International Outcomes of the Boston Type I Keratoprosthesis in Stevens–Johnson Syndrome

Jamie K. Alexander, MD, Samar K. Basak, MD,† Ma. Dominga B. Padilla, MD,‡ Fei Yu, PhD,* and Anthony J. Aldave, MD**

Purpose: To determine the factors influencing outcomes of Boston type I keratoprosthesis implantation in Stevens–Johnson syndrome (SJS) and to compare the results with those of individuals without SJS.

Methods: This is a multicenter, retrospective, comparative consecutive case series of patients undergoing keratoprosthesis implantation in Los Angeles, Kolkata, and Manila. Statistical analysis was performed to identify significant differences in visual acuity, complications, and retention between SJS and non-SJS populations.

Results: A total of 234 keratoprosthesis procedures were performed in 209 eyes, including 40 performed in 27 eyes of 26 patients with SJS. Procedures in patients with SJS were more frequently performed as repeat keratoprostheses (33% vs. 8%, $P < 0.001$) but less frequently in eyes with glaucoma (26% vs. 71%, $P < 0.001$) or multiple previous keratoplasties (15% vs. 59%, $P < 0.001$). A significantly greater percentage of individuals with SJS had a corrected distance visual acuity ≥20/200 12 months after surgery compared with individuals without SJS (100% vs. 67%, $P = 0.002$). Several postoperative complications were more common in SJS, including corneal stromal necrosis (59% vs. 8%, $P < 0.001$), corneal infiltrates (30% vs. 10%, $P = 0.009$), and persistent corneal epithelial defects (59% vs. 24% $P < 0.001$), which led to a higher retention failure rate (0.306/eye-year vs. 0.068/eye-year, $P < 0.001$) and secondary surgical procedures. However, after repeat implantation, eyes with SJS were no less likely to ultimately retain a keratoprosthesis (82% vs. 89%, $P = 0.34$).

Conclusions: The Boston type I keratoprosthesis is an effective means to restore vision in individuals with SJS. Although retention failure and several postoperative complications are more common in SJS, sight-threatening complications such as endophthalmitis and retinal detachment are not.

Key Words: Stevens–Johnson syndrome, Boston type I keratoprosthesis

(*Cornea* 2015;34:1387–1394)

Received for publication June 14, 2015; revision received July 27, 2015; accepted July 30, 2015. Published online ahead of print September 18, 2015.

From the *Stein Eye Institute, David Geffen School of Medicine at UCLA, Los Angeles, CA; †Disha Eye Hospitals, Kolkata, India; and ‡St Luke's Medical Center, Global City, Philippines.

The authors have no funding or conflicts of interest to disclose.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

Reprints: Anthony J. Aldave, MD, Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095 (e-mail: aldave@jsei.ucla.edu).

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Stevens–Johnson Syndrome (SJS) can devastate the ocular surface, with chronic inflammation leading to symblepharon formation and corneal conjunctivalization, neovascularization, and stromal scarring. Historically, penetrating keratoplasty performed in eyes affected by SJS has yielded poor outcomes secondary to allograft rejection and persistent epithelial defect formation with subsequent stromal ulceration and corneal perforation.[1] Solomon et al[2] reported that more complex reconstruction of the ocular surface with keratolimbal allografting produced lower survival of ambulatory vision in SJS compared with other causes of total limbal stem cell deficiency and 0% graft survival in SJS at 2 years. Cultured limbal epithelial transplantation using allogeneic donor tissue also requires systemic immunosuppression and has been shown by Shimazaki et al[3] to result in only 33% final corneal epithelialization in patients with SJS, significantly lower than in other ocular cicatrizing diseases. Although simplified limbal epithelial transplantation avoids systemic immunosuppression, this technique of ocular surface reconstruction cannot be used for many cases of ocular SJS because of bilateral ocular involvement and the need to obtain donor tissue from the fellow eye.[4] Recently, several authors have published series using autologous cultivated oral mucosal epithelial transplantation to stabilize the ocular surface and improve vision in patients with SJS, but the degree of visual recovery is variable and is typically limited to ambulatory vision.[5,6]

For visual rehabilitation in eyes with chronic recurrent cicatrization, keratoprosthesis surgery can provide sustained clarity of the visual axis. The Boston type I keratoprosthesis is the most frequently implanted keratoprosthesis worldwide. Other keratoprostheses that have been used in patients with SJS include the Boston type II keratoprosthesis and the osteo-odonto-keratoprosthesis; however, their use is limited to only a handful of centers and few surgeons across the globe. In contrast, more than 9000 Boston type I keratoprostheses have been implanted across more than 50 countries throughout the world, with visual outcomes, retention rates, and incidences of postoperative complications similar both within and outside North America.[7]

In early studies of the Boston type I keratoprosthesis (keratoprosthesis), procedures performed in eyes of patients with SJS resulted in the poorest outcomes among all indications for keratoprosthesis surgery, with discouragingly high rates of postoperative endophthalmitis and other vision-limiting complications.[8,9] Since then, advances in the keratoprosthesis design and postoperative management have improved outcomes across the board and expanded the

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indications for implantation.[10–14] However, only one study on the outcomes of Boston keratoprosthesis in SJS has been published to date, and included only 6 type I keratoprostheses and 10 type II keratoprostheses.[15] Although many other keratoprosthesis series have included a few patients with SJS, none have specifically focused on the outcomes of the Boston type I keratoprosthesis in patients with SJS, and none have had a sufficient number of procedures performed in patients with SJS to perform a meaningful comparison with outcomes in patients with other indications for keratoprosthesis implantation.

This study reports a large international series of Boston type I keratoprostheses implanted in patients with SJS and directly compares visual outcomes, retention rates, and complication rates with those of patients without SJS. Given that most of the procedures in patients with SJS were performed outside the United States, we anticipate that the results that we report are reflective of those that can be expected by keratoprosthesis surgeons in both developing and developed countries.

MATERIALS AND METHODS

After study approval was granted by the Institutional Review Board at The University of California, Los Angeles (study numbers 04-11-058-(01-13); 11-001336), informed consent was obtained for the collection and analysis of preoperative and postoperative data from each patient who underwent implantation of a Boston type I keratoprosthesis by one of the authors (A.J.A.) at the Stein Eye Institute between May 1, 2004, and July 1, 2013. After further study approval was granted by the Institutional Review Board at The University of California, Los Angeles (study number 11-001336-AM-00006), the Ethics Committee at Disha Eye Hospitals in Kolkata, India, and The Institutional Ethics Review Committee at St Luke's Medical Center, Global City, Philippines (EC reference No. RP-13027), deidentified data were collected from one surgeon (S.K.B.) at the Disha Eye Hospitals and one surgeon (M.D.B.P.) at the St Luke's Medical Center. Data collection was performed in a manner compliant with the Health Insurance Portability and Accountability Act (HIPAA), and the described research adhered to the tenets of the Declaration of Helsinki.

Preoperative Evaluation

Complete ocular histories and examinations, including indicated diagnostic testing, were performed for each patient to determine candidacy for keratoprosthesis implantation. Additional information was requested of other physicians involved in the patient's care when this information was considered necessary to determine either candidacy for keratoprosthesis implantation or the need for preceding or concurrent surgical procedures. The criteria used to determine candidacy for keratoprosthesis surgery at all 3 study sites were those that have been published previously.[10]

In eyes undergoing keratoprosthesis surgery for a primary indication of SJS, the following were considered exclusionary criteria: keratinization of the bulbar conjunctiva, significantly decreased tear production, and forniceal obliteration due to symblepharon formation. If eyelid surgery was successful in resolving bulbar conjunctival keratinization or forniceal foreshortening, candidacy for keratoprosthesis implantation was reconsidered.

Surgical Technique and Postoperative Management

Besides minor variations due to surgeon preference, each of the surgeons used the same previously published surgical technique.[10] Postoperatively, all patients were maintained on a regimen of topical steroids, topical antibiotics, and bandage soft contact lenses, which were exchanged on a monthly basis. Antibiotics were continued indefinitely, and topical steroids were tapered off in the months after surgery. Some patients were unable to be fit with a contact lens because of either socioeconomic or anatomic factors. In American patients for whom anatomic factors limited contact lens fitting, each was seen by a contact lens specialist in a university health care setting before abandoning contact lens use. Other oral and topical medications were used postoperatively for some patients, depending on the risk for or development of postoperative complications. For example, patients with a history of chronic conjunctival inflammation, such as SJS or sterile corneal necrosis, were frequently managed with an oral steroid in the early postoperative period.

Data were collected by reviewing each patient's chart for their ocular history, indication for a keratoprosthesis, intraoperative details including additional procedures performed, and postoperative outcomes including complications and their treatment. Corrected distance visual acuity (CDVA) was recorded at intervals of 6 months ($\pm$2 months) and each year ($\pm$2 months) after keratoprosthesis implantation. For repeat keratoprostheses, visual acuities were recorded in terms of time after the most recent keratoprosthesis implantation, not the initial keratoprosthesis. Complications were recorded on a per-eye basis, such that eyes that underwent repeat keratoprosthesis implantation would be included only once when calculating complication rates. The keratoprosthesis retention failure rate was expressed in terms of the number of implanted keratoprostheses that were removed per eye-years, which was calculated as the cumulative number of years that all keratoprostheses were retained. In eyes in which the keratoprosthesis was removed, the time that it remained in place before removal was included in the cumulative total, as was the time that a replacement keratoprosthesis, if performed, remained in place.

Data were entered into a Microsoft Excel spreadsheet (Microsoft, Redmond, WA) for statistical analysis, which was performed using SAS software version 9.4 (SAS, Inc, Cary, NC), with $P < 0.05$ considered statistically significant. Comparisons were made between the patients with SJS and those without from all 3 centers for the following: patient demographics; indications for keratoprosthesis surgery; comorbid ocular conditions; the incidence and rate of postoperative complications, including retention failure; and the percentage of eyes requiring postoperative procedures. The difference in the number of corneal transplants performed before

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keratoprosthesis implantation was compared using the Wilcoxon rank-sum test. Keratoprosthesis retention rates were evaluated using Kaplan–Meier survival analyses, and the differences in the retention rates were compared using the log-rank test. Using 2-tailed Fisher exact tests, eyes of patients with SJS in which the initial keratoprosthesis was retained were compared with eyes in which it was not.

RESULTS

Demographics and Preoperative Characteristics

A total of 234 Boston type I keratoprosthesis procedures were performed in 209 eyes of 201 patients by the 3 participating surgeons during the study period. Forty (17%) of the procedures were performed in 27 eyes of 26 patients with SJS: 18 procedures in 10 eyes of 9 patients in Los Angeles, 16 procedures in 11 eyes of 11 patients in Kolkata, and 6 procedures in 6 eyes of 6 patients in Manila. In addition, 194 procedures were performed in 182 eyes of 175 patients without SJS: 135 procedures in 125 eyes of 118 patients in Los Angeles, 52 procedures in 51 eyes of 51 patients in Kolkata, and 7 procedures in 6 eyes of 6 patients in Manila. The most common indication for keratoprosthesis implantation in non-SJS eyes was failed corneal transplant (56%). In patients with SJS, repeat keratoprosthesis implantation was a significantly more common indication than in patients without SJS (33% vs. 8%, $P < 0.001$) (Table 1). Mean follow-up duration after keratoprosthesis implantation was significantly shorter for procedures performed in patients with SJS (17.6 ± 16.2 months) compared with those performed in patients without SJS (29.3 ± 22.8 months; $P < 0.001$).

In regard to comorbid conditions, glaucoma was diagnosed preoperatively in significantly fewer operative eyes of patients with SJS than in patients without SJS (26% vs. 71%, $P < 0.001$), although the difference in the percentage of eyes that had undergone glaucoma surgery before keratoprosthesis implantation in each group was not significantly different. Additionally, eyes with SJS were also significantly less likely to have undergone multiple penetrating keratoplasties before keratoprosthesis implantation (15% vs. 59%, $P < 0.001$) (Table 1).

TABLE 1. Preoperative Characteristics of Patients Undergoing Keratoprosthesis Implantation

	Non-SJS	SJS	*P*
No. procedures	194	40	
No. eyes	182	27	
No. patients	175	26	
Sex (female; male)	75; 100	14; 12	0.3
Age, mean (range), yrs	60 (3–95)	50 (26–72)	<0.001
Follow-up, mo			
Mean (median)	29.3 (23.5)	17.6 (12.5)	0.001
SD (range)	22.8 (0.8–106.5)	16.2 (0.5–73.1)	
Primary indication for a keratoprosthesis			
Failed corneal transplant	109 (56.2%)	—	
SJS	—	27 (67.5%)	
Limbal stem cell deficiency	24 (12.4%)	—	
Chemical injury	18 (9.3%)	—	
Repeat keratoprosthesis	15 (7.7%)	13 (32.5%)	<0.001
Corneal vascularization	11 (5.7%)	—	
Mucous membrane pemphigoid	4 (2.1%)	—	
Aniridia	4 (2.1%)	—	
Thermal burn	3 (1.5%)	—	
Atopic keratoconjunctivitis	2 (1.0%)	—	
Other	4 (2.1%)	—	
Glaucoma	130 (71.4%)	7 (25.9%)	<0.001
Previous glaucoma surgery	45 (24.7%)	4 (14.8%)	0.334
Previous corneal transplant(s)			
0	42 (23.1%)	18 (66.7%)	<0.001
1	32 (17.6%)	5 (18.5%)	
2	54 (29.7%)	2 (7.4%)	
3	33 (18.1%)	0	
≥4	21 (11.5%)	2 (7.4%)	

Visual Outcomes

None of the patients with SJS and only 5% of the eyes of patients without SJS had a preoperative CDVA ≥ 20/200 (Table 2). At 6 months after surgery (the last keratoprosthesis implantation in eyes in which more than 1 was performed), 96% (22/23) of eyes of patients with SJS retaining a keratoprosthesis attained a CDVA ≥20/200, significantly higher than the 71% (120/169) of eyes of patients without SJS ($P = 0.01$). At 1 year after surgery, 100% (18/18) of the patients with SJS retaining a keratoprosthesis had a CDVA ≥20/200, significantly greater than the 67% (95/142) of patients without SJS with a CDVA ≥20/200 ($P = 0.002$). Although 100% of the patients with SJS retaining a keratoprosthesis at 2, 3, and 4 years after surgery had a CDVA ≥20/200, fewer than 10 eyes were measured at each time point, which limits the ability to draw any conclusions from the data.

Complications and Secondary Surgical Procedures

Several postoperative complications were more common in patients with SJS, including sterile corneal stromal necrosis (59% vs. 8%, $P < 0.001$), persistent corneal epithelial defects (59% vs. 24%, $P < 0.001$), and suspected and confirmed infectious corneal infiltrates (30% vs. 10%, $P = 0.009$). Each of the 3 centers demonstrated a higher incidence of fungal keratitis in eyes of patients with SJS: at Stein Eye Institute, 20% (2/10) of SJS eyes versus 2% (2/125) of non-SJS eyes; at Disha Eye Hospitals, 27% (3/11) of SJS eyes versus 2% (1/51) of non-SJS eyes; and at St Luke's Hospital, 17% (1/6) of SJS eyes versus 0% (0/6) of non-SJS eyes. Although 75% (6/8) of the corneal infiltrates in patients with SJS were culture positive for Candida species, only 17% (3/18) of infiltrates found in non-SJS eyes were culture positive for yeast.

Given the higher incidence of sterile corneal stromal necrosis, persistent corneal epithelial defects, and infectious keratitis in patients with SJS, it follows that several secondary

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TABLE 2. Preoperative and Postoperative CDVA in Eyes Retaining a Keratoprosthesis

	Baseline	6 Months	1 Year	2 Years	3 Years	4 Years	5 Years	At Last Follow-up
No. eyes								
SJS	27	23	18	9	3	1	0	22
Non-SJS	182	169	142	99	68	43	25	162
20/20–20/50								
SJS	0 (0%)	14 (60.9%)	7 (38.9%)	5 (55.6%)	1 (33.3%)	1 (100%)	—	9 (40.9%)
Non-SJS	1 (0.5%)	53 (31.4%)	45 (31.7%)	31 (31.0%)	21 (30.9%)	15 (34.9%)	9 (36.0%)	49 (30.2%)
20/60–20/100								
SJS	0 (0%)	5 (21.7%)	7 (38.9%)	3 (33.3%)	2 (66.7%)	0 (0%)	—	8 (36.4%)
Non-SJS	0 (0%)	49 (29.0%)	34 (23.9%)	18 (18.2%)	9 (13.2%)	5 (11.6%)	2 (8.0%)	33 (20.4%)
20/125–20/200								
SJS	0 (0%)	3 (13.0%)	4 (22.2%)	1 (11.1%)	0 (0%)	0 (0%)	—	4 (18.2%)
Non-SJS	9 (4.9%)	18 (10.7%)	16 (11.3%)	18 (18.2%)	13 (19.1%)	5 (11.6%)	4 (16.0%)	20 (12.3%)
20/250–20/400								
SJS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—	0 (0%)
Non-SJS	7 (3.8%)	9 (5.3%)	6 (4.2%)	4 (4.0%)	3 (4.4%)	4 (9.3%)	0 (0%)	12 (7.4%)
CF								
SJS	8 (29.6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—	0 (0%)
Non-SJS	53 (29.1%)	27 (16.3%)	21 (14.8%)	11 (11.1%)	6 (8.8%)	3 (7.0%)	4 (16.0%)	19 (11.7%)
HM								
SJS	9 (33.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—	1 (4.5%)
Non-SJS	61 (33.5%)	7 (4.1%)	8 (5.6%)	12 (12.1%)	10 (14.7%)	9 (20.9%)	1 (4.0%)	11 (6.7%)
LP								
SJS	10 (37.0%)	1 (4.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—	0 (0%)
Non-SJS	51 (28.0%)	4 (2.4%)	7 (4.9%)	2 (2.0%)	3 (4.4%)	1 (2.3%)	4 (16.0%)	9 (5.6%)
NLP								
SJS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	—	0 (0%)
Non-SJS	0 (0%)	2 (1.2%)	5 (3.5%)	3 (3.0%)	3 (4.4%)	1 (2.3%)	1 (4.0%)	9 (5.6%)
≥20/200								
SJS	0 (0%)	22 (95.7%)	18 (100%)	9 (100%)	3 (100%)	1 (100%)	—	21 (95.5%)
Non-SJS	10 (5.5%)	120 (71.0%)	95 (66.9%)	67 (67.7%)	43 (63.2%)	25 (58.1%)	15 (60.0%)	102 (63.0%)
P	0.367	0.01	0.002	0.055	0.547	1	—	0.001

CF, counting fingers; HM, hand movements; LP, light perception; NLP, no light perception.

surgical procedures were more commonly performed in patients with SJS, including keratoprosthesis replacement (33% vs. 4%, $P < 0.001$) and tarsorrhaphy (52% vs. 12%, $P < 0.001$) (Fig. 1). Similar rates of other complications of keratoprosthesis surgery were observed, including retroprosthetic membrane formation (37% vs. 49%), retinal detachment (11% vs. 12%), and cystoid macular edema (8% vs. 13%). Despite a significantly higher incidence of preoperative glaucoma in the non-SJS group, no difference was noted in the percentage of eyes that developed elevated intraocular pressure after keratoprosthesis implantation or the need for postoperative glaucoma surgery. Additionally, there was no difference in the percentage of eyes in patients with SJS and those without SJS who developed other sight-threatening complications such as endophthalmitis (0% vs. 2.2%, $P = 1$), retinal detachment (11.1% vs 11.6%, $P = 1$), or sterile vitritis (0% vs. 8.3%, $P = 0.23$) (Table 3).

Keratoprosthesis Retention

The mean duration of follow-up after keratoprosthesis implantation in the eyes of patients with SJS [17.6 months (range 0.5–73.1 months)] was significantly shorter than that of eyes of patients without SJS [29.3 months (range 0.8–106.5 months), $P = 0.001$]. Of 40 keratoprostheses implanted in eyes of patients with SJS, 55% (22/40) remained in place on each patient's final follow-up examination, significantly fewer than the 84% (162/194) of keratoprostheses retained in eyes of patients without SJS ($P < 0.001$). Similarly, retention failure occurred in a significantly higher percentage of eyes in patients with SJS (52%) than in eyes of patients without SJS (15%; $P < 0.001$). When the duration of follow-up in each group is taken into consideration, the retention failure rate was also significantly higher for procedures performed in eyes of patients with SJS (0.306/eye-year) than in eyes of patients without SJS (0.068/eye-year, $P < 0.001$) (Table 4). Most retention failures that occurred in patients with SJS were due to sterile corneal stromal necrosis (78%; 14/18), whereas the remainder were due to infectious infiltrates (22%; 4/18), all of which were secondary to yeast (Candida 2, budding yeast without speciation 1, mixed including yeast without further speciation 1) (Table 4).

The cumulative proportion of retention is lower at each time point for procedures performed in SJS eyes versus those

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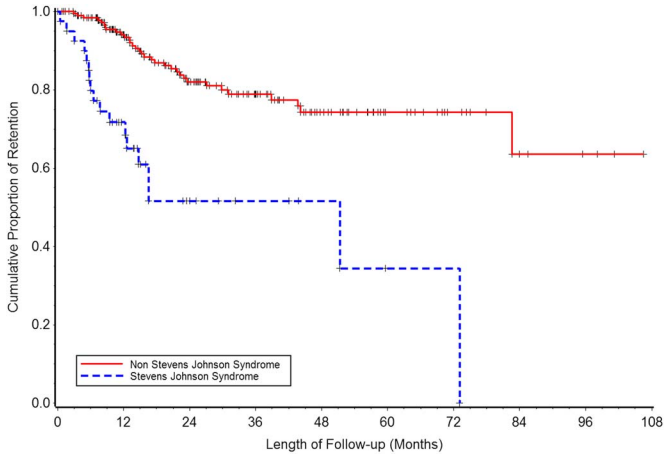

FIGURE 1. Kaplan–Meyer survival curve demonstrating cumulative proportion of keratoprostheses retained in patients with and without SJS.

performed in non-SJS eyes (see Table S1 Supplemental Digital Content 1, http://links.lww.com/ICO/A356). Although the keratoprosthesis retention rate was significantly lower in patients with SJS, there was no significant difference in the percentage of eyes in which a keratoprosthesis was retained at last follow-up (81% vs 89%; $P = 0.34$). Although the follow-up period in patients maintaining a keratoprosthesis with SJS (20.5 months; range 5.8–59.5 months) was shorter than that in patients without SJS (31.1 months; range 0.8–106.5 months), the difference was not statistically significant ($P = 0.08$). Procedures did fail sooner in eyes with SJS (14.1 months vs. 19.9 months, $P = 0.01$); however, in both groups, the mean follow-up period was longer than the mean time to procedure failure (Table 4).

TABLE 3. Postoperative Complications and Secondary Surgical Procedures (All Eyes With a Total of >6 Months of Follow-up)

	SJS	Non-SJS	*P*
No. eyes with >1 mo of follow-up	27	181	
Retroprosthetic membrane	10 (37.0%)	89 (49.2%)	0.303
YAG laser membranotomy	9 (33.3%)	68 (37.6%)	0.831
Surgical membranectomy	1 (3.7%)	13 (7.2%)	1
Sterile corneal stromal necrosis	16 (59.3%)	25 (8.3%)	<0.001
Keratoprosthesis replacement	9 (33.3%)	8 (4.4%)	<0.001
Elevated IOP (>25 mm Hg)	5 (18.5%)	32 (17.7%)	1
Glaucoma surgery	1 (3.7%)	11 (6.1%)	1
Corneal infiltrate	8 (29.6%)	18 (9.9%)	0.009
Persistent epithelial defect	16 (59.3%)	44 (24.3%)	<0.001
Tarsorrhaphy	14 (51.9%)	22 (12.2%)	<0.001
Infectious endophthalmitis	0	4 (2.2%)	1
Vitreous tap and injections	0	4 (2.2%)	1
Retinal detachment	3 (11.1%)	21 (11.6%)	1
Repair of retinal detachment	1 (3.7%)*	14 (7.7%)	0.698
Sterile vitritis	0	15 (8.3%)	0.227
Vitreous tap and injection	0	9 (5.0%)	0.609
Cystoid macular edema	2 (7.4%)	23 (12.7%)	0.75
Intravitreal injection	1 (3.7%)	17 (9.4%)	0.479

*Neither repaired because of serous retinal detachment (1), poor visual potential because of retinal detachment (1).

IOP, intraocular pressure; YAG, yttrium aluminum garnet.

Characteristics of SJS Eyes

An analysis of several clinical features before keratoprosthesis implantation and the average time from onset of SJS to initial keratoprosthesis implantation demonstrated that none was associated with retention failure in patients with SJS. Although the presence of bulbar conjunctival keratinization, lid malpositioning requiring previous or subsequent eyelid or other oculoplastic procedures, and a history of corneal perforation before keratoprosthesis implantation were all more common in eyes in which keratoprosthesis retention failure occurred, the difference was not statistically significant. However, the development of retention failure in 43% of eyes with bulbar conjunctival keratinization compared with 8% of eyes without demonstrated a trend toward statistical significance ($P = 0.08$) (Table 5).

Similarly, a number of interventions used around the time of keratoprosthesis implantation were not associated with a significant difference in the percentage of keratoprostheses that were retained. Specifically, the use of systemic immunosuppression before keratoprosthesis implantation, the performance of tarsorrhaphy at the time of keratoprosthesis implantation, and the use of systemic immunosuppression after keratoprosthesis implantation were not associated with a significant alteration in the retention failure rate in SJS eyes (Table 5). It should be noted, however, that approximately one third of keratoprosthesis procedures performed in patients with SJS were performed in eyes with a history of keratoprosthesis retention failure, and thus at an increased risk of repeat keratoprosthesis retention failure. Because tarsorrhaphies were performed in conjunction with a significantly greater percentage of repeat keratoprosthesis procedures (53.8%) as compared with initial keratoprosthesis procedures (18.5%; $P = 0.03$), they were disproportionately performed in eyes at a higher risk of corneal stromal necrosis and retention failure. Therefore, failure to observe a significant association between the performance of tarsorrhaphy at the time of keratoprosthesis implantation and keratoprosthesis retention may be due to selection bias in terms of the eyes in which tarsorrhaphies were or were not performed. Given the fact that there was no significant difference in the percentage of eyes that were treated with systemic immunosuppression after repeat keratoprosthesis procedures (53.8%) as compared with initial

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TABLE 4. Keratoprosthesis Retention Rates

	SJS	Non-SJS	*P*
Mean follow-up of all procedures (median, range), mo*	17.6 (12.5, 0.5–73.1)	29.3 (23.5, 0.8–106.5)	0.001
Retention failure			
Keratoprostheses removed (eyes)	14 of 27 (51.9%)	28 of 182 (15.4%)	<0.001
Keratoprostheses removed (procedures)	18 of 40 (45.0%)	32 of 194 (16.5%)	<0.001
Retention failure rate (procedures)†	18 per 58.75 eye-years, 0.306/eye-year	32 per 472.91 eye-years, 0.068/eye-year	<0.001
Mean time to failure (median range), mo*	14.1 (7.1, 0.5–73.1)	19.9 (15.5, 3.6–82.6)	0.011
Retention success			
Keratoprostheses retained (eyes)	22 of 27 (81.5%)	162 of 182 (89.0%)	0.335
Keratoprostheses retained (procedures)	22 of 40 (55.0%)	162 of 194 (83.5%)	<0.001
Mean follow-up of retained procedures (median, range), mo*	20.5 (14.8, 5.8–59.5)	31.1 (25.4, 0.8–106.5)	0.084

*Kruskal–Wallis test.
†Log-rank test.

keratoprosthesis procedures (59.3%; $P = 1$), there does not seem to be such a bias in terms of the selection of patients for systemic immunosuppression.

Final Outcomes of SJS Eyes Not Retaining Keratoprosthesis

In 5 patients with SJS, a keratoprosthesis was not replaced after removal: 3 from the United States, one from India, and the other from the Philippines (see Table S2 Supplemental Digital Content 2, http://links.lww.com/ICO/A357). In 3 of the 5 patients, the final postoperative CDVA is better than the preoperative CDVA; and in 2 patients, the final postoperative CDVA remains unchanged from the preoperative CDVA of LP. Of note, all retention failures in these patients occurred within 8 months of surgery (mean 5.5 months; range 2.2–7.7 months).

TABLE 5. Characteristics of Patients With SJS Associated With Keratoprosthesis Retention and Retention Failure

	Keratoprostheses Retained	Keratoprostheses Removed	*P*
Number (eyes; procedures)	13; 22	14; 18	
Preoperative characteristics (eyes)			
Time from SJS to initial procedure, yrs	13.7	12.0	0.913
Perforation at or before time of keratoprosthesis	4 (30.7%)	7 (50.0%)	0.44
Bulbar conjunctival keratinization	1 (7.7%)	6 (42.9%)	0.077
Lid malpositioning*	3 (23.1%)	4 (28.9%)	1
Perioperative characteristics (procedures)			
Tarsorrhaphy at the time of keratoprosthesis	7 (31.8%)	5 (27.8%)	1
Preoperative immunosuppression	3 (13.6%)	2 (11.1%)	1
Postoperative immunosuppression	13 (59.1%)	8 (44.4%)	0.525
Indication for removal (procedure)			
Sterile corneal necrosis	—	14	
Infectious corneal necrosis†	—	4	

*Requiring previous, concurrent, or subsequent oculoplastic procedures.
†Organisms including mixed (1), Candida (2), and budding yeast without speciation (1).

DISCUSSION

In the decade after the 1992 Food and Drug Administration's clearance of the Boston keratoprosthesis, patients with SJS were found to have the worst outcomes after keratoprosthesis surgery, with 0% achieving better than 20/200 vision at 5 years after implantation and 100% requiring either minor or major procedures for postoperative complications.[8] However, improved outcomes after changes in the keratoprosthesis design, surgical techniques, and postoperative management led to renewed interest in the use of the Boston keratoprosthesis for eyes with chronic cicatrizing ocular surface disease. In 2008, Dohlman et al published what remains the only study of Boston keratoprosthesis outcomes in patients with SJS, although only 6 of the 16 Boston keratoprostheses included in the study were type I keratoprostheses. The authors demonstrated longer conservation of visual acuity than previous reports, with 44% maintaining a visual acuity ≥20/70 at last follow-up (mean follow-up 3.6 ± 1.5 years; range 10.2 months–5.6 years) with no significant difference in visual acuity retention between both keratoprosthesis designs.[15]

We also report improved visual outcomes of the Boston type I keratoprosthesis in patients with SJS, with 100% of eyes with a retained keratoprosthesis demonstrating a CDVA ≥20/200 at 1 year, and 96% of eyes demonstrating a final CDVA ≥20/200 at an average of 20.4 months after latest keratoprosthesis implantation. At 6 months, 1 year, and last follow-up, a significantly greater percentage of patients with SJS retaining a keratoprosthesis maintained a CDVA ≥20/200 compared with patients who received a keratoprosthesis for other

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indications. The high percentage of eyes that experienced an improvement in vision is likely due in part, if not primarily, to the significantly lower percentage of patients with SJS with preoperative glaucoma as the diagnosis of preoperative glaucoma has been reported to be a risk factor for loss of 20/200 CDVA after keratoprosthesis surgery.[15] Of all eyes with severe ocular surface disease, those with autoimmune or iatrogenic disease have the lowest prevalence of glaucoma.[16]

In contrast to the encouraging visual outcomes that we report in patients with SJS after keratoprosthesis implantation, the keratoprosthesis retention failure rate was found to be 4.5 times higher than that for other indications. Over 3 quarters of these failures resulted from sterile corneal stromal necrosis, which has been documented to occur more frequently in eyes with chronic conjunctival inflammation.[8,10,17] In this study, 59% of the eyes of patients with SJS developed donor corneal stromal necrosis after keratoprosthesis surgery, necessitating donor cornea and keratoprosthesis replacement in 33% of eyes. These percentages are significantly higher than the 8% incidence of donor corneal stromal necrosis in eyes of patients without SJS, necessitating donor cornea and keratoprosthesis replacement in 4% of eyes. However, we believe that coverage of the donor cornea with either conjunctiva, in the form of tension-free, tarsal or bulbar conjunctival flaps, or extensive medial and lateral tarsorrhaphies, is the most effective means to prevent or manage corneal stromal necrosis, which often develops secondary to persistent corneal epithelial defects (Fig. 2).[18]

Previous studies provide conflicting data regarding whether or not cicatrizing conjunctival disease is an independent risk factor for infectious keratitis after keratoprosthesis surgery.[19,20] However, we report a significantly higher percentage of eyes of patients with SJS developing presumed microbial keratitis (30%) compared with eyes of patients without SJS (10%). The incidence of infectious keratitis in eyes of patients without SJS is consistent with the overall incidence of 3% to 17% reported in previous studies.[7,19–22] The three times greater incidence in eyes of patients with SJS is likely due in part to the significantly higher incidence of persistent epithelial defect formation in these eyes, given the significantly increased risk of infectious keratitis in the setting of a persistent corneal epithelial defect.[23]

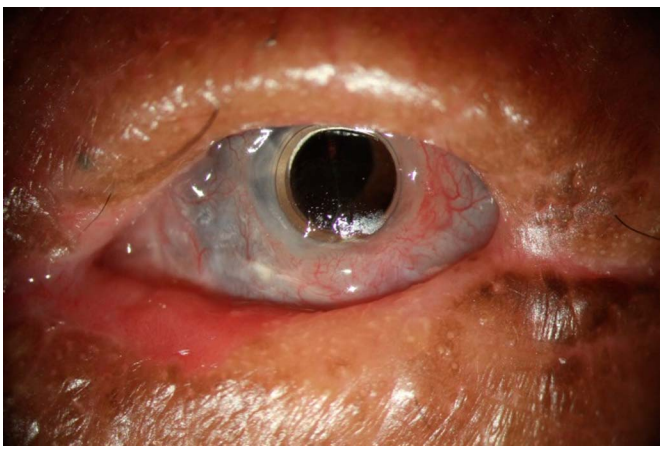

FIGURE 2. Slit-lamp photomicrograph of a 67-year-old man with SJS. Donor corneal necrosis developed 5 months after keratoprosthesis surgery, necessitating replacement of the donor cornea and keratoprosthesis. At the time of the second surgery, the donor cornea was covered with mobilized bulbar conjunctiva and extensive medial and lateral tarsorrhaphies were performed. After 2 years, the donor cornea remains covered by conjunctiva and the patient maintains 20/20 CDVA.

To determine the cause of the increased incidence of infectious keratitis, specifically fungal keratitis, in patients with SJS, we examined previously identified risk factors for fungal keratitis. Both use of topical vancomycin and contact lens wear were identified as risk factors for fungal keratitis and endophthalmitis after keratoprosthesis surgery in one series,[24] whereas the duration of topical vancomycin use but not contact lens wear was associated with an increased risk of fungal keratitis in another,[19] and neither was associated with an increased risk of fungal keratitis in a third series.[20] Of the 3 study centers, only the surgeon at Stein Eye Institute uses postoperative topical vancomycin, typically discontinued approximately 3 to 4 months after surgery. Thus, only 1 eye of a patient with SJS that developed fungal keratitis was concomitantly using vancomycin. However, 4 of the 6 eyes of patients with SJS in this series that developed fungal keratitis were using bandage contact lenses at the time of the diagnosis, which may have contributed to a higher rate of infectious keratitis. Patients operated at Disha Eye Hospitals are treated with amphotericin B (0.15%) eye drops 4 times daily for 10 days every 3 months because of an overall increased incidence of fungal keratitis in the region. Despite this, the percentage of eyes of patients with SJS and those without in Kolkata that developed fungal keratitis was essentially the same as in Los Angeles, where fungal keratitis is less common, although the incidence may have been even higher had antifungal prophylaxis not been used.

Previous studies have reported incidences of endophthalmitis after keratoprosthesis implantation between 1.7% and 13%,[9,13,14,21,25–27] with an even higher incidence in inpatients with a history of cicatricial conjunctival disease, particularly in SJS.[8,9] Although the overall rates of infectious endophthalmitis have been decreasing over time, 2 recent studies indicate continued concern for increased endophthalmitis rates among eyes with SJS and other underlying systemic inflammatory diseases such as rheumatoid arthritis.[25,28] However, in this multicenter multinational study, we report a relatively low 2.2% incidence of endophthalmitis in patients without SJS (mean follow-up 29 months). Even more encouraging is the fact that we report a 0.0% incidence of endophthalmitis in patients with SJS (mean follow-up of 18 months), supporting the results of the study by Sayegh et al[15] demonstrating the absence of postoperative endophthalmitis in 16 eyes of patients with SJS followed for a mean of 3.6 years after surgery.

In addition to endophthalmitis, several other postoperative complications that have previously been reported to occur more frequently in eyes with chronic cicatrizing conjunctivitis, such as retinal detachment, were not more commonly observed in patients with SJS in the series we

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report.[29] Similarly, none of the other commonly observed postoperative complications (retroprosthetic membrane, elevated intraocular pressure, sterile vitritis, or cystoid macular edema) developed at an increased frequency in eyes of patients with SJS after keratoprosthesis surgery.

In an effort to identify risk factors for keratoprosthesis retention failure in patients with SJS, we looked for an association with preoperative characteristics (such as time since onset of SJS or a history of corneal perforation) or anatomic factors (such as bulbar conjunctival keratinization or significant eyelid malpositioning) before keratoprosthesis implantation or the use of postoperative systemic immunosuppression. Although a trend toward a higher incidence of keratoprosthesis retention failure was associated with each of these factors, the association was not found to be significant for any. Those receiving systemic immunosuppression at or around the time of keratoprosthesis surgery in this study typically received prednisone, often in conjunction with azathioprine for the patients operated on at Disha Eye Hospitals. These untargeted immunosuppressives may not be specific to the underlying inflammation contributing to corneal stromal necrosis in eyes of patients with SJS, and thus a better understanding of the pathophysiology of both SJS and stromal necrosis may allow for more effective immunosuppressive regimens.

In summary, the Boston type I keratoprosthesis is an effective means of restoring vision in individuals with SJS. However, a significantly higher incidence of postoperative persistent corneal epithelial defect formation is associated with a significantly increased incidence of corneal stromal necrosis and infectious keratitis and subsequent retention failure. The incidence of these postoperative complications may be minimized by the coverage of the donor cornea with either conjunctival flaps or extensive medial and lateral tarsorrhaphies and avoidance of keratoprosthesis implantation in eyes with bulbar conjunctival keratinization, which is associated with an increased risk of keratoprosthesis retention failure.

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