Amniotic Membrane Transplantation in Acute Severe Ocular Chemical Injury: A Randomized Clinical Trial

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• PURPOSE: To compare the outcomes of conventional medical treatment vs combined medical treatment and amniotic membrane transplantation (AMT) in the management of patients with Roper-Hall grade IV ocular chemical injury.

• DESIGN: Randomized, parallel-controlled clinical trial.

• METHODS: SETTING: Single tertiary referral hospital. PATIENTS: Sixty eyes of 60 patients with Roper-Hall grade IV ocular chemical injury with a minimum follow-up of 12 months were enrolled in the study. INTERVENTION: Patients were randomly assigned to 2 groups: Group 1 (30 eyes) received topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline; Group 2 (30 eyes) received amniotic membrane transplant (AMT) on the entire ocular surface in addition to the medical treatment provided in Group 1. OUTCOME MEASURES: The main outcome measure was time to complete corneal epithelialization. Secondary outcome measures were best-corrected visual acuity (BCVA) and neovascularization in the central 5 mm of the cornea.

• RESULTS: Mean follow-up time was 20.3 ± 2.5 months (range 13-24 months). Corneal epithelial defects healed within 72.6 ± 30.4 (21-180) days in Group 1 vs 75.8 ± 29.8 (46-170) days in Group 2 ($P = .610$). Mean BCVA was 2.06 ± 0.67 (0.4-2.6) logMAR vs 2.06 ± 0.57 (1-2.9) logMAR in Groups 1 and 2, respectively ($P = .85$). Group 1 developed more central corneal neovascularization (22 eyes; 73.3%) compared to Group 2 (16 eyes; 53.3%); however, it was not statistically significant ($P = .108$).

• CONCLUSIONS: In comparison to conventional medical therapy, combined amniotic membrane transplantation and medical therapy does not accelerate corneal epithelialization or affect final visual acuity in severe chemical injuries. (Am J Ophthalmol 2019;199:209–215. © 2018 Elsevier Inc. All rights reserved.)

OCULAR CHEMICAL/THERMAL INJURIES ARE true ophthalmic emergencies and represent 8%-22.1% of traumatic ocular injuries.[1,2] The majority of victims are young and male. The severity of injury depends on the type of agent, its concentration, the extent of contact, and the duration of exposure.[1,2] Ideal treatments aim to maximize corneal re-epithelialization and minimize both adnexal structural abnormalities as well as corneal vascularization/conjunctivalization. Therapy should promote epithelial healing, reduce inflammation, and prevent tissue melting as well as scar formation.[1,2] Conventional medications include ascorbate (topical and systemic), citrates, oral tetracyclines, topical corticosteroids, lubricants, antibiotics, therapeutic contact lenses, and tenoplasty.[1,2]

The efficacy of amniotic membrane transplantation (AMT) in the management of acute-phase chemical injury is controversial. Most studies in support of this treatment are nonrandomized or noncomparative case series.[3–12] Three clinical trials have been conducted to determine the efficacy of AMT as a treatment for ocular chemical injury. Two of these trials determined AMT to have minimal efficacy in the care of patients during the acute phase of severe chemical injuries,[13,14] whereas 1 trial showed that AMT combined with standard medical therapy led to a shorter mean time to complete epithelialization vs standard medical treatment (although it was a similar mean time compared to umbilical cord serum with standard medical therapy).[15] The purpose of this randomized controlled clinical trial is to evaluate the effect of AMT in severe cases of chemical injury.

PATIENTS AND METHODS

THIS RANDOMIZED, PARALLEL-CONTROLLED CLINICAL trial was conducted at Labbafinejad Medical Center from August 2006 through January 2014. The study protocol

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was based on the tenets of the Declaration of Helsinki. It was approved by the institutional review board and ethics committee of the Ophthalmic Research Center, Shahid Beheshti University of Medical Sciences. All potential risks and benefits were clearly explained to patients before enrollment, and informed consent forms were obtained from all participants for both the treatment and participation in the research. This trial has been registered in Clinicaltrials.gov with reference number NCT00370812.

• **PARTICIPANTS:** Inclusion criteria were severe chemical injury (Roper-Hall grade IV)[16] and presentation no later than 7 days after injury. In bilateral cases, only the eye with more severe involvement was included. Sixty-nine eyes were enrolled initially. Patients with more than 12 months of follow-up were analyzed. Nine patients were excluded from the analysis because they presented more than 7 days after injury (7 patients) or they were lost to follow-up (2 patients). Thus, included in this study were 60 eyes of 60 patients (aged 12-49 years).

• **RANDOMIZATION AND MASKING:** Eligible eyes were allocated into 2 groups: a medical group, which received topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline (Group 1); and a surgical group, which received AMT in addition to topical preservative-free lubricating gel and drops, chloramphenicol, betamethasone, homatropine, oral vitamin C, and doxycycline (Group 2). Randomization was performed by a biostatistician using the random block permutation method according to a computer-generated randomization list. The block length varied randomly (4-8). The random allocation sequence was concealed from the study investigators via a sealed opaque envelope. However, it was not possible to mask study participants and personnel from knowing which treatment was received.

• **INTERVENTION:** Upon admission, until pH was verified to be neutral, injured eyes were irrigated with at least 2 liters of normal saline and all chemical particles were removed. A complete ophthalmic examination including best-corrected visual acuity (BCVA), pupillary examination, slit-lamp biomicroscopy, tonometry (if possible), and dilated funduscopy was performed. All patients received topical antibiotic (chloramphenicol Q1 0.5%, 4 times daily), corticosteroid (betamethasone Q1 0.1%, every 2 hours), and cycloplegic (homatropine Q1 2%, 3 times daily) drops. The antibiotic was continued until epithelialization was complete. The frequency of corticosteroid drop was decreased after 2 weeks, tapered over several weeks, and continued at a low maintenance dose for several months according to ocular surface inflammation. Patients also received Q1 500 mg oral vitamin C tablets (4 times per day) and Q1 100 mg doxycycline capsules (2 times per day). Preservative-free lubricating gels (Liposic; Bausch & Lomb, Rochester, New York, USA) and drops (Artelac; Bausch & Lomb, USA) every 3-6 hours were administered for several months. Increased intraocular pressure (IOP) was controlled with topical and systemic antiglaucoma medications. Patients were examined on postoperative days 1, 3, 7, 14, and 28; biweekly until 3 months; monthly until 1 year; and quarterly thereafter. At each visit, patients were evaluated for BCVA, slit-lamp findings, IOP measurement, and complications such as symblepharon formation. Corneal epithelial healing was assessed by fluorescein staining. Digital photography (SL-DC3; Topcon, Tokyo, Japan) was performed each follow-up visit. All clinical examinations were carried out by one of the authors (H.H.). If in Group 2 the amniotic membrane did not slough off spontaneously after 3 weeks, it was manually removed. Patients were requested to perform frequent and forceful blinking, separate the eyelids from the globe manually, wash their fornices with a balanced salt solution, and perform regular ductions and versions. At each follow-up visit, the fornices were carefully examined, and early symblephara were released with a glass rod. Patients were followed until they became a candidate for ocular stem cell transplantation (OSCT) and subsequent keratoplasty or keratoprosthesis placement. The ocular surface was allowed to quiet for at least 1 year following the chemical injury prior to OSCT. Ocular hypertension and eyelid malposition/forniceal reconstruction were addressed prior to OSCT.

• **SURGICAL TECHNIQUE:** All patients in Group 2 underwent surgery performed by the same surgeon (A.B.). All surgeries were performed under general anesthesia, and processed cryopreserved amniotic membranes (Tissue Bank, Imam Khomeini Hospital, Tehran, Iran) were used for all surgeries. One layer of amniotic membrane (stromal side down) was fixed to the limbus and 3 mm behind it using running 10-0 nylon sutures. Then a second layer (stromal side down) was fixed to the ocular surface from the upper lid margin to the lower lid margin, anchoring into the fornices using 3 6-0 polyglactin sutures.

• **OUTCOME MEASURES:** The main outcome measure was the time to complete corneal epithelialization. Secondary outcome measures were BCVA and neovascularization in the central 5 mm of the cornea. Patients were also assessed for the development of complications such as glaucoma and symblepharon formation.

• **SAMPLE SIZE:** To have an 80% power for detection of a difference of 14 days (based on previous trials[13–15]) in the mean corneal epithelial healing time between the groups as significant (for the 2-sided 5% level) with an assumed standard deviation of 20 days, 29 eyes in each group were required.

• **STATISTICAL METHODS:** Statistical analysis was performed using SPSS version 21 (IBM, Inc, Chicago, Illinois, USA). Data were presented as the mean

TABLE 1. Baseline Demographic Characteristics of the Patients With Severe Chemical Injury in 2 Treatment Groups

	Total	Medical Therapy	AMT + Medical Therapy	*P* Value
Age (y)				
Mean ± SD	25 ± 7	27 ± 7	24 ± 6	.054[a]
Median (range)	25 (12–49)	25 (12–49)	25 (12–35)	
Sex, n (%)				
M	56 (93.3%)	28 (93.3%)	28 (93.3%)	>.999[b]
F	4 (6.7%)	2 (6.7%)	2 (6.7%)	
Eye, n (%)				
Right	32 (53.3%)	15 (50.0%)	17 (56.7%)	.6[b]
Left	28 (46.7%)	15 (50.0%)	13 (43.3%)	
Injury, n (%)				
Alkali	33 (55.0%)	17 (56.7%)	16 (53.3%)	.795[b]
Acid	27 (45.0%)	13 (43.3%)	14 (46.7%)	

AMT = amniotic membrane transplantation.
[a]Based on *t* test.
[b]Based on χ^2 test.

value ± standard deviation and the level of significance was .05. To compare collected and baseline data, χ^2 or Fisher exact tests were used for qualitative data. The *t* test was used for quantitative data. To compare results between groups, the independent *t* test or Mann-Whitney *U* test was used based on normality test results.

RESULTS

OF THE 60 PATIENTS INCLUDED IN THIS STUDY 56 (93.3%) were male and 4 (6.7%) were female. The mean age of participants was 25 ± 7 years (range 12-49 years) (Table 1). There was not a significant difference between the mean age of Group 1 (27 ± 7 years, range 12-49 years) and Group 2 (24 ± 6 years, range 12-35 years) ($P = .054$) (Table 1). Twenty-seven (45%) patients had an acidic injury and 33 (55%) had an alkaline injury. The mean follow-up period was 20.3 ± 2.5 months (range 13-24 months) (Figure 1).

In Group 1, the corneal epithelial defect healed within 72.6 ± 30.4 days (range 21-180 days). For Group 2, the defect resolved in 75.8 ± 29.8 days (range 46-170 days) ($P = .610$) (Figure 2). Mean BCVA in Group 1 was 2.06 ± 0.57 (range 1–2.9) logMAR, vs 2.06 ± 0.67 (range 0.4–2.6) logMAR in Group 2 ($P = .85$). Group 1 developed more central corneal neovascularization (22 eyes; 73.3%) compared with Group 2 (16 eyes; 53.3%); however, this was not statistically significant ($P = .108$) (Table 2).

Chemical injuries due to alkaline agents had worse outcomes compared to acid-related injuries. Mean epithelial healing time was 81.3 ± 34.6 days vs 68.9 ± 22.1 days in alkali and acid injuries, respectively ($P = .016$). However, there was no significant difference between Groups 1 and 2 in terms of epithelial healing time when they were stratified based on type of injury. Likewise, alkali injuries induced significantly more symblephara compared to acid injuries ($P = .032$); however, there was no significant difference in treatment groups (Table 3).

Symblepharon developed in 11 (36.7%) eyes in Group 1 vs 9 (30%) eyes in Group 2 ($P = .584$). Three eyes (2 in Group 1 and 1 in Group 2) underwent tectonic penetrating keratoplasty following corneal perforation. Increased IOP was observed and controlled by medical therapy in 4 vs 6 eyes in Groups 1 and 2, respectively. One patient in Group 2 underwent laser cyclophotocoagulation secondary to refractive glaucoma. All patients underwent OSCT and subsequent keratoplasty to improve their ocular surface and vision after the last follow-up visit of the trial.

DISCUSSION

THE RESULTS OF THIS STUDY SHOW AMT TO SERVE NO ADDITIONAL benefit in regard to the duration of epithelial defect healing as well as several other secondary outcome measures for the treatment of severe acute ocular chemical injury. However, these data also show that routine medical therapy, which includes simple conservative measures such as frequent lubrication, topical corticosteroids, repeated forceful blinking, ductions and versions, manual separation of eyelids and globe, frequent irrigation, and mechanical release of early adhesions, leads to a relatively quiet, conjunctivalized cornea and deep fornices with minimal complications suitable for complementary ocular surface reconstructive surgeries, including stem cell transplantation.

Several mechanisms of action have been described for the amniotic membrane, including its anti-inflammatory, anti-angiogenic, and epitheliotrophic properties.[17] It has

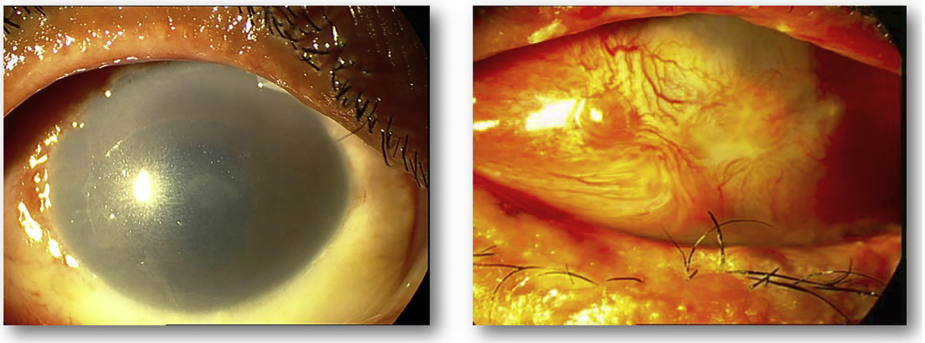

FIGURE 1. (Left) Total corneal opacity, severe limbal ischemia, and severe conjunctival involvement in a patient with severe chemical injury (Roper-Hall grade IV). (Right) Severe corneal conjunctivalization, neovascularization, and symblepharon formation in the same patient 6 months after injury.

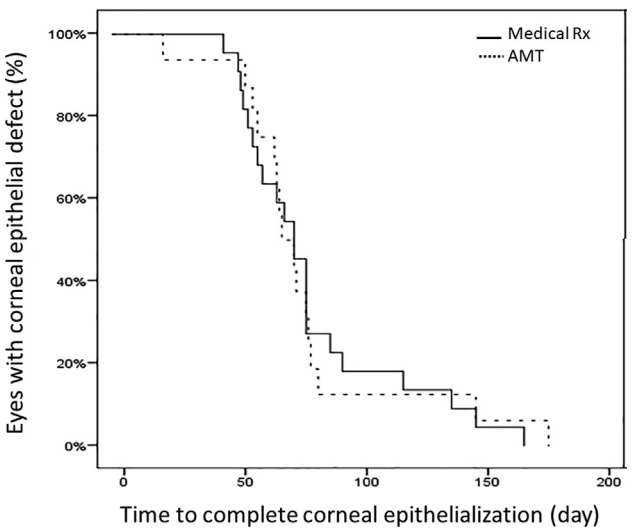

FIGURE 2. The Kaplan-Meier analysis for corneal epithelial defects in severe ocular injury. Kaplan-Meier survival curve comparing corneal epithelial defects in 2 treatment arms in patients with severe chemical injury.

been used after the removal of epithelial or subepithelial lesions (band keratopathy, scars, tumors), as well as for fornix reconstruction, treatment of persistent epithelial defects, corneal ulceration, conjunctival surface reconstruction, painful bullous keratopathy, partial or complete limbal stem cell deficiency (LSCD) (with or without stem cell transplantation), covering defects after removal of large conjunctival lesions, and bleb revision, as well as scleral thinning and pterygium.[18–20] AMT has also been used as a dressing for comfort after ocular surface injury and to prevent symblepharon formation.[1]

The role of AMT in the management of acute-phase chemical injury is controversial (Table 4).[3–15] This may be because despite the benefits of the anti-inflammatory and epithelial healing properties of this tissue, its tendency to decrease vascularization limits the ability for limbal stem cells to recover. In a prospective, noncomparative, interventional case series, Meller and associates[7] reported 13 eyes (11 patients), with acute chemical injury grades II-III (7 eyes) and grade IV (6 eyes), that received AMT within 2 weeks after injury. In this study, final visual acuity improvement was more significant in patients with grade II-III chemical injury vs those with grade IV. Arora and associates[3] performed AMT on 15 eyes of 15 patients with grade II-IV acute chemical injury and demonstrated that fresh amniotic membrane increases patient comfort and reduces inflammation, yet does not prevent the sequelae of LSCD. Kobayashi and associates[5] showed that AMT decreases pain in grade II-IV and facilitates rapid epithelialization. Joseph and associates[21] performed AMT on 4 eyes of 3 patients who suffered from severe chemical (n = 3) and thermal (n = 1) injury, yet concluded that this procedure did not restore the ocular surface or preserve the integrity of the eye in patients with severe acute injury. Finally, Westekemper and associates[11] performed a retrospective analysis on 72 eyes that received AMT for Roper-Hall grade I-IV ocular chemical injuries. At final visit (mean follow-up time was 36.4 months; median 18.5 months; range 1.3–117.3 months), 29 eyes had a BCVA of logMAR 0.2 or better. However, the incidence of complete 360-degree or partial LSCD occurred in 54 of the 72 eyes included in the study. Thus, this group concluded that AMT is an effective adjunctive treatment in the management of acute ocular chemical injury, yet LSCD is a common complication in those who present with severe injury.

Three randomized clinical trials that sought to determine the efficacy of AMT for acute chemical injury have been conducted.[13–15] Tamhane and associates[13] reported 44 ocular injury cases with grades II-IV (20 eyes treated with AMT within 3 weeks after the injury and 24 eyes considered as the control group). Their results showed that AMT improved pain and promoted early epithelialization in patients with moderate chemical injuries but not in

TABLE 2. Comparison of Different Outcomes of the Patients With Severe Chemical Injury in 2 Treatment Groups

	Total	Medical Therapy	AMT + Medical Therapy	95% CI	*P* Value (Intergroup Comparison)
Epithelial healing time (days)					
Mean ± SD	75.7 ± 30	72.6 ± 30.4	75.8 ± 29.8	-9.4 to 21.8	.610[a]
Median (range)	69 (21–180)	69 (21–180)	70 (46–170)		
Visual acuity (logMAR)					
Mean ± SD	2.06 ± 0.61	2.06 ± 0.57	2.06 ± 0.67	-0.31 to 0.32	.850[a]
Median (range)	1.79 (0.4–2.9)	1.79 (1–2.9)	2.6 (0.4–2.6)		
Central corneal neovascularization,[c] n (%)					
−	22 (36.7%)	8 (26.7%)	14 (46.7%)	5%–45%	.108[b]
+	38 (63.3%)	22 (73.3%)	16 (53.3%)		
Symblepharon formation, n (%)					
−	40 (66.7%)	19 (63.3%)	21 (70.0%)	18%–31%	.584[b]
+	20 (33.3%)	11 (36.7%)	9 (30.0%)		

AMT = amniotic membrane transplantation; CI = confidence interval.
[a]Based on Mann-Whitney test.
[b]Based on χ^2 test.
[c]Present (+) or absent (-).

TABLE 3. Comparison of Different Outcomes of the Patients With Severe Chemical Injury in 2 Treatment Groups Stratified Based on the Type of Injury

Injury	Present (+) vs Absent (−)	Total	Medical Therapy	AMT + Medical Therapy	*P* Value (Intergroup Comparison)
Epithelial healing time (days)					
Alkali (mean ± SD)		81.3 ± 34.6	82.6 ± 35.4	79.5± 32.7	.627[a]
Acid (mean ± SD)		68.9 ± 22.1	72.5 ± 24.9	64.8 ± 18.6	.485[a]
P value (intragroup comparison)		.016[a]	.128[a]	.172[a]	
Central corneal neovascularization, n (%)					
Alkali	−	10 (30.3%)	6 (18.2%)	4 (12.1%)	.465[b]
	+	23 (69.7%)	10 (30.3%)	13 (39.4%)	
Acid	−	12 (44.4%)	8 (29.6%)	4 (14.8%)	.252[b]
	+	15 (55.6%)	6 (22.2%)	9 (33.3%)	
P value (intragroup comparison)		.292[b]	.698[b]	.464[b]	
Symblepharon formation, n (%)					
Alkali	−	18 (54.5%)	9 (27.3%)	9 (27.3%)	.849[b]
	+	15 (45.5%)	7 (21.2%)	8 (24.2%)	
Acid	−	22 (81.5%)	12 (44.4%)	10 (37.5%)	0.557[b]
	+	5 (18.5%)	2 (7.4%)	3 (11.1%)	
P value (intragroup comparison)		0.032[b]	0.118[b]	0.259[b]	

AMT = amniotic membrane transplantation.
[a]Based on Mann-Whitney test.
[b]Based on χ^2 test.

those with severe injury. There was no difference in final visual outcome, decrease of corneal vascularization, symblepharon formation, or tear function between the 2 groups. The second clinical trial, performed by Tandon and associates,[14] evaluated 100 patients: 50 patients with grade II and III injury (moderate cases) and 50 patients with grade IV injury (severe cases); each group was randomized into control (n = 25) and AMT groups (n = 25). Their data showed epithelial healing to be significantly faster in the AMT group with moderate injury. However, in severe injury there was not a statistically significant difference in the rate of healing of the epithelial

TABLE 4. Major Clinical Studies on Amniotic Membrane Transplantation for Management of Acute Ocular Injury

Study	Year	Study Design	Injury Classification	AMT Eyes	Control Eyes	Conclusion
Meller et al[7]	2000	Case series	II-IV (R-H)	13	0	AMT was beneficial but does not prevent limbal stem cell deficiency
Sridhar et al[20]	2000	Case series	N/A	4	0	Warranted long-term studies
Joseph et al[21]	2001	Case series	Severe	4	0	AMT was not beneficial
Uçakhan et al[10]	2002	Case series	II-IV (R-H)	5	0	AMT was beneficial
Kobayashi et al[5]	2003	Case series	II-III (R-H)	5	0	AMT was beneficial
Arora et al[3]	2005	Case series	II-IV (R-H)	15	0	AMT was beneficial but did not prevent limbal stem cell deficiency
López-García et al[6]	2006	Case series	Moderate (Dua III-IV)	12	12	AMT was beneficial
Tejwani et al[9]	2007	Case series	Mild to Moderate (Dua II-IV)	24	0	AMT was beneficial in select cases
Prabhasawat et al[18]	2007	Case series	II-IV (R-H)	13	0	AMT was beneficial
Kheirkah et al[4]	2008	Case series	I-III (R-H)	5	0	AMT was beneficial
Gheorghe et al[12]	2016	Case series	N/A	28	0	AMT was beneficial
Westekemper et al[11]	2017	Case series	I-IV (R-H)	72	0	AMT was beneficial
Tamhane et al[13]	2005	Randomized controlled trial	II-IV (R-H)	24	24	AMT was not effective in severe cases
Tandon et al[14]	2011	Randomized controlled trial	II-IV (R-H)	50	50	AMT was not effective in severe cases
Sharma et al[15]	2016	Randomized controlled trial	III-V (Dua)	15	15	AMT was as effective as umbilical cord serum, in addition to standard medical therapy in both groups
Eslani et al (current study)	2018	Randomized controlled trial	IV (R-H)	30	30	AMT did not provide added benefit compared to standard medical treatment alone

AMT = amniotic membrane transplantation; R-H = Roper-Hall.

defect between groups. They concluded that owing to extensive limbal ischemia and stem cell deficiency, the role of AMT is limited in severe chemical injury. There was no difference between the 2 groups in terms of final visual outcome, symblepharon formation, corneal clarity, or vascularization. The most recent clinical trial sought to determine differences in efficacy between those who received standard medical treatment only and those who received umbilical cord serum (UCS) or AMT both, in addition to standard medical therapy.[15] This group evaluated 15 patients who received AMT in addition to standard medical therapy, 15 patients who received UCS in addition to standard medical therapy, and 15 patients who only received medical therapy. Ocular injuries were graded III-V via Dua's classification. They found that time to complete epithelialization was less for those who received AMT or UCS in comparison to those who received medical treatment alone. However, visual outcome, symblepharon formation, tear film status, and eyelid abnormalities were comparable among 3 groups 3 months postoperatively. Therefore, they concluded that UCS and AMT are equally efficacious in treatment of acute ocular chemical injury and lead to a significant decrease in time to complete corneal epithelialization. While the published clinical trials to date have looked at a range of severity, our group focused only on grade IV (Roper-Hall classification), allowing us to make more accurate conclusions.

Although there are indications where AMT has been beneficial, its role in the management of acute chemical injury has not been precisely defined. In milder chemical injuries (grade I-III) with better prognoses, AMT may not be necessary in addition to the standard of care, but it may provide benefit. In severe cases, the destruction and damage of the ocular surface is so extensive that AMT cannot overcome the extensive surface damage and inflammation. Moreover, in these extreme situations, the short-term benefits of AMT are unlikely to prevent secondary long-term complications after chemical injury. Given this, there may be a role for AMT in moderate but not severe cases of acute ocular chemical injury, yet more clinical trials should be conducted. Standard of care including frequent lubrication, repeated forceful blinking, ductions and versions, manual separation of eyelids and globe, frequent irrigation, and mechanical release of early

adhesions associated with routine medical therapy (topical and systemic ascorbate, oral tetracyclines, topical steroids, antibiotics, therapeutic contact lenses, etc) lead to a relatively quiet and conjunctivalized/vascularized ocular surface and deep fornices with minimal complications, suitable for complementary ocular surface reconstructive measures, including stem cell transplantation.

We chose complete epithelial healing as the main outcome measure. Although we assessed other objective outcome measures (eg, BCVA, corneal neovascularization, and symblepharon formation), we did not assess other subjective measures, such as pain, in this trial. Future trials are needed to shed more light on these important measures. In summary, our results show that in severe cases of chemical injury, there was no difference between combined AMT and medical therapy in comparison to medical therapy alone in terms of epithelial healing and final visual acuity.

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