Transepithelial corneal collagen crosslinking for keratoconus: Six-month results

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PURPOSE: To evaluate the safety and efficacy of corneal collagen crosslinking (CXL) using a transepithelial technique to treat keratoconus.

SETTING: Cornea and refractive surgery subspecialty practice.

DESIGN: Prospective clinical trial.

METHODS: Transepithelial CXL was performed in eyes with keratoconus using proparacaine with benzalkonium chloride (BAK) 0.01% to facilitate riboflavin absorption and riboflavin 0.10% without dextran. Eyes were randomized to receive ultraviolet-A treatment (365 nm, 3 mW/cm^2) with concurrent administration of riboflavin randomized to every 1 minute or every 2 minutes for 30 minutes. The principal outcomes included uncorrected (UDVA) and corrected (CDVA) distance visual acuities and topography-derived maximum keratometry (K) values. Patients were followed for 6 months.

RESULTS: Thirty eyes of 25 patients were treated. The mean maximum K value flattened by 0.9 diopter (D) (baseline 58.7 D; 6 months 57.8 D) (P=.01). The maximum K worsened by 2.0 D or more in 1 patient. The mean CDVA improved by 0.83 Snellen lines (P=.03). One patient lost 2 lines of CDVA. There were no differences in the UDVA, CDVA, or keratometry outcomes between the 1-minute instillation subgroup and the 2-minute instillation subgroup.

CONCLUSIONS: Transepithelial CXL resulted in a statistically significant improvement in maximum K values and CDVA at the 6-month follow-up. Further follow-up is necessary to ascertain the ability of transepithelial CXL to achieve long-term stabilization of the cornea in eyes with keratoconus.

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Keratoconus is a noninflammatory process that results in thinning and deformation of the cornea.[1] The cornea progressively distorts and loses its optical properties which result in visual impairment from irregular astigmatism, an increase in corneal aberrations, or stromal scarring.[2] The incidence of keratoconus is approximately 1 in 2000.[2] Keratoconus progresses between the second and fifth decades of life and may ultimately require corneal transplantation in 10% to 20% of cases.[3] It is the second most frequent indication for corneal transplantation, accounting for 18.1% of such procedures performed in the United States in 2012.[A] Other surgical treatments for patients with keratoconus include intrastromal corneal ring segment implantation, conductive keratoplasty,[4] and corneal collagen crosslinking (CXL).[5]

Collagen crosslinking is a promising treatment that may slow or stop the progression of keratoconus[5] and post-laser in situ keratomileusis (LASIK) ectasia.[6] Moreover, CXL may decrease the steepness of the cone and improve uncorrected (UDVA) and corrected (CDVA) distance visual acuities as well as subjective visual symptoms in some cases.[7–10]

As originally reported[5,11] as well as subsequently, most published trials of CXL used the standard technique in which the central corneal epithelium is first removed to allow maximum penetration of riboflavin into the corneal stroma. In transepithelial CXL, the

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corneal epithelium is not removed. This method offers possible advantages over traditional CXL. It may increase the safety profile by reducing the risk for infection and improve postoperative patient comfort. In addition, the lack of an epithelial defect may offer faster visual recovery, including a possible return to contact lens wear sooner.

The primary objective of this study was to evaluate the safety and efficacy of transepithelial corneal CXL performed with riboflavin 0.1% solution without dextran, proparacaine with benzalkonium chloride (BAK), and ultraviolet-A (UVA) crosslinking to reduce corneal curvature. In addition, we evaluated 2 riboflavin-dosing regimens to determine whether there were differences in outcomes.

PATIENTS AND METHODS

Patients with keratoconus were enrolled as part of a prospective randomized controlled clinical trial under a physician-sponsored Investigational New Drug.[B] This study was approved and monitored by an investigational review board, was compliant with the U.S. Health Insurance Portability and Accountability Act, and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from each patient before any required study procedure was performed.

Patients with a history of keratoconus or post-refractive corneal ectasia were evaluated for suitability and had the required screening procedures to determine study eligibility. The inclusion criteria included 18 years of age or older, a diagnosis of keratoconus or of corneal ectasia after corneal refractive surgery, a CDVA worse than 20/20, central or inferior steepening on a rotating Scheimpflug camera map (Pentacam, Oculus Optikgeräte GmbH), axial topography consistent with keratoconus or postoperative corneal ectasia, removal of contact lenses for 1 week before the screening refraction, and willingness and ability to comply with scheduled follow-up visits. In this report, only keratoconus patients are included.

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Each patient was randomized to administration of riboflavin every 1 minute or every 2 minutes for the duration of UVA exposure. Safety monitoring throughout the study included observations at appropriate times for subjective complaints, complications, adverse events, and clinically significant findings on ophthalmic examination.

The exclusion criteria included eyes classified as normal, atypical normal, or keratoconus suspect on the severity grading scheme; corneal pachymetry less than 350 μm at the thinnest point measured by the rotating Scheimpflug camera in the eye(s) to be treated; previous ocular condition that may predispose the eye to future complications (eg, herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, corneal dystrophy); clinically significant corneal scarring in the CXL treatment zone; history of chemical injury or delayed epithelial healing; pregnancy (including plan to become pregnant) or lactation during the course of the study; a known sensitivity to study medications; nystagmus or any other condition that would prevent a steady gaze during the CXL treatment or other diagnostic tests; and a current condition that, in the investigator's opinion, would interfere with or prolong epithelial healing.

Surgical Technique

On the day of surgery, each patient received proparacaine containing BAK 0.01% (Bausch & Lomb) every 5 minutes for 30 minutes with the goal of enhancing permeability of the epithelium to facilitate riboflavin absorption into the corneal stroma. Subsequently, riboflavin 0.10% in sterile water (Medio Cross hypotonic, Peschke GmbH) was administered every 2 minutes for 30 minutes with proparacaine–BAK 0.01% continued every 10 minutes, initially for 30 minutes. The patient was examined at the slitlamp, and this regimen was continued if complete saturation of riboflavin into the stroma had not been achieved. In some cases, if poor penetration was noted, a cellulose-sponge pledget soaked in riboflavin was placed on the cornea for 15 minutes with continued riboflavin administration every 2 minutes. Riboflavin dosing was continued until the investigator verified complete penetration of riboflavin through the corneal stroma on slitlamp examination (Figures 1 and 2). The cornea was exposed to UVA 365 nm light (UV-X system, IROC Innocross AG) for 30 minutes at an irradiance of 3.0 mW/cm^2, for a total dose of 5.4 J. Riboflavin drops were continued during the UVA treatment according to the randomization. In the 2-minute subgroup, riboflavin was applied to the cornea every 2 minutes. In the 1-minute subgroup, riboflavin was applied to the cornea every 1 minute. In both subgroups, proparacaine–BAK 0.01% was administered every 5 minutes for the duration of the UVA exposure. After the treatment, gatifloxacin (Zymaxid) and prednisolone acetate 1.0% (Pred Forte) were administered. Postoperatively, patients were prescribed gatifloxacin 4 times a day for 7 days, prednisolone acetate 1.0% 4 times a day for 2 weeks, and preservative-free artificial tears as needed.

Patient Assessment

Patients had complete examinations at baseline; on the day of treatment; and 1 day, 1 week, and 1, 3, 6, and 12 months after treatment. The 6-month results are presented here.

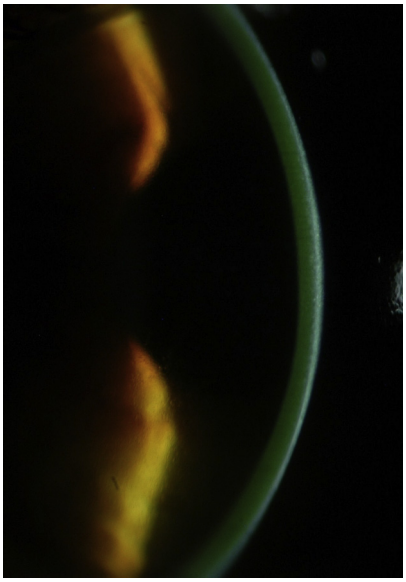

Figure 1. Transepithelial CXL immediately after riboflavin administration. Note good uptake into corneal stroma.

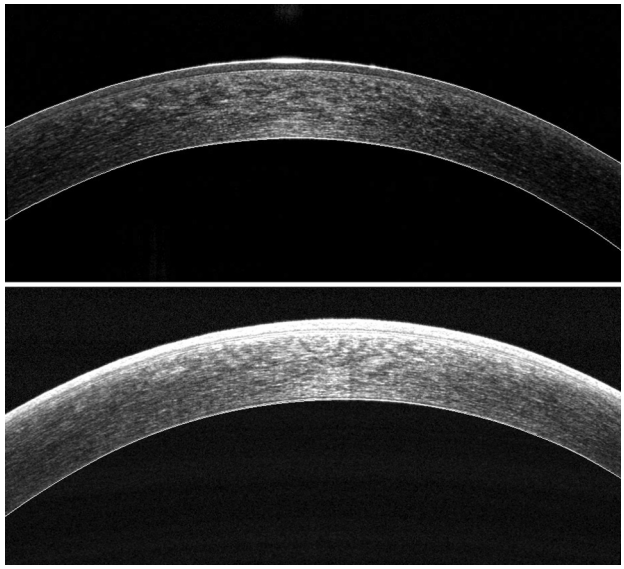

Figure 2. *Top*: Preoperative optical coherence tomography (OCT). *Bottom*: Postoperative OCT. Note good riboflavin uptake and hyperreflectivity of crosslinked tissue in the anterior stroma.

Outcome Measures

Visual Acuity The UDVA and CDVA were measured preoperatively and postoperatively at 1, 3, and 6 months. Visual acuity measurements were obtained under controlled lighting conditions using a modified Lighthouse Early Treatment Diabetic Retinopathy Study visual acuity test (2nd edition) with Sloan letters. Patients were tested 4 m from the visual acuity chart. If patients could not read any letters at 4 m, they were tested at 2 m. Visual acuity was recorded and analyzed as the logMAR value.

Topography Topography measurements were obtained using a rotating Scheimpflug camera (Pentacam). The Scheimpflug system generates a 3-dimensional model of the cornea and anterior segment. Topographic data were obtained preoperatively and 1, 3, and 6 months postoperatively. Maximum keratometry (K) and mean K values were recorded from the topography data generated by the Scheimpflug system.

Statistical Analysis

Statistical analysis was performed using PASW software (version 21, SPSS, Inc.). Three groups were analyzed as follows: the entire cohort, the 2-minute subgroup, and the 1-minute subgroup. A paired 2-tailed Student t test was used to compare the postoperative outcomes with the baseline values. For the primary outcome of the change in maximum K, power calculation showed that with a power of 0.8, α of 0.05, and standard deviation of 1.71, a difference of 1.3 D could be detected. An independent t test was used to compare baseline data and outcomes data between the 2-minute subgroup and the 1-minute subgroup at 6 months postoperatively. A P value less than 0.05 was used to determine statistical significance.

RESULTS

Thirty eyes of 25 patients (22 men) had transepithelial CXL and were followed for 6 months. The mean age of the patients was 31.8 years (range 18 to 58 years). The 2-minute subgroup comprised 12 eyes and the 1-minute subgroup, 18 eyes. No infections or other adverse reactions to treatment were recorded.

Visual Acuity Changes

Uncorrected Distance Visual Acuity Table 1 and Figure 3 show the UDVA over time. Although the mean UDVA improved from preoperatively to 6 months postoperatively in all patients, the change was not statistically significant (mean change −0.08 logMAR; $P=.114$). The UDVA improved by 2 or more Snellen lines in 11 eyes (36.7%); 5 eyes (16.7%) lost 2 or more Snellen lines of UDVA.

Corrected Distance Visual Acuity Table 1 and Figure 4 show the CDVA over time. The improvement in mean CDVA from preoperatively to 6 months postoperatively was statistically significant (mean change −0.08 logMAR; $P=.032$). The CDVA improved by 2 or more Snellen lines in 7 eyes (23.3%); 1 eye (3.3%) lost 2 Snellen lines of CDVA.

Topography

Table 2 shows the postoperative topographic measurements.

Maximum Keratometry There was a statistically significant decrease in the mean maximum K value

Table 1. Postoperative visual acuity in all eyes, the 1-minute subgroup, and the 2-minute subgroup.

Acuity/Group	Preop	Postop			*P* Value*	
		1 Month	3 Months	6 Months	Preop	Change, Baseline to 6 Months
UDVA					.102	.845
All eyes						
Mean logMAR ± SD	0.88 ± 0.41	0.79 ± 0.41†	0.79 ± 0.42	0.80 ± 0.40		
Snellen equivalent	20/153	20/122	20/124	20/127		
1-minute						
Mean logMAR ± SD	0.98 ± 0.39	0.91 ± 0.42	0.87 ± 0.40	0.91 ± 0.38		
Snellen equivalent	20/192	20/161	20/149	20/163		
2-minute						
Mean logMAR ± SD	0.73 ± 0.40	0.61 ± 0.33†	0.68 ± 0.42	0.64 ± 0.39		
Snellen equivalent	20/108	20/81	20/95	20/88		
CDVA					.386	.572
All eyes						
Mean logMAR ± SD	0.31 ± 0.23	0.28 ± 0.21	0.28 ± 0.25	0.23 ± 0.17†		
Snellen equivalent	20/41	20/38	20/38	20/34		
1-minute						
Mean logMAR ± SD	0.28 ± 0.18	0.24 ± 0.22	0.30 ± 0.30	0.22 ± 0.19†		
Snellen equivalent	20/38	20/35	20/40	20/33		
2-minute						
Mean logMAR ± SD	0.36 ± 0.30	0.33 ± 0.19	0.25 ± 0.17	0.25 ± 0.16		
Snellen equivalent	20/46	20/43	20/36	20/36		

CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity
*1 minute vs 2 minutes
†Significant change compared with preoperative baseline measurements

(−0.86 ± 1.71 D) from baseline to 6 months postoperatively (P=.010) (Figure 5). The maximum K decreased by 2.00 D or more in 6 eyes (20.0%), remained unchanged in 19 eyes (63.3%), and increased by 2.00 D or more in 1 eye (3.3%) (Figure 5).

Mean Keratometry The mean K decreased by −0.15 ± 1.21 D between baseline and 6 months postoperatively; however, the change was not statistically significant (P=.511) (Figure 6). The mean K value decreased by 2.00 D or more in 2 eyes (6.7%) and remained unchanged in 24 eyes (80.0%). It increased by 2.00 D or more in 1 eye (3.3%) (Figure 6). Of note, this occurred in the same patient who had an increase in the maximum K value of more than 2.00 D.

Comparison Between 1-Minute and 2-Minute Subgroups

There were no statistically significant differences in the baseline UDVA, CDVA, maximum K, or mean K between the subgroups (P=.102, P=.386, P=.072, and P=.560, respectively) (Tables 1 and 2). Similarly, there were no statistically significant differences in the changes in UDVA, CDVA, maximum K, or mean K between the subgroups 6 months after transepithelial CXL (P=.845, P=.572, P=.119, and P=.665, respectively) (Tables 1 and 2).

DISCUSSION

Collagen crosslinking is a promising treatment that may slow or stop the progression of keratoconus[5] and post-LASIK ectasia.[6] In addition, CXL may decrease the steepness of the cone and improve UDVA and CDVA in some cases. In transepithelial CXL, the corneal epithelium is not removed. This offers several potential advantages over traditional CXL; these include a reduced risk for infection, improved patient comfort in the early postoperative healing period, faster visual recovery, and an earlier return to contact lens wear. In addition, maintenance of the epithelium may decrease corneal thinning during the CXL procedure and allow treatment of more severe disease in cases in which corneal thickness may otherwise preclude treatment. Finally, maintenance of the epithelium may decrease corneal stromal haze postoperatively.[12,13]

In this randomized controlled clinical trial, the early outcomes of transepithelial CXL were analyzed. This study is one of the largest prospectively analyzed transepithelial treatment groups to date. In addition,

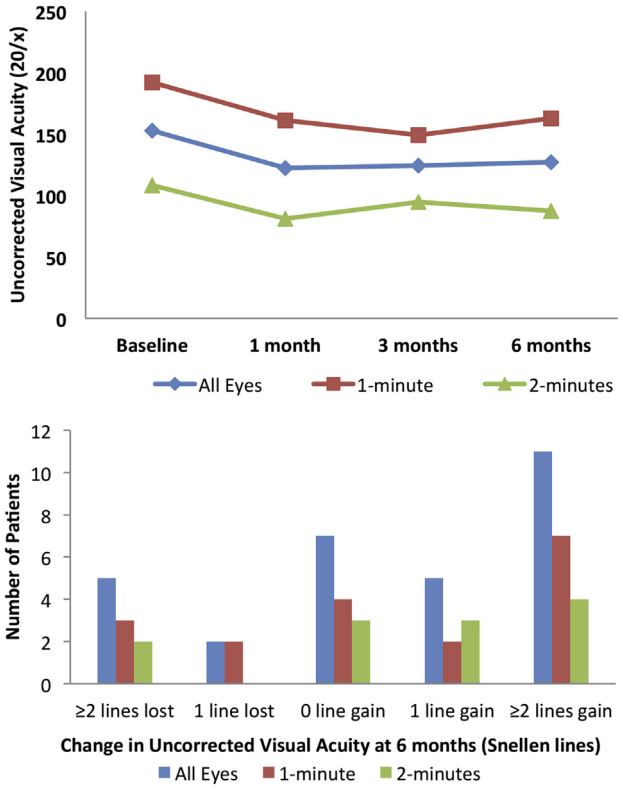

Figure 3. Change in UDVA over time and change in UDVA Snellen lines between baseline and 6 months postoperatively.

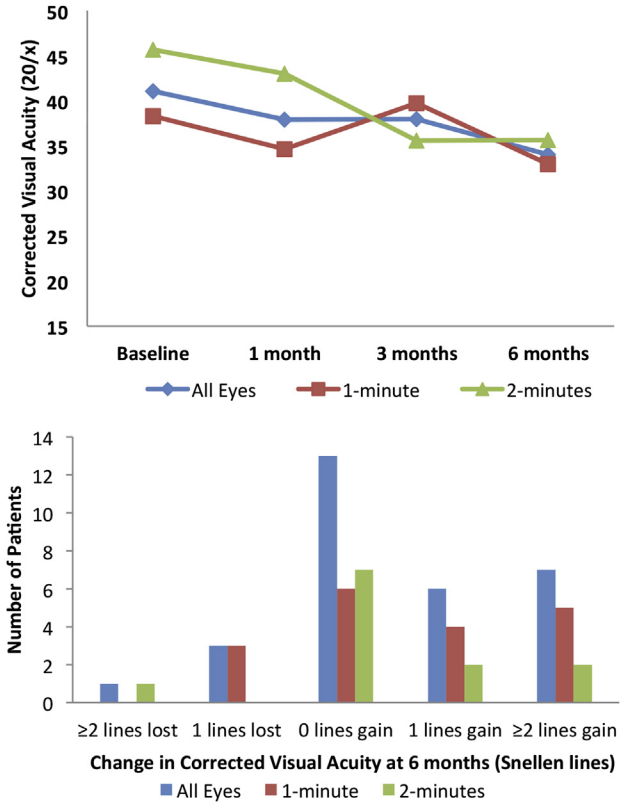

Figure 4. Change in CDVA over time and change in CDVA Snellen lines between baseline and 6 months postoperatively.

2 riboflavin-dosing regimens (1-minute or 2-minute administration during UVA treatment) were assessed to ascertain whether the dosing regimen influences the procedure outcomes.

There are several theoretical and practical hurdles that suggest transepithelial CXL would not be as effective in strengthening the cornea as CXL performed with epithelial removal. First, it is difficult for the large hydrophilic molecule of riboflavin to penetrate the lipophilic epithelium for diffusion into the corneal stroma. Next, both the epithelium and the riboflavin within the epithelial layer may absorb

Table 2. Postoperative topographic measurements by Scheimpflug imaging.

	Mean (D) ± SD					
		Postop			*P* Value*	
Parameter/Group	Preop	1 Month	3 Months	6 Months	Preop	Change, Baseline to 6 Months
Maximum K					.072	.119
All eyes	58.69 ± 7.80	57.99 ± 7.41	57.81 ± 7.47†	57.83 ± 6.98†		
1-minute	56.60 ± 7.45	56.17 ± 7.94	55.76 ± 7.09	56.14 ± 6.99		
2-minute	61.82 ± 7.54	60.72 ± 5.82	60.89 ± 7.21	60.36 ± 6.43†		
Mean K					.56	.665
All eyes	48.19 ± 5.14	48.01 ± 4.62	47.92 ± 4.57	48.04 ± 4.36		
1-minute	47.73 ± 4.96	47.53 ± 4.61	47.56 ± 4.30	47.67 ± 4.55		
2-minute	48.88 ± 5.54	48.73 ± 4.73	48.48 ± 5.10	48.61 ± 4.20		

K = keratometry
*1 minute vs 2 minutes
†Significant change compared with preoperative baseline measurements

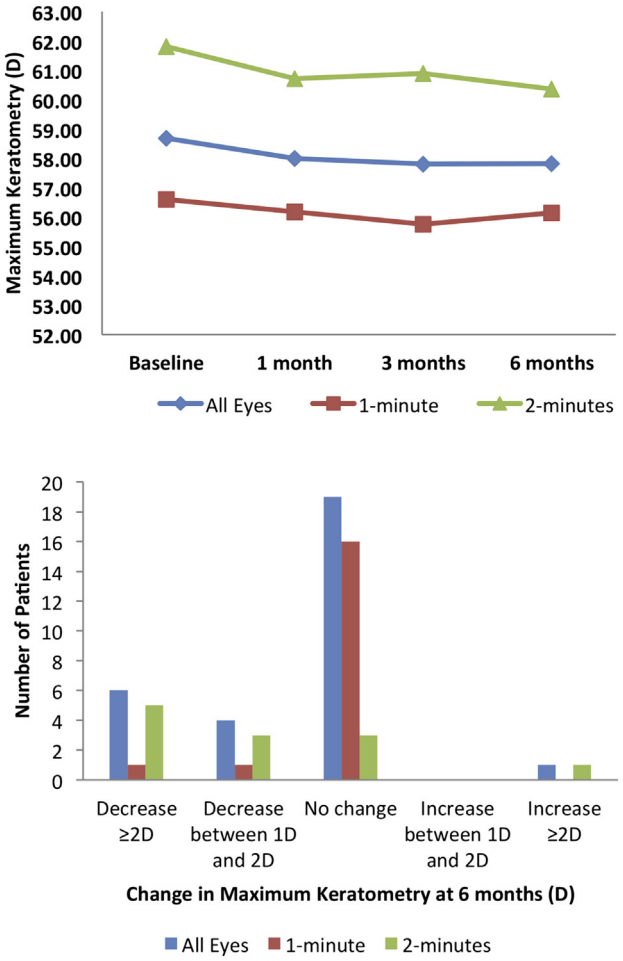

Figure 5. Change in maximum K over time and change in maximum K between baseline and 6 months postoperatively.

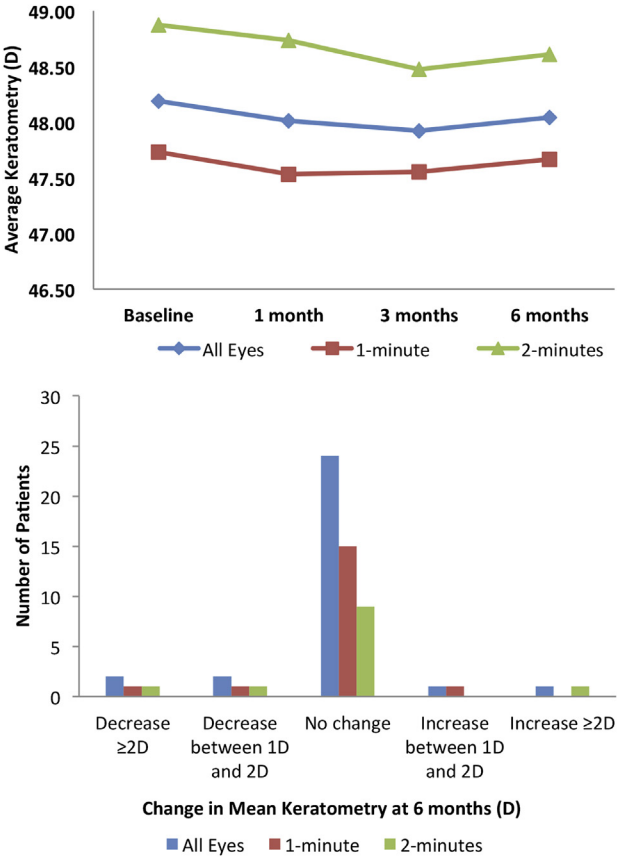

Figure 6. Change in mean K over time and change in mean K between baseline and 6 months postoperatively.

the incident UVA light and attenuate the UVA power in the corneal stroma. Thus, the actual crosslinking effect may be less deep and less complete at all levels compared to what occurs with equivalent dosing with the epithelium removed. Indeed, there is evidence that cytotoxic keratocyte damage is restricted to a 200 mm stromal depth.[12,13] Furthermore, the epithelium also acts as a barrier to oxygen diffusion to the stroma, which may limit the crosslinking that occurs through oxygen-dependent pathways.[14] Finally, the role of wound healing in the ultimate clinical effect of the procedure is unclear. In the standard CXL procedure, there is a typical corneal stromal haze and demarcation line that follows a generally consistent time course, peaking at 1 month through 3 months and diminishing over the course of a year.[15] Such haze is not generally seen in the transepithelial procedure. Whether this finding is a proxy for effective crosslinking, contributes to the actual clinical effect, or is simply an unwanted side effect remains to be seen.

With regard to stromal uptake of riboflavin, dextran has been included in most riboflavin formulations used clinically to date based on its efficacy in the standard CXL procedure with the epithelium removed. However, laboratory and clinical studies suggest that the inclusion of dextran in the riboflavin solution diminishes its ability to penetrate the epithelium. In a study of rabbit eyes,[12] the transepithelial crosslinking result was less efficacious than the result with the standard CXL procedure using riboflavin in dextran T500 solution. In other laboratory research using riboflavin in dextran solution,[16,17] stromal concentrations of riboflavin failed to reach quantities believed to be sufficient for a substantial CXL effect. Studies[18,19] have shown that removal of dextran from the riboflavin solution seems to facilitate penetration through the epithelium.

Furthermore, adjunctive agents have been shown to enhance the permeability of riboflavin through the epithelium. Benzalkonium chloride has been shown to increase epithelial permeability.[20–23] Similarly,

ethylenediaminetetraacetic acid (EDTA) has been shown to increase permeability to hydrophilic molecules such as riboflavin.[24,25] These modifications to the original CXL protocol seem to militate a more robust stromal diffusion and ultimate effect of the transepithelial CXL procedure.[19,25,26]

To date, published clinical results of transepithelial CXL efficacy have been mixed. However, the studies were not uniform in their design, specifically in the use of different riboflavin formulations and adjunctive agents. Caporossi et al.[24] used isotonic riboflavin with dextran, EDTA, and trometamol and reported initial improvement in UDVA and CDVA but a subsequent return to baseline and worsening of the maximum K value at 24 months of follow-up. Koppen et al.[27] used isotonic riboflavin with dextran and BAK and found a statistically significant improvement in CDVA at 6 months and 12 months and stable Placido disk topography; however, there was statistically significant worsening of the maximum K value on Scheimpflug imaging. Filippello et al.[25] used isotonic riboflavin with dextran, EDTA, and trometamol and found statistically significant improvement in UDVA, CDVA, and all topographic-derived values. Stojanovic et al.[19] used hypotonic riboflavin without dextran, increased the concentration of riboflavin to 0.5%, used BAK, and used mechanical disruption of the superficial epithelium. They report a statistically significant improvement in the UDVA, CDVA, and maximum K value. Salman[28] used isotonic riboflavin with dextran, EDTA, BAK, and trometamol and found a statistically significant improvement in UDVA and the maximum K value in a pediatric population. Leccisotti and Islam[29] used isotonic riboflavin with dextran, BAK, and EDTA and observed a statistically significant improvement in the CDVA and mean K value. Rechichi et al.[30] used a corneal disruptor device to create pockmarks in the epithelium, hypotonic riboflavin 0.1%, and the enhancers trometamol and sodium EDTA. They found a statistically significant improvement in UDVA and CDVA by 3 months, 6 months, and 12 months. There was a significant difference in the mean preoperative 3.0 mm, mean simulated K value, and steepest simulated K value between preoperatively and 12 months postoperatively.

In our study, we used riboflavin 0.1% solution without dextran and adjunctive administration of proparacaine with BAK to increase the permeability of the epithelium. Riboflavin penetration was good in all cases, with the time to complete penetration ranging from 30 to 80 minutes. Although this study has a follow-up of only 6 months, precluding analysis of the long-term stabilization effect of transepithelial CXL, we did find improvements in the visual acuity and topography-derived maximum K value.

The mean improvement in UDVA 6 months postoperatively was 0.8 Snellen lines; however, this was not statistically significant. The finding is consistent with results in other transepithelial CXL studies. Stojanovic et al.[19] reported significant improvement in UDVA at 12 months. Filippello et al.[25] reported significant improvement in UDVA throughout the 18-month follow-up. Rechichi et al.[30] found a statistically significant improvement in UDVA at 3 months, 6 months, and 12 months. Salman[28] observed significant improvement in UDVA at 1 year in a pediatric age group.

The mean improvement in CDVA at 6 months was 0.83 Snellen lines, a statistically significant result. This is consistent with results reported by Stojanovic et al.,[19] Filippello et al.,[25] Koppen et al.,[27] Leccisotti and Islam,[29] and Rechichi et al.[30] The CDVA improved by 2 or more Snellen lines in 7 eyes (23.3%), improved by 1 line in 6 eyes (20.0%), remained the same in 13 eyes (43.3%), worsened by 1 line in 3 eyes (10%), and worsened by 2 lines in 1 eye (3.3%). The patient who lost 2 Snellen lines of CDVA was a 27-year-old man who at baseline had a UDVA of 20/40, a CDVA of 20/25, and a maximum K value of 60.7 D. At 6 months, he was noted to have central superficial punctate keratopathy and the UDVA was 20/125, the CDVA was 20/40, and the maximum K value had increased slightly to 61.1 D.

As the key topographic indicator of the success of treatment, the maximum K value decreased significantly (by a mean of 0.86 D) over the course of 6 months. These results are again consistent with previously published data by Stojanovic et al.,[19] Filippello et al.,[25] Salman,[28] and Rechichi et al.[30] More specifically, in our study, the maximum K value decreased by more than 2.0 D in 6 eyes (20.0%), decreased between 1.0 D and 2.0 D in 4 eyes (13.3%), remained unchanged in 19 eyes (63.3%), increased by 1.0 to 2.0 D in 0 eyes, and increased by more than 2.0 D in 1 eye (3.3%). The patient with a more than 2.0 D increase in maximum K was a 39-year-old woman with a peripheral cone. At baseline, the UDVA was 20/400, the CDVA was 20/32, and the maximum K value was 55.9 D. At 6 months, the visual acuities were unchanged; however, the maximum K value had increased to 58.7 D. This may be explained in part by our findings in a previous study[31] in which there was more topographic flattening after CXL in centrally located cones and less flattening in cones located peripherally.

Statistical analysis showed no significant differences in the changes in UDVA, CDVA, or the mean and maximum K values between eyes randomized to riboflavin administration every 1 minute and eyes randomized to riboflavin administration every 2 minutes.

It is of interest to compare our transepithelial CXL results with the clinical results of standard CXL with removal of the epithelium. In our previous study of CXL outcomes,[7] patients with keratoconus had an improvement in UDVA and CDVA (mean change from 20/150 to 20/133 and from 20/49 to 20/36, respectively) from baseline to 1 year postoperatively. In the current transepithelial CXL study, the mean improvement in UDVA was from 20/153 at baseline to 20/127 at 6 months and the mean improvement in CDVA was from 20/41 to 20/34. In our previous study of standard CXL analyzed at the 6-month follow-up, the mean UDVA improved from 20/150 at baseline to 20/144 at 6 months and the mean CDVA improved from 20/49 to 20/36. In the current study, the topography-derived maximum K value flattened by a mean of 0.9 D. Our previous study of standard CXL found flattening of 2.0 D at 1 year and of 1.3 D at 6 months in the keratoconic population. Thus, in this study, the effect of transepithelial CXL on the clinical outcomes of cone flattening seems somewhat less than for standard CXL at 6 months, although there was little difference in the visual acuity outcomes.

A limitation of this study is the lack of a control group or treatment group with epithelial removal. Moreover, the study had a relatively short follow-up. Longer term follow-up is essential to determine the relative impact of the 2 procedures on the ultimate stabilization of the disease process, and further controlled clinical trials evaluating the 2 procedures are necessary to determine the relative risks and benefits of each. The study reported here is ongoing, and 12-month follow-up results will be reported in a future paper.

WHAT WAS KNOWN

- There are several theoretical hurdles that suggest that transepithelial CXL would not be as effective in strengthening the cornea as CXL performed with epithelial removal.
- Published clinical results of transepithelial CXL have been mixed; however, the studies were not uniform in their design.

WHAT THIS PAPER ADDS

- There was statistically significant flattening of the cornea after transepithelial CXL, but less than that of standard CXL.
- The mean CDVA improved after transepithelial CXL.
- Longer term follow-up and randomized controlled trials of transepithelial CXL and standard CXL are necessary to compare long-term corneal stabilization effects.

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