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Research Article

Long Term Refractive Stability of Combined ICR Implantation and Crosslinking in Irregular Astigmatism Due to Keratoconus

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Abstract

Purpose: To evaluate the long term refractive stability of combined femtosecond laser assisted intrastromal corneal ring (ICR) insertion with and corneal collagen crosslinking in keratoconus patients.

Setting: Roayah Eye Center, Alexandria and International Femto center, Cairo Egypt.

Designs: A prospective, multicenter noncomparative, and interventional clinical trial.

Methods: the study was conducted on moderate keratoconus patients with poor best spectacle-corrected visual acuity (BSCVA) and intolerance to contact lens wear, at age range between 18 to 35 years, a clear central cornea, and a peripheral corneal thickness of more than 450 microns at the planned incision sites.

Results: A statistically significant difference was reported between preoperative and postoperative uncorrected visual acuity, BSCVA, spherical equivalent, and K readings. There was no significant difference between pre- and postoperative pachymetry. No intraoperative complications was reported. Incidence and nature of postoperative adverse events were reports. Outcomes measures showed stability during various follow up periods.

Conclusions: ICR implantation with femtolaser assistance combined with corneal collagen crosslinking in keratoconus patients provides safe results and effective visual and refractive outcomes.

Keywords: *ICR Implantation; Crosslinking; Astigmatism; Keratoconus*

Introduction

Keratectectasia represents a group of corneal disorders characterized by an inherent state of tectonic corneal weakness leading to thinning, protrusion, irregular astigmatism, a resultant loss of visual acuity, and a rare risk for perforation. These disorders include both primary (keratoconus, keratoglobus, posterior keratoconus, and pellucid marginal degeneration) and secondary or iatrogenic corneal ectasia, which may follow corneal refractive procedures such as laser in situ keratomileusis (LASIK) [1].

Keratoconus and other ectatic disorders as pellucid marginal degeneration, keratoglobus, and posterior keratoconus have more or less similar clinical presentation. With the first 3 disorders may actually represent variations in the phenotypic expression of the same pathogenetic mechanism [2].

All these primary ectatic disorders have a common feature: corneal thinning with protrusion. The area of maximal thinning, relative to the location of maximal corneal protrusion, is helpful in differentiating these conditions. The resultant reduction in visual function can vary from mild to severe. Computer-assisted topographical analyses as well as scheimpflug based corneal imaging modalities as Pentcam have dramatically improved the sensitivity of detection of these ectatic disorders even in the early disease stage [2].

Reported estimates of the prevalence of keratoconus vary widely, but most fall between 50 and 230 patients per 100,000 people. Keratoconus is usually a bilateral disease but with asymmetric pattern. However, it has been convincingly shown that when diagnostic criteria and computer-assisted topographical analysis allow the detection of very early keratoconus in the fellow eye, the incidence of unilateral involvement is very unlikely to be reported [2,3].

Associations with systemic and ocular disorders have led to the development of many theories regarding the etiology of keratoconus. Nevertheless, the cause of this corneal disorder is still an enigma. Keratoconus may represent a general phenotype, the cause of which may be linked to variable clinical setting as long-term contact lens wear and atopy [1].

Keratoconus has a basic treatment algorithm. Visual correction begins with trial of spectacles, followed by rigid contact lens fitting. Failing these modalities, a surgical approach to restore a more normal corneal contour may be appropriate.

Contact lens-intolerant keratoconus patients without central scarring who have mild or moderate disease may be candidates for intracorneal ring (ICR) segment insertion. The ideal candidates for ICRs have low spherical equivalents and maximum keratometry readings less than 65D. The procedure works by flattening the central cornea, reducing astigmatism, and centering the cone. This in turn improves uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA). It also improves contact lens fit and comfort.

Intracorneal rings were first used to correct low myopia having the American Academy of Ophthalmology reports of safety and efficacy for the treatment of degrees from –1.0 to –3.0D in patients with a stable manifest refraction and less than 1D of astigmatism. However, they haven't gained popularity as other options for myopic correction such as LASIK and photorefractive keratectomy [4].

Corneal collagen crosslinking (CXL) is a outpatient procedure intended to halt the progression of keratectasia thus delaying if not eliminating the need for keratoplasty. The procedure uses ultraviolet (UV) light and riboflavin to strengthen the stromal collagen. Riboflavin (the photosensitizing agent), when exposed to UV, releases free radicals or reactive oxygen species into the surrounding stroma that cause corneal collagen hydrogen bond or crosslink formation [5-7].

The principal effects of crosslinking are localized to the anterior 300 μm of the stroma. A 328.9% increase in corneal rigidity has been shown in human corneas [6].

CXL is indicated in early progressive corneal ecstatic conditions, such as keratoconus and the associated variants. CXL requires a minimum corneal thickness of 400 μm after removal of the epithelium. Individuals with corneas thinner than 400 μm should not undergo CXL because of possible endothelial cell damage [8].

This study concerns the long-term safety and efficacy of combined CXL and use of the ICR segments for keratoconus management inserted with assistance from a femtosecond laser.

Materials and Methods

This prospective, noncomparative, interventional clinical trial was performed between July 2010 and March 2017at Roayah Eye Centre, Alexandria, Egypt and International Femto center, Cairo, Egypt. Inclusion criteria were: keratoconus with poor BSCVA less than 0.5 decimal and intolerance to contact lens wear, an age of 18 to 35 years, a clear central cornea, and a peripheral corneal thickness of more than 450 μm at the planned incision sites. Exclusion criteria were corneal opacity, severe keratoconus (keratometric values of more than 68.0D), acute hydrops, the presence of active or recent ocular infection or inflammation, and localized or systemic autoimmune or immunodeficiency diseases.

All patients were appropriately informed before their participation in the study and gave their written informed consent in accordance with institutional guidelines according to the Declaration of Helsinki.

Preoperatively, all patients were subjected to a detailed ocular and medical history and a complete ophthalmic examination that included UCVA, manifest refraction, BSCVA, slitlamp examination to exclude corneal opacity or inflammation, a fundus examination to report any posterior segment abnormalities, Scheimpflug imaging with Pentacam (Allegro Oculyzer, WaveLight AG, Germany) to measure keratometric readings and corneal thickness at the thinnest location, and anterior segment optical coherence tomography (OCT; Visante, Carl Zeiss Meditec, Inc., Dublin, CA) to measure corneal thickness at the planned incision sites.

To plan for ICR insertion, a nomogram was used to select the proper ring segments.

Careful placement and inspection of the laser system's contact glass was performed to ensure proper centration. The disposable contact glass applanates the cornea only minimally and maintains a precise focal distance between the laser emission aperture and the desired focal point. From this a tunnel of the desired depth and geometry is cut within the stroma.

Femtosecond laser (VisuMax, Carl Zeiss Meditec, Inc.) was used to create the tunnels and incisions with a wavelength of about 1,040 nm. The laser frequency was 500 kHz. With the software, it was possible to select the depth of the tunnels to be 80% of corneal thickness and parallel to the posterior surface of the cornea.

Incisions were made on the steepest corneal topographic axis or on the comatic axis, this is verified with manifest refraction. In all cases, two incisions were created. The number of tunnels depended on the desired number of segments to be inserted. One tunnel (180 degree) was created if one segment was planned for use; two tunnels (360 degree) were inserted if two segments were to be inserted.

The inner diameter of each tunnel was set to be about 5 to 5.5 mm; the outer diameter was 6.4 to 7 mm to have a tunnel width of 0.8mm. Energy used was about than 130 nano Joul, with a procedure time of about 13 to 18 sec for the femtosecond laser to create all tunnels and incisions.

All cases were operated on by the a group of 4 experienced surgeons. The procedure was performed under topical anesthesia (benoxinate eye drops every 5 min given 3 to 5 times). The patient was positioned on the patient supporting system in the exit position. The patient supporting system was moved with the patient to the observation position. Sterilization of both eyes was performed with povidone–iodine followed by draping and a speculum applied to the eye to be treated.

The Ring was placed after channel creation under full aseptic technique with the aid of a specific forceps and a Sinskey hook through dialing holes at both ends of the segments. Each segment was centered in the middle of its tunnel equidistant from both incisions. When a single segment was inserted, it was inserted inferiorly; two-segment implantation required the largest one to be inserted inferiorly (at the steep part).

Corneal Collagen Crosslinking

CXL was performed in patients with progressive keratoconus defined as a 1D increase in keratometric reading over a period of 6 months as documented with corneal topography. Contact lenses were placed at the end of procedure.

For CXL, the central corneal epithelium was removed to allow better diffusion of riboflavin into the stroma. A 0.1% riboflavin solution was applied every 5 min starting 30 min before irradiation. Irradiation was performed using a CXL device producing a UVA wavelength of 370 nm and an irradiance of 18 mW/cm^2 for 5 min (equal to a dose of 5400 mJ total energy) at a distance of 5 ± 0.5 cm. Riboflavin application continued during UVA irradiation.

Postoperative Treatment

The topical antibiotic moxifloxacin (Vigamox), steroids (prednisolone; PredForte), and artificial tears were used postoperatively. The artificial eye drops were used every hour during the first day and then every 4 hours for 1 month. The antibiotic dose was every hour for the first day, which then decreased to every 4 hours for 10 days. The systemic analgesic indomethacin was prescribed in cases with CXL.

Patients were instructed to avoid eye rubbing. Contact lenses were removed once epithelial healing was complete; this usually occurred on the third day after surgery. All cases were asked to come for a follow up at 1 week and 1, 3, 6, 12 and 24 months. During each follow-up ophthalmic examination, visual acuity measurement, refraction, and Pentacam images were obtained. Anterior segment OCT was done only once during follow up at 1 week to detect ICR segment depth and position. Any complications were recorded.

Statistical Analysis

Data were analyzed using the Predictive Analytics Software (PASW Statistics version 18 for Windows). Quantitative data were described using median, minimum, and maximum as well as mean and standard deviation. Comparison between different periods was assessed using an ANOVA test with repeated measures with Bonferroni correction. Significance test results were quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Results

This study included 1352 eyes of 917 keratoconus patients with moderate keratoconus. Only those who completed at least full 24 month follow-up were included in the statistical analysis. The patient age range was 18 to 37 years (mean ± SD, 23.77 ± 4.78). 64% of patients had bilateral ICR implantation. All patients in our study had CXL due to documented progression. Cases with no CXL due to no progression were excluded from statistical analysis of his report.

Operative and Postoperative Complications

No surgical complications occurred during surgery. Insertion was easy in most cases, with no need to use a mechanical spreader. There was also no need for sutures. In 28 eyes, intraoperative suction loss due to patient movement occurred. Suction was achieved again with no resultant decentration or other complications. All eyes showed excellent corneal tolerance with no extrusion, migration, or vascularization around the incision or the tunnels. In addition, neither corneal ulcers nor stromal necrosis superficial to the segment were seen. In one patient, the ICR segments broke while still in place. This patient showed no improvement in BCVA, although he did show improvement in UCVA by 4 lines. No postoperative infection or corneal melting occurred during follow up in any case. With the use of anterior segment OCT, 3 eyes were found to have their ICR segments inverted in the corneal tunnel, but no further corrections were necessary.

Visual Outcomes

Table 1 shows a comparison between the preoperative and postoperative UCVA, BCVA as well as keratometric values as measured by pentacam. All eyes showed improvement in UCVA. Patient satisfaction with UCVA and BCVA was met in all cases. There was no statistically significant difference between UCVA in the different follow-up periods.

	Preoperative	Postoperative 1 mo	Postoperative 12 mo	Postoperative 24 mo
UCVA	0.12 ± 0.29	0.66 ± 0.31 (P < 0.001)	0.69 ± 0.29 (P < 0.001)	0.67 ± 0.26 (P < 0.001)
BCVA	0.38 ± 0.20	0.76 ± 0.28 (P < 0.001)	0.81 ± 0.22 (P < 0.001)	0.76 ± 0.37 (P < 0.001)
Spherical Equivalent	-9.98 ± 4.7	-4.18 ± 2.12 (P < 0.001)	-3.54 ± 2.82 (P < 0.001)	-3.62 ± 2.90 (P <= 0.001)
K mean	54.23 ± 5.53	46.19 ± 4.93 (P < 0.033)	46.67 ± 4.87 (P < 0.005)	45.92 ± 4.61 (P < 0.05)
Pachymetry	445.19 ± 23.20	433.34 ± 66.52	441.21 ± 75.04	445.84 ± 68.14

Table: *Summary of preoperative and postoperative outcomes.*

Marked improvement in spherical equivalent in all patients was noted, especially for the cylindrical component as shown in Table 1.

There was a statistically significant difference between the preoperative period and other follow-up periods.

Using the Pentacam, pachymetry was measured at the thinnest location for all patients as shown in Table 1. No statistical significant difference existed between preoperative and postoperative pachymetry.

A comparison between early postoperative follow up and 3- and 6,12 and 24 month follow up showed no significant change in any of the previously mentioned parameters except for the mean BCVA improvement at months 3 and 6 compared with the 1 month BCVA (Figures 1-3). ocular response analyzer is done for all cases at 3rd months and showed a 16.7 and 21.7 % improvement of corneal hysteresis and corneal resistance factor respectively at 3rd follow up month (Figure 4). Both are indicators for corneal biomechanics improvement.

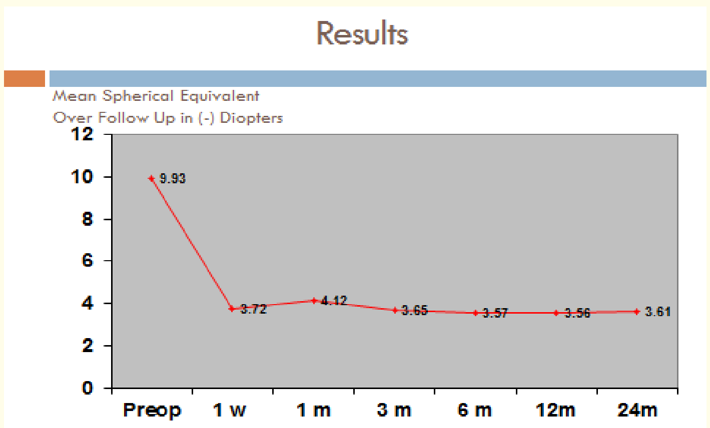

Figure 1: *Mean SE changed during follow up periods.*

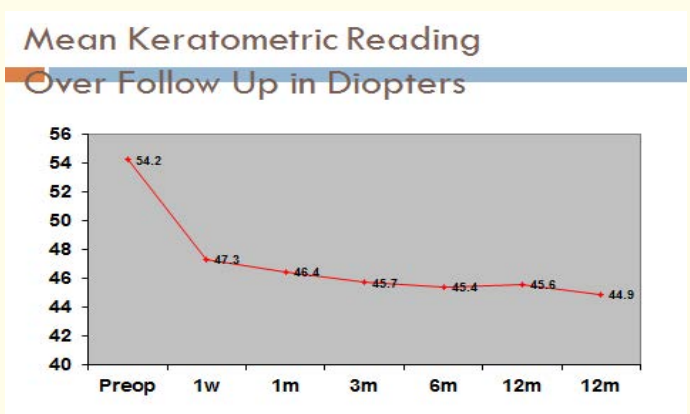

Figure 2

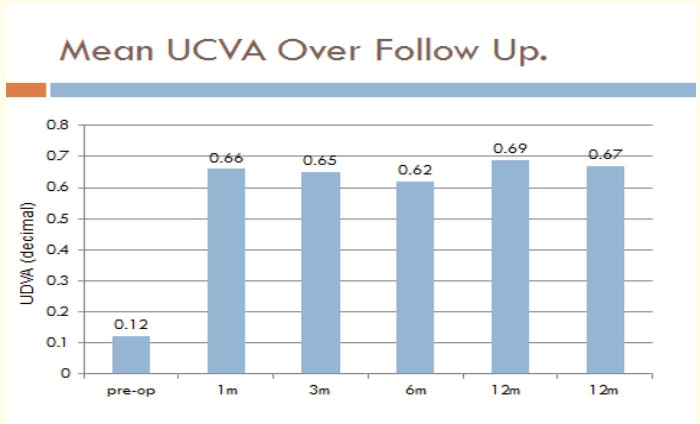

Figure 3

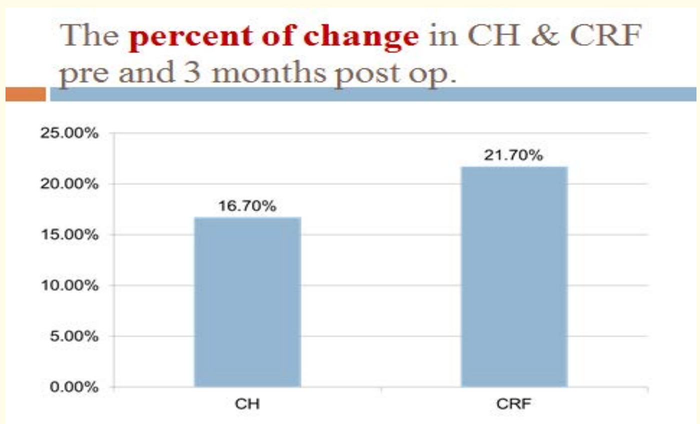

Figure 4

Discussion

ICRs can correct refractive errors in patients with intolerance to contact lenses. Crosslinking has been used to stop progression of keratoconus. ICR segments provide an interesting alternative aimed at delaying if not avoiding corneal grafting in keratoconus patients. The segments act by an "arc-shortening effect" on the corneal lamellae and by flattening the central cornea [9].

ICRs have been reported to improve the visual and refractive disorders in both keratoconus [9,10] and in post-LASIK keratectasia [11].

According to our experience the best indications for ICR segments are patients with mild to moderate keratoconus with a clear optical zone who are contact lens intolerant [9].

In our series, no surgical complications was encountered; all eyes showed excellent corneal tolerance with no segment extrusion, migration, or vascularization around the incision or the tunnels. The access incisions have seen to develop epithelial plugging at variable periods of follow up in 10 cases with tunnel haze in 15 cases. In addition, neither corneal ulcers nor stromal necrosis superficial to the segment were reported. One patient was found to have one of his ICR segments broken while still in place. This patient showed improvement in his UCVA although he maintained his preoperative BSCVA and did not wish to have this segment replaced.

The results demonstrate that the spherical equivalent error and astigmatism (refractive and keratometric) were reduced in all cases. The UCVA was significantly better than preoperative measurements at all examinations (p < 0.001). The BSCVA was 0.5 or better in 18/36 eyes (50%) at 1 week and in 21/36 (58%), 23/36 (64%), and 26/36 (72%) eyes at 1, 3, and 6 months, respectively. Sixty four percent of eyes had an improvement in BSCVA of 2 lines or more after 6 months of follow-up. No eye lost BSCVA lines. The topographic corneal shape (size and height of the cone) improved from baseline in all patients. The mean keratometry decreased approximately by 3 D, and the mean keratometric astigmatism decreased during the 6 months of follow up. The majority of patients (28/30) were satisfied with their surgical results. Visual side effects such as night glare or halos were reported in 6 patients but were well tolerated.

Our results support the results of Shabayek and Alió [12] who conducted a prospective study on the use of KeraRings in 21 keratoconic eyes and found significantly increased UCVA from 0.06 to 0.3 (p < 0.0001) and the BSCVA from 0.54 to 0.71 (p < 0.0003) and decreased the spherical equivalent by 2.28 D and the average keratometric values (K value) by 2.24 D (p < 0.001). There was no significant difference between the 3- and 6-month follow-up. Forty percent (8 eyes with a relatively low root-mean-square [RMS] of total higher-order aberrations [HOAs]) showed a nonsignificant increase in the RMS of total HOA; 60% (12 eyes with a relatively higher RMS of total HOA more than 3.0 m) showed a significant (p < 0.01) decrease in RMS of the total HOA due to a significant (p < 0.003) reduction in coma and coma-like aberrations. The amount of change in corneal curvature (biomechanical response) ranged from a decrease of 18% from its initial value to an increase of 2.75% and was not correlated to any preoperative parameter. Localized infectious keratitis occurred in only 1 eye (4.8%), and incision opacification occurred in 8 eyes (38%). One case showed difficult insertion of a ring segment and needed subsequent corneal suturing then developed bacterial keratitis that responded well to topical antibiotic therapy. Complication incidence in the aforementioned report seem to be more than ours, possibly due to the starting learning curve of the application of femtosecond laser techniques in ICRs as well as the use of less accurate pachymetry (ultrasound rather than anterior segment OCT) to assess incision sites.

Coskunseven*., et al*. [13] conducted another retrospective, noncomparative, interventional study on 32 keratoconic patients (50 eyes) who underwent ICR insertion using a femtosecond laser. All cases completed at least 1 year of follow-up. The UCVA, BSCVA, refraction, topographic findings, and adverse events were assessed. No intraoperative complications occurred. At postoperative day 1, segment migration to the incision site was seen in 3 eyes (6%). To avoid melting, the migrated segments were repositioned away from the incision site. Further second migration was not reported. At the last postoperative examination, there was a statistically significant reduction in the spherical equivalent refractive error compared with that observed at the examination before implantation (mean ± SD, –5.62 ± 4.15 D to –2.49 ± 2.68 D. The UCVA before implantation was 20/40 or worse in 47 eyes (94), whereas at the last follow-up examination, 14 (28%). Of 50 eyes had a UCVA of 20/40 or better (range, counting fingers to 20/25). Nine eyes (18%) maintained the pre-implantation BSCVA, whereas 39 eyes (68%) experienced a BSCVA gain of 1 to 4 lines at the last follow-up examination. Only in 2 eyes (4%; 2 patients) with stage III (advanced) keratoconus was there a decrease of up to 2 lines. Despite this deterioration in BSCVA, the patients did not want to remove the ICR segments because there was an increase in UCVA. No late postoperative complications were observed during the follow-up period. We have not faced segment migration in our cases, perhaps due to more accurate laser settings and proper preoperative planning based on exact corneal thickness measurements at the planned incision sites. Segment insertion exactly at the middle of the tunnel also may play a role in minimizing the risk for segment migration. None of our patients experienced UCVA or BCVA deteriorations-not even advanced cases of keratoconus. However, the advanced KC cases showed less promising visual results than mild and moderate cases.

Ertan., *et al*. [14] published a series of keratoconic patients who underwent Intacs (Addition Technology, Inc, Fremont, CA) implantation using a femtosecond laser. Intacs were implanted successfully in all eyes. At the end of the first postoperative year, 81.3% of eyes had improved UCVA, and 73.7% had improved BCVA.

Coskunseven [10] conducted a retrospective chart review of 531 patients (850 eyes) who underwent KeraRing insertion using a femtosecond laser for channel creation. Intraoperative and postoperative complications were recorded. Intraoperatively, there were 22 (2.7%) cases of incomplete channel formation. The rest of the intraoperative complications were system malfunction (5 eyes; 0.6%). In all cases, the error occurred 2 sec before the completion of the incision. In 2 of the cases, the procedure was restarted, and the error occurred again at exactly the same time. A 30-degree knife was then used to complete the incision. Endothelial perforation occurred in 5 eyes (0.6%), which presented intraoperatively as bubbles in the anterior chamber. Incorrect entry of the channel occurred in 2 eyes (0.2%). Vacuum loss occurred in 1 eye (0.1%). Vacuum was created again at the same conjunctival and corneal plane, and the same corneal markings were used. The channel was completed successfully at the same location and depth.

Postoperatively, he had 11 (1.3%) cases of segment migration, 2 (0.2%) cases of corneal melting, and 1 (0.1%) case of mild infection. The overall complication rate was 5.7% (49 cases out of 850 eyes). His most common complications were incomplete channel creation intraoperatively and segment migration postoperatively.

Layter on Coskunseven [12] studied the sequences of combined ICR segment implantation and UV/riboflavin–mediated CXL in progressive keratoconus. In this prospective comparative randomized consecutive study, CXL was followed by ICR segment implantation (Group 1) or ICR segment implantation was followed by CXL (Group 2). They found that ICR implantation followed by the UV/riboflavin–mediated corneal CXL resulted in greater improvement in keratoconus than CXL followed by ICR segment implantation. That can be explained as a stiffer cornea that has been treated by CXL exhibits a decreased flattening effect of ICR segment implantation. He concluded that, to achieve the maximum effect, ICR segment implantation should be performed first so the segments can reshape the cornea without restriction.

All previous studies used a different femtosecond laser device, the IntraLase femtosecond system (IntraLase Corp, Irvine, CA).

Kubaloglu., *et al.* [15] compared mechanical and femtosecond laser tunnel creation for ICR segment implantation in keratoconus. Theirs was a prospective randomized clinical trial in100 eyes of 90 patients with keratoconus and contact lens intolerance who had ICR implantation. The mechanical method was used in 50 eyes, and the femtolaser was used in 50 eyes. There was significant improvement in UCVA, BCVA, K readings, spherical equivalent, and manifest sphere and cylinder in both groups with no statistically significant differences between the 2 groups in visual or refractive results ($p > 0.05$). Anterior corneal perforation, superficial segment placement, and segment extrusion occurred in 1 eye in the mechanical group. Segment migration occurred in 1 eye in the femtosecond group due to frequent eye rubbing in one case with stage III keratoconus. Postoperative epithelial defect was more common in the mechanical group. Despite intraoperative complications in the mechanical group, the visual and refractive outcomes were similar to those in the femtosecond group.

Pinero., *et al*. [16] compared refractive and aberrometric outcomes of ICR segments for keratoconus using mechanical versus femtosecond-assisted procedures. A total of 146 consecutive eyes (106 patients) with the diagnosis of keratoconus (68 unilateral cases and 39 bilateral cases) were included. The refraction improved in both groups at 6 months ($p < 0.02$). The cornea on average was flatter in both groups at 6 months ($p < 0.01$). RMS astigmatism was reduced in the femtosecond group ($p = 0.03$), but there was an increase in some HOAs ($p = 0.03$). Significant differences were found between the 2 groups for eyes implanted with Intacs for primary spherical aberration, coma, and other HOAs, favoring the femtosecond group ($p < 0.01$). A significant negative correlation was found between the preoperative corneal aberrations and the postoperative BCVA in the mechanical group ($p < 0.04$). The study author concluded that ICR implantation using both mechanical and femtosecond laser-assisted procedures provide similar visual and refractive outcomes with more limited aberrometric corrections observed in the mechanical group.

Our study has some potential limitations. There was a small sample of treated eyes, the lack of a comparative group (e.g., keratoconic eyes after ICR insertion using mechanical devices), lack of data regarding higher order aberrations changes or corneal biomechanical properties and the absence of long-term follow-up data.

Conclusion

In conclusion, ICR implantation using a femtosecond laser appears to be a minimally invasive, safe, and easy procedure with good visual and refractive outcomes even on the long term. Future larger comparative studies focusing on the nomogram modification and the management of the possible complications of the technique are needed.

What this Paper Adds

ICR insertion with crosslinking can be safe and effective, providing good visual and refractive outcomes in patients with keratoconus.

Financial Disclosure

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