

ARTICLE



Efficacy and safety of intracorneal allogenic ring segment implantation in keratoconus: 1-year results

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BACKGROUND: To evaluate the safety and efficacy of corneal allogenic intrastromal ring segments in the management of keratoconus patients.

METHODS: The retrospective, nonrandomized, interventional case series consisted of 65 keratoconic eyes of 49 consecutive patients who had ring segment-shaped corneal allografts (KeraNatural®) implanted in intrastromal tunnels created using a femtosecond laser. The main outcome measures were uncorrected visual acuity (UCVA), corrected distant visual acuity (CDVA), refraction, keratometry, and pachymetry. Computed tomography scans of the corneal surfaces were also performed preoperatively as well as 3, 6 and 12 months postoperatively.

RESULTS: Mean age was 29.5 ± 7.3 years (median 29, range: 20–52 years). The mean UCVA improved from 0.91 ± 0.50 logMAR preoperatively to 0.40 ± 0.24 logMAR postoperatively at 6 month follow-up ($p < 0.01$) and the mean CDVA improved from 0.87 ± 0.20 logMAR preoperatively to 0.27 ± 0.06 logMAR postoperatively ($p < 0.01$). The mean spherical equivalent improved from -8.82 ± 4.57 to -3.45 ± 4.81 D ($p < 0.01$). Average Keratometry decreased from 49.23 ± 5.22 preoperatively to 45.63 ± 4.89 D postoperatively ($p < 0.01$). Mean anterior and posterior maximum elevation were also decreased significantly ($p < 0.01$). In one patient, dislocation of the graft towards the tunnel incision site and dehiscence at the tunnel entrance were observed in the first week of the operation. Yellow-white deposits were observed in the segment tunnels in five cases after 6 months.

CONCLUSION: This study demonstrated that implantation of corneal allograft ring segments is a viable alternative treatment for keratoconus with safety and good visual results.

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INTRODUCTION

Keratoconus, which is frequently observed bilaterally and is asymmetrical in the majority of patients represents a progressive corneal ectatic disease, manifesting itself with paraxial stromal thinning and weakening and leading to corneal protrusion, irregular astigmatism, and vision loss [1, 2]. While spectacles and contact lenses can be used to increase visual acuity in the early stages of keratoconus, invasive procedures such as penetrating keratoplasty (PKP) or deep anterior lamellar keratoplasty (DALK) may be required in advanced stages [3].

Some surgical alternatives such as intrastromal corneal ring segments (ICRS) have been tried to delay or avoid keratoplasty in patients with keratoconus with a clear cornea and contact lens intolerance. Despite the ICRSs' safety and effectiveness, many complications have been reported after these synthetic implants have been implanted [4–7]. In 2018, Soosan Jacob described corneal allogenic intrastromal ring segments (CAIRS) for the first time and they have attracted significant interest due to their full biocompatibility with real human corneas [8]. Jacob et al. described the acronym CAIRS to refer to any form of allogenic tissue ring segment (fresh, pre-cut, processed, packaged etc.) that is placed into intrastromal channels and started the manually cut variant of

CAIRS where the donor cornea is procured and subsequently cut to shape by a surgeon using a specially designed double-bladed circular trephine. More recently, an American eye bank (Lions VisionGift, Portland, OR, USA) has developed CAIRS in the form of ready-to-use corneal arcs and rings that are pre-cut, sterilized, and can be stored at room-temperature for up to 2 years (KeraNatural®). This shelf-stable and pre-cut allogenic graft benefits surgeons by removing variables surrounding donor tissue procurement, preparation time in the operating room, and provides an added safety level associated with the use of sterile tissues.

A new protocol (Istanbul nomogram) was developed in our clinic using this product in keratoconus patients [9]. The present study aims to evaluate the efficacy and safety of corneal allogenic intrastromal ring segments implantations in keratoconus subjects.

MATERIALS AND METHODS

Study design and population

Sixty-five eyes of consecutive 49 keratoconus subjects to whom prepared corneal stromal ring segments (KeraNatural®; Lions VisionGift, USA) and implanted between February 2020 and August 2021 at the Faculty of Medicine of Istanbul Medipol University (Istanbul, Turkey) were included in this retrospective observational study.

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In line with the principles of the Declaration of Helsinki, information about the advantages and risks of the said surgical procedure was provided to all subjects, and their consent for using their clinical data was received. Furthermore, the local ethics committee approved the research.

The inclusion criteria below were employed in patient selection: age 18 years or older with keratoconus, corrected distance visual acuity (CDVA) of less than 0.5 Snellen and contact lens intolerance or who did not prefer to use contact lenses were included in the study. All patients had underwent corneal crosslinking prior to KeraNatural ring segment implantation. Patient with a history of a previous eye surgery, eyes with post-LASIK corneal ectasia the presence of lesions other than keratoconus, central or paracentral scarring, a history of viral keratitis and a central corneal thickness less than 400 micron were excluded from the study.

Corneal crosslinking

An accelerated conventional corneal crosslinking CXL using 10 mW/cm² for 9 min to obtain a total energy of 5.4 J/cm². A topical anaesthetic agent, 0.5% proparacaine (Alcaine; Alcon Laboratories, Inc.) was initially applied and the corneal epithelium was debrided with a blunt spatula from a central 8.0 mm diameter area. Dextran-riboflavin (10 ml dextran-T-500 10% riboflavin-5-phosphate solution in 20% solution, Medicros, Neudorf, Germany) solution was instilled to the cornea for 30 min, one drop every 2 min. If intraoperative minimum corneal thickness was less than 400 µm, we used a hypotonic riboflavin solution (hypotonic eye drops; Medio Cross Medizin Produkte GmbH) to swell the cornea, and the cornea was 9 mW/cm² energy was exposed to UV-A (Pes-chke Meditrade, GmbH, Switzerland) light. Progression in a patient with keratoconus was defined as an increase in simulated maximum keratometry values of greater than 1.00 dioptres (D) in the preceding 12 months.

Preoperative and postoperative evaluation

A preoperative and postoperative slit-lamp examination, spherical equivalent of refraction, uncorrected distance visual acuity (UDVA), CDVA assessment, and dilated funduscopy were performed on all participants.

Postoperative evaluations were made at months 1, 3, 6 and 12. The measurement of UDVA and CDVA was carried out in decimal Snellen, and they were converted to the logarithm of the minimum angle of resolution (logMAR) to conduct statistical analyses. The anterior and posterior corneal curvature and elevation were measured using the Scheimpflug camera system Pentacam HR (Oculus Optikgeräte, Wetzlar, Germany). Flat (K1), steep (K2), mean (Kmean) and maximum (Kmax) keratometry values, corneal astigmatism in a 3-mm zone, and the thinnest-point pachymetry were noted. The best-fit sphere for the anterior (BFS ant) and posterior corneal surfaces (BFS post) in the central 8-mm region were acquired in all patients. Furthermore, the maximum elevations for the anterior and posterior corneal surfaces were noted in all subjects during every visit [anterior maximum elevation (AME) and posterior maximum elevation (PME)]. Data on corneal anterior mean elevation and posterior mean elevation were obtained from 9 points in the numerical elevation map in a 2-mm zone.

Surgical technique

The same surgeon carried out all surgeries under topical anaesthesia (AK). The iFS 150kHz, Intralase femtosecond laser platform (Abbott Medical Optics Inc, CA, USA) was utilized with the aim of creating a circular channel after marking the visual axis with an inked Sinskey hook. The first Purkinje reflex was selected as the central point and was marked under the WaveLight EX500 (Alcon Laboratories, Inc., Fort Worth, TX) biomicroscope. The circular channel parameters employed were an inner diameter of 4 mm and an outer diameter of 7.5 mm at a depth of 35% of the minimum pachymetry in a 7-mm central optical zone. The iFS laser default energy setting of 1.3 µJ was used for the intracorneal ring incision treatment method. Incisions with one entry into the channel were made on the tomographic cone location. The tunnel incision was dissected by moving the semi-circular dissector in the lamellar pocket with rotational motion. A corneal ring segment was placed in all cases at an arc length of approximately 160° (Fig. 1A, B). None of the cases needed wound suturing. Postoperatively, topical moxifloxacin 0.5% (Vigamox) and dexamethasone

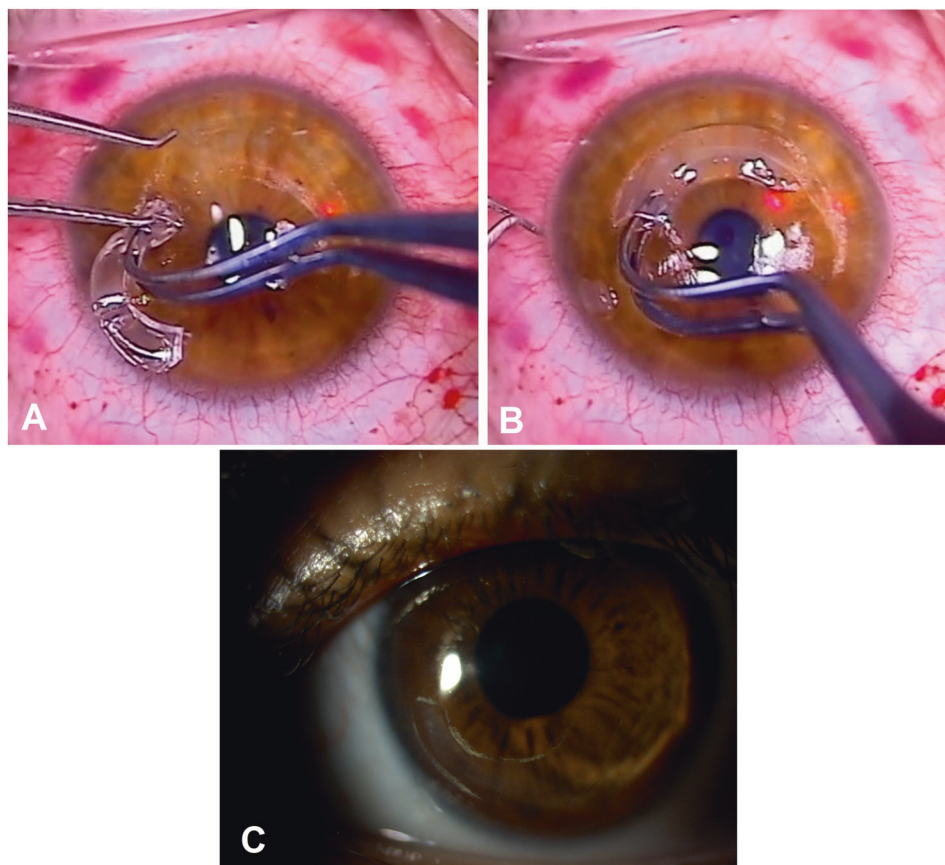


Fig. 1 Peroperative and postoperative anterior segment images. **A** A corneal ring segment was held with semi-circular forceps. **B** The corneal ring segment was implanted into channel **C**. Accumulation of yellow-white deposit along the inside and outside of the corneal allogenic intrastromal ring segments.

0.1% (Deksasine SE) eye drops were given five times a day for 2 weeks and then tapered to stop over the following 4 weeks.

Statistical analysis

Statistical analysis was carried out in the Statistical Package for the Social Sciences (SPSS version 21.0; IBM Corp., Armonk, NY, USA). Power analysis test was performed to determine the optimal sample size for the study. The Kolmogorov–Smirnov test was performed to assess normality assumption for clinical parameters and changes in clinical parameters. Repeated measures ANOVA was used when the assumption of normal distribution was met, and Friedman's test was used when normal distribution was not obtained. Pearson's correlation coefficient was employed for correlation. $P < 0.05$ were accepted as statistically significant.

RESULTS

There were 38 male (77.6%) and 11 female (22.4%) patients. Sixteen of them underwent bilateral implantation. A total of 65 eyes were included in the study. Seventeen eyes have undergone CXL in the last 12 months. Forty-eight eyes have had CXL 1–10 years ago. The average time between CXL and KeraNatural implantation surgery is 60.9 ± 42.1 months (Table 1). Since the KeraNatural implant surgery was performed in 13 patients less than 12 months after CXL, the progression of these patients could not be assessed. No progression was observed in the remaining patients who had been followed for at least 12 months.

The patients' mean age was 29.54 ± 7.34 years (range 20–52 years) and contact lens intolerance and a clear central cornea were

observed in all subjects. The baseline mean spherical equivalent was -8.82 ± 4.57 D, and the mean refractive cylinder was -4.35 ± 1.91 D. The baseline mean K1 value was 47.17 ± 4.97 D, K2 was 51.50 ± 5.67 D and Kmax was 59.20 ± 7.66 D. The patients did not have any intraoperative or major postoperative complications, including erosion, extrusion, melt or necrosis of the segments or corneal stroma. In one patient, dislocation of the graft towards the tunnel incision site and dehiscence at the tunnel entrance were observed in the first week of the operation, and this patient's graft was repositioned. In addition, punctate epithelial damage was observed in one patient between the area where the graft was placed and the centre of the cornea. Improvement was achieved with medical treatment. Yellow-white deposits were observed in the segment tunnels in five cases (7.6%) after 6 months (Fig. 1C). These channel deposits did not appear to affect the performance of the segment rings, visual level, or quality.

The increase in UCVA and CDVA was statistically significant after the first month postoperatively and remained stable for the remainder of the follow-up visits. UCVA in the 6th month improved at least 1 line in 91.7% of the eyes and remained stable in 8.3% of the eyes.

All patients had at least 1 line of vision gain in CDVA the 6th month (Fig. 2A, B). The mean CDVA improvement was 4 lines at postoperative 6 months (mean visual acuity changes was -0.42 ± 0.27 in logMAR). The detailed visual, refractive, and corneal tomographic outcomes of study patients during the preoperative and postoperative periods were presented in Table 1.

Table 1. Demographic characteristics, visual, refractive and corneal topographic outcomes of study patients during preoperative and postoperative period.

	Preoperative	1 Month	3 Month	6 Month	12 Month	P
Gender						
Male (%)	38 (77.6)					
Female (%)	11 (22.4)					
Age in years						
(mean $\pm$ SD)	29.54 ± 7.34					
Right eye (%)	34 (52.3)					
Left eye (%)	31 (47.7)					
Average duration between CLX and KeraNatural implantation	60.9 ± 42.1					
UCVA (logMAR)	0.91 ± 0.50	0.39 ± 0.28	0.38 ± 0.31	0.40 ± 0.24	0.36 ± 0.25	0.001 ^{a,b,c,d}
CDVA (logMAR)	0.87 ± 0.20	0.27 ± 0.06	0.36 ± 0.15	0.31 ± 0.09	0.36 ± 0.15	0.001 ^{a,b,c,d}
SE (D)	-8.82 ± 4.57	-3.92 ± 5.41	-3.55 ± 5.44	-3.45 ± 4.81	-2.32 ± 4.95	0.001 ^{a,b,c,d}
K1 (D)	47.17 ± 4.97	44.36 ± 5.24	44.28 ± 5.18	43.60 ± 4.84	42.96 ± 4.63	0.001 ^{a,b,c,d}
K2 (D)	51.50 ± 5.67	48.28 ± 5.45	48.26 ± 5.63	47.91 ± 5.20	47.81 ± 5.20	0.001 ^{a,b,c,d}
K max (D)	59.20 ± 7.66	56.75 ± 7.72	56.14 ± 7.70	55.83 ± 6.96	55.63 ± 6.14	0.001 ^{a,b,c,d}
K average (D)	49.23 ± 5.22	46.23 ± 5.25	46.17 ± 5.27	45.63 ± 4.89	45.23 ± 4.77	0.001 ^{a,b,c,d}
CCT (μ)	463.62 ± 54.88	449.69 ± 36.72	450.38 ± 48.74	447.46 ± 50.57	447.31 ± 56.35	0.18
AME (μ)	34.45 ± 11.67	20.27 ± 11.86	19.09 ± 11.62	19.09 ± 11.51	18.00 ± 10.07	0.001 ^(a,b,c,d)
PME (μ)	68.09 ± 6.27	54.72 ± 8.59	56.27 ± 8.41	59.18 ± 10.34	64.09 ± 9.03	0.01 ^{a,b}
BFS anterior (R)	7.55 ± 0.12	7.81 ± 0.13	7.81 ± 0.14	7.80 ± 0.12	7.79 ± 0.14	0.001 ^{a,b,c,d}
BFS posterior (R)	6.07 ± 0.08	6.25 ± 0.11	6.29 ± 0.11	6.39 ± 0.15	6.22 ± 0.10	0.001 ^{a,b,c}
Anterior elevation	9.30 ± 5.96	3.60 ± 5.67	2.84 ± 5.19	2.37 ± 6.19	2.17 ± 5.30	0.001 ^{a,b,c,d}
Posterior elevation	20.11 ± 3.63	15.49 ± 3.47	17.88 ± 2.78	18.96 ± 3.85	18.40 ± 3.69	0.05

All data were presented as mean or median $\pm$ standard deviation.

UCVA uncorrected distance visual acuity, log MAR log of the minimum angle of resolution, CDVA corrected distance visual acuity, SE spherical equivalent, K keratometry, CCT central corneal thickness, AME anterior maximum elevation, PME posterior maximum elevation, BFS best-fit sphere.

P values; repeated measures ANOVA or Friedman's test.

Comparative analysis based on Post hoc tests: ^a $p < 0.05$: preoperative vs. postoperative 1st month; ^b $p < 0.05$: preoperative vs. postoperative 3rd month; ^c $p < 0.05$: preoperative vs. postoperative 6th month; ^d $p < 0.05$: preoperative vs. postoperative 12th month. Bold values are statistically significant.

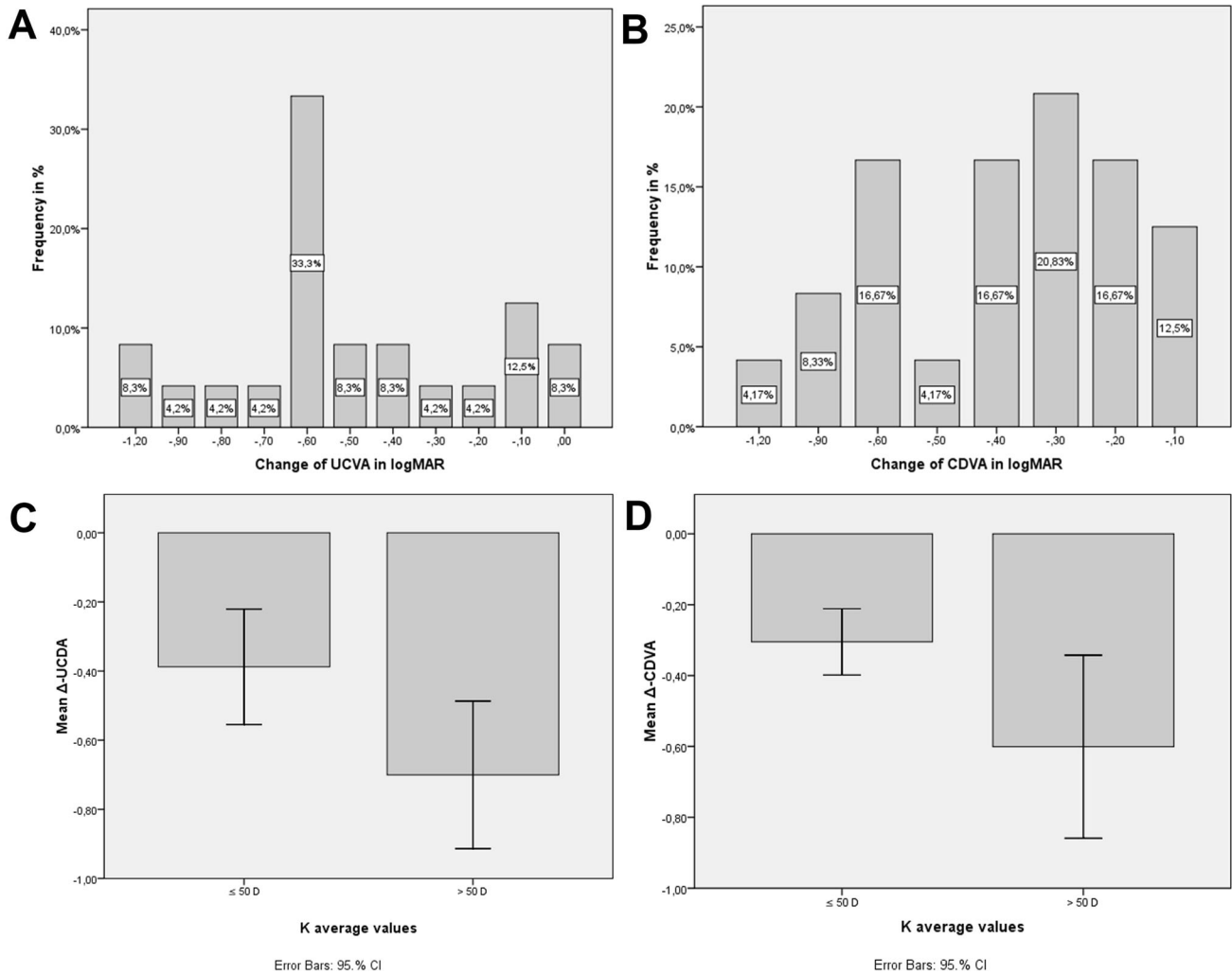


Fig. 2 Comparison of vision gain and vision improvement of patients after surgery. A Percentage graphs of the change in UCVA postoperative 6 months. **B.** Percentage graphs of the change in CDVA postoperative 6 months. **C** Comparison graph of UCVA improvement of the sub-groups in terms of K-average. **D** Comparison graph of CDVA improvement of the sub-groups in terms of K-average.

In brief, a significant enhancement was detected in the spherical equivalent, corneal astigmatism, K1, K2, Kaverage, Kmax, AME, PME, BFS ant, BFS post, and Ant Mean Elevation. A decrease was observed in PME from the first month postoperatively compared to the preoperative value, but this trend did not show statistical significance. While PME showed a statistically significant decrease compared to the preoperative values in the postoperative 1st and 3rd months, this significance was not observed in the postoperative 6th month and 1st year. There was no statistically significant change in central corneal thickness during the postoperative follow-up.

Upon comparing visual acuity results between the follow-up visits, logMAR levels of both UCVA and CDVA showed statistically significant improvement in the postoperative first month. UDVA and CDVA at every follow-up visit in the postoperative period were better compared to those in the preoperative period ($p < 0.01$). The study group was divided into two sub-groups according to the Kaverage value ≤ 50 D and > 50 D. UCVA and CDVA improvements at 1 month were statistically significantly better in the group with K average > 50 D ($p = 0.01$ and $p < 0.01$). the group with Kaverage value ≤ 50 D had a 3.8 line increase in the UCVA and 3 line increase in the CDVA while the group with Kaverage value > 50 D had a 7 line increase in UCVA and 6 line increase in the CDVA (Fig. 2C, D).

There was no statistically significant correlation between the alteration in the posterior maximum corneal elevation value and both UCVA change ($r = -0.251$, $p = 0.237$) and CDVA change ($r = -0.270$, $p = 0.202$) (Table 2). Also, there was no significant correlation between readings for K1, K2, Kmean, Kmax, and corneal elevation map changes and vision improvement lines ($p > 0.05$).

DISCUSSION

The findings of the present study suggest that changes in visual, refractive and corneal tomographic outcome occur in the first month following the corneal allograft intrastromal ring segment implantation. The keratometric power of the central cornea and refractive power decreased significantly following the implantation of the sterile corneal allografts. Furthermore, these favourable alterations remain stable during the postoperative first year.

The present study also shows that it is possible to avoid potential complications related to the implantation of a synthetic material with allogenic corneal ring segments. It is necessary to retain sufficient corneal stroma at a depth of approximately 80% above the synthetic implant for preventing extrusion and erosion [10, 11]. The implantation of a corneal allograft intrastromal ring segment at a mid-stromal depth or more superficially may decrease the said risks and can be related to a more significant

Table 2. Correlations between the visual acuity changes and topographic parameters changes in 6th months.

	Δ -AME	Δ -PME	Δ -BFS-anterior	Δ -BFS-posterior	Δ -elevation-anterior	Δ -elevation-posterior
Δ -UCVA						
<i>r</i>	0.191	-0.251	-0.127	0.285	0.214	0.116
<i>p</i>	0.371	0.237	0.556	0.177	0.316	0.591
Δ -CDVA						
<i>r</i>	0.118	-0.270	0.040	0.317	0.159	0.043
<i>p</i>	0.582	0.202	0.853	0.131	0.457	0.844

UCVA uncorrected distance visual acuity, CDVA corrected distance visual acuity, AME anterior maximum elevation, PME posterior maximum elevation, BFS best-fit sphere.

impact on the anterior corneal curvature through a spacer impact. In their series, Jacobs et al. utilized a full-thickness corneal stroma from the 6.7- to 7.5-mm optic zone of the donor cornea and observed a significant enhancement in UDVA, CDVA, spherical equivalent, and tomographic parameters [8]. The results obtained are directly proportional to the segment's thickness and inversely proportional to the segment's diameter [10]. In our study, the corneal ring segments were implanted at a depth of approximately 35% in the paracentral cornea between 4 to 7.5 mm in diameter. Further, we used only one segment on the keratoconus cone. Therefore, the ring segments were implanted more centrally and superficially.

There are several literatures about the necessity of removal of the INTACS due to some medical and refractive complications [4, 12–14]. Kanellopoulos et al. [4] reported that 6 implants had to be removed due to ring segment movement and exposure through the axial wound or corneal melting. In another study, Zare et al. [14] stated that 3 implant exposure through the wound occurred 3–5 months after implantation and 1 bacterial keratitis which they had to remove. Recently Hacıagaoglu et al. were published a retrospective results of 44 eye with keratoconus that had been implanted KeraNatural [9]. They reported only one case whose graft slipped towards the tunnel incision site in the early postoperative period, and they repositioned it [9]. Similarly, we did not have any intraoperative or major postoperative complications, in one case dislocation of the graft towards the implantation site and dehiscence at the tunnel entrance were observed in the first week of the operation, and this patient's graft was repositioned successfully.

Other complications of INTACS have been addressed in several studies are yellow-white deposit accumulation in the stromal channel [15, 16].

A recent study demonstrated the incidence of intrastromal channel deposits increases with longer follow-up and in patients with larger implants [16]. In our study yellow-white deposits were observed in the segment tunnels in 5 subjects after 6 months and these deposits did not appear to affect visual acuity level or quality as comparable with the other studies.

Although the regularization of the corneal anterior surface is the most significant factor in improving vision, how the posterior corneal elevation is affected after the corneal allogenic stromal ring segment implantation has not been studied yet. Some recent studies have stated alterations in the posterior corneal surface in early and advanced keratoconic eyes utilizing various topographic systems [17–19]. It is a known fact that there is a local protrusion in the anterior and posterior surfaces of keratoconic corneas and the posterior corneal surface contributes even more significantly to keratoconus, particularly in advanced cases [17–19].

A previous study showed a decrease in the posterior corneal curvature following the implantation of intracorneal ring segment implantation (INTACS) in post-laser-assisted in situ keratomileusis ectatic corneas [20]. Sögütlü et al. investigated only the anterior and posterior maximum elevation, whereas Rho et al. examined the

anterior and posterior elevation of the centre point and the anterior thinnest point [1, 2]. In their study, AME and PME decreased significantly after INTACS implantation [2]. In the present research, an average of 9 elevation points in central 2-mm areas were analysed since the alterations in question could be better described with average area parameters in patients with keratoconus. The findings of our research are consistent with the study by Sögütlü in this context. ICRSs are generally placed in the deep cornea at >70% of the corneal depth and can considerably impact the posterior corneal surface [2]. Rho et al. showed an increase in the posterior elevation of the centre point, whereas there was no prominent change in the posterior BFS [1]. Contrary to their study, our study revealed a significant decrease in PME, while posterior BFS was significantly increased. In addition, it was observed that the significant decrease in PME observed in the 1st and 3rd months did not continue in the 1st year. However, the statistically significant reduction in AME continued at 1 year. Posterior mean elevation decreased compared to preoperative values, but this decrease was not statistically significant. These results might be attributed to superficially-seated corneal allograft intrastromal ring segments.

The literature clearly demonstrates how ICRS implantation can improve visual acuity [21, 22]. Previous studies attempted to reveal a relationship between alterations in corneal parameters and visual outcomes following ICRS implantation [23]. Lyra et al. showed the best correlation between anterior corneal astigmatism and visual outcomes [23].

Another study detected a weak but statistically significant relationship between the maximum posterior corneal elevation and UDVA, and the spherical equivalent ($r = 0.18$ and $p = 0.02$) [2]. In our research, there was no statistically significant correlation between posterior maximum elevation changes and visual acuity. Furthermore, no statistically significant correlation was found between the other tomographic changes and visual acuity changes. However, despite the increasing trend in PME in the first year, it was observed that the increasing in visual acuity in the postoperative period continued. Evaluation of this increasing trend suggested that longer-term studies are needed to evaluate the effect on visual acuity and whether there is keratoconus progression. The study group was roughly divided into two sub-groups. Although the visual acuity was more significantly improved in the group with the Kaverage values ≥ 50 D, it would be more accurate to compare a further number of patients by classifying them according to keratoconus stages.

The present study has some limitations which are worth noting before interpreting. First, the strength of the study is limited by the relatively small sample size. Therefore, we cannot categorize the stages of keratoconus from 1 to 4 separately. Second, the follow-up data was limited by 12 months and long follow-up results are eagerly awaited. Another major limitation of this study is the absence of a control or comparison group. Therefore, there is a need for more studies to achieve a better understanding and verification of our initial findings and the impacts of nomograms and further customization.

In conclusion, the current research showed that the implantation of sterile, prepared corneal allogenic ring segments alters corneal tomographic parameters on the anterior and posterior surfaces and can improve visual acuity, offering a less invasive and safe surgical approach to the treatment of keratoconus.

SUMMARY

What was known before

- Acrylic segments have been used effectively for years to improve visual acuity in keratoconus patients.
- However acrylic ring segments are implanted at a depth of 80–85% due to the risk of extrusion.
- The disadvantage of this deep placement is that they have less effect on the resulting shape on the front surface

What this study adds

- This study shows that the corneal allogenic ring segment can be implanted to a shallower depth of 35%, which can provide a greater impact on the surface.
- This is an alternative treatment that is more biocompatible and less invasive choice of the keratoconus treatment.

DATA AVAILABILITY

Anonymised data for this study is available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

Concept—SAN, ECY, AK; Design—SAN, ECY, FK, CT; Supervision—ST, CT, AK; Funding—SAN, CT, AK; Materials—SAN, FK, CT, AK; Data Collection and/or processing—SAN, FK, CT; Analysis &/or interpretation—SAN, ECY, ST, AK; Literature search—SAN, ECY, ST, AK; Writing—SAN, ECY, AK; Critical review—SAN, ECY, FK, CT, ST, AK.

COMPETING INTERESTS

AK is a consultant of KeraNatural. The remaining authors have no conflicts of interest to disclose.

INFORMED CONSENT

Informed consent was obtained for the use of patient's images.

ADDITIONAL INFORMATION

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