

# A prospective, randomized clinical study comparing accelerated corneal collagen crosslinking with 5% NaCl hypertonic saline for bullous keratopathy in Asian eyes

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## Abstract

**Background:** We compared the clinical outcomes of accelerated corneal collagen crosslinking (CXL) and 5% NaCl hypertonic saline (HS) for the treatment of symptomatic bullous keratopathy (BK).

**Methods:** A randomized controlled trial was held at Department of Ophthalmology, Tokyo Dental College Ichikawa General Hospital, Chiba, Japan. Twenty-three eyes of 23 consecutive patients with symptomatic BK were enrolled. The etiology of BK included pseudophakic BK, previous keratoplasty, previous endotheliitis, previous glaucoma surgery, trauma, herpes infection, as well as unknown causes. Eleven eyes received epi-off accelerated CXL (with epithelial abrasion and 18mW/cm<sup>2</sup> ultraviolet A irradiation for 5 minutes) and 12 eyes received HS instillation. In addition to the usual ophthalmic examination, the best-corrected visual acuity (BCVA) and central corneal thickness (CCT) were determined. The CCT was measured using anterior segment optical coherence tomography before and up to 6 months after treatments. Subjective symptoms of pain, blurred vision, photophobia, and irritation were also recorded.

**Results:** The follow-up was completed for all patients in the CXL group. However, 6 patients in the HS group requested CXL treatments after 3 months. The BCVA was not significantly changed during the study periods in both groups. The CCT was significantly thinner in the CXL group compared to the HS group at 1 and 6 months ( $P = .015$  and  $0.144$ , respectively). Among the subjective symptoms recorded, irritation was significantly lower in the CXL group at 1 month ( $P = .013$ ).

**Conclusions:** Accelerated CXL may produce transient improvement in pain and corneal edema in patients with BK.

**Abbreviations:** BCVA = best-corrected visual acuity, BK = bullous keratopathy, CCT = central corneal thickness, CXL = corneal collagen crosslinking, HS = 5% NaCl hypertonic saline, UV = ultraviolet.

**Keywords:** bullous keratopathy, corneal cross-linking (CXL), corneal thickness, subjective symptoms

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## 1. Introduction

Bullous keratopathy (BK) is a condition that results from dysfunction and loss of corneal endothelial cells, leading to corneal edema, corneal opacification, and epithelial bullae formation. Patients usually initially present with decreased vision but, later, there is intense discomfort, pain, watering, irritation, photophobia due to rupture of bullae and exposure of corneal nerves.<sup>[1]</sup> Many therapeutic methods have been used to treat BK clinically. Although the most interventional treatment for BK is corneal transplantation or instillation of steroids and hypertonic saline (NaCl) eye drops,<sup>[2]</sup> applying a therapeutic bandage contact lens has also been considered to be effective.<sup>[3]</sup>

Corneal collagen cross linking (CXL) with riboflavin and ultraviolet (UV) -A radiation is a photochemical process that catalyzes the increase of cross-links between collagen fibers and extracellular matrices within the corneal stroma. The original procedure, introduced by Wollensak et al, named the “Dresden Protocol”, involves epithelial removal, riboflavin instillation, and UV-A with 3.0 mW/cm<sup>2</sup> of intensity for 30 minutes. This reaction results in increasing stiffness of the corneal stroma, keeping the configuration, preventing bulging of the cornea and, eventually, halting the progression of keratoconus.<sup>[3]</sup>

Another aspect of CXL is that it has been shown to decrease the water content of the corneal stromal layer.<sup>[4]</sup> It is known that CXL decreases the corneal thickness several months to years after the procedure.<sup>[5,6]</sup> Furthermore, some recent clinical studies with human subjects reported that CXL performed on BK patients reduced corneal edema and alleviated ocular pain.<sup>[1,7–11]</sup> In these reports, CXL was performed using the original procedure involving UV-A irradiation with 3.0 mW/cm<sup>2</sup> of intensity for 30 minutes.

Instead of the original procedure for CXL, some modified methods have been developed. Accelerated CXL, with a higher intensity of UV light, has facilitated a shorter UV irradiation time.<sup>[12–13]</sup> Because patients with BK are often elderly, time-consuming procedures are sometimes difficult to perform, and accelerated CXL may be more appropriate. The purpose of the present investigation was to assess the efficacy, safety, and clinical outcomes of accelerated CXL for the treatment of symptomatic BK, as well as comparing it with 5% NaCl hypertonic saline (HS) instillation.

## 2. Methods

### 2.1. General information

The investigation was planned as a randomized controlled trial and is registered in the Clinical Trial Registration System of the University Hospital Medical Information Network Center (UMIN000029302). The study protocol was approved by the institutional review board of Tokyo Dental College Ichikawa General Hospital, Tokyo, Japan. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

### 2.2. Inclusion criteria

Japanese patients with symptomatic BK, who visited the Department of Ophthalmology, Tokyo Dental College, Ichikawa General Hospital, were enrolled. The inclusion criterion included age older than 20 years-old, and diagnosed with symptomatic BK. The etiology of BK included pseudophakic BK, previous keratoplasty, previous endotheliitis, previous glaucoma surgery, trauma, herpes infection, as well as unknown causes. The profiles of the patients are summarized in Table 1.

### 2.3. Sample size

There is limited evidence quantifying the effectiveness of CXL for BK. The evidence available suggested CXL decreased the CCT

approximately 112.75 ± 52.3 μm (approximately 15% of the preoperative value). We used Sample Size Estimation (<http://www2.ccrb.cuhk.edu.hk/stat/Means.htm>) to calculate sample size with an independent dichotomous endpoint (2-sided test) using a Type I error probability set at 0.05 and a Type II error probability set at 0.2 (power 80%). The calculated sample size to see a difference in efficacy between the both groups was 13 for each group. And 23 patients with BK agreed to participate the trial during the research periods.

### 2.4. Randomization and grouping situations

All patients were randomly divided into 2 groups using a mathematical technique. Written informed consent was obtained from all patients. Randomization of protocols was performed using a simple randomization technique. Serial numbers assigned HS or CXL for each were randomized by randomization function of Microsoft Excel. Then, the number list was placed in a secure box in the office of ophthalmology. On admission into the study, eligible patients selected by doctors were assigned each of the treatments following the serial number list. Due to differences in administration, the doctors implementing the protocols could not be blinded. However, after completion of patient recruitment and data collection, all patient identifiers were removed.

## 3. Interventions

### 3.1. CXL procedure

CXL was performed under topical anesthesia using 0.4% oxybuprocaine hydrochloride eye drops before the procedure. A lid speculum was inserted, followed by removal of the central corneal epithelium (7.0–8.0 mm in diameter) using a blunt spatula. Then, 0.1% isotonic riboflavin in 20% dextran solution drops were instilled every 2 minutes for 20 minutes. After confirming stromal saturation of riboflavin by slit-lamp microscopy, the thinnest corneal stromal thickness was measured using an AL-3000 pachymeter (Tomey, Aichi, Japan). Then, UV-A was used to irradiate at an intensity of 18.0 mW/cm<sup>2</sup> for 5 minutes (accelerated CXL; KXL system; Avedro, Waltham, MA). Isotonic riboflavin was instilled continuously every 1 to 2 minutes during the UV-A irradiation. At the end of the procedure, a soft bandage contact lens was applied, and a drop of levofloxacin was instilled.

**Table 1**  
Patient profiles (before the investigation).

	CXL group	HS group	P value
Eyes	11 eyes of 11 cases	12 eyes of 12 cases	
Sex	6 females and 5 males	8 females and 5 males	.84
Age (years old)	73.2 ± 14.4	69.8 ± 16.8	.61
Etiology for BK	PBK 4 Previous KP 7 (Endotheliitis 1, previous TLE 1) Unknown 1	PBK 2 Previous KP 5 (Herpes 1, trauma 1) Unknown 6	
BCVA	1.24 ± 0.62	1.70 ± 0.59	.031
CCT (μm)	715.6 ± 137.7	844.3 ± 214.6	.16
Symptoms			
Pain	2.0 ± 2.3	3.1 ± 3.8	.35
Blurred vision	6.5 ± 3.2	6.5 ± 3.7	.84
Photophobia	3.8 ± 3.3	2.7 ± 2.5	.29
Irritation	2.5 ± 2.6	2.9 ± 2.8	.76

BCVA = best-corrected visual acuity, BK = bullous keratopathy, CCT = central corneal thickness, CXL = corneal crosslinking, HS = hypertonic saline, PBK = pseudophakic bullous keratopathy, TLE = trabeculectomy.

Postoperative medications included levofloxacin and 0.1% betamethasone eye drops, four times daily. The bandage contact lens was removed when we confirmed that re-epithelialization of the operated cornea was complete. After the epithelial defect had healed, levofloxacin eye drops were discontinued, and betamethasone was continued for 1 month.

### 3.2. Hypertonic saline (HS) instillation

In the HS group, 5% NaCl hypertonic saline (HS) drops were prescribed and patients were instructed to use them four times daily during the study period.

However, as the NaCl instillation was done as a control for the CXL and not expected to have significant efficacy, we settled the CXL as an ethical bailout. When the patients could not tolerate the subjective symptoms caused by HS instillation, the patients were allowed to undergo CXL from 3 months after starting HS instillation.

### 3.3. Outcome measures

Examinations were performed before and at 1, 3, and 6 months postoperatively. In addition to a usual ophthalmic examination, the best-corrected visual acuity (BCVA) and central corneal thickness (CCT) were examined. CCT was measured using anterior segment optical coherence tomography (CASIA SS-3000; Tomey, Aichi, Japan). Subjective symptoms were also recorded using a visual analog scale (0–10 for each item) at each visit. The VAS was based on a 100-mm scale; the extreme left side indicated none of symptoms and the extreme right, maximal. The patients were asked to put a check on the scale.

### 3.4. Times of treatments

The follow-up examination was completed in all 11 eyes of the patients in the CXL group. No patient requested to have additional treatment, such as a corneal endothelial transplantation, during the study. However, one patient underwent CXL at 3 months after starting HS instillation, and 5 patients underwent CXL after 6 months.

### 3.5. Statistical analysis

Statistical analysis was performed with JMP version 12.1.0. A Dunnett test was used for analyses of changes in the BCVA, CCT, and subjective symptoms, and Wilcoxon test was used for comparison between CXL and HS groups. The Wilcoxon test was also used to evaluate the difference for patients' age between CXL and HS groups. The Fischer exact test was used to evaluate the difference of gender between CXL and HS groups. A Dunnett test was performed for analyses of changes in the BCVA, CCT among cases who were initially treated with HS instillation, but requested and underwent subsequent CXL. A value of  $P < .05$  was considered statistically significant.

## 4. Results

In total, 23 eyes of 23 patients were enrolled for the investigation: 11 eyes (6 females and 5 males; average age:  $73.2 \pm 14.4$  years) received accelerated CXL, whereas 12 eyes of 12 patients (seven females and five males; average age:  $67.8 \pm 19.0$  years) received a prescription of hypertonic NaCl eye drops. The follow-up examination was completed in all 11 eyes of the patients in the

CXL group. No patient requested to have additional treatment, such as a corneal endothelial transplantation, during the study. However, one patient underwent CXL at 3 months after starting HS instillation, and five patients underwent CXL after 6 months (Fig. 1).

### 4.1. BCVA

CXL was uneventfully performed in all cases. Slit-lamp examinations showed no complications during the follow-ups for both groups. The mean BCVA was  $1.24 \pm 0.62$  (0.00–2.00) in the CXL group and  $1.70 \pm 0.59$  (–0.08 to –2.00) in the HS group before treatment ( $P = .031$ ). The mean BCVA did not significantly change from baseline within the follow-up period for both groups (Table 2).

### 4.2. CCT

The initial CCT was  $715.6 \pm 137.7 \mu\text{m}$  in the CXL group and  $844.3 \pm 214.6 \mu\text{m}$  in the HS group ( $P = .157$ ). The CCTs of both CXL and HS groups were not significantly decreased from the preoperative values in the follow-up periods; however, the CCT was significantly thinner in the CXL group compared to the HS group at 1 and 6 months ( $P = .015$  and  $.044$ , respectively; Fig. 2; Table 2).

### 4.3. Subjective symptoms

The total symptom score was  $13.5 \pm 8.5$  before the treatment and  $9.3 \pm 6.1$  at 1 month in the CXL group ( $P = .662$ ), whereas it was  $11.7 \pm 9.6$  and  $12.5 \pm 10.3$  in the HS group, respectively ( $P = 0.459$ ). The total symptom score did not significantly change from the initial values in both groups, and did not differ between the CXL and HS groups within the follow-up period.

When we analyzed each score, the irritation score was significantly less in the CXL group than in the HS group at 1 month ( $1.1 \pm 4.7$  vs.  $1.6 \pm 3.2$ , respectively;  $P = .012$ ); however, it returned to the preoperative value at 3 months after the procedure (Fig. 3). Other symptom scores such as pain, blurred vision, and photophobia did not significantly change during follow-ups for both groups.

### 4.4. Outcomes for subsequent CXL

Six eyes of 6 patients ( $71.0 \pm 20.7$ -years-old; 1 male and 5 females) who were initially treated with HS instillation, requested and underwent subsequent CXL. Five patients completed the 6-month follow-up period. One patient began to use not designed eye drops at 3 months, therefore we excluded her data from analysis. The BCVA was  $1.24 \pm 0.64$  and the CCT was  $687.4 \pm 224.7 \mu\text{m}$  (Suppl. Fig. 1, <http://links.lww.com/MD/D423>) before the CXL, respectively, and neither changed significantly up to 6 months after the CXL. Subjective symptoms were not evaluated in all six patients, so they were not analyzed.

## 5. Discussion

In the present study, we compared the effects of accelerated CXL (UV-A irradiation with an intensity of  $18.0 \text{ mW/cm}^2$  for 5 minutes) and HS instillation for the treatment of patients with BK. The results showed that the BCVA, CCT, and symptom scores were not significantly improved in either the CXL or HS

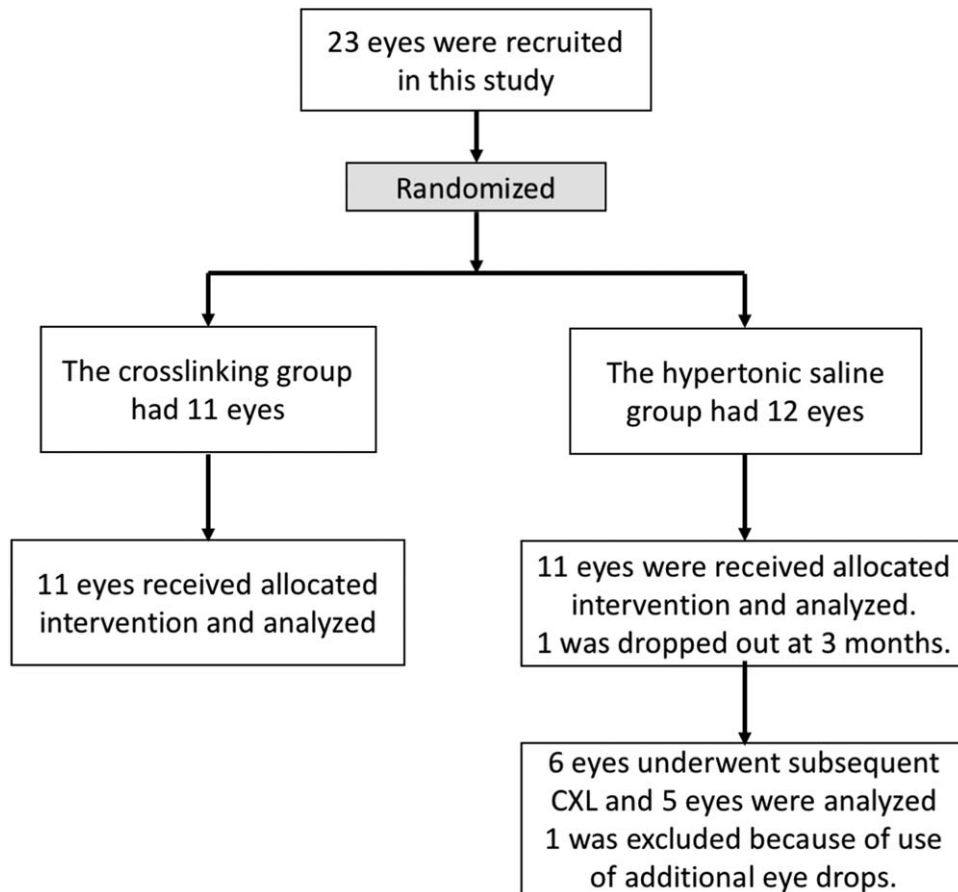


Figure 1. CONSORT flow diagram of patient selection and allocation.

groups; however, the CCT was significantly thinner at 1 and 6 months, and the irrigation score was significantly smaller at 1 month in the CXL group compared to the HS group. This difference disappeared thereafter. However, one of the patients in the HS group dropped out due to pain, and 5 patients

underwent CXL for 6 months after the completion of the HS instillation, and all participants in the CXL group completed the study.

For the treatment of keratoconus, whether accelerated CXL provides the identical crosslinking effect in the corneal stroma as

**Table 2**

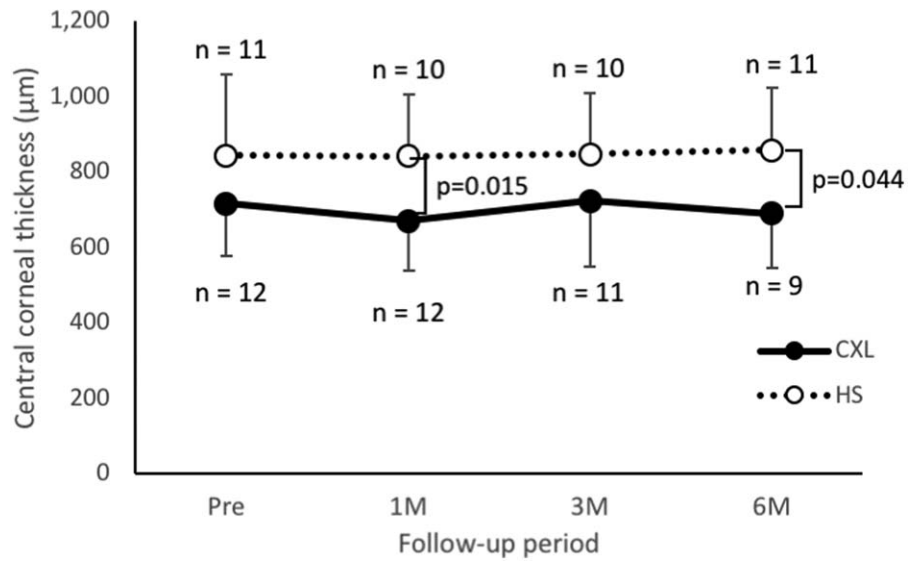
**Clinical outcomes of BCVA and CCT.**

		Pre-treatment	1 month	3 months	6 months
BCVA (logMAR) <i>P</i> value (number of eyes)	CXL	1.24 ± 0.62	1.15 ± 0.65	1.27 ± 0.45	1.44 ± 0.46
	<i>P</i> -value		0.961	0.999	0.741
		(n = 11)	(n = 10)	(n = 9)	(n = 11)
	HS	1.70 ± 0.59	1.66 ± 0.53	1.77 ± 0.26	1.64 ± 0.54
	<i>P</i> -value		0.996	0.971	0.988
	<i>P</i> -value (CXL vs HS)	0.031	0.030	0.013	0.111
CCT (μm) <i>P</i> value (number of eyes)	CXL	715.6 ± 137.7	669.6 ± 131.3	723.5 ± 173.3	690.2 ± 143.2
	<i>P</i> -value		0.818	0.999	0.958
		(n = 11)	(n = 10)	(n = 10)	(n = 11)
	HS	844.3 ± 214.6	841.8 ± 163.1	846.3 ± 163.0	858.0 ± 165.3
	<i>P</i> -value		1.000	1.000	0.996
	<i>P</i> -value (CXL vs HS)	0.157	0.015	0.067	0.044

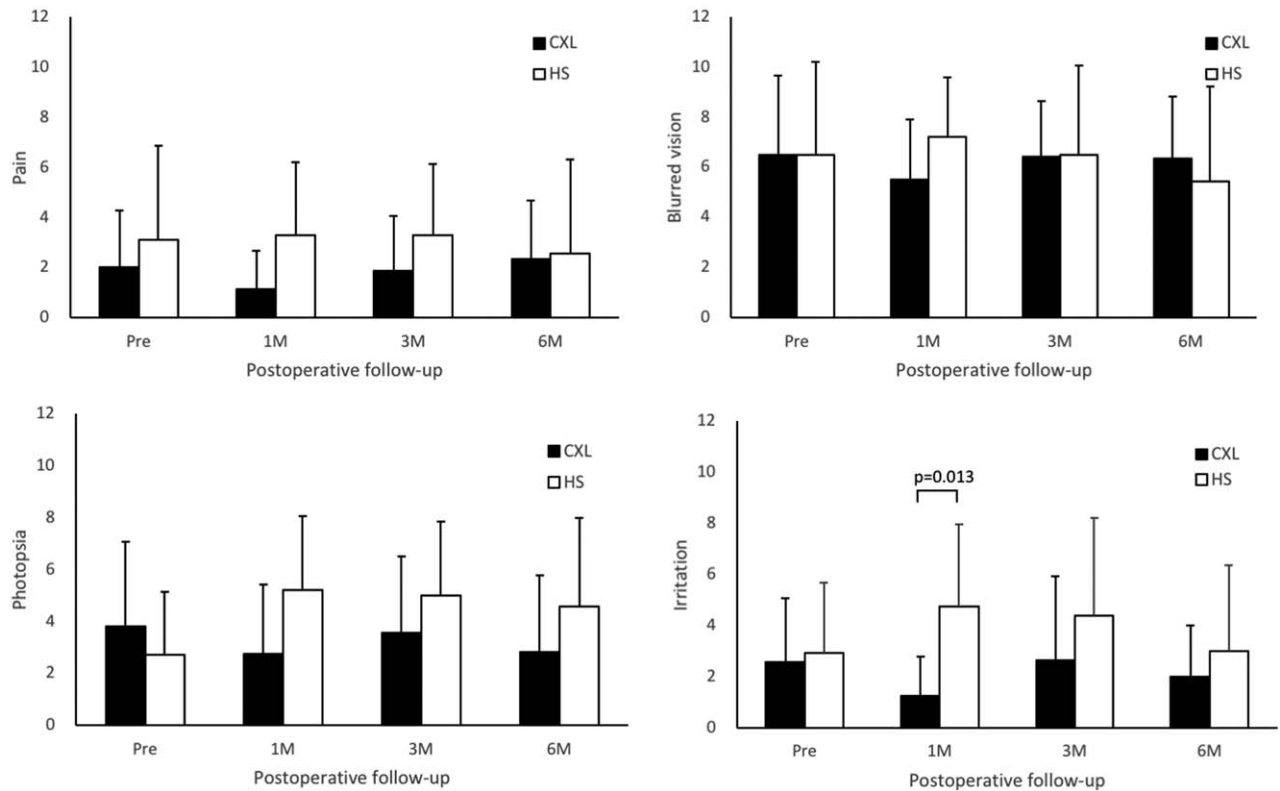
BCVA = best corrected visual acuity, CCT = central corneal thickness, CXL = corneal crosslinking, HS = hypertonic saline.

\**P* value under each average value indicates the comparison with preoperative value by Dunnett test.

\**P* value for CXL vs HS was calculated by chi-square test.



**Figure 2.** Change in the CCT. The initial CCT was not significantly different between the CXL group and the HS group. The CCTs of both CXL and HS groups were not significantly decreased from the initial values in the follow-up period; however, the CCT was significantly thinner in the CXL group compared to the HS group at 1 and 6 months. Pre, before treatment; 1M; 1 month; 3M, 3 months; 6M, 6 months; n, number of eyes. CCT = central corneal thickness, CXL = corneal crosslinking, HS = hypertonic saline.



**Figure 3.** Change in the subjective scores. The pain (top left), blurred vision (top right), and photopsia (bottom left) scores was not significantly changed both in the CXL and HS groups. The irritation (bottom right) score was significantly less in the CXL group than in the HS group at 1 month, but not significantly different between both groups at 3 and 6 months. The number of cases who answered the questionnaire for subjective scores was 10 before the treatment, 8 at 1 month, 7 at 3 months, and 6 at 6 months after the treatment in the CXL group, and 10, 11, 10 and 7 in the HS group, respectively. Pre, before treatment; 1M; 1 month; 3M, 3 months; 6M, 6 months. CXL=corneal crosslinking, HS=hypertonic saline.

conventional CXL has been a controversial issue. Several investigators<sup>[14–18]</sup> reported the outcomes of accelerated CXL using the same conditions of UVA irradiation as the present study, and compared it with conventional CXL for the treatment of keratoconus. Hashemi et al<sup>[17]</sup> and Chow et al<sup>[18]</sup> reported that accelerated CXL was less effective in the flattening effect on topography; however, they did not find any difference between the 2 procedures when monitoring other factors. However, we previously reported the outcomes of two different CXLs, the Dresden protocol and accelerated CXL (18.0 mW/cm<sup>2</sup> for 5 minutes), for Japanese patients with progressing keratoconus, and showed that the outcomes were similar.<sup>[19]</sup> We also showed that the depths of the demarcation lines occurring 1 month after the CXL were similar for both procedures, indicating similar crosslinked stromal areas between conventional CXL and accelerated CXL.<sup>[20]</sup>

The outcomes of the present study indicated that, for both treatments, the accelerated CXL and HS were not significantly effective treatments for the clinical symptoms of BK. However, the observations that the one patient in the HS group dropped out and requested CXL and the other 5 patients also requested CXL after the completion of the follow-up period, with these patients completing 6 months of follow-up for subsequent CXL, may indicate that the CXL was more effective in treatment for the improvement of subjective symptoms.

We speculate that the reason CXL was less effective in the present study compared to previous studies was probably due to the etiology of the BK of patients enrolled in our study. The etiology of the BK was limited to Fuchs' endothelial corneal dystrophy or pseudophakic BK in previous investigations. In contrast, the etiology of the BK of patients enrolled in the present study varied, including previous corneal transplants, glaucoma surgery, trauma, and/or endotheliitis. In these conditions, the elevation of intraocular cytokines may exacerbate corneal endothelial cell functions,<sup>[21,22]</sup> and the effect of the CXL could be overwhelmed by persistent intraocular inflammation.

However, it was noteworthy that the accelerated CXL treatment significantly decreased the CCT and subjective symptoms, even though the effect was only transient. For patients who cannot undergo corneal transplant surgery, for example, due to poor general conditions or having been diagnosed with dementia, accelerated CXL could be more effective than conservative treatment with eye drops, and it has also become a good alternative for conventional CXL or endothelial keratoplasty.

The limitation of the present study was that the number of enrolled eyes was small and also that the study design was not a randomized trial. The small sample size may obscure the difference of BCVA or CCT between before and after the treatment. On the other hand, the fact that we did not perform the sham treatment for both CXL and HS may have led some confounding factors that affect the outcomes, in particular, in analyses for subjective symptoms.

## 6. Conclusion

In conclusion, accelerated CXL may improve the corneal edema and subjective symptoms of BK. If we select only patients with Fuchs corneal endothelial keratopathy or pseudophakic BK, the effect could be more significant. Further investigations with a larger number of patients and limited etiology of BK and

comparison with the effect of Dresden protocol are therefore warranted.

## Author contributions

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**Validation:** Seika Den.

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**Writing – review & editing:** Naoko Kato, Seika Den, Kenji Konomi, Megumi Shinzawa, Jun Shimazaki.

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