Four-Stage Procedure for Keratoconus: ICRS Implantation, Corneal Cross-linking, Toric Phakic Intraocular Lens Implantation, and Topography-Guided Photorefractive Keratectomy

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ABSTRACT

PURPOSE: To evaluate a four-stage combined treatment for keratoconus including intrastromal corneal ring segment (ICRS) implantation followed by corneal cross-linking (CXL), toric phakic intraocular lens (IOL) implantation, and topography-guided photorefractive keratectomy (TG-PRK).

METHODS: In this retrospective interventional case series, 11 eyes of 7 patients with progressive keratoconus were treated with a four-stage procedure including the following: Keraring ICRS (Mediphacos Ltda, Belo Horizonte, Brazil) implantation followed by CXL, phakic IOL implantation, and TG-PRK (minimum 6 months between each stage). Minimum follow-up was 12 months after TG-PRK.

RESULTS: Both mean uncorrected distance visual acuity and corrected distance visual acuity (CDVA) improved from 0.025 decimal (20/800 Snellen) and 0.093 decimal (20/215 Snellen) preoperatively to 0.68 decimal (20/30 Snellen) and 0.73 decimal (20/27 Snellen), respectively, after the combined treatment ($P < .0001$). Mean postoperative CDVA of 0.73 decimal (20/27 Snellen) was similar to preoperative contact lens CDVA of 0.72 decimal (20/28 Snellen). Mean manifest refraction spherical equivalent reduced from 16.78 ± 3.58 to 0.59 ± 0.89 diopters ($P < .0001$) and mean refractive astigmatism reduced from 5.16 ± 1.86 to 0.82 ± 0.28 diopters ($P < .0001$).

CONCLUSIONS: This four-stage procedure appears to be an effective and safe approach for corneal stabilization and improvement of functional vision in patients with keratoconus. Larger case series with a longer follow-up are required to thoroughly evaluate the efficacy, safety, and stability of this combined approach.

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Corneal cross-linking (CXL) using riboflavin and ultraviolet-A (UVA) irradiation increases the biomechanical stability of the cornea and halts the progression of keratoconus.[1-8] Nevertheless, patients treated with CXL show minimal improvement inadequate to achieve functional visual acuity in most cases. In patients with low preoperative corrected distance visual acuity (CDVA), implantation of an intrastromal corneal ring segment (ICRS) is effective in improving visual, refractive, and keratometric parameters.[9-14] However, some patients with keratoconus may benefit from other adjuvant treatments including toric phakic intraocular lens (IOL) implantation and topography-guided photorefractive keratectomy (TG-PRK) to optimize the effects of ICRS and/or CXL.[15-22]

We recently reported a three-stage procedure for the management of progressive keratoconus involving ICRS implantation, followed by CXL and then phakic IOL implantation (minimum 6 months between procedures).[18] The case series of 14 eyes of 9 patients had a statistically significant improvement in mean uncorrected distance visual acuity (UDVA), mean CDVA, mean manifest refractive spherical equivalent (MRSE), mean refractive astigmatism, and mean steep and flat keratometry values. A separate study evaluated an alternative three-stage procedure of ICRS implantation followed by CXL and then TG-PRK in 16 eyes of 10 patients.[19] There was a significant improvement in mean UDVA and CDVA, MRSE, and mean steep and flat keratometry values. Similar findings have also been reported. Dirani et al.[20] showed that ICRS followed by CXL and then PRK improved visual acuity in patients with moderate keratoconus.

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In this case series, we present the results of a combined four-stage treatment for keratoconus comprising ICRS implantation followed by CXL, toric phakic IOL implantation, and TG-PRK.

PATIENTS AND METHODS

Study Design and Patients

This retrospective interventional case series comprised eyes with progressive keratoconus treated with a four-stage approach that had at least 1 year of follow-up after TG-PRK. Progressive keratoconus was defined as an increase in the topographic maximum keratometry (Kmax) readings of 1.00 diopters (D) or greater over at least 6 months.

Before their participation in the study, all patients were appropriately informed about the possible outcomes and the current clinical experience. All patients provided written informed consent in accordance with institutional guidelines and the tenets of the Declaration of Helsinki.

Inclusion criteria for the study were progressive keratoconus with clear corneas of at least 400 µm of corneal thickness at the thinnest point and contact lens intolerance. Exclusion criteria were no improvement in visual acuity with a diagnostic rigid or hybrid contact lens trial, anterior chamber depth from endothelium of less than 2.8 mm after ICRS implantation (which is expected to decrease the anterior chamber depth), history of herpetic eye disease, keratitis, corneal dystrophies, diagnosed autoimmune disease, systemic connective tissue disease, severe atopy, grade IV keratoconus, and endothelial cell density less than 2,500 cells/mm^2 (mean ± standard deviation = 2,881 ± 193 cells/mm^2).

Preoperative and postoperative examinations included UDVA, CDVA, manifest refraction, topographic findings (Orbscan II; Bausch & Lomb, Rochester, NY), specular microscopy (SP 3000P specular microscope; Topcon Corporation, Tokyo, Japan) measurements, and slit-lamp evaluation.

Surgical Technique

All surgical procedures were performed by the same surgeon (EC). All patients underwent a four-stage treatment in the following order: ICRS implantation, CXL, toric phakic IOL implantation, and TG-PRK. All surgical procedures were performed under sterile conditions and topical anesthesia with proxymetacaine hydrochloride 0.5% eye drops (Alcaine; Alcon Laboratories, Inc., Fort Worth, TX).

ICRS Implantation

During the first step of the four-stage procedure, one (9 eyes) or two (2 eyes) Keraring Si5 segments (Mediphacos Ltda, Belo Horizonte, Brazil) were implanted into the corneal stroma aiming at maximum flattening by embracing the steepest meridian of keratoconus, according to the topographic image. A 150-kHz femtosecond laser (Intralase, Irvine, CA) was used to create the ring channels. The surgical procedure of the Keraring segments implantation has been previously described.[14] Implantation of ICRS was uneventful in all cases.

CXL

After a 6-month postoperative interval, patients underwent an epithelium-off CXL treatment; the surgical procedure of CXL was performed as previously described.[2] The UVA irradiation was performed with a UV-X illumination system (version 1000; Peschke Meditrade GmbH, Huenenberg, Switzerland) with 3 mW/cm^2 surface irradiance for 30 minutes (5.4 J/cm^2). Before each procedure, the unit was calibrated with a UVA meter (Lasermate-Q, Laser 2000; Lasermate Group, Walnut, CA) at a working distance of 6 cm.

Toric Phakic IOL Implantation

Selection of a toric Visian Implantable Collamer Lens (ICL; STAAR Surgical Co., Monrovia, CA) was made at a minimum of 6 months after CXL treatment. In all cases in this series, the refractive target was -1.00 to -2.00 D of myopia, so that the final stage TG-PRK would be a relatively low myopic astigmatic treatment, and to avoid hyperopic surface ablation. The axis of alignment was calculated using the refractive astigmatism at that time point. To control for potential cyclotorsion when the patient was supine, the zero horizontal axis was marked at a slit lamp while the patient was sitting upright. Each patient received two Nd:YAG laser peripheral iridotomies 1 week before surgery. The toric phakic IOLs were sized according to the corneal white-to-white and anterior chamber depth measurements using the Orbscan II device. The phakic IOL was inserted through a temporal clear corneal incision and rotated to the correct axis with a Mendez axis marker (Asico LLC, Westmont, IL) as indicated by markings.

TG-PRK

The fourth step of the procedure was performed a minimum of 6 months after toric phakic IOL implantation. The excimer laser corneal treatment was performed with the Allegretto 400-Hz laser platform (Wavelight Laser Technologie AG; Alcon Laboratories, Inc., Fort Worth, TX). The surgical procedure was performed as previously described.[19] TG-PRK ablation was performed with a small optical zone (5.5- to 6-mm diameter) and large transition zone (9-mm diameter). The maximum stromal ablation depth was 50 µm and the attempted correction was approximately 80% of

the refraction. Mitomycin C 0.02% was applied after TG-PRK ablation for 30 seconds to avoid haze.

Statistical Analysis

All values are expressed as mean ± standard deviation; visual acuity is expressed in decimal (Snellen) and visual acuity lines are reported in logMAR equivalent. Normality was tested using the D'Agostino–Pearson normality test. Repeated-measures analysis of variance with Bonferroni posttest analysis was used for normally distributed data values. The Friedman test with the Dunn multiple comparison test was used for non-parametric data values. A P value of less than .05 was considered statistically significant.

RESULTS

The study enrolled 11 eyes of 7 patients (4 men and 3 women). Mean patient age was 25.5 ± 1.8 years (range: 23 to 28 years). Mean interval between ICRS and CXL was 7 months, mean interval between CXL and toric phakic IOL implantation was 8.2 months, and mean interval between toric phakic IOL implantation and TG-PRK was 6.4 months. All patients were observed for at least 1 year after TG-PRK.

Refractive Outcomes

Efficacy. Preoperatively, rigid contact lens CDVA was 0.6 (20/33) or better in all eyes, with a mean of 0.72 ± 0.37 (20/28), whereas mean (spectacle) CDVA was only 0.09 ± 4.0 (20/222).

The four-stage procedure produced a significant improvement in visual acuity, with all eyes achieving better postoperative UDVA than preoperative (spectacle) CDVA. After the four-stage procedure, mean UDVA improved from 0.02 ± 2.2 (20/1000) preoperatively to 0.68 ± 0.47 (20/29, $P < .0001$; Friedman test), whereas mean CDVA improved from 0.09 ± 4.0 (20/222) to 0.73 ± 0.27 (20/27, $P < .0001$). All 11 eyes achieved postoperative UDVA of 0.6 (20/33) or better, compared to 9 of 11 (82%) eyes having preoperative CDVA of 0.1 (20/200) or better (**Figure 1A**). The combined treatment resulted in a mean improvement of 14.3 of UDVA and 8.9 of CDVA. Mean postoperative (spectacle) CDVA of 0.73 (20/27) was similar to preoperative contact lens CDVA of 0.72 (20/28). The four-stage treatment was effective at maintaining postoperative (spectacle) CDVA compared to preoperative contact lens CDVA (**Figure 2A**).

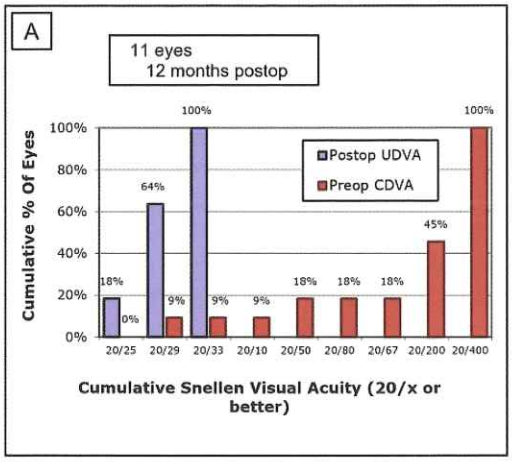
Figure 3 shows the improvement in UDVA and CDVA with each stage of treatment. ICRS implantation appears to improve UDVA and CDVA (Dunn multiple comparison test), ICL implantation, and TG-PRK appear to improve UDVA. CXL appears to show minimal effect on UDVA or CDVA. There is a narrow range of UDVA and CDVA at all time points after TG-PRK, with a minimum visual acuity of 0.5 (20/10), indicating the efficacy and stability of visual outcomes after the four-stage treatment.

Safety. All eyes had reduced (spectacle) CDVA preoperatively. There were no intraoperative or postoperative complications. No eye lost any line of CDVA. All eyes gained at least one line of CDVA after the four-stage procedure; the eye that had the least gain in CDVA had the best preoperative CDVA of 0.7 (20/29), with a final CDVA of 0.8 (20/25). In the other eyes, there was a significant improvement in CDVA, with 1 eye (9%) gaining one line, 1 eye (9%) gaining three lines, 3 eyes (27%) gaining six lines, and 6 eyes (55%) gaining seven or more lines (**Figure 1B**) of CDVA. Comparing postoperative (spectacle) CDVA to preoperative rigid contact lens CDVA, 8 of 11 eyes (73%) had no change, 2 eyes (18%) gained one line, and 1 eye (9%) lost one line (**Figure 2B**). Postoperative contact lens CDVA was not measured.

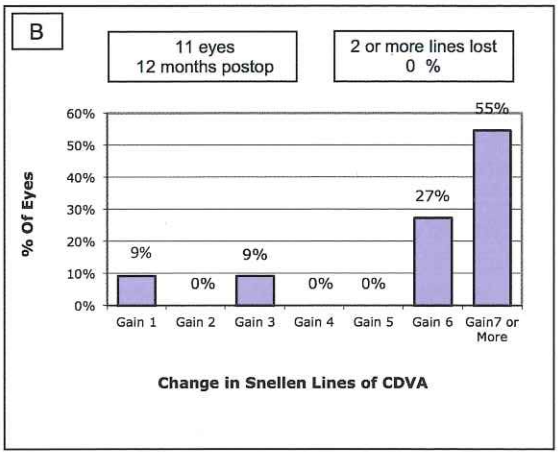
Spherical Equivalent Refraction. All eyes had high myopic astigmatism with a minimum MRSE of 11.25 D and a maximum of -22.13 D. Taken in context, the four-stage procedure has a predictable effect on the refractive outcome (**Figure 1C**). Part of the tendency for undercorrection is expected, given the target of the final stage TG-PRK was approximately 80% of the refractive error. The final MRSE for all eyes was within 1.375 D of target, with 4 eyes (27%) having a hyperopic MRSE (maximum +0.875 D; **Figure 1D**).

Mean MRSE reduced from 16.78 ± 3.58 D (range: -11.25 to 22.13 D) to 0.59 ± 0.89 D (range: 1.50 to +0.88 D) after the four-stage procedure ($P < .0001$). **Table A** (available in the online version of this article) shows the change in MRSE after each stage of the four-stage procedure. The improvement in MRSE is significant after ICRS implantation, phakic IOL implantation, and TG-PRK. The MRSE was stable after CXL with no significant change from 3 to 12 months after TG-PRK. Phakic IOL implantation had the greatest magnitude of effect on MRSE and the final stage of TG-PRK brought the MRSE close to plano.

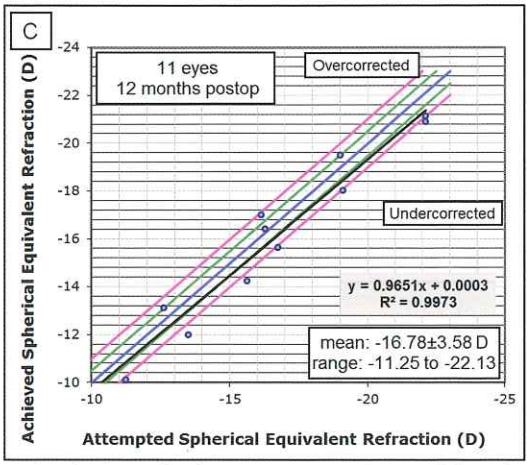
Refractive Astigmatism. The four-stage procedure resulted in a significant reduction in refractive astigmatism, from -5.16 ± 1.86 to -0.82 ± 0.28 D ($P < .0001$). **Table A** shows the change in refractive astigmatism after each stage of the four-stage procedure. The reduction of mean refractive astigmatism was greatest with ICRS implantation. CXL did not have a significant effect on astigmatism. Toric phakic IOL implantation reduced the range of residual refractive astigmatism to between -0.75 and -2.25 D. The final stage of TG-PRK further reduced the residual refractive astigmatism to a mean less than -1.00 D, with a final range between -0.50 and -1.25 D. The resid-



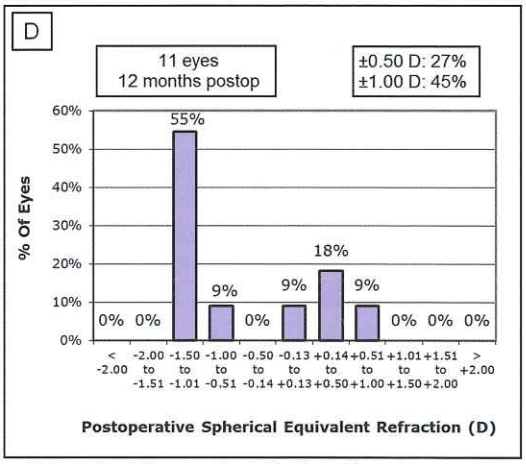
Uncorrected Distance Visual Acuity



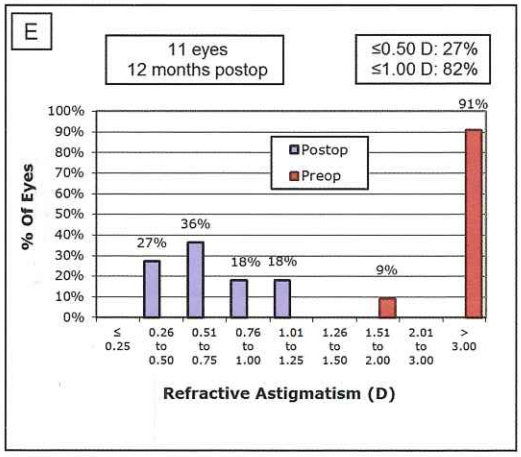
Change in Corrected Distance Visual Acuity



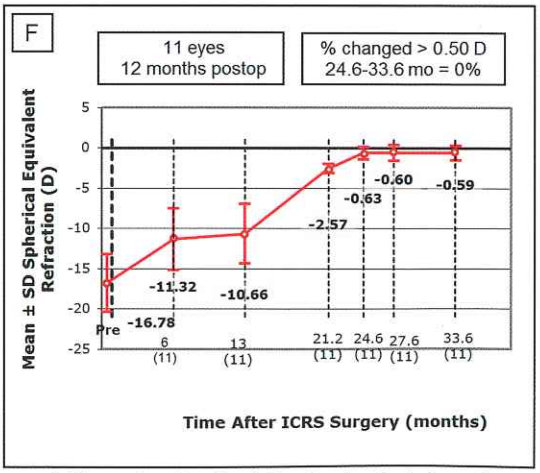
Spherical Equivalent Attempted vs Achieved



Spherical Equivalent Refractive Accuracy



Refractive Astigmatism



Stability of Spherical Equivalent Refraction

Figure 1. Refractive outcomes: (A) Efficacy (note Snellen decimal visual acuity [VA]), (B) Safety (comparing postoperative to preoperative corrected distance VA [CDVA]), (C) Predictability, (D) Accuracy, (E) Refractive Astigmatism, and (F) Stability. UDVA = uncorrected distance visual acuity; D = diopters

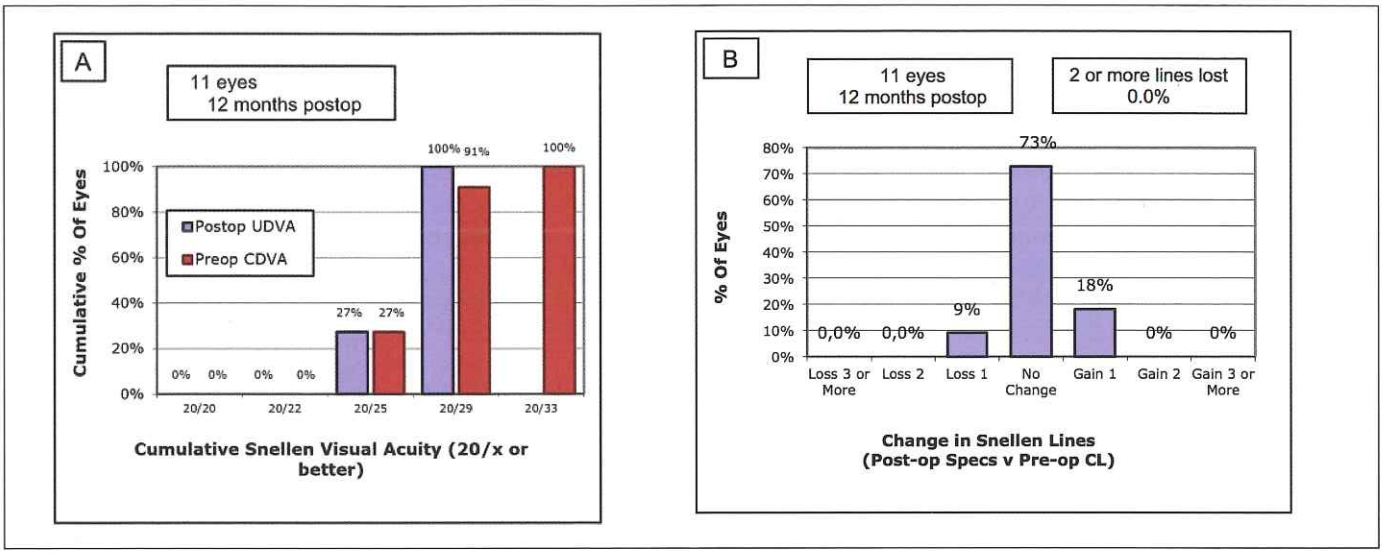


Figure 2. Efficacy (A) and safety (B) of four-stage procedure comparing postoperative corrected distance visual acuity (CDVA) to preoperative CDVA. CL = contact lens

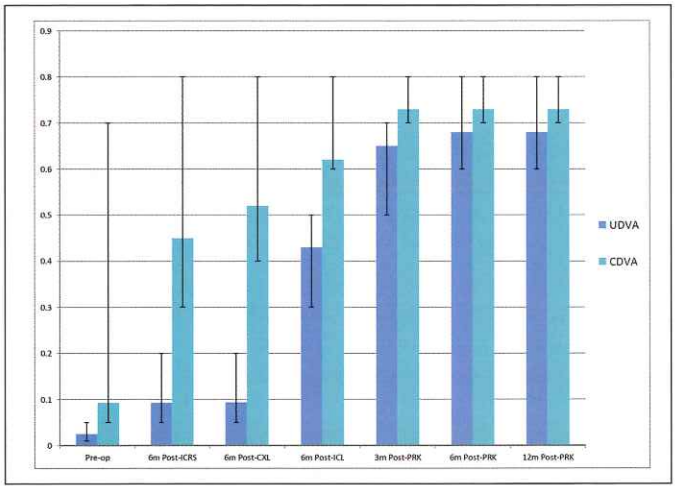


Figure 3. Mean uncorrected (UDVA) and corrected (CDVA) distance visual acuity at each time point during the four-stage procedure. Note that the error bars show the full range of values at each time point.

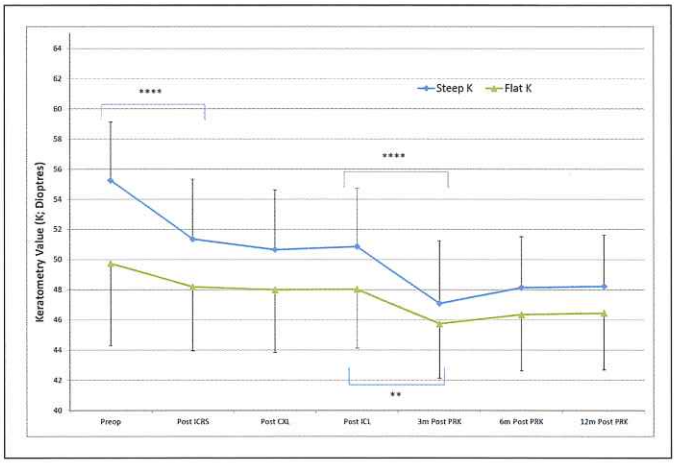


Figure 4. Mean flat and steep keratometry values (± standard deviation) at each time point during the four-stage procedure. $^{**}P < .01$, $^{****}P < .0001$.

ual refractive astigmatism was stable between 3 and 12 months after TG-PRK. Postoperatively, no eye had more than 1.25 D of astigmatism and 7 eyes had astigmatism of 0.75 D or less (**Figure 1E**).

Stability. The four-stage combined treatment resulted in stable refractive results in all eyes up to 1 year after TG-PRK. No eye had a change in MRSE of more than 0.50 D between 3 months after TG-PRK to 12 months after TG-PRK (**Figure 1F**).

KERATOMETRY

The change in flat, steep, and mean keratometry values is summarized in **Table B** (available in the online version of this article). With the four-stage procedure, mean flat keratometry reduced from 49.80 to 46.50 D ($P < .0001$), mean steep keratometry values reduced from 55.30 to 48.20 D ($P < .0001$), and mean keratometry value reduced from 52.50 to 47.30 D ($P < .0001$). A highly significant reduction in steep keratometry value was shown after ICRS implantation (-3.89 ± 1.25 D; $P < .0001$) and after TG-PRK (-3.77 ± 1.53 D; $P < .0001$). TG-PRK also produced a significant reduction in flat keratometry (-2.29 ± 1.79 D; $P < .01$). In contrast, there was a lower reduction in flat keratometry after ICRS implantation (-1.55 ± 2.14 D). **Figure 4** clearly shows the improvement in keratometry with the final stage TG-PRK. The regularization and reduction in corneal astigmatism are underestimated when considering the reduction in refractive astigmatism in isolation (a mean reduction in refractive astigmatism of -1.97 ± 2.30 D for ICRS implantation and -0.86 ± 0.72 D for PRK). It is important to note that both CXL and toric phakic IOL im-

plantation had no significant effect on flat, steep, or mean keratometry at 6 months after the procedure.

DISCUSSION

ICRS implantation has shown to be effective in improving visual acuity, causing flattening of the central corneal curvature.[9-11,13,14] However, patients with progressive keratoconus require CXL to strengthen the corneal tissue and stabilize the ectatic cornea.[1-8] ICRS implantation combined with CXL has been shown to increase visual acuity versus ICRS alone.[12,23] Regarding the sequence of treatment in combined ICRS and CXL for keratoconus, we have shown in a previous study that ICRS implantation followed by CXL resulted in greater improvement in keratoconus than CXL followed by ICRS implantation.[12] However, evidence suggests that adding a further treatment (implantation of a toric phakic IOL or TG-PRK) could help to optimize the effects of ICRS/CXL. Indeed, several authors have investigated the effects of adding phakic IOL implantation or PRK to ICRS/CXL.[17-21]

We previously investigated the effects of a triple procedure. In one study, we evaluated ICRS implantation, followed by CXL, and then toric phakic IOL implantation.[18] Findings showed that combined treatment led to a significant improvement in mean UDVA and CDVA, as well as significant reductions in mean MRSE, mean refractive astigmatism, and mean steep and flat keratometry values.[18] In another study, ICRS implantation followed by CXL and then TG-PRK showed a significant improvement in mean UDVA and CDVA, as well as significant reductions in MRSE and mean steep and flat keratometry values.[19]

Dirani et al.[20] showed that ICRS followed by CXL and then non–TG-guided PRK improved visual acuity in patients with moderate keratoconus. In a 1-year study of 41 eyes by Al-Tuwairqi et al.,[21] ICRS implantation followed by CXL and TG-PRK improved visual acuity and halted the progression of keratoconus.

In the current study, we evaluated the outcomes of a four-step treatment for progressive keratoconus. All of the parameters analyzed (UDVA, CDVA, MRSE, astigmatism, and keratometry) showed a significant improvement after completion of the four steps of the combined treatment. Similar to findings from our previous study of the triple procedure comprising ICRS implantation followed by CXL and TG-PRK, ICRS implantation appears to improve CDVA in particular with a more modest effect on UDVA, but CXL treatment does not improve UDVA or CDVA.[19] Toric phakic IOL implantation improves UDVA, whereas TG-PRK appears to improve UDVA in particular, with a lesser effect on CDVA. The analysis also showed that there was a significant improvement in mean MRSE after ICRS implantation, toric phakic IOL implantation, and TG-PRK, but not after CXL. Similarly, although there was an improvement in mean refractive astigmatism following each successive treatment, this improvement was significant only for ICRS versus preoperative. Additionally, keratometry values were significantly improved by ICRS implantation and TG-PRK, but were not significantly altered by CXL and phakic IOL implantation.

In this study, we did not perform same-day simultaneous CXL and TG-PRK and used a standard nomogram. CXL treatment can produce some improvement in topographic corneal irregularity and a small reduction in refraction. Moreover, CXL can flatten the corneal shape in keratometry over several years, meaning that a planned laser treatment may be enhanced or even over-flattened by additional CXL treatment later on. However, the attempted correction of TG-PRK ablation was approximately 80% of the refraction. Another important reason to use TG-PRK as the final stage procedure is that it can be used for fine-tuning the corneal irregularity and refraction after phakic IOL implantation. On the other hand, using TG-PRK on previous cross-linked corneas may affect its predictability due to the possible change of the ablation rate of the previously cross-linked corneas. Richoz et al. showed that CXL reduced the corneal ablation depth of the excimer laser.[24] Initial treatment with ICRS implantation improves corneal irregularity without removing corneal stroma, and phakic IOL implantation can treat high amounts of myopia and the regular component of astigmatism. One of the main limits of treatment in these thin corneas is that the stromal ablation with TG-PRK will be limited; therefore, it is an advantage to have a low residual refraction and irregularity prior to TG-PRK.

Because there has been little other research into the effects of a "quadruple procedure" for the treatment of keratoconus, it is difficult to discuss the current findings within the context of other studies. The purpose of this study was to take advantage of each separate technique to enhance visual and refractive outcomes. Although our findings did not show that each successive treatment always improved on the effects of the previous one across all parameters, the data show that staged treatment comprising ICRS, CXL, phakic IOL implantation, and TG-PRK resulted in a significant improvement in visual, refractive, and keratometry values in this group of patients.

The four-step procedure appears to be a safe and effective approach for corneal stabilization and improvement of functional vision in patients with keratoconus. However, larger studies with long-term follow-up are needed to further evaluate and confirm the benefits of a four-step procedure for the treatment of keratoconus.

AUTHOR CONTRIBUTIONS

Study concept and design (EC, DPS, GDK, IP); data collection (EC); analysis and interpretation of data (EC, DPS, MAG, OS); writing the manuscript (EC, DPS, MAG, OS, GDK, IP); critical revision of the manuscript (EC, MAG, OS, GDK, IP); statistical expertise (EC, MAG, OS); supervision (EC, DPS, MAG, GDK, IP)

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