Original Article

Human Amniotic Membrane: A Seal for Complex Retinal Detachments

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Abstract

Objectives: To evaluate the efficacy of human amniotic membrane (hAM) transplantation for complex retinal detachments (RD).

Materials and Methods: A retrospective analysis of consecutive patients who underwent vitreoretinal surgery with hAM transplantation for complex RD was conducted. The indications included high myopic macular hole (MH)-associated RD (n=5), traumatic large macular tears (n=4), combined RD with MH due to cicatricial retinopathy of prematurity (n=2) and severe retinitis (n=1), and morning glory syndrome (n=1). Surgical procedures, anatomical and functional results, and complications were noted.

Results: Thirteen eyes of 13 patients with a median age of 7 years (range, 0-65 years) were included. The follow-up was 15 months (range, 6-30 months). All eyes achieved MH sealing. Sealing occurred after a single surgery in 75% of eyes, while 25% required a second surgery due to hAM contraction/dislocation. The retina was attached and silicone oil could be removed in 92% of eyes during follow-up. The mean logarithm of the minimum angle of resolution visual acuity increased from 2.08±0.49 to 1.78±0.70 (p=0.07). Optical coherence tomography showed good integration of the hAM grafts with the retina, albeit without discernible retinal layer differentiation in any case.

Conclusion: Amniotic membrane grafting appears to be promising for anatomical sealing of MHs and posterior retinal tears in complex RDs such as those associated with degenerative myopia, severe trauma, tractional membranes, and retinal shortening, where conventional surgical techniques are likely to fail. Further research is needed to clarify the regenerative potential and functional capacity of hAM grafts in severe retinal pathologies.

Keywords: Human amniotic membrane, retinal detachment, macular hole, high myopia

Introduction

Human amniotic membrane (hAM) has been successfully used for decades for the treatment of ocular surface pathologies.[1] With its excellent anti-inflammatory, anti-fibrotic, and anti-angiogenic properties and low immunogenicity, hAM acts as an optimal biological support for damaged tissues and promotes re-cellularization.[2,3]

As in the anterior segment, *in vitro* studies have shown that hAM can provide a viable support matrix for retinal pigment epithelium (RPE) restoration.[4,5] Evidence suggests that human RPE cells can proliferate on a layer of hAM, forming a tightly organized monolayer of epithelial cells and secreting growth factors to maintain retinal homeostasis.[4,5]

Recently, research teams led by Rizzo et al.[6] reported successful *in vivo* applications of hAM for different retinal pathologies such as refractory macular hole (MH),[7,8] retinal detachment (RD) associated with MH,[9] posterior retinal breaks,[10,11] and age-related macular neovascularization.[12] Besides high rates of MH closure and retinal reattachment with hAM transplantation in these cases, the results were also very encouraging in terms of retinal regeneration. Amniotic membrane plugs exhibit promising integration into the retina, resulting in partial restoration of the outer retinal layers without any immunologic reactions.[6,9,10,12]

Current knowledge indicates that the use of hAM in vitreoretinal surgery is a novel and innovative technique that certainly has great potential but needs further investigation and understanding. In this report, we present our experience regarding the feasibility and efficacy of hAM transplantation in complex vitreoretinal pathologies in adult and pediatric eyes.

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Materials and Methods

A retrospective chart review was performed for consecutive patients undergoing vitreoretinal surgery with hAM transplantation for complex RDs associated with various pathologies from January 2019 to December 2022. The study received approval from the Gazi University Ethics Committee (protocol no: E.711694, date: 27.07.2023) and followed the principles of the Declaration of Helsinki.

Preparation of Amniotic Membranes

The hAM grafts were prepared under sterile conditions from a human placenta obtained shortly after elective caesarean delivery. Serological screening of donors was performed to exclude the risk of transmissible infections such as human immunodeficiency virus, hepatitis virus types B and C, and syphilis. The placenta was first washed free of blood clots with sterile saline solution. Then the amniotic membrane was separated from the rest of the chorion and rinsed with sterile saline solution containing 100 U/mL of benzyl penicillin, 200 µg/mL of ciprofloxacin, and 2.5 µg/mL of amphotericin B.[13,14] After incubating the amniotic membrane in this saline-antibiotic solution for 24 hours, it was flattened on a sterile ophthalmic drape, then cut into pieces (often 3x4 cm) and stored in plates containing a 1:1 mixture of glycerin and Dulbecco's modified Eagle medium at -80 °C for later use.

Surgical Procedures

All surgical procedures were performed by the same experienced vitreoretinal surgeon (Ş.Ö.). The patients underwent a standard 3-port, 23-gauge (G) pars plana/plicata or limbal vitrectomy with or without lens surgery. A complete vitrectomy with adequate vitreous base shaving was performed along with membrane/internal limiting membrane (ILM) peeling, retinotomy, or retinectomies as necessary.

The dimensions of the hAM graft were adjusted with vitreoretinal scissors before insertion into the vitreous cavity. Depending on the size of the graft, it was introduced to the vitreous cavity either through a 23-G valved trocar or directly through the sclerotomy following transient removal of one of the trocars. Once in the vitreous cavity, the hAM graft was gently manipulated under fluid or perfluorocarbon liquid and transplanted through the MH or retinal break into the subretinal space, with the graft edges positioned under the edges of the defective area as much as possible, and with the chorion side facing the RPE. The orientation of the graft was determined mainly by identifying the adhesiveness of the tissue using a retinal forceps, as described by Caporossi et al.[9]

In three cases, the hAM grafts were placed over the retina. The first one was a case of cicatricial retinopathy of prematurity (ROP) in which a large hAM graft was placed over the MH to address PVR/RD. The second was a case of morning glory syndrome where the hAM graft was inserted into the colobomatous disc under perfluorocarbon liquid to fill the anomalous disc pit. In the last case, the hAM graft placed during primary surgery had contracted and two new grafts were placed in a sandwich-type fashion, with one in the subretinal space and the other in an epimacular position.

After positioning the grafts appropriately, fluid-air exchange was performed, followed by silicone oil injection. All patients were instructed to maintain face-down position for 5 days.

Data Collection

The following data were obtained for each case: demographics, clinical features, indication for hAM use, surgical procedure(s) performed, complications, pre- and postoperative best corrected visual acuity (BCVA), anatomic outcomes, and length of follow-up.

Due to the difficulty of obtaining raster scans and the frequent lack of visibility of MH alignment on the RPE using optical coherence tomography (OCT) in detached retinas, MH size was determined intraoperatively by estimating its approximate average diameter in optic disc diameters (DD) after assuring retinal reattachment. Postoperative hAM graft appearance and microstructural regeneration of the retinal layers were assessed using spectral domain-OCT whenever possible. Axial length was measured using optical biometry (IOL Master 500; Carl Zeiss Meditec, Germany) or contact ultrasound biometry (A-scan).

BCVA was assessed with age-appropriate Snellen-equivalent methods and converted to logarithm of the minimum angle of resolution (logMAR) values for statistical analyses. In infants or younger patients for whom acuity testing was not possible, response to light stimuli and ability to fix and follow a penlight or an object were assessed.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics v22.0 (IBM Corp, Armonk, NY, USA) and statistical significance was set at a 2-tailed p value <0.05. Categorical data were reported as the number of cases and percentages, while normally distributed continuous data (tested with Shapiro-Wilk test) were reported as means with standard deviations and non-normal data as medians and ranges. Due to the non-normal distribution of some variables and a relatively small sample size, comparisons of continuous data were carried out with the non-parametric Mann-Whitney U and Wilcoxon signed rank tests.

Results

Thirteen eyes of 13 patients (9 male, 4 female) were included. The median age at presentation was 7 years, ranging from 3 months to 65 years. Nine (69.2%) were pediatric cases aged 14 years or younger. The mean length of follow-up was 15±9.3 months (range, 6-30 months).

The indications for hAM graft transplantation were as follows: five eyes (38.5%) suffered from a high myopic MH-associated RD (mean axial length: 29.8±5.3 mm; mean spherical equivalent: -15.5±7.4 diopters). Four eyes (23.5%) had trauma-related RD with large macular tears with or without peripheral tears and proliferative vitreoretinopathy (PVR), including one case of shaken baby syndrome. Three eyes (17.6%), two with cicatricial ROP and one with cytomegalovirus retinitis, had combined tractional and rhegmatogenous RD associated with MH with or without posterior retinal tears. One eye (5.9%) had total bullous RD associated with morning glory syndrome without MH or retinal break. At the time of hAM transplantation, the majority of cases (84.6%) were phakic (2 adults and 9 pediatric cases). Of these, both adults underwent combined phacoemulsification and vitrectomy surgery, whereas all except two pediatric patients underwent lens-sparing vitrectomy. One had cytomegalovirus retinitis and the other had trauma-related severe PVR/RD. Detailed characteristics of all cases are given in Table 1 and two cases are illustrated in Figures 1 and 2.

Table 1. Preoperative clinical characteristics, postoperative outcomes, and complications of the study population

No/sex	Age	Pathology	Previous intervention	Preop BCVA	Surgery and tamponade	Complications	Clinical remarks	Final BCVA
1/F	65 y	High myopic MH, RD	-	20/400	PPV, hAM (sub-MH), SO	-	SO removal (18 mo), MH sealed, R attached	20/100
2/M	2 y	High myopic MH, RD, PVR grade C1	-	LP	SB-PPV, hAM (sub-MH), SO	-	SO removal (15 mo), MH sealed, R attached	F/F
3/M	4 y	High myopic MH, RD, PVR grade C1	-	CF 1m	PPV, subretinal band removal, hAM (sub-MH and under retinotomy site), SO	hAM (sub-MH) contraction, RD	Re-PPV with double-layer hAM (4 mo), SO removal (3 mo), MH sealed, R attached	CF 1m
4/F	2.5 y	High myopic MH, RD	-	LP	SB, PPV, hAM (sub-MH), SO	-	SO removal (3 mo), MH sealed, R attached	F/F
5/F	8 mo	High myopic MH, RD	-	LP	SB, PPV, hAM (sub-MH), SO	hAM contraction, subretinal SO, RD	Re-PPV with sub-MH hAM, MH sealed, SO removal (4 mo)	F/F
6/M	7 y	Trauma, MH, post tear, peripheral tear, RD, PVR grade C2	SB, PPV (x2), ILMP, SO	HM	PPV, hAM (sub-MH and under post tear)- SO	-	hAM stable, MH sealed, R attached under SO; SO could not be removed due to persistent PVR	HM
7/M	40 y	Trauma, MH, RD, PVR grade C2	PPV, Retinectomy, SO	CF 1m	PPV, ILMP, Retinotomy, hAM (sub-MH), SO	-	SO removal (3 mo), MH sealed, R attached	20/250
8/F	52 y	Trauma, high myopia, MH, Post tears (x3), RD	-	LP	PPV, ILMP, hAM (sub-MH and under post tears), SO	-	SO removal (24 mo), MH sealed, R attached	HM
9/F	3 mo	Trauma (shaken baby), persistent MH, RD	PPV, ILMP, SO	NA	PPV, hAM (sub-MH), SO	-	SO removal (3 mo), MH sealed, R attached	F/F
10/M	26 y	Cicatricial ROP, MH, RD, PVR grade C1	SB, PPV, SO	20/400	PPV, ILMP, hAM (large epi-MH), SO	-	SO removal (3 mo), MH sealed, R attached	20/400
11/M	14 y	Cicatricial ROP, MH, RD, PVR grade C3	SB, PPV, ILMP, SO	CF 1m	PPV, Retinectomy, hAM (sub-MH), SO	hAM dislocation, PVR-RD	Re-PPV with sub-MH hAM, MH sealed (27 mo), re-PPV with 360° retinotomy for PVR-RD (24 mo), SO removal (18 mo), R attached	20/400
12/M	13 y	CMV retinitis, MH, post tears, RD	SB, PPV, air for TRD	HM	PPV, hAM (sub-MH and under post tears), SO	-	hAM remained stable and MH sealed, re-PPV, SO for recurrent retinitis with hemorrhage, TRD (1 mo), SO removal (3 mo), R partially attached	HM
13/M	5 y	Morning glory anomaly, total RD	-	LP	PPV, Internal drainage, hAM (in colobomatous disc pit), SO	hAM mobilization during SO removal	SO could not be removed due to hAM mobilization and immediate RD; hAM remained stable, R attached under SO (6 mo)	LP

BCVA: Best corrected visual acuity, CF: Counting fingers, CMV: Cytomegalovirus, F: Female, M: Male, F/F: Fix/follow, hAM: Human amniotic membrane, HM: Hand motions, ILMP: Internal limiting membrane peeling, LP: Light perception, M: Male, MH: Macular hole, mo: Months, NA: Non-applicable, No: Patient number, Post: Posterior, PPV: Pars plana vitrectomy, Preop: Preoperative, PVR: Proliferative vitreoretinopathy, R: Retina, RD: Retinal detachment, ROP: Retinopathy of prematurity, SB: Scleral buckling, SO: Silicone oil, TRD: Tractional retinal detachment, y: Years

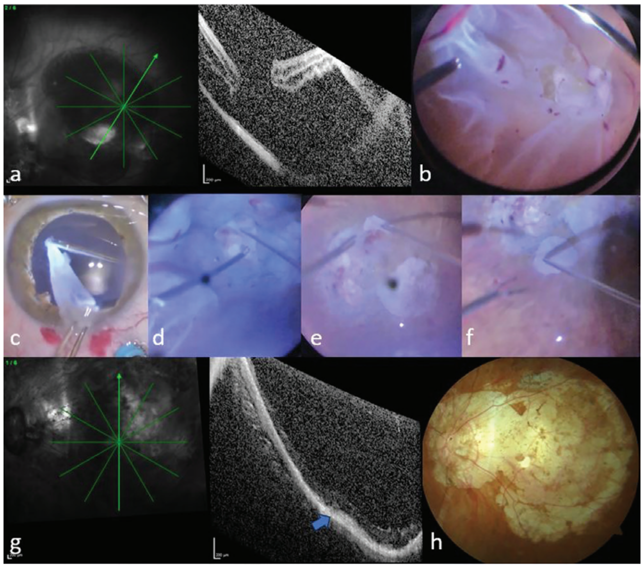

Figure 1. Case 8. A 52-year-old female patient with degenerative myopia (axial length: 35 mm) presented after an episode of psychosis and self-mutilation with macular hole-related posterior pole retinal detachment (a) which progressed to total rhegmatogenous retinal detachment with multiple posterior breaks in a few days in the left eye (b). The patient had previously experienced a similar trauma resulting in the loss of her right eye. Following phacoemulsification, a large piece of amniotic membrane was introduced through the anterior chamber (c) and placed under the large macular break (d). Two smaller pieces were then placed under the remaining posterior breaks (e, f). The surgery ended with the application of endolaser to a temporal peripheral retinal break and 360° periphery and silicone oil tamponade. Two years after silicone oil removal, the retina remained attached, and the patient achieved ambulatory vision. The optical coherence tomography image shows the amniotic membrane graft (arrow) overlaid by thin retina (g). The entire retina displayed extensive atrophy with no observable distinction between layers. The amniotic membrane grafts were not discernible in the fundus view, which exhibited significant posterior staphyloma and chorioretinal atrophy (h)

The estimated MH size ranged from 0.5 to 3 DD, with a mean of 1.5±0.9 DD. Overall, MH sealing was achieved in all cases with hAM transplantation, after a single surgery in 9 eyes (75%) and a second surgery in 3 eyes (25%). Three eyes required repeat surgery due to immediate graft dislocation (n=1) or graft contraction in the early postoperative period (n=2) (Figure 2). The mean MH size in these eyes was not significantly different from the remaining eyes (p=0.37). The contracted grafts were observed to have remained in place, still adhered to the RPE. However, their rapid shrinkage created a space for fluid leakage that resulted in MH reopening and RD recurrence. A second intervention including removal of the contracted graft via the MH and transplantation of larger grafts (submacularly in case 5 and in a sandwich-type fashion in case 3) provided successful re-sealing of the MH. Of 12 eyes, the retina was attached and silicone oil could be removed from 11 eyes (91.7%) by the final follow-up. The hAM grafts, including ones over the retina, remained securely in place following silicone oil removal. Silicone oil could not be removed in one eye despite a well-adherent hAM graft and stable sealing of the MH due to persistent PVR/RD (case 6). The hAM grafts placed under posterior tears and at the retinotomy site in four eyes remained stable, with no PVR

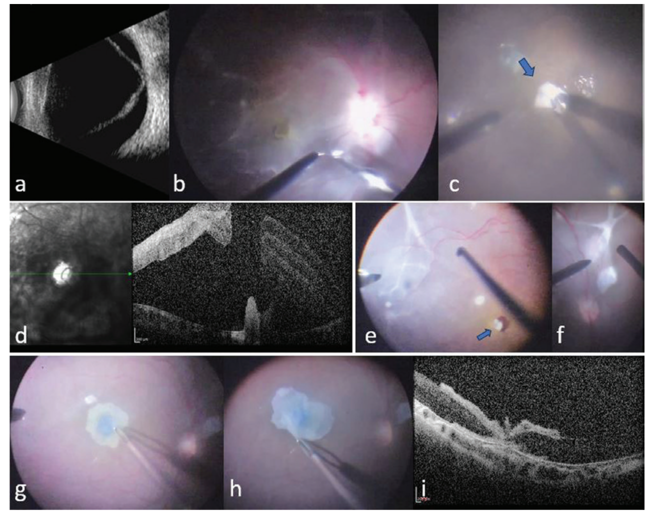

Figure 2. Case 3. A 4-year-old male patient diagnosed with Knobloch syndrome presented with retinal detachment (RD) associated with a high myopic macular hole (MH). During surgery, two amniotic membrane grafts were utilized, with one placed under the MH and the other one under the inferonasal retinotomy area created for the removal of subretinal bands. At postoperative 2 weeks, the graft contracted, resulting in reopening of the MH and subsequent RD. The graft was observed to have remained in place, still adhered to the RPE (d, e). The graft placed under the retinotomy area remained stable and was effectively closing that area (f). For the second surgery, two oversized amnion grafts were placed in a sandwich-like manner, with one positioned in the subretinal area (g) and another placed directly on top of the retina (h). The procedure was followed by tamponade with silicone oil. The retina remained attached during a 3-month follow-up period after silicone oil removal (i)

development in these areas, providing successful sealing of these defects without the need for laser retinopexy.

In one patient with morning glory syndrome (case 13), the subretinal fluid had totally resorbed after primary vitrectomy with hAM transplantation and the retina remained attached under silicone oil for 4 months. However, the graft immediately became mobile during silicone oil removal surgery and RD recurred intraoperatively. As a result, the subretinal fluid was once again drained with a 39-G cannula, the retina was attached, and a multi-layered hAM graft was placed and stabilized in the colobomatous disc pit and tamponaded with silicone oil. The patient has been followed up for 6 months since the surgery without any recurrence of RD or silicone-oil related complications.

Overall, vision improved in 8 eyes (61.5%) and remained unchanged in 5 eyes (38.5%) after surgery. The mean preoperative BCVA for the 9 eyes (69%) with measurable vision was 2.08±0.49 logMAR (Snellen equivalent 20/2400) and improved slightly to 1.78±0.70 logMAR (Snellen equivalent 20/1200) at the final visit. However, the difference did not reach statistical significance (p=0.07).

OCT images were available for evaluation in 8 patients (61.5%), all of whom demonstrated good integration of the hAM grafts with the retina. Retinal layer differentiation was not discernible in any case. In four eyes (cases 1, 6, 7, 8), a thin to medium-thickness layer of new tissue grew over the hAM graft without stratification of the retinal layers. The remaining four eyes (cases 3, 10, 11, 12) had hAM grafts completely filling the defective area like a plug, and there was no apparent growth of new retinal tissue.

None of the eyes showed signs of infection, inflammation, or rejection during the follow-up period.

Discussion

Posterior tears and MHs that are large and persistent or are associated with high myopia, posterior staphyloma, or RD pose significant challenges for vitreoretinal surgeons. Cases involving severe retinal shortening or tractions, such as PVR or cicatricial ROP, are particularly difficult to manage with conventional techniques, necessitating the use of novel sealing materials. In the pursuit of an effective sealing material, vitreoretinal surgeons have explored various options, including fragments of the ILM or lens capsule,[15,16,17] and autologous neurosensory retina transplantation.[18,19,20] However, each of these approaches has its own set of advantages and disadvantages, and none of them has emerged as the clear gold standard. More recently, hAM has emerged as a popular option for sealing in the vitreoretinal surgeon's toolkit.

The technique of using hAM was first introduced by Rizzo et al.[6] in 2019 for the treatment of complex MHs, and later the same team pioneered its application in different clinical scenarios.[7,8,9,10,11,12,21] In their initial study, the authors reported a 100% closure rate with improvement in visual acuity and time-dependent regeneration of the retinal layers over the hAM graft in 14 eyes with persistent MH or RD.[6] Encouraged by these results, we began to apply hAM transplantation for even more complex vitreoretinal cases where there was no reasonable alternative to closing retinal defects and where anatomic failure was highly likely. Accordingly, the main pathology of concern in this study was complicated RDs associated with high myopic MHs, traumatic MHs and posterior tears, tractional membranes, and severe PVR. Notably, half of the study group had previously undergone surgeries with adequate ILM peeling, rendering ILM flap techniques unsuitable. Of those undergoing primary repair, one was a severe trauma case with multiple large macular tears in which ILM peeling alone would not be sufficient to close the defects and reattach the retina. The remaining cases had high myopia, and creating ILM flaps was challenging due to very poor staining and high risk of iatrogenic retinal tears, although attempts were made to peel off as much of the ILM as possible. Also, given that more than half were pediatric cases and lens-sparing surgery was preferred, the use of lens capsule materials was not possible. Autologous retinal transplant could have been an alternative option, particularly in cases where a peripheral retinotomy was performed. However, besides being more technically challenging and carrying a higher risk of recurrent PVR/RD, it was often difficult to obtain adequate viable tissue in our cases due to extensive fibrosis in the peripheral retina or previous retinectomies.

Despite the inherent complexity of the study cases, the use of hAM grafts yielded encouraging anatomic outcomes. The final MH closure rate was 100%, achieved after one or two surgeries. Also, hAM grafts successfully sealed retinal breaks/retinotomy sites without the need for additional laser retinopexy, and no PVR development was observed in those areas.

While overall success was consistent with previous studies reporting complex MH closure rates ranging from 76.5% to 100% after hAM transplantation,[6,7,9,22,23,24,25] repeated surgeries were needed in our patient cohort due to graft-related complications. Previous studies by Caporossi et al.[7] and Huang et al.[23] reported cases of graft dislocation/contraction resulting in recurrence of MHs. Caporossi et al.[7] suggested that the likely cause of the failure was incorrect graft orientation with the epithelial layer facing the RPE, whereas Huang et al.[23] noted larger hole size as the possible cause. Although we did not observe a significant difference in the MH sizes between stable and unstable grafts, it is likely that the grafts in these eyes were not adequately large and unexpectedly rapid shrinkage led to MH reopening in two of them. Regarding the case with graft dislocation, in addition to suboptimal graft sizing, incorrect graft orientation and poor postoperative positioning may have been potential contributors. Determining graft orientation is particularly challenging with hAM grafts. There are several tips that can be used, such as observing the chorion layer, which tends to stick to the forceps, or identifying the villi present on the chorion layer using high magnification. However, these tips are not always helpful in the vitreous cavity. When the orientation of the graft is incorrect, it may lead to weak adhesion, increasing the risk of dislocations and possibly rapid contractions, which can negatively impact surgical success. Other than these three cases, hAM instability was also noted in the case of morning glory syndrome as soon as silicone oil support was removed during surgery, requiring reposition of the graft and re-injection of silicone oil. Caporossi et al.[26] reported the only other similar case in the literature, where two surgeries with gas and silicone oil tamponade failed and a third surgery was performed with a larger amniotic graft and silicone oil. Although the authors reported successful retinal reattachment under silicone oil, they only provided 3-month follow-up data and did not remove the oil. These cases suggest that hAM graft alone may not offer a permanent solution to fluid leakage caused by such large optic nerve defects in the short-term. However, long-term follow-up is required to evaluate its efficacy in providing adequate stabilization to allow silicone oil removal.

In contrast to several studies that have reported substantial improvements in visual acuity following successful closure of macular defects through hAM grafting,[6,9,10,22,23,24,25] the functional outcomes of our study were not in line with the favorable anatomic outcomes. Specifically, the increase in visual acuity was only modest and did not reach statistical significance. This outcome may be attributed to the fact that the majority of our study participants had limited retinal functional reserve, such as cases of infantile high myopia, ROP, severe retinitis, and traumatic cases with a history of multiple failed surgeries. Moreover, accurate measurement of visual acuity was often challenging in pediatric cases with low vision, and amblyopia was also a limiting factor that may have contributed to the overall poor functional outcomes. Nevertheless, given the intricate nature of the underlying pathologies, achieving anatomic success was the primary goal in these cases.

The potential of hAM for promoting retinal regeneration, although exciting, remains controversial. While early studies by Rizzo et al.[6] and Caporossi et al.[8] showed promising results, with tissue ingrowth and differentiation of retinal layers over the hAM graft, recent studies have failed to replicate these findings. Ventre et al.[27], Huang et al.[23], and Yadav et al.[28] reported that the external layers remained disorganized after follow-up periods ranging from 1 to 13 months. In our study with follow-up periods ranging from 6 to 30 months, we observed either a thin new tissue growth over the hAM without recognizable layers, or no growth at all. Concerns have also been raised about the permanent placement of an exogenous tissue in the subretinal space, as it appears not to dissolve over time according to previous studies.[23,25] To address this issue, Garcin et al.[22] proposed epiretinal placement of hAM grafts with the chorion facing the vitreous to avoid injuring the RPE and neuroretina during manipulations and improve photoreceptor layer recovery. However, despite successful MH closure, they also reported mostly persistent external limiting membrane and ellipsoid zone defects at 1 year. Discrepancies between studies may be due to heterogeneous baseline characteristics, with certain cases having more limited regeneration potential than others. Different types and sizes of hAM used and possible damage to viable cells during manipulations may also have contributed to the differing results.

Study Limitations

Our study was limited by a small sample size, retrospective design, and heterogeneity of underlying pathologies. Additionally, the suboptimal visual acuity measurements and OCT documentation inherent to pediatric patients may have affected the interpretation of results in terms of retinal regeneration and functional recovery.

Conclusion

This study presents the largest series of hAM graft use in unique pediatric challenges, such as complex RD associated with cicatricial ROP, infantile high myopia, shaken baby syndrome, and morning glory syndrome. While more research is needed to elucidate the regenerative effects of hAM grafts on the retina, they appear to be a safe, viable, and relatively simple option to achieve anatomic sealing of complex defects in both adult and pediatric cases.

Ethics

Ethics Committee Approval: The study received approval from the Gazi University Ethics Committee (protocol no: E.711694, date: 27.07.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: Ş.Ö., Concept: E.Ö.Z., Ş.Ö., Design: E.Ö.Z., Ş.Ö., Data Collection or Processing: E.Ö.Z., E.Y., H.B.Ö., Analysis or Interpretation: E.Ö.Z., E.Y., Ş.Ö., H.B.Ö., Literature Search: E.Ö.Z., Writing: E.Ö.Z.

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