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Flattening effect of corneal cross-linking depends on the preoperative severity of keratoconus

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Abstract

A retrospective observational study was conducted to validate the effect of corneal cross-linking (CXL) on eyes with progressing keratoconus, depending on severity.

In total, 45 eyes of 33 patients (age: 23.9 ± 6.8 years, range: 14–42 years) with progressive keratoconus who underwent CXL were enrolled. Examinations were performed at pre-, 1, 3, 6, and 12 months after surgery. In addition to a slit lamp microscopy, measurement of visual acuity, the steepest keratometric value (Kmax), the thinnest corneal thickness (TCT), and the corneal endothelial cell density (ECD) were assessed. Change in Kmax (ΔKmax) was calculated by subtracting the preoperative Kmax from the 12-month postoperative Kmax.

CDVA, TCT, and ECD did not change significantly throughout the follow-up period. Kmax was 56.4 ± 7.2 D preoperatively and 54.3 ± 5.6 D at 12 months after CXL ($P = .174$). The average value of ΔKmax was −2.23 ± 4.31 D at 12 months after CXL. ΔKmax was negatively correlated with preoperative Kmax ($\rho = -0.5517$, $P = .0001$), and positively correlated with preoperative TCT ($\rho = 0.4791$, $P = .0012$). However, no correlation was observed between Kmax and patient age or the decrease ratio of ECD.

The more flattening was obtained after CXL in cases with the more advanced keratoconus. No complication, including corneal endothelial damage, was observed even in advanced cases.

Abbreviations: ΔKmax = change in Kmax, CDVA = corrected distance visual acuity, CXL = corneal crosslinking, ECD = the corneal endothelial cell density, Kmax = the steepest keratometric value, TCT = the thinnest corneal thickness, UV-A = ultraviolet-A.

Keywords: advanced keratoconus, corneal cross-linking, keratoconus management, the later stages

1. Introduction

Corneal collagen cross-linking (CXL) is a method to halt the progression of corneal ectasia in patients with keratoconus.[1] Given the low cost and simplicity of the procedure, CXL has been applied in many countries worldwide, including developing countries, where prescribing contact lenses and/or undergoing keratoplasty are difficult due to financial or social reasons.

Many previous clinical studies have suggested that CXL may be effective not only in halting the progression of keratoconus but also in regressing the protrusion of the cornea, although to a limited extent.[2–7] Greenstein et al[8] showed that visual acuity and corneal topography indices improved 1 year after standard epithelial-off CXL. Kirgiz et al[9] also showed that flattening of anterior keratometric values affected the improvement in visual acuity after accelerated CXL. Thus, corneal flattening and closing to a symmetric configuration are recognized in some cases after CXL.

Recently, several authors have indicated that flattening of the protruded cornea may occur in more advanced cases; Koller et al[10] reported that significant flattening occurred during the first year after CXL, and cases with preoperative Kmax more than 54.00 D had a higher tendency to be flattened after CXL. Chen et al[11] showed that higher preoperative keratometry was associated with greater corneal flattening after epithelial-on CXL. Chan et al[12] also showed similar results after accelerated CXL. Other investigations indicated that patients with lower pretreatment visual acuity are more likely to benefit from CXL (with respect to visual acuity), and patients with more central cones benefit more in terms of cone flattening.[13,14]

However, in treatment of patients with advanced keratoconus, reports do not describe improvements in visual function after CXL, even though marked corneal flattening was observed. Rather, there is concern about the occurrence of delayed stromal scars or corneal endothelial cell damage, especially when treating a thin cornea. Moreover, higher incidence and prevalence rates, earlier onset, and greater severity in certain Asian groups versus white populations have been reported.[15] Thus, the aim of the present study was to validate the effect of CXL on eyes with progressing keratoconus, depending on severity, in a Japanese (East Asian) population, and to exclude the possibility of serious complications.

Editor: Giovanni Tarantino.

Funding/support: Eye Lens Private Limited provided support for this study and is a distributor of the products and/or procedures presented herein.

The authors do not have any conflicts of interest.

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Medicine (2017) 96:40(e8160)

Received: 9 July 2017 / Received in final form: 1 September 2017 / Accepted: 4 September 2017

http://dx.doi.org/10.1097/MD.0000000000008160

2. Patients and methods

A retrospective observational study was conducted. The patients who underwent CXL for progressing keratoconus at Tokyo Dental College Ichikawa General Hospital, Tokyo, Japan, approved by the institutional review board, were reviewed. The study was conducted in accordance with the tenets of the Declaration of Helsinki.

2.1. Patients

In total, 45 eyes of 33 consecutive Japanese patients (6 females, 27 males, age: 23.9 ± 6.8 years, range: 14–42 years) with progressive keratoconus, who underwent CXL using riboflavin and ultraviolet-A irradiation (UV-A) were enrolled. Inclusion criteria were as follows: an increase in the spherical equivalent or cylinder power of the manifest refraction by 1.0 D or more, and/or an increase in the steepest simulated keratometric value evaluated on computerized videokeratography (Kmax) by 1.0 D during the last 2 years. Eyes with a thin cornea, estimated to be <400 μm at the thinnest part at the start of UV-A irradiation, were excluded. Patients younger than 14 years were also excluded. Written informed consent was obtained from all patients and also from their guardians if the patients were under 20 years of age.

2.2. CXL procedure

CXL was performed under topical anesthesia with oxybuprocaine hydrochloride 0.4% 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. After that, 0.1% isotonic riboflavin in dextran 20% solution drops were instilled every 2 minutes for 20 minutes. After confirming stromal saturation of riboflavin by slit-lamp examination, the thinnest corneal stromal thickness was measured using an AL-3000 pachymeter (Tomey, Aichi, Japan). If the stromal thickness was <400 μm, 0.1% hypotonic riboflavin or distilled water was instilled until the minimal thickness reached 400 μm.[16] Then, UV-A was irradiated at 18.0 mW/cm^2 intensity for 5 minutes (KXL system; Avedro, Waltham, MA; accelerated CXL). Isotonic riboflavin was instilled continuously every 1 minute during UV-A irradiation. At the end of the procedure, a soft bandage contact lens was applied, and a drop of levofloxacin was instilled. Postoperative medications included levofloxacin and betamethasone 0.1% eye drops, 4 times daily. The bandage contact lens was removed when we confirmed that reepithelialization of the operated cornea was complete. After the epithelial defect healed, levofloxacin eye drops were discontinued, and betamethasone was continued for 1 month.

2.3. Examinations

Examinations were performed before and at 1, 3, 6, and 12 months after the procedure. In addition to a typical ophthalmic examination, the corrected distance visual acuity (CDVA), the steepest keratometric value (Kmax), the thinnest corneal thickness (TCT), and the corneal endothelial cell density (ECD) were assessed at each visit. The keratometric value and pre- and postoperative pachymetry were measured using a CASIA (SS-3000; Tomey). The change in Kmax (ΔKmax) was calculated by subtracting the preoperative from the postoperative Kmax at 12 months.

2.4. Statistical analysis

A Wilcoxon test was used for analyses of changes in CDVA, TCT, ECD, and Kmax. The Spearman rank correlation was used to evaluate the correlation between ΔKmax and CDVA, TCT, ECD, and Kmax. A P value <.05 was considered to indicate statistical significance. Suppose that for a 1.0 D of flattening of the Kmax with 5.0 D of expected population variance, the number of patients may be sufficient at N = 40 to achieve >80% power.

3. Results

The mean CDVA was 0.32 ± 0.39 (-0.1 to 1.5), Kmax was 53.0 ± 6.46 D (42.0–71.9 D), TCT was 401.0 ± 53.6 μm (278–482 μm), and ECD was 2821.7 ± 359.3 cells/mm^2 (1792–3597 cells/mm^2) before the procedure. The mean CDVA did not differ significantly from baseline within the follow-up period. The change in CDVA from before to 12 months after the CXL was 0.06 ± 0.25 (logMAR). The average Kmax also did not significantly change from before to 12 months after CXL. TCT and ECD did not change significantly after CXL. Summarized data before and after CXL are described in Table 1. The final CDVA was gained 3 lines or more in 9 eyes (20.0%), 2 lines in 4 eyes (8.9%), not changed in 25 eyes (55.6%), lost 2 lines in 4 eyes (8.9%), and lost 3 lines or more in 3 eyes (6.7%).

Mild stromal haze after CXL treatment was observed in 10 eyes (22.2%). One eye (2.2%) showed corneal stromal scarring, but improved spontaneously after 3 months. No eye showed a vision-threatening complication.

3.1. ΔKmax

The average value of ΔKmax was -2.23 ± 4.31 D at 12 months after the procedure. When we analyzed the correlation between ΔKmax and the preoperative Kmax, patient age, preoperative TCT, and the decrease ratio in ECD, a statistically significant

Table 1

CXL outcomes.

	Pre	1 mo	3 mo	6 mo	12 mo
CDVA (LogMAR)	0.32 ± 0.39	0.30 ± 0.31 *P* = .9868	0.29 ± 0.34 *P* = .8767	0.29 ± 0.36 *P* = .9901	0.28 ± 0.36 *P* = .9699
Kmax, D	56.4 ± 7.2	55.8 ± 6.1 *P* = 1.0000	55.2 ± 6.0 *P* = .9502	54.9 ± 5.5 *P* = .9548	54.3 ± 5.6 *P* = .1947
TCT, μm	401.0 ± 53.6	410.8 ± 49.4 *P* = .8251	405.8 ± 46.5 *P* = .9879	410.2 ± 40.2 *P* = .8495	411.0 ± 43.2 *P* = .8131
ECD, cells/ mm^2	2821.7 ± 359.3	2641.9 ± 482.9 *P* = .2059	2771.4 ± 322.8 *P* = .9774	2675.0 ± 411.5 *P* = .3422	2850.5 ± 347.2 *P* = .9983

P values indicate comparison with preoperative value.

CDVA = corrected distance visual acuity; ECD = endothelial cell density; Kmax = steepest keratometric value; Pre = before CXL; TCT = thinnest corneal thickness.

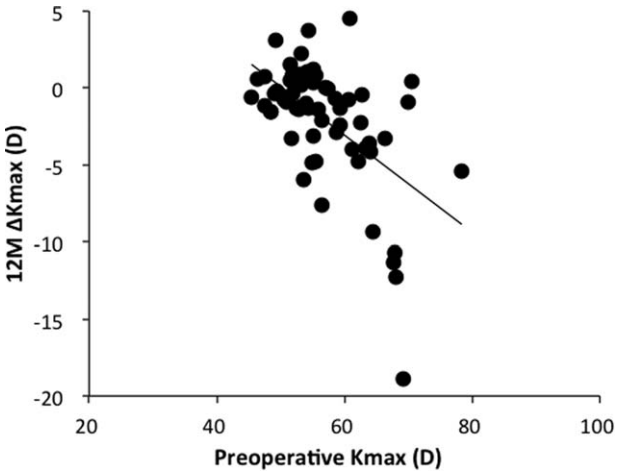

Figure 1. Correlation between change in steepest keratometric value (ΔKmax) at 12 months and the preoperative steepest keratometric value (Kmax). ΔKmax at 12 months correlated negatively with preoperative Kmax ($\rho = -0.5517$, $P = .0001$).

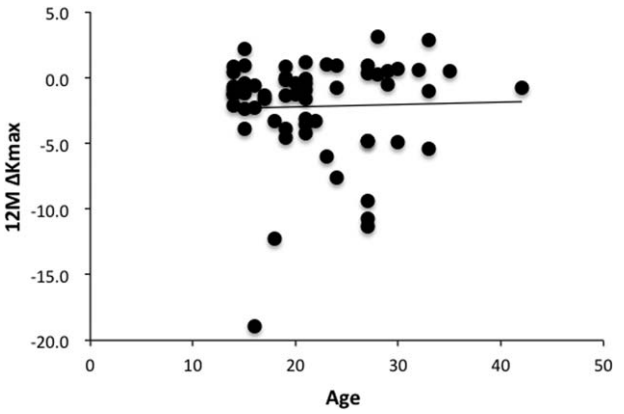

Figure 3. Correlation between change in steepest keratometric value (ΔKmax) at 12 months and patients' age. ΔKmax at 12 months and patients' age were not significantly correlated ($\rho = 0.1144$, $P = .4653$).

negative correlation was observed between ΔKmax and the preoperative Kmax ($\rho = -0.5517$, $P = .0001$; Fig. 1), and a positive correlation was observed between ΔKmax and the preoperative TCT ($\rho = 0.4791$, $P = .0012$; Fig. 2). No significant correlation was observed between ΔKmax and patient age ($\rho = 0.1144$, $P = .4653$; Fig. 3), the change in CDVA ($\rho = 0.1227$, $P = .4506$; Fig. 4), or the decrease ratio in ECD ($\rho = 0.0233$, $P = .8961$; Fig. 5).

4. Discussion

Our results indicated that ΔKmax was significantly negatively correlated with preoperative Kmax and positively correlated with preoperative TCT, indicating that CXL had a greater flattening effect in more advanced keratoconus. Corneal endothelial cell damage was not observed even in cases with advanced keratoconus.

The eyes enrolled in the present investigation had relatively thin corneas, with 401.0 ± 53.6 (278–482) μm preoperative TCT, compared with previous reports. This is probably because at Ichikawa General Hospital, we perform the greatest number of corneal transplants in Japan. Patients who are sent to our institution tend to have relatively advanced keratoconus, and are considering undergoing transplants or some other surgical intervention. Another possibility is that the keratoconus tends to be early onset, and to show greater severity in Asians.[14]

The more advanced keratoconus cases showed the greatest ΔKmax, or more flattening of the cornea after CXL. We had first considered that younger patients had earlier progression, probably resulting in smaller ΔKmax, and older patients had slower progression, probably contributing to larger ΔKmax, where a higher failure rate has been reported previously. However, no significant correlation was observed between ΔKmax and patient age. Likewise, the preoperative CDVA did not affect the ΔKmax after CXL. Chan et al[12] speculated as one reason that relatively deeper penetration of cross-linking in advanced keratoconus with thinner cornea may result in a relatively larger proportion of the cornea being crosslinked, exerting a stronger strengthening effect.

Although many investigators have reported that the corneal thickness decreased and corneal curvature flattened after CXL, the mechanisms of the flattening and thinning of the cornea after CXL have not been fully determined. The cornea of the keratoconus eye shows gradual changes, according to clinical severity. Transparency of the cornea requires uniform orientation

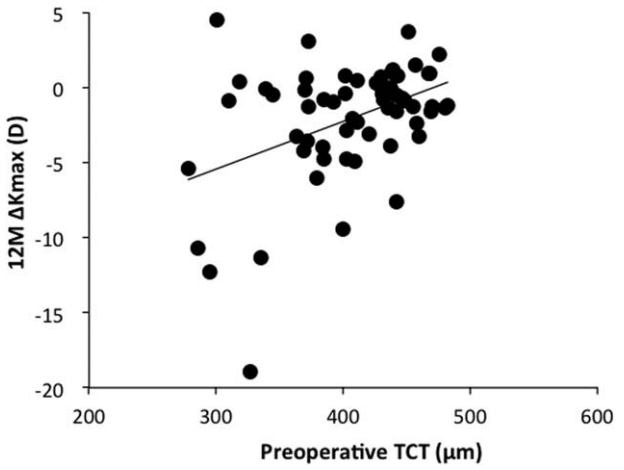

Figure 2. Correlation between ΔKmax at 12 months and preoperative thinnest corneal thickness (TCT). ΔKmax at 12 months correlated positively with preoperative TCT ($\rho = 0.4791$, $P = .0012$).

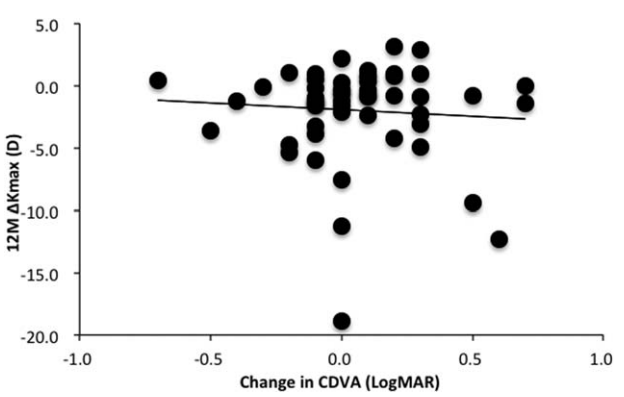

Figure 4. Correlation between change in steepest keratometric value (ΔKmax) at 12 months and change in corrected distant visual acuity (CDVA). ΔKmax at 12 months and CDVA were not significantly correlated ($\rho = 0.1227$, $P = .4506$).

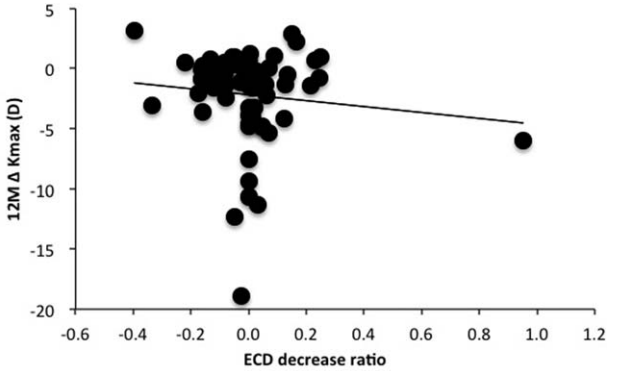

Figure 5. Correlation between change in steepest keratometric value (ΔKmax) at 12 months and decrease ratio of endothelial cell density (ECD). ΔKmax at 12 months and decreased ratio of ECD were not significantly correlated ($\rho = 0.0794$, $P = .6217$).

of collagen fibers in the corneal matrix, and normal expression of proteoglycans is essential for this organized architecture. The constitution of the collagen and proteoglycans have been reported to be altered in keratoconus eyes,[17] and we frequently observe idiopathic opacity at the apex of the cone in advanced keratoconus eyes. In such eyes, the effect of CXL, and the concentration of newly generated cross-links, was not equal to that in early keratoconus,[18] possibly contributing to more flattening of the cone. Several cases with corneal scars after CXL have been reported,[19–23] and Raiskup et al[24] reported that higher keratometric values and thinner corneas could be considered predictive factors for the development of such corneal scarring; this may be consistent with the theory above.

Also, in the present investigation, advanced keratoconus cases tended to show idiopathic corneal opacity preoperatively, and the opacity could be augmented after CXL to some extent, although we did not quantify or compare the density before and after CXL. However, no eye showed vision-threatening stromal scarring in the present investigation. In addition, although the present investigation included eyes with relatively advanced keratoconus, showing very thin corneas ($<350\,\mu m$), no eye revealed marked endothelial damage after CXL. This result suggests that CXL can be performed safely and is advantageous, as long as we follow the protocol during the procedure.

The strength of the present investigation is that we could show that the efficacy and safety of the accelerated CXL for the Asian keratoconus that were supposed to be relatively progressive, and also that more flattening effect was observed in the more advanced keratoconus. On the contrary, the limitation of the present study was that the observation period was only 1 year. Continuing follow-up, especially for cases that revealed stromal opacity or remarkable flattening, is required.

In conclusion, we found CXL to be effective in halting the progression of keratoconus and even inducing significant regression in advanced cases. As long as we follow the protocol for the procedure and keep the corneal thickness above $400\,\mu m$ during the UV-A, no case with marked corneal endothelial loss was observed. However, we should pay attention to the occurrence of corneal opacity, especially when treating cases with advanced keratoconus, and further long-term observation is needed.

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