

# Role of amniotic membrane transplantation in symblepharon

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## 羊膜移植治疗睑球黏连的临床观察

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### 摘要

**目的:**评估羊膜移植 (AMT) 在治疗睑球黏连中的应用效果。

**方法:**这项无对照干预性病例研究于 2013/01 ~ 2015/12, 包括连续就诊的 12 名患者共 14 眼。患者均接受永久性羊膜移植,以治疗睑球黏连,使用冷冻保存或冷冻干燥的羊膜 (AM)。这 12 例 (14 眼) 患者,年龄在 26 ~ 62 岁,平均 43.38±11.25 岁,其中 8 例 (4 名男性,4 名女性) 10 眼为翼状胬肉切除术后继发,4 例患者 (1 名男性,3 名女性) 斜视手术后继发。所有患者距上次手术至少 6mo。术后以恢复深度稳定的穹窿为手术成功,无瘢痕或炎症发生,6mo 的随访期间无眼球运动的限制。

**结果:**随访期平均为 7±4.2mo (6-9mo)。在所有 14 只眼中,手术后 3wk 均观察到 AM 完全上皮化,手术部位无炎症表现。总共 14 眼中有 8 眼 (成功率 57%) 显示穹窿重建成功,穹窿深,无复发。有 4 眼 (29%) 表现出部分成功,中度深度的穹窿和适度瘢痕。有 2 眼 (14%) 显示重建失败,穹窿完全闭合。有 7 眼手术后视力改善,7 眼视力保持稳定。AMT 术后并发症少,14 眼中 1 眼 (7%) 发生严重的结膜反应和眼球运动受限。而在术后前 3mo 中,14 眼中有 2 眼发生化脓性肉芽肿 (14%), 予以手术切除,局部糖皮质激素注射。

**结论:**单用 AMT 是一种治疗睑球黏连安全有效的方法。考虑到与角膜缘切除有关的潜在不良反应,AMT 也是一种有效的重建穹窿以修复各种眼表疾病所致睑球黏连的方法。

**关键词:**羊膜移植; 睑球黏连; 翼状胬肉; 斜视; 穹窿重建

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### Abstract

• **AIM:** To evaluate the use of amniotic membrane transplantation (AMT) in symblepharon.

• **METHODS:** This non-comparative interventional case study was conducted from January 2013 to December 2015 and included a consecutive series of 14 eyes of 12 patients. Patients were selected for permanent AMT. The amniotic patches were grafted for the treatment of symblepharon. Cryo-preserved or freeze-dried amniotic membrane (AM) was used. Regarded to the 14 eyes (12 patients), their age was ranged from 26-62y, with the mean age of 43.38±11.25, 10 eyes of 8 patients (4 males/4 females) were presented with symblepharon secondary to previous pterygium surgery, and 4 eyes of 4 patients (1 male/3 females) were presented with symblepharon secondary to previous strabismus surgery, at least 6mo after the last surgery. The outcome of success was defined as restoration of a stable-depth fornix and being free of scar or inflammation, and no motility restriction during the follow up of 6mo.

• **RESULTS:** The mean follow-up period was 7±4.2mo (range 6-9mo). In all 14 eyes, complete epithelialization of AM was observed 3wk after surgery, resulting in a non-inflamed appearance of the surgical site. Eight eyes out of total 14 eyes showed successful fornix reconstruction with success rate (57%), the fornix was deep, and no recurrence was observed. Four eyes (29%) showed partial success with moderate depth of the fornix and moderate scar. Two eyes (14%) showed failure of reconstruction of the fornix with complete fornix obliteration. The visual acuity improved after surgery in 7 eyes while remained stable in 7 eyes. Post-operative complications from the AMT was very limited as severe conjunctival reaction and motility restriction was occurred only in one eye out of 14 eyes (7%) and pyogenic granuloma occurred in 2 eyes out of 14 eyes (14%) in the first 3mo after surgery and was managed with surgical excision, with local corticosteroid injection.

• **CONCLUSION:** AMT alone is a safe and effective method for symblepharon. Considering the potential adverse effects associated with limbal excision, also, AMT is an effective method of fornix reconstruction for the repair of symblepharon in a variety of ocular surface disorders.

• **KEYWORDS:** amniotic membrane transplantation; symblepharon; pterygium; strabismus; fornix reconstruction

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## INTRODUCTION

Conjunctival epithelium is non-keratinized consists of two phenotypical distinct cell types, stratified squamous non-goblet cells (90% -95%) and goblet cells (5% -10%), in addition to occasional lymphocytes and melanocytes. The conjunctival epithelium plays an important role in ensuring the optical clarity of the cornea by providing lubrication to maintain a smooth, refractive surface, and by producing mucins critical for tear film stability<sup>[1]</sup>.

The conjunctiva also protects the eye against mechanical stress and infectious agents. It, furthermore, contributes water and electrolytes to the tear fluid. The squamous cells produce cell membrane-tethered mucins, while the goblet cells secrete the gel-forming mucins, both of which help to maintain a protective tear film. The superficial surface of the squamous cells is covered by the membrane-tethered mucins mucin-1 (MUC1), mucin-4 (MUC4) and mucin-16 (MUC16), which are essential for tear stability and make up the glycocalyx<sup>[2]</sup>.

Conjunctival stem cells continuously regenerate the conjunctiva by giving rise to both stratified squamous non-goblet and goblet cells, thereby maintaining a healthy tear film. Disorders that damage these stem cells cause varying extent of keratinization, which disrupts the protective tear film and ultimately leads to limbal stem cell deficiency (LSCD) and visual impairment or blindness. The location of the conjunctival epithelial stem cells has been investigated in several studies on mouse, rat, rabbit, and human tissue, yet no real consensus has been reached. The conjunctival stem cells have been suggested to reside in the limbus bulbar conjunctiva, medial canthal, fornical conjunctiva, palpebral conjunctiva and mucocutaneous junction<sup>[3]</sup>.

Although the conjunctival stem cells may not solely be located to one single region, their relative number generally appears to be the highest in the fornix. A large number of disorders can lead to scarring of the conjunctiva through chronic conjunctival inflammation. Scarring varies in severity and can be self-limited, such as in chemical/thermal burn, iatrogenic for example postoperative as in recurrent pterygium surgeries or post strabismus surgeries and infectious diseases due to adeno- and herpes viruses, or progressive, as in cicatrizing conjunctivitis, which consists of several diseases including ocular cicatricial pemphigoid, Stevens-Johnson syndrome, atopic keratoconjunctivitis and Sjögren's syndrome<sup>[4]</sup>.

Treatment depends on the disease etiology and severity, but can include various anti-inflammatory, immunomodulatory and immunosuppressive drugs. One of the most common complications of scarring of the conjunctiva is symblepharon formation where there is adhesion between the bulbar and

palpebral conjunctiva. Surgical treatment of symblepharon includes removal of the scar tissue and the surgical defect is then covered with a tissue substitute to prevent re-obliteration. These include mechanical physical or chemical approaches and the grafting of conjunctival or mucous membranes<sup>[5]</sup>.

Surgical techniques for restoration of a diseased conjunctiva have utilized different conjunctival substitutes, including conjunctival autografts, amniotic membrane (AM), buccal mucosal grafts and tissue engineered conjunctival epithelial equivalents. An obvious limiting factor when using autografts is the size of the defect to be covered, as the amount of healthy conjunctiva is limited<sup>[6-7]</sup>.

AM was first used in ophthalmology 76 years ago. AM constitutes the innermost layer of the fetal membranes. AM is particularly suited for clinical use as it supports epithelialization, reduces scarring, suppresses the immune response, reduces pain, and decreases inflammation<sup>[8-10]</sup>.

AMs are commercially available in two forms either cryopreserved or freeze-dried. In cryopreserved type, the AM cryopreserved in a basal cell medium at -80°C. Hence it kills all the AM cells, so the AM grafts function primarily as a matrix and not by virtue of transplanted function. The freeze-dried AM can be sterilized by gamma-irradiation; however, AM treated this way may release a less amount of growth factors than conventionally cryopreserved membranes<sup>[8,11]</sup>.

## SUBJECTS AND METHODS

This non-comparative interventional case study was conducted from Jan. 2013 to Dec. 2015 and included a consecutive series of 14 eyes of 12 patients.

The study was approved by the institutional review board and was conducted in accordance with the principles of the Declaration of Helsinki.

Patients were selected for permanent amniotic membrane transplantation (AMT). The amniotic patches were grafted for the treatment of symblepharon. Cryo-preserved or freeze-dried AM was used.

Regarded to the 14 eyes (12 patients), their age were ranged from 26-62y, with the mean age of 43.38y (SD:11.25), 10 eyes of 8 patients (4 males/ 4 females) were presented with symblepharon secondary to previous pterygium surgery, and 4 eyes of 4 patients (1 male/ 3 females) were presented with symblepharon secondary to previous strabismus surgery, at least 6mo after the last surgery.

**Inclusion Criteria** All patients were presented with post-surgical symblepharon after at least 6mo from last operation.

**Exclusion Criteria** 1) post-surgical symblepharon less than 6mo after the last operation; 2) patients with previous corneal perforation (as indicated by entangled iris tissue in the wound of previous operation); 3) symblepharon secondary to immune diseases; 4) patients with punctual occlusion, and patients had positive regurgitation test from the punctum.

**All the Patients were Subjected to the Following** Full history includes: name, age, sex, duration of the disease, past history of previous ocular surgeries, or trauma to the

affected eye and medical history of previous medications either topical or systemic. The patients were submitted to the full medical examination for any possible systemic disorders. (*e.g.* diabetes, hypertension and neurological disorders). Ophthalmological examination of the patients was carried out using slit – lamp biomicroscopy (SHIN NIPPON, Japan) including; morphological appearance of the lesion, affection of medial rectus muscle and any associated symblepharon or corneal scars.

Examination of the corneal epithelium, stroma, and the endothelium. Epithelial defect was examined as regards site, size, shape, number, depth and edge. Diagnostic dyes, as fluorescein or Rose Bengal, were used, as well as determination of the break up time and Schirmer's tests were also carried out. Corneal sensitivity was assisted by using twisted tips of a cotton piece touching the central corneal zone of the patient. Serological tests including conjunctival smear and corneal scrapping for culture and sensitivity test.

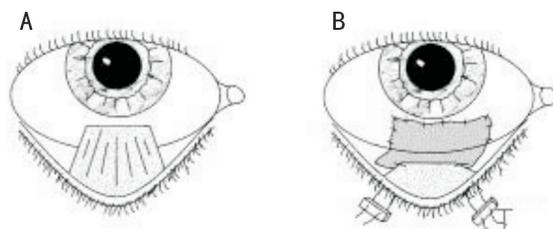
Visual acuity was tested using Snellen's chart and intra-ocular pressure measurement by applanation tonometer (SHIN NIPPON, Japan). Fundus examination using indirect ophthalmoscopy (KEELER, England). Regurgitation tests were carried in every patient by pressing on the site of the lacrimal sac. Upper and lower lids, lacrimal glands and punctum were assessed.

**Protocol of Tissue Preparation** Selection of the donor: a detailed medical and behavioral history together with signed consent was obtained from the donor mother. Serological tests were carried out by both enzyme-linked immuno sorbent assay (ELISA) and polymerase chain reaction (PCR) for HIV, hepatitis B, C. Under a lamellar flow hood, the placenta obtained shortly after caesarean delivery, was first washed, free of blood clots with balanced saline solution containing 50µg/mL of penicillin, 50µg/mL of streptomycin, 100µg/mL of neomycin, and 2.5µg/mL of amphotericin B (Fungizone® 50 mg, Bristol Myers Squibb, USA). The inner amniotic membrane was separated from the rest of the chorion by blunt dissection (through the potential spaces between these two tissues). The membrane was then cut into 4×4 cm<sup>2</sup> pieces and placed in a sterile vial containing Dulbecco's Modified Eagle's medium and glycerol at a ratio of 1:1 (vol/vol). For cryopreserved AM, the vials were frozen at -80°C to be used within less than 1mo.

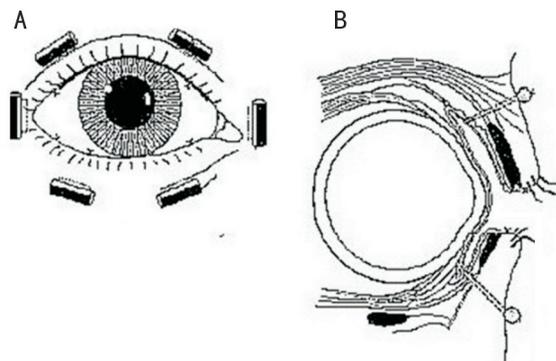
The membrane was defrosted immediately before use by warming, the container to room temperature for 10min.

**Surgical Techniques** All patients were anesthetized with a peri-bulbar block. Eyes with severe symblepharon obliterating the fornix to the extent that the speculum could not be inserted, one 4-0 black silk suture was placed at the lid margin through the tarsal plate of each lid as a traction. Those eyes in which symblepharon were not severe were opened with a lid speculum.

Once the eye was opened, the conjunctiva was incised from



**Figure 1 Schematic drawing of amniotic membrane transplantation for reconstruction of the lower fornix after symblepharon lysis** A: Preoperative demonstration of the scar tissue extending from the palpebral aspect of the fornix to the bulbar perilimbal area; B: Amniotic membrane graft (grey) is sutured to cover the bulbar conjunctival defect.



**Figure 2 Schematic diagram showing double armed 4-0 silk fornix, retaining sutures tied over bolsters, anchoring the amniotic membrane to the lid margins** A: Sites of sutures; B: Sagittal view of the suture in upper and lower lid.

the peri-limbal region between the normal conjunctiva and the beginning of the cicatrix. If the cicatrix was focal, such an incision was made for <180° and relaxing incisions were then made at the border of the cicatrix toward the fornix. For traction suture 7-0 Vicryl sutures were used at the superior or inferior limbal sclera to redirect the globe, so that the cicatrix could be better exposed. Meticulous dissection by scissors was then done to separate and remove all of the subconjunctival fibrovascular tissue in each bulbar conjunctiva up to the fornix in each quadrant.

After the globe was rotated by the 7-0 traction suture and the removal of cicatrix, the incised conjunctival edge was invariably and naturally recessed to the deep fornix or the tarsus. The AM was thawed and laid down on the bare sclera with the stromal side facing down. If the symblepharon was focal and fornix shortening was limited, the membrane was secured to recessed conjunctiva by an interrupted 8-0 Vicryl suture with episcleral bites (Figure 1). If the symblepharon was diffuse and fornix shortening involved nearly the entire fornix, the membrane was secured to the recessed conjunctiva by a running 8-0 Vicryl suture and the graft was pushed to the deep fornix by a muscle hook and anchored there by passing one double-armed 4-0 black silk suture per quadrant through the full thickness of the lid and securing it to the skin with a bolster made of silicone tubing (Figure 2). The remaining AM was then flattened and secured on the bare sclera by interrupted 8-0 Vicryl sutures with long episcleral

bites. Care was taken to avoid trapping blood under the membrane.

**Postoperative Evaluation and Follow up** Postoperatively all patients received topical combination of tobramycin and dexamethasone eye drops 5 times daily and Tobradex eye ointment twice daily, and tapered off in a period of 4 to 6wk, until full epithelialization of the AM was evident, as determined on the first postoperative visit when no fluorescein staining was demonstrated over the AM. Sutures were usually removed from the 2<sup>nd</sup> week postoperatively.

The outcome of success was defined as restoration of a stable-depth fornix and being free of scar or inflammation, and no motility restriction on the follow up of 6mo (Figure 3). Partial success was defined as focal recurrence of scar tissue without inflammation, whereas failure was defined as the return to inflamed and scarred tissue in the area of surgery and obliteration of the fornix at the last follow up period.

**Statistical Analysis** Collected data were entered into an excel sheet and stored in excel format using Microsoft Excel 2007. For statistical analysis, Statistical package for social science (SPSS) software version 17 was used.

The following tests were used; descriptive analysis of the results in the form of percentage distribution for qualitative data; minimum, maximum, mean and standard deviation calculation for quantitative data. *P* values less than 0.05 were considered significant.

## RESULTS

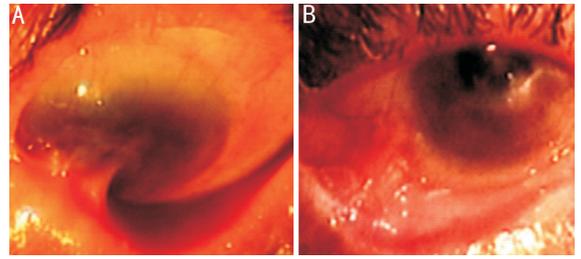
Fourteen eyes of 12 patients (5 males/ 7 females) were presented with symblepharon. The mean follow-up period was  $7 \pm 4.2$  mo (range: 6 – 9mo). In all 14 eyes, complete epithelialization of AM was observed 3wk after surgery, resulting in a non-inflamed appearance of the surgical site.

Eight eyes out of total 14 eyes showed successful fornix reconstruction with success rate (57%), while 4 eyes (29%) showed partial success and 2 eyes (14%) showed failure of reconstruction of the fornix with complete fornix obliteration (Table 1). The visual acuity improved after surgery in 7 eyes while remained stable in 7 eyes.

Post-operative complications from the AMT was very limited as severe conjunctival reaction and motility restriction was occurred only in one eye out of 14 eyes (7%) and pyogenic granuloma occurred in 2 eyes out of 14 eyes (14%) in the first 3mo after surgery and was managed with surgical excision, with local corticosteroid injection

Ten eyes of symblepharon secondary to previous pterygium surgery (4 males/ 4 females, mean age: 43.38y) showed successful fornix reconstruction in 6 eyes (3 males/ 2 females); the fornix was deep, and no recurrence was observed. Two eyes (1 male/ 1 female) showed partial success with moderate depth of the fornix and moderate scar. Two eyes (1 male/ 1 female) showed failure of reconstruction of the fornix with complete fornix obliteration.

Four eyes of symblepharon secondary to previous strabismus surgery, (1 male/ 3 females, mean age: 31.5y) showed successful fornix reconstruction in 2 eyes (1 male/ 1 female),



**Figure 3 Symblepharon secondary to previous pterygium** A: Symblepharon before surgery; B: After AMT surgery for the symblepharon.

**Table 1 Post-operative success rate of symblepharon** *n* = 14

Results of the operations	No.	%
Complete remission	8	57
Partial success	4	29
Failure	2	14

with no recurrence in the follow up period (6mo). Partial success with moderate fornix depth was observed in 2 eyes (2 females) in the last follow up time.

There was no statistical difference in the recurrence rate and the complications between the cryopreserved AM and freeze-dried AM after  $\chi^2$  test.

## DISCUSSION

AM, the innermost layer of fetal (or placental) membrane, consists of a thick basement membrane and an avascular stroma. The function is to protect fetus from unwanted maternal insults during development. It has been commonly recognized that the incision made *via* the skin of the fetus during fetal surgery performed in the third trimester does not bear any scarring after birth. The phenomenon of “scar-less fetal wound healing” remains to be elucidated. It is not clear if AM carries the same feature as the fetal tiss<sup>[12]</sup>.

There are a number of action mechanisms that may explain the effectiveness of AM used in ocular surface reconstruction. The AM's basement membrane facilitates migration of epithelial cells, reinforces adhesion of basal epithelial cells, and promotes epithelial differentiation, and prevent epithelial apoptosis. The AM's stroma contains growth factors, anti-angiogenic and anti-inflammatory proteins<sup>[13]</sup>.

The formation of symblepharon may destabilize the tear film by interfering with eyelid blinking and tear meniscus formation, by reducing the size of goblet cell-containing conjunctiva, by facilitating mechanical trauma caused by lid malposition and misdirected lashes, and by limiting the ocular motility. Symblepharon as such further aggravates the underlying pathology and directly accounts for the patient's symptoms of discomfort. Furthermore, without being first corrected, such symblepharon is a major obstacle, if not a contraindication, for the ensuing corneal transplantation and ocular surface reconstruction<sup>[14-15]</sup>.

When a large symblepharon is surgically removed, the conjunctival defect is normally healed by the surrounding conjunctiva with granulation and scarring, which may lead to

disfiguring and motility restriction of the extraocular muscles or the lid blinking. To avoid such potential problems, conjunctival autograft from the same eye or the fellow eye is frequently used. However, some patients might not have healthy conjunctival tissue to spare and further removal of the uninvolved conjunctiva might put the patient at additional risks. Procedures of symblepharon correction are numerous, suggesting that each variation has its limitations. Conventional therapies should possess the dual actions of restoring the normal conjunctival tissue in the symblepharon-lysed area and preventing the underlying cicatricial processes leading to re-adhesion<sup>[15-16]</sup>.

In this study, AMT was used in 14 eyes of 12 patients with symblepharon, secondary to previous surgery (10 eyes had symblepharon secondary to previous pterygium surgery and 4 eyes secondary to previous strabismus surgery). The mean follow-up was  $7 \pm 4.2$  mo. Cryo-preserved or dried AM was applied alone after lysis of symblepharon and release of the adherent conjunctiva. The degree of success of the outcome was measured by formation of a deep fornix, with complete epithelialization of AM without inflammation and partial improvement of the ocular motility. This was achieved in 8 eyes of the 14 eyes (57%). Partial success was reported in 4 eyes (29%), in which moderate fornix depth was achieved with moderate ocular motility, but without inflammation or severe scarring.

Failure was reported in 2 eyes (14%) in which persistence of adhesion between the lid and the bulbar conjunctiva still present with very shallow fornix and restricted ocular motility. In these cases the host scar tissue was not removed but rather recessed to the fornix after symblepharon lysis. Thus, the remaining scar tissue may be responsible for the failure in these patients.

Strube *et al*<sup>[17]</sup>, in 2011, did a retrograde study series on 80 eyes with postoperative restrictive strabismus (post pterygium, retinal detachment, orbital floor fracture, dermoid cyst and strabismus surgeries) to evaluate the success rate of AMT in treatment ocular misalignment and restore orthophoria and normal ocular motility. This goal achieved in 87% of the cases. These results are higher than ours, as the success rate is defined as achievement of complete fornix reconstruction compared to this study where success rate is achieved only after orthophoria and free ocular motility.

Solomon *et al*<sup>[11]</sup> did a study to evaluate AMT for fornix reconstruction after symblepharon due to previous ocular surface disorders. Seventeen eyes were included in this study. Four eyes had ocular-cicatricial pemphigoid, two eyes had symblepharon after pterygium excision, four eyes had chemical or mechanical trauma, two eyes had strabismus surgery, two eyes (one patient) had Stevens-Johnson syndrome, one eye had toxic epidermal necrolysis, and two eyes (one patient) had chronic allergic conjunctivitis. The mean follow-up period was ranged 9-24 mo. Complete fornix reconstruction was demonstrated in 12 of 17 eyes (70.6%), whereas 2 eyes had a partial success, and 3 eyes (3 patients)

had recurrence of symblepharon with restricted motility. In eyes that demonstrated partial success or failure, the underlying etiology was either an autoimmune disorder or chemical burn. The most successful outcome was observed in eyes with symblepharon associated with previous pterygium or strabismus surgeries (69.4%). These results are compatible with our results.

Nakamura *et al*<sup>[18]</sup>, reported successful fornix reconstruction in 9/10 eyes with symblepharon using sterilized, freeze-dried amniotic membrane (FD-AM) with a mean follow up period of  $13.5 \pm 3.8$  mo. The complete healing took 1 to 6 wk. These results are matching to our results.

Tseng *et al*<sup>[19]</sup>, had non-comparative interventional study to investigate the role of AMT with application of mitomycin C for fornix reconstruction in cicatricial ocular surface diseases. Sixteen patients (8 females, 8 males; 18 eyes) with a mean age of  $41 \pm 23.4$  y (range: 3-79) and suffering from severe chemical/thermal burn (7 eyes), multiple recurrent pterygia and pseudo pterygia (5 eyes), Stevens-Johnson syndrome (4 eyes), and ocular cicatricial pemphigoid (2 eyes) were consecutively enrolled. All except for 2 eyes had prior surgical attempts of surgical reconstruction, including 6 eyes with a mucous membrane graft (MMG), but still presented with symblepharon and persistent ocular surface inflammation. The mean epithelial healing time was  $4.2 \pm 1.9$  wk. The best results achieved in with eyes with post pterygium symblepharon with success rate (65%) and the least with previous chemical burn (28%). The success rate in this study is matching with our study results but the mean epithelial healing time in this study ( $4.2 \pm 1.9$  mo) is delayed compared to our study (3 wk), this is due to the application of MMC.

In conclusion AMT alone is a safe and effective method for symblepharon. Considering the potential adverse effects associated with limbal excision, also, AMT is an effective method of fornix reconstruction for the repair of symblepharon in a variety of ocular surface disorders.

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