One-Year Clinical Outcomes of a Two-Step Surgical Management for Keratoconus—Topography-Guided Photorefractive Keratectomy/Cross-Linking After Intrastralional Corneal Ring Implantation

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Purpose: To present the results of same-day topography-guided photorefractive keratectomy (TG-PRK) and corneal collagen cross-linking (CXL) after intrastromal corneal ring (ISCR) implantation in patients with keratoconus.

Methods: Thirty-three patients (41 eyes) aged between 19 and 45 years were included in this prospective study. All patients underwent a femtosecond laser–enabled (Intralase FS; Abbott Medical Optics, Inc.) placement of intracorneal ring segments (Kerarings; Mediphacos, Brazil). Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and keratometry readings remained stable for 6 months. Same-day PRK and CXL was subsequently performed in all patients.

Results: After 12 months of completion of the procedure, mean UDVA in log of minimal angle of resolution was significantly improved (0.74±0.54–0.10±0.16); CDVA did not improve significantly but 85% of eyes maintained or gained multiple lines of CDVA; mean refraction spherical equivalent (−3.03±1.98 to −0.04±0.99 D), all keratometry readings were significantly reduced, from preoperative values, but coma did not vary significantly from preoperative values. Central corneal thickness and corneal thickness at the thinnest point were significantly (P<0.0001) reduced from 519.76±29.33 and 501.87±31.50 preoperatively to 464.71±36.79 and 436.55±47.42 postoperatively, respectively. Safety and efficacy indices were 0.97 and 0.88, respectively. From 6 months and after 1 year of follow-up, further significant improvement was observed only for UDVA (P<0.0001).

Conclusions: Same-day combined TG-PRK and CXL after ISCR implantation is a safe and effective option for improving visual acuity and visual function and ceases progression of the ectatic disorder. The improvements recorded after 6 months of follow-up were maintained or improved upon 1 year after the procedure.

Key Words: Keratoconus—Corneal collagen cross-linking—Distance visual acuity—Satisfaction—Intrastralional corneal ring implantation.

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Keratoconus is a progressive non-inflammatory, asymmetric, and usually bilateral ectatic disease of the cornea characterized by localized corneal thinning, visual distortion, corneal steepening, and central corneal scarring. Its onset is generally at puberty but often progresses until the fourth decade of life, when it usually stabilizes. Its prevalence in the general population is reported to be about 1 in 2,000 (0.0005%) people, and 1 in 1,750 white Europeans aged between 10 and 44 years are affected with the disease and this estimate rises to 1 in 450 (0.002%) in South Asians. In Saudi Arabia, an incidence of 20/100,000 (0.002%) was reported in one province a decade ago, and an increase in the number of referrals because of keratoconus has also been observed.

Corneal collagen cross-linking (CXL) uses riboflavin and UV-A irradiation to strengthen the cornea by augmenting the crosslinks between collagen fibrils, thereby stabilizing the condition and effectively stalling the progression of keratoconus and pellucid marginal degeneration. CXL alone may prevent topographic and refractive progression but it leads to minimal improvement in vision quality of patients and induces corneal flattening. However, a combination of various techniques like conductive keratoplasty, photorefractive keratectomy (PRK), intrastromal corneal ring (ISCR) implantation plus PRK, non–topography-guided PRK after ISCR implantation, and simultaneous wavefront-guided PRK with CXL maximizes the results by providing an overall additive effect on visual acuity, keratometry, and stability of the condition.

Same-day simultaneous topography-guided PRK and CXL was shown to be superior to sequential CXL with later PRK in the visual rehabilitation of progressing keratoconus. Despite the reported safety and improvements in visual functions associated with same-day combined surgical approach, few studies have followed up the patients beyond 6 months postoperatively and the procedure is uncommon among practitioners in the Middle East despite the increasing number of keratoconus referrals. This study aim to evaluate the efficacy of ISCR implantation followed no less than 6 months later by same-day topography-guided photorefractive keratectomy (TG-PRK) combined with CXL for visual rehabilitation in patients with keratoconus (two-step procedure). To enable the comparison of the outcomes of this study with those of other studies, to enhance easy recognition, and to allow the reader to quickly find some basic information, the results were reported using the standards outlined for reporting outcomes of refractive surgery but often ignored by researchers.
SUBJECTS AND METHODS

Subject Population
Forty-one eyes of 33 patients with keratoconus (24 men [72.7%] and 9 women [27.3%]) of mean age 28.4±6.7 years (range: 19.45 years) were randomly recruited from a pool of patients seeking relief from their ocular condition and who were scheduled to undergo a combined surgical procedure for management of their existing keratoconus condition. Informed consent was obtained after the hospital research review board approved the study protocol. The study conformed to the tenets of the Declaration of Helsinki (1975), as revised in Edinburgh 2000.

All patients underwent ISCR implantation and were followed up for at least 6 months and at most 9 months, until stabilization of refraction was achieved before same-day TG-PRK and CXL was performed. These patients were included if the patients were interested in the study, were intolerant to contact lens wear or were not interested in participating in the study, showed moderate keratoconus, poor spectacle vision, and progression in keratoconus observed over the previous 6 months. The exclusion criteria were the presence of any of the following conditions: central or paracentral corneal scarring; central pachymetry less than 400 μm, as measured by the Galilei Dual Scheimplug Analyzer (Ziemer, Switzerland), pregnancy or lactation; severe dry-eye disease; systemic autoimmune disease; and/or a history of herpetic keratitis. Keratoconus was graded based on Amsler–Krumeich classification in accordance with the distribution area of the ectasia as has been described by Gómez-Miralles et al. However, progression of keratoconus was defined as one or more of the following changes over a period of 6 months: an increase of ≥1.00 D in K-max, an increase of ≥1.00 D manifest cylinder, or an increase of ≥0.50 D in manifest refraction spherical equivalent. All patients were seeking relief from symptoms arising from their refractive errors.

Data Collection
Clinical evaluation of general and ocular health was performed preoperatively. For all patients, one Optometrist assessed the following visual parameters, preoperatively, after 6 and 12 months of performing the two-step procedure (ISCR implantation followed by same-day TG-PRK and CXL): uncorrected distance visual acuity (UDVA [log of minimal angle of resolution; logMAR]); corrected distance visual acuity (CDVA [logMAR]); mean manifest objective cylinder; mean objective sphere; central corneal thickness (CCT) by ultrasound pachymeter; topographical keratometry values; and corneal coma-like root mean square assessed over a 4.5 mm of pupil size. The keratometry values and coma were obtained using the Schwind Corneal wavefront Analyzer (Schwind Eye-tech-Solutions; GmbH & Co., Kleinostheim, Germany). All data were entered into a Microsoft Excel 2007 spreadsheet (Microsoft, Inc, Redmond, WA). The means, standard deviations, and minimum and maximum values were calculated and presented descriptively using standard graphs and tables used for reporting refractive surgery results as recommended by Waring et al.

Surgical Procedures
All procedures—the first step (ISCR) and the second step (PRK and CXL)—in all patients were performed at the Elite Medical Centre Riyadh, by the same Ophthalmologist (W.S.A.-T.) under conditions similar to what is used in refractive surgery suites. As a first step, all eyes underwent femtosecond laser–enabled Intralase FS 150 kHz (Intralase Corp./Abbott Medical Optics, Inc., Abbott Park, IL) placement of ICRs using the Keraring (Mediphacos, Brazil) with a 1.30 μl default energy setting. Segment sizes were determined according to the nomogram provided by the manufacturer. Depth of the ring channels was set at 75% to 80% of the thinnest pachymetry reading, and the tunnel was programmed for an inner diameter of 4.4 mm and an outer diameter of 5.6 mm, the entry cut thickness was 1 μm (at the steepest topographic axis). At the end of the surgery, dicyfenac sodium 0.1% (Voltaren) and tobramycin/dexamethasone eye drops were administered, a bandage contact lens (Air Optix Ciba Vision of material, lotrafilcon B, diameter 14.0 mm, base curve 8.6 mm, and Dk of 140 barrers) was fitted, and slitlamp examination was conducted. Approximately 3 to 5 days later, the bandage contact lens was removed after the epithelial defect at the site of incision had closed.

Following stabilization of refraction after ISCR implantation, the patients underwent a second step of topography-guided PRK followed by same-day riboflavin–UV-A CXL during same session. Transepitheelial mode to remove the epithelium was performed in all cases by phototherapeutic keratectomy (PTK) using the Schwind Amaris laser platform (Schwind Eye-tech-Solutions; GmbH & Co.), so as to smooth the anterior irregular cornea. To minimize tissue ablation and reduce the risk of iatrogenic ectasia, the PTK ablation was performed to remove 50 μm of the central 6.5 mm of corneal epithelium before performing TG-PRK treatments with a 6-mm optical zone. We aimed to reduce irregular astigmatism by normalizing the cornea while treating part of the refractive error. Corneal wavefront errors were calculated using the topography data from the Corneal Wavefront Analyzer, a standard eye model, and ray tracing. The Schwind Corneal Wavefront Analyzer measures the difference between the anterior topography and the best sphere and converts the corneal plane from its current state to the best sphere. This profile was shown to be reliable and with it, we tried to achieve emmetropia in one surgical step. The instrument also has the capability of selective treatment for coma or spherical aberration alone. The aim of this treatment was to normalize the cornea by reducing irregular astigmatism while treating part of the refractive error. Mitomycin C (0.02 mg/mL) was then applied for 30 sec for all TG-PRK procedures. Shortly after PRK, the CXL treatment was initiated by instilling 0.1% riboflavin solution in the center of the cornea every 2 to 3 min for 30 min to saturate the cornea. During the procedure, the absorption of riboflavin across the corneal stroma and anterior chamber was confirmed through examination under the slitlamp. Hypotonic riboflavin (0.1% with no dextran) was used for 10 min to induce corneal swelling to at least 400 μm, but when the stromal bed thickness was less than 400 μm, isotonic riboflavin was used. Thinnest and CCT were continuously monitored using ultrasonic pachymeter to ensure that none dropped below 400 μm. The UV-A irradiation was performed at the central 8.0 mm diameter of the cornea using a UVX system (Peshke, Inc.) of wavelength 365 nm for 30 min at irradiance of 3 mW/cm², total energy 5.4 J/cm²; during this time, riboflavin drops were instilled every 2 min. After CXL, the corneal surface was irrigated with a cold balanced salt solution kept at 4°C, same antibiotic and corticosteroid eye drops administered, a bandage contact lens was fitted until full re-epithelialization (between 3 and 5 days) before it was removed, and the eyes were examined at the slitlamp. Postoperative medication included 0.1% dicyfenac sodium
(Voltaren) eye drops four times a day for 2 days and tobramycin/dexamethasone drops four times daily. Corneal haze was subjectively quantified on a slitlamp by the following grading scale: 0 for no corneal haze or totally transparent cornea; 1 for slight corneal haze or slight loss of transparency; 2 for moderate haze and iris details seen; and 3 for exaggerated haze or when iris details are hardly seen. The Safety Index was calculated as the ratio: post-keraring placement UDVA divided by baseline CDVA (both in logMAR units). The Efficacy Index was calculated as the ratio: post-keraring placement UDVA divided by the baseline CDVA (both in logMAR units). A satisfaction questionnaire that was used in a previous study was completed by every patient.

Statistical Analysis

The normality of data distribution was checked by the Kolmogorov–Smirnov test. To study the differences in outcome parameters preoperative, 6 months and after 1 year postoperative, a repeated-measures analysis of variance was conducted for mean values of all tested parameters except for CCT and coma, where a Student t test analysis was used to compare the baseline with 1 year postoperative outcome values. All statistical analyses were conducted using the GraphPad Prism software (version 6.00; Graph pad Software, Inc., La Jolla, CA). Differences were considered to be statistically significant when the P value was less than 0.05, and with 40 eyes the study had a power of 85% as calculated using the G* Power software 3.1.10 version. For satisfaction analysis, a score of 12 or more and less than 12 indicated that patient was satisfied and dissatisfied, respectively.

RESULTS

Of the 41 eyes that underwent the two-step procedure, 39 eyes (95.1%) had paracentral cones and 2 eyes (4.9%) had a central cone (i.e., when the apex—the highest point on the posterior elevation toric ellipsoid float—is between the 3- and 5-mm circles or within the central 3-mm circle, respectively). The mean follow-up period after the second step procedure was 14.8±5.2 months (range: 10–24 months). Table 1 shows the preoperative (baseline) and postoperative (at 6 months and after 1 year follow-up) visual and refractive outcomes.

Visual Outcomes

There was a statistically significant improvement in UDVA (P<0.0001) at final follow-up postoperatively. Post hoc analysis showed that between 6 months postoperative and after 1 year of completing the second procedure, measured UDVA also improved (P<0.0001) and CDVA remained unchanged (Table 1). At the final follow-up visit, approximately 61% of the eyes (28 eyes) achieved at least 20/25 monocular UDVA (Fig. 1) and no eyes lost more than two Snellen lines of CDVA. Safety and efficacy indexes for the 41 eyes were 0.97 and 0.88, respectively.

Refractive Outcomes

All refractive components were statistically significantly reduced (P<0.0001, for all comparisons) after 6 months and after 1 year of follow-up, but between both follow-up intervals, no statistically significant differences were observed in all refractive outcomes (P>0.05, for all comparisons) as shown in Table 1. The changes in refractive astigmatism and mean refraction spherical equivalent (MRSE) 1 year postoperatively are plotted in Figures 3 and 4, respectively. The figures show that in 71% of eyes (21 eyes), refractive astigmatism was ≤1.00 D (Fig. 3) and the MRSE was within 1.0 D of emmetropia in 73.2% (30 eyes) of eyes (Fig. 4).

Figure 5 shows the achieved spherical equivalent correction plotted at 1 year postoperatively against the attempted correction.

TABLE 1. Mean Preoperative (Baseline), 6 Months Postoperative, and 1 Year Postoperative Intrastromal Corneal Ring Implantation Followed by Same-Day Topography-Guided Photorefractive Keratectomy Combined With Corneal Collagen Cross-Linking Data and the Results of Comparative Analysis

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Baseline</th>
<th>6 mo Postop</th>
<th>P*</th>
<th>12 mo Postop</th>
<th>P*</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDVA (logMAR)</td>
<td>0.74±0.54 (0.05 to 3.00)</td>
<td>0.12±0.26 (−0.10 to 2.00)</td>
<td>&lt;0.0001</td>
<td>0.10±0.16 (−0.10 to 0.40)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CDVA (logMAR)</td>
<td>0.04±0.12 (−0.10 to 0.48)</td>
<td>0.04±0.11 (−0.10 to 0.48)</td>
<td>&gt;0.05</td>
<td>0.05±0.10 (−0.10 to 0.48)</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>MRSE (D)</td>
<td>46.13±2.10 (41.45 to 51.51)</td>
<td>43.03±2.37 (38.15 to 48.23)</td>
<td>&lt;0.001</td>
<td>43.20±2.29 (39.10 to 47.34)</td>
<td>&lt;0.001</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kmax (D)</td>
<td>47.39±1.80 (40.40 to 48.54)</td>
<td>41.46±1.20 (37.56 to 45.12)</td>
<td>&lt;0.001</td>
<td>41.50±2.02 (37.13 to 44.78)</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Kmin (D)</td>
<td>44.96±1.83 (41.13 to 50.03)</td>
<td>42.24±2.12 (38.02 to 46.29)</td>
<td>&lt;0.001</td>
<td>42.35±2.11 (38.12 to 45.66)</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Sphere (D)</td>
<td>−1.93±2.20 (−7.00 to 2.00)</td>
<td>0.20±0.87 (−1.25 to 2.50)</td>
<td>&lt;0.0001</td>
<td>0.34±1.04 (−1.25 to 2.75)</td>
<td>&lt;0.0001</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Manifest Cyl (D)</td>
<td>−2.20±1.47 (−6.00 to 0.00)</td>
<td>−0.81±0.80 (−2.75 to 0.00)</td>
<td>&lt;0.0001</td>
<td>−0.76±0.74 (−2.25 to 0.50)</td>
<td>&lt;0.0001</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Topographic astigmatism (D)</td>
<td>−2.33±1.36 (−6.20 to −0.30)</td>
<td>−1.57±0.96 (−3.88 to −0.27)</td>
<td>&lt;0.0001</td>
<td>−1.70±0.93 (−3.94 to −0.48)</td>
<td>&lt;0.0001</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

For CCT and coma, results are one-way measures analysis of variance. *P* values of post hoc analysis of repeated-measures analysis of variance 6 months postoperative versus baseline, 1 year postoperative versus baseline.

**P** values of post hoc analysis of repeated-measures analysis of variance 1 year postoperative versus baseline.

***P** values of post hoc analysis of repeated-measures analysis of variance 6 months postoperative versus 1 year postoperative.

CCT, central corneal thickness; CDVA, corrected distance visual acuity in logMAR; D, dioptr; MRSE, mean refraction spherical equivalent; UDVA, uncorrected distance visual acuity in logMAR.
In this figure, the solid line represents the slope while the short dashed lines and the long dashed lines represent points within ±1.00 D and within ±1.5 D (i.e., standard deviation of attempted MRSE), respectively. It shows a weak correlation that was close to being statistically significant ($R^2 = 0.09$, $P = 0.055$). The difference between means of attempted and achieved spherical equivalent refraction was $-0.12 \pm 1.5$ D with a 95% confidence interval range of $-2.98$ and $2.74$ D ($P = 0.5909$). Seven eyes (17%) achieved emmetropia (MRSE = +0.50 to −0.25 D) at the final follow-up.

**Keratometer and Corneal Thickness Values**

There was a statistically significant reduction in all $K$ values (mean $K_{	ext{flat}}, K_{	ext{steep}},$ and $K_{	ext{average}}$; $P < 0.0001$ for all), at the final follow-up visit, but no significant change was observed between all $K$ values obtained at 6 months and after 12 months of completing the procedure ($P > 0.05$, for all comparisons) (Table 1). Central corneal thickness and CT at the thinnest point were statistically significantly reduced from preoperative values at 6 months and at 12 months postoperatively ($P < 0.0001$, for both comparisons) but did not change between both follow-up visits ($P > 0.05$, for 6 months versus after 12 months). However, coma, which was standardized at a wavefront diameter of 6 mm for all eyes, was significantly reduced at 6 months but remained similar to preoperative values after 12 months of completing the procedure ($P > 0.05$, Table 1).

**Improvement in Visual Acuity and Refraction**

The follow-up period in these eyes revealed that the visual and refractive outcomes, which improved at 6 months, were maintained up to 1 year after the two-step surgical procedure. Except for UDVA, there were no statistically significant changes in the CDVA, spherical, cylindrical error between 6 and 12 months after surgery as shown in Table 1. Figure 6 shows the improvement in mean spherical equivalent refraction from at both postoperative follow-up intervals.

**Complications**

Four eyes (9.8%) were undercorrected, 4 (9.8%) were overcorrected, and 3 eyes (7.3%) had coma that exceeded 1.5 μm. None of the tested eyes had any visible haze during the whole follow-up and none had any serious complication 1 year postoperatively.
Subjective Questionnaire Outcomes

Thirty-three patients (completion rate, 80.5%) completed the questionnaire. Majority of the patients (26/33, 78.8%) reported that they were satisfied with the outcome of their procedure; 7 patients (21.2%) stated that they were not satisfied. Two of the subjects who were dissatisfied were the ones who had coma that was ≥1.5 µm postoperatively.

DISCUSSION

In this prospective study, we wanted to determine whether the treatment of early stage keratoconus by ISCR followed up not less than 6 months and at most 9 months later by same-day TG-PRK plus CXL (two-step procedure) leads to improvement in visual outcomes even after 1 year. We also sought to show the results using a protocol that should be used but is not commonly used for reporting graphical results of post-keratoconus surgical treatment. This protocol would enhance easy, practical, and more accurate comparison of the outcomes with those of future studies. Intrastromal corneal ring implantation with the aid of a femtosecond laser was performed as a first-step procedure. We found very satisfactory refractive outcomes in the efficacy index (0.88), which was slightly better than that reported in a previous study after 6 months of follow-up but lower than the 1.6 reported in another study of 1-year postoperative outcomes. Predictability was very good as 80.5% of treated eyes were within the SD (±0.45) of the attempted MRSE, and there was no statistically significant difference between the attempted and achieved MRSE values. The MRSE was −0.50 D after 12 months of surgery, with a majority (73%) of the eyes being within ±1.00 D. In addition, mean manifest astigmatism decreased significantly (from −2.20 to −0.76 D) after 12 months of the procedure. Regarding visual outcomes, the efficacy was good (0.98) as more than 60% of eyes had a postoperative UDVA of 20/25 or better (Fig. 1). Although approximately 85% of eyes maintained or gained multiple lines CDVA (Fig. 2), 15% of eyes (15%) lost one or two lines of CDVA. Overall, the CDVA improved after 12 months of the procedure but this improvement did not reach a statistically significant level, which was the target for performing this procedure in two steps (Table 1).
The efficacy and predictability of the combined procedure in the treatment of keratoconus are supported by recent reports. Table 2 summarizes the main results of the studies of TG-PRK plus CXL. Generally, it has been shown that combining TG-PRK with CXL lead to greater improvements in visual functions and halts progression of the disease. In the sequence, Li et al.\textsuperscript{29} suggested that PRK followed by CXL was better than CXL followed by PRK because removing the cross-linked stiffer anterior cornea may minimize the benefit of CXL in the latter procedure. Wavefront-guided PRK combined with CXL showed similar improvements in the visual outcomes at 6 months that were maintained through 12 months postoperative,\textsuperscript{18} which were similar to our result. The satisfactory visual, keratometry, and topography results, which were also shown in the current study after 6 and 12 months of this two-step procedure, further confirm that the combined procedures complement one another and that the improvements in vision were maintained or sometimes improved upon, after 12 months of the procedure. Generally, same-day combined surgical procedures are more effective than sequential treatments in improving the corneal shape in patients with keratoconus.\textsuperscript{24,29,30} However, practitioners were cautioned on the likelihood of overcorrecting patients during the surface normalization.\textsuperscript{31} In this study, four eyes were overcorrected.

Our results showed a significant reduction in the preoperative topographic astigmatism, $K_{\text{steep}}$, $K_{\text{flat}}$, and $K_{\text{average}}$ values 12 months after the two-step procedure. In addition, we observed that the combined therapy significantly improved UDVA and CDVA was the same and this was the target during the procedure. Similarly, CCT and CT at thinnest point were further reduced by approximately 55.06 and 68.56 $\mu$m, respectively, at the completion
of the procedure (Table 1). There was a significant reduction in coma (which is the hallmark of keratoconus) from 1.08 μm preoperatively to 0.83 μm at 6 months postoperatively. However, despite the mean reduction in coma observed after 12 months of completion of the procedure, the coma root mean square values measured at final visit was similar to baseline values. A possible explanation for this could be the instrument used in the assessment of corneal aberrations in this study. Most wavefront analysers are based on the Hartmann–Shack principle, including the Schwind Ocular Wavefront Analyser, which has a wavefront sensor with a resolution of 210 μm and a maximum of 1,452 measuring points, but the Schwind Corneal Wavefront Analyser used in this study obtains measurements by calculating corneal topography data with ray tracing and a standardized eye model. Both instruments are reliable and have been recommended for use in refractive surgery, even though the Hartmann–Shack device was favored.

Although studies have shown similar significant improvements in most of the tested visual functions, they have been conducted on a different population sample and/or have not agreed on all findings, partly because of the variation in the surgical protocol, and data collection/analysis method or follow-up duration. Additionally, many of these studies have been performed on a few eyes and have used a format which is different from that recommended in presenting their graphic data, thus making it difficult to directly compare results between studies. This study has been carried out in a population different from those of previous studies and with a high incidence of keratoconus.

We have also recruited more eyes than in previous studies and have monitored the changes from 6 months up until 12 months after the procedure—a follow-up period that is longer than those of previous studies.

The impact of CXL combined with TG-PRK in patients’ self-reported quality of life has been reported previously using various validated tools. Labiris et al. in a controlled study, reported that CXL combined with TG-PRK offered an improved self-reported quality of life in patients after treatment, but the scores of the patients with keratoconus were significantly lower than those of the matched healthy controls. The authors concluded that the technique should be implemented as soon as possible for the treatment of keratoconus. Analysis of the questionnaire scores used in the current study also showed that many of the patients (79%) were satisfied with the outcome of the procedure. No eye progressed as evidenced from the keratometry readings shown in Table 1. The use of a different assessment questionnaire in our study makes it difficult to directly compare our results with those of Labiris et al.

Despite the observed significant visual improvements in this study, it lacked a control group and neither corneal endothelial cell counts nor corneal biomechanical properties were assessed. Future studies should consider monitoring these parameters for a long term to better understand the changes observed using the two-step surgical procedure. In this study, we were concerned with the changes that were observed on completion of the second step procedure, and as such, measurements of the reported parameters were obtained only after the procedure has been completed. It has been shown that the addition of the second step improves visual outcomes beyond the improvements observed after the first step procedure and we have shown that between 6 and 12 months after the procedure, there were further improvements in CDVA while other visual functions were almost stable. We also waited for 6 months after the first step before the second step procedure was performed, but in future, earlier intervention can be considered, provided the stability of refraction is confirmed in two or three visits of the patient. Additionally, the authors reason that a better biomechanical strength could be achieved without inducing any refractive surprises, if a flash CXL (half dose: 30 min riboflavin plus 15 min UV@3 mW/cm²) is used rather than the full CXL, which is commonly used in keratoconus.

In summary, the study reaffirms that ISCR implantation followed no less than 6 months later by same-day TG-PRK/CXL (two-step procedure)—for the treatment of moderate keratoconus—is a safe and effective procedure that offers patients functional visual acuity and satisfactory vision, which were maintained with almost no postsurgical complication. It also seems to halt the progression of the disorder and studies with much longer follow-up

### TABLE 2. Summary of Authors and Their Study Results for PRK Combined With Cross-linking in the Management of Keratoconus in Relation to the Findings of the Current Study

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sample Size</th>
<th>Follow-up Period</th>
<th>Treatment Modality</th>
<th>Major Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kanellopoulos and Binder</td>
<td>2007</td>
<td>2 eyes</td>
<td>18 mo</td>
<td>CXL+TG-PRK</td>
<td>Significant improvement in vision</td>
</tr>
<tr>
<td>Kyriopoulos et al.</td>
<td>2009</td>
<td>12 eyes</td>
<td>10.69 mo</td>
<td>Customized TG-PRK+same-day CXL</td>
<td>Significant improvement in vision</td>
</tr>
<tr>
<td>Kanellopoulos</td>
<td>2009</td>
<td>127 eyes (group 1)</td>
<td>36 mo</td>
<td>CXL+TG-PRK 6 mo after vs CXL+TG-PRK same day (Athens Protocol)</td>
<td>Significant improvement in both but better in group 2</td>
</tr>
<tr>
<td>Krueger and Kanellopoulos</td>
<td>2010</td>
<td>1 eye</td>
<td>30 mo</td>
<td>Athens Protocol</td>
<td>Significant improvement in CDVA, UDVA unchanged</td>
</tr>
<tr>
<td>Iovieno et al. (retrospective)</td>
<td>2011</td>
<td>5 eyes</td>
<td>6 mo</td>
<td>PRK+CXL same day</td>
<td>Significant improvement in UDVA, no CDVA lines lost</td>
</tr>
<tr>
<td>Lin et al.</td>
<td>2012</td>
<td>72 eyes</td>
<td>12 mo</td>
<td>PRK/CXL</td>
<td>Significant improvement in UDVA, CDVA but 16.5% lost lines in CDVA</td>
</tr>
<tr>
<td>Alessio et al.</td>
<td>2013</td>
<td>34 eyes</td>
<td>24 mo</td>
<td>PRK+CXL vs CXL alone</td>
<td>Combined procedure better than CXL alone</td>
</tr>
<tr>
<td>Coskunseven et al.</td>
<td>2014</td>
<td>16 eyes</td>
<td>6 mo</td>
<td>PRK+CXL 6 mo after</td>
<td>Significant improvement in vision</td>
</tr>
<tr>
<td>Kanellopoulos and Asimellis</td>
<td>2014</td>
<td>231 eyes</td>
<td>3 yrs</td>
<td>Athens Protocol</td>
<td>Combined technique could lead to overcorrection</td>
</tr>
<tr>
<td>Zeraid et al.</td>
<td>2014</td>
<td>21 eyes</td>
<td>6 mo</td>
<td>CXL+TG-PRK same day</td>
<td>Significant improvement in vision</td>
</tr>
</tbody>
</table>

CDVA, corrected distance visual acuity; CXL, corneal collagen cross-linking; TG-PRK, topography-guided photorefractive keratectomy; UDVA, uncorrected distance visual acuity.
periods are needed. Practitioners are encouraged to adopt a standardized protocol for reporting their results and to aid easy visualization and direct comparison of results between studies.

REFERENCES