding [17]. In some cases, endodiathermy or laser were utilized to mark the retinal tissue and applied to the bleeding sites [15, 19].

The graft can be harvested using 23 Ga or 25 Ga vertical scissors, holding it by one of its edges with 23 Ga or 25 Ga forceps. Once harvested, the graft is displaced to the hole site, using a 23Ga or 25Ga silicone tipped cannula and stabilizing it with perfluorocarbon fluids (PFs). Graft dislocation is prevented by lowering the intraocular pressure setting to reduce turbulence in the fluid stream [15, 19, 21 - 29]. Afterward, a PFs-silicone oil exchange is carried out. A prone position is prescribed to the patient for one week, and the silicone oil was removed after approximately four months [19].

Some variants of the original technique have been published [12 - 28]. The site where the graft is harvested depends on the surgeon's preference. It has been obtained outside the vascular arcades from the superior, superotemporal, temporal, inferotemporal, inferior, inferonasal, or nasal areas [11, 13, 15, 19]. A bimanual technique is recommended to harvest the graft, and it has been performed on the retina immediately internal to the area where the laser barricade was applied.

The autologous graft size should be approximately 1.5 to 2 times larger than the MH's diameter [13, 15, 19]. It has been positioned above or below the MH edges [17, 19]. Tamponades used have included PFs, C_3F_8 gas, silicone oil, SF_6, and air [12 - 28].

1.2. Anatomical Outcomes

The publications to date on ART are isolated case reports or case series. The most extensive case series have been published by Moysidis *et al.* [19].

Table **1** shows the baseline characteristics of the cases included in the published case series. Most MH cases had a minimum diameter larger than 500 μm and at least one previously failed vitrectomy. Authors have reported ART in first-time operations in those cases with chronic, large macular holes. One of the patients had retinal detachment related to a large macular hole. Common indications to perform ART were those cases that had undergone several surgeries.

Table 1. Autologous retinal transplant in MH. Baseline characteristics and postoperative follow-up of the different case series.

Publication	Number of Cases	Prior Surgeries	Follow-up Time (Months)	MH Minimum Diameter (μm ± SD)
Ding *et al.*	5	1	6	_
Wu *et al.*	6	2.3 ± 0.5	25.3 ± 15.6	538 ±184.9
Thomas *et al.*	2	2-3	3-12	_
Tanaka *et al.*	7	0	16	643
Grewal *et al.*	41	1-3	11.1 ± 7.7	825 ± 422.5
Chang *et al.*	10	2-3	12	1404.2 ± 562.9
Moysidis *et al.*	130	1.7 ± 0.2	8.6 ± 1	837 ± 34
Li *et al.*	10	2-3	≥ 3	1192.6 ± 467.5
Yamada *et al.*	4	1-2	6	>400
Lumi *et al.*	4	0->1	13-23	828
Tabandeh *et al.*	2	>1	3-6	>2000
Rojas *et al.*	13	>1	12	964.4 ± 709.77

MH: Macular Hole SD: Standard Deviation.

Table **2** shows the anatomical results of the published series. Closure rates range from 66.7% to 100%. Grewal *et al.* [15] reported MH closure in 36 of 41 included cases in their series. Moysidis *et al.* [19] reported an 89% anatomical closure rate in a series of 130 cases.

Several findings have been described in OCT analysis during follow-up in patients that have undergone ART surgery. Hyperreflectivity of the transplanted graft internal layers has been observed in the first weeks after surgery. It decreases after a few weeks [17, 19, 22]. After several months, progressive alignment of neurosensory layers of the graft and host retina has been described.

Another finding observed by OCT imaging is vertical, hyperreflective, and irregular lines that represent bridging or transitional tissue between the transplanted graft and the host retinal tissue and the presence of a wooly-like, hyperreflective tissue in the surface of the graft that tends to decrease during follow-up [17].

Table 2. MH closure rate and decrease of the EZ and ELM defects.

Publication	Percentage of Cases with MH Closure	Baseline EZ Defect (μm ± SD)	Final EZ Defect (μm ± SD)	p	Baseline ELM Defect (μm ± SD)	Final ELM Defect (μm ± SD)	p
Ding *et al.*	100	_	_	_	_	_	_
Wu *et al.*	66.7	_	_	_	_	_	_
Thomas *et al.*	100		_		_	_	_
Tanaka *et al.*	100	1089 ± 403.8	921 ± 129.1	0.09	_	_	_
Grewal *et al.*	87.8	1777.3 ± 513.8	1370 ± 556.9	0.007	1681.5 ± 429	1408.5 ± 571.2	0.017
Chang *et al.*	90		60% *	0.003	_		_
Moysidis *et al.*	89	_	50% *	_	_	54% [†]	_
Li *et al.*	80	_	_	_	_	_	_
Yamada *et al.*	100	_	_	_	_	_	_
Lumi *et al.*	100	_	_	_	_	_	_
Tabandeh *et al.*	100	_	_	_	_	_	_
Rojas *et al.*	77	1277.4 ± 538.78	478.5 ± 589.5[‡]	_	_	_	_

MH: Macular Hole SD: Standard Deviation EZ: Ellipsoid Zone ELM: External Limiting Membrane * percentage of cases with continuity restoration of the EZ [†] percentage of cases with continuity restoration of the ELM [‡] Six patients showed full recovery of the myoid/ellipsoid layers at the end of the follow-up. The remaining four showed a reduction of 44.9% of the defect.

The OCT analysis showed complete structural integration of the retinal transplant into the adjacent retina in some cases. In other cases, the transplant was integrated into the retina, but not all layers could be recognized [15, 17, 19, 22].

Grewal *et al.* [15] reported a significant decrease in the External Limiting Membrane (ELM) and Ellipsoid Zone (EZ) and defects at the end of follow-up compared to baseline (p < 0.05).

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Vascularization and reperfusion of the retinal graft were observed within six weeks of transplantation by OCT-angiography, as reported by Tabandeh *et al.* [28].

Grewal *et al.* [15] reported a significant decrease in the External Limiting Membrane (ELM) and Ellipsoid Zone (EZ) and defects at the end of follow-up compared to baseline (p < 0.05).

1.3. Functional Outcomes

Best-Corrected Visual Acuity (BCVA) improved in at least three lines in 43% and at least five lines in 29% of the cases, as reported by Moysidis *et al.* [19]. All series showed a significant improvement at the end of follow-up compared with baseline preoperative BCVA (Table **3**). Four of the series have documented sensitivity by microperimetry with improvement in fixation [18, 19, 22, 23].

Table 3. Preoperative and postoperative BCVA. Microperimetry and mfERG findings.

Publication	Preoperative BCVA*	Final BCVA	p	Microperimetry	mfERG
Ding *et al.*	2.4 ± 0.6	1.46 ± 0.5	< 0.05	_	_
Wu *et al.*	1.30	1.10	_	_	_
Thomas *et al.*	1.30-2.00**	0.90-1.3	_	_	_
Tanaka *et al.*	1.00	0.70	0.001	Recordable sensitivity in 5 cases in the graft's zone	_
Grewal *et al.*	1.11 ± 0.6	1.03 ± 0.5	0.005	_	_
Chang *et al.*	1.65 ± 0.43	0.87 ± 0.50	0.001	_	_
Moysidis *et al.*	1.30	0.90	< 0.001	Increase in fixation. 6.7 ± 1.9 dB sensitivity [‡]	Recordable b wave amplitude [§§]
Li *et al.*	2.01 ± 0.3	1.32 ± 0.3	0.000	Non-recordable sensitivity in the graft's zone [§]	_
Yamada *et al.*	1.88 ± 0.47	1.17 ± 0.21	_	12° fovea area showed retinal sensitivity of fixation view point at final visit	_
Lumi *et al.*	3.87	0.62	_	Median sensitivity in the area of the transplant of 4dB (range 1.8 -12.4dB)	mfERG showed the abnormal function of the central ring and normal function of the second ring in 3 cases
Tabandeh *et al.*	2.00- 1.00**	1.00 -0.88	_	_	_
Rojas *et al.*	0.92 ± 0.28	0.75 ± 0.29	0.034	_	_

BCVA: Best-Corrected Visual Acuity mfERG: multifocal electroretinogram * LogMAR (logarithm of the minimum angle of resolution) units were used to describe BCVA ** Snellen notation was converted to LogMAR units [‡] Average sensitivity decibels in 12 cases [§] Sensitivity improvement in the autologous graft's adjacent zone [§§]mfERG performed in 3 patients. Recordable b wave amplitude in the graft's zone.

Microperimetry findings showed that spatially, the functional regions were located in the transplants' peripheral regions while no function was detected in the region corresponding to the foveal center. Fixation was relatively unstable and eccentric in all patients, located either in the nasal or nasal-superior perifoveal region or near the transplant border [17].

Tanaka *et al*. [18] reported that five of the seven eyes included in their series showed a positive response to light stimuli in the graft retinas when examined with microperimetry. In contrast, the two eyes with unchanged visual acuity had a negative response to light in the graft.

Moysidis *et al*. [19] reported a recordable b wave in the autologous graft's area while Lumi *et al*. [22] reported abnormal function of the central ring and normal function of the second ring in three cases by multifocal electroretinogram (mfERG).

The reconstitution of the EZ on optical coherence tomography (OCT) was associated with a better final visual outcome ($p=0.02$) [14].

1.4. Complications

The largest case series of ART published by Moysidis *et al*. [19] reported some complications that are shown in Table **4**.

Table 4. Complications.

Complication	Percentage (n)
Intraoperative complications	
Graft dislocation	3.8% (n=5)
Undersized graft	2.7% (n=2)
Damage to the RPE	0.8% (n= 1)
Postoperative complications*	
Retinal detachment	3.8% (n=5)
Endophthalmitis	0.8% (n=1)
Damage to the RPE	2.7% (n=2)
Subretinal or vitreous hemorrhage	6.6% (n=5)

* Of the phakic patients, 12% underwent phacoemulsification surgery during follow-up.

Grewal *et al*. [15] reported an RD in one case and a vitreous hemorrhage as major postoperative complications in their series. Tanaka *et al*. [18] reported in one eye that the harvested retina seemed to have been incorrectly transplanted upside down with unchanged visual acuity in the follow-up period. Macular edema occurred in another eye three months after transplantation that was successfully treated with a steroid injection. Rojas *et al*. [29] reported during the follow-up that one patient developed mild posterior proliferative vitreoretinopathy, and another demonstrated a macular epiretinal membrane. In other series, no significant intraoperative and postoperative complications were reported [12, 14, 16, 21 - 23].

2. DISCUSSION

ART is a novel technique that has shown its usefulness in treating both primary and refractory MH cases.

Nonetheless, several issues regarding the best tamponade and techniques are still debated [11 - 29].

Regarding tamponade use, different tamponade types have been used to keep the graft in place to prevent its dislocation. PFs have been used for a few days as a tamponade. They probably also have the advantage of increasing oxygen diffusion to the ART, contributing to its viability, thus favorably impacting functional outcomes postoperatively [15, 19]. Nonetheless, silicone oil or PFs as tamponades have the main disadvantage of often requiring a second surgery to remove them [19]. A second surgical procedure may entail additional risks both at an ocular and systemic level for the patient.

Some authors have used gas or air to overcome the disadvantage of performing a second procedure using PFs or silicone oil [15, 19]. Hernandez-Da Mota *et al*. [17] described a technique using only air as a tamponade, placing the transplanted tissue below the MH's edges. The graft did not dislocate, fully integrating with the adjacent retina after a few months. Moreover, Lumi *et al*. [22] reported that a better recovery of the ellipsoid zone was seen in OCT in subretinally positioned graft cases.

Another unsolved issue is defining which ART technique could be less traumatic and has greater anatomic and functional success. In relation to performing the less traumatic surgical procedure, one of the crucial steps in ART is harvesting the graft. It requires delimiting the graft's harvest area first with a laser barricade and circumferentially cutting the graft. It can be harvested, previously inducing a localized RD in the selected area for obtaining the graft, injecting saline solution into the subretinal space with a 41Ga needle. It is also possible to harvest the graft without prior induction of an RD [15, 19].

In addition, harvesting the graft without previously inducing an RD could be less traumatic for the photoreceptors; nonetheless, it carries the potential risk of traumatizing the choroidal vessels with the scissors, causing significant bleeding, and thus complicating the surgery [19]. PFs have also been used to stabilize the graft once it has been harvested, moving it over the retinal surface to the hole with another instrument, generally, a silicone-tipped cannula [11, 15].

Displacing the graft under PFs may rub the graft's inner face against the retinal surface, resulting in potential damage and loss of photoreceptors. Moreover, it could have a harmful impact on the final visual outcome in these patients.

Bimanual techniques have been used to overcome this disadvantage [11, 15, 19]. They do not require the displacement of the graft under PFs, thus avoiding photoreceptors' damage and using air or SF_6 gas as tamponades [17]. With these tamponades, it has been observed that the graft remained in the MH site without dislocating.

Interestingly, several postoperative changes have been documented by OCT [11 - 29]. First, hyperreflectivity of the internal retinal layers suggests edema, and it has been reported in the first weeks after ART has been performed [15, 17]. Likely, the edema present in the transplanted graft in the first postoperative days and weeks contributes to the graft pressing against the MH's edges, closing it hermetically. Together with the RPE pump's action, the hermetic closure would probably

keep the graft between the edges of the hole without dislocating, thus allowing its eventual integration with the receptor tissue.

The internal retinal layers hyperreflectivity, observed in the first postoperative weeks, may occur due to the arterial circulation interruption of the superficial and deep retinal plexuses after the graft is harvested [17]. Conversely, the transplanted graft's external retinal layers do not show this hyperreflectivity, possibly because when placed in the MH area, they begin to receive blood supply from the choriocapillaris immediately [17]. Furthermore, retinal vascular plexuses at the MH edges have shown the structural formation of new loops from the perifoveal capillary network that project towards the transplanted graft by OCT-angiography during follow-up [28].

This reperfusion process likely involves localized upregulation of angiogenic pathways by an ischemic retinal graft [28]. Authors have hypothesized that a large ischemic area retinal graft produces enough angiogenic stimulus to initiate angiogenesis, resulting in neovascularization and anastomosis between the superficial and deep vascular plexuses, reperfusing the graft. As the retinal graft reperfuses, ischemic signaling diminishes, downregulates angiogenic drive, and decreases further angiogenesis [28].

Another OCT finding that has been observed is the preservation of the EZ and ELM continuity, which may be a potential imaging biomarker of the viability of the transplanted photoreceptors and visual improvement [11, 15, 19].

In addition, the integration of the autologous graft into the recipient tissue has also been documented in different publications using OCT imaging, and it is noteworthy that the transplanted tissue undergoes structural changes until the integration into the recipient retina is completed [11, 17, 15, 19, 22].

Functional outcomes include, in addition to the improvement in BCVA in the different published series, fixation and sensitivity documented by microperimetry and a b wave recordable by mfERG in the graft area [18, 19, 22, 23]. Nonetheless, Lumi *et al*. [22] reported that the functional regions were located in the transplants' peripheral areas. Simultaneously, no function was detected by microperimetry in the region corresponding to the foveal center. As shown by mfERG and microperimetry, functional integration suggests some gradual functional integration of the transplants' outer regions [22].

How the transplanted retinal tissue's functionality is achieved and maintained in the postoperative period is the subject of speculation. Several hypotheses have been proposed to explain the graft's integration and possible neuronal reconnection with the retinal receptor tissue to achieve and maintain the transplanted graft functionality [33 - 41].

One hypothesis proposes the formation of new synapses in the bipolar cells of the recipient tissue. These newly formed synapses would reconnect with the outer plexiform layers and the transplanted tissue's photoreceptors' terminal plates. Peng *et al*. [33, 34] documented this process in an animal model of retinitis pigmentosa [RP]. They described that bipolar cells'

synapsis reconnected with the cones in the rods' absence. This process is known as ectopic synaptogenesis [33 - 41].

Furthermore, Lorach *et al*. [41] transplanted retinal tissue from healthy rats into the subretinal space of rats with RP. They were able to document, using immunohistochemistry and confocal microscopy, the formation of synaptic outgrowths of the bipolar cells in the retinal receptor tissue. The colocalization of the dendrites with the synaptic ribbons present in the synaptic endplates of the transplanted tissue's photoreceptors in the external plexiform layer was observed.

Noticeably, ectopic synaptogenesis has not been described in humans to the best of our knowledge. Probably, imaging techniques, such as adaptive optics to visualize *in vivo* details at the retinal tissue's cellular level, could be performed and may contribute to elucidating how ART integrates into the receptor's retina [19].

Lastly, all the published series' limitations include the lack of a control group to compare the ART technique, their retrospective nature, and the variability between the different techniques [11 - 29]. Designing prospective, comparative, and multicentric studies that include variables obtained with retinal autofluorescence, mfERG, microperimetry, and adaptive optics is warranted. Moreover, post-mortem histopathology in animal models may explain how the transplanted graft's retinal layers align and integrate with the recipient's retinal tissue [19].

CONCLUSION

The ART technique for the treatment of MH is a new technique that effectively induces a high percentage of MH's closure, especially those refractory to conventional surgery, and has a low incidence of complications [11 - 29].

Significant visual improvement was documented in the published case series [11 - 29]. Furthermore, evidence of the retinal graft functionality by microperimetry and mfERG has been described. However, there is still a lack of knowledge about the mechanisms involved in the graft's functional improvement and integration with the recipient retina in humans [19].

The ART technique is an additional surgical alternative to those previously described for some MH cases, which expands the treatment options and offers functional improvement in patients with this macular disease.

LIST OF ABBREVIATIONS

RD	=	Retinal Detachment
ART	=	Autologous Retinal Transplantation
MH	=	Macular Hole
SD	=	Standard Deviation
EZ	=	Ellipsoid Zone
ELM	=	External Limiting Membrane
OCT	=	Optical Coherence Tomography
RPE	=	Retinal Pigment Epithelium
PF	=	Perfluorocarbon Fluids
BCVA	=	Best-Corrected Visual Acuity

mfERG = Multifocal Electroretinogram

LogMAR = Logarithm of the Minimum Angle of Resolution.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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