ARTICLE

Corneal crosslinking without epithelial removal

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Purpose: To evaluate the effect of riboflavin–ultraviolet (UV)-A corneal crosslinking (CXL) without epithelial removal on ectatic corneal disease.

Setting: Woolfson Eye Institute, Atlanta, Georgia, USA.

Design: Prospective observational study.

Methods: Patients were treated with a new riboflavin formulation without epithelial removal, then exposed to UV light (365 nm) at 4 mW/cm^2 with on-off cycling for 30 minutes. Uncorrected (UDVA) and corrected (CDVA) distance visual acuities, maximum corneal curvature (maximum keratometry [Kmax]), total higher-order aberrations (HOAs), and coma were measured at 3, 6, 12, and 24 months postoperatively. Progression was defined as an increase of more than 1 diopter (D) in Kmax and loss of more than 1 line of CDVA.

Results: Five hundred twelve eyes of 308 patients with keratoconus or forme fruste keratoconus and 80 eyes of 55 patients with ectasia after laser in situ keratomileusis (LASIK) were treated with the new riboflavin formulation without epithelial removal; 229 patients received bilateral treatments, 95 of which were simultaneous. The mean UDVA and CDVA improved by 1 to 1.5 Snellen lines at 1 and 2 years postoperatively ($P < .0001$). Mean Kmax decreased by 0.48 D at 2 years postoperatively ($P = .0002$). Mean total HOAs and coma decreased by 36% ($P < .0001$) and 37% ($P = .0002$), respectively, at 2 years postoperatively. Kmax decreased more than 1 D in three times as many eyes as it increased more than 1 D ($P < .0001$). No eyes progressed, and there was no loss of effect between 1 and 2 years postoperatively. No vision-threatening events were observed. Pain typically resolved within 24 hours, and visual acuity returned to preoperative levels in 1 to 2 days.

Conclusion: Epithelium-on CXL using this new protocol halted the progression of keratoconus and ectasia after LASIK. It was safer and provided more rapid visual recovery than CXL with epithelial removal, allowing routine bilateral, simultaneous treatment.

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Corneal crosslinking (CXL) was first described for the treatment of keratoconus in 2003.[1] Lack of permeability of the corneal epithelium to riboflavin formulations available at the time led to the removal of corneal epithelium as part of the original Dresden protocol for CXL.

Closure of the epithelial defect after epithelium-off (epi-off) CXL has been reported to require a mean of 3.24 days ± 1.4 (SD)[2] and 5.09 ± 0.77[3] days. Delayed epithelial closure (beyond 5 days) has been reported in 3.5% of eyes with epi-off CXL, and complete healing required more than 10 days in 0.8% of eyes.[3]

Epi-off CXL causes severe pain, which persists for up to 1 week after treatment and leads to corneal haze or scarring, affecting up to 99% of eyes.[2–6] Regrowth and hypertrophy of the epithelium prevents return of preoperative visual acuity for weeks to months after treatment.[3]

Removal of the corneal epithelium can lead to sterile infiltrates that are seen in up to 7.6% of eyes[2–4,7–9] and cause visually significant corneal scarring in 2.9% of eyes.[2]

There are also multiple published reports of infectious keratitis after epi-off CXL because of gram-positive bacteria,[10–15] gram-negative bacteria,[15–17] fungi,[15,18] herpes simplex virus,[15,19,20] Acanthamoeba,[15,21] and even microsporidia.[22] The incidence of infectious keratitis has been reported to be 0.3%[3] in one study and 1.3% in another.[23] It can lead to corneal perforation with severe visual loss and the need for corneal transplantation.[10,18,21,23] Even partial disruption of the epithelium has led to significant complications.[24]

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Past investigators, seeking a less invasive treatment, have sought to saturate the corneal stroma with riboflavin without epithelial removal by the inclusion of preservatives, ethylenediaminetetraacetic acid, tris(hydroxymethyl)aminomethane, partial epithelial disruption and iontophoresis.[25] However, after initial enthusiastic reports, long-term follow-up showed loss of effect between 1 and 2 years after epithelium-on (epi-on) CXL using a commercially available transepithelial riboflavin formulation.[26,27] More recently, successful epi-on CXL with a riboflavin solution containing vitamin E has been reported but not confirmed.[28]

We now report 2-year results of corneal CXL using a new system that does not require epithelial removal.

PATIENTS AND METHODS

Patients

The participants in this clinical trial were enrolled in a physician-sponsored study approved and monitored by Quorum IRB (Seattle Washington; CT01024322) and registered with clinicaltrials.gov (NCT01956474). Eyes were included if they had a clinical diagnosis of keratoconus, form fruste keratoconus, or ectasia after LASIK, and the minimum corneal thickness measured by a Scheimpflug corneal tomographer (Pentacam, Oculus, Inc.) was at least 300 μm. Eyes with other significant anterior or posterior segment pathology were excluded. Mild to moderate apical scarring was allowed. Bilateral simultaneous treatments were permitted.

Examination Procedures

After informed consent was obtained, the patients had a complete eye examination, including measurement of uncorrected (UDVA) and corrected (CDVA) distance visual acuities (Snellen) after manifest refraction by an experienced refractionist, as well as testing with a Scheimpflug corneal tomographer and a wavefront aberrometer (iTrace, Tracey Technologies).

Treatment Protocol

For treatment, the patients were seated at a slitlamp and, after instillation of proparacaine, the corneal epithelium was gently brushed for approximately 15 seconds with a specially designed, patent-pending, sterile sponge (CXL Ophthalmics LLC) hydrated with proparacaine to increase epithelial permeability without disrupting the epithelium.[29]

With the patient in the supine position and a speculum inserted, one drop of a proprietary transepithelial riboflavin formulation was then applied every 2 minutes by saturating the specially designed, flexible, sterile sponge placed on the cornea.[29] This proprietary, sterile sponge-loading device has a unique shape, material, and pore size designed to maximize contact of the riboflavin solution with the cornea and increase penetration of riboflavin into the corneal stroma without creating epithelial defects.

The riboflavin formulation did not contain dextran. It was optimized at a specific concentration, pH, and osmolarity to enhance absorption and it contained sodium iodide, which acted as an excipient. After 15 to 20 minutes, the patients were evaluated at the slitlamp with both white and cobalt blue light, and the amount of riboflavin in the corneal stroma was estimated by comparison to standardized photographs that had been calibrated via animal studies to permit estimation of the stromal riboflavin concentration.[29] If the stromal riboflavin concentration was not adequate ($>\sim$15 μg/gm)[29] or saturation was not uniform, saturation time was extended. Most eyes were sufficiently saturated in 15 minutes, and over 95% were saturated in less than 30 minutes.

Eyes were rinsed briefly with a balanced salt solution to remove riboflavin from the surface of the cornea. The patients were then exposed to ultraviolet (UV) light (365 nm) at 4 mW/cm^2 cycled off and on for 30 minutes using a proprietary light (CXL Ophthalmics LLC) without additional application of riboflavin. Hydration of the cornea was maintained during UV light exposure with artificial tears.

A fluoroquinolone antibiotic and prednisolone acetate 1% were prescribed four times a day for 1 week postoperatively.

Outcome Measures

Examinations were performed at 1 day, 1 week, 1 month, and 3, 6, 12, and 24 months postoperatively. Patients were allowed to resume contact lens wear 1 week after treatment. Soft and scleral contact lenses were removed at least 3 days before, and rigid gas-permeable lenses were removed at least 2 weeks before all examinations. Outcome measures were UDVA, CDVA, maximum keratometry (Kmax) measured by the Scheimpflug corneal tomographer, total higher-order aberrations (HOAs) and coma (measured by a wavefront aberrometer). Progression after treatment was defined as an increase of more than 1 D (diopter) Kmax and a loss of more than 1 line of CDVA in the same eye.

The 12-month and 24-month data analyses included only eyes with preoperative and 12-month or 24-month examinations, respectively. Trends over time were studied using the consistent cohort (eyes with preoperative and 3-, 6-, 12-, and 24-month examinations) to avoid artifacts created by analyzing different eyes at different timepoints. Aberrometry was not performed on all patients because the aberrometer was not available at all treatment sites.

Statistical Methods

Snellen acuities were converted to logarithm of the minimum angle of resolution (logMAR) notation. Because the distribution of the logMAR values, Kmax values, total HOAs, and coma values are unknown and have not been studied in detail, tests of the hypothesis that the paired differences were not equal to zero were conducted using the Wilcoxon signed-rank test. For testing the differences in multinomial probabilities (percentage of eyes with Kmax decreases <1 D and increases >1 D), the normal approximation was used in a Student *t* test. Error bars in figures and standard deviation reported in the tables are based on the raw values for each timepoint, rather than the differences between timepoints. Therefore, these error bars and plots should not be used to assess the statistical significance of the true differences in these values between timepoints.

RESULTS

Patients and Demographics

The study comprised 512 eyes of 308 patients with keratoconus or forme fruste keratoconus and 80 eyes of 55 patients with ectasia after LASIK, who underwent epi-on CXL between October 17, 2013 and May 16, 2016, and were followed through February 20, 2017. Table 1 shows the baseline characteristics of the study population. The baseline characteristics of eyes that were examined at 12 months and 24 months postoperatively were not significantly different from those that were not examined at 12 months and 24 months postoperatively.

Overall, 229 patients had bilateral treatment, and 95 of these had simultaneous treatments. Minimum corneal thickness measured by the Scheimpflug corneal tomographer was 302 μm, and there were 58 eyes with a minimum corneal thickness less than 400 μm. Documentation of progression was not required for inclusion in the study;

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Table 1. Preoperative demographics of the study population.

Diagnosis/Parameter	Baseline			
	Eyes (N)	Mean ± SD	Median	Range
Keratoconus				
Sphere (D)	512	−1.71 ± 3.66	−0.75	−18.75, 11.00
Cylinder (D)	512	−3.05 ± 2.17	−2.75	−13.25, 0.75
Axis (°)	512	89.4 ± 44.5	90.0	0, 180
SE (D)	512	−3.24 ± 3.89	−2.25	−19.38, 10.63
UDVA (20/–)	512	385 ± 633	100	20, 2000
LogMAR UDVA	512	0.834 ± 0.599	0.699	0.000, 2.000
CDVA (20/–)	512	57 ± 164	30	15, 2000
LogMAR CDVA	512	0.247 ± 0.290	0.176	−0.125, 2.000
K1 (D)	508	46.20 ± 4.84	45.10	36.30, 66.70
K2 (D)	508	49.96 ± 5.77	48.60	40.50, 72.90
Kave (D)	508	48.08 ± 5.19	46.73	38.65, 68.10
Kmax (D)	508	56.48 ± 8.62	54.80	42.60, 90.90
CT (μm)	508	474.8 ± 54.9	474.0	302, 651
Total HOAs (μm)	308	1.200 ± 1.367	0.760	0.058, 14.257
Coma (μm)	308	0.976 ± 1.240	0.576	0.012, 13.586
Age (y)	512	30.0 ± 9.6	29.0	10, 60
Male sex, n/N (%)	512	389/512 (76.0%)	—	—
Ectasia				
Sphere (D)	80	−0.62 ± 3.27	−0.25	−14.00, 7.00
Cylinder (D)	80	−3.39 ± 2.37	−2.88	−16.00, −0.25
Axis (°)	80	92.1 ± 35.5	90.5	10, 175
SE (D)	80	−2.31 ± 3.25	−1.63	−15.25, 4.88
UDVA (20/–)	80	440 ± 673	150	20, 2000
LogMAR UDVA	80	0.907 ± 0.616	0.875	0.000, 2.000
CDVA (20/–)	80	51 ± 82	30	20, 400
LogMAR CDVA	80	0.232 ± 0.290	0.176	0.000, 1.301
K1 (D)	80	43.30 ± 5.37	42.30	30.70, 57.30
K2 (D)	80	46.84 ± 5.58	45.55	36.70, 68.00
Kave (D)	80	45.15 ± 5.37	44.05	33.70, 62.65
Kmax (D)	80	54.01 ± 6.86	53.35	43.80, 72.90
CT (μm)	80	453.9 ± 62.9	457.5	305, 603
Total HOAs (μm)	59	0.793 ± 0.887	0.588	0.041, 5.105
Coma (μm)	59	0.573 ± 0.676	0.381	0.006, 3.316
Age (y)	80	45.1 ± 8.8	45.0	29, 66
Male sex, n/N (%)	80	49/80 (61.2%)	—	—

CDVA = corrected distance visual acuity; CT = minimum corneal thickness; HOAs = higher-order aberrations; K1 = flat keratometry; K2 = steep keratometry; Kave = average keratometry; Kmax = maximum keratometry; LogMAR = logarithm of the minimum angle of resolution; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

however, progression was documented by medical history in 283 (92%) patients and by progressive increase in myopic spherical equivalent (>1 D), cylinder (>1 D), or Kmax (>1 D) in the previous 2 years in 172 (56%) patients with keratoconus or forme fruste keratoconus.

Efficacy

At 12 months and 24 months, there were significant improvements in UDVA, CDVA, Kmax, coma, and HOAs (Tables 2 and 3). At 12 months, 31 eyes gained more than 2 lines of CDVA, whereas only 4 eyes lost more than 2 lines (Table 4). At 24 months, 18 eyes gained more than 2 lines of CDVA, whereas only 1 eye lost more than 2 lines of CDVA (Table 4). The consistent cohort (115 patients with examinations at all timepoints) showed initial improvement in UDVA, CDVA, and Kmax and no regression from 1 to 2 years after treatment (Figures 1 and 2).

Because keratoconus in pediatric patients has been found to progress more rapidly than in adults,[30,31] outcomes of pediatric subjects (18 years of age or younger) were evaluated. At 12 months, there was a significant improvement in UDVA, CDVA, HOAs, and coma (n = 26) (Table 5). Although the cohort was small at 24 months, there was an improvement in all outcome parameters, and statistical significance was reached for CDVA (n = 12) (Table 6). Figures 3 and 4 show UDVA, CDVA, and Kmax for the pediatric consistent cohort (n = 11). After an initial improvement in UDVA and Kmax, there was some regression (20/105 to 20/136 and 56.16 to 56.41, respectively); however, neither of these measures returned to pretreatment values, and no eyes met the criteria for progression. Corrected distance visual acuity (likely

Table 2. Outcomes of epithelium-on corneal crosslinking at 12 months in all eyes (N = 341).

Parameter	Preop Value	Postop Value	Change	*P* Value
UDVA				
LogMAR	0.867	0.719	+1.5 lines	<.0001
Snellen	20/147	20/105		
CDVA				
LogMAR	0.236	0.148	+1 line	<.0001
Snellen	20/34	20/28		
Kmax (D)	55.64	55.19	−0.45	<.0001
Total HOAs (μm)*	1.210	0.874	−28%	<.0001
Coma (μm)*	1.002	0.711	−29%	<.0001

CDVA = corrected distance visual acuity; HOAs = higher-order aberrations; Kmax = maximum keratometry; LogMAR = logarithm of the minimum angle of resolution; UDVA = uncorrected distance visual acuity
*n = 217 eyes at preop and 12-month examinations (aberrometry was not performed on all patients)

Table 3. Outcomes of epithelium-on corneal crosslinking at 24 months in all eyes (N = 133).

Parameter	Preop Value	Postop Value	Change	*P* Value
UDVA				
LogMAR	0.838	0.692	+1.5 lines	<.0001
Snellen	20/138	20/98		
CDVA				
LogMAR	0.258	0.150	+1 line	<.0001
Snellen	20/36	20/28		
Kmax (D)	56.58	56.11	−0.48	.0002
Total HOAs (μm)*	1.453	0.931	−36%	<.0001
Coma (μm)*	1.185	0.747	−37%	.0002

CDVA = corrected distance visual acuity; HOAs = higher-order aberrations; Kmax = maximum keratometry; LogMAR = logarithm of the minimum angle of resolution; UDVA = uncorrected distance visual acuity
*n = 83 eyes at preop and 24-month examinations (aberrometry was not performed on all patients)

the most important outcome metric) continued to improve throughout the study (Figure 3).

Kmax

Kmax increased by more than 1 D in 24 (7.0%) of 341 eyes at 12 months postoperatively; however, Kmax decreased by more than 1 D in 3 times as many eyes (72 [21.1%] of 341) ($P < .0001$) (Figure 5). At 24 months postoperatively, Kmax increased by more than 1 D in 11 (8.3%) of 133 eyes, but decreased by more than 1 D in more than 3 times as many eyes (35 [26.3%] of 133 eyes) ($P < .0001$) (Figure 5). In eyes with an increase of more than 1 D Kmax, there was a mean gain of 0.9 lines of CDVA at 12 months postoperatively and 0.7 lines of CDVA at 24 months postoperatively (Figures 6 and 7). These findings suggest that the increase in Kmax observed in some eyes was a result of random measurement variation rather than progression of disease.

Table 4. Change in lines of CDVA from preoperative examination to 12-month and 24-month examinations.

	Number of Eyes (%)	
Diagnosis/Δ CDVA Lines	12 Months	24 Months
Keratoconus		
<−2	4 (1.4%)	1 (0.9%)
−2	9 (3.0%)	3 (2.6%)
−1	34 (11.5%)	9 (7.8%)
0	83 (28.0%)	32 (27.8%)
1	93 (31.4%)	38 (33.0%)
2	46 (15.5%)	17 (14.8%)
3	9 (3.0%)	8 (7.0%)
4	4 (1.4%)	0 (0%)
5	3 (1.0%)	3 (2.6%)
>5	11 (3.7%)	4 (3.5%)
Ectasia		
<−2	0 (0%)	0 (0%)
−2	1 (2.2%)	1 (5.6%)
−1	6 (13.3%)	2 (11.1%)
0	16 (35.6%)	5 (27.8%)
1	13 (28.9%)	4 (22.2%)
2	5 (11.1%)	3 (16.7%)
3	2 (4.4%)	1 (5.6%)
4	1 (2.2%)	1 (5.6%)
5	0 (%)	0 (0%)
>5	1 (2.2%)	1 (5.6%)

Δ = change in; CDVA = corrected distance visual acuity

Progression after Treatment

Progression after treatment was defined as an increase in Kmax of more than 1 D and loss of more than 1 line of CDVA in the same eye. No patients met these criteria for failure of CXL to halt progression of disease (Figures 6 and 7).

Safety

There were three adverse events after CXL in this study. One eye with advanced ectasia after LASIK

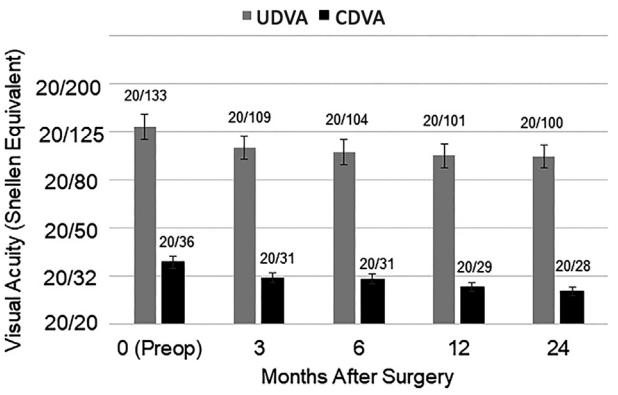

Figure 1. Trend in visual acuities over 24 months after CXL. Columns show UDVA and CDVA obtained at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 115). Error bars represent standard error of the mean (CDVA = corrected distance visual acuity; CXL = corneal crosslinking; UDVA = uncorrected distance visual acuity).

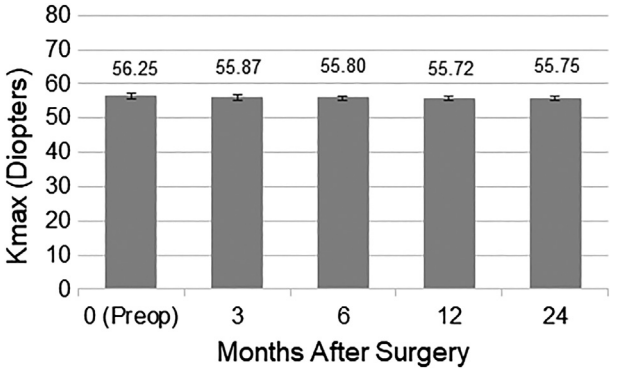

Figure 2. Trend in Kmax over 24 months after CXL. Columns show Kmax measured at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 115). Error bars represent standard error of the mean (CXL = corneal crosslinking; Kmax = maximum keratometry).

(Kmax = 72.8 D and CDVA = 20/400) developed hydrops 23 months after CXL and was treated with keratoplasty. Pathologic examination of the cornea confirmed the presence of a break in Descemet membrane.

Another eye developed corneal edema 15 months after CXL. There were no signs of inflammation to suggest a diagnosis of disciform herpes simplex keratitis; however, this eye was treated with topical prednisolone acetate and oral valcyclovir. The edema resolved, leaving this eye with a UDVA of 20/400, unchanged since the preoperative examination. The CDVA improved from 20/30 preoperatively to 20/20 at 24 months postoperatively, and Kmax decreased 1.5 D from 58.2 D preoperatively to 56.7 D at 24 months postoperatively.

A third patient presented with localized anterior scleritis 1 month after CXL. Treatment with topical and oral steroids resulted in resolution of the inflammation. The UDVA in this eye improved from 20/50 preoperatively to 20/30 at 24 months postoperatively, and the CDVA improved from 20/25 to 20/20 at 24 months postoperatively. Kmax increased 0.6 D from 58.5 D to 59.1 D during the same period.

Thirty (5%) of the 592 eyes presented with small epithelial defects (less than 2.0 mm diameter) on the day after treatment, but almost all resolved by the next day, and no epithelial defects persisted beyond 2 days postoperatively. No corneal scarring was seen in any eyes. There were no sterile infiltrates and no cases of infectious keratitis. Discomfort typically lasted less than 24 hours, and visual acuity returned to preoperative levels in 1 to 2 days. Eyes with keratoconus and those with ectasia had similar outcomes.

Table 6. Outcome of epithelium-on corneal crosslinking for keratoconus in pediatric eyes at 24 months (N = 12).

Parameter	Preop Value	Postop Value	Change	*P* Value
UDVA (Snellen)	20/160	20/120	+0.5 lines	.3750
CDVA (Snellen)	20/46	20/29	+1.5 lines	.0098
Kmax (D)	56.70	56.31	−0.39	.4360
Total HOAs (μm)*	1.096	0.907	−18%	.3828
Coma (μm)*	0.838	0.661	−21%	.3828

CDVA = corrected distance visual acuity; HOAs = higher-order aberrations; Kmax = maximum keratometry; UDVA = uncorrected distance visual acuity
*n = 9 eyes (aberrometry was not performed on all patients)

Table 5. Outcome of epithelium-on corneal crosslinking for keratoconus in pediatric eyes at 12 months (N = 26).

Parameter	Preop Value	Postop Value	Change	*P* Value
UDVA (Snellen)	20/108	20/75	+1 line	.0162
CDVA (Snellen)	20/45	20/27	+1.5 lines	<.0001
Kmax (D)	56.14	55.71	−0.43	.1171
Total HOAs (μm)*	1.281	0.919	−28%	.0289
Coma (μm)*	1.070	0.721	−33%	.0055

CDVA = corrected distance visual acuity; HOAs = higher-order aberrations; Kmax = maximum keratometry; UDVA = uncorrected distance visual acuity
*n = 19 eyes (aberrometry was not performed on all patients)

DISCUSSION

The epi-on corneal CXL technique used in this study produced a significant improvement in UDVA, CDVA, Kmax, HOAs, and coma in patients with keratoconus and ectasia after LASIK, 92% of whom had progressive disease by history, change in manifest refraction, increase in cylinder, or increase in Kmax preoperatively. We did not observe any progression after treatment (defined as an increase in Kmax of >1 D and loss of >1 line of CDVA), and the percentage of eyes with an increase in Kmax seen at 1 year in this study was actually slightly lower than that reported for epi-off CXL (7.0% vs 7.6%, respectively).[2]

The reduction in HOAs was also greater in the present study than reported for epi-off CXL at 2 years (−36% versus −17%), and the reduction in coma was greater than that reported for epi-off CXL (−37% versus −11%).[9] At 1 year, a slight increase in HOAs was reported previously with epi-off CXL (+2.1%),[9] whereas a significant decrease was

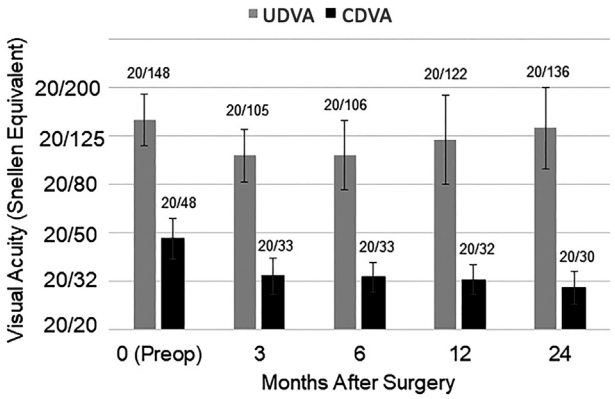

Figure 3. Trend in pediatric visual acuities over 24 months after CXL. Columns show UDVA and CDVA measured at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 11). Error bars represent standard error of the mean (CDVA = corrected distance visual acuity; CXL = corneal crosslinking; UDVA = uncorrected distance visual acuity).

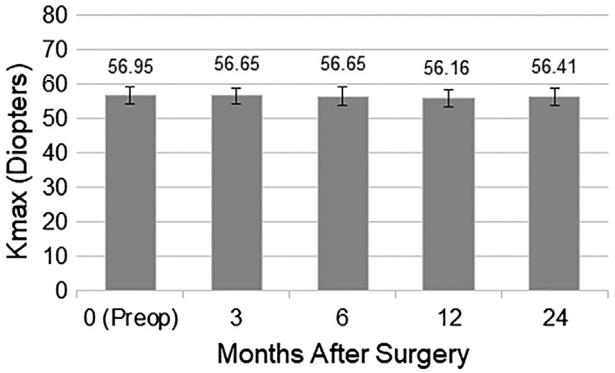

Figure 4. Trend in pediatric Kmax over 24 months after CXL. Columns show Kmax obtained at 3, 6, 12, and 24 months after CXL for eyes in the consistent cohort (n = 11). Error bars represent standard error of the mean (CXL = corneal crosslinking; Kmax = maximum keratometry).

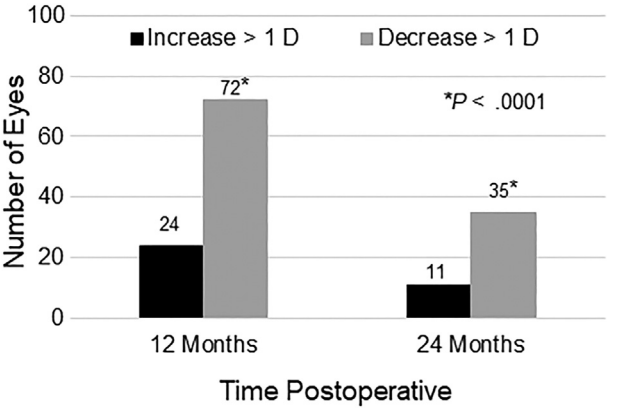

Figure 5. Eyes with more than 1 D change in Kmax 12 and 24 months after CXL. Columns show the number of eyes with an increase or decrease in Kmax at 12 and 24 months after CXL (CXL = corneal crosslinking; Kmax = maximum keratometry).

noted in the present study (−28%). Similarly, a slight decrease in coma was reported with epi-off CXL at 1 year (−2.5%),[9] compared to the statistically significant reduction in coma seen in the present study (−29%). These objective, quantitative measurements that reflect quality of vision suggest that the effect of epi-on CXL observed in this study is greater than that of epi-off CXL performed according to the classic Dresden protocol.

The technique for epi-on CXL in this report is fundamentally different in several ways from the classic Dresden protocol and previous long-term reports of epi-on CXL (Table 7). The ability to perform CXL without epithelial removal makes it inherently safer than epi-off CXL, reducing the risk of infectious keratitis, sterile infiltrates, delayed epithelial healing, corneal scarring, and corneal perforation. Postoperative pain lasts for only 1 day; visual acuity returns to preoperative levels in 2 to 3 days; and contact lens wear can be resumed in 1 week. The enhanced safety and rapid visual recovery make bilateral treatments appropriate.

One unique feature of the technique described herein is the use of a calibrated pictoral comparison chart that allowed us to be confident that the riboflavin concentration in the study eyes was at least 15 μg/g of stromal tissue, and more typically, over 25 μg/g, as shown by independent laboratory studies of this transepithelial CXL technology.[29] The UV light was pulsed using a patented duty cycle long enough to allow oxygen, which is known to be essential for optimal CXL,[32] to penetrate deeply and diffuse into the cornea during the dark phase, and increase the efficacy of CXL.[33–36] Riboflavin drops were also rinsed from the surface of the eye and not added during light exposure, to minimize absorption of ultraviolet-A (UVA) before it could penetrate the corneal stroma, resulting in a more uniform concentration of riboflavin in the stroma and a more uniform delivery of UVA to the stroma.[37,38]

Although it is not clear what role each of these protocol components played in producing the clinical outcomes we observed, the effect is undeniable. Both UDVA and CDVA improved to about the same extent as they did in reported studies of epi-off CXL—without any of the risks of epithelial removal. Moreover, there was no evidence of loss of effect between 1 and 2 years after treatment, as reported with previous epi-on CXL (Figures 1 and 2).[26, 27] Even pediatric eyes showed an improvement in UDVA, CDVA, Kmax, total HOAs, and coma at 12 months and 24 months postoperatively (Tables 5 and 6).

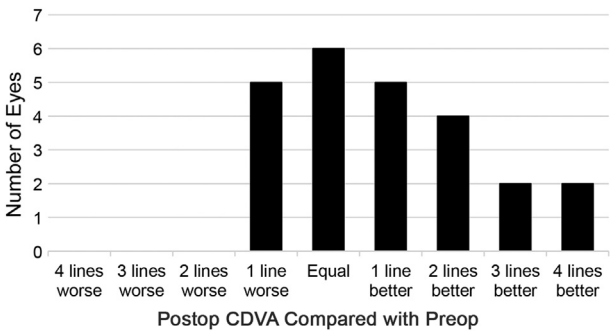

Figure 6. Corrected distance visual acuity in eyes with a more than 1 D increase in maximum keratometry 12 months after corneal crosslinking. Columns show the number of eyes with a change in CDVA as shown on the horizontal axis (n = 24) (CDVA = corrected distance visual acuity).

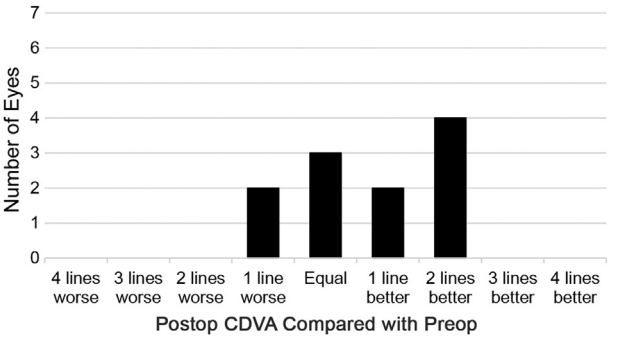

Figure 7. Corrected distance visual acuity in eyes with a more than 1 D increase in maximum keratometry 24 months after corneal crosslinking. Columns show the number of eyes with a change in CDVA as shown on the horizontal axis (n = 11) (CDVA = corrected distance visual acuity).

Table 7. Differences in technique compared with the classic Dresden CXL protocol and previous epi-on protocols.

Parameter	Present Study	Dresden[1]	Previous Epi-on[26,27]	Previous Epi-on[28]
Epithelial preparation	Yes	No	No	No
Soaking sponge	Yes	No	No	No
Silicone ring for soaking	No	No	No	Yes
Riboflavin solution components				
Dextran	No	Yes	Yes	Yes
NaI	Yes	No	No	No
TRIS–EDTA	No	No	Yes	No
Vitamin E	No	No	No	Yes
Slitlamp confirmation of adequate saturation w/calibrated comparison chart	Yes	No	No	No
UVA light irradiance (mw/cm^2)	4.0	3.0	3.0	Variable
Total UVA dose (J/cm^2)	3.6	5.4	5.4	Variable
Diameter of light (mm)	12	9	9	8
Rinsing of riboflavin from surface of the eye before light exposure	Yes	No	No	Yes
Riboflavin application during light phase	No	Yes	Yes	No
Pulsing	Yes	No	No	No

CXL = corneal crosslinking; EDTA = ethylenediaminetetraacetic acid; epi-on = epithelium-on; NaI = sodium iodide; TRIS = tris(hydroxymethyl)aminomethane; UVA = ultraviolet-A

We did not observe progression after treatment in this trial; however, it is possible that the ectatic process will continue in some eyes, despite CXL. If this occurs, we believe that epi-on CXL can be repeated with safety similar to that of a primary procedure and a high likelihood of achieving improved vision. We have limited experience with retreatments; however, our preliminary results (unpublished data) indicate that retreatment using this epi-on CXL system is safe and can further improve UDVA, CDVA, and Kmax. There is also a published report of improved vision with epi-on CXL after epi-off CXL failed to halt progression of corneal ectasia after LASIK.[39]

Epi-on CXL as performed in this study causes minimal pain that predictably lasts less than 24 hours. Oral and topical pain relievers are required for less than 24 hours, if at all. Because the surface of the cornea is not disrupted, vision is reduced by only a small amount and only for 1 to 2 days, allowing patients to perform activities of daily life and drive safely in about 2 days—even after bilateral simultaneous CXL. Contact lens wear can be resumed, if necessary, within a week after epi-on CXL. There is no scarring from delayed epithelial closure, stromal melting, corneal perforation, noninfectious keratitis, or infectious keratitis.

Adverse events in this study were rare. Hydrops in one eye 23 months after CXL was clearly a result of the underlying, severe ectasia, rather than CXL (preoperative CDVA = 20/400 and Kmax = 72.8). There was no indication of corneal endothelial cell damage, even though 58 corneas with a minimum corneal thickness of 302 μm to 400 μm were treated, suggesting that previous calculations of 400 μm as the minimum corneal thickness required to avoid endothelial cell damage during CXL[40] do not apply to this epi-on CXL system. It is also noteworthy that the total energy delivered by this system (3.6 J/cm^2) is significantly less than that delivered under the Dresden protocol (5.4 J/cm^2).

In summary, we report a safe, effective method of epi-on CXL that halts the progression of ectatic corneal disease—as evident by an improvement in UDVA, an improvement in CDVA, a decrease in Kmax, a reduction in total HOAs, and a reduction in coma without any observed treatment-related complications. The improvement in visual acuity is apparent at 3 months postoperatively and stable for 2 years, without regression from year 1 to year 2. The increased safety, enhanced patient convenience, rapid return of visual acuity, lack of complications, and possibility of retreatment, if necessary, make this technique preferable to epi-off CXL for the treatment of ectatic corneal disease.

WHAT WAS KNOWN

- The corneal epithelium prevents absorption of topical riboflavin.
- Traditional CXL requires removal of the corneal epithelium, which can lead to vision-threatening complications.

WHAT THIS PAPER ADDS

- A new CXL technique without epithelial removal effectively stopped progression of keratoconus and ectasia after LASIK.
- The new technique avoided the potential complications of epithelial removal for CXL.

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