Effect of Corneal Allogenic Intrastromal Ring Segment (CAIRS) Implantation Surgery in Patients With Keratoconus According to Prior Corneal Cross-linking Status

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ABSTRACT

PURPOSE: To compare the effects of corneal allogenic intrastromal ring segment (CAIRS) implantation on topographical measurements and visual outcomes of patients with keratoconus with and without corneal cross-linking (CXL) prior to the time of implantation.

METHODS: Sixty-seven eyes with corneal allograft intrastromal ring segment implantation (KeraNatural; Lions VisionGift) due to advanced keratoconus were included in the study. Thirty-seven eyes had no CXL and 30 eyes had had CXL before being referred to the authors. The changes in spherical equivalent (SE), uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), steep keratometry (K1), flat keratometry (K2), mean keratometry (Kmean), maximum keratometry (Kmax), and thinnest pachymetry were retrospectively analyzed 6 months after the implantation.

RESULTS: The median age was 29 years in the CXL group and 24.0 years in the non-CXL group ($P > .05$), respectively. All topographical and visual parameters before implantation were similar in both groups ($P > .05$ for all parameters). At 6 months, CDVA, K1, and Kmean showed higher improvement in the non-CXL group than the CXL group ($P = .030$, .018, and .039, respectively).

CONCLUSIONS: CAIRS surgery has a flattening effect on both the corneas with and without CXL. The cornea with prior CXL treatment had less flattening effect due to the stiffening effect of prior CXL.

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Keratoconus is an ectatic corneal disease that causes progressive corneal thinning, irregular astigmatism, corneal fibrosis, and vision loss.[1] Treatment options vary according to the stage and progression of the disease.[2] In the early stages, spectacles and different types of contact lenses are used to improve vision.[3] Corneal cross-linking (CXL) is used to halt progression and delay or prevent the need for corneal transplantation.[4] Intracorneal ring segments (ICRS) can be implanted to flatten the corneal profile, achieve better visual acuity and reduce contact lens intolerance.[5] In patients with severe corneal thinning, and/or protrusion, deep anterior lamellar keratoplasty and penetrating keratoplasty are the main alternatives.[6] Recently, a new and different strategy has been included as an option for managing keratoconus. It consists of implanting corneal tissue from a donor into the corneal stroma of a recipient.[7]

Our study about the KeraNatural corneal allograft (Lions VisionGift) with the Istanbul nomogram has been described as a safe and effective surgery that enhances visual performances in patients with keratoconus.[8] CAIRS may be applied to corneas that have had CXL and those that have not, but the influence on outcomes of prior CXL has not been evaluated yet.

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This study compared the effects of allograft corneal ring segments on topographical measurements and visual outcomes of eyes with keratoconus 6 months after implantation between eyes with or without prior CXL.

PATIENTS AND METHODS

This retrospective study was conducted in Medipol University, Ophthalmology Department, Istanbul, Turkey, following the principles of the Declaration of Helsinki, and, in adherence with the institutional ethics committee, consent for using their clinical data was obtained from all patients.

PATIENTS

Inclusion criteria were patients with keratoconus 20 years or older with a minimum corneal thickness of at least 400 µm at the implantation area, a clear cornea, asymmetric non-central cones, and documented contact lens intolerance history. The diagnosis of keratoconus and cone pattern were determined according to corneal tomography (Pentacam; Oculus Optikgeräte GmbH). Exclusion criteria were history of corneal or intraocular surgery except CXL, viral keratitis, presence of glaucoma or any retinal disease, connective tissue or systemic autoimmune diseases, and pregnancy or lactation during the study. The CXL history of the patients was obtained from the medical records. In all cases, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), anterior and posterior segment examination with a slit-lamp biomicroscope, and corneal tomography were performed before and after surgery. Postoperative follow-up was performed 1 and 6 months after surgery.

SURGICAL METHOD

All surgical steps were performed by the same surgeon (AK) according to the previously described Istanbul nomogram under topical anesthesia.[8] The center of the patients' pupil was marked under a surgical microscope of a clinical excimer laser (VisX S4, CustomVue; S4IR Abbott Medical Optics Inc). A circular annular tunnel at 200 µm depth with 4-mm inner and 7.5-mm outer diameter was created around (concentric to) the cone location for implantation of the allograft ring segment with a femtosecond laser (iFS 150kH, Intralase; Abbott Medical Optics, Inc). The tunnel incision was dissected with a modified C-hook separator with rotational motion. An allograft corneal ring segment (KeraNatural) was implanted as a single ring segment (160 degrees) into the tunnel with modified C-hook forceps. Centration was checked and the surgery finished. No wound suturing was needed. Postoperative treatment consisted of topical moxifloxacin 0.5% (Vigamox; Alcon Laboratories, Inc) administered four times a day for 1 week and 0.1% dexamethasone (Maxidex; Alcon Laboratories, Inc) and preservative-free artificial tears administered five times a day for 4 weeks and then tapered. No intraoperative or postoperative complication was seen due to the surgery.

STATISTICAL ANALYSES

The statistical analysis was performed with the SPSS package program version 25.0 (SPSS, Inc). A P value less than .05 for all tests was considered significant. The descriptive statistics are presented as mean and standard deviation values. The Kruskal-Wallis test was used to compare continuous data, when appropriate. The paired *t*-test was used for statistical analysis of within-group comparisons for different time points and for between-group comparisons at the last follow-up visit.

RESULTS

This study included 67 eyes of 47 patients with advanced keratoconus. The median age was 27 years (range: 20 to 52 years) and 34 (72%) of the patients were men. There were 30 eyes in the CXL group and 37 eyes in the non-CXL group. The comparison of preoperative visual and topographical features of the patients are shown in **Table 1**. There was no statistically significant difference between the groups before surgery.

NON-CXL GROUP

Table 2 shows visual acuity, refractive, and topographical outcomes of the non-CXL patients. There were statistically significant differences in SE, UDVA, CDVA, flat keratometry (K1), steep keratometry (K2), and mean keratometry (Kmean) in both 1 month and 6 months results compared to preoperative measurements ($P < .05$). Maximum keratometry (Kmax) and thinnest pachymetry did not change postoperatively compared to preoperative measurements.

CXL GROUP

Table 3 shows changes of visual acuity, refractive, and topographic measurements at different time points for the CXL group. A significant enhancement was detected in SE, K1, K2, and Kmean at the postoperative first month compared to preoperative values ($P < .05$) and only SE had significant difference at 6 months compared to preoperatively. There was a statistically significant increase in UDVA and CDVA after the first month postoperatively and they remained stable for 6 months of follow-up ($P < .05$).

BOTH GROUPS

Evaluation of the final results showed that non-CXL eyes had a statistically significant higher increase in CDVA than CXL eyes (three lines versus two lines)

TABLE 1

Comparison of Preoperative Clinical and Topographic Features of the CXL and Non-CXL Groups[a]

Parameter	CXL	Non-CXL	*P*
Median age (years)	29	24	.072
SE (D)	-7.28 ± 5.66	-7.26 ± 4.62	.983
Sphere (D)	-4.87 ± 4.93	-4.74 ± 4.20	.909
Cylinder (D)	-4.76 ± 2.74	-4.71 ± 2.38	.954
UDVA (decimal)	0.20 ± 0.17	0.17 ± 0.16	.763
CDVA (decimal)	0.28 ± 0.20	0.31 ± 0.18	.503
K1 (D)	47.43 ± 5.24	47.11 ± 4.36	.925
K2 (D)	51.69 ± 5.99	51.33 ± 5.22	.865
Kmean (D)	49.46 ± 5.55	49.11 ± 4.66	.900
Kmax (D)	57.22 ± 6.68	58.38 ± 7.24	.528
Pachymetry (µm)	437 ± 38	454 ± 45	.156

CDVA = corrected distance visual acuity; CXL = corneal cross-linking; D = diopters; K1 = flat keratometry; K2 = steep keratometry; Kmax = maximum keratometry; Kmean = mean keratometry; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

[a]All values are given as mean ± standard deviation except age.

TABLE 2

Topographical and Visual Changes of Non-CXL Eyes[a]

Parameter	Preoperative	1 Month Postoperative	6 Months Postoperative	*P*
SE (D)	-7.26 ± 4.62	-0.85 ± 4.92	-1.32 ± 3.96	< .001 (preop vs 1 month); .899 (1 vs 6 month); < .001 (preop vs 6 month)
Sphere (D)	-4.74 ± 4.20	0.74 ± 4.71	0.88 ± 3.89	< .001 (preop vs 1 month); .989 (1 vs 6 month); < .001 (preop vs 6 month)
Cylinder (D)	-4.71 ± 2.38	-3.38 ± 2.46	-4.17 ± 2.62	.065 (preop vs 1 month); .380 (1 vs 6 month); .630 (preop vs 6 month)
UDVA (decimal)	0.17 ± 0.16	0.55 ± 0.26	0.49 ± 0.22	< .001 (preop vs 1 month); 0.477 (1 vs 6 month); < .001 (preop vs 6 month)
CDVA (decimal)	0.31 ± 0.18	0.65 ± 0.22	0.68 ± 0.27	< .001 (preop vs 1 month); .808 (1 vs 6 month); < .001 (preop vs 6 month)
K1 (D)	47.11 ± 4.36	42.67 ± 4.81	42.67 ± 3.99	< .001 (preop vs 1 month); 1.0 (1 vs 6 month); < .001 (preop vs 6 month)
K2 (D)	51.33 ± 5.22	46.58 ± 5.01	46.45 ± 4.72	< .001 (preop vs 1 month); .993 (1 vs 6 month); < .001 (preop vs 6 month)
Kmean (D)	49.11 ± 4.66	44.52 ± 4.80	44.45 ± 4.20	< .001 (preop vs 1 month); .998 (1 vs 6 month); < .001 (preop vs 6 month)
Kmax (D)	58.38 ± 7.24	56.17 ± 7.13	55.66 ± 6.29	0.358 (preop vs 1 month); .945 (1 vs 6 month); .212 (preop vs 6 month)
Pachymetry (µm)	454 ± 45	452 ± 36	446 ± 44	.970 (preop vs 1 month); .814 (1 vs 6 month); .676 (preop vs 6 month)

CDVA = corrected distance visual acuity; CXL = corneal cross-linking; D = diopters; K1 = flat keratometry; K2 = steep keratometry; Kmax = maximum keratometry; Kmean = mean keratometry; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

[a]All values are given as mean ± standard deviation.

and a statistically significant greater decrease in K1 (4.43 versus 2.85 diopters [D]) and Kmean (4.65 versus 3.26 D). There was no statistically significant difference between both groups in UDVA, SE, K2, Kmax, or pachymetry ($P > .05$) (**Table 4**).

DISCUSSION

In the current study, the effects of allograft corneal ring segments on topographical measurements and visual outcomes of keratoconic eyes 6 months postoperative were analyzed. The findings of this study

TABLE 3

Topographical and Visual Changes of CXL Eyes[a]

Parameter	Preoperative	1 Month Post-implantation	6 Months Post-implantation	*P*
SE (D)	-7.28 ± 5.66	-2.46 ± 5.08	-3.15 ± 4.45	.006 (preop vs 1 month); .897 (1 vs 6 month); .019 (preop vs 6 month)
Sphere (D)	-4.87 ± 4.93	-0.73 ± 5.22	-0.53 ± 5.09	.021(preop vs 1 month); .991 (1 vs 6 month); .015 (preop vs 6 month)
Cylinder (D)	-4.76 ± 2.74	-3.45 ± 2.10	-4.93 ± 3.47	.265 (preop vs 1 month); .226 (1 vs 6 month); .978 (preop vs 6 month)
UDVA (decimal)	0.20 ± 0.17	0.42 ± 0.25	0.44 ± 0.28	.006 (preop vs 1 month); .970 (1 vs 6 month); .002 (preop vs 6 month)
CDVA (decimal)	0.28 ± 0.20	0.54 ± 0.23	0.54 ± 0.26	.001 (preop vs 1 month); .999 (1 vs 6 month); < .001 (preop vs 6 month)
K1 (D)	47.43 ± 5.24	43.55 ± 4.35	44.73 ± 4.30	.016 (preop vs 1 month); .694 (1 vs 6 month); .107 (preop vs 6 month)
K2 (D)	51.69 ± 5.99	47.66 ± 5.06	48.13 ± 4.90	.032 (preop vs 1 month); .957 (1 vs 6 month); .053 (preop vs 6 month)
Kmean (D)	49.46 ± 5.55	45.48 ± 4.45	46.34 ± 4.46	.019 (preop vs 1 month); .836 (1 vs 6 month); .066 (preop vs 6 month)
Kmax (D)	57.22 ± 6.68	55.28 ± 6.26	54.11 ± 6.65	.565 (preop vs 1 month); .830 (1 vs 6 month); .209 (preop vs 6 month)
Pachymetry (μm)	437 ± 38	449 ± 42	452 ± 41	.564 (preop vs 1 month); .972 (1 vs 6 month); .391 (preop vs 6 month)

CDVA = corrected distance visual acuity; CXL = corneal cross-linking; D = diopters; K1 = flat keratometry; K2 = steep keratometry; Kmax = maximum keratometry; Kmean = mean keratometry; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

[a]All values are given as mean ± standard deviation.

TABLE 4

Comparison of Changes in Clinical and Topographic Features of Prior CXL and Non-CXL Eyes 6 Months After CAIRS[a]

Parameter	CXL (Δ)	Non-CXL (Δ)	*P*
SE (D)	3.66 ± 4.25	5.52 ± 3.17	.128
Sphere (D)	3.36 ± 3.77	5.23 ± 3.59	.086
Cylinder (D)	0.42 ± 2.92	0.57 ± 2.40	.870
UDVA (decimal)	0.21 ± 0.22	0.30 ± 0.19	.059
CDVA (decimal)	0.24 ± 0.18	0.36 ± 0.21	.030
K1 (D)	-2.85 ± 2.40	-4.43 ± 2.82	.018
K2 (D)	-3.71 ± 2.41	-4.87 ± 3.46	.163
Kmean (D)	-3.26 ± 2.16	-4.65 ± 3.00	.039
Kmax (D)	-3.53 ± 3.81	-2.20 ± 5.08	.445
Pachymetry (μm)	6.86 ± 10.01	-5.65 ± 33.13	.096

CAIRS = corneal allogenic intrastromal ring segment implantation; CDVA = corrected distance visual acuity; CXL = corneal cross-linking; D = diopters; K1 = flat keratometry; K2 = steep keratometry; Kmax = maximum keratometry; Kmean = mean keratometry; SE = spherical equivalent; UDVA = uncorrected distance visual acuity

[a]All values are given as mean ± standard deviation.

provide a unique perspective on the effects of allograft corneal ring segments, particularly in relation to the timing of CXL. Accordingly, eyes without CXL prior to allograft corneal ring segment surgery yielded distinct outcomes compared to cases with prior CXL.

Intracorneal ring segments have been shown to be an effective method of treating keratoconus, with many recent studies reporting significant improvements in visual acuity, refraction, and keratometric readings.[9] Nicula et al[10] compared the sequence of intrastromal corneal ring implantation followed by CXL and CXL followed by intrastromal corneal ring implantation and the first sequence proved to be more effective in reducing Km and SE values. In a later study, Coskunseven et al[11] reported ICRS implantation followed by CXL resulted in better results in topographic and visual acuity measurements than CXL followed by ICRS implantation in patients with keratoconus. Their assumption about these results is, although each treatment step individually flattens the cornea, CXL treatment causes a stiffer cornea and decreases the flattening effect of subsequent ICRS implantation, thus restricting its effect and decreasing the maximum flattening potential. Similar to these results, in our research we saw that the non-CXL group had greater decrease in Kmean and greater increase in CDVA. It is controversial whether CAIRS is similar to ICRS in terms of its mechanism of action, although both techniques involve adding material to the midperiphery. ICRS are polymethylmethacrylate rings that act as a spacer between the corneal lamellae, and cause shortening of the central arc in proportion to the ring thickness.[12] Ganesh and Brar[13] theorize that intrastromal lenticule implantation, involving the addition of natural corneal tissue, acts more like a filler and appears to cause local elevation at the midperiphery and relative flattening at the center, without actually causing as much tension or pull on the corneal lamellae as ICRS does. However, they also stated, based on only 6 eyes, it is difficult to draw any conclusion regarding effects of tissue addition and CXL. Our study is more robust because it includes 67 patients with keratoconus.

Jacob et al[7] described a novel technique of CAIRS surgery to improve the biocompatibility and biointegration of the inlay compared to ICRS. Their study indicated CAIRS implantation with CXL is a safe and efficient method for patients with keratoconus. However, they also stated that longer term studies are needed to confirm the initial results and examine the effects of nomograms and further personalization. Recently, Nacaroglu et al[14] described the Istanbul nomogram and showed that implantation of sterile inlays prepared by an eye bank offers a safe surgical approach in the treatment of keratoconus by improving visual acuity and changing the corneal tomography parameters on the anterior and posterior surfaces. In the current study, using the same nomogram previously published by the authors, it was aimed to compare the visual and topographic changes of CXL-treated and CXL-naive patients to decide on the timing.

CXL is known to induce stiffness in the cornea,[15,16] which can impact the effects of subsequent procedures such as allograft corneal ring segment surgery. The results of this study align with the anticipated effects of CXL in relation to allograft corneal ring segments. The cross-linking likely contributed to a stiffer cornea in the CXL group, potentially reducing the overall effectiveness of the allograft ring segments. This observation highlights the importance of understanding the dynamic relationship between these procedures and their potential interactions. It is important to acknowledge the inherent complexities associated with combining treatments for keratoconus. The findings of this study highlight the multifaceted nature of corneal biomechanics and the influence of treatment sequence on outcomes.

A systematic review and meta-analysis by Riau et al[17] reviewed 9 studies about femtosecond laser–assisted corneal tissue implantation for keratoconus treatment. According to this meta-analysis, no study reported the occurrence of graft rejection and persistent haze formation. The implantation of donut-shaped, concave, convex, or planar lenticules appeared to expand the stromal volume of thin ectatic corneas and flattened the cones, and significantly improved UDVA, CDVA, and SE. CXL was performed simultaneously in two of the studies.[7,13] Most of the remaining studies are small case series or case reports and CXL was not performed.[18-23] In this meta-analysis, the authors stated that it is not clear whether CXL is required and whether the CXL should be performed in the lenticule only or the entire cornea. In a study using a rabbit model, Damgaard et al[24] showed that CXL of lenticules limited the flexibility of the lenticular stroma to natural tissue remodeling of the recipient corneas, which in turn stabilized the refractive status of the corneas earlier and reduced the refractive regression over time. In our study, it was observed that the improvement was better in eyes without prior CXL. However, the combination of corneal ring segments, along with CXL, may offer additional benefits compared to implantation alone.[25] Furthermore, if CXL is not performed, the disease might progress. Hence, close follow-up is essential and CXL should be performed when deemed necessary. Another approach involves delaying CXL until corneal remodeling stabilizes, which opens up the possibility of tailored photorefractive keratectomy combined with CXL for enhancing CDVA if necessary.[26]

It is essential to acknowledge limitations of this study. The relatively short follow-up period of 6 months might not provide a complete understanding of the long-term effects of these interventions on patients with keratoconus. Additionally, the small sample size limits the generalizability of the results. A larger study with extended follow-up and prospective design that includes two groups, CXL after CAIRS and CAIRS after CXL, would be valuable in confirming and expanding upon the findings presented here.

The current study sheds light on the distinct impact of prior CXL on the effects of allograft corneal ring segment surgery in patients with keratoconus. We found a higher effectiveness of CAIRS in eyes without stiffening by prior CXL. Future research could delve deeper into the mechanisms underlying these interactions, exploring how corneal biomechanics influence the outcomes of combined interventions.

AUTHOR CONTRIBUTIONS

Study concept and design (ST, AK); data collection (BY, CT, FFNKP, YK); analysis and interpretation of data (BY, CT); writing the manuscript (BY, FFNKP, YK); critical revision of the manuscript (CT, ST, AK); statistical expertise (BY)

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