Femtosecond laser-assisted peripheral additive stromal keratoplasty for treatment of primary corneal ectasia: Preliminary outcomes

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Purpose: To report the preliminary results of a new surgical modality for the treatment of primary corneal ectasia, which consists of implanting allogeneic corneal tissue into the peripheral corneal stroma using a femtosecond laser system or femtosecond laser-assisted peripheral allogeneic stromal additive keratoplasty or FA-PASAK. Methods: This prospective, noncomparative case series includes patients with primary corneal ectasia including keratoconus and pellucid marginal degeneration. In the operating room, one or two ring or crescent-shaped allogeneic corneal segments were prepared using a handmade double-bladed punch, which were then implanted by a specially designed device, into stromal channels in the peripheral recipient cornea fashioned with a femtosecond-laser system. Results: A total of 15 eyes of 13 patients with mean age of 31.73 years were operated. There were significant improvements in uncorrected (0.68 to 0.3 logMAR) and corrected (0.44 to 0.16 logMAR) visual acuity, mean sphere, mean spherical equivalent refractive error, and mean keratometry (steep, flat, and average). Topographic and refractive astigmatism did not change significantly. Complications included a single case of bacterial keratitis secondary to epithelial defect, which was controlled with topical antibiotics eventually leading to an uncorrected vision of 20/25 one year after surgery. Conclusion: The use of allogeneic corneal ring or crescent shape segments may be a safe and cost-effective treatment for primary corneal ectasia, whereas a nomogram is necessary to be devised for general use of the technique.



Key words: Allogenic, cornea, ectasia, keratoconus

Keratoconus (KCN) and pellucid marginal degeneration (PMD) are bilateral, asymmetrical, noninflammatory, and progressive ectatic corneal conditions, characterized by stromal thinning leading to distortion of the corneal surface.^[1-3] In severe cases with irregular astigmatism where contact lenses cannot be used, or when corneal stromal opacity is present, lamellar or penetrating keratoplasty is the mainstay of treatment.^[4] Due to the costs and complications of corneal transplantation, research is ongoing to delay or replace it with simpler methods, such as intracorneal ring segments (ICRSs). Although long-term studies have shown the effectiveness of these implants in delaying corneal transplantation,[5-8] melting of corneal stroma over the polymethyl methacrylate (PMMA) implants, migration of synthetic rings to the incision site, and corneal ulcers are major concerns. These complications are not uncommon, both when the ring is manually inserted into the cornea or when the procedure is femtosecond laser-assisted.[9-12]

The use of allogeneic corneal tissue to change corneal strength and shape was first proposed by Barraquer in 1965.^[13] With the availability of excimer lasers to correct refractive errors, these methods replaced that of Barraquer for the purpose of refractive corrections. Nevertheless, in recent years,

Received: 12-Dec-2020 Accepted: 30-Apr-2021 Revision: 30-Jan-2021 Published: 25-Sep-2021 with the availability of femtosecond lasers the implantation of donor tissue has been re-considered, with the advantages of providing corneal tissue donor material in various shapes and sizes, with superior biological compatibility as compared to PMMA and possibly lower cost.

In 2015, Liu *et al.*,^[14] using femtosecond laser, examined the transfer of allogeneic corneal lenticules into the corneal stroma of monkeys. They found that that this method is safe and could be used to increase corneal stromal thickness and change corneal refractive power. In 2018 and 2019, a few reports on different methods using xenogeneic, allogeneic, and autogenic corneal tissues were published to correct different types of corneal ectasia or refractive errors.^[15–20] But there are still many questions in this regard.

The current study aimed to investigate the visual outcomes and complications of implanting differently shaped allogeneic corneal segments in the peripheral stroma of ectatic corneas.

Methods

This prospective noncomparative case series was approved by the Ethics Committee of our institute and followed the tenets of

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Cite this article as: Jafarinasab M, Hadi Y. Femtosecond laser-assisted peripheral additive stromal keratoplasty for treatment of primary corneal ectasia: Preliminary outcomes. Indian J Ophthalmol 2021;69:2663-8.

the Declaration of Helsinki. The surgical procedure, alternative options, possible complications, and benefits of each procedure were fully explained to patients and all included subjects studied and signed the informed consent form before surgery.

Patients with definite signs of KCN or PMD based on slit-lamp examination, retinoscopy, topography, and tomography, who were referred to our center from March 2018 to December 2019, were evaluated for inclusion into the study. Inclusion criteria were subjects over 18 years of age with KCN between Amsler-Krumeich stages 1 and 4^[21] and unsatisfactory vision with glasses or contact lenses. Exclusion criteria consisted of the history of any corneal surgery of the same eye (including implantation of synthetic rings inside the cornea), corneal refractive surgery, corneal transplantation, corneal crosslinking, central corneal scars, and any other ocular comorbidity that could affect the final visual outcomes. Preoperative examinations included measuring uncorrected distance visual acuity (UDVA), refraction and spectacle-corrected distance visual acuity (SCDVA), new topography and tomography of the cornea, and a complete ophthalmic examination at the slit lamp.

Surgical Technique

All operations were performed by the same surgeon (MJ). First, in a laser clinic under sterile conditions and local anesthesia, using the Z6 Femto LDV™ (Ziemer Ophthalmic Systems, Port, Switzerland) (3 nJ; spot spacing, 5 µm), a 360° stromal channel was created at a depth of 300–400 μm or 70%–80% of corneal thickness. Inner diameter was 4.9-5.9 mm and outer diameter was 7.1-9.6 mm. The laser created two entry cuts on the topographic steep axis of the cornea, 1.2–1.8 mm long. To accommodate the almost 350-µm thickness of the implanted segments, the width of the channel and the length of the cuts were sized 20% larger than the width of the allogeneic segments. Next, in the operating room, the appropriate tissue was prepared from fresh anterior corneal buttons from DSAEK donor tissues, the endothelium (posterior lamellae) of which had been used on the same day or within the last few days while the anterior lamellae were preserved appropriately. Since this study was a pilot study and we did not have a specific nomogram, we used a fixed cap thickness. A single, slow pass of 400-µm microkeratome yielded the corneal caps. Using a specially designed double-bladed trephine, the DSAEK button (anterior lamellae) was punched in the form of a ring and then cut to the preferred size [Fig. 1]. We used another form of double-bladed trephine to cut the cornea in the shape of a crescent [Fig. 1] for use in patients with PMD. A specially designed hand-held helical or pigtail lamellar dissector with a hole in its tip was passed through the femtosecond laser-dissected channel. An 8-0 silk suture was threaded through the hole of the dissector, passed through one end of the corneal segment and tied. When the pigtail dissector was pulled backward through the channel, the corneal segment was drawn into the channel. The dissector was brought out and the suture was cut at the end [Fig. 2].

After intraoperative adjustments with the aid of a maloney keratoscope, entry cuts were closed with 10-0 nylon sutures. At the conclusion of the procedure, a silicone-hydrogel bandage contact lens (Alcon Laboratories, Inc., Fort Worth, TX, USA) was placed on the cornea. Postoperatively patients were prescribed betamethasone 0.1% eye drops (Sina Darou, Tehran, Iran) four

times a day, nonpreserved Levofloxacin 0.5% eye drops (Sina Darou, Tehran, Iran) four times a day, and nonpreserved artificial tears Artelac (Baush and Lomb, Rochester, NY USA) six times a day. Levofloxacin drops were discontinued 7 days postoperatively and betamethasone drops tapered off over 4 weeks. Bandage contact lenses were removed 3 days after surgery. The corneal sutures were removed no later than one month after the operation. Patients were visited regularly on the first day, first week, and first month after surgery and then every three months. At each visit, they underwent detailed ophthalmic examinations, including refraction, SCDVA and UDVA measurement, intraocular pressure monitoring, topography (TOMEY Version 4.2C, Tomey GmbH, Nürnberg, Germany), and thorough slit lamp examination to detect any possible complications.

Statistical Analysis

Statistical analysis was performed by using SPSS software for windows version 16.0 (IBM Corp., Armonk, NY, USA). Data were recorded as mean ± standard deviation.

Our data followed a normal distribution. The differences between any two time points were analyzed using paired sample *t*-tests. A *P* value < 0.05 indicated statistical significance.

Results

A total of 15 eyes from 13 patients including 7 women and 6 men with mean age of 31.73 (range 18–52) years met the study criteria and were operated. Table 1 reports details of patient demographics and follow-up period. Mean follow-up time was 5.73 (range 3–12) months.

CDVA change before and after surgery in individual cases is shown in Fig. 3. Mean uncorrected and corrected distance visual acuity (logMAR) significantly improved from 0.68 to 0.3 and 0.44 to 0.16 at last postoperative visit, respectively (P < 0.005). Mean sphere was - 4.8 D (range, -17.00 to + 1.00) preoperatively and + 0.08 D (range, -15 to + 3.75) postoperatively; the reduction in sphere was statistically significant (P < 0.001). Mean pre- and postoperative refractive astigmatism were comparable at – 5.1 and – 4.2 D, respectively, (P value 0.2). Mean pre- and postoperative topographic astigmatism were also comparable at -4.1 and -3.7 D, respectively (P value 0.57). Mean SE refractive error was - 7.08 D preoperatively, which was significantly reduced to -2.07 D at last visit (P < 0.001). Mean flat, steep, and average K-readings at the central 3-mm area were all reduced significantly, from 46.6 D to 42.1 D (P < 0.001), from 48.69 D to 43.98 D (P < 0.001), and from 48.96 D to 43.98 D (P < 0.001), respectively [Fig. 4]. Visual, refractive, and keratometric data before and after surgery are summarized in Table 2.

Table 1: Patient's demographics and follow up time			
Eye (N) R/L	15 (7/8)		
Mean age (y) +/-SD, Min/Max	31.2±7.85 (18/52)		
F (%)	6 (40%)		
M (%)	9 (60%)		
Mean F/U (m), Min/Max	5.73±3.15 (3/12)		

SD=standard deviation; F/U=follow up; F=female; M=male; (%)=percentage; (y)=years; (m)=months





Figure 1: Prepare a semicircular segment. (a) A complete ring is punched from the cornea. (b) The ring is cut to the desired size segment. (c) Passed a helical or pigtail hand-held dissector through femtosecond created stromal channel, the segment is tied to the pigtail's hole and is pulled back into the channel. (d) 3 months later, the segment became transparent

No intraoperative complications occurred in any of the eyes. There was no instance of allogeneic corneal rejection and no infection or melting of the donor or recipient tissue within the stromal canal during the follow-up period. In one case, a corneal ulcer was diagnosed on the third postoperative day outside the surgical area due to an epithelial defect. The patient was admitted and routine care was provided including sampling for smear and culture and prompt initiation of topical treatment with fortified antibiotic eye drops (vancomycin and ceftazidime). The culture was reported positive for staphylococcus epidermidis, and after observing a good clinical response, we discharged the patient. On an outpatient basis, the corneal ulcer continued to respond favorably leaving a mild, superficial scar on the paracentral cornea. The patient's final SCDVA reached 20/25, 6 months after the operation.

Discussion

Various interventions have been designed to delay or replace corneal transplantation in patients with KCN or PMD. ICRSs were designed to flatten central corneal curvature and achieve refractive improvement leaving the optical center of the cornea intact. Many reports have demonstrated the efficacy of ICRSs in attaining this purpose.^[5-8,22] However, the use of these synthetic rings is associated with the risk of corneal melting, infection, implant migration, late intrusion into the anterior chamber,^[9-11] as well as limitation of use in corneas thinner than 350 µm at



Figure 2: Crescent shape segment implantation in a patient with pellucid marginal degeneration. (a) and (b) A crescent shape corneal segment is punched. (c) Final position of the segment

Table 2: Comparison o	f preoperative and p	postoperative visual,	refractive and	topographic parameters

Parameter	Preoperative	Postoperative	Р
UDVA (logMAR)±SD	0.65±0.22	0.31±0.14	0.00
CDVA (LogMAR)±SD	0.38±0.23	0.15±0.14	0.002
Sphere (D)±SD	-3.46±3.96	1.20±1.9	0.000
Refractive astigmatism	5.1±2.8	4.1±2.6	0.114
Spherical equivalent (D), mean±SD	-6.03±3.68	-0.86±1.64	0.000
Topographic astigmatism (D), mean±SD	4.52±3.21	3.8±2.8	0.427
Steepest K (3mm central)(D), mean±SD	50.55±3.48	45.37±3.61	0.000
Flat K (3 mm central)	46.00±3.79	41.51±4.34	0.000
Average K (3 mm central)	48.26±3.26	43.43±3.75	0.000

UDVA=uncorrected distance visual acuity; SD=standard deviation; CDVA=corrected distance visual acuity; D=diopters





the thinnest point or 400 μ m at the anticipated site of ICRS implantation.^[22]

In recent years, various methods have been used to transfer allogeneic or autogenic corneal tissue to change corneal strength and shape and treat conditions, such as aphakia, hyperopia, and corneal ectasia. These studies, most of which have used lenticules, have shown the safety and efficacy of such procedures.^[14-18] This is an unpublished study so there is no reference to be cited. Journal reviewers didn't disapprove to mention this unpublished work, however if it is against journal's policies to mention a work without any references to be cited we could delete this paragraph altogether.

In the current study, using the remaining anterior corneal button of DSAEK donor tissues, we prepared allogeneic corneal ring segments and placed them in channels created in the patient's ectatic cornea using a femtosecond laser. Our results showed a significant improvement in UDVA, SCDVA, spherical equivalent, and flat, steep, and average K-readings in the central 3-mm zone. In addition to becoming flat, corneal topography became more regular [Fig. 5]

Jacob et al.[20] conducted a study in which 24 KCN eyes were included. An allogeneic ring segment called corneal allogeneic intrastromal ring segment was prepared using a two-bladed trephine and implanted into mid-depth femtosecond laser-assisted created channels in the patient's cornea followed by accelerated corneal cross-linking. Mean follow-up was about 12 months and, similar to our study, there was significant improvement in SCDVA, spherical equivalent, and steepest keratometry. Our series did not perform corneal cross-linking to prevent the effect of hyperopic shift caused by corneal cross-linking on the final refractive results on one hand, and to avoid an added risk of corneal infection due to epithelium removal and prolonged operative time, on the other hand. Corneal cross-linking may be performed if there are signs of disease progression during the follow-up period. However, we used crescent shape lenticles in PMD patients for the first time with favorable results



Figure 4: Pre- and postoperative average karatometry of 3-mm central corneal area of individualsD = Diopter

In the study by Jacob et al.,^[20] refractive astigmatism did not change significantly after surgery, while topographic astigmatism showed a significant decrease. However, in our study, neither of the two types of astigmatism showed a significant change. There are possible reasons why SCDVA improved in our patients despite no significant change in the amount of astigmatism. One of the most important reasons is the displacement of the steepest point of the cornea toward the center, as well as a more regular corneal topography. Another reason may be a decrease in third- and fourth-order aberrations due to reduction of myopia and achieving a more regular corneal surface. But unfortunately, no aberrometry was performed pre- or postoperative to prove this theory. Since in patients with corneal ectasia, unlike those with usual refractive errors, the primary goal of surgical intervention is not to obtain spectacle independence, but to restore vision with the help of glasses that are tolerable; in this study, our criterion for effectiveness of the procedure was the improvement in SCDVA.

Biological rings increase corneal thickness at the location of implantation and since they are soft and malleable, concerns are reduced regarding its displacement inside the cornea or damage to adjacent tissues such as Descemet's membrane. This may imply their ability for use corneas of various thicknesses, however, further studies are needed to ascertain this. None of our patients reported symptoms such as glare or halo, which are not uncommon with synthetic ICRSs. This could be because the refractive index of allogeneic segments is the same as that of the recipient cornea, and that the implants are not rigid and unlike synthetic types they have no sharp edge [Fig. 6]. Coincidentally, two of our patients had a synthetic ICRS in the fellow eye and interestingly both of them were more satisfied with the eye receiving allogeneic ring. However, no conclusion can be deduced from these two cases and well-designed randomized studies are needed to compare biological rings with their artificial counterparts.



Figure 5: Preoperative (right raw) and postoperative (left raw) corneal topographies. (a) 320° near-complete ring segment. (b) 270° one ring segment. (c) 160° two-ring segment. (d) Crescent shape segment



Figure 6: Anterior segment optical coherence tomography (AS-OCT) showing the intrastromal allogeneic corneal segments position and demarcation lines. Note that the cross section of these segments becomes square after punching, but after being implanted into the cornea, it is deformed under pressure and the cross-sectional area becomes oval. Corneal epithelium is thinner over the ring area and thicker in the center (white star). Posterior surface of the cornea exhibited more curvature changes than the anterior surface (white arrow)

So far, neither our study nor similar studies have reported any case of corneal stromal rejection against the implanted material. Since we used DSAEK buttons, in the absence of endothelium and epithelium, which are known to be more antigenic, one does not expect other types of corneal graft rejection. Processing of the transplanted corneal tissue with gamma irradiation may further diminish the allogenicity of donor corneal material.^[23]

Biological rings or segments may be procured from remnants of donor corneas already used for lamellar or penetrating keratoplasty, anterior corneal buttons leftover from DSAEK surgery, or even corneal donors unsuitable for optical keratoplasty. Such recycling of donor material residues or corneal tissues that do not meet transplantation requirements can help significantly reduce treatment costs.

Limitations of our study include a small number of subjects, limited follow-up period, and no use of pre- and postoperative aberrometry. While our study and similar ones show that allogeneic intrastromal corneal segments or lenticules may become a promising treatment option for corneal ectasia, there are unanswered questions in this regard. There is yet no clear nomogram to determine the diameter, thickness and number of allogeneic rings required as well as the optical zone and depth of insertion, which makes the results less predictable. It is also technically challenging to prepare and insert these flexible segments within the recipient corneal channel. It requires the use of new and special devices, such as two-bladed trephines in different sizes or shapes, which can punch rings or crescents in different dimensions and/or specially designed pigtails for implantation.

Conclusion

In summary, based on the preliminary results of our study, employing intrastromal corneal allogeneic ring segments for KCN and PMD may be an effective, low-risk, simple, and economic option. Further studies should be conducted employing larger sample size, longer follow-up, and more accurate instruments for better evaluation of this new method. Financial Support and Sponsorship Nil

Conflicts of Interest

There are no conflicts of interest.

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