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Adjuvant Role of Amniotic Membrane Transplantation in Acute Ocular Stevens–Johnson Syndrome

A Randomized Control Trial

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Purpose: To evaluate the adjuvant role of amniotic membrane transplantation (AMT) in cases of acute ocular Stevens–Johnson syndrome (SJS).

Design: Prospective randomized controlled clinical trial.

Participants: Twenty-five patients (50 eyes) with acute ocular SJS who presented within 4 weeks of onset of symptoms were recruited.

Methods: The eyes were randomized into 2 groups that underwent either AMT with medical therapy (MT; n = 25) or standard MT alone (n = 25). The patients were evaluated at presentation and during follow-up at 1 week and 1, 3, and 6 months. The parameters evaluated were the best-corrected visual acuity (BCVA), Schirmer test, tear film breakup time (TBUT), conjunctival congestion, corneal haze, vascularization, conjunctivalization, and limbal stem cell involvement. Lid edema, symblepharon, ankyloblepharon, ectropion, entropion, trichiasis, and metaplastic lashes also were analyzed.

Main Outcome Measures: Maintenance of BCVA and stable ocular surface.

Results: At the end of 6 months, the mean BCVA was significantly better in the AMT group (0.068±0.10 logMAR units) compared with the MT group (0.522±0.52 logMAR units; $P = 0.042$). The mean TBUT in the AMT and MT groups was 9.92±4.1 and 6.96±4.5 seconds, respectively ($P = 0.015$). The mean Schirmer test results in the AMT and MT groups were 15.4±6.3 and 8.64±5.4 mm, respectively ($P < 0.001$). Conjunctival congestion persisted in 44% (11/25) in the MT group compared with 4% (1/25) in the AMT group ($P = 0.03$) at the end of the 6-month follow-up. No case in the AMT group demonstrated corneal haze, limbal stem cell deficiency, symblepharon, ankyloblepharon, or lid-related complications. Among eyes in the MT group, corneal haze occurred in 44% (11/25; $P = 0.001$), corneal vascularization and conjunctivalization in 24% (6/25; $P = 0.03$), symblepharon in 16% (4/25; $P = 0.12$), ankyloblepharon in 4% (1/25; $P = 1.00$), ectropion and entropion in 8% (2/25; $P = 0.47$), and trichiasis and metaplastic lashes in 24% (6/25; $P = 0.03$) eyes.

Conclusions: Amniotic membrane transplantation is a useful adjunct to conventional MT in maintaining BCVA and a stable ocular surface in cases of acute ocular SJS. Furthermore, the adjunctive use of AMT also helps to prevent intermediate-term ocular cicatricial sequelae. *Ophthalmology 2015;■:1–8 © 2015 by the American Academy of Ophthalmology.*

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are acute vesiculobullous disorders affecting the skin and mucosal surfaces of the body.[1,2] In this disease spectrum, SJS involves less than 10% of body surface area, the SJS–TEN complex involves 10% to 30% of body surface area, and TEN involves more than 30% of body surface area.[3] The common drugs that incite this idiosyncratic delayed hypersensitive reaction include anticonvulsants, antibiotics, nonsteroidal anti-inflammatory drugs, and allopurinol.[4]

Ocular manifestations occur in 50% to 81% of the patients who have epidermal necrolysis, and one third of them demonstrate long-term ocular sequelae.[5–7] The primary goal of the therapy in acute ocular SJS–TEN is control of acute inflammatory reaction, restoration of an intact ocular surface, and prevention of long-term complications. Conventional medical therapy (MT) in the acute stage comprises topical administration of antibiotics, steroids, and lubricants. It also has been recommended that the fornices be frequently swept with a glass rod in the acute stage. Amniotic membrane transplantation (AMT) has been tried in the acute stage in a few studies because its application decreases inflammation and promotes healing.[8–12] However, no prospective randomized trial has compared the adjuvant role of AMT with conventional MT in cases of acute ocular SJS–TEN. Herein we compare the anatomic and visual

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outcomes in cases of acute SJS−TEN undergoing either AMT in conjunction with conventional MT or conventional MT alone using a prospective randomized controlled trial.

Methods

A prospective, randomized, controlled trial was conducted at a tertiary care center (Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, India). The study is registered at the Clinical Trials Registry−India (identifier, CTRI/11/0052255). Ethical clearance was obtained from the institutional review board, and the study conforms to the tenets of the Declaration of Helsinki. Twenty-five patients (50 eyes) with acute ocular SJS−TEN seeking treatment within 4 weeks of the onset of symptoms were recruited from the Dermatology Department of All India Institute of Medical Sciences from May 7, 2013, through May 15, 2014. They were randomized into 2 groups using a computer-generated random number table. Group 1 (n = 25) underwent AMT with standard MT, and group 2 (n = 25) received standard MT alone. Written informed consent was obtained from all patients. Patients with corneal infection, who were younger than 12 years, and who were unable to undergo AMT for systemic reasons were excluded from the study.

All patients were isolated in a sterile room. Patient examinations were carried out at the bedside to assess visual acuity (handheld Snellen chart); ocular surface (tear film breakup time [TBUT] assessment followed by the Schirmer test); adnexa (lid edema, lid membrane, symblepharon, ankyloblepharon, conjunctival inflammation); and fundus. Visual acuity was measured at the bedside using a handheld Snellen chart kept at 6 m at the time of initial presentation. Patients' refractive error was corrected at the bedside to note best-corrected visual acuity (BCVA) as a baseline parameter. Hence, at all follow-up points, the BCVA was repeatable and could be compared with the baseline values. At the time of the initial presentation, all patients were examined at the bedside using a portable slit lamp. As soon as the patient was ambulatory, he or she was examined using a routine slit lamp. In all cases, routine slit-lamp evaluation was carried out 1 week after presentation. The eyes were categorized as having mild, moderate, and severe disease based on the initial presentation.[6] A conjunctival swab was obtained under sterile conditions and sent for bacterial culture and sensitivity. Standard MT was started in both eyes of all patients. Intensive topical corticosteroids were administered every 2 hours for 1 week, which then were continued 4 times daily for 3 more weeks.

After obtaining informed consent, simple randomization was carried out using a computer-generated random number table (Fig 1). The random number sequence was generated by the statistician, the participants were enrolled by the dermatologist (N.K.), and treatment was assigned by the ophthalmologist (N.S.). No blinding was carried out.

Conventional Medical Treatment

Conventional MT consisted of topical antibiotics (chloramphenicol 0.5% and polymyxin B sulphate 10 000 IU 4 times daily for 1 week), topical steroids (prednisolone acetate 1% every 2 hours daily for 1 week followed by 4 times daily for 3 weeks), and topical lubricants (carboxymethyl cellulose 5 mg/ml 6−8 times daily, ointment hypromellose 2%, and sodium chloride 0.5% 3 times daily for 6 months). The fornices were swept 2 to 3 times daily for the first month, followed by once daily until the inflammation subsided.[11,13]

Amniotic Membrane Preparation and Surgical Technique

The method of amniotic membrane preparation and preservation has been described previously.[14] The amniotic membrane was obtained under sterile conditions after elective cesarean delivery from a donor who was seronegative for human immunodeficiency virus, hepatitis B surface antigen, hepatitis C virus, and syphilis. 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 nitrocellulose paper discs (5 cm in diameter). The pieces were stored in a 1:1 mixture of glycerol and Dulbecco's modified Eagle's medium at −70° C. The amniotic membrane was thawed before proceeding to transplantation in eyes. A modification of previously described techniques was used while performing the AMT.[15] The procedure was performed at the bedside under topical anesthesia in the isolation room, where aseptic precautions were maintained. The conjunctival surface of the eyes was dried using cotton swab sticks. Instead of sutures, fibrin glue (Tisseel VH fibrin sealant; Baxter AG, Vienna, Austria) was applied over the ocular surface, and the membrane was transferred with the stromal side touching the surface of the eye, covering the cornea and the entire ocular surface. Fibrin and thrombin components of the glue were injected together beneath the amniotic membrane over the conjunctival surface. Iris repositor was used to cause apposition of the amniotic membrane all around for 5 minutes. The Precision UV bandage contact lens (Ciba Vision, Duluth, GA;14.5-mm diameter, 74% water content vasurfilcon A material) was applied after 5 minutes to allow the amniotic membrane to adhere properly to the ocular surface. We ensured that the amniotic membrane was glued to the conjunctiva in the fornices as well as to the upper and lower tarsal conjunctiva by a sweeping movement, which was carried out with a lens spatula so as to cause apposition of the amniotic membrane to the ocular surface. A symblepharon ring then was applied in all cases.

The patients were followed up at 1 week and at 1, 3, and 6 months. The primary outcome measures evaluated were BCVA, TBUT, and Schirmer test results. The secondary outcome parameters evaluated were conjunctival congestion, corneal haze, corneal vascularization and conjunctivalization, symblepharon, ankyloblepharon, ectropion, entropion, trichiasis, and metaplastic lashes.

Statistical Analysis

Keeping the power of study as 80% and the level of significance as 0.05, the primary outcome measures were the mean BCVA and ocular surface markers (TBUT and Shirmer test results). Statistical analysis was carried out using SPSS software version 11.0 (SPSS, Inc., Chicago, IL). Data are expressed as median (range), percentage, and mean ± standard deviation, as appropriate. Nominal data were compared using the chi-square test or Fisher exact test, as appropriate. Nonparametric quantitative data were compared using Kruskal−Wallis and Mann−Whitney *U* tests. One-way analysis of variance was used to compare intergroup means for parametric quantitative data, and Bonferroni correction was used to analyze posttest results.

Results

Twenty-five patients (50 eyes) were recruited between May 7, 2013, and May 15, 2014, to undergo either conventional MT alone or in conjunction with AMT. The patients were followed up until