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Factors affecting outcomes of corneal collagen crosslinking treatment

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CLINICAL STUDY

Abstract

Purpose To assess the effects of preoperative patient characteristics on clinical outcomes of corneal crosslinking (CXL) treatment in patients with progressive keratoconus.
Methods This retrospective study comprised 96 eyes of 96 patients who had unilateral CXL treatment for progressive keratoconus. All patients underwent a complete ophthalmological examination and corneal topography at baseline and 1 year. Subgroup analyses were performed according to the age (<30 and ≥ 30 years), gender, preoperative corrected distance visual acuity (CDVA, <0.3 and ≥ 0.3 logMAR (log of the minimum angle of resolution)), preoperative maximum keratometry (K, <54 and ≥ 54 D), baseline topographic cone location (central, paracentral, and peripheral), and preoperative thinnest pachymetry (<450 and $\geq 450\,\mu$m) to determine the associations between preoperative patient characteristics and outcomes (changes in visual acuity and maximum keratometry) of CXL treatment.
Results In the entire study population, mean CDVA and maximum K significantly improved after CXL treatment ($P < 0.001$). Patients with a preoperative CDVA of 20/40 Snellen equivalent or worse (≥ 0.3 logMAR) experienced more visual improvement after CXL treatment ($P < 0.001$). However, an age ≥ 30 years and a baseline thinnest pachymetry less than $450\,\mu$m were found significantly associated with more flattening in maximum keratometry ($P = 0.024$, $P = 0.005$ respectively). Gender, preoperative maximum K, and baseline topographic cone location did not show significant effect on postoperative visual acuity and maximum keratometry ($P > 0.05$).
Conclusions In patients with progressive keratoconus, age, baseline visual acuity, and baseline thinnest pachymetry seem to affect the success of the CXL treatment.

Introduction

Keratoconus is a non-inflammatory ectatic corneal disorder.[1] Major clinical findings are progressive stromal thinning and visual deterioration secondary to irregular astigmatism, myopia, and central corneal scarring.[1,2] Conservative treatment modalities such as spectacles and gas permeable rigid contact lenses become insufficient for visual rehabilitation in advanced stages of keratoconus and 10–20% of the patients need corneal transplantation.[2]

Wollensak *et al*[3,4] introduced corneal collagen crosslinking (CXL) using riboflavin and ultraviolet A (UVA) as a new hope for treatment of progressive keratoconus. Studies concluded that CXL is an effective procedure to arrest the progression of keratoconus by increasing biomechanical stability of the cornea.[4–6] Moreover, significant improvements in visual acuity and keratometry (K) readings after CXL treatment could be considered as a regression in disease severity.[7–10]

Although the efficacy of CXL treatment has been shown in many studies, there is little evidence about the influence of preoperative patient characteristics on clinical outcomes of CXL treatment.[8–10] In this study, we aimed to assess the effects of initial demographic and topographic properties on outcomes of CXL treatment in patients with progressive keratoconus at 1-year follow-up.

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Materials and methods

Study population

This retrospective study comprised 96 eyes of 96 patients who underwent unilateral CXL treatment for progressive keratoconus. The study was performed in adherence to the tenets of the Declaration of Helsinki and local ethics committee approved the methodology. Inclusion criteria were biomicroscopic examination and corneal topography consistent with keratoconus, inferior–superior ratio on topographic map >1.5, at least 18 years of age, thinnest corneal pachymetry of $\geq 400\,\mu m$. Progression was defined as $\geq 1\,D$ steepening of maximum keratometry or an increase of $\geq 1.00\,D$ in manifest cylinder or an increase of $\geq 0.50\,D$ in manifest refraction spherical equivalent in 2 years. Eyes with prior corneal surgery or scarring were excluded from the study.

Examinations

All patients underwent detailed ophthalmological examinations that included corrected (including contact lens) distance visual acuity (CDVA) measurement with Snellen charts, slit-lamp biomicroscopic examination, applanation tonometry, and dilated funduscopic examination. Visual acuity in Snellen format was converted to the logMAR (log of the minimum angle of resolution) equivalent for statistical analysis.[11] The mean CDVA was noted at baseline and 1 year after CXL treatment.

New generation anterior segment tomography devices are capable of determining the topography and pachymetry of the entire cornea.[12–14] In this study, corneal topography (Allegro Oculyzer, WaveLight AG, Erlangen, Germany) was conducted with undilated pupils under scotopic conditions by a single experienced technician. Scans were taken in automatic mode with proper quality. Maximum keratometry and corneal pachymetry at the thinnest location were recorded at baseline and 1 year after CXL treatment.[13,14] Cone location was determined according to the topographic coordinates of maximum keratometry as follows: central cone (maximum K within the central 3 mm optical zone), paracentral cone (3–5 mm optical zone), and peripheral cone (outside the central 5 mm optical zone).

Subgroups and cutoff values were created in accordance with the current literature as follows: age (<30 and ≥ 30 years), gender, preoperative CDVA (<0.3 and ≥ 0.3 logMAR), preoperative maximum K (<54 and $\geq 54\,D$), baseline topographic cone location (central, paracentral, and peripheral cone), and preoperative thinnest pachymetry (<450 and $\geq 450\,\mu m$) to analyze the relationship between preoperative patient characteristics and improvements in CDVA and maximum K after CXL treatment.

Surgical procedure

CXL was performed under sterile conditions using topical anesthesia as described by Wollensak.[4] Central 9.0 mm corneal epithelium was removed by mechanical debridement. Isotonic riboflavin solution (0.1% in 20% dextran T500 solution) was instilled every 2 min for 30 min until riboflavin absorption was observed in the corneal stroma and anterior chamber under biomicroscopic examination. Then, the cornea was exposed to UVA irradiation at the wavelength of 365 nm and surface irradiance of 3 mW/cm². During the UVA exposure, isotonic riboflavin solution instillation was continued every 2 min for 30 min. Postoperatively, a soft contact lens was placed until corneal epithelial healing completed. Topical antibiotic and corticosteroid drops were administered and continued four times daily for 1 week and 2 weeks, respectively.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences software version 16.0 (SPSS Inc, Chicago, IL, USA). Results were expressed as mean ± SD. A paired t-test was used to analyze the changes in mean CDVA and maximum K between baseline and 1 year. Comparison of the quantitative data (changes in mean CDVA and maximum K) between two groups was performed by independent samples t-test. However, non-parametric tests (Wilcoxon signed ranks test and Mann–Whitney U-test) were used to analyze the effects of preoperative topographic cone location on mean CDVA and maximum K. A P-value less than 0.05 was considered statistically significant at 95% confidence interval.

Results

Ninety-six eyes of ninety-six patients who had unilateral CXL treatment for progressive keratoconus were included in this retrospective study. The study group consisted of 39 (40.6%) male and 57 (59.4%) female with a mean age of 29.42 ± 9.34 years (Table 1). All patients had 1-year follow-up. In the entire cohort, mean CDVA significantly improved from 0.39 ± 0.29 logMAR (20/49 Snellen) to 0.28 ± 0.22 logMAR (20/38 Snellen; Table 2, $P<0.001$) and the maximum K significantly decreased from $54.54 \pm 5.50\,D$ to $53.52 \pm 5.18\,D$ between baseline and 1 year after CXL treatment (Table 2, $P<0.001$).

The effects of preoperative patient characteristics on changes in CDVA and maximum K after CXL treatment were assessed.

Subgroup analyses according to the preoperative patient data

Age *Patients with <30 years of age (n=54):* The mean CDVA significantly improved from baseline 0.34 ± 0.23 logMAR (20/43 Snellen) to 0.21 ± 0.15 logMAR (20/32 Snellen) at 1-year after CXL treatment ($P<0.001$), whereas improvement in maximum K (from 53.62 ± 4.90 D to 53.06 ± 5.03 D) was not statistically significant ($P=0.61$).

Patients with ≥30 years of age (n=42): The improvement in mean CDVA was not statistically significant (from 0.44 ± 0.35 logMAR, 20/55 Snellen, to 0.36 ± 0.27 logMAR, 20/45 Snellen, $P=0.074$) between baseline and 1 year, whereas maximum K significantly decreased after CXL treatment (from 55.72 ± 6.12 D to 54.12 ± 5.37 D, $P<0.001$).

Comparison of the postoperative changes in CDVA and maximum K between groups: After CXL treatment, the patients with ≥30 years of age experienced more flattening in maximum K compared with that of the patients with <30 years of age ($P=0.024$), whereas there was no significant difference between two groups in terms of change in CDVA ($P=0.442$).

Gender *Males (n=39):* The mean CDVA (from 0.35 ± 0.25 logMAR, 20/44 Snellen, to 0.27 ± 0.22 logMAR, 20/37 Snellen, $P=0.034$) and maximum K (from 53.95 ± 6.04 D to 53.28 ± 6.06 D, $P=0.005$) significantly improved between baseline and 1 year after CXL treatment.

Table 1 Demographic data of the study group ($n=96$)

Characteristic	Value
Gender	
Male, *n (%)*	39 (40.6)
Female, *n (%)*	57 (59.4)
Age, years (mean ± SD)	29.42 ± 9.34
18–29, *n (%)*	54 (56.2)
30–50, *n (%)*	42 (43.8)

Females (n=57): There were significant improvements in mean CDVA (from 0.41 ± 0.32 logMAR, 20/51 Snellen, to 0.28 ± 0.22 logMAR, 20/38 Snellen, $P=0.001$) and maximum K (from 54.94 ± 5.18 D to 53.69 ± 4.53 D, $P=0.001$) after CXL treatment.

Comparison of the postoperative changes in CDVA and maximum K between groups: There were no significant differences regarding the changes in CDVA and maximum K between males and females ($P=0.501$, $P=0.183$, respectively).

Preoperative CDVA *CDVA <0.3 logMAR (n=39):* The mean CDVA did not show significant improvement (from 0.16 ± 0.06 logMAR, 20/28 Snellen, to 0.16 ± 0.13 logMAR, 20/28 Snellen, $P=0.905$), whereas the decrease in maximum K was statistically significant (from 52.42 ± 4.12 D to 51.66 ± 3.92 D, $P=0.002$).

CDVA ≥0.3 logMAR (n=57): The mean CDVA (from 0.54 ± 0.29 logMAR, 20/69 Snellen, to 0.36 ± 0.23 logMAR, 20/45 Snellen, $P<0.001$) and maximum K significantly improved after CXL treatment (from 55.98 ± 5.94 D to 54.80 ± 5.57 D, $P=0.001$).

Comparison of the postoperative changes in CDVA and maximum K between groups: The patients with a worse baseline visual acuity (CDVA ≥0.3 logMAR) showed significant improvement in CDVA 1 year after CXL treatment compared with that of the patients with a better baseline visual acuity (CDVA <0.3 logMAR; $P<0.001$). However, comparing two groups, the change in maximum K was not statistically significant at 1 year ($P=0.316$).

Preoperative maximum keratometry *Maximum K <54 D (n=52):* The baseline CDVA (from 0.28 ± 0.17 logMAR, 20/38 Snellen, to 0.21 ± 0.17 logMAR, 20/32 Snellen, $P=0.009$) and maximum K significantly improved (from 50.54 ± 2.10 D to 49.74 ± 2.31 D, $P=0.003$) after CXL treatment.

Maximum K ≥54 D (n=44): After CXL treatment, mean CDVA (from 0.51 ± 0.35 logMAR, 20/64 Snellen, to 0.35 ± 0.25 logMAR, 20/44 Snellen, $P=0.002$) and maximum K significantly improved (from 59.26 ± 4.51 D to 58.00 ± 3.89 D, $P=0.003$).

Table 2 Changes in visual acuity and topographic data between baseline and 1 year after CXL treatment in the entire cohort ($n=96$)

	Baseline	1 Year	P-value
CDVA (logMAR, mean ± SD) (Snellen equivalent)	0.39 ± 0.29 (20/49)	0.28 ± 0.22 (20/38)	**<0.001**
Maximum keratometry (diopters, mean ± SD)	54.54 ± 5.50	53.52 ± 5.18	**<0.001**
Thinnest pachymetry (μm, mean ± SD)	460.11 ± 47.15	430.65 ± 61.90	**<0.001**

Abbreviations: CDVA, corrected distance visual acuity; CXL, corneal collagen crosslinking. Bold values indicate statistical significance = $P<0.05$, paired *t*-test.

Comparison of the postoperative changes in CDVA and maximum K between groups: There were no significant differences between two groups in terms of change in CDVA and maximum K after CXL treatment ($P = 0.099$, $P = 0.332$, respectively).

Preoperative cone location. The study group comprised only eyes with central and paracentral cones.

Central cone (n = 72): There were significant improvements in mean CDVA (from 0.43 ± 0.32 logMAR, 20/53 Snellen, to 0.30 ± 0.23 logMAR, 20/39 Snellen, $P < 0.001$) and maximum K (from 55.75 ± 5.68 D to 54.54 ± 5.36 D, $P < 0.001$) 1 year after CXL treatment.

Paracentral cone (n = 24): There were no significant improvements in mean CDVA (from 0.24 ± 0.09 logMAR, 20/34 Snellen, to 0.21 ± 0.18 logMAR, 20/32 Snellen, $P = 0.239$) and maximum K (from 50.90 ± 2.92 D to 50.47 ± 3.05 D, $P = 0.057$) at 1-year follow-up.

Comparison of the postoperative changes in CDVA and maximum K between the groups: The changes in mean CDVA and maximum K after CXL treatment did not show significant differences between two groups ($P = 0.176$, $P = 0.160$, respectively).

Preoperative thinnest pachymetry Thinnest pachymetry $< 450\,\mu m$ (n = 45): The baseline mean CDVA (from 0.44 ± 0.35 logMAR, 20/55 Snellen, to 0.32 ± 0.23 logMAR, 20/41 Snellen, $P = 0.012$) and *maximum K* (from 57.79 ± 5.52 D to 56.10 ± 5.17 D, $P < 0.001$) significantly improved after CXL treatment.

Thinnest pachymetry $\geq 450\,\mu m$ (n = 51): The mean CDVA (from 0.34 ± 0.23 logMAR, 20/43 Snellen, to 0.24 ± 0.21 logMAR, 20/34 Snellen, $P = 0.001$) significantly improved, whereas maximum K (from 51.67 ± 3.67 D to 51.25 ± 4.02 D, $P = 0.124$) did not show significant improvement after CXL treatment.

Comparison of the postoperative changes in CDVA and maximum K between groups: The maximum K significantly decreased in thinner corneas (pachymetry $< 450\,\mu m$) compared with that of the relatively thicker corneas (pachymetry $\geq 450\,\mu m$; $P = 0.005$), whereas there was no significant difference between the groups with respect to improvement in CDVA ($P = 0.627$).

Postoperative changes in mean CDVA and maximum K according to the preoperative factors are demonstrated in Figures 1 and 2.

Discussion

CXL using photosensitizer riboflavin and UVA-light has been introduced as a promising new treatment for progressive keratoconus to reduce the need for corneal transplantation.[4] The treatment, as a photo-oxidative procedure, enhances biomechanical stability of the cornea because of synthesis of well-structured collagen and new lamellar interconnections in the cornea.[5,6,15] Numerous clinical studies agreed that CXL treatment provides significant improvements in visual acuity and maximum keratometry as well as halting the progression of keratoconus.[7,8,16,17] However, it is still unclear whether baseline demographic and topographic characteristics influence postoperative outcomes. Therefore, we sought effects of age, gender, preoperative CDVA, preoperative
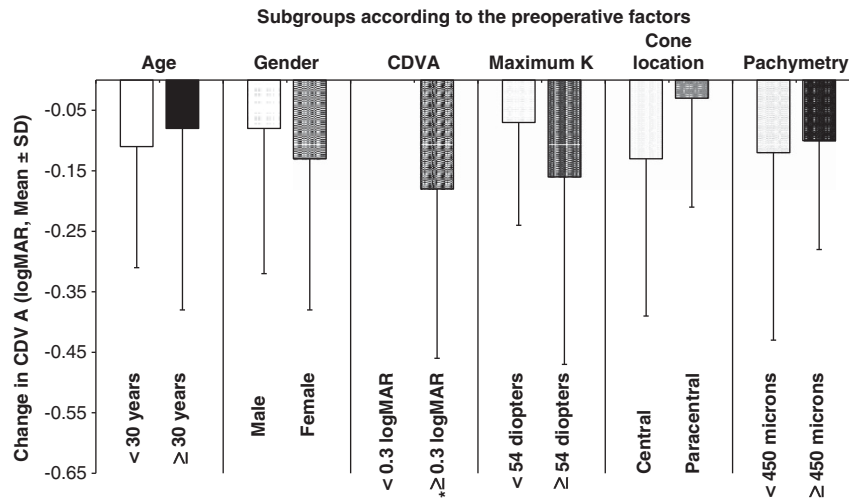

Figure 1 Change in mean corrected distance visual acuity (CDVA) between baseline and 1 year after CXL treatment in subgroups (*indicates statistically significant difference between two groups, $P < 0.05$).

Subgroups according to the preoperative factors
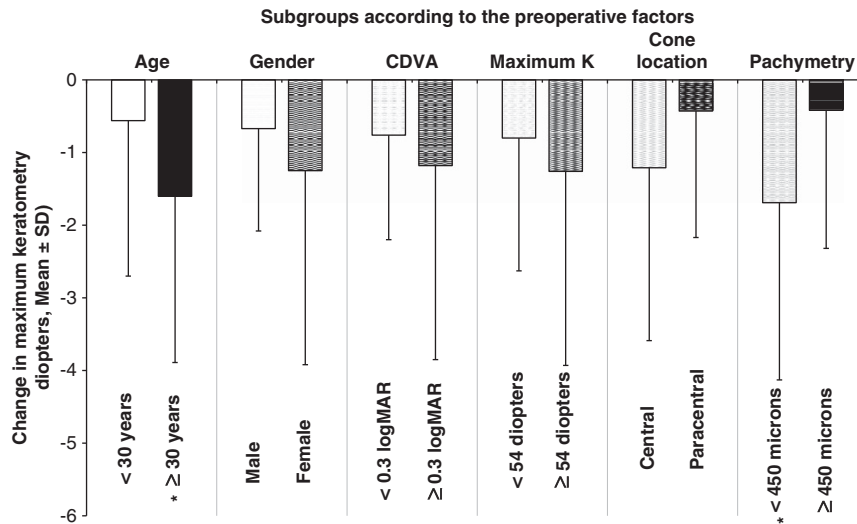

Figure 2 Mean decrease in maximum keratometry between baseline and 1 year in subgroups (*indicates statistically significant difference between two groups, $P < 0.05$).

maximum K, topographic cone location, and preoperative thinnest corneal pachymetry on improvements in CDVA and maximum K at 1 year after CXL treatment. In the entire study group, the improvements in CDVA and maximum keratometry after CXL treatment were in agreement with the previous studies.[9,10,18–20]

In the current literature, a small number of studies investigated the effects of preoperative patient characteristics on outcomes of CXL treatment. Koller et al[21] evaluated the effects of maximum K, preoperative CDVA, and age on complication and failure rates of CXL treatment for primary keratectasia. They suggested that age older than 35 years and a preoperative CDVA better than 20/25 (Snellen equivalent) were significant risk factors for complications (percentage of eyes losing two or more Snellen lines) and a preoperative maximum K > 58 D was identified a significant risk factor for failure (percentage of eyes with continued progression). On the contrary, another study by Koller et al[22] demonstrated that a preoperative maximum K of > 54.00 D was a significant positive preoperative predictor of corneal flattening 1 year after CXL treatment. Similarly, a multifactorial analysis by Greenstein and colleagues revealed that patients with initial worse CDVA ($\leq 20/40$ Snellen equivalent) and a higher keratometry (≥ 55 D) were most likely to benefit from CXL treatment.[23]

In our study, a preoperative CDVA $\leq 20/40$ Snellen equivalent was found significantly related with postoperative visual improvement. Furthermore, patients with an age ≥ 30 years and a thinnest corneal pachymetry less than 450 μm significantly experienced more flattening in maximum K. However, gender, preoperative maximum K, and preoperative topographic cone location did not affect postoperative changes in

mean CDVA and maximum K. Another study by Greenstein et al[24] demonstrated more topographic flattening in eyes with centrally located cones compared with that of the peripherally located cones 1 year after CXL treatment, whereas differences among cone groups were not found statistically significant with respect to change in visual acuity.

It has been concluded that CXL is a safe and effective procedure for the treatment of progressive keratoconus, whereas it is still unclear which patients are more likely to benefit from the treatment. In clinical practice, it can be valuable to predict success of the treatment to give patients satisfactory information about postoperative course.

In conclusion, our study evaluated baseline demographic and topographic data to determine preoperative predictors of CXL treatment efficacy. Age, preoperative CDVA, and thinnest corneal pachymetry appear to influence the efficacy of CXL treatment.

Summary

What was known before
- Previous studies demonstrated the efficacy of corneal collagen crosslinking (CXL) treatment in patients with keratoconus.
- Preoperative predictors of CXL efficacy were not completely elucidated.

What this study adds
- Patients with an older age ($\geq$ 30 years), a worse baseline corrected visual acuity ($\leq 20/40$ Snellen equivalent), and a thinner baseline pachymetry (< 450 μm) most likely to benefit from CXL treatment.
- Preoperative corrected visual acuity was significantly related with visual improvement, whereas age and baseline thinnest corneal pachymetry showed a significant effect on flattening of maximum keratometry.

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