Corneal Collagen Cross-Linking for Ectasia after LASIK and Photorefractive Keratectomy

Long-Term Results

Olivier Richoz, MD, Nikolaos Mavrankanas, MD, Bojan Pajic, MD, PhD, Farhad Hafezi, MD, PhD

Purpose: To report the long-term results of corneal collagen cross-linking (CXL) in ectasia after LASIK and photorefractive keratectomy (PRK).

Design: Retrospective, interventional cases series.

Participants: Twenty-six eyes of 26 patients (18 male, 8 female) with postoperative ectasia after LASIK (23 eyes) and PRK (3 eyes) were included with a mean age of 35±9 years at the time of treatment and a mean follow-up of 25 months (range, 12–62 months).

Methods: All consecutive patients treated with CXL for progressive ectasia after LASIK or PRK at the Institute for Refractive and Ophthalmic Surgery, Zurich, Switzerland between 2004 and 2010 were included.

Main Outcome Measures: Corrected distance visual acuity (CDVA), maximum keratometry readings (K_max), minimum radius of curvature (R_min), and 6 corneal topography indices were assessed in this study.

Results: Mean CDVA before CXL was 0.5 logarithm of the minimum angle of resolution (logMAR) units, which improved to a mean of 0.3 logMAR units (P<0.001). Corrected distance visual acuity improved 1 line or more in 19 cases and remained unchanged in 7 patients. Mean K_max after CXL of 50.9±4.9 diopters (D) was significantly lower (P<0.001) than mean pre-CXL K_max of 52.8±5 D. The R_min after CXL was increased significantly (P = 0.006), whereas the index of surface variance (P = 0.03), the index of vertical asymmetry (P = 0.04), the keratoconus index (P = 0.03), and the central keratoconus index (P = 0.016) were reduced significantly.

Conclusions: Ectasia after LASIK and PRK was arrested by CXL with stabilization or improvement of CDVA and K_max after a mean follow-up of 25 months. There were improvements in 4 topography indices, suggesting a more regular corneal surface.

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Iatrogenic ectasia after refractive laser surgery, a progressive stromal thinning and steepening of the cornea resulting in refractive aberrations and visual loss, increasingly has been reported since its first description by Seiler et al in 1998. All excimer laser procedures remove corneal tissue, weakening corneal biomechanics. Iatrogenic keratectasia is a sight-threatening complication after LASIK, occurring in 0.1% of cases, and is less frequent after photorefractive keratectomy (PRK). The major risk factors for ectasia after refractive laser surgery are deep ablation, residual stromal thickness of less than 250 μm, retreatments, and pre-existing abnormal corneal topography such as forme fruste keratoconus and pellucid marginal degeneration.

Corneal collagen cross-linking (CXL) has emerged as an effective technique to delay or arrest progression of keratoconus and postoperative ectasia. Corneal collagen cross-linking increases the stromal biomechanical stability by creating additional chemical bonds using ultraviolet A light and riboflavin as photomediator. These biomechanical changes can be detected either directly or via changes in corneal topography. Corneal collagen cross-linking also improves stromal collagen resistance to endogenous protease, a proposed cause of ectasia. Before CXL emerged, treatment options for iatrogenic ectasia were limited to intracorneal ring segments to try to stabilize the cornea mechanically and to lamellar or penetrating keratoplasty. Hafezi et al investigated the effect of CXL on iatrogenic keratectasia and observed an improvement in corrected distance visual acuity (CDVA) in 9 of 10 cases, improved keratometric readings in 5 of 10 cases, and reduction in cylinder in all patients. Salgado et al similarly showed regression of corneal ectasia and improvement of spherical equivalent with a 6-month follow-up. Recently, Hersh et al reported 1-year outcomes of a prospective, randomized clinical trial on CXL in both keratoconus and ectasia patients, showing significant improvement in CDVA and reduced maximum keratometric values; however, the CXL results were less notable in ectasia patients.

The results of these studies, evaluating the efficacy, stability, and safety of corneal CXL for ectasia, are limited by short follow-up. The study evaluated the effect of CXL in the treatment of ectasia after LASIK and PRK with a follow-up period of up to 62 months (mean, 25 months).

Patients and Methods

This was a retrospective study of all consecutive patients treated with CXL for progressive ectasia after LASIK or PRK at the Institute for Refractive and Ophthalmic Surgery, Zurich, Switzerland...
land, between 2004 and 2010. The study was approved by the local institutional review board and adhered to the tenets of the Declaration of Helsinki. All patients provided written informed consent.

Ectasia was defined as topographic steepening of 5 diopters (D) or more compared with immediate postoperative appearance, loss of 2 lines or more of Snellen acuity, and a change in manifest refraction of 2 D or more of either sphere or cylinder. Progression was defined by an increase of maximum keratometry readings ($K_{max}$) of the anterior corneal surface, at 3.0 mm from the apex, of at least 1.0 D in corneal topographies over a maximum of 12 months. Central corneal thickness (CCT) by optical and ultrasonic pachymetry was at least 300 μm with the exception of 1 patient with CCT of 297 μm. None of the patients had a history of corneal surgery, chemical injury, or delayed epithelial healing or was pregnant or lactating during the treatment.

The main outcome measures were: CDVA, $K_{max}$, minimum radius of curvature, and 6 quantitative descriptors of corneal topography (Pentacam topography; Oculus Instruments, Wetzlar, Germany), including index of surface variance, index of vertical asymmetry, keratoconus index, central keratoconus index, center keratoconus index, index of height asymmetry, and index of height decentration.

**Corneal Collagen Cross-Linking Surgical Technique**

Corneal collagen cross-linking was performed using the standard protocol except for 8 patients with CCT thinner than 400 μm, in whom hypo-osmolar riboflavin solution was used before surgery. After topical anesthesia with tetracaine 1% and oxybuprocaine 0.4%, the central 8.0 mm of corneal epithelium were debrided using a hockey knife. Riboflavin solution (0.1% solution 10 mg riboflavin-5-phosphate in 10 ml dextran-T-500 20% solution) was instilled every 3 minutes for 30 minutes for complete stromal penetration, confirmed by green aqueous fluorescence with blue light slit-lamp biomicroscopy. Ultraviolet A irradiation then was applied using UV-X (Peschke Meditrade, Cham, Switzerland). Before treatment, the intended 3-mW/cm$^2$ surface irradiance (5.4 J/cm$^2$ surface dose after 30 minutes) was calibrated using an ultraviolet A meter (LaserMate-Q, LASER 2000; Coherent Inc, Santa Clara, CA) at a working distance of 10 cm. During treatment, riboflavin solution was applied every 5 minutes; tetracaine 1% and oxybuprocaine 0.4% drops were given if necessary.

At the end of the procedure, ofloxacin ointment (Floxaich; Bausch & Lomb, Madison, NJ) was applied every 2 hours and at night until full corneal re-epithelialization occurred. Then, fluorometholone 0.1% drops (FML Liquifilm; Allergan Inc, Irvine, CA) were administered twice daily for 6 weeks.

**Examination**

Preoperative and postoperative examinations included CDVA, slit-lamp evaluation, Goldmann applanation tonometry, corneal topography, and minimal and central corneal thickness by Scheimpflug imaging (Pentacam; Oculus Instruments, Wetzlar, Germany), ultrasonic pachymetry (Tomey Corporation, Nahoya, Japan). Visual acuity was recorded and analyzed as the logarithm of the minimum angle of resolution (logMAR) value. Scheimpflug imaging was not available at the beginning of the study, but was performed in the last 18 of 26 cases. The $K_{max}$ reading was performed in all cases using corneal topography. Because of high intraindividual variation associated with $K_{max}$, 3 keratometry readings were performed and the highest of the 3 was chosen. For ultrasound pachymetry, the thinnest measurement was chosen, with each single measurement representing the mean of 5 consecutive measurements.

**Statistical Analysis**

Statistical analysis was performed using PASW Statistics software version 18 (SPSS, Inc, Chicago, IL). A paired 2-tailed Student’s t test was performed to analyze the postoperative outcome changes compared with baseline values. A $P$ value less than 0.05 was used to determine statistical significance. The Wilcoxon test was used for keratoconus index and index of height asymmetry.

**Results**

Twenty-six eyes of 26 patients (18 male, 8 female) with progressive ectasia after LASIK (23 eyes) and PRK (3 eyes) were included. The mean ± standard deviation (SD) patient age at CXL treatment was 35±9 years (range, 23–46 years). Twenty-five of 26 eyes had a central CCT by optical and ultrasonic pachymetry of at least 300 μm; 1 eye had a CCT of 297 μm. Fifteen patients (58%) had unidiagnosed keratoconus, 3 patients (12%) had undiagnosed pellucid marginal degeneration, and 3 patients (12%) had a deep stromal ablation. In 4 cases (15%), the cause of the ectasia was not clear.

Mean ± SD follow-up was 25±13 months (range, 12–62 months). Mean ± SD CDVA was 0.5±0.3 logMAR before CXL (range, 0.1–1.0) and improved to 0.3±0.14 logMAR (range, 0.1–0.6 logMAR) after treatment. Total mean ± SD CDVA improved to 0.2±0.16 logMAR ($P<0.001$). Corrected distance visual acuity improved (gain of ≥1 line) in 19 cases and remained stable in 7 patients. No patient showed deterioration (lost ≥1 line).

Mean ± SD $K_{max}$ after CXL of 50.9±4.9 diopters (D) (range, 45.4–64.4 D) was significantly lower ($P<0.001$) than mean $K_{max}$ before CXL (52.8±5.2 D; range, 45.1–65.5 D). Mean ± SD $K_{max}$ improvement was 1.9±1.9 D (range, –0.6 to 7.7 D). There was no significant correlation between $K_{max}$ and CDVA before ($r=0.12$, $P=0.53$) or after ($r=0.1$, $P=0.6$) treatment. In 19 patients, $K_{max}$ improved (more than 1 D improvement) and in 7 patients was stable (less than 1-D change). In the 4 cases with follow-up longer than 3 years, both $K_{max}$ and CDVA remained stable. Mean ± SD CCT was 9±17 μm thinner (range, –27 to 32 μm) after CXL ($P=0.007$).

The 3 cases of ectasia occurring after PRK all showed forme fruste keratoconus before surgery and the following characteristics after CXL: mean preoperative $K_{max}$ improved from 50.1 D to 49.7 D. Corrected distance visual acuity remained stable in 2 patients and improved by 0.03 logMAR for the third patient. Statistical comparisons between the groups of LASIK and PRK patients are limited by the small number of the latter.

The minimum radius of curvature was increased significantly after CXL. The index of surface variance, the index of vertical asymmetry, the keratoconus index, and the central keratoconus index were reduced significantly. There was no significant change in the index of height asymmetry or index of height decentration. The results and $P$ values are summarized in Table 1, Figures 1 and 2 show preoperative and postoperative topographies and their difference maps.

No serious complications were reported during the follow-up period. A corneal demarcation line was observed at a depth of approximately 250 to 300 μm in all cases undergoing CXL after 2005, when the initial observation on the existence of such a line was submitted. A haze was visible in the anterior stroma, up to 80% of thickness, in all eyes, but disappeared within 12 months after CXL. One case with preoperative CCT by ultrasonic pachymetry of 400 μm had endothelial irregularity and endothelial opacities at presentation that cleared within 12 months after CXL with a stable endothelial cell count of 2350 cells/mm. The patient showing a preoperative thickness of 297 μm was treated using...
hypo-osmolar riboflavin solution and showed no signs of endothelial damage.

Discussion

This study of CXL for ectasia after refractive surgery, with 23 cases occurring after LASIK and 3 cases occurring after PRK, offers a longer follow-up (mean, 25 months; maximum, 62 months) when compared with the existing literature. Results of CXL for PRK-induced ectasia have not been published previously.

This study found an improvement in CDVA in 19 of 26 patients after CXL, with a mean improvement of 0.2 logMAR. In a previous report, an improvement in CDVA was shown in 9 of 10 patients after CXL, but a recent report by Hersh et al11 showed only a 0.07-logMAR increase in CDVA at 1 year after CXL. Corneal collagen cross-linking has been proven very effective in halting the progression of keratoconus and iatrogenic ectasia, but visual recovery,

Table 1. Results and P Values of Minimum Radius of Curvature and 6 Corneal Topography Indices

<table>
<thead>
<tr>
<th>Index</th>
<th>Before Corneal Collagen Cross-Linking</th>
<th>After Corneal Collagen Cross-Linking</th>
<th>Change</th>
<th>Standard Deviation</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>KI</td>
<td>1.26</td>
<td>1.24</td>
<td>–0.022</td>
<td>±0.06</td>
<td>0.029*</td>
</tr>
<tr>
<td>IHA</td>
<td>31.1</td>
<td>25.4</td>
<td>–5.66</td>
<td>±21.88</td>
<td>0.149</td>
</tr>
<tr>
<td>ISV</td>
<td>99.17</td>
<td>92.28</td>
<td>–6.89</td>
<td>±12.21</td>
<td>0.029*</td>
</tr>
<tr>
<td>IVA</td>
<td>1.19</td>
<td>1.11</td>
<td>–0.081</td>
<td>±0.156</td>
<td>0.043*</td>
</tr>
<tr>
<td>CKI</td>
<td>1.05</td>
<td>1.03</td>
<td>0.014</td>
<td>±0.022</td>
<td>0.016*</td>
</tr>
<tr>
<td>IHD</td>
<td>0.089</td>
<td>0.08</td>
<td>–0.009</td>
<td>±0.023</td>
<td>0.117</td>
</tr>
<tr>
<td>R_{min}</td>
<td>6.39</td>
<td>6.54</td>
<td>0.146</td>
<td>±0.196</td>
<td>&lt;0.0061*</td>
</tr>
</tbody>
</table>

CKI = central keratoconus index; IHA = index of height asymmetry; IHD = index of height decentration; ISV = index of surface variance; IVA = index of vertical asymmetry; KI = keratoconus index; R_{min} = minimum radius of curvature.

*Statistically significant.

Figure 1. Topographies obtained (Top left) before and (Top middle, Bottom left, and Bottom middle) after corneal collagen cross-linking (CXL) showing regression of maximum keratometry reading (K_{max}) over 3 years. The difference map visualizes the regression over more than 5 diopters. OD = right eye.
Although statistically significant, usually is modest.\textsuperscript{11,25,26} It also seems that the visual outcome in patients with iatrogenic ectasia has been inferior compared with that of keratoconus patients after CXL.\textsuperscript{11}

Mean $K_{\text{max}}$ was significantly lower at 50.9 D ($P<0.001$) when compared with mean $K_{\text{max}}$ before CXL of 52.8 D. In 19 eyes, $K_{\text{max}}$ improved by more than 1 D, and in 7 eyes, it was stable. This is consistent with a previous report of 10 ectasia patients treated with CXL that showed a $K_{\text{max}}$ reduction from 54.5 D to 52.6 D. However, another report of 22 eyes with ectasia that had undergone LASIK showed no significant difference in $K_{\text{max}}$ before or after treatment (1.00 D decrease in $K_{\text{max}}$; $P = 0.08$). Vinciguerra et al\textsuperscript{27} also reported no significant topographic changes (average keratometry, flat keratometry, or steep keratometry) in patients with iatrogenic keratectasia. Those results suggest that ectatic corneas may have a less robust response to CXL as opposed to keratoconic corneas. Although the cause for this potential difference in not clear, several explanations have been suggested. One is that CXL preferentially strengthens the anterior stroma, including the LASIK flap, which does not contribute to the mechanical stability of the cornea. The riboflavin diffusion may be reduced in corneas that have undergone LASIK, affecting the CXL result. Differences in the pathophysiologic features of keratoconus and ectasia occurring after refractive surgery also may account for a less pronounced CXL effect.\textsuperscript{11,28}

Corneal topography indices are elevated in ectasia patients with the exception of the minimum radius of curvature, the inverse of corneal steepness, and therefore are expected to decrease. A decrease in corneal indices after CXL may indicate improvement of the corneal irregularities. In 18 of 26 eyes for which Scheimpflug imaging was available, the results showed a statistically significant increase in the minimum radius of curvature and statistically significant decreases in the index of surface variance, the index of vertical asymmetry, the keratoconus index, and the central keratoconus index after CXL therapy. There were no significant changes in the index of height asymmetry or index of height decentration.

The increase in the minimum radius of curvature in the present study is consistent with decreases in $K_{\text{max}}$ after CXL in many studies.\textsuperscript{8,26,27,29–31} Decreases in the index of surface variance indicate a decrease in the curvature variation compared with the mean curvature of the cornea, and decreases in the index of vertical asymmetry suggest a reduction of the difference between the superior and inferior corneal curvature. The decrease of this index may correspond to a decrease of the inferior-to-superior ratio.\textsuperscript{32–34} The significant improvement in the keratoconus and central

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{topographies.png}
\caption{Topographies obtained before and after corneal collagen cross-linking (CXL) in a patient with bilateral iatrogenic ectasia and their respective difference maps for (Top row) the right eye (OD) and (Bottom row) the left eye (OS). N = nasal; T = temporal.}
\end{figure}
keratoconus indices reflect the reduction of the corneal steepening after CXL. Improvement in those parameters may explain the visual recovery and reverse of refractive aberrations in some ectasia patients.

Previous studies from Koller et al. and Greenstein et al. showed similar results. Koller et al found significant improvement in 4 of 7 Pentacam topography indices (central keratoconus index, keratoconus index, index of height asymmetry, and minimum radius of curvature) 1 year after CXL. Greenstein et al. found changes in the index of surface variance, index of vertical asymmetry, keratoconus index, and minimum radius of curvature at 1 year after CXL, but the results were significant only in the subgroup of keratoconus patients, and not in the ectasia patients.

No serious complications were reported during the follow-up period, apart from an early corneal haze, which disappeared within 12 months after CXL, and a patient with an endothelial irregularity and preoperative CCT of 400 μm, which cleared after 12 months with a normal endothelial cell count. The direct irradiation by ultraviolet-A light normally is limited to the anterior 300 μm of corneal stroma, protecting the endothelium, iris, and lens. No permanent haze, stromal scars, sterile infiltrates, corneal edema, lamellar keratitis, infectious or herpetic keratitis, or iritis were described. The overall risk of corneal infection with CXL is low, possibly because of a bactericidal effect and an antibiotic prophylaxis occurring after CXL.

In conclusion, CXL arrested the progression of ectasia occurring after LASIK and PRK and improved the CDVA and K max with a mean follow-up of 25 months. There were improvements in 4 topography indices, suggesting a more regular corneal surface. In the light of these results and the absence of major complications, but also in the absence of other minimally invasive therapeutic options, the use of CXL in iatrogenic ectasia is recommended without restrictions.

References

29. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and cor-

Footnotes and Financial Disclosures

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