A Novel Technique for Amniotic Membrane Transplantation in Patients with Acute Stevens-Johnson Syndrome

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ABSTRACT **Cryopreserved amniotic membrane (AM) transplantation is an emerging technique that is becoming the gold standard for the management of acute Stevens-Johnson syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN). We describe a novel surgical technique utilizing a single, large sheet of AM (5 x 10 cm) and a custom-made forniceal ring, which facilitates AM placement. Our technique is easy to use and minimizes suturing and manipulation of ocular tissues, resulting in decreased operative time. This technique may be applied in the management of multiple ocular surface disease processes, including chemical or thermal burns, severe ocular graft versus host disease (GVHD), and other autoimmune diseases.**

KEY WORDS **amniotic membrane, cryopreserved amniotic membrane, ocular surface, Stevens-Johnson syndrome, transplantation**

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I. INTRODUCTION

Stevens-Johnson syndrome (**SJS**) and its more severe variant, toxic epidermal necrolysis (**TEN**) present with widespread exfoliation of the skin and mucous membranes, which can lead to significant ocular involvement and morbidity. If acute ocular surface inflammation is not recognized and treated, cicatrization ensues, leading to photophobia, intractable dry eye, chronic pain, corneal scarring, and vision loss.[1] In fact, progressive conjunctival scarring and corneal damage are the most disabling long-term complications for SJS and TEN survivors.[2,3] The incidence is approximately 2-6 cases per million per year, but can be significantly higher in children, at up to 35.5 cases per million per year.[4-6]

Cryopreserved amniotic membrane transplantation (**AMT**) is an emerging technique that is becoming the gold standard in the management of acute SJS/TEN.[7,8] Amniotic membrane (**AM**) arises from the innermost placental membrane and contains a single layer of epithelial cells that are often nonviable in commercially available AM, a thick basement membrane, and a stroma. The basement membrane supports host epithelial cell migration, adhesion, and differentiation, and it inhibits epithelial cell apoptosis. The stroma is rich in cytokines, growth factors, and protease inhibitors,[9,10] providing AM with anti-inflammatory and antiscarring actions. Thus, AM serves as a biological bandage by suppressing inflammation, promoting epithelialization, and thereby preventing sight-threatening sequelae. AM typically dissolves over a period of 1-2 weeks; thus, more than one application may be necessary during the acute phase of the disease.

It is well understood that early intervention with AM during the acute stage of SJS is beneficial,[10] and there are two current methods of applying AM. The first involves PROKERA® (Bio-Tissue, Doral, FL). This product consists of AM stretched across the lumen of a polycarbonate ring, and it is placed on the eye in a way similar to a contact lens. Its advantages include easy bedside insertion without sedation[11] and easy replacement if the membrane melts. However, this device only covers the cornea and surrounding bulbar conjunctiva,

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leaving the rest of the conjunctiva, fornices, and eyelid margins exposed. The second method involves utilizing multiple, pre-cut 3.5 cm or 5 cm square pieces of cryopreserved AM and suturing or gluing these pieces together on the ocular surface and eyelids.[8,12] The advantage of this technique is complete coverage of the mucosal surface of the eye with AM. The disadvantage is that the technique is time-consuming, requires sedation (especially in children), and allows gaps to form between AM sheets in coverage of the ocular surface.

We describe a novel surgical technique utilizing a single, large sheet of AM (5 x 10 cm) and a custom-made forniceal ring for AMT in ocular SJS. This technique combines the ease of application provided by PROKERA® and the complete ocular surface coverage of the multiple AM sheet technique, while minimizing suturing and manipulation of ocular tissues to decrease operative times significantly. Our technique can be applied in the management of multiple ocular surface disease processes, including chemical or thermal burns, severe ocular graft versus host disease (**GVHD**), and other autoimmune diseases.

II. DESCRIPTION OF THE TECHNIQUE

Because all the patients in our series were children, the procedure was performed under general anesthesia. First, a custom-made symblepharon ring is fashioned from sterile intravenous (**IV**) tubing (Ultra™ Small Bore Extension Sets, Reference Number MX453HL, Smiths Medical, Dublin, OH). The size of the ring is tailored to each patient to ensure proper apposition of the AM to ocular surfaces. The distance between the superior and inferior orbital rims is measured, and this distance is used to estimate the diameter of the ring. The length of IV tubing can be adjusted if it is too small or too large, as proper sizing is necessary for expansion of the AM to the fornices while simultaneously allowing for proper eyelid closure. The length of IV tubing is cut with one blunt edge and one oblique edge, and the oblique end is threaded into the other using a clamp (Figure 1A).[13]

Next, the patient is prepared for the surgical procedure. The periocular skin is cleansed with either betadine 10% or saline, depending on the degree of periocular skin inflammation. A few drops of 5% betadine solution are placed in each of the fornices. To protect the fragile skin, drapes without adhesive are utilized to create a sterile field in the periocular region. The eyelashes are then trimmed to facilitate membrane contact with the eyelid margins. Erythromycin ointment (or any antibiotic-based ointment) may be smeared onto the eyelashes, which facilitates clumping of the lashes, thus preventing individual lashes from falling onto the ocular surface.

AMT is initiated with a continuous 5 x 10 cm sheet of cryopreserved AM (Custom Piece, Amniograft, Bio-Tissue, Doral, FL) placed over the entire mucosal ocular surface. This AM is separated from the nitrocellulose paper at one edge and is placed over the upper eyelid with the stromal side facing the skin (Figure 1B). It is anchored to the skin and orbicularis, using two, 6-0, polypropylene mattress sutures 2-3 mm superior to the lash line, and styrofoam bolsters from the suture packaging protect the skin (Figure 1C). Alternatively, larger gauge IV tubing cut longitudinally can be used to make the bolsters. Once anchored superiorly, the AM is completely separated from the nitrocellulose paper. Given that AM is extremely thin and tends to wrap around itself and clump together, the sheet is swept from the center to the edges using a blunt, 19-gauge cannula while balanced salt solution is administered to maintain moisture (Figure 1D). With the AM covering the anterior eyelids and ocular surface, an eyelid retractor (i.e., Conway or Demarres) is used to lift the AM-covered upper eyelid off the ocular surface. This lifting motion pulls the AM into the upper fornix, and the custom-made symblepharon ring is inserted into the upper fornix over the AM (Figure 1E), thereby further pushing the membrane into the fornix. Next, the lower eyelid is retracted, and the ring-AM complex is inserted into the lower fornix. A muscle hook can also be used to tuck the ring into position. The AM is then brought over the lower eyelid margin and anchored to the skin with 6-0, polypropylene sutures and bolsters (Figure 1F). Excess AM is trimmed with scissors. Antibiotic ointment is applied over the eyelid and ocular surface, and the sterile draping is removed.

III. OUTCOME DATA

A retrospective chart review of consecutive cases of AMT performed in patients with acute SJS at Boston Children's Hospital (**BCH**) was conducted with institutional review board approval. Cases were identified through billing records between 2011 and 2015. Nine cases were identified, each performed by one of the two attending physicians who manage SJS patients at BCH, assisted by second-year ophthalmology residents and/or pediatric ophthalmology fellows. The first five cases were performed utilizing two separate 3.5 x 3.5 cm pieces of AM. These pieces were sutured together, with one end anchored along the upper eyelid margin and one end anchored along the lower end with running sutures. The central portion was then anchored on the ocular surface. The last four cases utilized one large piece of AM with the technique presented here. A summary of patient data is given in Table 1.

We compared surgical times of AMT with a single piece of AM as presented here versus the traditional technique of suturing multiple pieces of AM.[12] As shown in Table 1, surgical times were reduced with the single-piece AM technique. On average, surgical duration was reduced by 60% (Figure 2A). AMT with multiple pieces of AM took an average of 199.6 ± 35 minutes versus an average of 84 ±322 minutes (P=.016, Mann-Whitney U test) for AMT with a single piece of AM.