Simultaneous Topography-Guided Photorefractive Keratectomy Followed by Corneal Collagen Cross-linking for Keratoconus

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Purpose: To present the long-term results after simultaneous photorefractive keratectomy followed by corneal collagen cross-linking for keratoconus.

Design: Prospective, interventional, consecutive case series.

Methods: In this study, 26 patients (31 eyes) with progressive keratoconus were included. All patients underwent customized topography-guided photorefractive keratectomy immediately followed by corneal collagen cross-linking with the use of riboflavin and ultraviolet A irradiation. Epithelium was removed by transepithelial phototherapeutic keratectomy in all cases.

Results: Mean follow-up was 19.53 ± 3.97 months (range, 12 to 25 months). Mean preoperative spherical equivalent was −2.3 ± 2.8 diopters (D), whereas at the last follow-up examination, it was significantly (P < .001) reduced to −1.08 ± 2.41 D. Logarithm of the minimal angle of resolution uncorrected and best-corrected visual acuity were reduced significantly by 0.46 and 0.084 (P < .001), respectively, at the last follow-up examination. Finally, mean steep and flat keratometry readings were reduced by 2.35 (P < .001) and 1.18 (P = .013) at the last follow-up examination.

Conclusions: Simultaneous photorefractive keratectomy followed by corneal collagen cross-linking seems to be a promising treatment alternative in our series of keratoconic patients.

ORNEAL ECTATIC DISORDERS, THE MOST COMMON of which is keratoconus, represent a group of conditions characterized by a bilateral state of tectonic corneal weakness that can lead to thinning of the cornea, production of myopia and irregular astigmatism, and visual acuity deterioration.

Treatment options comprise 2 general approaches: first, vision restoration by means of spectacles or rigid gas permeable contact lenses, and second, restoration of the tectonic integrity of the cornea by means of intracorneal ring segments and corneal collagen cross-linking (CXL). In advanced cases of keratoconus, lamellar or penetrating keratoplasty are considered essential treatment possibilities to improve patients’ quality of life.

CXL is a minimally invasive technique using riboflavin and ultraviolet A irradiation for the enhancement of corneal rigidity. In particular, CXL augments the biomechanical strength of the cornea by inducing interfibrillar cross-links of the stroma, resulting in the stabilization of the disorder. Results are extremely promising, but poor vision quality in patients remains largely unchanged, with minimal improvement.

Several combined procedures have been proposed to optimize the CXL result (such as conductive keratoplasty followed by CXL), but it seems that the most effective is the combined topography-guided photorefractive keratectomy (PRK) followed by CXL. In this case series, we present the long-term results of simultaneous customized topography-guided surface ablation followed by CXL in patients with keratoconus.

METHODS

IN THIS STUDY, 26 PATIENTS (31 EYES; CONSECUTIVE series), 18 men and 8 women, with progressive keratoconus were included. Mean age was 29.3 ± 8.5 years (range, 19 to 49 years). Inclusion criteria were progressive keratoconus (keratoconus was described as progressive when there was an increase in the cone apex keratometry of −0.75 diopters [D] or an alteration of −0.75 D in the spherical equivalent refraction in the last 6 months), expected corneal thickness at the apex of the cone after PRK more than 400 μm, and no other corneal pathologic signs.

Clinical Evaluation: Preoperative evaluation consisted of general and ocular health history assessment; corneal topography (iTrace; Tracey Tech, Houston, Texas,
USA); assessment of uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), and manifest refraction; scotopic pupillometry; central ultrasound pachymetry (Corneo-Gage Plus; Sonogage, Inc, Cleveland, Ohio, USA) and slit-lamp examination of the anterior and posterior segments of the eyes. Patients’ preoperative and postoperative data are shown in the Table. All data were analyzed for normality. Because not all variables followed normal distribution, the Wilcoxon signed-rank paired test (PASW Statistics 18; SPSS, Inc, Chicago, Illinois, USA) was used. All diagrams and frequency analyses were performed by Microsoft Excel 2007 (Microsoft, Inc, Redmond, Washington, USA). Harris notation was used to calculate the mean values of refractions in the Table.

**SURGICAL PROCEDURE:** All procedures were performed in our institution by the same surgeon (G.D.K.) under sterile conditions. After topical anesthesia with tetracaine 1% and oxybuprocaine 0.4% eyedrops, the epithelium was removed by transepithelial phototherapeutic keratectomy (PTK). The transepithelial PTK ablation was performed in an 8.0-mm zone in an intended depth of 50 μm. A solid-state laser with a wavelength of 213 nm (Pulzar Z1; CustomVis, Perth, Washington, USA) was used for the PRK procedure. The wavelength is generated using a major neodymium:yttrium–aluminum–garnet laser system of 1064 nm, and through special cultivated crystals, the 213 nm is used finally. The customization was performed based on the topographic data obtained by the iTrace technology. System software allows using a percentage of customization from 0% to 100%.

**TABLE.** Preoperative and Last follow-up Refractive, Visual, and Keratometric Data in Keratoconic Patients after Combined Topography-Guided Photorefractive Keratectomy and Corneal Collagen Cross-linking

<table>
<thead>
<tr>
<th></th>
<th>MRSE (D)</th>
<th>UCVA (logMAR)</th>
<th>BCVA (logMAR)</th>
<th>Steep and Flat Keratometry (D)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>–2.3 ± 2.8</td>
<td>0.21 ± 0.18</td>
<td>0.81 ± 0.65</td>
<td>49.8 ± 5.3</td>
</tr>
<tr>
<td>Range</td>
<td>1.63 to –12.88</td>
<td>0.54 to –0.06</td>
<td>2 to 0.1</td>
<td>67.7 to 42.7</td>
</tr>
<tr>
<td>Mean refraction (range)</td>
<td>–2.06/–0.48@77°</td>
<td>20/33</td>
<td>20/131</td>
<td>44.39 ± 4.8 (62.75 to 37.1)</td>
</tr>
<tr>
<td><strong>Postoperative data (mean follow-up, 19.53 ± 3.97 mos; range, 12 to 25 mos)</strong></td>
<td></td>
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<tr>
<td>Mean ± SD</td>
<td>–1.08 ± 2.41</td>
<td>0.12 ± 0.15</td>
<td>0.35 ± 0.36</td>
<td>47.46 ± 4.3</td>
</tr>
<tr>
<td>Range</td>
<td>2.5 to –8.75</td>
<td>0.46 to –0.04</td>
<td>1.2 to –0.04</td>
<td>53 to 57.48</td>
</tr>
<tr>
<td>Mean refraction (range)</td>
<td>–0.81/–0.54@74°</td>
<td>20/27</td>
<td>20/46</td>
<td>43.21 ± 3.4 (53 to 37.48)</td>
</tr>
</tbody>
</table>

BCVA = best-corrected visual acuity; D = diopters; K = keratometrics; logMAR = logarithm of the minimal angle of resolution; mos = months; MRSE = manifest refraction spherical equivalent; SD = standard deviation; UCVA = uncorrected visual acuity.

**FIGURE 1.** Bar graph showing change in best-corrected visual acuity (BCVA; safety) before and after photorefractive keratectomy followed by corneal collagen cross-linking for keratoconus confirming that approximately 50% of patients gained 1 line or more of BCVA at the last follow-up examination. PostOp = after surgery.
Because of continuous flattening after CXL, as shown in previous studies, the relevant attempted correction was up to 60% of sphere and cylinder of patient refractive error, whereas customization was adjusted from 0% to 100%. Using 0% would be equivalent to a conventional laser treatment, and 100% would be equivalent to a full customized treatment. Adjusting this percentage could lower the maximum depth of tissue removed (upper limit, 50 μm). Treatment modifications (attempted correction and percentage of customization) were based on preoperative corneal pachymetry, corrected distance visual acuity, and manifest refraction to arrive to a maximum ablation depth of 50 μm.

Next, riboflavin (0.1% solution of 10 mg riboflavin-5-phosphate in 10 mL dextran-T-500 20% solution) was applied every 3 to 5 minutes for approximately 30 minutes until the stroma was penetrated completely and aqueous was stained yellow (riboflavin shielding). A commercially available ultraviolet A system (UV-X illumination system, version 1000; IROC AG R&D, Zürich, Switzerland) with Koehler optics was used for ultraviolet A irradiation. Before treatment, the intended 3-mW/cm² surface irradiance (5.4 J/cm² surface dose after 30 minutes) was calibrated using the ultraviolet A meter YK-34UV (Lutron Electronic Enterprise CO, LTD, Taipei, Taiwan), which is supplied with the UV-X device. During treatment, riboflavin solution was applied every 3 to 5 minutes to ensure saturation.

After the treatment, a bandage contact lens was applied until the epithelium healed completely, followed by application of fluorometholone 0.1% eyedrops (FML Liquifilm; FALCON pharmaceuticals, Ltd, Fort Worth, Texas, USA) twice daily for 2 weeks.

RESULTS

All values are expressed as mean ± standard deviation and range. Visual acuity is expressed as logarithm of minimal angle of resolution (logMAR) visual acuity. All values presented statistically significant differences between preoperative and last postoperative period. Patient postoperative data at the last follow-up examination are shown in the Table.

FIGURE 2. Bar graph showing uncorrected visual acuity (UCVA; efficacy) before and after photorefractive keratectomy followed by corneal collagen cross-linking for keratoconus representing an increase in the percentage of eyes that achieved UCVA 20/100 or better at the last follow-up examination.

FIGURE 3. Box plot showing flat and steep keratometric readings after photorefractive keratectomy followed by corneal collagen cross-linking before surgery, at 1, 3, 6, and 12 months after treatment, and at the last follow-up, showing a significant decrease that remained stable throughout the follow-up. PreOp = before surgery; PostOp = after surgery.
Mean follow up was 19.53 ± 3.97 months (range, 12 to 25 months). Mean preoperative spherical equivalent was −2.3 ± 2.8 D, whereas at the last follow-up examination, it was reduced significantly \((P < .001)\) to −1.08 ± 2.41 D. LogMAR UCVA and BCVA were reduced significantly by 0.46 and 0.084 logMAR units \((P < .001)\) at the last follow-up examination. There were no intraoperative or postoperative complications.

Regarding the method’s safety, 48\% (15/31) of eyes gained 1 line or more of UCVA at the last follow-up examination (Figure 1). At the last follow-up examination, 10\% (3/31) of eyes lost 1 line of BCVA. As shown in Figure 2, 58\% (18/31) of eyes were had UCVA of 20/100 (Snellen) or better after surgery, whereas at the last follow-up, 87\% (27/31) of eyes had UCVA of 20/100 (Snellen) or better. Mean steep and flat keratometry readings were reduced by 2.35 D \((P < .001)\) and 1.18 D \((P = .013)\), respectively (Figure 3). The stabilization of uncorrected distance and corrected distance visual acuity is demonstrated in Figure 4. Additionally, spherical equivalent refractive changes in the follow-up period can be seen in Figure 5. Patient topographic improvement can be seen using the iTrace technology (Figure 6).

In 50\% (16/31) of the eyes, a posterior linear stromal haze corresponding to the central treated area of the cornea was detectable by slit-lamp examination 1 year after surgery. During the follow-up period, this finding gradually became less dense and demonstrated an anterior movement (Figure 7, Top left and Top right). This finding can be graded as mild haze (grade 1) according to the Fantes anterior stromal haze scale.11

In these eyes, using corneal confocal microscopy, we detected an area with high reflectance at the level of the posterior stroma characterized by spindle-shaped and hyperreflective structures (Figure 7, Bottom). The reflectance was located adjacent to the endothelial cell layer 1 year after surgery and gradually moved anteriorly throughout the follow-up. The highly reflective spindle-shaped structures have been linked with migration and activation of keratocytes, which become transformed during locomotion, assuming spindle- or needle-shaped morphologic features.12

**DISCUSSION**

CXL is a safe and effective technique for the management of ectatic disorders. It has been proven that CXL...
FIGURE 6. Two examples (Left and Right) of comparative topographic maps before (Bottom right) and after (Upper right) photorefractive keratectomy followed by corneal collagen cross-linking treatment for keratoconus showing significant improvement (difference topographic map left).
is effectual in stopping the progression of keratoconus by quasi-freezing of the cornea,\textsuperscript{13} and in many cases helps to avoid corneal transplantation. Nevertheless, a patient’s basic problem, which is the deterioration of their vision, remains. CXL combined with topography-guided PRK has been developed to achieve an important goal: to offer patients stability of their disorder and at the same time to assist them in achieving functional vision.

In this article, we report the long-term results of topography-guided PRK followed by CXL. All of our patients showed topographic progression of their ectasia over a period of 6 months (although 1 of our patients was 49 years of age). In our case series, all the parameters analyzed—spherical equivalent refraction, UCVA, BCVA, and mean keratometrics—showed a significant improvement that remained stable throughout the follow-up period. The safety index of the combined procedure was 1.21 at the last follow-up examination. No eye has lost more than 2 lines of UCVA at the last follow-up period. None of our patients showed topographic or clinical signs of keratoconus progression during the follow-up period. All patients showed marked improvement of corneal irregularity and visual acuity.

The epithelium was removed in all cases by transepithelial PTK. It is known that transepithelial PTK uses an excimer laser ablation to remove the epithelium and to smooth the anterior irregular cornea.\textsuperscript{14,15} The aim of transepithelial PTK was epithelial removal and anterior cornea smoothening to decrease further the irregular astigmatism.
In 50% of our patients, a posterior linear stromal haze developed that was detectable by slit-lamp biomicroscopy. The posterior haze gradually moved anteriorly and became less dense during the follow-up period. This finding could be attributed to the interaction between CXL and photoablation, which results in keratocyte activation. This may explain the high reflectance revealed in our case series, because our patients underwent photoablation in combination with CXL, and thereby photoablation may have induced keratocyte activation, causing posterior stromal hyperreflectance formation. Furthermore, the hyperreflective structures could be associated with increased collagen deposition, collagen disorganization, and excessive production of extracellular material from the activated kerocytes.

The aim of customized PRK was to remodel the shape of the cornea and to decrease irregular astigmatism. Customization could be a percentage of the fully customized treatment for reducing the maximum depth of tissue removed over the corneal irregularity. A maximum ablation depth of 50 μm has been chosen in all cases to achieve a decrease in astigmatism, but also to avoid removing a significant amount of tissue that would jeopardize the biomechanical integrity of the cornea. It has been demonstrated that even with a relatively small correction, because of the thickness limitations, patients may benefit substantially.

CXL alone is effective in achieving a cessation of the keratoconus progression. However, studies confirm a visual acuity improvement that is not always considered sufficient to meet patients’ needs. It seems that PRK followed by CXL is an improved version of CXL alone, because it combines halting of ectasia and significant vision improvement. This combined treatment seems to be more appropriate for patients with early keratoconus staging, because in more advanced cases, thinning of the cornea could limit the possibility of tissue removal by topography-guided PRK.

One of the limitations of our study is the lack of control group. The existence of a control group could facilitate the comparison between CXL alone and topography-guided PRK followed by CXL.

In conclusion, long-term results confirm the advantages of the combined PRK and CXL procedure. This combined treatment is capable of offering patients a functional vision and stabilization of the ectatic disorder. Further follow-up and additional cases must be reviewed to draw final conclusions about the benefit of this surgical technique in keratoconic patients.

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