Open

ARTICLE

Transepithelial accelerated corneal crosslinking for keratoconus eyes with maximum keratometry values larger than 58 diopters

Ling Sun, MD, PhD, Jing Zhao, MD, PhD, Xiaoyu Zhang, MD, PhD, Yang Shen, MD, PhD, Mi Tian, MD, PhD, Xingtao Zhou, MD, PhD

Purpose: To evaluate the safety and efficacy of transepithelial accelerated corneal crosslinking (CXL) for advanced keratoconus eyes with maximum keratometry (Kmax) values >58 diopters (D).

Setting: Department of Ophthalmology, Eye and ENT Hospital, Fudan University, Shanghai, China.

Design: Prospective parallel control study.

Methods: 41 keratoconus eyes from 41 patients (mean age, 21.93 ± 5.48 years) who underwent transepithelial accelerated CXL were included prospectively. The enrolled eyes were divided into 2 groups according to their Kmax values (Group A, Kmax ≥58.0 D; Group B, Kmax <58.0 D). The examinations including assessment of uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), corneal topography, and corneal endothelial cell density count were conducted preoperatively, at 1 day, 1 month, 3 months, 6 months, and 1 year postoperatively.

Results: All 41 eyes finished 1 year follow-up. No statistical difference was noted between the mean UDVA and CDVA in both groups throughout the follow-up duration. At 1-year postoperative follow-up, the CDVA increased by ≥2 lines in 45% (9/20) and 28.6% (6/21) eyes in Groups A and B, respectively. The mean preoperative Kmax in Groups A and B were 62.51 ± 3.34 D and 49.98 ± 4.32 D, respectively, and that at postoperative 1-year follow-up were 61.94 ± 4.11 D and 50.24 ± 4.72 D, respectively. The Kmax values of 30% (6/20) eyes in Group A and 4.8% (1/21) eyes in Group B decreased by more than 1 D. Deduction of flat K, steep K, mean K, and Kmax showed no significant difference between the 2 groups at 1-year postoperative follow-up. Moreover, 20% (4/20) and 23.8% (5/21) of eyes in Groups A and B, respectively, showed progress at postoperative 1-year follow-up.

Conclusions: Transepithelial accelerated CXL can safely treat advanced keratoconus eyes with Kmax values ≥58.0 D with some extent of efficacy and has similar progressive rate as Kmax values <58.0 D.

J Cataract Refract Surg 2022; 48:208–214

Keratoconus is characterized by progressive corneal expansion, which consequently results in cornea thinning, highly irregular astigmatism, and visual loss. The conventional treatment methods for keratoconus include the use of frame spectacles and contact lens; severe cases may need lamellar or penetrating keratoplasty.[1] Corneal crosslinking (CXL) is widely accepted by ophthalmologists as a technique that improves the corneal biomechanics and delays or prevents the development of corneal keratoconus and ectasia.[2–4]

The Dresden protocol is a popular clinical procedure for performing conventional CXL. This protocol involves the debridement of the corneal epithelium and stromal saturation with riboflavin for 30 minutes; thereafter, the cornea is continuously irradiated with 365 nm UV-A light at 3 mW/cm^2 irradiance for 30 minutes.[2] According to this

Submitted: December 16, 2020 | Final revision submitted: April 5, 2021 | Accepted: April 26, 2021

From the Department of Ophthalmology, Eye and ENT Hospital, Fudan University, Shanghai, China (Sun, Zhao, Zhang, Shen, Tian, Zhou); NHC Key Laboratory of Myopia, Fudan University, Shanghai, China (Sun, Zhao, Zhang, Shen, Tian, Zhou); Shanghai Research Center of Ophthalmology and Optometry, Shanghai, China (Sun, Zhao, Zhang, Shen, Tian, Zhou).

L. Sun and J. Zhao contributed equally to this work.

Supported in part by the National Natural Science Foundation of China (grant no. 81770955); the National Natural Science Foundation of China for Young Scholars (grant no. 11702063); Joint research project of new frontier technology in municipal hospitals (SHDC12018103); Joint research project of new frontier technology in municipal hospitals (SHDC12018103); Project of Shanghai Science and Technology (grant no. 20410710100); and Clinical Research Plan of SHDC (SHDC2020CR1043B). The sponsors and funding organizations had no role in the design or conduct of this research.

Corresponding author: Xingtao Zhou, MD, PhD, Department of Ophthalmology, Eye & ENT Hospital, Fudan University, 83 FenYang Rd, Shanghai 200031, China. Email: doctzhouxingtao@163.com.

0886-3350/$ - see frontmatter
https://doi.org/10.1097/j.jcrs.0000000000000733

protocol, a maximum keratometry value (Kmax) of >58 diopters (D) is not recommended because of the high risk for surgical failure.[5] However, several studies have demonstrated the standard CXL technique seemed to be safe and effective for advanced keratoconus cases, although with a slightly high rate of progression.[6–8]

Currently, transepithelial accelerated CXL, which retains the corneal epithelium (epithelial-on CXL) and uses high-power irradiation with less irradiation time, has been applied for treating keratoconus.[9,10] Various transepithelial accelerated procedures were reported. The irradiation power could increase from 3 mW/cm^2 to 7-45 mW/cm^2, and corneal epithelium could be preserved by riboflavin formulations with the omission of dextran and/or the addition of chemical agents known to loosen epithelial junctions (such as benzalkonium chloride or ethylenediaminetetraacetic acid) or iontophoretic delivery of riboflavin through the use of a mild electrical.[11]

As reported previously, epithelium-on CXL eliminates the need for epithelial removal and prevents associated complications, such as severe pain, corneal haze, corneal infiltrates, and infectious keratitis.[12–15] However, few reports have demonstrated that clinical outcomes for keratoconus with epithelium-on CXL are not as promising as those with epithelium-off CXL.[9,16] A recent study showed that epithelium-on CXL was an effective treatment for patients with advanced keratoconus, and a higher preoperative Kmax value correlated with a greater extent of corneal flattening after CXL.[17] Although the number of studies on conventional CXL for progressive keratoconus with Kmax ≥58.0 D is increasing, to our knowledge, no study has assessed the effectiveness of transepithelial accelerated CXL for keratoconus with Kmax ≥58.0 D.

Therefore, this study aimed to analyze the safety and efficacy of transepithelial accelerated CXL for advanced keratoconus eyes with Kmax ≥58.0 D.

METHODS

Patients

All patients admitted at the Department of Ophthalmology of EENT Hospital of Fudan University between January 1, 2017, and December 31, 2017, were prospectively recruited. The enrolled eyes were diagnosed with progressive keratoconus at our clinic. Progression was determined by an increase in Kmax by at least 1.0 D in the preceding 6 months. Other inclusion criteria were the following: minimal corneal thickness was equal to or larger than 400 μm and clear cornea without visible scar on slitlamp examination. In contrast, the exclusion criteria were the following: previous ocular trauma or surgery, other ocular disease or systemic disease that may affect the cornea, and taking vitamin C (ascorbic acid) supplements within 1 week of the crosslinking treatment.

Routine preoperative examinations were performed to exclude patients with contraindications. The enrolled eyes were divided into 2 groups according to their Kmax values. Eyes in Group A had Kmax ≥58.0 D, whereas those in Group B had Kmax <58.0 D. All patients fully understood the procedure and provided signed informed consent. This study was approved by the Ethical Committee of EENT Hospital of Fudan University Review Board and followed the tenets of the Helsinki Declaration.

Surgical Techniques

All operations were performed by the same surgeon (Z.X.T.). After induction of topical anesthesia with 4% oxybuprocaine, 0.1% riboflavin (ParaCel; Avedro, Inc.) was applied to the cornea for 4 minutes, following which, 0.25% riboflavin (VibeX Xtra; Avedro, Inc.) was applied for 6 minutes. The cornea was irradiated with UV-A light at 45 mW/cm^2 for 5 minutes and 20 seconds, and pulsed illumination was performed using the KXL CXL system (Avedro, Inc.). After the last operation, a bandage contact lens (ACUVE OASYS; Johnson & Johnson Vision) was placed over the cornea and removed on postoperative day 1. The postoperative topical medication regimens were identical for each eye—0.3% levofloxacin, 4 times per day for 3 days; 0.1% fluorometholone eyedrops, tapered from 6 times per day to 1 time per day over 18 days; and a preservative-free tear drops, 4 times per day for 1 month.

Follow-up

The patients were followed up at 1 day, 1 month, 3 months, 6 months, and 1 year postoperatively. Follow-up examinations included assessment of uncorrected distance visual acuity (UDVA), subjective refraction, corrected distance visual acuity (CDVA), corneal topography with the Pentacam anterior segment analysis diagnosis system (Oculus Optikgeräte GmbH), and corneal endothelial cell density (ECD) count using endothelial biomicroscopy (Nidek Co., Ltd.). The failure rate of transepithelial accelerated CXL was defined as the percentage of eyes in which the Kmax value increased by more than 1.00 D relative to the preoperative value.

Statistical Analyses

Data are expressed as mean ± SD. The Shapiro-Wilk test was used to determine whether the data were normal distribution. The *P* value was determined using the paired *t* test and single-factor repeated-measures analysis of variance. The univariate linear regression was used to assess the relationship between Kmax or change in Kmax and other different variables. Visual acuity was examined using Snellen charts. For statistical analysis, the Snellen visual acuity was converted to the corresponding logMAR value using standard conversion tables. *P* values <0.05 were considered statistically significant. All statistical analyses were performed using SPSS software (v. 16.0; SPSS, Inc.).

RESULTS

Forty-one eyes from 41 patients (23 males, 18 females; mean age, 21.93 ± 5.48 years [range, 10–34 years]) were included in this study. Group A consisted of 20 eyes with Kmax ≥58.0 D, whereas Group B consisted of 21 eyes with

Table 1. Baseline Patient Data.

Parameter	Group A Kmax ≥58 D, mean ± SD	Group B Kmax <58 D, mean ± SD
Patients (n)	20	21
Eyes (n)	20	21
Age (y)		
Mean ± SD	23.00 ± 4.03	21.48 ± 6.15
Range	13, 30	10, 34
UDVA (logMAR)	0.92 ± 0.47	0.77 ± 0.49
CDVA (logMAR)	0.40 ± 0.23	0.13 ± 0.16
Kmax (D)	62.51 ± 3.34	49.98 ± 4.32
TCT (μm)	449.06 ± 17.67	482.21 ± 32.91
ECD (cells/mm^2)	3426.40 ± 377.61	3198.70 ± 432.02

ECD = endothelial cell density; Kmax = maximal keratometry; TCT = thinnest corneal thickness

Table 2. Visual and Topographic Characteristics Before and After Transepithelial Accelerated CXL for Keratoconus Eyes in Group A (Kmax ≥58 D) (Mean ± SD).

Parameter	Preop	Postop				*P* value
		1 mo	3 mo	6 mo	1 y	
UDVA (logMAR)	0.92 ± 0.47	0.75 ± 0.37	0.75 ± 0.44	0.77 ± 0.37	0.68 ± 0.36	>.274
CDVA (logMAR)	0.40 ± 0.23	0.39 ± 0.17	0.32 ± 0.20	0.32 ± 0.20	0.31 ± 0.20	>.099
SE (D)	−8.37 ± 3.65	−6.65 ± 5.12	−6.53 ± 3.20	−5.81 ± 2.86	−6.70 ± 3.49	>.062
Flat K (D)	50.37 ± 2.88	50.90 ± 3.47	50.53 ± 3.28	50.51 ± 3.26	50.57 ± 3.15	1.000
Steep K (D)	53.72 ± 3.07	53.91 ± 3.51	53.49 ± 3.29	53.77 ± 3.30	53.69 ± 3.34	1.000
Mean K (D)	51.97 ± 2.82	52.36 ± 3.31	51.96 ± 3.12	52.08 ± 3.13	52.08 ± 3.09	1.000
Kmax (D)	62.51 ± 3.34	63.11 ± 4.52	61.19 ± 3.96	62.02 ± 3.94	61.94 ± 4.11	>.153
TCT (μm)	449.06 ± 17.67	449.75 ± 20.55	445.00 ± 21.84	450.56 ± 20.30	445.19 ± 17.29	>.562
ECD (cells/mm^2)	3426.4 ± 377.61	3472.4 ± 469.25	3270.2 ± 438.03	3171.6 ± 396.89	3246.1 ± 329.29	>.190

ECD = endothelial cell density; Flat K = keratometry at flat axis; Kmax = maximal keratometry; Mean K = mean keratometry; SE = spherical equivalent; Steep K = keratometry at steep axis; TCT = thinnest corneal thickness
Bonferroni adjustments were applied for multiple testing between different time points, and *P* value <.05 was considered to be of statistical significance

Table 3. Visual and Topographic Characteristics Before and After Transepithelial Accelerated CXL for Keratoconus Eyes in Group B (Kmax <58 D) (Mean ± SD).

Parameter	Preop	Postop				*P* value
		1 mo	3 mo	6 mo	1 y	
UDVA (logMAR)	0.77 ± 0.49	0.61 ± 0.47	0.52 ± 0.40	0.57 ± 0.40	0.55 ± 0.38	>.092
CDVA (logMAR)	0.13 ± 0.16	0.08 ± 0.09	0.06 ± 0.09	0.08 ± 0.11	0.05 ± 0.09	>.051
SE (D)	−4.13 ± 3.08	−4.35 ± 2.86	−4.29 ± 2.65	−4.18 ± 3.17	−4.22 ± 3.21	1.000
Flat K (D)	43.44 ± 2.03	43.57 ± 2.58	43.55 ± 2.17	43.60 ± 2.30	43.59 ± 2.46	1.000
Steep K (D)	45.58 ± 2.33	46.11 ± 2.81	45.58 ± 2.46	45.89 ± 2.51	45.99 ± 2.73	>.195
Mean K (D)	44.47 ± 2.07	44.79 ± 2.55	44.67 ± 2.16	44.69 ± 2.27	44.75 ± 2.45	>.477
Kmax (D)	49.98 ± 4.32	51.02 ± 5.68	50.35 ± 5.09	50.24 ± 4.48	50.24 ± 4.72	>.204
TCT (μm)	482.21 ± 32.91	479.95 ± 35.00	478.84 ± 32.87	483.74 ± 35.17	484.74 ± 35.25	>.195
ECD (cells/mm^2)	3198.7 ± 432.02	3151.0 ± 414.48	3223.8 ± 419.59	3233.3 ± 365.07	3200.5 ± 397.83	1.000

ECD = endothelial cell density; Flat K = keratometry at flat axis; Kmax = maximal keratometry; Mean K = mean keratometry; SE = spherical equivalent; Steep K = keratometry at steep axis; TCT = thinnest corneal thickness
Bonferroni adjustments were applied for multiple testing between different time points, and *P* value <.05 was considered to be of statistical significance

Kmax <58.0 D. Table 1 summarizes the baseline patient data between the 2 groups.

All surgeries were uneventful, and patients experienced moderate corneal epithelial edema on postoperative day 1. However, no severe or persistent complications occurred in any of the 41 eyes during subsequent follow-up periods, and no patients underwent further treatment because of obvious eye pain, photophobia, and red eye postoperatively.

The UDVA and CDVA among each visit throughout the follow-up duration showed no statistically significant difference in both groups (Tables 2 and 3). At 1-year postoperative follow-up, the UDVA increased by ≥2 lines in

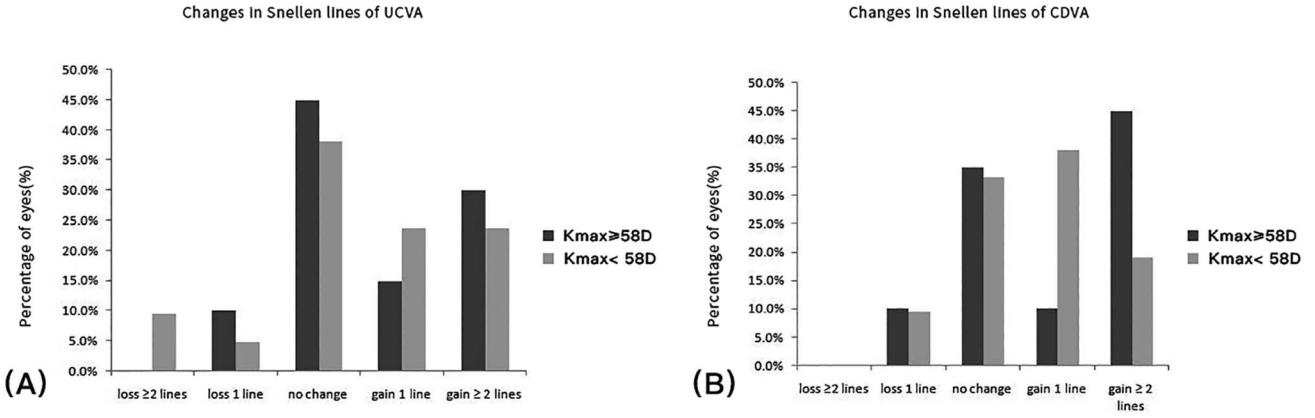

Figure 1. Changes in Snellen lines (%) of UDVA (*A*) and CDVA (*B*) at 1-year postoperative follow-up in both groups.

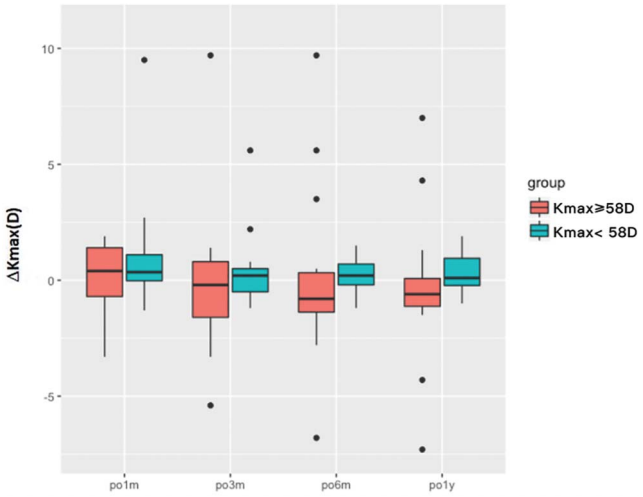

Figure 2. Difference in ΔKmax between Groups A (Kmax ≥58 D) and B (Kmax <58 D) at each postoperative visit. ΔKmax is defined as the difference in Kmax preoperative and each postoperative follow-up.

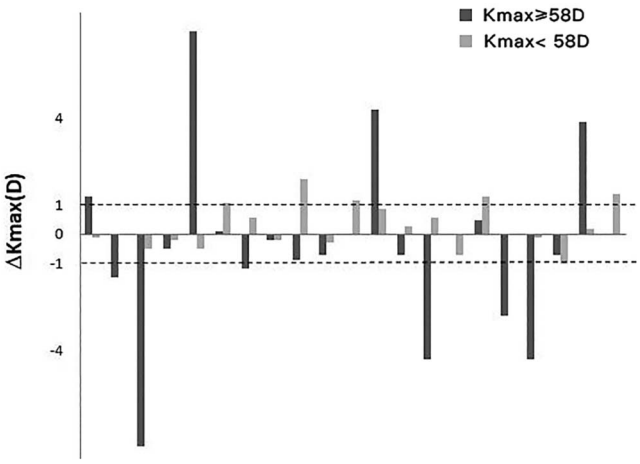

Figure 3. Changes in Kmax (ΔKmax) for individual patients in Groups A (Kmax ≥58 D) and B (Kmax <58 D) at 1-year postoperative follow-up. ΔKmax is defined as the difference in Kmax preoperative and 1-year postoperative follow-up. Dashed lines indicate 1 D of change.

30% (6/20) and 23.8% (5/21) eyes in Groups A and B, respectively (Figure 1, A). CDVA increased by ≥2 lines in 45% (9/20) and 28.6% (6/21) eyes in Groups A and B, respectively (Figure 1, B).

The flat K, steep K, mean K, and Kmax values of both groups at each visit were showed in Tables 2 and 3. There was no significant difference in the preoperative and postoperative changes of flat K, steep K, mean K, and Kmax values between the 2 groups (Figure 2).

At 1-year postoperative follow-up, the Kmax values of 30% (6/20) eyes in Group A and 4.8% (1/21) eyes in Group B decreased by more than 1 D. Progress (increase in Kmax by >1 D) occurred in 20% (4/20) eyes in Group A and 23.8% (5/21) eyes in Group B at 1 year postoperatively (Figure 3). The mean age of patients with progress was 24.5 ± 3.70 years and 21 ± 1.58 years in Groups A and B, respectively.

The thinnest corneal thickness and endothelial cell density count showed no significant change among each follow-up time point in both Groups A and B (Tables 2 and 3).

No significant correlations could be found between the preoperative Kmax value and the change of ECD, CDVA, and UDVA at 1-year postoperative follow-up (Table 4). No significant correlation could be found between change in Kmax at 1 year postoperatively and age (Table 5). In Group B, a significant correlation was detected between change in Kmax at 1-year postoperative follow-up and preoperative Kmax (Table 5).

DISCUSSION

Several studies have shown that CXL is expected to stop the progression of keratoconus, preserve visual acuity, and delay or obviate the need for more extensive surgical interventions such as keratoplasty; however, it could not take effect in each case.[4,18,19] A few studies have reported that the failure rate of CXL was higher in advanced keratoconus eyes with Kmax ≥58.0 D than those with Kmax <58 D.[7,8] Koller et al. demonstrated that changing the inclusion parameter––Kmax values from 65 D to <58 D––would reduce the failure rate to 2.8%.[5] Most of these were observed with conventional CXL that were performed according to the Dresden protocol. To our knowledge, this study was the first to analyze the safety and efficacy of transepithelial accelerated CXL for treating advanced keratoconus eyes with Kmax ≥58.0 D.

All operations performed in this study were uneventful, and no corneal infection, haze, and other complications in the eyes were noted at 1-year postoperative follow-up in both groups. The corneal endothelial cell density count and thinnest corneal thickness did not change significantly throughout the postoperative follow-up duration in both groups. These results indicated that the safety of transepithelial accelerated CXL for keratoconus with Kmax ≥58 D was comparable to that with Kmax <58 D. Considerable changes and variations in corneal thickness have been reported previously depending on the instrument used for corneal measurements. Ivarsen et al. showed that corneal thickness reduced significantly by 1 year postoperatively after standard CXL in patients with advanced keratoconus, and this result was congruent with that reported by other studies.[7] Giacomin et al. reported that the mean central ultrasonic pachymetry readings significantly decreased after standard CXL from 388.20 ± 49.61 μm to 379.25 ± 48 μm at 48 months postoperatively and that the difference was less than 9 μm, which may not be clinically significant.[8] Early changes in corneal thickness may be related to initial stromal compaction due to the CXL treatment, whereas progressive corneal thinning could be associated with the progression of keratoconus. Consequently, the risk for corneal perforation and vision loss becomes higher. Thus, stable postoperative corneal thickness after transepithelial accelerated CXL observed in the present study indicated that it was a safe procedure for treating patients with advanced keratoconus.

Table 4. Regression Coefficients of Kmax on Change of Eye Parameters After 1-Year Follow-up.

Group	UDVA (logMAR)	CDVA (logMAR)	SE (D)	Flat K (D)	Steep K (D)	Mean K (D)	TCT (μm)	ECD (cells/mm^2)
Group A: Kmax ≥58 D								
B	0.029	−0.014	0.485	0.013	0.035	0.027	−1.358	21.287
β	0.227	−0.162	0.346	0.118	0.060	0.053	−0.404	0.133
P value	.380	.522	.160	.914	.807	.828	.086	.610
R^2	0.052	0.026	0.120	0.001	0.004	0.003	0.163	0.018
Group B: Kmax <58 D								
B	0.002	−0.003	0.037	0.063	0.083	0.068	0.563	42.439
β	0.020	−0.109	0.115	0.414	0.451	0.448	0.178	0.342
P value	.933	.647	.619	.069	.046	.047	.453	.140
R^2	<0.001	0.012	0.013	0.172	0.204	0.201	0.032	0.117
Overall								
B	−0.003	−0.008	0.148	0.018	−0.001	0.009	−0.517	−3.532
β	−0.065	−0.286	0.330	0.115	−0.005	0.055	−0.300	−0.050
P value	.703	.082	.040	.486	.975	.742	.063	.770
R^2	0.004	0.082	0.085	0.013	<0.001	0.003	0.090	0.002

B = coefficient; β = standardized coefficient; ECD = endothelial cell density; Flat K = keratometry at flat axis; Kmax = maximal keratometry; Mean K = mean keratometry; SE = spherical equivalent; Steep K = keratometry at steep axis; TCT = thinnest corneal thickness

The endothelial cell density count was a crucial aspect to investigate because more advanced cases may have a higher risk for ECD loss due to thinner baseline corneas. The present study showed that the ECD count did not change significantly throughout the postoperative follow-up duration in Kmax ≥58 D group. This result was similar to study reported by Giacomin et al. at 48-month postoperative follow-up.[8] A few larger changes in ECD were found in both studies, which might be influenced by cornea irregularity in advanced stages of keratoconus as it led to count difficulty and reduced repeatability. Moreover, this statistical result might also be affected by the small sample size examined in the study, and therefore, further investigation with a lager sample size was needed.

In this study, the UDVA, CDVA, and corneal K values showed no statistical difference throughout the follow-up duration in both Groups A and B; moreover, there was no statistically significant difference in the changes of various K values between 2 groups at different follow-up time points. In addition, the Kmax of 30% eyes in Group A and 4.8% eyes in Group B decreased by >1 D after 1 year postoperatively. These results indicated that the progression of keratoconus in eyes with Kmax ≥58 D might be stopped after transepithelial accelerated CXL. Furthermore, Chen et al. found that a higher preoperative maximum K value correlated with greater corneal flattening after epithelium-on CXL, and they hypothesized that this outcome could be partly attributable to the relatively deep crosslinking in eyes with advanced keratoconus.[17] Contrary to the report of Koller et al., although the risk for treatment failure might be slightly high, our results showed that transepithelial accelerated CXL might indeed be effective to treat keratoconus eyes with Kmax >58.00 D.[5] Therefore, advanced keratoconus with Kmax >58.00 D should not exclude CXL as a treatment.

Table 5. Regression Coefficients of Demographic Characteristics and Baseline Eye Parameters on ΔKmax From Baseline to Postoperative 1-Year Follow-up.

	Group A (Kmax ≥58 D)				Group B (Kmax <58 D)				Overall			
Parameters	B	β	*P* value	R^2	B	β	*P* value	R^2	B	β	*P* value	R^2
Age	0.128	0.162	.508	0.026	−0.011	−0.086	.718	0.007	0.016	0.036	.828	0.001
UDVA (logMAR)	0.300	0.045	.860	0.002	0.128	0.074	.757	0.005	<0.001	<0.001	1.000	<0.001
CDVA (logMAR)	−2.590	−0.244	.315	0.059	0.701	0.133	.576	0.018	−1.960	−0.248	.127	0.062
SE (D)	0.164	0.197	.420	0.039	0.033	0.130	.585	0.017	0.129	0.219	.181	0.048
Flat K (D)	−0.031	−0.027	.912	0.001	0.105	0.264	.260	0.070	−0.065	−0.120	.469	0.014
Steep K (D)	0.120	0.109	.658	0.012	0.065	0.188	.429	0.035	−0.035	−0.074	.653	0.006
Mean K (D)	0.058	0.050	.839	0.002	0.093	0.240	.309	0.058	−0.049	−0.094	.570	0.009
Kmax (D)	0.013	0.013	.959	<0.001	0.084	0.447	.048	0.200	−0.028	−0.088	-.537	0.008
TCT (μm)	0.019	0.133	.587	0.018	−0.005	−0.205	.386	0.042	0.008	0.115	.487	0.013
ECD (cells/mm^2)	0.001	0.066	.795	0.004	<0.001	0.105	.667	0.011	<0.001	0.012	.942	<0.001

B = coefficient; β = standardized coefficient; ECD = endothelial cell density; Flat K = keratometry at flat axis; Kmax = maximal keratometry; Mean K = mean keratometry; SE = spherical equivalent; TCT = thinnest corneal thickness

Various studies have reported a significant decrease in K values after standard CXL.[19,20] In contrast, transepithelial accelerated CXL causes less corneal flattening than standard CXL.[21] Although corneal flattening was reported after standard CXL, few studies have reported significant improvement in UDVA or CDVA postoperatively, similar to this study.[7,8] Nevertheless, in the present study, UDVA increased by ≥2 lines in 30% and 23.8% eyes, whereas CDVA increased by ≥2 lines in 45% and 28.6% eyes in Groups A and B, respectively. These might be due to the absence of corneal haze after epithelium-on CXL, which was confirmed by a less extent of keratocyte apoptosis and inflammation.[22,23] Few experts have highlighted that the main goal of CXL was to stop keratoconus progression and maintain visual acuity. Therefore, it is rational to consider the indication for CXL on the stable maintenance of visual acuity rather than on the degree of keratometry changes.[24] In this regard, transepithelial accelerated CXL could be performed in select cases for treating advanced keratoconus to maintain visual acuity and delay or avoid the need for a more extensive surgery.

In this study, the progression rate of keratoconus was 20% in Group A and 23.8% in Group B at 1-year postoperative follow-up. These rates were similar to those reported in the study of Kuechler et al., which showed that keratoconus progressed in 23% eyes with Kmax ≥58.0 D 1 year after standard CXL.[6] Surprisingly, the failure rate in patients with severe keratoconus was not higher than that in patients with mild to moderate keratoconus examined in our study. One reason for this observation might be that the mean age of patients with progressive keratoconus in Group A was a little older than those in Group B. The progression of keratoconus is known to slow with age. Moreover, the observed difference might have been further affected by the small sample size examined in this study and therefore warrants further investigation with a lager sample size.

This study had few limitations. First, the sample size was small, which might have affected the statistical efficacy; therefore, we will continue to enroll more patients for further analysis. Second, the follow-up time may not be sufficient to evaluate the long-term efficacy of transepithelial accelerated CXL. Third, both children and adults were enrolled in this study, which warrants a subgroup analysis in future studies with a large sample size as this would yield more detailed information.

In summary, this study shows that in extremely steep and advanced keratoconus eyes with Kmax values ≥58.0 D, transepithelial accelerated CXL could be a safe treatment procedure with some extent of efficacy. Further studies with a relatively large sample size and extended follow-up duration are needed to validate the present findings.

Acknowledgements

The authors thank Editage for English language editing.

WHAT WAS KNOWN

- According to Dresden protocol for CXL, a maximum keratometry value (Kmax) of >58 D was not recommended because of the high risk for surgical failure.
- Transepithelial accelerated CXL was an effective treatment for patients with advanced keratoconus, and a higher preoperative Kmax value correlated with a greater extent of corneal flattening after CXL.

WHAT THIS PAPER ADDS

- In extremely steep and advanced keratoconus eyes with Kmax values ≥58.0 D, transepithelial accelerated CXL could be a safe treatment procedure with some extent of efficacy.

REFERENCES

1. Tuft SJ, Moodaley LC, Gregory WM, Davison CR, Buckley RJ. Prognostic factors for the progression of keratoconus. Ophthalmology 1994;101:439–447
2. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003;135:620–627
3. Saffarian L, Khakshoor H, Zarei-Ghanavati M, Esmaily H. Corneal cross-linking for keratoconus in Iranian patients: outcomes at 1 year following treatment. Middle East Afr J Ophthalmol 2010;17:365–368
4. Vinciguerra R, Romano MR, Camesasca FI, Azzolini C, Trazza S, Morenghi E, Vinciguerra P. Corneal cross-linking as a treatment for keratoconus: four-year morphologic and clinical outcomes with respect to patient age. Ophthalmology 2013;120:908–916
5. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009;35:1358–1362
6. Kuechler SJ, Tappeiner C, Epstein D, Frueh BE. Keratoconus progression after corneal cross-linking in eyes with preoperative maximum keratometry values of 58 diopters and steeper. Cornea 2018;37:1444–1448
7. Ivarsen A, Hjortdal J. Collagen cross-linking for advanced progressive keratoconus. Cornea 2013;32:903–906
8. Giacomin NT, Netto MV, Torricelli AA, Marino GK, Bechara SJ, Espíndola RF, Santhiago MR. Corneal collagen cross-linking in advanced keratoconus: a 4-year follow-up study. J Refract Surg 2016;32:459–465
9. Çerman E, Toker E, Ozarslan Ozcan D. Transepithelial versus epithelium-off crosslinking in adults with progressive keratoconus. J Cataract Refract Surg 2015;41:1416–1425
10. Sun L, Li M, Zhang X, Tian M, Han T, Zhao J, Zhou X. Transepithelial accelerated corneal collagen cross-linking with higher oxygen availability for keratoconus: 1-year results. Int Ophthalmol 2018;38:2509–2517
11. Lytle G. Advances in the technology of corneal cross-linking for keratoconus. Eye Contact Lens 2014;40:358–364
12. Sharma A, Mohan K, Niranakari VS. Endothelial failure after collagen cross-linking with riboflavin and UV-A: case report with literature review. Cornea 2013;32:e180–e181
13. Bagga B, Pahuja S, Murthy S, Sangwan VS. Endothelial failure after collagen cross-linking with riboflavin and UV-A: case report with literature review. Cornea 2012;31:1197–1200
14. Cassagne M, Laurent C, Rodrigues M, Galinier A, Spoerl E, Galiacy SD, Soler V, Fournié P, Malecaze F. Iontophoresis transcorneal delivery technique for transepithelial corneal collagen crosslinking with riboflavin in a rabbit model. Invest Ophthalmol Vis Sci 2016;57:594–603
15. Koppen C, Vryghem JC, Gobin L, Tassignon MJ. Keratitis and corneal scarring after UVA/riboflavin cross-linking for keratoconus. J Refract Surg 2009;25:S819–S823
16. Soeters N, Wisse RP, Godefrooij DA, Imhof SM, Tahzib NG. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. Am J Ophthalmol 2015;159:821–e3
17. Chen S, Chan TC, Zhang J, Ding P, Chan JC, Yu MC, Li Y, Jhanji V, Wang Q. Epithelium-on corneal collagen crosslinking for management of advanced keratoconus. J Cataract Refract Surg 2016;42:738–749
18. Lang SJ, Messmer EM, Geerling G, Mackert MJ, Brunner T, Dollak S, Kutchoukov B, Böhringer D, Reinhard T, Maier P. Prospective, randomized,

double-blind trial to investigate the efficacy and safety of corneal cross-linking to halt the progression of keratoconus. BMC Ophthalmol 2015;15:78
19. Richoz O, Mavrakanas N, Pajic B, Hafezi F. Corneal collagen cross-linking for ectasia after LASIK and photorefractive keratectomy: long-term results. Ophthalmology 2013;120:1354–1359
20. Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. Ophthalmology 2014;121:812–821.
21. Bouheraoua N, Jouve L, Borderie V, Laroche L. Three different protocols of corneal collagen crosslinking in keratoconus: conventional, accelerated and iontophoresis. J Vis Exp 2015;105:53119
22. Hayes S, O'Brart DP, Lamdin LS, Doutch J, Samaras K, Marshall J, Meek KM. Effect of complete epithelial debridement before riboflavin-ultraviolet-A corneal collagen crosslinking therapy. J Cataract Refract Surg 2008;34:657–661
23. Wollensak G, Iomdina E. Biomechanical and histological changes after corneal crosslinking with and without epithelial debridement. J Cataract Refract Surg 2009;35:540–546
24. Caporossi A, Baiocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. J Cataract Refract Surg 2006;32:837–845

First author:
Ling Sun, MD, PhD

Department of Ophthalmology, Eye and ENT Hospital, Fudan University, Shanghai, China