

Amniotic membrane transplantation as an adjunct to medical therapy in acute ocular burns

Radhika Tandon,¹ Noopur Gupta,¹ Mani Kalaivani,² Namrata Sharma,¹ Jeewan S Titiyal,¹ Rasik B Vajpayee^{1,3}

¹Cornea & Refractive Surgery Services, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India
²Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India
³Centre for Eye Research Australia, University of Melbourne, Melbourne, Australia

Correspondence to

Dr Radhika Tandon, Cornea & Refractive Surgery Services, Dr Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India; radhika_tan@yahoo.com

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ABSTRACT

Aims To evaluate the role of amniotic membrane transplantation in patients with acute ocular burns.

Methods In a prospective, randomised, controlled clinical trial, 100 patients with grade II to IV acute ocular burns (Roper Hall Classification) were recruited. 50 patients with grade II–III burns were graded as moderate burns, and 50 patients with grade IV burns were graded as severe burns. Both groups were individually randomised into control group (n=25) and study group (n=25). The corresponding grade of ocular surface burn by Dua classification was noted. The eyes in the study group underwent amniotic membrane transplantation in addition to conventional medical therapy. In the control group, conventional medical therapy along with mechanical release of early adhesions as and when necessary was instituted. Rate of healing of corneal epithelial defect, visual acuity, extent of corneal vascularisation, corneal clarity and formation of symblepharon were compared in both groups.

Results In patients with moderate ocular burns treated with amniotic membrane transplantation, the rate of epithelial healing was significantly better than the group treated with standard medical therapy alone (p=0.0004). There was no overall difference in the final visual outcome, symblepharon formation, corneal clarity and vascularisation with or without amniotic membrane transplantation.

Conclusions Amniotic membrane transplantation in eyes with acute ocular burns promotes faster healing of epithelial defect in patients with moderate grade burns. There seems to be no definite long-term advantage of amniotic membrane transplantation over medical therapy and mechanical release of adhesions in terms of final visual outcome, appearance of symblepharon and corneal vascularisation when compared in a controlled clinical setting.

INTRODUCTION

The main aim of management of acute ocular burns (thermal or chemical) is to promote epithelial healing, reduce inflammation and prevent progressive tissue melting to minimise scarring sequelae and severe visual loss with medical or surgical therapy, or both.¹ Various medical and surgical modalities are available,² of which medical management is reasonably effective in controlling the disease in large number of cases. The role of amniotic membrane transplantation (AMT) in the management of acute ocular burns has been studied by various authors,^{3–5} but no prospective controlled studies have been reported except the results of the preliminary study, which was carried out at our centre.⁶ AMT improves

corneal re-epithelialisation and hastens recovery after chemical burns. Amniotic membrane is effective in reducing inflammation and its consequences, and may partially restore limbal stem cell function in ocular burns.^{3–4} Autolimbial or allolimbial transplantation with or without amniotic membrane transplantation, combined with systemic immunosuppression and topical instillation of autologous serum, have all evolved from the better understanding of ocular surface regeneration. The efficacy of AMT as an adjunct to medical therapy in cases of acute ocular burns in a large, prospective, randomised controlled clinical trial and the utility of a new classification system (Dua classification) which has been acclaimed to aid in better management and predictive outcome of ocular injuries were studied.

Patients and methods

The study was approved by the Ethics Committee of the All India Institute of Medical Sciences (AIIMS), New Delhi, India. The study was conducted as a prospective, randomised controlled clinical trial and was retrospectively registered with Clinical Trials Registry—India (CTRI) with the registration number CTRI/2009/091/001018. The sample size of 100 cases was calculated based on the expected number of patients who we could recruit during a 2-year study period as anticipated from our past clinic and emergency records.

Patients

Patients presenting with acute chemical or thermal ocular burns (Roper-Hall Grade II–IV) at Rajendra Prasad Centre for Ophthalmic Sciences, AIIMS were included in the study. The study included 100 eyes of 100 patients with acute ocular burns treated at a tertiary care hospital from October 2003 to December 2005. Grades II and III burns were classified as a ‘moderate’ burns group, while Grade IV burns was taken as a ‘severe’ burns group. An equal number of patients (50 patients each) were recruited with moderate and severe burns. Stratified randomisation was done in patients with moderate and severe burns respectively into a control group (n=25) and study group (n=25). Patients in the control group were treated with conventional medical therapy including mechanical release of any adhesions if necessary, while patients comprising the study group were treated with AMT in addition to the conventional therapy.

A detailed ophthalmic workup included a thorough history with special emphasis on the nature, situation and causative agent of the injury. The preliminary treatment and any delay in first-aid treatment were noted in all patients. All patients

were initially subjected to first aid therapy, which included copious irrigation with normal saline for a minimum of 30 min or as appropriate to normalise the ocular surface pH and removal of any particulate matter or debris from the fornices.

After obtaining informed consent, the patients were randomised using a treatment assignment list prepared with the help of a table of random numbers. A stratified randomisation system was followed (figure 1). Serial numbers were given to the cases, and concealed randomisation using sealed envelopes was followed to decide whether a subject would receive either AMT combined with conventional medical therapy (study group) or conventional medical therapy alone (control group). Patients with bilateral involvement were randomised as individuals, and the right eye was randomised.

Medical treatment

All patients included in the study were started on conventional medical therapy, which included topical prednisolone acetate (1%) every 6 h; ofloxacin(0.3%) every 6 h; sodium ascorbate (10%) every 4 h, sodium citrate (10%) every 4 h and preservative-free tear substitutes every 2 h; homatropine (2%) twice daily and oral vitamin C (500 mg) every 6 h for 2–4 weeks. Antiglaucoma therapy including timolol maleate 0.5% drops and/or oral acetazolamide was prescribed if required. Medications were self-administered by the patients except in cases where symblepharon release was required. Patients in the study group received medical therapy in addition to amniotic membrane transplantation while the control group received medical therapy alone.

Preparation of amniotic membrane and surgical method

The method of amniotic membrane preparation and preservation has been described previously.⁶ Amniotic membrane was obtained under sterile conditions after Caesarian section delivery from a seronegative donor (HIV, hepatitis B surface antigen,

hepatitis C virus, syphilis) after obtaining informed consent. The membranes (amnion and chorion) were separated from the placenta under strict asepsis and then cleaned, processed and preserved. The amniotic membrane was cut into pieces and wrapped onto the nitrocellulose paper discs (5 mm in diameter) The pieces were stored in a 1:1 mixture of glycerol and Dulbecco modified Eagle medium at -70°C.

AMT was performed by a single surgeon (RT) within 2 days of presentation to the hospital. The amniotic membrane was thawed before proceeding to transplantation in eyes with ocular burns. The membrane was transferred onto the entire ocular surface with the epithelial side facing up and stromal side of the membrane touching the surface of the eye. Perilimbal, interrupted 8-0 Vicryl sutures (Ethicon, Johnson & Johnson, Ahmedabad, India) were applied to anchor the underlying conjunctiva and episclera to the membrane. Additional vicryl sutures were applied along the lid margins for further anchorage and stability. Hence, the amniotic membrane was spread fully on the ocular surface up to the fornices, so as to serve as a patch for the entire ocular surface.

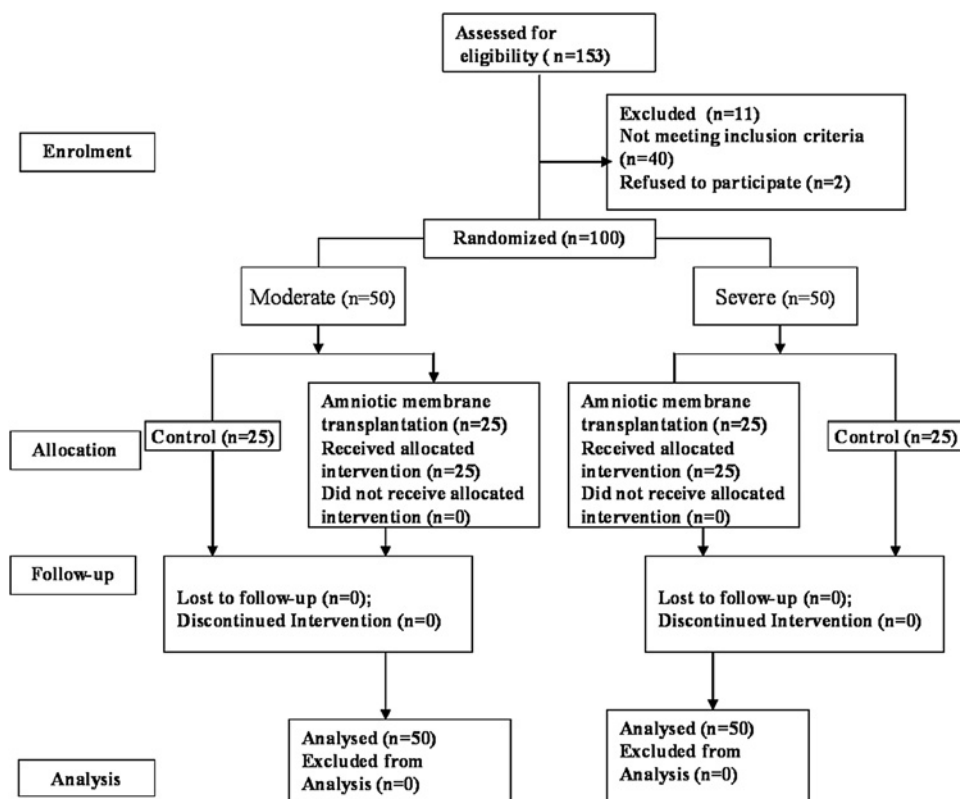
Examinations

Baseline evaluation

Visual acuity was recorded using Snellen charts and was converted into decimals and equivalent values on a log scale. Detailed ophthalmic examination was performed with the aid of a slit lamp, noting the extent of the burn, limbal ischaemia in clock hours and the presence or absence of symblepharon. The conjunctival involvement was estimated by dividing the bulbar and fornicial conjunctiva into quadrants and determining the area of involvement; palpebral conjunctiva was not included in calculation.

Cornea was examined for extent of haze, grade of clarity, size of epithelial defect and corneal vascularisation. Corneal clarity was given a value from 0 to 4 according to the standard classification.

Figure 1 Consolidated Standards of Reporting Trials diagram showing the randomisation and flow of participants through each stage of the randomised trial.



For the purpose of final analysis, we have reversed the corneal clarity grading to the corneal haze grading by subtracting the corneal clarity grading number from 4, such that we obtained a modified classification on the basis of corneal haze (table 1).

The size of the epithelial defect was measured on the slit lamp aided by fluorescein staining (Haag-Streit AG, Koeniz, Switzerland), and the area of the epithelial defect was obtained by the product of the dimensions of the largest diameter and the diameter perpendicular to it. Anterior segment fluorescein angiography was carried out whenever possible.

The classification of injury severity was done by the Roper Hall Classification (RHC) system.⁷ Disease severity was also done simultaneously by a new, modified classification system proposed by Dua *et al*,⁸ which takes into account the extent of limbal involvement in clock hours, the percentage of conjunctival involvement and subsequently tabulating an analogue scale for recording the clinical status and grade of ocular surface burn.

Follow-up

The patients were examined at day 1, day 7, weekly until 1 month, biweekly until 3 months and monthly thereafter. The patients were called for follow-up more frequently, if the condition of the eye so required. The patients were carefully examined at each follow-up visit for complications such as symblepharon and suture granuloma, which were then eventually treated. Visual acuity, status of transplanted membrane, ocular surface, size of corneal epithelial defect, extent of corneal vascularisation and anterior chamber inflammation were assessed at each visit.

Digital photographs at each visit were obtained and stored for independent comparative assessment by masked observers. Epithelial defect size was calculated independently using image-analysis software (Image-Pro Plus, version 4.5, Media Cybernetics, Silver Spring, Maryland). In patients with the amniotic membrane in situ, margins of the epithelial defect, if discernible under the membrane, were measured and recorded. Percentage reduction in the size of epithelial defect as compared with the baseline measurements was computed.

Primary outcome measure:

- a. rate of healing of epithelial defect.

Secondary outcome measures:

- a. visual outcome;
- b. corneal clarity and vascularisation, if any;
- c. prevention of symblepharon.

Statistical analysis

Data analysis was carried out using STATA 9.0 (College Station, Texas). Data were described as number (%) or median (range). Continuous response variables were compared between the groups using the Wilcoxon ranksum test, since the data were non-normal. Categorical response variables were analysed between the groups using the χ^2 test/Fisher exact test as appropriate. A *p* value less than 0.05 was considered statistically significant.

Table 1 Modified grading of corneal clarity on the basis of corneal haze

Grade	Characteristic
0	No corneal haze
1	Iris details visible
2	Pupillary margin visible, iris details not visible
3	Pupillary margin not visible
4	Cornea totally opaque

RESULTS

The baseline demographic and clinical characteristics of the patients in the control and study group are outlined in table 2. The age of the patients varied from 4 to 52 years in the moderate burns group and from 3 to 61 years in the severe burns group. The majority of the patients presenting with ocular burns were young adults and below 40 years of age (96% in the moderate burns group and 92% in the severe burns group). Thirteen females (two with moderate burns and 11 with severe burns) and 87 males participated in the study. Alkali burn was the commonest type of chemical injury (72 of 100 eyes) followed by acid injury (20 of 100 eyes) and thermal injury (eight of 100 eyes).

The ocular surface burn was also graded into six grades according to a classification system described by Dua *et al*, essentially subclassifying RHC Grade IV into Dua 4, 5 and 6 grades. There were 24 and 26 patients, respectively (table 3), in Grade II and III ocular burns in both Dua and RHC. Grade IV ocular burn by RHC comprised a total of 50 patients, who were subdivided into three grades under Dua classification system (Figure 2). There were 12, 16 and 22 patients in Grade 4, 5 and 6 by Dua Classification respectively.

In patients with moderate burns, the primary outcome variable of healing of the epithelial defect in the control group (0.8 mm²/day; range=0.43–5.1 mm²/day) and in the study group (2.45 mm²/day; range=0.48–5.8 mm²/day) was statistically significant (*p*=0.0004). Hence, patients of ocular burns who were treated with amniotic membrane transplantation showed a faster healing rate than patients who were treated with conventional medical therapy alone in the moderate burns group.

In patients with moderate burns, the average time taken for the epithelial defect to heal was 21 days in the control group and 15 days in the study group. The difference was not statistically significant (*p*=0.56). In the severe burns group, the time taken for healing of the epithelial defect in controls ranged from 14 to 90 days, the average being 60 days. In the study group, the time taken by the epithelial defect for complete healing ranged from 12 to 90 days, the average being 30 days. The difference was not statistically significant (*p*=0.219).

At the final follow-up, secondary outcome variables (table 4) such as visual acuity, corneal clarity and vascularisation, and development of symblepharon were also compared between the two groups, and the difference was not statistically significant.

Corneal vascularisation was measured according to the number of quadrants involved. The outcome in terms of corneal vascularisation was also studied in the different grades of burns. It was found that with increasing grade of ocular burn, the number of quadrants of corneal vascularisation also increased. The difference was statistically significant (*p*=0.001).

Corneal vascularisation was not evident in any case at presentation. At the final follow-up visit, it was absent in 25 patients (12 in control group and 13 in AMT group) with moderate burns. It was present in one quadrant in 15 patients (30%), in two quadrants in nine patients (18%) and circumferentially (four quadrants) in one patient (2%), with moderate burns. Corneal vascularisation was characteristically present in all patients with severe burns (100%) at the final follow-up visit. It was present in one quadrant in five patients (10%), in two quadrants in eight patients (16%), in three quadrants in six patients (12%) and in all four quadrants in 31 patients (62%), with severe burns.

In the moderate burns group, two patients of the study group had to undergo a procedure other than amniotic membrane

Table 2 Baseline characteristics in the two groups

Baseline variables	Moderate		Severe	
	Control (n=25)	Amniotic membrane transplantation (n=25)	Control (n=25)	Amniotic membrane transplantation (n=25)
Age†	25 (4–45)	18 (5–52)	14 (3–61)	13 (6–60)
Sex*				
Male	23 (92.00)	25 (100.00)	21 (84.00)	18 (72.00)
Female	2 (8.00)	0 (0.00)	4 (16.00)	7 (28.00)
Mode of injury*				
Alkali	18 (72.00)	17 (68.00)	18 (72.00)	19 (76.00)
Acid	6 (24.00)	4 (16.00)	4 (16.00)	6 (24.00)
Thermal	1 (4.00)	4 (16.00)	3 (12.00)	0 (0.00)
Duration at presentation† (days)	3 (0–14)	6 (1–15)	7 (1–15)	7 (1–15)
Visual acuity†				
Logmar	0.8 (0.13–4)	0.5 (0–3)	2 (0.3–4)	3 (0.2–4)
Lid involvement*				
0 (absent)	9 (45.00)	5 (27.78)	9 (36.00)	12 (48.00)
1 (present)	11 (55.00)	13 (72.22)	16 (64.00)	13 (52.00)
Symblepharon*				
0 (absent)	25 (100.00)	24 (96.00)	20 (80.00)	20 (80.00)
1 (present)	0 (0.00)	1 (4.00)	5 (20.00)	5 (20.00)
Conjunctival involvement† (%)	0 (0–25)	20 (0–50)	25 (0–100)	25 (0–100)
Size of epithelial defect (mm ²)†	22.8 (4–144)	42 (3.4–100)	144 (16–144)	144 (25–144)
Corneal haze† (%)	20 (0–100)	20 (0–80)	80 (20–100)	77.5 (50–100)
Grade of corneal clarity†	1 (0–4)	1 (0–2)	3 (1–4)	3 (0–4)
Corneal vascularisation	0	0	0	0
Limbal ischaemia† (clock hours)	2 (1–6)	5 (2–6)	10 (7–12)	9 (7–12)

*Data presented as number (%).

†Data presented as median (range).

transplantation which included granuloma excision and repeat amniotic membrane grafting. One patient of the control group underwent a large-diameter lamellar keratoplasty. The difference was not statistically significant ($p=0.39$). In the severe burns group, 19 patients of the control group and 18 patients of the study group had to undergo further procedures. These procedures mainly included limbal stem cell transplantation and large diameter lamellar keratoplasty. The difference was not statistically significant ($p=0.89$).

At the final follow-up, symblepharon was present in one patient of the study group and three patients of the control group as a consequence of the moderate ocular burn. The difference was not statistically significant ($p=0.29$). In the severe burns group, 17 patients of the study group and 16 patients of the control group developed symblepharon as a consequence of the ocular burn. The difference was not statistically significant ($p=0.89$).

The average follow-up of patients with acute ocular burns was 13.2 ± 3.8 months. No complications were encountered in any patient during the period of the study.

DISCUSSION

Amniotic membrane transplantation has been used for ocular surface reconstruction in acute chemical and thermal injury and reported to be effective in a number of studies,^{9–11} but a controlled, prospective study involving a large number of patients is lacking.⁶ The present study was designed to assess the potential efficacy of AMT involving 100 patients with

moderate and severe ocular burns and to compare the results with a control group.

This was a follow-on study, and we aimed to eliminate the fallacies of the preliminary trial conducted at our centre.⁶ The present study involved a larger number of patients with a longer follow-up period. In the preliminary trial, some of the baseline variables were significantly worse in the AMT group compared with controls. This fallacy was attributed to the small sample size and the randomisation strategy which was followed.⁶ A stratified random sampling method was used in the follow-on study, which ensured that equal numbers of patients with moderate and severe burns could be recruited. Moreover, all baseline parameters in the control and study group were comparable and similar for all grades of ocular burns. Additionally, Dua classification was also used to ensure a more detailed subclassification of grade IV burns based on the exact extent of limbal ischaemia and conjunctival involvement to prognosticate outcome in various degrees of severe burns.

Table 3 Distribution of patients by Roper Hall and Dua Classification

Roper Hall	Dua					Total
	2	3	4	5	6	
II	24	–	–	–	–	24
III	–	26	–	–	–	26
IV	–	–	12	16	22	50
Total	24	26	12	16	22	100

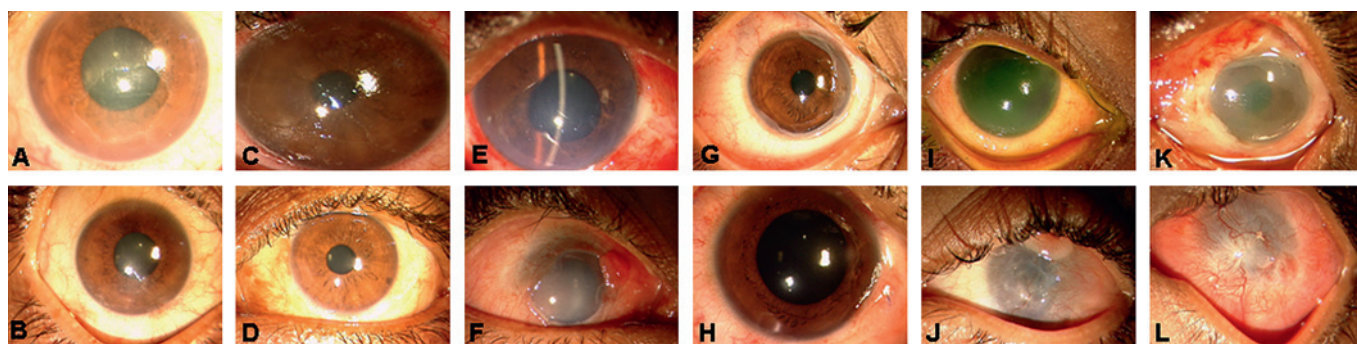


Figure 2 Representative photographs of patients with severe ocular surface burns (Grade 4 Roper Hall Classification and the equivalent Dua 4, 5, 6 ocular burn). The upper row shows the clinical pictures of the patients at presentation, and the lower row shows the corresponding slit-lamp photographs of the same patient at final follow-up visit: A–D: Grade 4 chemical burns (6–9 clock hours of limbal ischaemia); E–H: Grade 5 chemical burns (9–11 clock hours of limbal ischaemia); I–L: Grade 6 chemical burns (12 clock hours of limbal ischaemia); A, B, E, F, I, J: patients treated with standard medical therapy; C, D, G, H, K, L: patients who underwent amniotic membrane transplantation.

The results of the current study have again demonstrated that AMT promotes epithelial healing in patients with moderate ocular burns in comparison with a control group, as reported previously by us.⁶ The rate of epithelial healing in patients with moderate burns was significantly faster in patients who received AMT. In patients with severe burns, the AMT-treated group had a slightly faster healing rate of the epithelial defect, but the difference was not statistically significant. The role of AMT for severe burns seems limited, because these burns are associated with extensive limbal ischaemia and stem cell deficiency. There was no statistically significant difference in outcome in patients with severe burns who underwent AMT as compared with patients who were managed conservatively on medical therapy. This could be due to aggressive medical management on an

inpatient basis under close observation, monitoring and use of manual techniques to break and prevent any symblepharon. The power of the study for the primary outcome variable in cases of severe burns was found to be 21%. The prognosis of Dua Grade 6 burns remains poor, as all of these patients had total epithelial defect with 12 clock hours of limbal involvement and 100% conjunctival involvement. Moreover, in such cases the final outcome should only be assessed after ocular surface reconstruction procedures such as autolimbal or allolimbal transplantation^{12–14} with¹⁵ or without amniotic membrane transplantation^{16–18} combined with systemic immunosuppression. Another prospective controlled trial involving a larger sample size of patients with severe ocular burns is recommended to determine the efficacy of AMT in such patients.

Table 4 Effect of therapy on outcome variables

Response variable	Moderate			Severe		
	Control (n=25)	AMT (n=25)	p Value	Control (n=25)	AMT (n=25)	p Value
Primary outcome variable						
Epithelial healing rate†	0.8 (0.43 to 5.1)	2.45 (0.48 to 5.8)	0.0004‡	2.4 (0.27 to 4.8)	2.8 (1 to 4.8)	0.275
Secondary outcome variables						
Visual acuity†						
LogMAR	0.3 (0 to 2)	0.2 (0 to 1.8)	0.531	2 (0.2 to 4)	1.8 (0 to 4)	0.709
Lid involvement*	0 (0.00)	0 (0.00)	—	0 (0.00)	1 (4.00)	0.500
Presence of symblepharon*	3 (12.00)	1 (4.00)	0.609	16 (64.00)	17 (68.00)	1.00
Corneal haze† (%)	0 (0 to 100)	10 (0 to 50)	0.983	75 (0 to 100)	80 (50 to 100)	0.272
Duration taken for epithelial healing (days)†	21 (7 to 90)	15 (7 to 70)	0.433	60 (14 to 90)	30 (12 to 90)	0.219
Corneal haze†	0 (0 to 2)	1 (0 to 3)	0.983	3 (0 to 4)	2 (0 to 4)	0.272
Grade of corneal haze*						
0	13 (52.00)	12 (48.00)	0.706	2 (8.00)	2 (8.00)	0.538
1	9 (36.00)	10 (40.00)		4 (16.00)	4 (16.00)	
2	3 (12.00)	2 (8.00)		6 (24.00)	8 (32.00)	
3	0 (0.00)	1 (4.00)		8 (32.00)	9 (36.00)	
4	0 (0.00)	0 (0.00)		5 (20.00)	2 (8.00)	
Corneal vascularisation*						
0	12 (48.00)	13 (52.00)	0.432	0 (0)	0 (0)	0.804
1	7 (28.00)	8 (32.00)		2 (8)	3 (12)	
2	5 (20.00)	4 (16.00)		3 (12)	5 (20)	
3	0 (0.00)	0 (0.00)		3 (12)	3 (12)	
4	1 (4.00)	0 (0.00)		17 (68)	14 (56)	

*Data presented as number (%).

†Data presented as median (range).

‡p<0.01, statistically significant.

AMT, amniotic membrane transplantation.

The results of the study should be interpreted, keeping in mind that even patients on conventional medical therapy were carefully managed and closely monitored. The authors feel that there was no difference in formation of symblepharon with or without AMT, as patients on medical therapy alone were actively managed, and symblepharon formation was prevented by manual release and proper therapy modulation as and when required.

Ocular surface reconstruction procedures are being extensively used in patients of ocular burns for rehabilitation and improving visual outcome in such cases.¹¹ With the advent of LSCT¹⁹ and amniotic membrane grafting^{18 20 21} prognosis of less severe grades of burns is enhanced. In our study, AMT was beneficial in patients with 50–75% limbal involvement and resulted in improved outcome in Grade IV burns by Dua classification.

The prognosis of Dua Grade VI burns is poor, and the use of AMT for Grade VI burns is limited. This may be due to the presence of chronic ocular surface inflammation in these cases which could affect the success of AMT and limbal transplantation procedures. It is simply not enough to note the healing of the epithelial defect, but to ascertain the nature and morphology of the covering epithelium. Impression cytology is a good method to monitor the inflammatory status of the ocular surface that is assessed by expression of the MHC class II inflammatory marker HLA-DR by the conjunctival epithelium,²² and also to assess whether the covering epithelium is corneal or conjunctival in origin. There is a significant upregulation of the expression of HLA-DR in eyes with severe burns, and this affects the final outcome in patients with ocular surface burns.²²

Published literature on the efficacy of AMT in acute ocular burns is inadequate in terms of number of patients and comparison with controls. Various studies reported varying degrees of success, and a randomised, controlled trial was much needed. A large number of retrospective reviews^{3 4 21} are available which report favourable outcome with AMT in acute ocular burns. Prospective, non-controlled studies^{5 10 23 24} have also been conducted and have reported that AMT can effectively reduce the inflammation of the cornea at the acute stage of burn injury and prevent complications such as corneal ulcer and perforation. Larger case series^{9 10 25} involving two to five eyes have shown contradictory results. A study by Joseph *et al*²⁵ showed failure of AMT in ocular burns because all patients had severe burns with total epithelial defect and 100% limbal ischaemia.

AMT promoted healing of the ocular surface in all patients, as complete epithelialisation was achieved in all cases. It helps in corneal and conjunctival differentiation and regeneration. This action of amniotic membrane is by virtue of the epithelial basement membrane layer providing a mechanical support and acting as an internal splint. In addition, the amniotic membrane has beneficial biological properties such as secretion of cytokines, growth factors and protease inhibitors which decrease surface inflammation and prevent fibrosis and symblepharon formation. AMT stabilises the ocular surface and provides a conducive surface for further procedures such as auto-limbal and allo-limbal transplantation, lamellar or penetrating keratoplasty.

AMT can be considered as a useful surgical option in moderate chemical burns with non-healing epithelial defects. It may also be used judiciously in severe cases where close monitoring and follow-up are not possible, and compliance with medication is not satisfactory.

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Competing interests None.

Patient consent Obtained.

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