Saudi Journal of Ophthalmology (2014) 28, 198—202

Original Article

Ocular surface rehabilitation Application of human amniotic membrane in high-risk penetrating keratoplasties

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Abstract

Background: Human amniotic membrane is a versatile tool for management of ocular surface disorders. This study evaluates the effect of cryopreserved human amniotic membrane (hAM) on one-year survival of penetrating keratoplasties (PKP) in high-risk recipients.
Method: This is a retrospective noncomparative cohort study of 58 consecutive eyes undergoing PKP with concurrent placement of a self-retained cryopreserved hAM (PROKERA®) at a tertiary care center from January 2009 to July 2010.
Results: Mean patient age was 66.7 ± 17.2 years and 30 (54%) were males. 51 eyes were pseudophakic and one aphakic. 27 eyes were glaucomatous; 24 had glaucoma drainage device and 2 had previous endocyclophotocoagulation. 12 patients had PKP for the first time and 46 had repeat PKP (average number of prior PKP = 1.63 ± 1.1, range: 1–5).
Risk factors for graft failure included repeat PKP (79.3%), corneal neovascularization (51.7%), preexisting glaucoma (46.6%), and presence of anterior synechiae (37.9%). Both First Transplant and Repeat Transplant groups had similar survival rates until 6 months after transplant (75% vs 74%, odds ratio = 1.06, $p = 1.00$). At 12 months, First Transplant group showed a better survival rate (67% vs 43%, odds ratio = 2.60, $p = 0.20$). Eyes with >3 risk factors had a higher graft failure rate (odds ratio = 5.81, $p = 0.003$).
Conclusion: Survey of the literature suggests that high-risk PKP with concurrent hAM placement demonstrate comparable graft survival. Presence of multiple risk factors is associated with poor survival.

Keywords: Penetrating keratoplasty, Graft rejection, Immunomodulation, Anti-angiogenesis, Amniotic membrane, ProKera

http://dx.doi.org/10.1016/j.sjopt.2014.06.010

Introduction

The human amniotic membrane (hAM) has become a versatile tool in the management of ocular surface disorders. It is the inner most layer of the placenta, consisting of the maternal outer chorion and the fetal inner amnion. The hAM is comprised of a monolayer epithelium, a basement membrane, and an avascular stromal matrix. Initial indication was reported by De Rotth in 1940 for repair of conjunctival defects;[1] in the late 20th and early 21st centuries, the indications for hAM transplant rapidly expanded, as investigators discovered that the immunologically naïve hAM plays important roles in wound healing.

The unique properties of hAM are amply documented in the literature. It has been demonstrated to reduce the inflammatory response, induce suppression of interleukin alpha and interleukin 1 beta in epithelial cells,[2–6] support survival of the transplanted limbal epithelial stem cells via growth factors,[7]

Received 19 March 2014; received in revised form 1 June 2014; accepted 15 June 2014; available online 2 July 2014.

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Peer review under responsibility of Saudi Ophthalmological Society, King Saud University

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and via clearance of polymorphonuclear cells and inhibition of proteinase activity.[8,9] Induction of apoptosis of T lymphocytes and modulation of activated macrophages by hAM were found to play important roles in tissue remodeling.[10–14] Insults to the ocular surface, such as surgeries, trauma, or burns, may potentiate deleterious cascades resulting in decreased vision and patient comfort. The hAM has been shown to reduce scar tissue formation by trapping and preventing polymorphonuclear infiltration into the corneal stroma[15] and by downregulation of the transforming growth factor beta signaling system and myofibroblast differentiation of normal fibroblasts.[16,17] Other groups explored the utility of hAM as a bioactive substrate in limbal stem cell expansion and transplantation with varying results.[18–23] Interestingly, the anti-inflammatory activities and modulation of macrophages have been replicated in water-soluble hAM extract,[24] cryopreserved hAM tissue,[25] and a covalent complex of hyaluronan and the heavy chain of inter-α-inhibitor purified from hAM extract,[26] greatly expanding the versatility of hAM.

Presently, there are various commercially available preserved hAMs for ophthalmic applications. Bio Tissue Inc. (Doral, FL, USA) provides AmnioGraft®, AmnioGuard™, and PROKERA® via cryopreservation method. IOP Ophthalmics Inc. (Costa Mesa, CA, USA) supplies the free-dried alternatives, Ambio2™, Ambio5®, and AmbioDisk™. Recently, lyophilized extract of the fresh hAM (AMX®), prepared by Keera srl and distributed by Treviso Tissue Bank, Italy, has been made available in Europe. However, the literature on AMX® efficacy is rather scant.[27] Table 1 compares these tissues.

Although utility of hAM is widely reported for many ocular surface applications,[28,29] its use in corneal transplant is limited. Despite the fact that corneal transplantation is now the most successful human organ transplantation, routinely performed without HLA typing or systemic immunosuppression, the long-term success of penetrating keratoplasty (PKP) is dictated by risk factors.[30–38] Having multiple risk factors, such as preoperative diagnosis of corneal opacity, corneal neovascularization, presence of anterior synechiae, prior rejection, coexisting glaucoma, and recipient gender and age at time of transplant, predisposes the patient to graft rejection and failure.[39–50] Data from the literature suggest that topical steroids may be inadequate for high-risk recipients, systemic steroids and immunomodulatory therapies pose significant adverse effects, and newer therapeutic strategies are being explored to improve survival of high-risk transplants.[51–60]

The unique properties of hAM suggest that it may be an adjuvant therapy to reduce the risks of graft rejection in high-risk PKP. Accordingly, we set forth to investigate whether high-risk PKP recipients would benefit from hAM placement. In this retrospective series, we evaluate the failure rates of PKP when performed in conjunction with cryopreserved hAM placement in patients with high-risk features and compare our graft failure rates to those reported in the literature.[30,34,44–50]

Materials and methods

The study population consisted of 58 eyes of 56 patients who underwent PKP with placement of self-retained hAM devices (PROKERA®, Bio-Tissue, Inc., Doral, FL). PROKERA® is a class II medical device comprised of cryopreserved hAM clipped into a dual polymethyl methacrylate symblepharon ring system, where the stromal aspect is in contact with the corneal epithelium. It was selected because its placement can be performed without sutures and bioadhesives, reducing confounding factors. A retrospective chart review was conducted for demographics and pre- and post-operative findings. The main outcome measure was clinical determination of graft failure. Study protocol was approved by the Institutional Review Board; and strict adherence to the principles of the Declaration of Helsinki was followed.

All surgeries and preoperative/postoperative cares were performed by a single surgeon (SCY). Briefly, the donor button was prepared using a Barron punch and coated with viscoelastic device for protection. A Hessburg-Barron vacuum trephine and corneal scissors were used to excise the host corneal button. The graft was secured to the host bed with interrupted 10-0 nylon sutures; subsequently, ophthalmic viscoelastic device was irrigated and the anterior chamber was reformed with balanced salt solution. All suture knots were buried. Subconjunctival injections of cefazolin, tobramycin, and dexamethasone were given. Thereafter, a self-retained amniotic membrane device was placed over the corneal button. Postoperative care for these patients was provided by the same surgeon, and included standard regimen of antibiotic and steroid drops, as well as follow-up visits at postoperative (PO) day 1, PO week (POW) 1, PO month (POM) 1, POM 3, 6, 9 and 12.

Inclusion criteria were eyes with at least 12-month postoperative follow-up visits and having two or more risk factors for graft rejection and failure,[5–9,36] identified preoperatively. Risk factors are high-risk indications for transplant, corneal stromal neovascularization of two or more quadrants, history

Table 1. Comparison of commercially available preserved human amniotic membrane for ophthalmic applications.

Company	IOP Ophthalmics, Inc.	Bio Tissue, Inc.	Keera, srl
Preparation	De-epithelialized, dehydrated, sterilized with irradiation	Epithelialized, cryopreserved	Lyophilized extract of the fresh human amniotic membrane
Storage	Stored free-standing at 10–27 °C, good for 2 years	Attached to nitrocellulose paper, cryopreserved at −80 °C, good for 2 years	Soluble powder form, stored in dry environment at 18–20 °C
Activation	Activated with saline solution or bioadhesive agent	Thaw to room temperature before use	Dilution with sterile BSS
Delivery/ fixation method	Bioadhesive or suture fixation for Ambio™, contact lens for Ambiodisk™	Bioadhesive or suture fixation for AmnioGraft® and AmnioGuard™, self-retained symblepharon ring for PROKERA®	Topical using eye drop dispenser
Availability	Worldwide	Worldwide	Europe