Efficacy and safety of intracorneal allogenic ring segment implantation in keratoconus

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Article

Keywords:

Posted Date: September 15th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1974653/v1

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Version of Record: A version of this preprint was published at Eye on June 16th, 2023. See the published version at https://doi.org/10.1038/s41433-023-02618-5.
Abstract

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 to 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). 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). Dislocation of the graft towards the implantation site and swelling at the tunnel entrance were observed in one case. Yellow white deposits were observed in the segment tunnels in five case 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.

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 (ICRSs) 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 ring segments for the first time and they have attracted significant interest due to their full biocompatibility with real human corneas [8]. In this technique, the donor cornea must be procured and subsequently cut to shape by a surgeon using a specially designed double-bladed circular trephine [8]. More recently, an American eye bank (Lions VisionGift, Portland, OR, USA) has developed ready-to-use corneal arcs and rings that are precut, 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 (Table 1). The present study aims to evaluate the efficacy and safety of corneal allogenic intrastromal ring segments implantations in keratoconus subjects.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Corneal allograft intrastromal ring segment surgery and laser parameter of Istanbul Nomogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 180° arc, corneal full stromal tissue</td>
<td></td>
</tr>
<tr>
<td>• 2 mm wide</td>
<td></td>
</tr>
<tr>
<td>• Channel diameters and depth</td>
<td></td>
</tr>
<tr>
<td>i) Inner diameter: 4mm</td>
<td></td>
</tr>
<tr>
<td>ii) Outer diameter: 7.5 mm</td>
<td></td>
</tr>
<tr>
<td>iii) Depth: 200 µm</td>
<td></td>
</tr>
<tr>
<td>• Incision cut energy: 1.3 µj</td>
<td></td>
</tr>
<tr>
<td>• Ring energy: 1.3 µj</td>
<td></td>
</tr>
<tr>
<td>• Incision cut length: 1.5 mm</td>
<td></td>
</tr>
<tr>
<td>• Incision axis: Cone location</td>
<td></td>
</tr>
<tr>
<td>• Cones</td>
<td></td>
</tr>
<tr>
<td>i) Asymmetric cone: single segment implantation</td>
<td></td>
</tr>
<tr>
<td>ii) Central cone: symmetric two segment implantation</td>
<td></td>
</tr>
</tbody>
</table>

**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.

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. Patient with a history of a previous eye surgery, the presence of lesions other than keratoconus, central or paracentral scaring, a history of viral keratitis and a central corneal thickness less than 400 micron were excluded from the study.

**Preoperative and postoperative evaluation**

A preoperative and postoperative slit-lamp examination, spherical equivalent of refraction, uncorrected distance visual acuity (UDVA), CDVA assessment, and dilated fundoscopy 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 was 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 anesthesia (AK). The iFS 150kH, 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 by 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 topographic cone location. The tunnel incision was dissected by moving the semicircular dissector in the lamellar pocket with rotational motion. A corneal ring segment was placed in all cases at an arc length of approximately 160 degrees. None of the cases needed wound suturing. Postoperatively, topical moxifloxacin 0.5% (Vigamox) and dexamethasone 0.1% (Deksasine SE) eye drops were given five times a day for the period of two weeks and then tapered to stop over the following four weeks.

**Statistical Analysis**

Statistical analysis was carried out in the Statistical Package for the Social Sciences (SPSS version 21.0; IBM Corp., Armonk, N.Y., USA). 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. 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 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 implantation site and swelling 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 center of the cornea. Improvement was achieved with medical treatment. Yellow white deposits were observed in the segment tunnels in five case (7.6%) after 6 months (Fig. 1). These channel deposits did not appear to affect the performance of the segment rings, visual level or quality.

The increase in UCVA and CDVA were statistically significant after the first month postoperatively and remained stable for the remainder of the follow-up visits. UCVA at 6th months 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 at 6th months (Figs. 2 and 3). 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 topographic outcomes of study patients during preoperative and postoperative period were presented in Table 2. In brief, a significant enhancement was detected in the spherical equivalent, corneal astigmatism, K1, K2, Kaverage, Kmax, AME, PME, BFS ant, BFS post, Ant Mean Elevation. A decrease was observed in PME from the first month postoperatively compared to 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.
Table 2
Visual, refractive and corneal topographic outcomes of study patients during preoperative and postoperative period

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>1 Month</th>
<th>3 Month</th>
<th>6 Month</th>
<th>12 Month</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCVA (logMAR)</td>
<td>0.91 ± 0.50</td>
<td>0.39 ± 0.28</td>
<td>0.38 ± 0.31</td>
<td>0.40 ± 0.24</td>
<td>0.36 ± 0.25</td>
<td>0.001</td>
</tr>
<tr>
<td>CDVA (logMAR)</td>
<td>0.87 ± 0.20</td>
<td>0.27 ± 0.06</td>
<td>0.36 ± 0.15</td>
<td>0.31 ± 0.09</td>
<td>0.36 ± 0.15</td>
<td>0.001</td>
</tr>
<tr>
<td>SE (D)</td>
<td>-8.82 ± 4.57</td>
<td>-3.92 ± 5.41</td>
<td>-3.55 ± 5.44</td>
<td>-3.45 ± 4.81</td>
<td>-2.32 ± 4.95</td>
<td>0.001</td>
</tr>
<tr>
<td>K1 (D)</td>
<td>47.17 ± 4.97</td>
<td>44.36 ± 5.24</td>
<td>44.28 ± 5.18</td>
<td>43.60 ± 4.84</td>
<td>42.96 ± 4.63</td>
<td>0.001</td>
</tr>
<tr>
<td>K2 (D)</td>
<td>51.50 ± 5.67</td>
<td>48.28 ± 5.45</td>
<td>48.26 ± 5.63</td>
<td>47.91 ± 5.20</td>
<td>47.81 ± 5.20</td>
<td>0.001</td>
</tr>
<tr>
<td>K max (D)</td>
<td>59.20 ± 7.66</td>
<td>56.75 ± 7.72</td>
<td>56.14 ± 7.70</td>
<td>55.83 ± 6.96</td>
<td>55.63 ± 6.14</td>
<td>0.001</td>
</tr>
<tr>
<td>K average (D)</td>
<td>49.23 ± 5.22</td>
<td>46.23 ± 5.25</td>
<td>46.17 ± 5.27</td>
<td>45.63 ± 4.89</td>
<td>45.23 ± 4.77</td>
<td>0.001</td>
</tr>
<tr>
<td>CCT (µ)</td>
<td>463.62 ± 54.88</td>
<td>449.69 ± 36.72</td>
<td>450.38 ± 48.74</td>
<td>447.46 ± 50.57</td>
<td>447.31 ± 56.35</td>
<td>0.18</td>
</tr>
<tr>
<td>AME (µ)</td>
<td>34.45 ± 11.67</td>
<td>20.27 ± 11.86</td>
<td>19.09 ± 11.62</td>
<td>19.09 ± 11.51</td>
<td>18.00 ± 10.07</td>
<td>0.001</td>
</tr>
<tr>
<td>PME (µ)</td>
<td>68.09 ± 6.27</td>
<td>54.72 ± 8.59</td>
<td>56.27 ± 8.41</td>
<td>59.18 ± 10.34</td>
<td>64.09 ± 9.03</td>
<td>0.01(a,b)</td>
</tr>
<tr>
<td>BFS Anterior</td>
<td>7.55 ± 0.12</td>
<td>7.81 ± 0.13</td>
<td>7.81 ± 0.14</td>
<td>7.80 ± 0.12</td>
<td>7.79 ± 0.14</td>
<td>0.001</td>
</tr>
<tr>
<td>BFS Posterior</td>
<td>6.07 ± 0.08</td>
<td>6.25 ± 0.11</td>
<td>6.29 ± 0.11</td>
<td>6.39 ± 0.15</td>
<td>6.22 ± 0.10</td>
<td>0.001</td>
</tr>
</tbody>
</table>

All data were presented as mean or median ± 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 1th Month; b: p < 0.05: preoperative vs. postoperative 3th Month; c: p < 0.05: preoperative vs. postoperative 6th Month; d: p < 0.05: preoperative vs. postoperative 12th Month.
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 ($p < 0.01$).

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 3). Also there was no significant correlation between readings for K1, K2, Kmean, Kmax and corneal elevation map changes and vision improvement lines ($p > 0.05$).

### Table 3
Correlations between the visual acuity changes and topographic parameters changes in 6th months

<table>
<thead>
<tr>
<th></th>
<th>$\Delta$-AME</th>
<th>$\Delta$-PME</th>
<th>$\Delta$-BFS-anterior</th>
<th>$\Delta$-BFS-posterior</th>
<th>$\Delta$-elevation-anterior</th>
<th>$\Delta$-elevation-posterior</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta$-UCVA</td>
<td>0.191</td>
<td>-0.251</td>
<td>-0.127</td>
<td>0.285</td>
<td>0.214</td>
<td>0.116</td>
</tr>
<tr>
<td>$r$</td>
<td>0.371</td>
<td>0.237</td>
<td>0.556</td>
<td>0.177</td>
<td>0.316</td>
<td>0.591</td>
</tr>
<tr>
<td>$p$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta$-CDVA</td>
<td>0.118</td>
<td>-0.270</td>
<td>0.040</td>
<td>0.317</td>
<td>0.159</td>
<td>0.043</td>
</tr>
<tr>
<td>$r$</td>
<td>0.582</td>
<td>0.202</td>
<td>0.853</td>
<td>0.131</td>
<td>0.457</td>
<td>0.844</td>
</tr>
<tr>
<td>$p$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

The findings of present study suggest that changes in visual, refractive and corneal topographic 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 favorable 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 [9, 10]. The implantation of a corneal allograft intrastromal ring segment at a midstromal depth or more superficially will probably not have the said risks and can be related to a more significant 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 topographic parameters [8]. The results obtained are directly proportional to the segment’s thickness and inversely proportional to the segment’s diameter [9]. 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 of diameter. Further, we used only one segment on the keratoconus cone. Therefore, the ring segments were implanted more centrally and more superficially.

There are several literatures about the necessity of removal of the INTACS due to of some medical and refractive complications [4, 11–13]. Kanellopoulos et al. [4] reported that 6 implants had to be removed due to ring segment movement and exposure through axial wound or corneal melting. In another study Zare et al. [13] have stated that 3 implant exposure through the wound that occurred 3 to 5 months after implantation and 1 bacterial keratitis which they had to remove. We did not have any intraoperative or major postoperative complications, in one case dislocation of the graft towards the implantation site and swelling at the tunnel entrance were observed in the first week of the operation, and this patient’s graft was repositioned successfully.

Another complications of INTACS have addressed in several studies are yellow-white deposit accumulation in the stromal channel [14, 15].

The recent study demonstrated the incidence of intrastromal channel deposits increases with longer follow-up and in patients with larger implants [15]. 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. A number of recent studies have stated alterations in the posterior
corneal surface in early and advanced keratoconic eyes by means of various topographic systems [16–18]. It is a known fact that there is a local protrusion in anterior and posterior surfaces of keratoconic corneas and the posterior corneal surface contributes even more significantly to keratoconus, particularly in advanced cases [16–18].

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 [19]. Söğütlü et al investigated only the anterior and posterior maximum elevation, whereas Rho et al examined the anterior and posterior elevation of the center 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 analyzed 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 Söğütlü 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 center 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 [20, 21]. Previous studies attempted to reveal a relationship between alterations in corneal parameters and visual outcomes following ICRS implantation [22]. Lyra et al. showed the best correlation between anterior corneal astigmatism and visual outcomes [22].

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 $p = .02$) [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 topographic changes and visual acuity changes. However, despite the increasing trend in PME in the first year, it was observed that the increase 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 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. 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 a safe surgical approach to the treatment of keratoconus.

Declarations

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

The authors received no financial support for the research, authorship, and/or publication of this article.

Funding

This study received no financial assistance.

Conflict of Interest

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

Authorship 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.

References


Figures

Figure 1
Accumulation of yellow white deposit along the inside and outside of the corneal allogenic intrastromal ring segments

Figure 2

Percentage graphs of the change in UCVA postoperative 6 months
Figure 3

Percentage graphs of the change in CDVA postoperative 6 months