• Clinical Research •

Simultaneous versus sequential corneal cross-linking and intracorneal ring segments implantation for keratoconus: two-year study

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Abstract
● **AIM:** To compare simultaneous corneal collagen cross-linking (CXL) with intracorneal ring segment (ICRS) implantation versus successive ICRS followed by CXL and detect the impact of the timing of CXL after ICRS implantation in the successive method.

● **METHODS:** This is a retrospective study of the records of three groups of patients. Group 1 of 28 patients were operated on with simultaneous ICRS implantation and CXL, group 2 of 32 patients had ICRS implantation followed by CXL after 1mo, and group 3 of 38 patients had ICRS implantation followed by CXL after 3mo. The three groups had follow-up visits after 6, 12, and 24mo.

● **RESULTS:** The preoperative data, age, and gender differences among 3 groups revealed no significant differences. The postoperative spherical equivalent and best-corrected visual acuity were improved significantly in all groups compared to the baseline, which were more evident in groups 1 and 2. The differences between preoperative and postoperative mean values of mean of K readings (Km) and maximum K reading (Kmax) at 6mo were 4.66 and 4.1 D in group 1, 4.43 and 4.64 D in group 2, but 3.2 and 3.4 D in group 3, respectively. The spherical aberrations and the vertical coma showed significant postoperative changes in all groups, and trefoil showed nonsignificant changes.

● **CONCLUSION:** Simultaneous and sequential ICRS implantation and CXL at 1mo has similar Km and Kmax better postoperative changes than when both surgeries were done at three-month intervals.

● **KEYWORDS:** keratoconus; cross-linking; intracorneal ring; aberrations
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INTRODUCTION

Keratoconus (KC) is a progressive, bilateral ectatic corneal state characterized by progressive thinning of the stroma with steepening and even scarring of the corneal tissue, thus leading to severe visual impairment if left untreated[1-2]. Early detection of KC and proper management are crucial to stop the disease progression[3].

Several treatment options are available for visual improvement or disease progression stoppage. The two popular procedures identified over the past years are corneal collagen cross-linking (CXL) and intrastromal corneal ring segments (ICRS)[4].

ICRS implantation is a beneficial treatment procedure for KC. It is considered an effective and stable technique[5]. It is a minimally invasive technique that improves visual acuity, with a high success rate and a low complication rate compared to penetrating keratoplasty[6]. It was first proposed for treating low degrees of myopia, then used to correct corneal ectasia depending on the arc-shortening effect within the cornea; the additional volume of ICRS redistributes the biomechanical stress of the corneal lamellae, thus flattening the central cornea[7].

Also, the corneal changes induced by ICRS can be roughly predicted by the Barraquer "thickness law". You achieve a flattening effect when you add material to the cornea's periphery or remove an equal amount of material from the central area. On the contrary, a steeped surface curvature is obtained when a material is added to the corneal center or removed from its periphery. The corrective is directly related to the implant's thickness and is inversely related to its diameter. The thicker and the smaller the device, the higher the corrective result[8].

The femtosecond laser allows for simple and safe ICRS implantation, faster tunnel creation, precise depth, width, centration control, and fast postoperative recovery. Although ICRS decreases astigmatism and corneal abnormalities, it does not eliminate or halt disease progression[7-9]. It has been proven that ICRS regularize the ectatic corneal surface, while CXL arrest its progression in cases of KC[10]. Combined ICRS and CXL can be considered as an effective treatment option for KC[11]. Corneal CXL means photopolymerization of the stromal fibrillar tissue to increase its stiffness and resistance to the corneal ectasia through the combined action of the photosensitizing substance (riboflavin) and ultraviolet-A (UV-A) to strengthen the cornea and halt the progression of KC. Since introducing the Dresden protocol, other modified CXL protocols have been recommended to optimize the treatment's success[12]. Topography-guided photorefractive keratectomy combined with CXL was used to reduce the higher-order aberrations with better visual results in KC patients with adequate corneal pachymetry[13].

Combined CXL and ICRS procedures could act synergistically, producing potential additive outcomes. So, this study aimed to assess and compare the visual, corneal topography, and higher-order aberrations outcomes of the simultaneous CXL with ICRS implantation versus successive ICRS followed by CXL and to detect the impact of the timing of CXL after ICRS implantation in the successive method.

PARTICIPANTS AND METHODS

Ethical Approval The study was designed as a retrospective study and was registered by the institutional review board of the Faculty of Medicine of Minia University, Egypt (323-4-2022). Informed consent was collected from each participant before using his data.

The participants were recruited from the records of Roaa Eye Center, Minya, Egypt patients. The patients included in the study were divided into three groups who met the eligibility criteria for ICRS implantation and CXL. Group 1 underwent ICRS implantation and corneal CXL in the same setting. Group 2 underwent ICRS implantation followed by corneal CXL after 1mo. Group 3 underwent ICRS implantation followed by corneal CXL after 3mo.

Inclusion Criteria The included patients met the following criteria. They were between 18 and 35 years old, both genders and had been diagnosed with KC according to Pentacam KC grading. They have a clear cornea and an average thinnest corneal thickness of at least 400 µm. Also, they have been operated on without intraoperative or postoperative complications.

Exclusion Criteria The patients were excluded from the study if they had one or more of the following findings: the average thinnest corneal thickness of less than 400 µm, corneal opacity, very steep cornea more than 62 D, severe dry eye disease, herpetic keratitis, acute hydrops, corneal dystrophy, atopy, collagen diseases, autoimmune disease, ocular pathology other than KC, previous history of refractive or corneal surgery, pupillary diameter more than 6 mm, and pregnant females were excluded from the study. Also, patients who failed to attend the follow-up visits or had postoperative complications were excluded.

Ophthalmologic Examination Data on preoperative and postoperative examinations were collected. Follow-up was completed for patients with postoperative follow-up visits of less than two years.

Operative Details

Intracorneal ring implantation segment technique The surgery was performed in the operating room. Preoperatively, antibiotics (moxifloxacin) and topical anesthetic eye drops (benoxinate hydrochloride 0.4%) were instilled. The patient was positioned lying flat under the operating microscope, followed by applying a lid speculum, marking the center of the cornea, and customization of femtosecond laser ring implantation parameters using Intralase FS 60. The parameters included the depth of incision (75% of the corneal thickness at the ring site), the angle of incision (the steep angle), inner (5 mm) and outer diameters (6 mm), and laser energy (1.8 mJ). The tunnel dissection was performed then the intrastromal ring(s) (Keraring by Mediphacos Company, Brazil) was inserted. The number, arc length, and thickness of the ICRS were selected according to the Keraring manufacturer's nomogram based on the distribution and shape of the ectatic area and the refractive error. All patients had two segments with 6 mm diameter and variable thickness between 150 and 300 µm and arc between 90° and 160°.

Collagen cross-linking CXL was performed according to the accelerated protocol. The eye was anaesthetized with topical eye drops (benoxinate hydrochloride 0.4%), and the central 8 mm of the corneal epithelium was removed mechanically after applying ethyl alcohol 20% for 20s to loosen the epithelial layer. The epithelium-off CXL was performed after inserting the intracorneal rings at the same session in group one or postponed for another in groups two and three.

Isotonic riboflavin 0.1% (VibeX Rapid™, Avedro, Waltham, MA, USA) was instilled every 2min for 10min. UV-A irradiation (Avedro) was applied at a pulsing rate (1s on/off) with an intensity of 30 mW/cm^2 for eight minutes, with a cumulative dose of 7.2 J/cm^2.

After the surgical procedure, the eye was rinsed with a balanced salt solution, an antibiotic eye drop was applied, and a bandage contact lens was inserted. Postoperatively, antibiotics, steroids, and artificial tears eye drops were prescribed for 2wk, and the bandage contact lens was removed after complete epithelial healing.

Table 1 Changes in the spherical equivalent and best corrected visual acuity (logMAR)

Studied Variables	Preoperative	After 6mo (*P*)	After 12mo (*P*)	After 24mo (*P*)
Group 1				
SE, D	-4.44±2.85	-1.88±1.26 (<0.001)	-1.89±1.29 (<0.001)	-1.9±1.28 (<0.001)
UDVA	0.28±0.19	0.24±0.3 (<0.001)	0.24±0.33 (<0.001)	0.24±0.33 (<0.001)
BCVA	0.21±0.31	0.16±0.21 (<0.001)	0.16±0.23 (<0.001)	0.16±0.24 (<0.001)
Group 2				
SE, D	-4.63±2.76	-1.59±1.23 (<0.001)	-1.59±1.25 (<0.001)	-1.6±1.25 (<0.001)
UCVA	0.27±0.22	0.22±0.21 (<0.001)	0.22±0.2 (<0.001)	0.22±0.2 (<0.001)
BCVA	0.19±0.14	0.12±0.18 (<0.001)	0.12±0.18 (<0.001)	0.12±0.19 (<0.001)
Group 3				
SE, D	-4.31±2.23	-2.19±0.91 (<0.001)	-2.19±0.92 (<0.001)	-2.3±0.65 (<0.001)
UCVA	0.29±0.12	0.24±0.12 (<0.001)	0.24±0.11 (<0.001)	0.24±0.11 (<0.001)
BCVA	0.21±0.23	0.17±0.14 (<0.001)	0.17±0.15 (<0.001)	0.18±0.12 (<0.001)

SE: Spherical equivalent; BCVA: Best corrected visual acuity; UCVA: Uncorrected visual acuity. The *P*-value is between every follow-up period's data and the preoperative data.

Imaging and follow-up The data of the Scheimpflug image examination with Pentacam (Oculus, Wetzlar, Germany), refractive error, and visual acuity measurements were collected. The keratometric readings with the mean K (Km) and maximum K reading (Kmax) were studied. The higher-order aberrations of the cornea at 5 mm diameter were obtained from the Zernike analysis map of the pentacam to study the spherical aberrations, coma, and trefoil. These data were obtained from preoperative and postoperative visits at 6, 12, and 24mo following the simultaneous procedure in group 1 and following the second procedure in groups 2 and 3.

Statistical Analysis The SPSS software version 20 was used to analyze the collected data. The normality test was performed using the Shapiro-Wilk test. The data are presented as mean±standard deviation for quantitative data, but the percentage is used for the quantitative data. The one-sample *t*-test is used for normally distributed data, and the Mann-Whitney test is used for non-normally distributed data to compare the differences between the preoperative and postoperative parameters. ANOVA was used to compare the three groups. The *P*-value was considered statistically significant when less than 0.05.

RESULTS

This study was performed on 28 eyes of 28 patients who had concurrent ICRS and CXL as group 1, 32 eyes of 32 patients who had ICRS followed by CXL after 1mo as group 2, and 38 eyes of 38 patients who had ICRS followed by CXL after 3mo as group 3. The data was collected for groups 2 and 3 after the CXL procedure. The normality test of the data revealed that they were normally distributed. The majority of patients in the three groups were female (75% in group 1, 72% in group 2, and 77% in group 3) without statistically significant differences between them (*P*=0.12). The mean age of group 1 was 28.9±4.5y; for group 2, it was 27.6±5.1y; and for group 3, it was 29.2±3.2y, and the *P* value was insignificant (0.2).

The three groups were comparable, with no significant differences regarding the preoperative spherical equivalent (SE), K reading, and corneal thickness. The preoperative data concerning the three groups' refractive, topometric, and higher-order aberrations had no statistically significant differences.

The postoperative SE, uncorrected distant visual acuity (UDVA) and best-corrected visual acuity (BCVA) improved significantly in all groups compared with the preoperative measurements (Table 1). However, the amount of change was not the same, as groups 1 and 2 showed more changes than group 3 after 6mo and remained stable until 24mo postoperatively.

Statistical analysis of the topographic data revealed that the postoperative measurements of the keratometry readings at 6, 12, and 24mo had all highly significant differences when compared with the preoperative readings (Tables 2-4). The main difference between the groups was the amount of change in the K readings. The flat and steep K after 6mo showed about 3 D change in the three groups, which remained nearly stable in groups 1 and 2, but in group 3, the change decreased after 12mo and remained stable afterwards. The main differences between groups were in Km and Kmax. The differences between preoperative mean values and postoperative mean values of Km and Kmax at 6mo in group 1 were 4.66 and 4.1 D, and in group 2, were 4.43 and 4.64 D but in group 3, were 3.2 and 3.4 D, respectively. After 12mo, these differences showed minimal changes in groups 1 and 2, but in group 3, the differences became 3.6 and 3.8 D in Km and Kmax, respectively. The changes were the same after 24mo in all groups. For the thinnest location changes between groups, there were no noticeable differences. Higher-

Table 2 Keratometric and higher order aberrations changes of group 1

Studied variables	Preoperative	After 6mo (*P*)	After 12mo (*P*)	After 24mo (*P*)
K1, D	49.6±2.8	46.2±5.2 (<0.001)	46.2±5.3 (<0.001)	46.4±5.5 (<0.001)
K2, D	55.13±3.6	51.8±4.8 (<0.001)	51.78±4.6 (<0.001)	51.78±4.7 (<0.001)
Km, D	52.36±3.3	47.7±5.1 (<0.001)	47.7±4.8 (<0.001)	47.7±4.9 (<0.001)
Kmax, D	57.64±2.1	53.54±2.4 (<0.001)	53.54±2.8 (<0.001)	53.55.3.2 (<0.001)
Thinnest location, µm	413.8±24.62	415.7±28.51 (<0.001)	415.6±32.12 (<0.001)	412.9±31.63 (<0.001)
Spherical aberrations	-0.982±0.67	-0.572±0.53 (<0.001)	-0.571±0.55 (<0.001)	-0.571±0.56 (<0.001)
Vertival coma	1.032±0.491	0.492±0.624 (<0.001)	0.492±0.646 (<0.001)	0.492±0.658 (<0.001)
H. coma	-2.801±0.986	-2.13±0.762 (0.03)	-2.14±0.691 (0.01)	-2.14±0.698 (0.01)
Trefoil	-0.159±0.512	-0.097±0.292 (0.016)	-0.097±0.298 (0.015)	-0.097±0.299 (0.016)

K1: Flat K reading; K2: Steep K reading; Km: Mean of K readings; Kmax: Maximum K reading; H. coma: Horizontal coma. The *P*-value is between every follow-up period's data and the preoperative data.

Table 3 Keratometric and higher order aberrations changes of group 2

Studied variables	Preoperative	After 6mo (*P*)	After 12mo (*P*)	After 24mo (*P*)
K1, D	48.4±3.7	45.9±4.2 (<0.001)	45.9±4.3 (<0.001)	45.9±4.3 (<0.001)
K2, D	53.26±4.5	47.8±3.2 (<0.001)	47.7±3.9 (<0.001)	47.7±3.9 (<0.001)
Km, D	51.33±4.6	46.9±3.5 (<0.001)	46.9±3.8 (<0.001)	46.8±3.7 (<0.001)
Kmax, D	54.35±5.7	49.71±4.3 (<0.001)	49.72±3.6 (<0.001)	49.72±4.1 (<0.001)
Thinnest location, µm	427.6±22.36	434.7±25.32 (<0.001)	434.2±23.29 (<0.001)	432.3±23.39 (<0.001)
Spherical aberrations	-1.082±0.82	-0.651±0.92 (<0.001)	0.651±0.94 (<0.001)	0.651±0.98 (<0.001)
Vertival coma	1.015±0.572	0.568±0.475 (<0.001)	0.568±0.475 (<0.001)	0.567±0.477 (<0.001)
H. coma	-2.426±1.232	-2.07±1.16 (0.011)	-2.07±1.15 (0.012)	-2.07±1.15 (0.012)
Trefoil	-0.173±0.371	-0.178±0.418 (0.52)	-0.178±0.418 (0.51)	-0.178±0.418 (0.52)

K1: Flat K reading; K2: Steep K reading; Km: Mean of K readings; Kmax: Maximum K reading; H. coma: Horizontal coma. The *P*-value is between every follow-up period's data and the preoperative data.

Table 4 Keratometric and higher order aberrations changes of group 3

Studied variables	Preoperative	After 6mo (*P*)	12mo (*P*)	24mo (*P*)
K1, D	47.3±3.2	45.4±3.6 (<0.001)	45.6±3.9 (<0.001)	45.6±4.2 (<0.001)
K2, D	53±3.9	50.2±3.1 (<0.001)	50.1±2.9 (<0.001)	50.1±3.8 (<0.001)
Km , D	50.1±3.7	46.9±3.5 (<0.001)	46.5±3.3 (<0.001)	46.5±3.4 (<0.001)
Kmax, D	54.1±4.9	50.7±3.8 (<0.001)	50.3±4.1 (<0.001)	50.3±4.2 (<0.001)
Thinnest location, µm	443±28.7	448.3±26.8 (<0.001)	446.9±31.2 (<0.001)	446.2±25.9 (<0.001)
Spherical aberrations	-0.906±0.491	-0.537±0.624 (<0.001)	-0.642±0.362 (<0.001)	-0.644±0.491 (<0.001)
Vertival coma	1.022±0.465	0.446±0.482 (<0.001)	0.449±0.482 (<0.001)	0.452±0.632 (<0.001)
H. coma	-2.632±1.12	-2.132±0.98 (0.018)	-2.141±1.11 (0.019)	-2.142±0.99 (0.019)
Trefoil	-0.163±0.492	-0.158±0.321 (0.14)	-0.158±0.321 (0.14)	-0.158±0.329 (0.14)

K1: Flat K reading; K2: Steep K reading; Km: Mean of K readings; Kmax: Maximum K reading; H. coma: Horizontal coma. The *P*-value is between every follow-up period's data and the preoperative data.

order aberrations study of the cornea focused on changes in the spherical aberrations, trefoil, and coma (Tables 2-4). For the spherical aberrations, there was a statistically significant increase after 6mo postoperatively in all groups compared to preoperative data. Compared to 6mo postoperatively, the spherical aberrations after 12mo were the same in groups 1 and 2 but increased in group 3, and these changes were the same after 24mo. However, trefoil showed non-significant changes all over the study period except in group 1, which showed a statistically significant decrease. The marked changes in the higher-order aberrations were in the vertical coma, which improved significantly by about 50% compared to the preoperative values. The horizontal coma showed minimal but significant changes in the three groups. The differences between the groups in the higher-order aberrations were insignificant.

DISCUSSION

ICRS has been established for managing myopia and astigmatism with flattening of the corneal center, and it has been proven effective in managing KC[14]. Corneal cross-linking is frequently added to the management plan by many ophthalmic surgeons to stop the condition's progression[15]. It is even better than performing topography-guided photorefractive keratectomy with CXL in terms of UDVA and Kmax, as a recent study comparing the results of the two surgeries has concluded[16]. The two surgeries are frequently used to improve the visual outcome and protect the patients from advancing to the level they require keratoplasty operation. Comparing the results of performing ICRS or CXL alone with the results of combined ICRS with CXL revealed that the combined approach has yielded much better refractive and keratometry results[17-18].

Some surgeons prefer implanting the ICRS with CXL on the same day to decrease the cost, effort, and time for both the patient and the surgeon. However, many others prefer doing the two surgeries separately at one, three, or six-month intervals. Some believe that ring extrusion is more frequent if both surgeries are done on the same day. Thus, postponing CXL is preferable[19]. Performing CXL before ICRS implantation has been studied before by Coskunseven *et al*[20], who concluded that the effect of the ring implantation was less effective if performed after CXL, which may be due to the increased stiffness of the cornea decreasing the flattening effect of the rings.

In our study, we studied three groups: a simultaneous group as group 1 and two sequential groups, group 2 with an interval of 1mo and group 3 with an interval of 3mo. Many previous researchers have studied the differences in simultaneous and consensual CXL and ICRS implantation outcomes. One short-term study with a 6-month follow-up by Hersh *et al*[21] found that concurrent and sequential treatment after 3mo showed equivalent outcomes in keratometry changes and improved corrected distance visual acuity (CDVA). In our study, CDVA and SE in groups 1 and 2 revealed much better improvement than in group 3. Changes in keratometric readings were better in groups 1 and 2 as well.

Another earlier study by El-Raggal[22] reported no differences between concurrent and sequential techniques regarding CDVA and refractive errors. However, he found that the concurrent group had more reduction in keratometry values.

This is similar to our results, where the Km and Kmax reduction was greater in the concurrent group than in the sequential group after 3mo. Interestingly, after 1mo, the sequential group showed comparable keratometry changes to the concurrent group.

Our results demonstrated that the changes in the keratometry readings and the refraction of the patients in the concurrent and after-one-month groups were better than after the three-month group and had nearly similar effects. The ICRS continues to change the corneal tissues for up to 9wk as reported by a study done by *in vivo* confocal microscopy[23]. CXL has its full effect on the appearance of the demarcation line after 1mo, as studied by anterior segment optical coherence tomography[24].

In groups 1 and 2, we suggest that the time required for the CXL to give its full effect is the same as needed for the full impact of the ICRS to take place. Thus, they add to each other's flattening and stabilizing effect. The cornea becomes stiff when the ICRS gives its full effect. In group 3, the CXL gives its effect later, which may be affected by the elastic properties, and a slight bulge in the cornea may occur before it becomes stiff. Another explanation for group 1's better results is the pooling of the riboflavin in the ring tunnels during CXL, which augments its effect, as reported by a previous study[25]. The tunnel in group 3 becomes fibrosed after 3mo, giving no space for riboflavin pooling, leading to a poorer effect than in group 1. For group 2, we believe that the channel around the implanted ring segments is still open, giving space for riboflavin pooling like in group 1, so they have similar results better than group 3.

The higher-order aberrations of the studied patients showed that the spherical aberrations and the vertical coma were the most affected in all groups, with no differences between the groups. A recent study found that vertical coma was also the most affected parameter[26]. However, another study showed that all lower and higher-order aberrations are improved after ICRS implantation[27]. We believe any change in the higher-order aberrations is mainly due to the effect of ICRS implantation. From the above-presented data, the concurrent and sequential groups after 1mo had similar better effects than the three-month group in terms of mean and maximum k readings. Hence, surgeons who prefer not to do ICRS followed by CXL on the same day or those who believe concurrent procedures are the best can perform CXL after 1mo, not more, to get the same results as the concurrent surgeries.

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Availability of Data and Materials: The data supporting this study's findings are available upon request from the corresponding author.

Conflicts of Interest: Omar I, None; **Safwat Elhiny R,** None.

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