Original Article

Combined umbilical cord patching with amniotic membrane graft for corneal surface reconstruction

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ABSTRACT

Background: Umbilical cord patch (UCP) grafts have been successfully used for glaucoma shunt tube coverage and conjunctival surface reconstruction. In recent years, the technique has emerged as a novel alternative for the reconstruction of corneal perforation and descemetocele. This study aimed to evaluate the effectiveness of combined UCP grafting and human amniotic membrane (HAM) transplantation for the management of corneal perforation or descemetocele.

Methods: This prospective, non-comparative, interventional case series included nine eyes of nine patients with corneal descemetoceles and 28 eyes of 28 patients with corneal perforations, all in a clinically quiescent state. UCP grafting and HAM transplantation were combined to treat all patients. We re-examined the patients daily throughout the first week, weekly for 1 month, and then monthly for the first 6 months using slit-lamp examination and anterior segment optical coherence tomography.

Results: We included 37 eyes with descemetocele or corneal perforation in a clinically quiescent state. The mean (standard deviation) ages of patients with corneal descemetocele and corneal perforation were 56.3 (18.8) years and 54.3 (18.1) years, respectively. The male-to-female ratios in patients with corneal descemetocele and corneal perforation were 56% to 44% and 61% to 39%, respectively. Postoperative corneal thickness increased significantly in eyes with descemetocele compared to preoperative values ($P < 0.001$). Postoperative best-corrected distance visual acuity improved significantly compared to preoperative values in eyes with descemetocele or corneal perforation (both $P < 0.001$), with relief of accompanying ocular symptoms. We did not observe any recurrence or complications such as rejection, infection, suture-related problems, or severe inflammation and all had a formed anterior chamber up to the final follow-up visit.

Conclusions: Combined UCP grafting and HAM transplantation could be a promising alternative treatment for corneal perforation or descemetocele in clinically quiescent eyes, providing satisfactory reconstruction and functional outcomes. Further studies with robust designs, larger sample sizes, and longer follow-up are needed to verify the efficacy and safety of this modified surgical technique in enhancing vision and restoring anterior segment anatomical integrity in compromised corneas.

KEYWORDS

umbilical cord, allograft, biologic dressing, amniotic membrane dressing, amniotic membrane, corneal perforation, Descemet Membrane, Descemetocele, visual acuities

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INTRODUCTION

Corneal perforation and descemetocele are potentially blinding complications of various pathologies that induce corneal melting, including ocular surface disease, autoimmune disorders, microbial keratitis, and trauma [1, 2]. They may cause significant morbidity and require prompt intervention to prevent additional adverse events [1, 2].

Management of corneal perforation comprises a broad spectrum of therapies, such as bandage contact lenses, gluing, and human amniotic membrane (HAM) transplantation [1]. Penetrating keratoplasty is an efficient treatment; however, because of a shortage of corneal donors, corneal demand exceeds the corneal supply [3]. Moreover, despite the satisfactory success rate of corneal allograft transplantation, infective corneal perforations pose a significant risk to corneal transplantation because of possible graft rejection following recent corneal infections [4-6].

HAM is used as a scaffold for human limbal epithelial cell culture and for reconstructing the ocular surface using cultured cells [7]. It has been used for corneal reconstruction over the past 20 years. HAM acts as a graft or temporary patch by promoting corneal epithelialization and preventing stromal inflammation, angiogenesis, and scarring [8]. Typically, multiple layers of HAM are used to treat deep corneal ulcers or perforations [9]. However, because of its weak tectonic support, HAM carries the risk of early dissolution or dislocation before the healing of corneal perforation [10].

The umbilical cord patch (UCP) has emerged as a novel technique for reconstructing corneal perforations and descemetoceles [11, 12]. It is easier to manipulate and has been successfully used for tube shunt coverage and conjunctival surface reconstruction [13]. The UCP contains a high concentration of biological signaling agents, such as high molecular weight hyaluronic acid, heavy chain–hyaluronic acid complex, and pentraxin 3, which are recognized as the most important factors underlying the anti-inflammatory, anti-scarring, and anti-angiogenic effects of the UCP [4].

The advantage of UCP grafting over HAM transplantation alone is that it has prolonged adherence without dissolution, thus allowing sufficient time for corneal healing. Additionally, it has therapeutic effects in managing deep ulcers and perforations by minimizing inflammation and enhancing epithelialization [14]. One previous study discussed the role of combined UCP grafting and HAM transplantation in managing corneal perforation or descemetocele in eyes with active keratitis [4]. However, most prior research has emphasized the role of HAM transplantation [8-10].

To our knowledge, no study has used combined UCP grafting and HAM transplantation to manage corneal perforation or descemetocele with eyes in a clinically quiescent state. Therefore, we aimed to evaluate the efficacy of combined UCP grafting and HAM transplantation in treating these eyes.

METHODS

This prospective, non-comparative, interventional case series received ethical approval from the Institutional Review Board (IRB) of Mansoura Ophthalmology Center, Mansoura University, Faculty of Medicine, Egypt (Code number: MS.18.11.370) and was conducted from June 2020 to February 2022. All participants provided written informed consent before recruitment. We included clinically quiescent eyes with corneal descemetocele or perforation. The enrolled patients complained of ocular pain, reduced vision, red eye, excessive lacrimation, foreign body sensation, and photophobia. Eyes with active corneal infection were excluded from this study.

All patients underwent detailed ophthalmological examination, including an assessment of best-corrected distance visual acuity (BCDVA) and a detailed slit-lamp examination (SL-7F; Topcon, Tokyo, Japan). In eyes with descemetocele, swept-source anterior segment optical coherence tomography (AS-OCT) (Topcon Corp., Tokyo, Japan) was performed.

The following procedure was slightly modified to prepare the HAM and UCP. Briefly, after obtaining written informed consent, human placentas containing the umbilical cord were promptly obtained following cesarean deliveries. Donors seropositive for hepatitis B, hepatitis C, syphilis, and human immunodeficiency virus type 1 and 2 were excluded. After blunt dissection from the chorion, the HAM was saline-washed before being cut into 3×3-cm sections. The average HAM thickness measured using AS-OCT was approximately 100 μm. The umbilical vessels and loose jelly tissues were removed, and the UCP was then flattened and divided into 2×2-cm sections. The average UCP thickness measured using AS-OCT was approximately 500 μm. The HAM and UCP were cleaned with saline containing 50 g/mL penicillin, 50 g/mL streptomycin, and 2.5 g/mL amphotericin B [4]. They were then placed in sterile tissue culture medium and maintained at 8°C for a month.

The eyes were treated using combined UCP grafting and HAM transplantation. Following the application of peribulbar and topical anesthesia, the necrotic tissue was removed from the base and surrounding areas of the

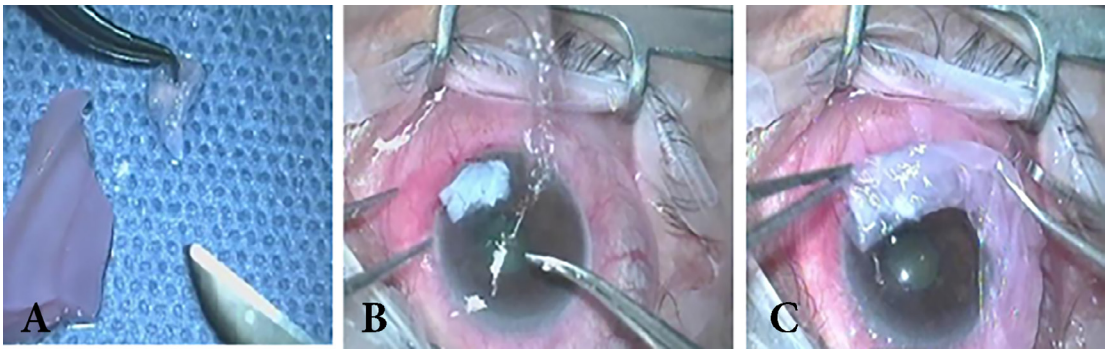

Figure 1. Fashioning and suturing of the umbilical cord patch and human amniotic membrane graft: Surgical microscope view shows (A) the umbilical cord patch with an average thickness of 500 µm, (B) cut to the size and depth of the defect and anchored to the cornea with the epithelial side facing upward using 10-0 nylon interrupted sutures (Ethilon; Ethicon Inc., Somerville, NJ, USA). (C) Finally, a large piece of human amniotic membrane with an average thickness of 100 µm and the epithelium facing upward is placed over the entire cornea as a temporary patch and secured to the perilimbal episclera using four interrupted 7-0 sutures (Vicryl; Ethicon).

corneal perforation or descemetocele. The UCP was then cut to the size and depth of the defect and stitched to the cornea with 10-0 nylon interrupted sutures (Ethilon; Ethicon Inc., Somerville, NJ, USA), with the epithelium facing upward. Finally, a larger section of HAM, with the epithelium facing upward, was placed over the entire cornea as a temporary patch and secured to the perilimbal episclera using four interrupted 7-0 sutures (Vicryl; Ethicon Inc.) (Figure 1).

Postoperatively, topical antibiotic/steroid eye drops—tobramycin 0.3%/dexamethasone 0.1% (Tobradex®; Eyevance® Pharmaceutical LLC, Fort Worth, TX, USA)—were used 5 times per day for 1 month with gradual tapering for the next 2 months, combined with preservative-free lubricant eye drops and topical 1% cyclopentolate hydrochloride for 2 weeks.

The patients were then monitored daily for the first week, weekly for the first month, and monthly for the next 6 months. Two weeks postoperatively, the episcleral sutures fixing the HAM were removed, and bandage contact lenses (PureVision, Bausch & Lomb Inc., Rochester, NY, USA) were placed to decrease the foreign body sensation induced by corneal sutures. The corneal sutures fixing the UCP graft were removed after 1 month. At each follow-up visit, BCDVA and slit-lamp examinations were performed in all eyes. Additionally, in eyes with descemetocele, corneal thickness was measured and recorded using AS-OCT at baseline and at the 3-month postoperative visit.

IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) was used for data analysis. The Shapiro–Wilk test and histograms were used to evaluate the normality of data distribution. Numerical data, presented as means and standard deviations (SDs), were compared using the paired Student's *t*-test. Categorical variables are presented as frequencies and percentages. *P*-values < 0.05 were deemed statistically significant.

RESULTS

Our study included 37 eyes in a clinically quiescent state, including 28 with corneal perforations and nine with corneal descemetoceles (Table 1).

The causes of descemetocele were post-bacterial keratitis (44%) (two eyes with *Pseudomonas aeruginosa* and two eyes with *Staphylococcus aureus*), post-corneal alkali burn (22%), post-fungal keratitis (22%) (*Candida albicans*), and autoimmune disorders (11%) (rheumatoid arthritis). The causes of corneal perforation were post-bacterial keratitis (39%) (seven eyes with *Pseudomonas aeruginosa* and four eyes with *Staphylococcus aureus*), post-corneal alkali burn (25%), autoimmune disorders (21%) (four eyes due to rheumatoid arthritis and two eyes with ocular cicatricial pemphigoid), and post-fungal keratitis (14%) (three eyes with *Candida albicans* and one eye with *Aspergillus fumigatus*) (Table 1).

In the descemetocele series, the mean (SD) preoperative lesion diameter, preoperative corneal thickness, postoperative corneal thickness, and duration for complete healing were 4.3 (3.5) mm, 87.4 (24.1) µm, 209.1 (23.0) µm, and 2.4 (1.1) weeks, respectively. The location of the lesion was central in 78% of the eyes and paracentral in 22%. Corneal thickness increased significantly compared to the preoperative values ($P < 0.001$) (Table 2).

In the corneal perforation series, the mean (SD) preoperative lesion diameter and duration for complete healing were 5.6 (3.0) mm and 4.3 (1.5) weeks, respectively. The location of the lesion was central in 54% of the eyes and paracentral in 46% (Table 2).

Table 1. Demographics and characteristics of patients with corneal descemetocele or perforation

Variable		Descemetocele (n = 9)	Corneal perforation (n = 28)
Age (y), Mean ± SD		56.3 ± 18.8	54.3 ± 18.1
Sex (Male / Female), n (%)		5 (56) / 4 (44)	17 (61) / 11 (39)
Underlying Cause	**Bacterial keratitis, n (%)**	4 (44)	11 (39)
	Chemical burn, n (%)	2 (22)	7 (25)
	Autoimmune disorder, n (%)	1 (11)	6 (21)
	Fungal keratitis, n (%)	2 (22)	4 (14)

Abbreviations: n, number; y, years; SD, standard deviation; %, percentage.

Table 2. Clinical data of patients with corneal descemetocele or perforation

Variable		Descemetocele (n = 9)	Corneal perforation (n = 28)
Preoperative lesion diameter (mm), Mean ± SD		4.3 ± 3.5	5.6 ± 3.0
Preoperative corneal thickness (µm), Mean ± SD		87.4 ± 24.1	-
Corneal thickness after 3 months (µm), Mean ± SD		209.1 ± 23.0	-
***P*-value**		**< 0.001**	-
Duration for complete healing (w), Mean ± SD		2.4 ± 1.1	4.3 ± 1.5
Preoperative BCDVA (decimal), Mean ± SD		0.07 ± 0.02	0.06 ± 0.02
Postoperative BCDVA (decimal), Mean ± SD		0.18 ± 0.05	0.13 ± 0.04
***P*-value**		**< 0.001**	**< 0.001**
Location of lesion, n (%)	**Central**	7 (78)	15 (54)
	Paracentral	2 (22)	13 (46)

Abbreviations: n, number; mm, millimeter; SD, standard deviation; µm, micrometer; w, weeks; BCDVA, best-corrected distance visual acuity. *P*-values < 0.05 are shown in bold (* the paired *t*- test was used).

Postoperative BCDVA significantly improved compared with preoperative values in eyes with either descemetocele or corneal perforation (both $P < 0.001$) (Table 2). All participants reported a marked improvement in pain, ocular discomfort, and photophobia from the first postoperative day. Intraoperatively, we reported no eyes with inadvertent perforation, and through the final follow-up visit, we did not note any recurrence or complications, such as rejection, infection, suture-related problems, or severe inflammation. All had a formed anterior chamber.

Representative Cases

Case 1: A 55-year-old woman presented with central corneal descemetocele in her right eye after a 30-day history of pain, photophobia, tearing, and foreign body sensation. There was a central deep corneal ulcer measuring 3×4 mm, and preoperative radial AS-OCT showed a 72-µm central corneal thickness [15]. The patient used topical cyclopentolate (Cyclogyl, Alcon Laboratories, Inc., Fort Worth, TX, USA), topical moxifloxacin ophthalmic solution 0.5% (Vigamox®, Alcon Laboratories), and platelet rich plasma eye drops for 3 weeks before combined UCP grafting and HAM transplantation. One month after surgery, the stromal thickness at the descemetocele site increased to 94 µm, as measured by radial AS-OCT in the central area. The UCP graft was fully epithelialized [15].

Case 2: A 14-year-old boy presented with a central corneal perforation following severe alkali chemical burns (Figure 2A). Combined UCP grafting and HAM transplantation was performed (Figure 2B). Two weeks later, an anterior chamber was formed (Figure 2C). The UCP graft was fully epithelialized at the 1-month postoperative examination (Figure 2D). Four months later, the patient underwent penetrating keratoplasty to avoid the possible high-risk graft rejection when penetrating keratoplasty is performed immediately after a chemical burn.

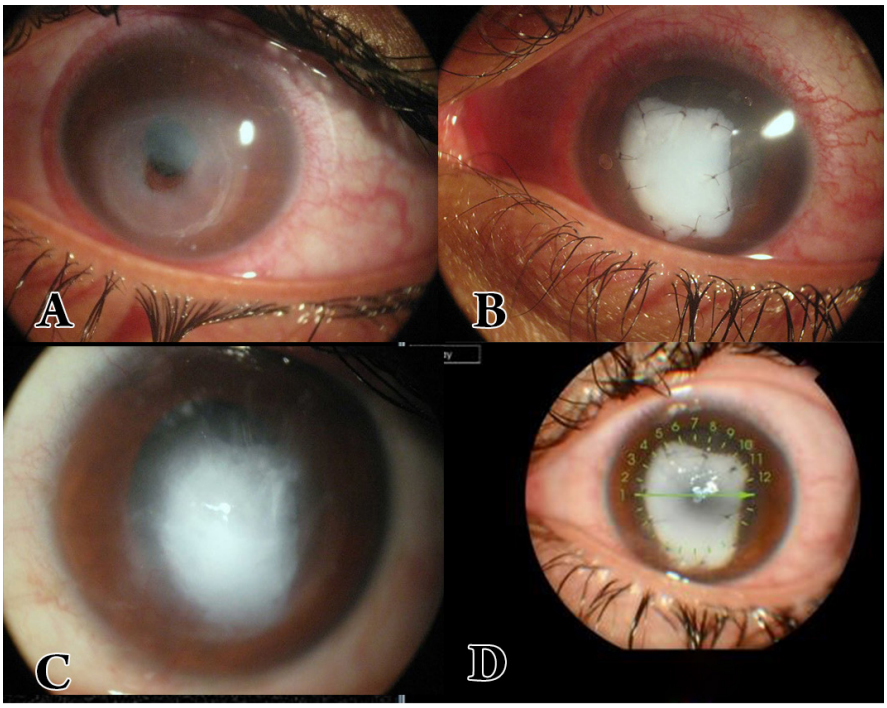

Figure 2. (A) Central corneal perforation following severe alkali chemical burn. Combined umbilical cord patch and human amniotic membrane graft are applied. (B) Two weeks postoperatively, the episcleral sutures fixing the HAM were removed, and a bandage contact lense (PureVision, Bausch & Lomb Inc., Rochester, NY, USA) was placed to decrease the foreign body sensation induced by corneal sutures. (C) Anterior chamber is formed. (D) The umbilical cord patch is fully epithelialized at the 1-month postoperative examination.

DISCUSSION

This case series revealed the effectiveness of UCP grafting with HAM transplantation in clinically quiescent eyes with corneal descemetocele or perforation. Postoperative corneal thickness significantly increased in eyes with descemetocele. BCDVA significantly improved in eyes with descemetocele or corneal perforation, with a marked improvement in the accompanying ocular symptoms. No recurrence or complications were detected during the study period.

Corneal thinning and perforation are potentially blinding complications that compromise corneal surface integrity and markedly deteriorate visual acuity [16, 17]. HAM transplantation has been widely used for treating a range of ocular surface disorders over the last few decades; however, it still has certain drawbacks [18-20]. Thus, we applied combined UCP grafting and HAM transplantation because UCP is thicker, more compact, and more durable than HAM transplantation alone [4], with the benefit of non-immunogenicity [4, 21], which allows its use even in active keratitis [4].

In a multicenter, randomized clinical trial, Sheha et al. [21] applied an HAM-UCP graft to cover glaucoma drainage device tubes. They found that the HAM-UCP graft was well tolerated and demonstrated excellent host-tissue integration. The HAM-UCP graft had superior host-tissue integration and less graft thinning than the pericardial patch graft [21]. Likewise, in the current case series with different clinical applications for UCP grafting and HAM transplantation, we noted acceptable host-tissue integration and no clinical evidence of graft rejection or infection. Thus, combined UCP grafting and HAM transplantation could be an alternative in eyes with corneal perforation or descemetocele requiring urgent tectonic keratoplasty based on the clinical judgment of the ophthalmic surgeon.

Pain and ocular discomfort may be caused by ocular surface disease with corneal perforation or descemetocele [22, 23]. Initial symptoms of pain, ocular discomfort, and photophobia markedly improved in our case series starting from the first postoperative day, with notable improvement in corneal thickness [15]. We found that combined UCP grafting and HAM transplantation is an alternative treatment for deep corneal ulcers with perforation or descemetocele, with satisfactory anatomical and functional corneal reconstruction and relief of accompanying ocular symptoms.

Xie et al. [4] applied UCP grafting and HAM transplantation in four eyes with descemetocele and seven with corneal perforation. Within the first postoperative month, they recorded improvement in corneal thickness

and smoothing of the corneal surface in all participants. Ten eyes showed improvement in vision and one eye remained unchanged. Eyes with infectious keratitis were in the active phase and received concurrent antimicrobial treatment. They did not observe any recurrence or side effects during the follow-up [4]. Using a similar technique [4], we treated 37 eyes: 28 with corneal perforation and nine with corneal descemetocele. Likewise, our patients experienced a significant improvement in BCDVA and corneal thickness in eyes with descemetocele. However, in our study, the eyes did not have active keratitis or require concomitant antimicrobial treatment.

In this series, most eyes with descemetocele were diagnosed with post-bacterial keratitis (44%), while chemical burns represented 22%, post-fungal keratitis 22%, and autoimmune disorders 11% of eyes. In the case series by Ozdemir et al. [24], bullous keratopathy was the most common cause of descemetocele (26%), followed by herpetic keratitis (31%), corneal ulcers (17%), dry eye (9%), and others (6%). In addition, in the case series by Xie et al. [4], nearly half of the eyes (55%) had herpes simplex keratitis, followed by exposure keratitis (18%), fungal keratitis (18%), and bacterial keratitis (9%).

Solomon et al. [25] used HAM transplantation for eyes with deep ulcers, descemetoceles, and non-traumatic corneal perforations. They found favorable surgical results in 28 (82%) eyes, with complete epithelialization within 3 weeks and stable corneal thickness for the first 2 months [25]. Using combined UCP grafting and HAM transplantation in our series, the mean (SD) duration for complete healing of corneal descemetocele was 2.4 (1.1) weeks, with a significant increase in postoperative corneal thickness and improvement in BCDVA compared to preoperative assessments.

Previous histological research by Resch et al. [26] found that HAM was limited to the corneal surface following transplantation, or that it might be integrated into the intraepithelial, subepithelial, or intrastromal planes of host corneal tissue. In a case report observing the superficial localization of HAM, Nubile et al. [27] noted intrastromal and subepithelial HAM integration patterns, which offered stable tectonic support in a perforated eye. Solomon et al. [25] inferred that the efficacy of HAM transplantation in healing small corneal perforations is well established; however, HAM is incapable of promoting corneal stability in individuals with significant corneal thinning [25]. Thus, HAM transplantation alone may not be appropriate as the only therapy for central corneal thinning and perforation because of its relatively rapid dissolution and insufficient duration for corneal surface healing. However, it might be an appropriate temporizing therapy to resolve eye inflammation before keratoplasty, thus boosting the success of vision rehabilitation [9]. Using combined UCP grafting and HAM transplantation, we found good host-tissue integration with epithelialized and stable corneal surfaces in eyes with corneal perforation or descemetocele, and all had a formed anterior chamber with no evidence of immunogenicity up to the 6-month follow-up.

HAM transplantation has been used to treat infectious scleritis [28], with most articles discussing the use of various tissue grafts in conjunction with HAM transplantation. Zheng et al. [29] successfully used fascia lata grafts and HAM after surgical debridement for infectious scleritis. Siatiri et al. [30] reported a case of necrotizing infectious scleritis caused by *Pseudomonas aeruginosa,* and HAM transplantation with scleral grafting and tenonplasty restored the globe integrity and managed inflammation [30]. Although we reported no eyes with infectious scleritis, and all included eyes were clinically quiescent, UCP grafting with HAM transplantation achieved promising functional and anatomical outcomes in our series.

In the case series of Peng et al. [31], single or multiple HAM patches were unsuccessful in re-epithelializing the ocular surface in patients with severe ocular burn-induced anterior segment necrosis, despite the presence of a residual portion of the healthy limbus. Consequently, they used the tenonplasty technique combined with HAM transplantation for patients with intractable ocular burn-induced anterior segment necrosis and reported stabilization of the ocular surface [31]. Likewise, we used UCP grafting combined with HAM transplantation as it provides a thicker graft [21] with enhanced support. The eyes achieved complete epithelialization with promising anatomical and functional outcomes within 6 months of follow-up.

We found a significant increase in postoperative BCDVA compared with preoperative values in eyes with descemetocele or corneal perforation. Likewise, Xie et al. [4] noted vision enhancement in more than 90% of eyes. The BCDVA of six eyes improved by at least two Snellen lines. Four of the remaining five eyes were enhanced from hand motion to finger counting, but one eye remained unaffected. Thus, they found that the UCP graft was an effective treatment in their case series [4]. Similarly, we found that this technique is an effective and safe surgical treatment for restoring the functional and anatomical status of eyes with corneal perforation or descemetocele.

The use of UCP grafts is invaluable in countries with a deficiency in corneal tissues and eye bank services [32, 33]. The UCP graft might be regarded as a viable option for corneal repair because of its accessibility and effectiveness [34]. Thus, we speculate that it could serve as the initial step in restoring ocular integrity, controlling inflammation, and preventing infection. Subsequently, a corneal transplant may be performed to enhance vision. This stepwise method is favored over performing a tectonic corneal transplant at the time of perforation [4] or active infection with a descemetocele.

HAM coverage of the entire cornea combined with a UCP graft acts as a substrate for the regeneration of defective epithelium [35, 36], as we found epithelialized and stable corneal surfaces in eyes with corneal perforation

or descemetocele. The basement membrane of the HAM is comparable to that of the conjunctival or corneal basement membrane, mainly because of its collagen composition [35, 36]. The basal membrane of HAM supports the adhesion and differentiation of corneal epithelial cells, facilitates their migration, and prevents apoptosis [35]. Thus, combined UCP grafting and HAM transplantation brings together stable tectonic support of the UCP graft and the ability of HAM to provide a substrate for corneal and conjunctival epithelial cell growth, making this technique a potentially promising approach in treating compromised corneas.

To our knowledge, this study is the first to combine UCP grafting with HAM transplantation as a promising alternative for managing corneal perforation or descemetocele in clinically quiescent eyes. However, our study had some limitations, as it was a single-center study with a small sample size and a lack of a control group. Moreover, we did not document corneal thickness using AS-OCT at the 6-month follow-up examination, we did not measure the corneal thickness of eyes with corneal perforation, and we did not record details and grading of improvement in ocular surface symptoms. Hence, multicenter studies with larger sample sizes, regular monitoring of corneal thickness, and assessment of subjective and objective improvement of ocular surface symptoms and signs in a similar case setting are required to confirm our preliminary findings.

CONCLUSIONS

Combining UCP grafting with HAM transplantation is a promising alternative for restoring corneal surface integrity, providing satisfactory reconstruction, and increasing postoperative BCDVA in eyes with descemetocele or corneal perforation. Thus, it might be considered a reasonable temporizing measure to delay and improve the success rate of keratoplasty. Likewise, it could help overcome corneal graft shortages in the management of these ocular emergencies. We recommend further studies with larger patient samples and longer follow-up periods to assess the efficacy and safety of this modified surgical technique in enhancing vision and restoring anterior segment anatomical integrity.

ETHICAL DECLARATIONS

Ethical approval: This study received ethical approval from the Institutional Review Board (IRB) of Mansoura Ophthalmology Center, Mansoura University, Faculty of Medicine, Egypt (Code number: MS.18.11.370). All participants provided written informed consent before recruitment.
Conflict of interest: None.

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