Intracorneal Ring Segments Followed by Simultaneous Topography-Guided Removal of Epithelium and Stroma With Accelerated Collagen Cross-Linking For Keratoconus (I-TRESK/CXL)

Rohit Shetty, PhD, FRCS*, Neeraj Ashok Israni, MD*, Saurabh Ramuka, MD*, Zelda Dadachanji, MD*, Abhijit Sinha Roy, PhD†, Rohan Mehra, MD*, and Vaitheeswaran Ganesan Lalgudi, MD*

**Purpose:** The aim of this study was to assess the visual, topographic, and aberrometric outcomes of a novel tissue sparing technique, topography-guided removal of epithelium, and stroma in keratoconus (TRESK) along with accelerated collagen cross-linking (CXL), 1 month after Intacs insertion.

**Design:** Prospective interventional study.

**Methods:** Forty-eight eyes (45 patients) with keratoconus underwent femto-assisted Intacs insertion. After 1 month, TRESK and CXL (9 mW/cm² for 10 minutes) was done. TRESK is a centered trans-PTK (phototherapeutic keratectomy) with center and area of ablation at the location of the steepest tangential anterior curvature and area of the cone respectively. Total ablation (epithelium plus stroma) was limited to 75 µm. Postoperative measurements were performed 1 month after Intacs, 6 weeks after Intacs followed by TRESK/CXL, and at the final visit 12 months after Intacs followed by TRESK/CXL.

**Results:** For all eyes studied, uncorrected distance visual acuity and corrected distance visual acuity (CDVA) (logMAR) improved from preoperative means of 1.05 ± 0.05 and 0.31 ± 0.03 logMAR to postoperative means of 0.52 ± 0.05 (P < 0.001) and 0.20 ± 0.02 logMAR (P = 0.009), respectively. The mean preoperative sphere, cylinder and mean refractive spherical equivalent decreased from −4.52 ± 0.98 D, −4.81 ± 0.25 D, −6.93 ± 0.99 D to −0.77 ± 0.53 D (P = 0.029), −3.13 ± 0.24 D (P = 0.002), and −2.34 ± 0.53 D (P = 0.021), respectively with a mean keratometric flattening of 5.06D (P < .0001) at the final visit. In total, 2.08% of the eyes lost 1 Snellen line of CDVA. Sixty-eight percent and 27% of the eyes gained 2 Snellen lines or more of uncorrected distance visual acuity and CDVA, respectively.

**Conclusions:** Simultaneous TRESK with CXL done 1 month after Intacs insertion (I-TRESK) in keratoconus eyes provided significant visual gain with refractive and topographic improvement. This novel procedure involving customized PTK before CXL is safe, easy to plan and perform, and provides good outcomes.

**Key Words:** cross-linking, customized phototherapeutic keratectomy, Intacs, keratoconus

**K**eratoconus is a progressive form of corneal ectasia characterized by steepening along with thinning of the central or paracentral cornea. This leads to myopia and irregular astigmatism which affect quantity and quality of vision and worsens with disease progression. Initially, spectacles or contact lenses alone are sufficient for visual rehabilitation. Intra corneal ring segments (ICRS) are passive spacing agents, which flatten the cornea by shortening of arc length. ICRS is indicated in keratoconus patients for visual rehabilitation, when spectacles are inadequate and contact lenses are not tolerated.

ICRS implantation in different stages of keratoconus has been shown to improve uncorrected and corrected distance visual acuities. Long-term follow-up studies following ICRS alone have documented progression of keratoconus. Thus, additional corneal collagen cross-linking (CXL), which has been proven to stabilize corneal ectasia, has to be done after or before ICRS or simultaneously.

ICRS alone is seldom sufficient for adequate visual rehabilitation and many patients require glasses or contact lenses or additional procedures as toric implantable collamer lens (implantable collamer lens) or topography-guided or wave-front-guided photorefractive keratectomy (PRK). In a contact lens intolerant patient, none of the above methods excepting topography or wave-front-guided PRK can reduce corneal aberrations, which is very essential for improving the quality of vision. Keratoconus eyes have altered inflammatory and biomechanical profile, hence ablating keratoconic corneas is considered counterintuitive to the principle of safe management. Though some evidence has shown long-term safety of such ablative procedures in keratoconic eyes, it is essential to work on customizing these ablations by decreasing the surface area and volume of ablation in order to minimize the mechanical insult to keratoconic eyes.

Thus, we need to focus on strategies to improve the visual gain with ICRS procedure without ablating as much tissue as topography/wave-front-guided PRK ablates. ICRS followed by CXL was shown to have better visual gain than ICRS alone. In keratoconus eyes, when CXL is performed using PTK (phototherapeutic keratectomy) for epithelial removal compared to the manual method, better outcomes have been reported (Cretan protocol). This utilizes the difference in epithelial thickness
distribution in keratoconic eyes, that is, a thinner epithelium in the cone compared with periphery. A uniform 50 μm PTK ablates a few microns of stroma under the cone, leading to flattening. In the Cretan protocol, this 50 μm PTK is centered on the geometric center of the cornea. Owing to varying position of the cone and varying epithelial thickness in the cone region in keratoconus, this standard PTK cannot produce consistent flattening in the cone region in all patients.

We recently published a novel trans-PTK procedure called TREK (topography-guided removal of epithelium in keratoconus). With TREK, customized specific depth of stromal ablation is possible under the cone with the ability to shift the center and size of ablation to the center and size of the cone respectively, thus minimizing the area of ablation. TREK followed by CXL resulted in significant visual, topographic and aberrometric outcomes. Because we are removing stromal tissue in addition to epithelium, we have renamed TREK as topography-guided removal of epithelium, and stroma in keratoconus (TRESK). Inspired by this possibility, we performed TRESK and CXL after Intacs placement (I-TRESK) to gain better visual outcome after Intacs in keratoconus eyes.

METHODS

This was a prospective, interventional study conducted in Narayana Nethralaya Eye Hospital, India. It was approved by the ethics committee of the hospital and procedures were performed after receiving the written informed surgical consent from the patients or their parents when the patients were younger than 18 years of age. The study adhered to the tenets of the Declaration of Helsinki. Patients with all stages (Amsler-Krumeich keratoconus severity scale) of progressive keratoconus between 12 and 35 years of age with unsatisfactory spectacle-corrected vision and/or contact lens intolerance, and with clear central cornea were included in the study. Progression of keratoconus was defined as an increase of 1.0 diopter (D) or more in 2 or more keratometry values in the steep meridian between 2 axial curvature maps or a decrease in corneal thickness of 5% or more at the thinnest point between 2 pachymetry maps on Pentacam (Oculus Optikgerate GmbH, Wetzlar, Germany) in the preceding 6 months. Exclusion criteria included presence of other ocular co-morbidities affecting vision, active allergic eye disease, pregnancy, any prior ocular surgery, or central scarring of the cornea.

All the cases included in the study were operated by a single surgeon (RS) in 2 stages (Intacs first followed by simultaneous TRESK and CXL after 1 month) under topical anesthesia. Intacs (Addition Technology Inc SA, Lombard, IL) planning was done using our decision making nomogram. The channels were created by using femtosecond laser (Wavelight FS200). Femto channels were planned with platform length of 1.5 mm and width of 1.2 mm. Channels for regular rings had inner diameter of 6.9 mm and outer diameter of 7.9 mm, while SK rings had 6.1 mm and 7.1 mm, respectively. Intacs was placed inside the created channels and a bandage contact lens (BCL) (Pure Vision, Bausch and Lomb, Rochester, NY) was placed. BCL was removed on the first postoperative visit. Patients were given postoperative topical antibiotics (Moxifloxacin 0.5%, Alcon Laboratories, Inc. Fort Worth, TX, for 2 weeks), steroid (Fluorometholone 0.1%, Alcon Inc, Fort Worth, TX, USA, tapered over 4 weeks), and lubricant (Sodium Hyaluronate 1%, Allergan, Inc., India, for 4 weeks).

After 1 month, patients were taken up for simultaneous TRESK and CXL. Patients underwent anterior segment optical coherence tomography (RTVue OCT; Optovue Inc, Fremont, California, USA), and minimum epithelial thickness over the cone area was measured. Maximum ablation depth by trans-PTK was calculated as 25 microns over the minimum epithelial thickness in the region of the cone or a total of 75 microns (epithelium plus stroma), whichever was lesser of the two. The laser system used was Schwind Amaris 1050 RS (Schwind eye-tech solution, Kleinostheim, Germany). Data were obtained from both the RTVue and the topographer. While the minimum/apical epithelial thickness from RTVue determines the depth of the trans-PTK procedure, location of Kmax and the size of the cone on tangential topography maps determine the ablation offset and the long and short axis of the ablation zone respectively. In a central cone, the ablation would be centered and in a peripheral cone, it would be decentered to fit the location and dimensions of the cone. Additionally, this ablation is guided by cyclotorsion compensation as well, ensuring only the exact area planned is ablated. The details of the planning are as described in our previous published report.

After PTK, surrounding epithelium was manually scraped. Epithelial debridement did not extend to the corneal area over the Intacs. CXL was done with 0.1% riboflavin drops using the Mosaic system (Avedro Inc, Waltham, MA, USA). Details of the CXL procedure are summarized in Table 1. After a thorough eye wash with sterile balanced salt solution, a sterile BCL (Pure Vision), Bausch and Lomb, Rochester, NY) was placed. Postoperative antibiotic eye drops (moxifloxacin 0.5%, Alcon Laboratories, Inc. Fort Worth, TX, for 2 weeks) and lubricant (Sodium Hyaluronate1%, Allergan, Inc., India, for 6 weeks) were prescribed. The BCL was removed only after the epithelium healed, following which steroid eye drop (Flurometholone 0.1%, Alcon Inc, Fort Worth, TX, USA, tapered over 6 weeks) was prescribed.

Uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), refraction [sphere, cylinder, and
mean refractive spherical equivalent (MRSE)] and Pentacam was done preoperatively, 1 month after Intacs implantation, 6 weeks after combined TRESK and CXL (I-TRESK/CXL), and on the final postoperative visit (1 year post-I-TRESK/CXL) of all patients.

Flat and steep keratometry (K1 and K2), maximum anterior axial keratometry (Kmax), thinnest pachymetry (TCT), and ante
coronal aberrations (e.g., coma, spherical aberration and root mean square (RMS) of lower (LOA), and higher order aberrations (HOA) of the central 6 mm diameter of cornea) were evaluated using Zernike polynomials up to the sixth order from Pentacam.

After combined TRESK and CXL (I-TRESK/CXL), and on the final postoperative visit (1 year post-I-TRESK/CXL) of all patients.

Flat and steep keratometry (K1 and K2), maximum anterior axial keratometry (Kmax), thinnest pachymetry (TCT), and anterior corneal aberrations (e.g., coma, spherical aberration and root mean square (RMS) of lower (LOA), and higher order aberrations (HOA) of the central 6 mm diameter of cornea) were evaluated using Zernike polynomials up to the sixth order from Pentacam.

MedCalc v18.2.1 (MedCalc Inc., Ostend, Belgium) was used for statistical analyses. The primary objective of this study was to describe the outcomes of this novel tissue sparing technique at the end of 1 year, in terms of safety and efficacy. In addition to the above, subgroup comparison was done between those patients who had single ring vs double ring implantation and between those with mild-to-moderate and severe stages of keratoconus in terms of keratometric flattening and visual outcomes. Amsler Krumeich stage 4 was considered severe stage and stages 1 to 3 were clubbed together as mild-moderate stages.

All continuous variables are described as mean ± standard error (mean, minimum, maximum). Kolmogorov-Smirnov test was done on all variables to determine normality of distribution and accordingly parametric or nonparametric tests were performed to study the changes of variables over different time points. Data from multiple time points were assessed with post hoc analysis of variance. For multiple comparisons, Bonferroni adjustment of the P value was done automatically by the statistical analysis software. For comparison between nonpaired data, unpaired t test was done after confirming normality. A P value less than 0.05 was considered statistically significant.

**RESULTS**

A total of 48 eyes (45 patients) were included in the study. Mean age of the patients enrolled was 23.39 ± 0.62 (13, 35) years. The number of male and female patients were 29 and 16, respectively. By Amsler Krumeich classification, 33 eyes were mild-moderate grade and 15 were grouped under severe keratoconus. Mean ablation depth (epithelium plus stroma) was 68.39 ± 0.75 μm (57, 75). The mean offset was 0.63 ± 0.11 mm (0.22, 2.12) at 234.33 ± 20.98 degrees (90, 320). The ablation zone was an elliptical zone with a mean major [4.02 ± 0.12 mm (2.47, 5)] and a minor [3.82 ± 0.14 mm (2.34, 5)] diameter.

Mean preop logMAR UDVA improved from 1.05 ± 0.05 (0.30, 1.78) to 0.52 ± 0.05 (0.0, 1.30) at the final visit (P < 0.0001). Mean preop logMAR CDVA improved from 0.31 ± 0.03 (0.0, 0.78) to 0.20 ± 0.02 at the final visit (P = 0.002). Mean sphere, cylinder and MRSE also showed significant reduction at the final visit. Table 2 shows the change in trend of vision and refraction parameters from preoperative through 1 month after Intacs and 6 weeks after I-TRESK/CXL, till the final visit. For all variables with significant P values, significance existed between preoperative and final postoperative time points. For sphere and MRSE, there was also a significant decrease in their means between post-Intacs 1 month and 6 weeks after I-TRESK/CXL, and logMAR UCVA change showed significance between post-Intacs 1-month and final visit as well. None of the variables showed significant differences between 6 weeks after I-TRESK/CXL and the final visit, showing stability of these variables in the postoperative period.

There were no cases of intraoperative or postoperative complications. In total, 79.2% of eyes attained postop CDVA of 20/40 or better at the final visit, with 27% of eyes gaining at least 2 or more lines and 48% of eyes gaining at least 1 line of CDVA. Two eyes lost a line each of CDVA following Intacs and 6 weeks after I-TRESK/CXL, but at the final visit, 1 of the 2 eyes reached preop CDVA, whereas the other continued to have loss of 1 line of CDVA. There was no eye which had loss of 2 or more lines of CDVA at any point of time in the cohort.

Efficacy is defined as number of eyes reaching >20/40 UDVA. Eleven out of 48 eyes (22.92%) reached 20/40 or better postoperative UDVA. While 8 eyes (16.67%) had >20/80 preoperative UDVA, 33 eyes (68.76%) attained >20/80 UDVA at the final visit. One eye (2.08%) following Intacs and 2 eyes (4.17%) at 6 weeks post I-TRESK/CXL lost 1 line of UDVA, but at the final visit, there was no eye with loss of any lines of UDVA. These results are depicted in Figures 1 and 2.

Safety index, defined as the ratio of mean postop CDVA to preop CDVA was 1.32, indicating a gain of 32% in CDVA. Efficacy index, defined as the mean postoperative UDVA/mean preoperative UDVA was 0.67 indicating that 67% of eyes attained postoperative UDVA that was better than or equal to the preoperative UDVA.

Table 3 summarizes the outcomes of anterior corneal topography and aberrations (preoperative, 1 month after Intacs, 6 weeks after I-TRESK/CXL and at the final postoperative visit). K1, K2, and Kmax reduced by ~4.75D (P < 0.001), ~5.37D (P < 0.001) and ~6.81D (P < 0.001) between the preoperative and the final follow-up, respectively. K1, K2, and Kmax also had a significant reduction of ~1.96D (P = 0.0001), ~1.57D (P = 0.0001), and 2.99D (P < 0.001), respectively between post-Intacs and 6 weeks after I-TRESK/CXL, signifying keratometric reduction by the
additional procedure of TRESK/CXL. Axis of K1 was statistically similar throughout \((P = 1)\). None of them had a significant change between 6 weeks post I-TRESK/CXL and the final visit. Example of topographic change in an eye undergoing Intacs followed by TRESK/CXL is shown in Figures 3 and 4. As a result of the TRESK/CXL part, the pachymetry of these eyes too changed. The mean standard error (range) of corneal thicknesses before and after TRESK/CXL in our patients were 472.5 ± 5.81 (458, 490) and 443 ± 6.21 \(\mu m\) (438, 465), respectively \((P < 0.05)\).

Mean spherical aberration reduced by 47.4\% (from \(-1.54 \mu m\) to \(-0.81 \mu m, P = 0.001)\). Mean horizontal and vertical coma reduced from \(-0.68 \mu m\) to \(-0.41 \mu m (P = 0.478)\) and \(-3.21 \mu m\) to \(-1.95 \mu m (P = 0.001)\). Astigmatism 0° and 45° decreased and increased by 0.48 \(\mu m\) \((P = 0.755)\) and 0.27 \(\mu m\) \((P = 1.0)\), respectively, by the final follow-up, though the change was insignificant. RMS of LOA and HOA significantly reduced from 17.16 ± 1.08 \(\mu m\) \((7.49, 38.04)\) to 11.66 ± 0.87 \(\mu m\) \((3.58, 27.30)\) \((32.0\%\) reduction) \((P < 0.001)\) and 4.54 ± 0.28 \(\mu m\) \((2.11, 8.98)\) to 3.24 ± 0.25 \(\mu m\) \((1.16, 7.48)\) \((28.63\%\) reduction) \((P = 0.006)\). For all aberrations with a significant \(P\) value, significance existed between pre- and final time points. Additionally, HORMS, LORMS, and SA had a significant reduction at 6 weeks post I-TRESK/CXL and HORMS and SA continued to have a significant reduction between 6 weeks post I-TRESK/CXL and the final visit also.

Visual and topographic outcomes were compared between severe keratoconus eyes and mild-moderate staged eyes. Out of 48 eyes in the cohort, 15 were classified as severe keratoconus (group 2) and the rest (33 eyes) were mild-moderate.

The means preop logMAR UDVA and CDVA of group 1 \((0.97 ± 0.06, 0.26 ± 0.03)\) and group 2 \((1.25 ± 0.08, 0.45 ± 0.05)\) have improved to 0.46 ± 0.05 \((P < 0.001)\), 0.17 ± 0.02 \((P = 0.01)\) and 0.71 ± 0.10 \((P = 0.0005)\), 0.27 ± 0.05 \((P = 0.014)\), respectively. Mean logMAR UDVA gain in group 1 was 0.51 ± 0.10 and in group 2 was 0.54 ± 0.06 \((P = 0.85)\), which had no statistical difference, and mean logMAR CDVA gain in group 1 was 0.09 ± 0.2 and in group 2 was 0.18 ± 0.07 \((P = 0.20)\). Though the mean logMAR CDVA gain was higher in group 2 (severe keratoconus) compared to group 1, the difference was not statistically significant (Table 4).

Comparison of the mean reduction in Kmax, Kmean, sphere, cylinder, and MRSE from preoperative to final visit in group 1 and group 2 are mentioned (Table 4). While there was no difference in mean cylinder reduction, sphere and MRSE reduction reached
## TABLE 3. The Mean ± Standard Error (Minimum, Maximum) of Keratometry and Wavefront Aberrations

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Post-Intacs 1 Month</th>
<th>Post-I-TRESK/CXL 6 Weeks</th>
<th>Post-I-TRESK/CXL Final Visit</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>K1 (D)</td>
<td>50.41 ± 0.93 (40.9, 65.1)</td>
<td>48.02 ± 0.87 (39.3, 59.4)</td>
<td>46.06 ± 0.78 (38.0, 56.1)</td>
<td>45.66 ± 0.73 (38.0, 53.7)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>K2 (D)</td>
<td>55.05 ± 1.05 (43.5, 68.2)</td>
<td>51.34 ± 0.93 (40.9, 60.9)</td>
<td>49.77 ± 0.88 (38.3, 60.8)</td>
<td>49.68 ± 0.84 (38.7, 59.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Kmean (D)</td>
<td>52.73 ± 0.97 (42.6, 66.65)</td>
<td>49.68 ± 0.89 (40.45, 60.05)</td>
<td>47.92 ± 0.81 (38.15, 59.25)</td>
<td>47.67 ± 0.77 (38.35, 57.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Axis of K1</td>
<td>80.48 ± 9.59 (1.5, 177)</td>
<td>90.65 ± 9.92 (0.9, 178.4)</td>
<td>76.68 ± 9.12 (4.9, 177)</td>
<td>82.45 ± 9.08 (6.6, 179.1)</td>
<td>1.00</td>
</tr>
<tr>
<td>Kmax (D)</td>
<td>63.49 ± 1.45 (48.17, 79.5)</td>
<td>51.34 ± 0.89 (40.45, 60.05)</td>
<td>49.77 ± 0.88 (38.3, 60.8)</td>
<td>49.68 ± 0.84 (38.7, 59.6)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Vertical coma (μm)</td>
<td>–3.21 ± 0.29 (–8.52, 0.34)</td>
<td>–2.25 ± 0.25 (–6.36, 1.80)</td>
<td>–2.19 ± 0.28 (–6.59, 1.87)</td>
<td>–1.95 ± 0.24 (–6.18, 1.09)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Spherical aberration (μm)</td>
<td>–1.54 ± 0.23 (–5.89, 1.18)</td>
<td>–1.65 ± 0.21 (–5.10, 0.45)</td>
<td>–1.10 ± 0.18 (–4.59, 0.65)</td>
<td>–0.81 ± 0.19 (–4.64, 1.35)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Astigmatism 0° (μm)</td>
<td>–1.73 ± 0.42 (–6.79, 3.21)</td>
<td>–1.14 ± 0.31 (–5.05, 2.51)</td>
<td>–1.09 ± 0.38 (–6.69, 3.48)</td>
<td>–1.25 ± 0.40 (–5.69, 3.59)</td>
<td>0.755</td>
</tr>
<tr>
<td>Astigmatism 45° (μm)</td>
<td>–0.01 ± 0.53 (–7.03, 6.75)</td>
<td>0.30 ± 0.37 (–4.45, 5.75)</td>
<td>0.08 ± 0.43 (–5.64, 6.38)</td>
<td>–0.28 ± 0.43 (–6.01, 5.44)</td>
<td>1.00</td>
</tr>
<tr>
<td>RMS LOA (μm)</td>
<td>17.16 ± 1.08 (7.49, 38.04)</td>
<td>15.50 ± 0.88 (5.20, 26.04)</td>
<td>12.60 ± 0.88 (4.83, 25.21)</td>
<td>11.66 ± 0.87 (3.58, 27.30)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>RMS HOA (μm)</td>
<td>4.54 ± 0.28 (2.11, 8.98)</td>
<td>3.85 ± 0.24 (1.21, 7.15)</td>
<td>3.53 ± 0.26 (1.00, 7.16)</td>
<td>3.24 ± 0.25 (1.16, 7.48)</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

All eyes underwent Intacs followed by topography-guided removal of epithelium and stroma in keratoconus (I-TRESK) with corneal cross-linking. D indicates diopter; HOA, higher order aberrations; K1, flat axis keratometry; K2, steep axis keratometry; Kmax, maximum keratometry; Kmean, mean keratometry; LOA, lower order aberrations; RMS, root mean square.

*P < 0.05 was considered statistically significant.

**FIGURE 3.** Effect of Single Intacs SK ring placed inferiorly on the topography. A is the preoperative status (UDVA < 20/200, CDVA – 20/120), B is 1-month post Intacs alone (UDVA – 20/80, CDVA – 20/60). C is A minus B. CDVA indicates corrected distance visual acuity; UDVA, uncorrected distance visual acuity.

**FIGURE 4.** Effect of TRESK+ CXL on the topography. A is the status 1-month post Intacs (UDVA- 20/80, CDVA- 20/60). B is 6 weeks post TRESK+ CXL (UDVA- 20/40, CDVA- 20/30). C is A minus B. Additional effect of TRESK/CXL on topography and visual gain can be seen here. CDVA indicates corrected distance visual acuity; CXL, collagen cross-linking; TRESK, topography-guided removal of epithelium, and stroma in keratoconus; UDVA, uncorrected distance visual acuity.
DISCUSSION

Intacs is known to slow down the progression of keratoconus and improve UDVA and CDVA by flattening the cornea which are shown by studies. However, recent studies with longer follow-ups have established that insertion of Intacs alone does not stop the progression of keratoconus. There is also an unpredictability associated with the outcomes in terms of the amount of visual gain. Different additional procedures, such as CXL or wave-front-guided PRK and toric implantable collamer lens are being done in order to maximize the visual gain in association with Intacs placement. In visual rehabilitation in keratoconus, the aim should mostly be to improve the quality of vision and provide a good CDVA. However, to compare visual outcomes with other studies, we have included UDVA change too, alongside CDVA.

While comparing outcomes across studies, it is important to try and match the grade of keratoconus (Amsler-Krumeich) studied, type of ICRS implanted and the baseline UDVA and CDVA. Different studies group different Amsler-Krumeich grades as severe keratoconus or moderate keratoconus. Some use Amsler grade 2 and 3 as moderate and 4 as severe, whereas some others use 1 and 2 as moderate and 3 and 4 as severe or advanced. Flattening varies with different ICRS use and some studies have shown that Ker-keratoplasty has better outcomes compared to Intacs. It is known that a higher preop keratometry (Kmean) leads to a greater flattening postop (Table 4 in the results section proves the same) and those with poor preop UDVA/CDVA tend to gain more lines postop. But, in spite of gaining a greater number of lines, the final UDVA or CDVA attained is lesser compared to those who had a better baseline UDVA or CDVA to begin with. In our study as well, as shown in results, when we compare the outcomes between mild-moderate and severe keratoconus, the mean postop UDVA and CDVA attained at final visit is lower in the severe keratoconus group (0.71 and 0.27 in grade 4 compared to 0.46 and 0.17 logMAR in grades 1–3). When we exclude Amsler-Krumeich grade 3 from mild-moderate keratoconus group, the final UDVA and CDVA attained changes (for grades 1–3, mean postop UDVA & CDVA in the same parameters are 2.52 ± 0.52 (P = 0.0004), 1.76 ± 0.27 (P = 0.0001), 1.06 ± 0.49 (P = 0.25), 0.83 ± 0.42 (P = 0.38), and 1.48 ± 0.56 (P = 0.08). Isolating visual outcomes of Amsler Krummich grade 1 and 2 alone (Kmean < 53D), mean pre-op logMAR UDVA and CDVA were 0.85 ± 0.07 and 0.21 ± 0.03. In the final visit, they improved to 0.39 ± 0.04 (P < 0.0001) and 0.13 ± 0.01 (P = 0.018).

Comparing eyes with single (group A) and double ring (group B) implantation, there were 24 eyes in each group. Preoperative Kmean (keratometric mean) of group A was 50.42 ± 1.15D and group B was 56.80 ± 1.54D (P = 0.0020). The mean reduction in Kmax, sphere, cylinder, MRSE, HORMS, and vertical coma from preoperative to final visit in group A and group B are shown in Table 5. Double ring implantation had significantly better reduction of sphere and MRSE, whereas single ring group had marginally better cylinder reduction (not significant) and significantly better reduction of HORMS and vertical coma. In spite of the above differences, mean logMAR gain from preoperative to final visit between group A and B in UDVA (0.49 and 0.53, P = 0.68) and CDVA (0.12 and 0.14, P = 0.58) were not significant.

**TABLE 4.** The Mean ± Standard Error of Change in the Mean logMAR UDVA, CDVA, Sphere, Cylinder, MRSE, Kmean and Kmax between preoperative and Final visit in Mild-Moderate and Severe Keratoconus Groups

<table>
<thead>
<tr>
<th></th>
<th>Mild-moderate (Grade 1,2,3)</th>
<th>Severe (Grade 4)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ logMAR UDVA</td>
<td>−0.51 ± 0.10</td>
<td>−0.54 ± 0.06</td>
<td>0.85</td>
</tr>
<tr>
<td>∆ logMAR CDVA</td>
<td>−0.09 ± 0.02</td>
<td>−0.18 ± 0.07</td>
<td>0.20</td>
</tr>
<tr>
<td>∆ Sphere (D)</td>
<td>2.76 ± 0.86</td>
<td>5.97 ± 2.09</td>
<td>0.09</td>
</tr>
<tr>
<td>∆ Cylinder (D)</td>
<td>1.55 ± 0.62</td>
<td>2.22 ± 0.29</td>
<td>0.28</td>
</tr>
<tr>
<td>∆ MRSE (D)</td>
<td>3.53 ± 0.81</td>
<td>7.08 ± 1.96</td>
<td>0.05</td>
</tr>
<tr>
<td>∆ Kmean (D)</td>
<td>−4.31 ± 0.40</td>
<td>−6.82 ± 0.85</td>
<td>0.004*</td>
</tr>
<tr>
<td>∆ Kmax (D)</td>
<td>−6.68 ± 0.70</td>
<td>−11.93 ± 1.01</td>
<td>0.0002*</td>
</tr>
</tbody>
</table>

CDVA indicates corrected distance visual acuity; Kmax maximum keratometry; Kmean mean keratometry; MRSE mean refractive spherical equivalent; UDVA uncorrected distance visual acuity. ∆ denotes final – preoperative values of the variables.

*P < 0.05 was considered statistically significant.

**TABLE 5.** The Mean ± Standard Error of Change in the Mean LogMAR UDVA, CDVA, Sphere, Cylinder, MRSE, Kmean, and Kmax between Preoperative and Final Visit in Single vs Double Ring Groups

<table>
<thead>
<tr>
<th></th>
<th>Single Ring Group</th>
<th>Double Ring Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆ Log Mar UDVA</td>
<td>−0.49 ± 0.06</td>
<td>−0.53 ± 0.08</td>
<td>0.68</td>
</tr>
<tr>
<td>∆ Log Mar CDVA</td>
<td>−0.12 ± 0.03</td>
<td>−0.14 ± 0.03</td>
<td>0.58</td>
</tr>
<tr>
<td>∆ Sphere (D)</td>
<td>2.05 ± 0.66</td>
<td>5.14 ± 1.28</td>
<td>0.03*</td>
</tr>
<tr>
<td>∆ Cylinder (D)</td>
<td>1.90 ± 0.35</td>
<td>1.5 ± 0.34</td>
<td>0.241</td>
</tr>
<tr>
<td>∆ MRSE (D)</td>
<td>3.01 ± 0.62</td>
<td>5.89 ± 1.24</td>
<td>0.03*</td>
</tr>
<tr>
<td>∆ Kmean (D)</td>
<td>−4.67 ± 0.45</td>
<td>−5.46 ± 0.71</td>
<td>0.35</td>
</tr>
<tr>
<td>∆ Kmax (D)</td>
<td>−7.98 ± 1.01</td>
<td>−9.05 ± 1.11</td>
<td>0.48</td>
</tr>
<tr>
<td>∆ HORMS (µm)</td>
<td>−1.78 ± 0.21</td>
<td>−0.84 ± 0.22</td>
<td>0.005*</td>
</tr>
<tr>
<td>∆ Vertical Coma (µm)</td>
<td>2.09 ± 0.32</td>
<td>0.46 ± 0.20</td>
<td>0.001*</td>
</tr>
</tbody>
</table>

CDVA indicates corrected distance visual acuity; HORMS, higher order aberrations RMS; Kmax, maximum keratometry; Kmean, mean keratometry; MRSE, mean refractive spherical equivalent; UDVA, uncorrected distance visual acuity. ∆ denotes final – preoperative values of the variables.

*P < 0.05 was considered statistically significant.
alone. Although the order of performing CXL was under a lot of debate, recent meta-analysis has shown that CXL done either simultaneously with Intacs or following Intacs has better outcomes, compared to doing CXL before.5 Several authors have performed CXL either immediately following Intacs10 or 1 month16 or 3 months8 or 6 months37 following Intacs insertion and reported additional visual gain with CXL.

Ertan et al22 performed trans-epithelial CXL for mild to moderate keratoconus at a mean of 3.98 months following Intacs. At 3 months post-Intacs, there was a mean reduction of 2.08D (P < 0.05), 0.47D (P > 0.05), 2.22D (P < 0.05) and 1.27D (P < 0.05) in sphere, cylinder, Kmean, and Kmax, respectively. They reported an additional mean reduction of 0.5 D(P < 0.05), 0.15 D (P > 0.05), 0.35 D (P > 0.05), and 0.76D (P < 0.05) in the same parameters and a gain of 1.2 (P < 0.05) and 0.36 (P < 0.05) Snellen lines of UDVA and CDVA, respectively at 2 months after CXL. Similarly, 4.5 months after Kera-ring implantation in mild to moderate keratoconus, El Awady et al8 noted 2.8D (P < 0.05) after TRESK/CXL, we further had 1.76 in Kmean, sphere, cylinder, and MRSE. Additionally, 6 weeks (P < 0.05) Snellen lines of UDVA and CDVA, respectively at 2 months after CXL. Similarly, 4.5 months after Kera-ring implantation in mild to moderate keratoconus, El Awady et al8 noted 2.8D (P < 0.05), 2.1D (P < 0.05), and 2.5D (P < 0.05) reduction in MRSE, cylinder and Kmean. After Kera-ring implantation, mean UDVA and CDVA were 0.23 ± 0.17 and 0.39 ± 0.18 (decimal). Following CXL, the mean CDVA improved to 0.41 ± 0.18 (P = 0.18) with an insignificant reduction of 0.11D (P > 0.05) in MRSE.

In our study, when we look at outcomes of mild-moderate subgroup of keratoconus, 1 month after Intacs, our patients had a mean reduction of 2.41 ± 0.40 (P = 0.001), 1.57 ± 0.67 (P = 0.17), 0.87 ± 0.36 (P = 0.15), and 2.01 ± 0.62 (P = 0.02) in Kmean, sphere, cylinder, and MRSE. Additionally, 6 weeks after TRESK/CXL, we further had 1.76 ± 0.27 (P = 0.0001), 1.06 ± 0.49 (P = 0.25), 0.83 ± 0.42 (P = 0.38), and 1.48 ± 0.56 (P = 0.08) in the same parameters and final logMAR UDVA and CDVA of 0.46 ± 0.05 (P < 0.001), 0.17 ± 0.02 (P = 0.01), respectively. The additional reduction in spherical equivalent and Kmean are higher compared with previous studies.

Nicula et al17 studied 71 eyes [41 eyes (group 1-CXL done 6 months after ICRS), 30 eyes (group 2-ICRS placed 6 months after CXL)] across all grades of keratoconus and reported that ICRS-first group had significantly better outcomes. Six months after CXL (final visit) in group 1, there was an additional 0.9D (P = 0.003) flattening of Kmean, while the spherical equivalent and cylinder remain unchanged. In the final visit in our group (including all grades), compared to the values attained 1 month post Intacs, we had an additional 1.27D (P = 0.15), 0.59D (P = 0.42), 1.56D (P = 0.02) and 1.99D (P < 0.0001) reduction in sphere, cylinder, MRSE, and Kmean (Tables 2 and 3). Baseline UDVA and CDVA were not mentioned by Nicula et al, but around 50% and 75% of the eyes attained UDVA and CDVA of ≥20/50. In our study, we had 46% and 96% of the eyes attaining a UDVA and CDVA ≥20/60 (Fig. 2).

Coskunseven et al13 compared 2 sequences as ICRS (Kera- ring)-first and CXL-first in 48 eyes of 43 patients and reported overall better improvement in mean K, MRSE and CDVA in the ICRS-first group. In this group (preoperative Kmean-52.06 ± 4.93D), he performed ICRS first followed by CXL after 7 months and documented final findings 6 months after CXL. He noted mean reduction of 4.2D, 2.4D and 3.98D in MRSE, cylinder and Kmean and means final UDVA and CDVA of 0.32, and 0.55 (decimal). Our study (with similar baseline Kmean= 52.73 ± 0.97) had a mean reduction of 4.59D, 1.7D, and 5.06D in the same parameters. Our final UDVA and CDVA were comparable though our baseline UDVA was lesser.

A study by Elbaz et al29 was on a similar concept as that of our study. They performed femto-based Intacs insertion for mild to moderate keratoconus followed by same day 50 μm PTK of 7 mm diameter and then either standard or accelerated CXL. Fifty μm PTK was based on the idea of ablating a small depth of stroma under the cone taking advantage of a thinner epithelium over the cone. Since our study utilized accelerated CXL, we will compare the outcomes of our study (subgroup of mild-moderate keratoconus) with the outcomes of the accelerated CXL group of Elbaz et al. The mean differences from baseline to final visit in MRSE, refractive cylinder, Kmean, Kmax, UDVA, and CDVA in the study by Elbaz et al were 1.89D, 1.53D, 1.69D, 3.62D, 0.30 logMAR, and 0.12 logMAR, respectively. The same parameters in our subgroup (grades 1–3) were 3.38D, 1.62D, 4.31D, 6.61D, 0.51 logMAR, and 0.09 logMAR units, respectively. These improvement in outcomes are predominantly due to the novel technique of PTK adopted in our study. In a standard central 50 μm PTK centered on the corneal apex for all patients, it is not possible to customize a specific depth of stromal ablation under the cone as the effect of PTK of the stroma in cone region is altered by epithelial thickness in the region of the cone27 and the position of the cone. For a central cone with epithelial thickness of 35 to 40 μm, standard 50 μm PTK will ablate around 10 to 15 μm of stroma in cone region causing a flattening of around 1–1.5D. But for a relatively peripheral cone or a central cone with overlying epithelium of 45–50 μm, standard PTK will not have any corneal flattening effect. By decentralizing our ablation center to center of the cone, minimizing ablation zone to area of the cone and altering PTK depth as 25 μm over the thinnest epithelial thickness,28 we can consistently obtain 20 to 25 μm of stromal ablation in cone region, causing an additional flattening of 2–2.5D, which is reflected in the differences in outcomes between our study and the study done by Elbaz et al.

We performed TRESK and CXL 1 month after Intacs placement. We found an additional significant reduction in sphere, MRSE, UDVA, Kmean, Kmax, HORMS at the end of 6 weeks post-TRESK and post-CXL compared with the measurements of 1-month post Intacs (Tables 2 and 3). There is an argument that the refractive and topographic effect of Intacs lasts up to 6 months.38 In our study, we have seen stability in refractive and topographic parameters between 6 weeks following I-TRESK/CXL and the final follow-up (12 months). In a study by Legare et al39 comparing outcomes between ICRS alone and ICRS with simultaneous CXL, they found that Kmean and Kmax stabilized in ICRS/CXL group between 1 and 3 months, but continued to flatten up to 1 year in the ICRS alone eyes. Early CXL following ICRS makes the cornea stiffer, thereby preventing further flattening effect of ICRS. The additional significant improvement in refractive and topographic parameters seen in our study following the TRESK/CXL step and the stability in parameters from 6 weeks onwards shows that the result achieved by this modified PTK (TRESK)/CXL is not significantly influenced by the longer-lasting effect of Intacs.

The additional UDVA and CDVA gain in our study following TRESK/CXL is not just because of the flattening leading to decrease in spherical equivalent, but is also importantly contributed by decrease in HORMS. There is a significant reduction in HORMS and SA values and borderline reduction in vertical coma...
between 1-month post-Intacs and 6-weeks post-TRESK/CXL. HORMS and SA continued to have a significant reduction in the follow-up period leading to the final follow-up. HORMS reduction is necessary for an improvement in CDVA as spherical equivalent change alone cannot cause a CDVA change. This is the reason for the delay in CDVA improvement noted in our study. While keratometric flattening and spherical equivalent change stabilized at 6 weeks following TRESK/CXL, UDVA also stabilized, whereas CDVA continued to improve as the HORMS reduction continued. In our study, since the follow-up in between 6-week post-TRESK/CXL and the final visit was not possible by majority of patients, we are not certain as to when the HORMS related corneal remodeling process was completed.

Simultaneous corneal topography/wave-front-guided ablation along with CXL following varying time intervals after ICRS placement have been studied. Most of them were performed in Amsler-Krumeich grade 1–2. Kremer et al.,17 Al-Tuwairqui et al.,16 and Lee et al18 have reported final UDVA and CDVA of logMAR 0.26 and 0.12, 0.08 and 0.02, and 0.17 and 0.07, respectively following topography/wave-front-guided PRK with CXL after Intacs. These range from 20/30 to 20/25 for UDVA and 20/25 for CDVA. They do not provide close to zero sphere or cylinder outcomes, as the primary target is only to correct close to 50% of cylinder in topography-guided PRK ablations. Hence, spectacle-free or contact lens-free vision cannot be guaranteed in most cases. When we look at outcomes of our subgroup of grades 1–2 patients, we have a final logMAR UDVA and CDVA of 0.39 and 0.13, which amount to 20/50 UDVA and 20/25 CDVA. This outcome is definitely comparable in terms of quantity and quality of vision.

With I-TRESK/CXL, we ablate an elliptical area of mean diameter (4 – 3.5) which constitutes a surface area (calculating area of ellipse as 0.25π * major * minor) of 11.9 mm². This elliptical ablation is essentially an astigmatic ablation as the long and short axis are different and additionally, since it is decentered, it is also an ablation pattern specifically targeting the higher order aberrations. The maximum stromal ablation is 25 μm and it is restricted to the area of the cone. In comparison, the topography/wave-front-guided protocols ablate an average of 50 μm of stromal tissue in a diameter of 8.5 to 9 mm (surface area 63.6 mm²).14,16 This constitutes a significantly higher volume of tissue ablation in a biomechanically weaker20 and inflamed tissue.19,40 Though some evidence shows safety of these ablations, our effort must continue to find alternatives which create significantly lesser mechanical and inflammatory damage.21

In our group (grades 1 – 4) of 48 eyes, we had only 1 eye which had loss of 1 line of CDVA at the final visit. This was not because of haze, which was a factor in the 2 eyes that lost a line of UDVA and CDVA at 6-weeks post-TRESK/CXL. It is because of adjustment errors in sphero-cylindrical correction of irregular cornea. There was no other intra/postoperative complication either during Intacs implantation or during TRESK/CXL. Sixty-seven percent of our patients gained a postop UDVA equal to or better than preop CDVA and more than 80% had a final CDVA ≥ 20/40. Though the eyes in severe grades gained significant lines of CDVA, they could not attain a final CDVA ≥ 20/40 because of their poor baseline (preop mean CDVA logMAR grade 4: 0.45 vs grade 1–3: 0.26 logMAR). If we consider only mild-moderate grades, 90.90% were able to reach CDVA ≥ 20/40. Additionally, no eye lost 2 or more lines of CDVA at any stage.

Some limitations exist in our study. Longer time of follow-up will be desirable, but it is limited with current setting of our patients having to travel long distances to visit our center. We could not have adequate follow-up in an intermediate time point sufficient enough to draw conclusions on the intermediate term trends. We have not performed vector analysis which could have helped interpret changes in cylinder better. Future directions include the studying of how different ablation zone sizes of modified PTK affect outcomes with I-TRESK/CXL and finding out the ideal time (simultaneous or 1 month or 3–6 months) for performing the TRESK/CXL step after Intacs. These would help improve and maximize the outcomes with this novel technique called I-TRESK/CXL.

In practices where there is non-affordability to wave-front-guided or topography guided platforms and its diagnostics, or when quality of scans obtained for such treatments are of insufficient quality, or when the amount and axis of cylinder to be treated is doubtful due to significant coma creating differences between refractive and topographic cylinder axis, or in patients desiring better visual outcomes with corneas thinner than 450 μm (where PRK is not advisable), it is possible to go ahead with I-TRESK/CXL as an effective alternative that can provide comparable outcomes.

In summary, I-TRESK/CXL is a novel technique of using Intacs for better visual gain in keratoconus eyes. I-TRESK/CXL involves performing a modified form of customizable PTK specific to the cone area along with accelerated CXL, 1 month after Intacs surgery. In the current era of constantly evolving knowledge, although this procedure may not be the best available method of visual rehabilitation along with halting the progression of keratoconus, it will definitely be one of the better and simpler options to choose from in the time to come, as it ablates considerably lesser volume of tissue compared to PRK while providing comparable outcomes.

REFERENCES


