

Mucous Membrane Grafting For Lid Margin Keratinization in Stevens–Johnson Syndrome: Results

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Purpose: To study the efficacy of mucous membrane grafting as a surgical technique to address lid margin keratinization, an important cause for chronic blink-related microtrauma in Stevens–Johnson syndrome (SJS).

Methods: The keratinized strip of conjunctiva along the lid margin was excised and replaced by lip mucous membrane using fibrin glue in 54 eyes of 31 patients with lid margin keratinization after SJS. This was a retrospective case series carried out between April 2005 and November 2006.

Results: In 50 of 54 eyes (92.6%), there was improvement or stabilization in patient comfort, conjunctival hyperemia, ocular surface staining characteristics, and best-corrected visual acuity over a mean follow-up period of 6 months.

Conclusions: The authors describe the method of mucous membrane grafting for addressing lid margin keratinization, one of the important causes for persistent inflammation in SJS. This procedure not only improves patient comfort and visual acuity by reducing surface inflammation but also possibly prevents further deterioration of ocular surface in SJS.

Key Words: Stevens–Johnson syndrome, lid margin keratinization, blink-related microtrauma, mucous membrane grafting

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Stevens–Johnson syndrome (SJS), although an acute self-limiting disorder of the skin and mucous membrane, leads to chronic cicatricial changes in the eye.¹ The ocular manifestations in the acute stage include ocular inflammation and tarsal ulceration. Corneal complications include epithelial defect, infiltration, and ulceration and are reported in 18%–20% of cases.^{2–4} Although self-limiting, the chronic continuing process of inflammation in SJS has been well documented.^{5,6}

In SJS, a disturbance in all 3 components of the tear film occurs. The mucin layer is disturbed by destruction of the conjunctival cells, aqueous layer by scarring around the ductules, and the meibum is affected by meibomian gland metaplasia. The lid margin changes occurring include meibomian gland metaplasia, trichiasis, punctal scarring, and lid margin keratinization. In addition, the presence of symblepharon alters the stability of the tear film. The blink-related microtrauma because of the lid margin keratinization (Fig. 1), which is worsened by the lipid and aqueous tear deficiencies, leads to continuous insult to the limbal stem cells.⁷

Destruction of limbal stem cells results in replacement of corneal epithelium by conjunctival epithelium. This destruction to limbal stem cells is ongoing in SJS because of persistent inflammation. The preexisting primary damage to the limbal stem cells determines the further course of the disease—either squamous metaplasia or conjunctivalization.⁸ The prime causes for this inflammation include dry eye, lid margin changes, and conjunctival inflammation secondary to underlying pathophysiology. The management of each of these factors in altering the chronic course of the disorder cannot be overemphasized.

Intervention in both the acute and chronic stages of SJS has been described in literature. Amniotic membrane transplantation performed within the first 2 weeks of onset of SJS is believed to reduce the incidence of chronic sequelae.^{8–12}

The treatment of dry eye and eyelid abnormalities such as trichiasis and entropion is well established in the management of chronic ocular sequelae of SJS. Corneal transplantation in patients with SJS with severe ocular surface disease carries a very poor prognosis with a high rate of infection (up to 40%). The occurrence of persistent epithelial defects often progresses to corneal melting, infiltration, and perforation. Transplanted limbal epithelial cells or keratoepithelioplasty in these chronically inflamed eyes result in graft rejection and loss of donor epithelial cells, often resulting in progressive conjunctivalization and visual loss.^{13,14}

The issue of lid margin keratinization, which could be a very important cause for persistent ocular surface inflammation in these eyes, has invariably been overlooked. It accounts for a deterioration of the ocular surface over years and also contributes to the high failure rates of attempts at surface reconstruction and visual rehabilitative procedures.¹⁴ Large-diameter contact lenses do prevent the constant rubbing of the lids on the limbus and the cornea, thus eliminating the sandpaper effect of the lids on the ocular surface.⁸ However, contact lens fitting may be a problem in the presence of

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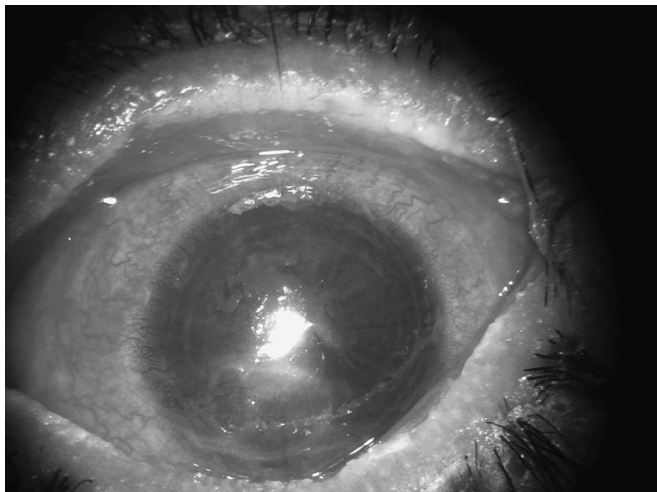


FIGURE 1. Severe lid margin keratinization.

symblypharon, and compliance is particularly poor in this condition. The long-term use of bandage contact lenses is not without complications. The use of mucous membrane grafting for lid margin keratinization has been mentioned earlier.^{8,9} To the best of our knowledge, there are no published reports on the clinical results of this procedure with fibrin glue as described herein.

The aim of this study was to analyze the results of excision of the strip of keratinized conjunctiva along the lid margin and replacement using oral mucous membrane harvested from the lip. We present the results of this procedure, done in 54 eyes of 31 patients with SJS.

PATIENTS AND METHODS

Approval of the institutional review board was obtained for this study, which adhered to the tenets of the Declaration of Helsinki. We studied 54 eyes of 31 patients with SJS who underwent mucous membrane grafting for lid margin keratinization. The diagnosis of SJS was based on a confirmed history of the acute onset of high fever, serious mucocutaneous illness with skin eruptions, and involvement of at least 2 mucosal sites including the ocular surface. A routine ophthalmic examination was done for all patients. A total of 300 patients with SJS were examined at our institute during the study period from April 2005 to November 2006, of which 54 eyes of 31 patients were selected for the surgical procedure as described below.

Preoperative Evaluation

Ocular surface evaluation included assessment of

1. Symptoms (scored from 1 to 10 in terms of increasing severity). The symptoms were graded on the subjective basis of severity of interference with daily activities pre- and postoperatively, with respect to irritation and photophobia. This was graded on a scale from 0 to 10.
2. Conjunctival hyperemia (indicative of ocular surface inflammation) graded from 0 to 3 (0, absent; 1, mild; 2, moderate; and 3, severe).
3. Fluorescein corneal staining scores from 0 to 9. The grading scale for fluorescein corneal staining was done

based on the intensity of staining graded from 0 to 3. (0, no staining; 1, mild staining; 2, moderate staining; and 3, confluent staining). This scoring was done for each third of the cornea divided vertically.

4. Schirmer I test was graded as 1 to 4 (1: < 5 mm, 2: 5 to 10 mm, 3: 11 to 15 mm, 4: >15 mm).
5. Corneal changes were graded⁸ from 1 to 3 based on corneal vascularization (0: no vascularization, 1: neovascularization confined to peripheral cornea, 2: neovascularization up to pupillary margin, 3: neovascularization crossing the center).

In addition, the best-corrected visual acuity was compared pre- and postoperatively.

Eyes with lid margin keratinization as the primary ocular involvement were included in the study. Lid margin keratinization was looked for after eversion of the lids. Changes were graded as minimal roughening (mild) not causing any surface changes, keratinization extending 1 mm into the tarsal conjunctiva (moderate), and keratinization extending more than 1 mm into tarsal conjunctiva (severe). All eyes in our study included for surgery manifested lid margin changes (moderate to severe) severe enough to cause symptoms, conjunctival hyperemia, ocular surface staining, and/or corneal vascularization.

Those with extensive symblephara, associated entropion, and ocular surface cicatrization, which would necessitate additional surgical procedures, were excluded from the study. Eyes with no wetting of Schirmer strip after punctal occlusion and presence of extensive ocular surface keratinization were excluded from the study. A localized small patch of corneal or conjunctival keratinization was not considered to be a contraindication to surgery. Surgery was undertaken at least a month after the onset of SJS (3 months to 10 years).

Management of trichiatric lashes by electroepilation and punctal occlusion for dry eye wherever appropriate was done along with the use of lubricants, usually before mucous membrane grafting. The preoperative parameters were graded after these procedures were performed and compared postoperatively. Preoperative evaluation of the lip mucosa to confirm its good health (pink, without any evidence of infection and submucosal scarring) was done with subsequent use of chlorhexidine mouthwash 4 times a day for 5 days.

Surgical Technique

An informed consent was taken from each patient before surgery. Being an extraocular procedure, both eyes were operated upon at the same time for bilateral cases. All but 2 surgeries were performed under general anesthesia. Oral endotracheal intubation was done with the tube secured to one side, allowing adequate exposure of the lip mucosa. The eye and the mouth were prepared with betadine solution and draped.

Lid sutures were taken using 4-0 silk and lids everted. The lid margin was marked using a marker to indicate the extent of excision to be carried out so as to encompass the entire corneal diameter. It was important to remember that the eye tends to rest in the exotropic position under general anesthesia and thus causes a lateralization of the graft if done with respect to the center of the cornea. In general, up to 15–20 mm of the central keratinized lid, margin was marked and dissected with the tarsal conjunctiva as a flap to a width of

5 mm for each lid. Hemostasis was achieved with judicious use of cautery. After completing the same for all the 4 lids, the eyes were kept closed and attention was shifted to the lip mucosa.

An area of 30–40 × 10 mm was marked out on the stretched lower lip mucosa, and submucosal infiltration of 5 mL xylocaine adrenaline (1:1,600,000) given. The marked out area was dissected using a 15 blade on Bard Parker handle, and the harvested graft was washed in antibiotic solution. The edges of the raw lip mucosa were approximated using continuous 5-0 vicryl sutures. After confirming hemostasis, attention was redirected to the eye after change of gloves and surgical instruments.

The harvested graft was first freed of any underlying fatty tissue by sharp dissection and thinned out to the extent possible to allow good stretchability of the graft. This was then divided into 4 parts per lid each measuring 15–20 × 5 mm for each to match the dissected area on the lid. One edge of the mucosa was sutured to the lid margin using 8-0 vicryl continuous suture with exteriorization of the knots. Fibrin glue (Baxter Tisseel Kit) was reconstituted, and the 2 components were applied to the raw tarsal surface; the mucosa was stretched and stuck over the tarsus. After confirming good apposition, the conjunctival flap was excised off. The procedure was repeated for all 4 lids, and surgery was completed by patching the eyes with antibiotic eye ointment (Figs. 2A–D).

Postoperative management included the use of topical antibiotic eyedrop 4 times daily for a week along with frequent application of lubricants. No topical steroids were used. Patients were examined on day 1, weeks 1 and 6, and subsequently every 3 months. Postoperative chlorhexidine mouthwash was continued for a week after surgery.

RESULTS

Of the 31 patients who underwent surgery, 16 were males and 15 were females. The mean age of the patients was 21.32 years, ranging from 4 to 50 years. All but 2 patients were younger than 35 years. Nine of 31 were children younger than 15 years (29.03%). The mean follow-up was 6 months, ranging from 1 month to 14 months. The mean duration from onset of SJS to surgical intervention was 3.78 years ± 2.05 years. Nine patients underwent the procedure in only one eye as the other eye was either phthisical or completely keratinized (asymmetric involvement). One patient was advised surgery in only one eye because of lack of lid margin keratinization in the other eye.

In 50 of 54 eyes (92.6%), there was marked improvement (a difference of greater than 5 in the subjective scoring) in symptoms on the first day and was maintained till last follow up (Figs. 3A, B). In 1 patient (2 eyes), although there was improvement in symptoms and a reduction in corneal staining, photophobia significant enough to interfere with daily activities persisted after surgery. In the second patient (2 eyes), there was considerable residual peripheral lid margin keratinization rubbing on the cornea and the rest of the ocular surface causing persistence of symptoms. These 2 patients underwent revision mucous membrane grafting with complete excision and replacement of residual lid margin keratinization after which there was marked improvement in symptoms.

In 50 of 54 eyes, there was an improvement in conjunctival hyperemia. Before surgery, grade 1 conjunctival hyperemia was noted in 12 eyes, grade 2 in 26 eyes, and grade 3 in 16 eyes. This improved to grade 0 in 5 eyes, grade 1 in 36 eyes, grade 2 in 9 eyes, and grade 3 in 4 eyes (Table 1). Conjunctival

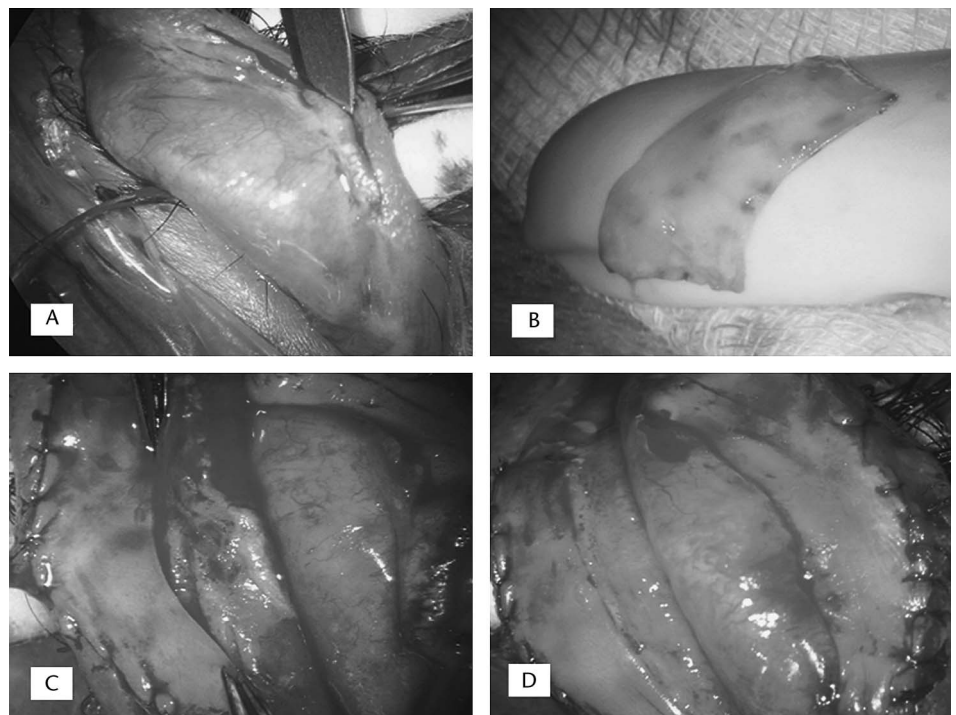


FIGURE 2. A, Excision of the strip of keratinized lid margin from the lid margin up to 5 mm, encompassing the entire length of keratinization, 15–20 mm per lid. B, Harvested lip mucosa freed of underlying fatty tissue. C, Securing lip mucosa to lid margin using 8-0 vicryl suture and stretching and adhering the graft using fibrin glue. D, Final appearance of the lids after surgery.

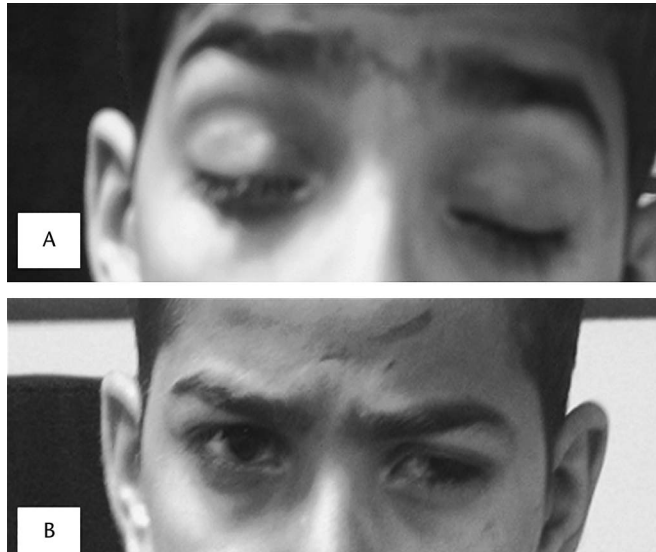


FIGURE 3. A, Inability to open eyes preoperatively with frontalis overaction. B, Improvement in photophobia after surgery (3 months postoperatively).

hyperemia improved from a mean grade of 2 preoperatively to a mean grade of 1 postoperatively.

The change in total score of fluorescein corneal staining after surgery was studied. An improvement in the score was noted in all eyes. Data was not recordable in 3 eyes. Staining score improved by more than 6 in 17 eyes (33.33%), 3–6 in 27 eyes (52.94%), and <3 in 7 eyes (13.73%; Table 2). Schirmer I test was also compared pre- and postoperatively (Table 3). This showed a considerable increase in the percentage of patients in the groups between 5 and 15 mm of wetting among eyes with recordable data (27.57% preoperatively vs. 59.45% postoperatively).

Corneal changes were noted to be of grade 1 in 22 eyes, grade 2 in 16 eyes, and grade 3 in 16 eyes preoperatively. This improved by 1 grade in 4 eyes with a decrease in corneal vascularization and remained stable in 46 eyes. It worsened in the 4 eyes in which there was a drop in visual acuity because of continued progression of inflammation. Impression cytology was not performed in these eyes to corroborate clinical findings.

In 50 of 54 eyes (92.6%), the visual acuity was maintained or improved after surgery. Visual acuity improved in 28 eyes (56%; Table 4) and was maintained in 22 eyes (44%). Among the eyes with an improvement in visual acuity, 16 eyes (57.14%) improved by 2 lines. Of these 16 eyes, 7 eyes (43.75%) had an improvement in visual acuity of 5 lines or

TABLE 2. Comparison of Fluorescein Staining Scores Pre- and Postoperatively

Improvement	No. Eyes, n (%)
>6	17 (33.33)
3 to 6	27 (52.94)
<3	7 (13.73)

more. In the 4 eyes of 3 patients in whom the visual acuity reduced, continued progression of underlying inflammation was observed. Subsequent conjunctivalization of the cornea in both eyes of 1 patient required keratoprosthesis for visual rehabilitation. In 1 eye of another patient, there was development of an epithelial defect with continued inflammation and subsequent healing with vascularization causing a subsequent 2-line drop in Snellen visual acuity. At presentation, visual acuity was noted to be less than 6/18 in 23 eyes, which improved to 15 eyes with a visual acuity of less than 6/18 after surgery.

Postoperatively, in all eyes, the area of keratinization abruptly stopped short of the grafted mucous membrane (Fig. 4). Although there was minimum amount (<1 mm) of retraction of the mucous membrane in the follow-up period along the lid margin, keratinization along the edge of the mucous membrane was no longer in contact with the ocular surface to cause discomfort or inflammation.

No complications related to mucous membrane grafting were encountered intra- and postoperatively.

DISCUSSION

Lid margin keratinization is a unique problem commonly associated with SJS. The tarsal ulceration that occurs in the acute phase leads to destruction of the mucocutaneous junction with subsequent overgrowth of the keratinized skin into the tarsal conjunctiva.⁸ Attending to this ulceration in the acute stage within 2 weeks of onset of SJS by the use of amniotic membrane transplantation shows good results with no subsequent scarring.^{8,10–12} However, most patients only seek advice of an ophthalmologist after the subsidence of acute phase, which makes intervention in the first 2 weeks difficult. Also, with other life-threatening disturbances, administration of general anesthesia for an ophthalmic procedure may prove risky.

The subsequent occurrence of lid margin keratinization can be likened to a pterygium, with keratinization extending into the tarsal conjunctiva. Excision of the keratinized area with replacement by mucous membrane helps restore the

TABLE 1. Pre- and Postoperative Comparison of Conjunctival Hyperemia

Grade	Preoperatively, n (%)	Postoperatively, n (%)
0	0	5 (9.2)
1	12 (22.3)	36 (66.7)
2	26 (48.1)	9 (16.7)
3	16 (29.6)	4 (7.4)

TABLE 3. Comparison of Pre and Postoperative Schirmer I Test Scores

Score	<5 mm	5–10 mm	11–15 mm	>15 mm
Preoperatively, n (%)	15 (51.72)	7 (24.13)	1 (3.44)	6 (20.7)
Postoperatively, n (%)	11 (29.73)	16 (43.24)	6 (16.21)	4 (10.81)

Data was not recordable in 25 eyes preoperatively and 17 eyes postoperatively.

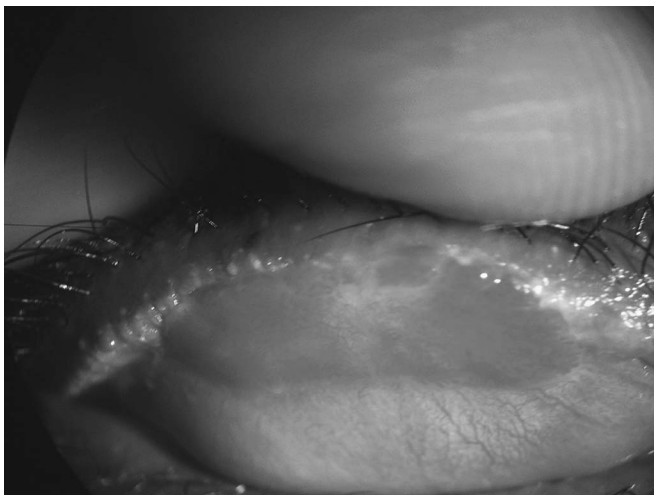
TABLE 4. Improvement in Snellen Best-Corrected Visual Acuity After Surgery (n = 28)

Lines of Best-Corrected Visual Acuity	No. Eyes
1	12
2	1
3	5
4	3
5	4
>5	3

intactness of the mucocutaneous junction and prevents crossover of the keratinized epithelium, thus acting as a barrier. This is proved by the stopping short of the keratinized area adjacent to the transplanted mucous membrane as seen in our cases.

Usually, the keratinization extends 2–3 mm into the tarsal conjunctiva and excision up to 5 mm of the tarsal conjunctiva will suffice. In case of adequate availability of oral mucosa, the length of the strip can be up to 20 mm to cover as much of the length of the lid margin as possible. Our study demonstrates the effectiveness of the use of mucous membrane grafts in the management of lid margin keratinization in cases of SJS.

Though mucosal sites are involved in SJS, the oral mucosal lesions like the skin lesions are probably self-limiting making it possible to harvest mucosa from the lip.¹⁵ Mucous membrane from the lip can be harvested with ease and does not leave behind any significant scarring or deformity. Also, the presence of goblet cells in the lip mucosa can contribute to the mucin in the eye with stabilization of the tear film to some extent as noted by the improvement in Schirmer wetting values.⁹ The use of fibrin glue for sticking the mucous membrane not only reduces the intraoperative time but also eliminates the need for suturing along the inner edge, which itself can cause a considerable amount of surface irritation in

**FIGURE 4.** Keratinization stopping short of transplanted mucous membrane.

the immediate postoperative period. In the 2 cases done under local anesthesia because of lack of medical fitness for general anesthesia, the procedure was performed without the use of sutures using fibrin glue, for ease and speed of completion.

Most of the patients in our series were young. Discomfort because of symptoms of irritation and photophobia caused considerable interference in their daily activities. This occurred because of superficial punctate keratopathy secondary to dry eye and the sandpaper effect of the lid margin changes on the cornea. This also compromised visual acuity because of the corneal roughening. The symptomatic improvement with alleviation of photophobia after the procedure helped these patients perform routine and work-related activities with comfort. It improved the visual acuity because of improvement of the corneal surface and absence of photophobia in operated eyes.

Our study pointed to an improvement in wetting of Schirmer strips after mucous membrane grafting and an improved tolerance of the strip in the eye after surgery. The improvement in photophobia after surgery facilitated insertion of the strip into the eye accounting for the increase in data after surgery. Data were not recordable in children uncooperative for the test. The improvement in the tear volume could be secondary to contribution of mucin from the lip mucosa accounting for better tear film stability. The high values noted preoperatively were probably because of a reflex tearing rather than indicative of high tear volumes.

It has been shown in the past that the inflammation and stem cell loss occurring in SJS are a chronic continuous process.^{5,6} In our series, we noted a considerable reduction in the conjunctival hyperemia, stabilization of the corneal changes, and a marked improvement in corneal staining after surgery. In fact, a decrease in corneal vascularization was noted in 4 eyes. This needs to be followed over a longer duration. Impression cytology studies will also help corroborate the changes occurring because of squamous metaplasia versus limbal stem cell deficiency. It is thus possible that with correction of the lid margin keratinization, there can be a reversal of squamous metaplastic changes, although the conjunctivalization because of preexisting limbal stem cell deficiency cannot be expected to recede. Yet continued mechanical and secondary inflammatory insult on the limbal stem cells can possibly be reduced with this procedure. This procedure may also improve the results of further interventions for visual rehabilitation by reducing inflammation and blink-related microtrauma.

It is extremely important to address all issues contributing to inflammation to minimize this continued process. With better understanding of the process of blink-related microtrauma, the need to eliminate the sandpaper effect of the lids on the cornea cannot be overemphasized.

The procedure of mucous membrane grafting when performed with concurrent management of other causes of ocular surface inflammation in eyes affected by SJS may go a long way in maintaining ocular surface stability and prevent further damage to the limbal stem cells. This preparatory step may enable better results for visual rehabilitation procedures, such as lamellar or penetrating keratoplasty in such otherwise high-risk grafts.

We believe that our study is the first large series of cases of mucous membrane grafting for lid margin keratinization using fibrin glue in SJS. In sum, mucous membrane grafting is a viable approach to management of lid margin keratinization in SJS. However, it is important to identify and address all causes contributing to ocular surface inflammation and forms a part of a comprehensive approach to the ocular sequelae of SJS.

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