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Effects and safety of combined corneal collagen crosslinking and intrastromal corneal ring segment treatment in patients with keratoconus: a retrospective study

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Abstract

Purpose To evaluate the safety and efficacy of different time-point combinations of intrastromal corneal ring segment (ICRS) implantation using femtosecond technology) and corneal collagen crosslinking (CXL) for the treatment of moderate-to-severe keratoconus (KCC).

Methods This study included 69 eyes of 69 patients with keratoconus who underwent ICRS and CXL treatment at an Eye Hospital between March 2020 and March 2023. The patients were divided into two groups: Group 1 ($n = 33$ eyes of 33 patients), which received ICRS and CXL treatment in one session, and Group 2 ($n = 36$ eyes of 36 patients), which included treatment with ICRS for at least 6 months following CXL application. Preoperative and postoperative evaluations included visual acuity, autorefractometer refraction, corneal tomographic measurements using the Sirius (CSO) Scheimpflug camera and the TONOREF™ III device, and documentation of observed complications. Uncorrected visual acuity (UCVA) and best-corrected spectacle visual acuity (BCVA) were measured in each eye individually, and visual acuity was assessed using the logarithm of the minimum angle of resolution (logMAR).

Results In Group 1, mean UCVA improved from 0.81 ± 0.34 to 0.45 ± 0.25 ($p < 0.01$), and mean BCVA improved from 0.76 ± 0.35 to 0.38 ± 0.20 ($p < 0.01$). In Group 2, mean UCVA improved from 0.71 ± 0.32 to 0.43 ± 0.30 ($p < 0.01$), and mean BCVA improved from 0.65 ± 0.25 to 0.31 ± 0.23 ($p < 0.01$). Both groups showed significant reductions in manifest spherical and cylindrical refraction ($p < 0.01$). Group 1 exhibited greater reductions in maximum keratometry (Kmax), flat keratometry (K1), steep keratometry (K2) ($p < 0.05$), and astigmatic aberration compared with group 2 ($p < 0.01$). The use of simultaneous or separate CXL and ICRS does not significantly increase the incidence of complications.

Conclusions Both combined and separate CXL and ICRS treatments resulted in significant improvement in UCVA and BCVA and reduced manifest refraction. Although improvements were observed in groups 1 and 2 in terms of K1, K2, and Kmax at 6 months, the improvements were more pronounced in Group 1. These results highlight the potential benefits of simultaneous ICRS + CXL treatment and underscore the importance of optimising the timing of CXL treatment to achieve the best visual outcomes.

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Introduction

Keratoconus is typically characterised as a bilateral, progressive corneal ectasia that frequently results in the development of irregular astigmatism [1]. The incidence of this condition varies from 50 to 230 cases per 100,000 individual, depending on the specific geographical location [2]. Clinical manifestations encompass a spectrum of manifestations, ranging from minor refractive errors to pronounced irregular astigmatism, and may even include corneal scarring and notable visual impairment following hydrops.

Corneal collagen cross-linking (CXL) has been established as an effective method for halting keratoconus progression by strengthening stromal collagen bonds [3, 4]. However, while CXL stabilises the cornea, many patients still require additional interventions to improve visual acuity, especially in moderate-to-severe cases. In patients with keratoconus, rigid gas-permeable contact lenses are commonly used to enhance visual acuity, and they can be effective even in advanced cases [5]. Spectacles may also be beneficial in mild cases. Intrastromal corneal ring segment (ICRS) is a treatment method that provides visual rehabilitation in patients with keratoconus by reshaping the cornea, leading to significant improvements in vision [6–8]. When corneal rings are not an option, keratoplasty remains a last resort, but it is associated with significant risks, including graft rejection and infection [9]. Regarding ICRS implantation, recent advancements in implant designs and the use of femtosecond lasers for corneal tunnelling have aimed to simplify the procedure, reduce the risks associated with implantation, and enhance both efficacy and patient comfort [10].

The primary objective of intrastromal ICRS surgery is to enhance visual acuity while simultaneously minimising refractive error and mean keratometry through corneal reshaping. Although previous studies have demonstrated the individual benefits of CXL and ICRS, the timing and combination of these treatments remain a topic of debate. Some studies have suggested that simultaneous treatment offers superior results in corneal flattening and visual outcomes, whereas others have found no significant difference compared with staged procedures [11–16].

This study aimed to assess refractive changes, corneal topography characteristics, and visual acuity in patients who underwent combined CXL and ICRS treatment in a single session compared with patients who received CXL treatment followed by ICRS treatment for at least six months of time difference. Additionally, it contributes to the debate on the ideal sequence and timing of CXL and ICRS treatment.

Materials and methods

This retrospective, non-randomised study evaluated patients diagnosed with moderate or severe keratoconus who received femtosecond-assisted ICRS combined with CXL treatment at different time points. The study period was from March 2020 to March 2023. In accordance with the tenets outlined in the Declaration of Helsinki, all patients were duly informed of the benefits and potential hazards associated with surgical intervention and provided explicit consent for participation in the clinical investigations. This study was approved by the ethics committee of Kahramanmaraş Sütçü İmam University(Decision no: 2023/03).

The patients underwent thorough ophthalmological examination before and after surgery. This examination encompassed uncorrected (UCVA) and best-corrected spectacle visual acuity (BCVA) visual acuity, manifest and cycloplegic refraction, intraocular pressure measurement, and funduscopic examination. Keratoconus diagnosis and staging were performed using a Sirius Scheimpflug imaging device camera (CSO, Italy). In this study, keratoconus was classified using both the Amsler-Krumeich staging system and the José Alfonso phenotype classification system. According to Amsler-Krumeich, keratoconus was defined as mild if the central corneal power was less than 45 diopters (D), moderate if it ranged between 46 and 52 D, advanced if it ranged between 53 and 59 D, and severe if it exceeded 59 D [17]. Patients were also classified into the following phenotypes according to the José Alfonso system: round (central), oval (paracentral), globus (extensive), and nipple (small, steep cones) phenotype [17]. Additionally, keratoconus severity was further categorised by Amsler-Krumeich as stage 1 for mild keratoconus, stage 2 for moderate keratoconus, and stages 3–4 for advanced or severe keratoconus [18]. Patients who met the following criteria were eligible for inclusion: they had to be at least 18 years old, have progressed during the previous year, demonstrated by a shift in the steepest K reading of 1.0 Dpt or more, and have been diagnosed with moderate to severe keratoconus according to the Keratoconus Study classification system, which uses the steepest K readings [19]. Furthermore, the study included individuals who exhibited intolerance towards inflexible gas-permeable contact lenses and possessed maximum K values within the range of 48 to less than 65 Dpt. Keratoconus is considered progressive when, within a period of less than 1 year, one or more of the following changes are observed: an increase in astigmatism of 1.0 D or more, significant alterations in the orientation of refractive axes, an increase of 1.0 D or more

in the optical power of the steepest corneal meridian, or a decrease of 25 µm or more in corneal thickness [18].

The exclusion criteria were as follows: corneal topography analysis of the eye to be treated indicating a corneal thickness of less than 350 µm; or corneal thickness of less than 400 µm mm at the narrowest point where the ICRS is anticipated to be positioned. Acute hydrops, corneal haze, or opacities, Kmax>65 Dpt, pregnancy or breast-feeding, and the presence of ongoing or new ocular infection or inflammation were among the exclusion criteria. Furthermore, the exclusion criteria included individuals who declined to participate in the research or failed to adhere to established protocols for subsequent actions.

Group 1 (*n*=33 patients, 33 eyes) received ICRS and CXL treatment in a single session, whereas Group 2 (*n*=36 patients, 36 eyes) received ICRS treatment at least 6 months after the initial CXL procedure. The Bioring (Biotech, India) device was surgically inserted in both groups of patients using local anaesthesia and the assistance of a femtosecond laser (Visumax, Zeiss, Germany). The investigator ascertained the dimensions, symmetry, and insertion angle of the ICRS by analysing the refractive and tomographic data of each individual patient in accordance with the Bioring nomogram supplied by Biontech. The patients underwent comprehensive ophthalmological examination and tomographic evaluation at specific time intervals following the surgical procedure, specifically on the first day, first week, third month, and sixth month.

Surgical technique
ICRS implantation procedure
ICRS implantation was performed using a Visumax femtosecond laser (Zeiss, Germany) (Fig. 1). The laser
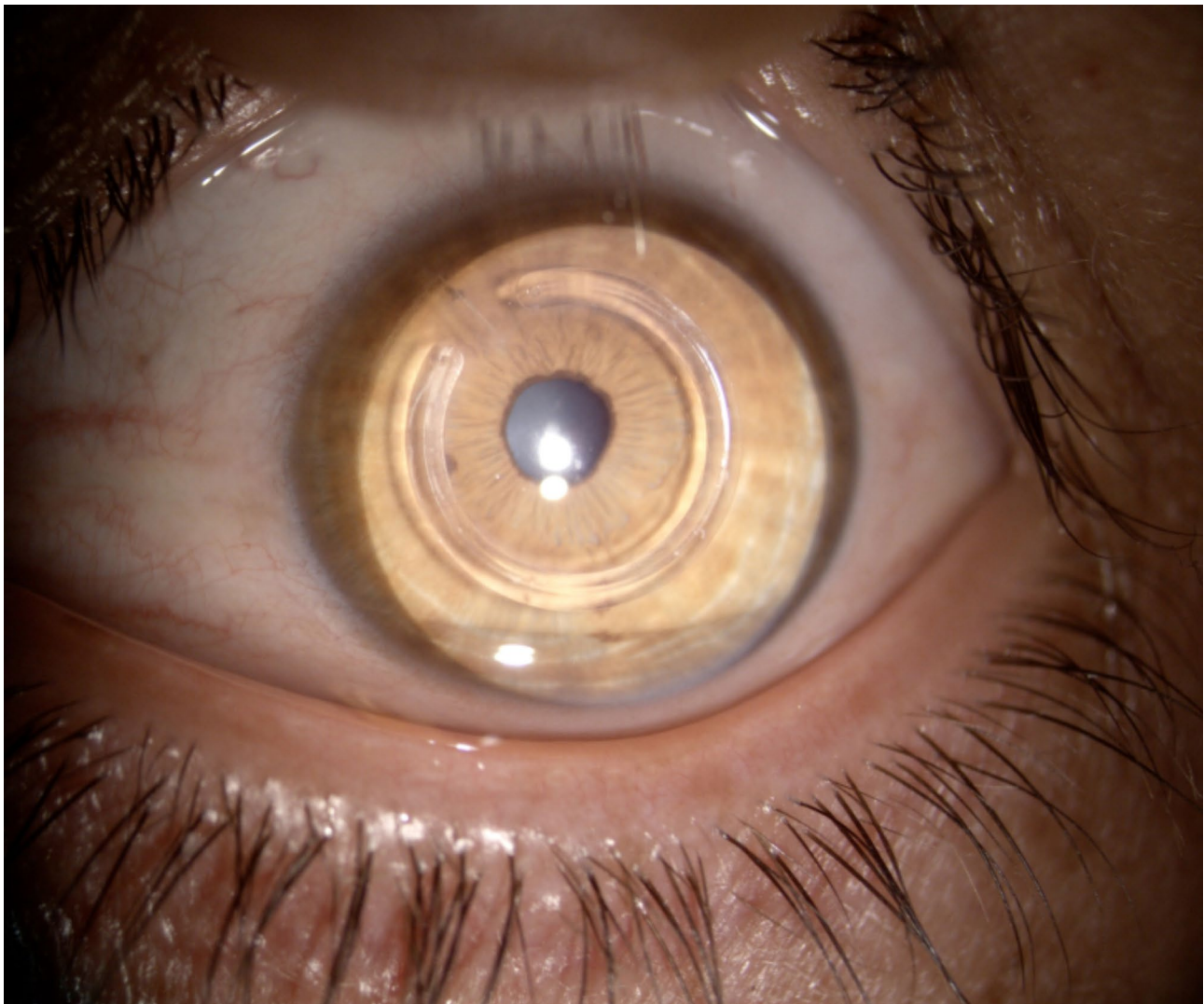
Fig. 1 Anterior segment photograph of a patient who underwent ICRS implantation using a femtosecond laser, showing the positioning and integration of the ring segment within the cornea

parameters were set with an average energy of 5 milli-joule (mJ), with a depth adjusted to 70-80% of the corneal thickness [11]. These parameters were customised for each patient based on factors such as corneal thickness, keratoconus stage, and surgeon preference. The dimensions, symmetry, and insertion angle of the ICRS were determined by analysing the refractive and tomographic data in accordance with the Bioring nomogram. After ICRS implantation, the patient was immediately prepared for CXL.

CXL procedure

The following ICRS implantation, the CXL procedure was performed. Proparacaine hydrochloride (0.5%) (Alcaine; Alcon Laboratories, Puurs, Belgium) was administered, and the cornea was disinfected before the procedure. The central 8.0-mm area of the corneal epithelium was removed using a crescent knife (Beaver–Visitec International Inc., Waltham, MA). The cornea was then soaked in riboflavin 0.1% dextran-free plus hydroxypropyl-methylcellulose solution (VibeX Rapid, Avedro Inc.) at 5-min intervals for 30 min to ensure proper penetration into the corneal stroma. The CXL procedure was executed using the CCL Vario crosslinking system (Peschke Trade, Gdask, Poland). UV-A radiation with a power density of 9 mW/cm² was applied for 10 min [20]. In cases in which the central corneal thickness (CCT) was 400 μm or less, hypotonic riboflavin drops were applied for 5–10 min. Corneal pachymetry was measured preoperatively, after epithelial removal, and at 10-minute intervals using an ultrasound (US) instrument (SP-2000, Tomey, Inc.). If the CCT remained below 400 μm, the procedure was halted. Following the completion of CXL, a bandage contact lens was typically removed after corneal epithelialization, which occurred between days 3 and 5.

Postoperative care

Dexamethasone eye drops (0.1%) were administered four times daily, with gradual tapering over 2 weeks. Moxifloxacin drops were administered four times daily for one week, and preservative-free artificial tears were provided as needed during follow-up visits. The same methodology was applied for the initial CXL treatment in patients who underwent sequential procedures, but with adjustments for timing and sequence.

Outcome measures

The Lighthouse Early Treatment Diabetic Retinopathy Study visual acuity test (2nd version) with Sloan letters was used to measure both UCVA and BCVA. This test was performed in a room with controlled lighting and from a distance of >4 m. UCVA and BCVA measurements were individually documented for each eye of the subjects. The logarithms of the minimum angle-of-resolution (logMAR) measurements were calculated. Astigmatism values were determined using refraction measurements, specifically with the TONOREF™ III (NIDEK, Japan), which combines autorefraction, keratometry, tonometry, and pachymetry measurements. Measurements were acquired using the manifest and cycloplegic refraction techniques. Astigmatism in both eyes was measured individually.

Corneal tomographic parameters were analysed using a Sirius tomography device. This device was used before and 6 months after surgery. The examination of corneal tomography parameters involved consideration of the following measurements:

1. Keratometric (Curvature) Values: A comparative analysis was performed to evaluate differences in keratometry readings, including the flat meridian (K_1), steep meridian (K_2), and maximum curvature (Kmax) of the anterior corneal surface. The analysis also considered the curvatures of both the anterior and posterior corneal surfaces, providing a comprehensive assessment of the corneal curvature at both central and peripheral regions.
2. Elevation indices: Corneal sphericity (Q value) and root mean square (RMS) values were compared. The cornea's centre-to-periphery curvatures were measured by asphericity. The RMS value indicates abnormalities on the corneal surface.
3. Pachymetry Indices: Preoperative and postoperative measurements of the thinnest corneal thickness (TCT) and central corneal thickness (CCT) were made to assess the effect of surgery on corneal thickness.
4. Keratoconus analysis was performed on vertex (elevation-based) data and curvature asymmetry. The Keratoconus vertex front (KVf) determines height-based vertices, and the surface asymmetry index front–back (SIf/SIb) assesses curvature asymmetry.

These measurements were taken preoperatively (pre-CXL values were taken as first measurements in patients who received CXL first and subsequently ICRS) and 6 months postoperatively. Multiple data acquisitions were conducted to confirm the repeatability of the measurements. The data were analysed using mean values and standard deviations.

Statistical analysis

Data analysis was performed using the SPSS 25.0 software (IBM Corp., Armonk, NY, USA). Quantitative data are presented as mean±standard deviation, whereas qualitative data are presented as numbers and percentages. The independent sample t-test was used to assess disparities between the two groups. The paired t-test was

used to examine differences between the groups before and after treatment. The statistical significance of the results was set at 5%. *P* values were used to determine statistical significance. Results were deemed statistically significant when the *p*-value was less than 0.05. In addition, multivariate and regression analyses were performed. Multiple regression analysis was used to determine the effects of UCVA and BCVA on eye topographic parameters. This investigation involved the computation of the correlation and beta coefficients.

Results

A retrospective analysis was performed on patients who underwent CXL and corneal ring implantation at the Eye Hospital between March 2020 and March 2023. The study enrolled 69 eyes. Group 1 included 33 eyes of 33 patients (15 males, 18 females) who received ICRS and CXL treatment in one session. Group 2 consisted of 36 eyes from 36 individuals (17 males, 19 females) and included treatment with ICRS for at least 6 months following CXL application. The mean ages of the participants in Group 1 was 24.90 ± 8.86 years, whereas the mean age of the participants in Group 2 was 25.58 ± 6.11 years. The distribution of patients in Groups 1 and 2 according to keratoconus severity was as follows: Group 1 included 15 patients with moderate keratoconus and 18 patients with severe keratoconus. Group 2 included 16 patients with moderate and 20 with severe keratoconus. The keratoconus phenotypes of Group 1 (15 oval, 11 round, 7 nipple+globus) and Group 2 (19 oval, 9 round, 8 nipple+globus) were compared using the José Alfonso classification. The chi-square test revealed no significant difference between the groups ($p=0.738$). In this study,

one patient in the first group and two patients in the second group underwent ICRS removal due to insufficient visual recovery at the end of the 6th month.

For Group 1, mean UCVA, as measured using the Snellen chart LogMAR was 0.81 ± 0.34 compared to 0.45 ± 0.25 6 months postoperatively($p<0,01$). Similarly, mean BCVA preoperatively and 6 months postoperatively were 0.76 ± 0.35 and 0.38 ± 0.20 ($p<0,01$) respectively. In Group 2, mean UCVA changed from 0.71 ± 0.32 to 0.43 ± 0.30 ($p<0,01$) 6 months postoperatively. BCVA improved from 0.65 ± 0.25 to 0.31 ± 0.23 ($p<0,01$) 6 months postoperatively.

For Group 1, the mean preoperative spherical refraction value was -5.80 ± 3.03 preoperatively compared to -2.10 ± 2.58 6 months postoperatively ($p<0.01$). Similarly, the mean cylindrical refraction value was -6.64 ± 4.64 preoperatively, and -3.28 ± 2.52 after 6 months postoperatively ($p<0.01$). For Group 2, the mean spherical refraction value was -4.62 ± 3.55 preoperatively compared to -1.96 ± 2.59 6 months postoperatively($p<0.01$). The mean manifest cylindrical refraction value was -5.31 ± 3.23 preoperatively compared to -3.04 ± 1.71 6 months postoperatively($p<0.01$).

There were no significant differences in demographic and clinical characteristics between the preoperative and postoperative groups (Table 1). Additionally, there were no statistically significant variations in topographic values between the two groups preoperatively, indicating that they were similar before the operation (Table 2).

There were no significant differences in the Kmax, K_1 and K_2 values between the two groups before surgery. However, a comparison of the groups 6 months postoperatively showed that the decrease in Kmax, K_1, and K_2 values was more pronounced in Group 1 (Table 2).

Preoperatively, there were no statistically significant differences between the two groups in CCT ($p=0.354$) and TCT ($p=0.216$). However, 6 months postoperatively, both values showed significant differences between the groups, with Group 1 exhibiting a more pronounced reduction in both CCT ($p=0.034$) and TCT ($p=0.015$) compared with Group 2. Comparison of preoperative elevation indices, curvature asymmetry, and vertices (elevation-based) data between groups 1 and 2 revealed no significant differences. Similarly, no statistically significant differences were observed between groups 1 and 2 at 6 months postoperatively (Table 2).

Both Group 1 and Group 2 showed significant improvements in UCVA, BCVA, manifest spherical refraction, manifest cylindrical refraction, Kmax, K_1, K_2, topography cylindrical value, CCT, KVf, Q anterior, Q posterior, and astigmatic aberration compared with preoperative and 6 months postoperative values ($p<0.01$) (Table 3). Both Group 1 and Group 2 showed statistically significant reductions in astigmatic aberration ($p<0.01$

Table 1 Demographic and clinical characteristics of the study groups

Parameter	Group 1	Group 2	*p* value
Number of Patients	33	36	0,871
Age	24,90 ± 8,86	25,58 ± 6,11	0,623
Gender (male)	15 (45,4%)	17 (47,2%)	0,316
UCVA (logMAR), Preoperatively	0,81 ± 0,34	0,71 ± 0,32	0,091
UCVA (logMAR), 6 months postoperatively	0,45 ± 0,25	0,43 ± 0,30	0,617
BCVA, Preoperatively	0,76 ± 0,35	0,65 ± 0,25	0,071
BCVA, 6 months postoperatively	0,38 ± 0,20	0,31 ± 0,23	0,719
Manifest Spherical Refraction Value , Preoperatively	-5,80 ± 3,03	-4,62 ± 3,55	0,215
Manifest Spherical Refraction Value, 6 months postoperatively	-2,10 ± 2,58	-1,96 ± 2,59	0,523
Manifest Cylindrical Refraction Value, Preoperatively	-6,64 ± 4,64	-5,31 ± 3,23	0,093
Manifest Cylindrical Refraction Value, 6 months postoperatively	-3,28 ± 2,52	-3,04 ± 1,71	0,149

UCVA: Uncorrected Visual Acuity, BCVA: Best-corrected Spectacle Visual Acuity logMAR=logarithm of the minimum angle of resolution

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Table 2 Characteristics and statistical comparison of the topographic data of the study groups

Parameter	Group 1	Group 2	P value
TCT (µm), Preoperatively	419.12 ± 60.60	413.33 ± 44.31	0.216
TCT (µm), 6 months postoperatively	385.59 ± 64.17	408.55 ± 44.29	**0.015**
CCT (µm), Preoperatively	433.63 ± 62,17	431,75 ± 47,69	0,354
CCT (µm), 6 months postoperatively	399.81 ± 77.73	411,77 ± 48,32	**0.034**
K max (D), Preoperatively	59.10 ± 7.85	60.76 ± 5.57	0.219
K max (D), 6 months postoperatively	58.25 ± 7.38	59.94 ± 4.73	**0.025**
K_1 ant (D), Preoperatively	47.13 ± 4.55	48.05 ± 2.69	0.078
K_1 post (D), Preoperatively	6.32 ± 0.37	6.41 ± 0.31	0.119
K_1 ant (D), 6 months postoperatively	44.74 ± 3.89	46.30 ± 2.29	**0.003**
K_1 post (D), 6 months postoperatively	6.35 ± 0.45	6.42 ± 0.40	0.121
K_2 ant (D), Preoperatively	51.39 ± 5.95	52.07 ± 3.32	0.095
K_2 post (D), Preoperatively	6.72 ± 0.38,	6.79 ± 0.35	0.108
K_2 ant (D), 6 months postoperatively	47.49 ± 4.63	48.74 ± 2.77	**0.005**
K_2 post (D), 6 months postoperatively	6.82 ± 0.36	6.85 ± 0.33	0.117
Topography Cylindric, Preoperatively	-3.48 ± 3.21	-3.97 ± 1.64	0.115
Topography Cylindric, 6 months postoperatively	-2.25 ± 2.06	-2.28 ± 1.62	0.367
Slf (D), Preoperatively	7.06 ± 4.55	7.95 ± 4.47	0.408
Slf (D), 6 months postoperatively	7.17 ± 4.50	7.31 ± 3.79	0.535
Slb (D), Preoperatively	1.91 ± 1.22	2.31 ± 1.03	0.718
Slb (D), 6 months postoperatively	1.58 ± 1.06	1.91 ± 1.09	0.309
KVf (µm) Preoperatively	38.75 ± 18.50	42.05 ± 13.51	0.134
KVf (µm) 6 months postoperatively	32.15 ± 14.74	36.61 ± 11.73	0.862
KVb (µm), Preoperatively	88.60 ± 46.15	99.13 ± 34.58	0.360
KVb (µm) 6 months postoperatively	88.63 ± 45.14	103.02 ± 32.86	0.152
RMS ant, Preoperatively	0.26 ± 0.10	0.29 ± 0.14	0.063
RMS ant, 6 months postoperatively	0.24 ± 0.10	0.26 ± 0.11	0.199
Q ant, Preoperatively	-1.24 ± 1.31	-1.10 ± 1.29	0.687
Q anterior, 6 months postoperatively	-1.77 ± 0.97	-1.96 ± 1.34	0.089
Q post, Preoperatively	-1.46 ± 1.52	-1.13 ± 1.31	0.823
Q post, 6 months postoperatively	-2.58 ± 1.40	-2.05 ± 1.39	0.692

If *p* values are <0.05, they are highlighted in bold font. CCT: central corneal thickness; TCT: thinnest corneal thickness; RMS: root mean square; Slf, symmetry index front; Slb: symmetry index back; KVf: keratoconus vertex front; KVb: keratoconus vertex back; Kmax: Maximum Kerotometry, K_1: Flat K, K_2: Steep K, ant: Anterior, post: Posterior

Table 3 Statistical comparison of the groups before and after the procedure

Parameters	Group 1 *p* values	Group 2 *p* values
UCVA	***p* < 0,01**	***p* < 0,01**
BCVA	***p* < 0,01**	***p* < 0,01**
Manifest Spherical Refraction Value	***p* < 0,01**	***p* < 0,01**
Manifest Cylindrical Refraction Value	***p* < 0,01**	***p* < 0,01**
CCT	**0,045**	**0,036**
TCT	0,051	0,71
Kmax	***p* < 0,01**	***p* < 0,01**
K1	***p* < 0,01**	***p* < 0,01**
K2	***p* < 0,01**	***p* < 0,01**
Topography cyl	***p* < 0,01**	***p* < 0,01**
Slf	0,016	0,029
Slb	**0,038**	***p* < 0,01**
KVf	***p* < 0,01**	***p* < 0,01**
KVb	0,988	0,205
Q ant	***p* < 0,01**	***p* < 0,01**
Q post	***p* < 0,01**	***p* < 0,01**
Astigmatic aberration	***p* < 0,01**	**0,031**

If *p* values are <0.05, they are highlighted in bold font

and *p* = 0.031, respectively). However, the reduction in astigmatic aberration was more pronounced in Group 1.

Discussions

Keratoconus is a progressive corneal condition characterised by thinning and bulging. The primary treatment goals are halting progression and improving visual acuity. Corneal collagen cross-linking (CXL) is the only proven method to stop disease progression, whereas intrastromal corneal ring segments (ICRS) can enhance visual acuity by reshaping the cornea [21, 22]. Our study demonstrated significant improvements in visual acuity and refractive outcomes, consistent with previous findings on the efficacy of ICRS in patients with moderate and advanced keratoconus [23, 24].

Keratoconus management focuses on two key goals: halting disease progression and improving visual acuity. CXL is the only proven treatment to stop the progression of keratoconus [25], whereas ICRS is effective in enhancing visual acuity by reshaping the cornea. Alfredo et al. [26] reported significant short-term improvements in visual, refractive, and topographic outcomes after ICRS implantation. However, their study also indicated that over 5 years, ICRS may not be as effective in controlling progressive keratoconus in younger patients with documented disease progression.

In our study, the simultaneous application of CXL and ICRS resulted in greater reductions in both CCT and TCT compared with the other groups, which is consistent with previous research showing early decreases in corneal thickness following CXL [27]. While studies have shown that these early reductions in corneal thickness

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are often temporary, with recovery occurring over time [28], our study did not include a long-term follow-up, so we could not determine whether the thinning observed in our patients was temporary or permanent.

There are different opinions in the literature regarding the optimal sequence and timing of CXL and ICRS procedures. Some studies have suggested that performing ICRS after CXL is beneficial [14, 29], while others have argued that performing CXL before ICRS reduces its effectiveness because CXL stiffens the cornea, making visual rehabilitation less effective when ICRS is applied to a stiffer cornea [29, 30]. As a result, some researchers have advocated for the simultaneous application of ICRS and CXL, suggesting that it may have a more positive effect [14, 31]. According to a report by Peter et al. [16], there was no significant difference between the safety and effectiveness of ICRS and CXL treatment in one session and ICRS at least 3 months after the application of CXL. Henriquez et al. [32] Demonstrated that ICRS implantation six months after CXL is an effective and safe treatment for keratoconus. In a study conducted by El-Raggal et al. [29], it was determined that sequential CXL+ICRS in the same session improved corneal morphology more effectively than ICRS performed six months after CXL. Legare et al. demonstrated that both combined ICRS+CXL and individual ICRS treatments for keratoconus were secure and efficient [15]. Moreover, the ICRS alone group outperformed the ICRS+CXL group in terms of spherical squalane, Kmax, and overall higher-order aberration. A study by Renesto et al. [33] demonstrated that ICRS placement with or without preceding CXL had no effect on refractive, topographic, pachymetric, tonometric, or corneal biomechanical findings at 24-month follow-up. According to our research, both the group treated with concurrent CXL and ICRS implantation and the group that received CXL treatment before ICRS were safe and effective. Although no statistically significant difference was observed between the group of patients treated with concurrent CXL and ICRS implantation and the group that received CXL treatment prior to ICRS, a more pronounced improvement in astigmatic aberration, Kmax, and K_2 was noted in the concurrent group. It is considered that in studies with larger sample sizes, this difference might reach statistical significance.

The complications of ICRS include mechanical complications (late or early segment migration and extrusion), inadequate vision recovery, and progression of existing keratoconus. These undesirable consequences may require the removal of the ring. In a study of 572 eyes, the explantation rate of ICRS(specifically, Intacs) was 6.1%. Medical complications accounted for 2.6% of explantations, including microbial keratitis (3%), inflammation (31%), persistent photophobia (3%), and persistent foreign-body sensation (6%). Refractive or topographic

issues led to 3.5% of explantations, primarily due to optical side effects like halo and diplopia (14%), lack of subjective improvement (23%), and preparation for additional procedures, such as penetrating or deep anterior lamellar keratoplasty (9%), conductive keratoplasty (9%), and photorefractive keratectomy (6%) [34]. The incidence of complications after ICRS is decreasing because of technological and surgical evolution and advancements in technology and surgical techniques [35]. In the present investigation, removal of the ring was required in one participant from the first group (3.03%) and in two participants from the second group (5.56%) because of inadequate visual recovery. Despite the limited sample size, the corneal ring complications observed were in agreement with those documented in the existing literatüre [34]. Furthermore, our findings suggest that the application of simultaneous or separate CXL and ICRS does not significantly impact the incidence of complications.

This study has several limitations. Caution should be exercised when interpreting the results because of the retrospective and non-randomised design of the study. Furthermore, the efficacy of the two treatment modalities may be constrained by the use of a restricted sample size, potentially impeding the extrapolation of the findings to a broader population. Another significant constraint was the duration of the follow-up period, which lasted 6 months. As noted, this follow-up was too short to make assumptions about long-term outcomes, particularly for a progressive disease like keratoconus. In the context of progressive diseases, such as keratoconus, an extended follow-up duration could offer a more comprehensive and expansive understanding. Ultimately, it should be noted that although the study assessed multiple corneal parameters, the absence of measurements of biomechanical parameters, specifically corneal hysteresis and corneal resistance factor, can be viewed as a limitation.

Conclusion

This study evaluated the results of patients with keratoconus in whom ICRS and CXL were applied sequentially, and the ICRS groups were applied to patients who had previously received CXL. Both treatment approaches significantly improved uncorrected and corrected visual acuity and astigmatism. These results demonstrate that the application in both combinations is effective. Furthermore, our findings suggest that the application of simultaneous or separate CXL and ICRS does not significantly impact the incidence of complications. The group that underwent CXL along with ICRS showed a more significant improvement in corneal tomography values. This result did not indicate a better treatment option in our study. However, the results suggest that the difference could be significant in larger groups of randomised

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controlled studies with larger samples and longer follow-up periods.

Abbreviations

BCVA	Best-corrected spectral visual acuity
CCT	Central Corneal Thickness
CXL	Corneal Collagen Crosslinking
ICRS	Intrastromal Corneal Ring Segment
KVb	Keratoconus Vertex Back
KVf	Keratoconus Vertex Front
logMAR	Logarithm of the Minimum Angle of Resolution
RMS	Root Mean Square
SIb	Symmetry Index Back
SIf	Symmetry Index Front
TCT	Thinnest Corneal Thickness
UCVA	Uncorrected Visual Acuity
UV	Ultraviolet

Author contributions
Ali Dal: Conceptualization, methodology, data collection, writing – original draft, and final approval of the manuscript. Mehmet Canleblebici: Data analysis, review, and editing of the manuscript. Bünyamin Kutluksman: Manuscript review, and final approval. Murat Erdağ: Supervision, manuscript review, and final approval.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the tenets of the Declaration of Helsinki. The ethics committee of Kahramanmaraş Sütçü İmam University approved the study (Decision No: 2023/03). All participants provided written informed consent before inclusion in the study.

Consent for publication
Written informed consent was obtained from all participants prior to their participation in the publication of this study.

Competing interests
The authors declare no competing interests.

Clinical trial number
Not applicable.

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