Combined Phototherapeutic Keratectomy, Intracorneal Ring Segment Implantation, and Corneal Collagen Cross-Linking in Keratoconus Management

Guillermo Rocha, MD, FRCSC, FACS,†‡ Tarek Ibrahim, MD, PhD,*§ Eric Gulliver, BSc (Hons),¶ and Kylee Lewis, BSc¶*

Purpose: To evaluate the efficacy, predictability, and safety of combined corneal collagen cross-linking (CXL), intracorneal ring segment (ICRS) implantation, and superficial phototherapeutic keratectomy (PTK) in patients with keratoconus.

Methods: Fifty-five eyes received ICRS implantation, followed by CXL and PTK combination treatment. Patients were followed up for 6 months. Primary outcomes included Logarithm of the Minimum Angle of Resolution (LogMAR) uncorrected distance VA (UDVA) and corrected distance VA (CDVA), sphere, cylinder, mean spherical equivalent, index of surface variance, index of vertical asymmetry, keratoconus index, central keratoconus index, index of height asymmetry, and index of height decentration. Secondary outcomes were higher-order aberrations (HOAs), including HOA total, coma, spherical, secondary astigmatism, and trefoil.

Results: At 6 months, there was a statistically significant improvement in UDVA, CDVA, sphere, and cylinder compared with baseline ($P < 0.001$). UDVA improved in 14% of the eyes to 20/25 and 96% had at least 20/40 or better spectacle corrected vision; 30.9% of the eyes were within ±0.5 diopter (D), 45.5% of the eyes were within ±1.0 D, and 74.5% of the eyes were within ±2.0 D. For CDVA, 1 eye (2%) lost 3 lines (but gained UDVA), 11% lost 1 line, 38% showed no change, and 49% gained between 1 and 8 lines of vision. Eighty-eight United Arab Emiratespercent of the eyes had at least 1 line of UDVA visual improvement, 79% improved by ≥2 lines, and 69% improved by ≥3 lines. HOA total, coma, spherical aberration, and secondary astigmatism showed improvements of −0.87 ($P < 0.001$), −0.84 ($P < 0.001$), −0.10 ($P = 0.002$), and −0.15 ($P = 0.035$), respectively.

Conclusions: A combined procedure of ICRS implantation, CXL, and PTK is effective, predictable, and apparently safe for patients diagnosed with moderate keratoconus.

Key Words: cross-linking, INTACS, keratoconus, Pentacam, higher-order, aberrations

(*Cornea* 2019;38:1233–1238)

Measuring the success of keratoconus treatment relies on how effective the selected therapy is in halting disease progression, in addition to confronting the optical insufficiency of the irregular cornea.[1] Recently, corneal collagen cross-linking (CXL), intracorneal ring segment (ICRS) implantation, and excimer laser refractive surgery have taken an increasing role in disease stabilization and improving functional vision.[2,3]

Early studies examined combined topography-guided photorefractive keratectomy (t-PRK) and CXL, aiming for both visual acuity (VA) rehabilitation and corneal stability.[4–10] t-PRK or wavefront-guided photorefractive keratectomy (PRK) can potentially reduce irregular astigmatism, improving spectacle corrected distance VA (CDVA).[11–15]

Kanellopoulos[11] and Richoz et al[16] have discussed the possible advantages of simultaneous treatment, in which PRK is followed sequentially by CXL, resulting in reduced time off work, faster visual rehabilitation, no removal of previously cross-linked corneal tissue,[16] and unmodified tissue ablation rates. The main risk associated with combining PRK with CXL in keratoconus is that corneal stromal tissue removal in PRK might render the cornea less stable biomechanically, acting against the stabilizing effect of CXL. For this reason, most investigators have limited the depth of tissue removal to a notional 50 μm maximum depth, such that only a partial refractive correction is achieved and optical zone diameters are reduced in many cases.[14–16]

Previously, we reported improvement in visual performance and keratometry after intracorneal ring implantation (INTACS Corneal Inserts; Addition Technology, Inc, AJL Ophthalmic, S.A., Sunnyvale, CA).[2,17] Our group has also observed corneal stabilization and improved topography, tomography, and reduced higher-order aberrations (HOAs)

Received for publication February 13, 2019; revision received June 3, 2019; accepted June 5, 2019. Published online ahead of print July 16, 2019.

From the *Ocular Microsurgery & Laser Centre, Brandon, MB, Canada; †Department of Ophthalmology, Max Rady College of Medicine, University of Manitoba, MB, Canada; ‡Brandon Regional Health Centre, Prairie Mountain Health, MB, Canada; §Eye Consultant Centre, Visiting Consultant, Dubai, United Arab Emirates; and ¶Max Rady College of Medicine, University of Manitoba, MB, Canada.

G. Rocha acknowledges receiving Bausch + Lomb speaker fees, T. Ibrahim is a consultant for Bausch + Lomb, and E. Gulliver and K. Lewis have no financial interest or proprietary interest in any material or method mentioned. Michelle Dalton, ELS, provided editorial support for this manuscript; this support was funded by the investigators.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.corneajrnl.com).

Ethics approval: Research Ethics Board, University of Manitoba, Canada.

Correspondence: Tarek Ibrahim, MD, PhD, Ocular Microsurgery & Laser Centre, 144-6th St, Brandon, MB, Canada R7A 3N2 (e-mail: tarekan@yahoo.com).

after epithelium-off CXL in eyes with keratoconus and postlaser in situ keratomileusis ectasia.[18,19] More recently, our research showed that the combination of wavefront-guided photorefractive keratectomy with epithelium-off CXL resulted in improved visual function, enhanced topography/tomography indices, and reduced HOA in eyes with keratoconus and postlaser in situ keratomileusis ectasia.[20]

In this study, we evaluate the effect of combined ICRS, phototherapeutic keratectomy (PTK), and epithelium-off CXL on visual function, corneal topography, corneal tomography, and HOAs in eyes with moderate keratoconus.

METHODS

This retrospective study reviewed the charts of all patients with keratoconus who had undergone combined INTACS implantation, PTK, and epithelium-off CXL between March 2010 and July 2016. All patients provided written informed consent before surgery in accordance with the Declaration of Helsinki. Parental consent was obtained in cases where patients were younger than 18 years at the time of surgery. The study was approved by the Research Ethics Board of the University of Manitoba, MB, Canada.

Inclusion criteria included the presence of keratoconus as evidenced clinically and topographically/tomographically through the Pentacam (Oculus, Wetzlar, Germany) and iTrace (Tracey Technologies, Houston, TX), contact lens intolerance, and clear central cornea. Eyes with moderate keratoconus and corneal thickness ≥440 μm, peripheral corneal thickness of at least 450 μm, a maximum CDVA of 20/32, and keratometry readings ≤55.0 diopter (D), which is equivalent to an Amsler–Krumeich classification of stages 2 to 3, were considered for this approach. Before surgery, all eyes were at risk of progression or had proven changes consistent with progression. All patients complained of poor "satisfactory best-corrected" vision,[21] meaning they could have good corrected vision; however, either the overall quality of their vision was poor or they could not tolerate corrective lenses for extended periods.

Exclusion criteria included previous corneal refractive surgery, delayed epithelial healing, pregnancy, or nursing before surgical intervention. Patients with thin corneas (≤440 μm at the center), corneal central scarring or opacification, severe dry eye syndrome, history of herpetic eye disease, active anterior and posterior segment pathologies, or autoimmune disease were also excluded.

Preoperative Assessment

A full examination was performed on each patient, including uncorrected distance VA (UDVA), spectacle CDVA, manifest refraction, slit-lamp examination, tonometry, and fundoscopy. VA was measured using the ClearChart 2 Digital Acuity System (Reichert Technologies, Depew, NY) with Logarithm of the Minimum Angle of Resolution (LogMAR) optotype display. All examinations and manifest refractions were performed by 1 examiner (G.R.). The anterior segment was assessed with optical coherence tomography to evaluate epithelial thickness (R-TVue, Fremont, CA). Placido-based topography and total ocular aberrometry (iTrace ray tracing aberrometer/topography), in addition to Scheimpflug corneal tomography (Pentacam HF; Oculus GmbH, Wetzlar, Germany), were obtained. All HOAs were assessed at a 5-mm pupil.

Primary outcomes included UDVA, CDVA, sphere, cylinder, manifest spherical equivalent, index of surface variance, index of vertical asymmetry, keratoconus index (KI), central KI, index of height asymmetry, and index of height decentration. HOA included HOA total, coma, spherical, secondary astigmatism, and trefoil.

Surgical Planning

Three steps were used to individualize the treatment parameters for each eligible eye:

1. Assessment of manifest refraction, topography, tomography, and coma axis on aberrometry testing to determine the position of the cone.
2. Estimation of residual stromal thickness. The goal was to have an estimated residual stromal thickness of at least 390 μm (preferably 400 μm) after a maximum excimer laser central stromal ablation of 10 μm after epithelial removal.
3. INTACS segments were placed either inferiorly only or asymmetrically (thinner superior) based on our previously reported method.[20] Alignment was based on the concordance of the refractive, topographic, and perpendicular vertical coma axis, as previously described by Alfonso et al.[22]

All procedures were carried out at ImagePlus Laser Eye Centre in Winnipeg, Canada, by the same surgeon (G.R.). For the purposes of this study, follow-up was 6 months.

INTACS Implantation

The incision site was determined preoperatively based on the correlation of the axis location of the plus cylinder on manifest refraction, the topographical axis, the shape and location of the cone on the elevation map, and the axis perpendicular to the axis of the vertical coma. The IntraLase FS laser (Abbott Medical Optics Inc, Santa Ana, CA) was used to create the channel depth of 400 μm, with an internal diameter of 6.8 mm and external diameter of 7.8 mm. Regular INTACS implantation followed manufacturer's instructions, with no modifications for asymmetric segment thickness. INTACS severe keratoconus (SK) required a channel depth of 380 μm, 6.0-mm internal diameter, and 7.0-mm external diameter. A dissector was used to open the channel at its origin, then INTACS segments were placed starting with the thicker segment first. The incision was closed with a 10-0 nylon suture, which was removed approximately 2 months postoperatively or earlier if the suture loosened.

PTK Procedure

PTK was performed using the VISX Star S4 IR excimer laser system (Abbott Medical Optics Inc). Corneal epithelial thickness was calculated using optical coherence tomography

epithelial thickness maps on the central and thinnest points, with results (usually between 50 and 65 μm) used to plan the initial depth of the PTK circle at a 6.5-mm optical zone. The laser ablation was initiated centered on the pupillary center. With dim illumination, fluorescence was evident as the laser ablated the epithelium. When epithelial breakthrough occurred, usually at a depth between 40 and 50 μm, a dark spot corresponding to the Bowman layer was observed through the microscope. At this point, the ablation was continued at micron by micron steps until the central cornea was clear of epithelium. No more than 10 μm of the stroma was ablated, and the goal was to always leave at least 390 μm of residual stromal thickness. An Amoils brush (Hyperopic Amoils Epithelial Scrubber; Innovative Excimer Solutions Inc, Toronto, Canada) was used to remove an epithelial area out to 8.0 mm before CXL. Mitomycin C 0.02% was applied for 12 seconds, then washed with 10 mL balanced salt solution, and the CXL procedure was performed.

CXL Procedure

The CXL procedure was slightly modified from how it was initially described by Wollensak et al.[1] In brief, pilocarpine 2% was instilled. Riboflavin 0.1% in dextran solution was applied every 2 minutes for 30 minutes. When necessary, hypotonic riboflavin solution was used to ensure a corneal thickness of at least 400 μm before initiating Ultraviolet A (UVA) irradiation. The debrided area was then exposed to 370 nm wavelength UVA irradiation/9 mW/cm^2 for 10 minutes (IROC Innocross AG, Zug, Switzerland) while instillation of riboflavin continued in an alternating fashion every minute (dextran/hypotonic). After the procedure, topical antibiotic, steroid, and cycloplegic drops were instilled and a bandage contact lens was placed.

Postoperatively, topical moxifloxacin hydrochloride 0.5% (Vigamox; Alcon Laboratories, Ft. Worth, TX) was prescribed 4 times a day until epithelial closure; dexamethasone 0.1% (Maxidex; Alcon Laboratories) was prescribed 4 times a day and tapered weekly over a month, and frequent artificial tears were prescribed. The bandage contact lens was removed upon epithelial closure, which was between 5 and 7 days postoperatively.

Postoperative Assessment

A complete examination was performed postoperatively including UDVA, CDVA, refraction, and slit-lamp assessment. Placido-based topography, total ocular aberrometry, and Scheimpflug corneal tomography were repeated at the 6-month follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 25, International Business Machines Corp, Armonk, NY). The normality of all data samples was evaluated with the Shapiro–Wilk test. The paired sample 2-tailed *t* test was used to compare presurgical and postsurgical parameters.

RESULTS

A total of 55 eyes of 46 patients were included in the study. There were 40 male and 15 female eyes, with a median age of 33.7 years (range, 14–51 years). Slightly more right eyes (n = 30) were included than left eyes (n = 25). At baseline, mean UDVA and CDVA (spectacle corrected) values were 0.83 and 0.19 LogMAR, respectively. At baseline, only 2% of the UDVA measures were 20/32 or better; the remainder were 20/40 or worse. All patients received 6 months of follow-up before being exited from the study.

At 6 months, there was a statistically significant improvement in UDVA and CDVA (spectacle corrected) compared with baseline, by -0.39 ± 0.31 and -0.08 ± 0.17 LogMAR, respectively (95% confidence interval [CI]: ± 0.08 and ± 0.45, respectively; $P < 0.001$). Sphere and cylinder also showed statistically significant improvements at 6 months compared with baseline (1.48 ± 1.67 D and 2.12 ± 1.42 D, respectively; CI, ± 0.44 and ± 0.38, respectively; Table 1).

After 6 months, UDVA improved in 14% of the eyes to 20/25 and in 46% to 20/40. Sixty-six percent of the eyes achieved CDVA of 20/25, and 96% had at least 20/40 vision (Table 2). At 6 months, higher percentage of eyes showed near emmetropia manifest spherical equivalent compared with baseline. Full results are shown in Table 3.

Other keratometric endpoints improved as well, including index of surface variance by 19.6, index of vertical asymmetry by −0.23 mm, KI by 0.10, index of height asymmetry by 5.5 μm, and index of height decentration by 0.03 μm (all, $P < 0.001$). Full results are shown in Table 4.

Safety

The large majority of eyes either retained the same vision or had improved vision. Of the 55 eyes with CDVA data, 1 eye (2%) lost 3 lines (but gained UDVA); this was probably due to increase in higher-order aberrations, as well as mild anterior stromal haze, 11% lost 1 line of vision, 38% showed no change, and 49% gained between 1 and 8 lines (the latter in 1 patient). Four eyes did not have UDVA data; of the remaining 51 eyes with UDVA data, 88% of the eyes had at least 1 line of UDVA visual improvement, 79% improved by ≥2 lines, and 69% improved by ≥3 lines.

TABLE 1. Visual Acuity Outcomes, 6-Month Data

	Baseline (N = 55)	6 Months (N = 55)	Difference ± SD (CI)	*P*
UDVA* (LogMAR)	0.85	0.46	0.39 ± 0.31 (±0.08)	<0.001
CDVA (LogMAR)	0.19	0.11	0.08 ± 0.17 (±0.04)	<0.001
Sphere (D)	−4.42	−2.94	1.48 ± 1.67 (±0.44)	<0.001
Cylinder (D)	4.01	1.89	2.12 ± 1.42 (±0.38)	<0.001
MSE (D)	−2.41	−2.00	0.42 ± 1.75 (±0.46)	0.08

*N = 51 for UDVA.
MSE, manifest spherical equivalent.

TABLE 2. Efficacy of Combined PTK, CXL, and INTACS Treatment for Keratoconus

	Preop (% of Patients)		Postop (% of Patients)		
LogMAR	UDVA (N = 54)	CDVA (N = 55)	UDVA (N = 52)	CDVA (N = 55)	
At least 20/25	1.9	41.8	13.5	65.5	LogMAR ≤ 0.1
At least 20/32	1.9	66.5	30.8	83.6	LogMAR ≤ 0.2
At least 20/40	9.3	90.9	46.2	96.4	LogMAR ≤ 0.3

Specific MSE values for all eyes (n = 55) are shown in Table 3. At 6 months, approximately one-third of eyes (30.9%) were within ±0.5 D, with 45.5% within ±1.0 D, and 74.5% within ±2.0 D.

MSE, manifest spherical equivalent.

HOAs

Chart data were available for 15 eyes (13 patients; 9 male and 4 female). HOA total, coma, spherical aberration, and secondary astigmatism showed improvements of −0.87 ($P < 0.001$), −0.84 ($P < 0.001$), −0.10 ($P = 0.002$), and −0.15 ($P = 0.035$), respectively. Only trefoil had a nonsignificant improvement of −0.16 ($P = 0.15$; see Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/ICO/A864).

DISCUSSION

After evidence-based validation of the safety and efficacy of the standalone CXL procedure, combined approaches emerged to improve outcomes in keratoconus patients.[10,23–29] This study was designed to evaluate the combined effect of simultaneous ICRS, PTK, and CXL on visual outcomes in patients with keratoconus. Although partial PRK is commonly used to improve refractive error in combination with CXL in keratoconus management, we used PTK to minimize stromal ablation in an attempt to flatten the protruding area of the cone.[30–32]

We use a logical and consistent approach to keratoconus management. The goal is to identify which eyes will benefit from the different treatment options available. Our treatment decisions are based on 3 clinical questions: Was there progression, does the shape of the cornea need to be altered, and does the quality of vision need to be improved? If the eye can achieve satisfactory corrected vision with spectacles or contact lenses and is not at risk of or demonstrate progression, no further surgical intervention is needed. However, if progression is a concern, the cornea needs to be stabilized. In those situations, CXL is one of the treatment modalities offered. If the corneal shape is abnormal, treatment options including ICRS and t-PRK or wavefront-guided PRK can be considered. In our experience, eyes that can achieve better than 20/32 CDVA with corneal thickness >440 μm and keratometry readings ≤55 D are good candidates for combined CXL and PRK, depending on the refraction. Conversely, we strive to use ICRS when eyes are unable to achieve better than 20/32 CDVA.

TABLE 3. Percentage of Eyes Within Specific MSE Outcome, 6-Month Data

MSE (D)	Baseline; Percentage Within Specific MSE (N = 55)	6-Month; Percentage Within Specific MSE (N = 55)
±0.25	9.1	27.3
±0.50	18.2	30.9
±1.00	29.1	45.5
±1.50	34.5	58.2
±2.00	52.7	74.5

MSE, manifest spherical equivalent.

TABLE 4. Pentacam Indices Outcomes, 6-Month Data

μm/5 mm	Baseline (N = 55)	6 Months (N = 55)	Difference ± SD (CI)	*P*
ISV	104.24	84.62	19.62 ± 24.42 (±6.45)	<0.001
IVA (mm)	1.22	0.99	0.23 ± 0.27 (±0.07)	<0.001
KI	1.31	1.21	0.10 ± 0.06 (±0.02)	<0.001
CKI	1.06	1.06	0.001 ± 0.05 (±0.01)	0.85
IHA (μm)	29.62	24.09	5.53 ± 20.27 (±5.36)	0.048
IHD (μm)	0.13	0.10	0.03 ± 0.45 (±0.01)	<0.001

ISV, index of surface variance; IVA, index of vertical asymmetry; CKI, central keratoconus index; IHA, index of height asymmetry; IHD, index of height decentration.

This off-label combined procedure of ICRS implantation, CXL, and superficial PTK appears to be safe, effective, and predictable. We found significant improvements in UDVA, CDVA, and HOAs at 6 months postoperatively compared with baseline. The large majority of eyes either retained the same vision or had improved vision. HOA total, coma, spherical aberration, and secondary astigmatism showed improvements of −0.87 ($P < 0.001$), −0.84 ($P < 0.001$), −0.10 ($P = 0.002$), and −0.15 ($P = 0.035$), respectively. This is one of the major strengths in our study.

The addition of ICRS implantation in more advanced cases is needed for primary intervention. Vega-Estrada et al[33] recently analyzed visual outcomes after ICRS implantation for keratoconus in 631 eyes, which showed better results for patients starting with worse preoperative CDVA. It is still not clear when the intrastromal rings' effect reaches its peak. The effect of the INTACS and PTK likely plateaus 6 months after surgery.[34] In addition, several studies have shown that there is some regression of the effect achieved by implanting INTACS alone without additional CXL.[34,35] Therefore, if stability is observed after 6 months, it can be attributed to the prolonged effect of the CXL. This study has shown 6 months of improvement in nearly all of the primary measures after the combined treatment.

A number of studies have highlighted that same-day combination therapies may be superior to sequential combination therapies and individual treatments.[11,36] The combined same-day PTK, ICRS, and CXL procedure has the advantage of avoiding ablation on previously cross-linked corneas, which may remove cross-linked areas that do affect the total volume of modified stroma needed to prevent further future progression.[37] It also avoids de-epithelialization twice from separate procedures and the associated risks, such as

superficial stromal haze and scarring. The combined approach also is more efficient regarding patient scheduling, travel time, and time off work. It offers faster visual recovery, and it may have a synergistic effect making it more rewarding.[38] Yeung et al conducted retrospective reviews on a number of same-day combinations, including ICRS and CXL, and PTK, ICRS, and CXL.[27,29,34] Despite the presence of some differences with our study (ie, the ICRS incision site was based on the plus cylinder axis of the patient's manifest refraction in all cases, and the PTK depth used was a consistent 50-μm ablation), they also concluded that these techniques are safe and effective, with reduced corneal astigmatism and improved UDVA. In our study, however, we also included changes in HOA and found the combined procedure was able to statistically significantly improve all measured HOAs with the exception of trefoil.

We acknowledge that this study has several limitations. In a young, mobile, metropolitan population, achieving higher follow-up rates is a significant challenge, which is why we limited our study to 6 months of follow-up. A longer follow-up would have strengthened the outcomes. Another limitation is the small number of patients, which restricted the accrued HOA data. It would have been interesting to determine the effect of this combined treatment on the progression of keratoconus in the pediatric age group, where keratoconus behaves more aggressively and may even progress despite CXL treatment.[39] Unfortunately, we had only 2 cases of patients 18 years or younger; thus, we were unable to statistically isolate the effect of the intervention in this age group. At study inception, we opted to set a 5-mm zone from which to measure HOAs. We found during screening, however, that a larger than anticipated number of pupils were smaller than 5 mm, leaving us unable to capture their data per protocol. Finally, the differential contribution of the PTK and the INTACS insertion to the overall improvement in refraction and topographical flattening was not evaluated in our study. This merits further investigation in future studies.[40,41]

In conclusion, simultaneous ICRS, PTK, and CXL seem to be a promising treatment resulting in a rapid and marked improvement in VA and topography of keratoconus patients. The procedure is predictable, appears to be safe, and effective and provides added stability of the cornea offered by CXL, with additional benefits of improved vision and keratometric measures 6 months postoperatively. Longer follow-up with larger groups is needed to confirm these results.

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