Outcomes of a Single-Segment Intrastromal Corneal Ring in Early Keratoconus Versus Early Pellucid Marginal Degeneration

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Abstract

Purpose: To determine the effect of a single-segment intrastromal corneal ring segment (ICRS;Intacs-SK) on early keratoconus (KCN) or pellucid marginal degeneration (PMD).

Methods: It is a prospective interventional study. One-hundred-twenty-four eyes (99 patients) with KCN and 36 eyes (26 patients) with PMD at early stage (the maximum keratometric reading less than 55 diopters) were included to ICRS implantation using femtosecond laser at a tertiary university-based hospital and a private outpatient center. The uncorrected distance and spectacle-corrected visual acuity (UDVA and SCDVA), manifest spherical and cylindrical refractions, and keratometry indices were measured preoperatively and postoperatively, 1 week, 2 and 6 months.

Results: One week after surgery, significant improvements were observed in UDVA, SCDVA, cylinder and keratometry readings of both KCN and PMD groups (all $P < 0.05$) with no significant changes afterwards. No significant change occurred in the sphere refraction of PMD group ($P = 0.10$) in contrast to KCN group ($P < 0.001$). Corneal irregularity of KCN group in central 3 and 5 mm zones increased at 1 week (both $P < 0.001$) and then continued to decrease up to 6 months. However, the corneal irregularity of PMD group had significant reduction only at 1 week in 5-mm zone ($P = 0.02$) and 2 months in 3-mm zone ($P = 0.01$) postoperatively. The final efficacy indexes were 1.44 ± 0.71 and 0.87 ± 0.40 in KCN and PMD groups, respectively.

Conclusion: Visual acuity and keratometry values reached stability at 1 week, after one-segment Intacs-SK implantation in KCN and PMD groups. The short-term efficacy of the procedure was more in early KCN compared to early PMD.

Introduction

Keratoconus (KCN) and pellucid marginal degeneration (PMD) are the most common forms of non-inflammatory corneal ectatic disorders in which progressive corneal steepening causes increasing myopia and high irregular astigmatism. The diagnosis of PMD and its distinction from KCN have been an ongoing discussion. For most, this is nothing more than an academic exercise with little clinical significance, because most view these two entities as different points on a clinical continuum [1]. Although the ectasia of both KCN and PMD usually affects the inferior part of the cornea, the corneal protrusion of PMD is located above the area of thinning [2].

Different methods of visual rehabilitation in KCN and PMD, including spectacles, contact lenses and corneal transplantation, have been introduced. Intrastromal corneal ring segment (ICRS) implantation is considered a minimally invasive surgical procedure in the management of KCN and PMD that may defer the need for keratoplasty and restore contact lens tolerance [3].

Different types of intracorneal rings are available in the market that have variable curvatures, widths and zones of implantation. Modern ICRSs are incomplete rings. Intacs (AdditionTechnology, Fremont, California, USA) have a crescent-shaped arc length of 150 degrees and is subdivided into two models: standard Intacs and Intacs-SK [4]. Standard Intacs has external and inner diameters of 8.10 mm and 6.8 mm, respectively with a hexagonal transverse shape. Intacs-SK has an inner diameter of 6.0 mm and two thicknesses with a round cross section to minimize glare [5]. It is positioned closer to the visual axis and central cornea, consequently being more effective than standard Intacs in severe ectatic cases [5].

There are some studies comparing the effects of single-segment and double-segment implantation of Intacs [6–8]. Implantation of single-segment ICRS induces inferior flattening and superior steepening in contrast to double-segment ICRS which flattens the cornea both inferiorly and superiorly. Therefore, single-segment rings result in greater change in inferior-superior ratio and thus, more favorable outcomes compared with double-segment implantation, especially for cases of peripheral keratoconus [9].

To the best of our knowledge, no previous study evaluated the femtosecond-assisted implantation of single segment Intacs-SK besides the common usage of implantation of Intacs-SK in the early keratoconus. Therefore, this study aimed to assess

the femtosecond laser-assisted implantation of single-segment Intrastromal corneal ring (ICRS; Intacs® SK) in eyes with early stages of KCN or PMD.

Methods

This is a prospective interventional study on patients with diagnosis of keratoconus (KCN) or pellucid marginal degeneration (PMD) who underwent femtosecond-assisted single-segment Intacs® SK ICRS (Addition Technology Inc., Sunnyvale, USA) implantation at Rassoul Akram Hospital and Iranian Eye Clinic, Tehran, Iran from 2015 to 2019. The Ethics committee of Iran University of Medical Sciences approved the study (IR.IUMS.1398.544) and informed consent was obtained from all patients and the study adhered to the tenets of Declaration of Helsinki.

Included were patients with clear cornea who did not tolerate contact lens, the maximum keratometric reading less than 55.00 diopters (D), and the corneal thickness more than 450 µm at the incision site, keratoconus of stage I and II according to Amsler–Krumeich classification and mesopic pupil of less than 6.5 mm in diameter. Patients with severe dry eye, corneal scar, severe allergic conjunctivitis, previous ocular surgery, glaucoma, cataract, a history of herpes simplex keratitis, pregnancy, breast-feeding, and use of certain medications, such as Accutane (Isotretinoin, Accutane™ Roche®, Canada) were excluded.

The diagnosis of pellucid marginal corneal degeneration was made on the basis of slit lamp findings (ectasia above the area of maximum thinning in the inferior cornea). The diagnosis was confirmed by corneal topography ('butterfly' keratometry pattern, very steep peripheral inferior cornea, and high keratometric powers radiating from the center to the inferior oblique meridians), and refractive findings (against-the-rule astigmatism with loss of spectacle corrected distance visual acuity (SCDVA). Diagnosis of keratoconus was established by the combination of computed videokeratography for the anterior and posterior corneal surface (Orbscan II; Bausch & Lomb, Rochester, NY), keratometry readings, and corneal pachymetry. All eyes showed an inferior–superior corneal shape index > 1.40 Diopter (from an average of five points at 30 degree intervals located 3 mm from center).

Each study participant underwent a comprehensive ophthalmic evaluation, including subjective refraction, uncorrected Snellen distance visual acuity (UDVA), spectacle corrected Snellen distance visual acuity (SCDVA), IOP measurement with a calibrated Goldmann applanation tonometer and slit-lamp biomicroscopy at preoperative and postoperative visits. Corneal thickness at the incision site was measured using Orbscan pachymetry with Intracalc software. Topographical indices were measured by Orbscan II (Bausch & Lomb, Rochester, New York, USA) which include corneal dioptric power in the flattest meridian for the 3-mm central zone (flat keratometry), corneal dioptric power in the steepest meridian for the 3-mm central zone (steep keratometry), mean corneal power in the 3-mm central zone (mean keratometry), Simulated keratometric astigmatism (Sim-K), irregularity in the 3 and 5 mm zones, anterior chamber depth, anterior best fit sphere (BFS) and posterior BFS, preoperatively and 1 week, 2 and 6 months postoperatively. Furthermore, the efficacy index was defined as the ratio of the postoperative UDVA to the preoperative SCDVA. Safety index was calculated as the ratio of the postoperative SCDVA to the preoperative SCDVA. Visual acuities changed to Snellen in order to calculate safety and efficacy ratios.

Surgical Technique: All surgical procedures were performed by the first author (SJH) under topical anesthesia using 0.5 tetracaine eye drop (Anestocaine; Sina Darou, Tehran, Iran). Prep and drape were done by povidone iodine (BacterBye 10% povidone iodine; Kishmedipharma, Kish, Iran) after blepharostat placement and followed by conjunctival sac irrigation using normal saline. Intacs SK segment implantation was performed using a femtosecond laser LDV Z6 (Ziemer Ophthalmic Systems, Port, Switzerland). All intrastromal rings that were used in this study had 150-degree arcs and the thickness of the ring was selected on the basis of either corneal thickness at the incision site, distant corrected visual acuity, sphere, spherical equivalent, astigmatic power, location of the cone, manufacture nomogram and the surgeon's experience. Patients were placed under the laser system, and the femtosecond suction ring was centered at the pupil center. Suction was applied and the femtosecond laser was used to create a channel at the selected corneal depth (75% of the corneal thickness at the incision site), with an inner diameter of 6.0 mm and an outer diameter of 7.2 mm. The femtosecond laser was also used to

create an incision to insert the Intacs SK segment, preferably on the steepest axis. If the patient's SCDVA was better than 0.5 logarithm of the minimum angle resolution (LogMar), the axis of manifest refraction was used for this purpose. Under microscopic guidance, the Intacs SK segments were implanted inside the channels using forceps and Sinsky hooks placed through dialing holes at the ends of the segment, which was centered in the middle of its tunnel, equidistant from the incision. The incision site was not sutured. Postoperatively, a bandage contact lens (AIR optix AQUA; Base Curve: 8.6, Diameter: 14.2; CIBA VISION) was fitted for 24 hours. Levofloxacin eye drop was administered four times a day for one week. Betamethasone eye drop (Betasonit %0.1, betamethasone disodium phosphate; Sina Darou, Tehran, Iran) was given every 12 hours for 3 weeks, and artificial tears (Artelac™, Hypromellose; Bausch and Lomb, Montpellier, France) were administered every 4 hours for 4 weeks.

Statistical Analysis

Statistical analyses were performed with SPSS for Windows software version 22.0 (SPSS Inc., Chicago IL, USA). Quantitative data were described with means (standard deviation) and percentage in continuous and numerical data respectively. Snellen visual acuity was converted into logarithm of the minimum angle of resolution [LogMAR] for statistical analysis. Shapiro-Wilk test was used to assess whether variables had a normal distribution. Independent student *t*-test and Mann-Whitney U test were performed for parametric and non-parametric data respectively, to compare the preoperative values between KCN and PMD groups. Mixed model analysis was used to account for the inclusion of both eyes from some of the patients, which was performed to evaluate the changes of the main outcome measures including visual acuity, refraction and topographic indices after Intacs-SK implantation. P values less than 0.05 were considered statistically significant.

Results

One hundred-sixty eyes of 125 patients with mean age of 31.15 ± 7.81 years (range = 19–67) were enrolled. According to the Amsler–Krumeich classification, four-fifths of subjects (79.2%, 99/125 patients or 77.5%, 124/160 eyes) were assembled in early keratoconus (KCN) groups, including 77/124 eyes (62.1%) as stage 1 and 47/124 eyes (37.9%) as stage 2. One-fifth of (20.8%, 26/126 patients or 22.5%, 36/160 eyes) patients had pellucid marginal degeneration (PMD). Table 1 shows the baseline features of patients. The PMD and KCN groups did not differ in terms of sex, corneal thickness, ring thickness, incision axis, and depth of insertion while PMD group was significantly older than KCN group ($P = 0.01$) (Table 1).

Table 1
Baseline characteristics of 160 eyes from 125 patients with early keratoconus (KCN) or pellucid marginal degeneration (PMD) underwent single segment Intacs-SK implementation.

Variables	KCN Patient = 99 Eye = 124	PMD Patient = 26 Eye = 36	p-Value
Age	30.49 ± 65.66	34.38 ± 7.99	0.01 ^{a*}
Sex (female %)	32.3% (32/99)	30.8% (8/26)	0.88 ^b
Corneal thickness	537.66 ± 38.39	531.60 ± 36.98	0.46 ^c
Ring thickness	428.63 ± 36.74	432.86 ± 26.96	0.37 ^a
Depth of insertion	402.38 ± 21.24	399.29 ± 17.66	0.53 ^a
a: Mann-Whitney U test, b: Chi-Square test, c: Mixed model analysis, *: statistically significant			

Intacs-SK ring segment with 450μ thickness were implanted in 66.3% (104/160) of eyes, 400μ thickness in 23.8% (38/160) of eyes, 350μ thickness in 7.5% (12/160) of eyes and 300μ in 2.5% (4/160) of eyes.

Visual values and refraction

The mean preoperative visual acuities were not different between KCN and PMD groups (P for UDVA = 0.07, P for SCDVA = 0.21). Visual acuity results at the preoperative and postoperative examinations are summarized in Table 2. The mean UDVA of KCN group showed statistically significant improvement, from 0.77 ± 0.21 logMAR preoperatively to 0.46 ± 0.23 at the first postoperative week ($P < 0.001$) which continued to increase to 0.42 ± 0.22 ($P = 0.01$) logMar at month 2 while they remained stable at month 6 ($P = 0.62$). The mean preoperative SCDVA of KCN group was 0.47 ± 0.17 logMar that increased to 0.26 ± 0.15 logMar at week 1 ($P < 0.001$) and 0.21 ± 0.14 logMar at month 2 ($P < 0.001$). The changes between months 2 and 6 of the SCDVA in KCN group were not significant ($P > 0.99$). Similarly, preoperative UDVA and SCDVA of PMD group increased significantly at the first week, from 0.85 ± 0.17 logMar to 0.46 ± 0.29 logMar ($P < 0.001$) and from 0.42 ± 0.23 logMar to 0.24 ± 0.22 logMar ($P = 0.002$), respectively. The visual acuities of PMD group did not experience further improvement at 2 and 6 months after surgery (Table 2).

Table 2

Visual acuity and refractive indices in 124 eyes of 99 patients with keratoconus (KCN) and 36 eyes of 26 patients with pellucid marginal degeneration (PMD) underwent single segment Intacs-SK implementation.

Variables		Preoperative <i>Mean ± SD</i>	1 week <i>Mean ± SD</i>	2 months <i>Mean ± SD</i>	6 months <i>Mean ± SD</i>	Total p-value <i>b</i>	1 week vs. preop p-value <i>a</i>	2 months vs. 1 week p-value <i>a</i>	6 months vs. 2 months p-value <i>a</i>	6 months vs. preop p-value <i>a</i>
UDVA (LogMar)	KCN	0.77 ± 0.21	0.46 ± 0.23	0.42 ± 0.22	0.39 ± 0.20	< 0.001*	< 0.001*	0.01*	0.62	< 0.001*
	PMD	0.85 ± 0.17	0.46 ± 0.29	0.44 ± 0.26	0.42 ± 0.25	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
SCDVA (LogMar)	KCN	0.47 ± 0.17	0.26 ± 0.15	0.21 ± 0.14	0.19 ± 0.14	< 0.001*	< 0.001*	< 0.001*	> 0.99	< 0.001*
	PMD	0.42 ± 0.23	0.24 ± 0.22	0.21 ± 0.19	0.16 ± 0.17	0.001*	0.002*	> 0.99	> 0.99	0.001*
Spherical Equivalent (D)	KCN	-4.22 ± 2.99	-2.47 ± 2.76	-2.30 ± 2.65	-2.31 ± 2.73	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
	PMD	-2.96 ± 2.06	-1.37 ± 1.71	-1.27 ± 1.52	-0.99 ± 1.23	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
Sphere (D)	KCN	-2.34 ± 2.88	-1.19 ± 2.70	-1.06 ± 2.59	-0.98 ± 2.53	< 0.001*	< 0.001*	> 0.99	> 0.99	0.009*
	PMD	-0.72 ± 1.93	-0.13 ± 1.86	0.13 ± 1.55	0.25 ± 1.42	0.10	0.52	> 0.99	> 0.99	0.20
Cylinder (D)	KCN	-3.76 ± 1.61	-2.55 ± 1.63	-2.49 ± 1.62	-2.65 ± 1.47	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
	PMD	-4.47 ± 1.69	-2.47 ± 1.62	-2.79 ± 1.69	-2.47 ± 1.18	< 0.001*	< 0.001*	0.64	> 0.99	< 0.001*
Efficacy index	KCN	-	1.15 ± 0.57	1.27 ± 0.63	1.44 ± 0.71	-	-	-	-	-
	PMD	-	0.93 ± 0.39	1.01 ± 0.38	0.87 ± 0.40	-	-	-	-	-
Safety index	KCN	-	1.73 ± 0.73	1.95 ± 0.75	2.15 ± 0.83	-	-	-	-	-
	PMD	-	1.55 ± 0.60	1.70 ± 0.64	1.52 ± 0.45	-	-	-	-	-
a: Estimated marginal means by Mixed model linear analysis with Bonferroni correction for comparing with previous time point; b: Mixed model linear analysis; UDVA: uncorrected distance visual acuity; SCDVA: spectacle corrected distance visual acuity; LogMar: logarithm of the minimum angle of resolution; D: diopter; SD: Standard deviation, *: statistically significant										

Patients with PMD had statistically significant more cylinder ($P = 0.007$) and less myopia ($P = 0.007$) compared to patients with KCN, preoperatively while both groups were similar in terms of postoperative pattern of refractive changes (Table 2). In the KCN group, there were significant reductions in the spherical equivalent from -4.22 ± 2.99 D to -2.47 ± 2.76 ($P < 0.001$) D, spherical refraction from -2.34 ± 2.88 D to -1.19 ± 2.70 D ($P < 0.001$) and cylindrical refraction from -3.76 ± 1.61 D to -2.55 ± 1.63 D ($P < 0.001$).

1.63 ($P < 0.001$) D at the first week. The changes were not statistically significant at months 2 and 6 (Table 2). Likewise, the spherical equivalent of -2.96 ± 2.06 D and cylindrical refraction of -4.47 ± 1.69 D decreased to -1.37 ± 1.71 D ($P < 0.001$) and -2.47 ± 1.62 D ($P < 0.001$), respectively, after 1 week in PMD group while they remained stable at months 2 and 6 (Table 2). Spherical refraction of PMD group did not have a statistically significant change after surgery ($P = 0.10$).

Efficacy and safety

The efficacy index after 6 months was 1.44 ± 0.71 in KCN group and 0.87 ± 0.40 in PMD group, proposing that Intacs-SK alone achieved 144% of baseline SCDVA of KCN group and 87% of PMD group. The safety index was 2.15 ± 0.83 in KCN group and 1.52 ± 0.45 in PMD group after 6 months indicating 115% and 52% increase in visual acuity in KCN and PMD groups, respectively. The UDVA increased one line and more (up to 8 lines) in 95% (152/160) of eyes, remained at the preoperative level in 4.4% (7/160) of eyes (of these, five were grade 2 and two of them were in PMD group), and decreased 1 line in 0.6% (1/160) of eyes (which was KCN of the grade 2). Furthermore, the SCDVA increased one line and more (up to 6 lines) in 94.38% (151/160) of eyes, remained at the preoperative level in 4.4% (7/160) of eyes (three and two of them belonged to KCN grade 1 and 2 respectively and two eyes in PMD group). The SCDVA decreased 1 line in one eye (1/160, 0.6%) and 2 lines in another one (1/160, 0.6%), which belonged to PMD groups.

Topographic parameters

Topographic results are presented in Table 3. The changes of all tomographic parameters were statistically significant between preoperative values and post-operative measurements in both groups. The steep keratometry, flat keratometry, mean keratometry, posterior Best-Fit-Sphere (BFS), simulated keratometry (sim-k), and anterior chamber depth (ACD) decreased significantly after surgery and reached stability at postoperative week 1, in both KCN and PMD groups (Table 3). These parameters were not different between KCN and PMD groups, preoperatively ($0.11 \leq P \leq 0.88$) except flat ($P < 0.001$) and mean ($P = 0.008$) keratometry, which were statistically far steeper in KCN group than PMD group. Likewise, the preoperative anterior BFS of KCN and PMD groups was also similar to each other ($P = 0.23$). Although anterior BFS of KCN group decreased significantly from 43.96 ± 1.45 D to 42.86 ± 1.42 D after 1 week ($P < 0.001$), it rose again to 43.03 ± 1.41 at month 2 ($P = 0.001$) and then remained stable at month 6 ($P = 0.38$) (Table 3). On the other hand, anterior BFS of PMD group decreased from 48.57 ± 2.60 D to 45.89 ± 2.47 D after 1 week ($P < 0.001$) which remained stable at 2 and 6 months ($P > 0.99$) (Table 3).

Table 3

Topographic parameters in 124 eyes of 99 patients with keratoconus (KCN) and 36 eyes of 26 patients with pellucid marginal degeneration (PMD) underwent Intacs-SK implementation.

Variables		Preoperative <i>Mean ± SD</i>	1 week <i>Mean ± SD</i>	2 months <i>Mean ± SD</i>	6 months <i>Mean ± SD</i>	Total p-value <i>b</i>	1 week vs. preop p-value <i>a</i>	2 months vs. 1 week p-value <i>a</i>	6 months vs. 2 months p-value <i>a</i>	6 months vs. preop p-value <i>a</i>
Steep keratometry (D)	KCN	49.65 ± 3.14	46.97 ± 2.73	47.06 ± 2.80	47.32 ± 2.85	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
	PMD	48.57 ± 2.60	45.89 ± 2.47	46.19 ± 2.33	46.18 ± 1.62	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
Flat keratometry (D)	KCN	45.32 ± 2.74	44.14 ± 2.71	44.08 ± 2.57	44.25 ± 2.69	< 0.001*	0.001*	> 0.99	0.93	< 0.001*
	PMD	43.38 ± 2.22	43.02 ± 2.12	42.87 ± 2.15	43.35 ± 1.75	0.001*	0.004*	> 0.99	> 0.99	0.17
Mean keratometry (D)	KCN	47.48 ± 2.83	45.56 ± 2.61	45.57 ± 2.58	45.78 ± 2.69	< 0.001*	< 0.001*	> 0.99	0.90	< 0.001*
	PMD	46.06 ± 2.14	44.45 ± 2.07	44.53 ± 1.99	44.77 ± 1.53	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
Anterior BFS (D)	KCN	43.96 ± 1.45	42.86 ± 1.42	43.03 ± 1.41	43.25 ± 1.43	< 0.001*	< 0.001*	0.001*	0.38	< 0.001*
	PMD	48.57 ± 2.60	45.89 ± 2.47	46.19 ± 2.33	46.18 ± 1.62	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
Posterior BFS (D)	KCN	54.56 ± 2.27	53.09 ± 2.23	53.27 ± 2.20	53.39 ± 2.16	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
	PMD	53.94 ± 2.24	52.25 ± 2.08	52.79 ± 2.25	53.27 ± 2.16	< 0.001*	< 0.001*	0.08	> 0.99	0.001*
Sim-K (D)	KCN	-4.33 ± 1.61	-2.83 ± 1.57	-3.02 ± 1.42	-3.07 ± 1.30	< 0.001*	< 0.001*	0.13	> 0.99	< 0.001*
	PMD	-5.01 ± 2.27	-2.88 ± 2.02	-3.31 ± 2.06	-2.82 ± 1.42	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
Irregularity in central 3 mm	KCN	4.97 ± 1.68	4.81 ± 1.46	4.36 ± 1.36	4.21 ± 1.44	< 0.001*	> 0.99	< 0.001*	0.04*	< 0.001*
	PMD	4.43 ± 1.94	4.08 ± 1.30	3.79 ± 1.43	3.07 ± 0.83	0.003*	0.86	0.01*	> 0.99	0.009*
Irregularity in central 5 mm	KCN	5.11 ± 1.53	6.02 ± 1.42	5.38 ± 1.34	5.05 ± 1.29	< 0.001*	< 0.001*	< 0.001*	0.02*	> 0.99
	PMD	5.77 ± 5.38	5.95 ± 1.87	5.37 ± 1.70	4.99 ± 1.61	0.01*	0.02*	0.40	> 0.99	0.26

a: Estimated marginal means by Mixed model linear analysis with Bonferroni correction for comparing with previous time point; b: Mixed model linear analysis; D: diopter; SD: Standard deviation; Sim-K: simulated keratometric astigmatism; K: keratometry; BFS: best fit sphere, *: statistically significant

Variables		Preoperative <i>Mean ± SD</i>	1 week <i>Mean ± SD</i>	2 months <i>Mean ± SD</i>	6 months <i>Mean ± SD</i>	Total p-value <i>b</i>	1 week vs. preop p-value <i>a</i>	2 months vs. 1 week p-value <i>a</i>	6 months vs. 2 months p-value <i>a</i>	6 months vs. preop p-value <i>a</i>
Anterior chamber depth (mm)	KCN	3.21 ± 0.31	3.09 ± 0.32	3.11 ± 0.32	3.11 ± 0.32	< 0.001*	< 0.001*	> 0.99	> 0.99	< 0.001*
	PMD	3.20 ± 0.41	3.16 ± 0.43	3.15 ± 0.42	3.03 ± 0.75	< 0.001*	< 0.001*	0.08	> 0.99	0.003*
a: Estimated marginal means by Mixed model linear analysis with Bonferroni correction for comparing with previous time point; b: Mixed model linear analysis; D: diopter; SD: Standard deviation; Sim-K: simulated keratometric astigmatism; K: keratometry; BFS: best fit sphere, *: statistically significant										

The preoperative corneal irregularity of KCN and PMD groups in central 3 mm (P = 0.19) and 5 mm (P = 0.74) zones were not statistically significantly different. Although the corneal irregularity of PMD group had a trend of reduction up to months 6 after surgery in 3 mm zone, the changes were statistically significant only between week 1 and month 2 (decrease = 0.42 ± 0.58 , P = 0.01). The irregularity had a statistically significantly transient increase at week 1 in 5 mm zone (increase = 0.27 ± 6.36 , P = 0.02) and then decreased (Table 3). The corneal irregularity of 5 mm zone at month 6 was not statistically different from preoperative values in PMD group (P = 0.26) in contrast to 3 mm zone (P = 0.009) at month 6. The overall pattern of corneal irregularity of KCN group after Intacs-SK implantation was similar to PMD group, although this parameter was not stabilized at month 6 after surgery at both 3 and 5 mm zones and the reduction of irregularity between months 3 and 6 was statistically significant in KCN group (Table 3).

Adverse events and complication

No surgical complications, such as anterior chamber perforation, extrusion, migration, or visualization around the incision or the tunnels occurred. In addition, neither corneal ulcers nor stromal necrosis superficial to the segment were observed.

Discussion

In this study we assessed the outcomes of femtosecond laser-assisted single-segment Intacs-SK implantation in early stages of keratoconus and pellucid marginal degeneration. The current study showed that implantation of single-segment Intacs-SK could significantly improve the uncorrected and corrected visual acuity of eyes with mild KCN and PMD by decreasing the cylindrical refraction and keratometry (mean, steep and flat) values 1 week after surgery that remained stable afterward. The reduction of spherical refraction was significant only in eyes with keratoconus. Furthermore, the corneal irregularity at central 3 mm and 5 mm had a trend of increase at 1 week postoperatively, and then re-decrease up to months 6. The current study showed that the single-segment Intacs-SK was safer and more efficacious in early KCN than early PMD although this procedure had acceptable safety and efficacy indices in both groups.

The ICRSs are polymethylmethacrylate segments that generate an immediate response by interrupting the biomechanical cycle of the disease progression. The ICRSs act as a spacer in corneal lamella, induce an arc-shortening effect and decrease the steepness of the curvature of the central cornea by creating a second limbus of smaller diameter in the middle of the cornea [10]. It minimizes the sphero-cylindrical error and flattens the topographic analysis with a subsequent improvement of the visual acuities. The main advantages of ICRS are safety, stability, and individualized treatment of ectatic cornea depending on ring thickness, diameter, and centration [7, 11]. Additionally, the ICRS implantation is reversible and with its removal the topographic and refractive values return to its preoperative state makes dealing with complication less dreadful [10].

Previous studies demonstrated that Intacs implantation with femtosecond laser was an effective method in the management of patients with either keratoconus or pellucid marginal degeneration to reduce the SE refractive error and consequently improve the uncorrected and spectacle corrected visual acuities although some studies reported regression in the long term following short-term improvement [12, 13]. Change of refractive and visual outcomes over time after ICRS implantation has rarely been reported [11, 14]. All of them reported immediate improvement of visual and refractive outcome remaining unchanged in short period [11, 14]. Our results showed similar trend in which immediate significant improvement of visual acuity, refraction and keratometry values at first week followed by plateau status in both PMD and KCN groups.

The comparison of effects of single-segment and double-segment implantation of Intacs have been explored in some studies [6–8, 15]. Abad et al. [16] showed that the implantation of 150-degree single-segment Intacs-SK could decrease the steepness of the cornea as much the asymmetric double-segment Intacs-SK implantation did. The impact of single segment implantation on ectatic cornea may return to the asymmetric changes in such patients, which usually happens in the inferior part of the cornea. Implantation of single-segment ICRS accompanies with less corneal trauma which decreases the risk of infection, segment extrusion, glare, and halos. Our results were in agreement with Amanzadeh's [17] prospective case series of keratoconic eyes. Despite the fact that they used single-segment conventional Intacs in their study, the results of visual outcome of our study with Intacs-SK is comparable to those results. Fahd et al. [18] evaluated the efficacy and safety of a single-segment Intacs-SK in 30 eyes with moderate to severe keratoconus up to 6 months. Although, they reported significant improvement of visual and refractive outcomes after 1 month, no significant change was observed afterward [18]. Fahd and association [19] calculated corneal irregularity based on the topography differences between apex and steepest point to implement single-segment Intacs-SK and proposed the development of a topographically driven nomogram rather than a primarily refraction-based nomogram for single-segment rings implementation [19]. The effect of single-segment Intacs-SK on flattening of the steepest keratometry was more pronounced the larger the initial difference of keratometry of apex and steepest points and the larger the preoperative steepest keratometry [19]. This can explain the subtle discrepancies between our study and others' in terms of the amount of postoperative refractive and visual changes. Hence, customizing the ring segment size based on these measures might be a better option than relying purely on the preoperative manifest refraction [19]. Single-segment rings also maximize the reduction in lower-order astigmatism and corneal coma-like aberrations [19, 20].

The ICRS implantation is also effective and safe for patients with PMD [20–23]. Some case studies have explored the use of Intacs in PMD patients and the results have been promising [21–23]. Ertan et al. [21] assessed the 6-month outcomes of two-segment Intacs using femtosecond laser in 9 eyes with PMD. In this study, there was statistically significant improvement in UDVA, SCDVA, keratometry readings and cylindrical refractions [21]. However, no significant decrease was observed in spheric refraction [21]. More favorable outcomes were reported by one-segment 210 degree keraring and Myoring in patients with PMD that probably due to extended arc length and higher arc-shortening effect [14, 20]. Jabbarvand et al. [14] proposed that Myoring could be used in more advanced cases with higher myopia. Kubaloglu et al. [20] reported the mean reduction of 1 logMar of UDVA, 0.5 logMar of SCDVA, 2.5 diopter of steep keratometry and 2 diopter cylindrical refraction in 16 eyes with PMD, 3 years after single-segment 210-degree arc length Keraring implantation. However, they did not evaluate the early postoperative results earlier before 1 year [20]. Single-segment ICRS provide a localized flattening in a wide field of steep area and steepening in the superior cornea, instead of flattening seen with the implantation of double segments. Therefore, single segment ICRS induces a more regular optical zone and a greater improvement in SCDVA. Our results with single-segment Intacs are comparable with those by Kubaloglu et al. [20] with single-segment Keraring in terms of reduction of steep keratometry and cylindrical refraction although the decrease of flat keratometry and spherical refraction were much higher than our study. Moreover, our results were in agreement with Jabbarvand's study [14] in which no significant change was observed 1 month after surgery.

The effect of ICRS on visual, refractive and topographic outcomes depends on the severity of corneal ectasia. However, there continues to be controversy over which stage of KCN and PMD has the best outcomes after the ICRS. The contradictory results may be explained by fundamental differences including the type of ICRS used, the technique of tunnel creation and

the nomograms for ring selection. Some studies reported that in patients with more pronounced keratoconus, the mean reduction in keratometric values after Intacs or Keraring was higher compared with the mean reduction in patients with early stages [24, 25]. Boxer Wachler et al. [26] observed a greater reduction in spherical equivalent in those with more advanced keratoconus following Intacs implantation. It contradicts Ertan's study, in which higher stage of the KCN was associated with less improvement of uncorrected visual acuity despite flatter postoperative keratometry after Intacs implantation using femtosecond [25]. Different stages were similar in terms of change in corrected visual acuity, manifest spherical refraction, or manifest cylindrical refraction [25]. In the stage II group, the mean UCVA (1.15 to 0.63) and BCVA (0.48 to 0.28) improved significantly from preoperatively to postoperatively [25]. The mean preoperative spherical refraction (-5.94 to -3.29), cylindrical (-3.98 to -2.31) refraction, and mean K (50.26 to 47.49) values were statistically significantly lower postoperatively [25]. Similarly, Wild et al. [27] found out that patients with mild keratoconus are more likely to have a favorable outcome following Keraring implantation while the changes were more prominent in advanced groups. In the mild KCN group with maximum keratometry less than 48 D, the increase of SCDVA was 0.16 logMar while the sphere, cylinder and maximum keratometry decreased nearly 2 D [27]. They mentioned that patients with severe keratoconus failed to achieve significance in sphere or cylinder [27].

This article has several potential limitations including the small sample of eyes with pellucid marginal degeneration, the relatively short period of follow-up, the lack of analysis of corneal aberrations. Moreover, absence of data regarding contrast sensitivity, contact lens intolerance, or qualitative outcomes can be other reservations in concluding sufficient results.

In conclusion, the implantation of single-segment Intacs-SK using femtosecond laser is safe and effective to address early stages of keratoconus and pellucid marginal degeneration with significant improvement in UDVA, SCDVA and topography profile of corneal.

Declarations

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Ethics approval: Approval was obtained from the ethics committee of Iran University of Medical Sciences approved the study (IR.IUMS.1398.544). The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

Consent to participate: Informed consent was obtained from all individual participants included in the study.

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Authors' contributions: Conceptualization: Leila Ghisian, Ali Hadavandkhani, Hosein Aghaei, Leila Ghiasian; Methodology: Leila Ghisian, Parya Abdolalizadeh, Fatemeh Nadjafi Semnani, Mohammad Ebrahim Jafari; Formal analysis and investigation: Parya Abdolalizadeh, Fatemeh Nadjafi Semnani, Mohammad Ebrahim Jafari; Writing - original draft preparation: Parya Abdolalizadeh, Fatemeh Nadjafi Semnani, Seyed Mahyar Hashemian, Mahsa Sadat Hashemian; Writing - review and editing: Leila Ghiasian, Ali Hadavandkhani, Seyed Javad Hashemian, Parya Abdolalizadeh, Hosein Aghaei; Funding acquisition: Seyed Javad Hashemian; Resources: Seyed Javad Hashemian, Leila Ghiasian, Hosein Aghaei, Ali Hadavandkhani; Supervision: Seyed Javad Hashemian; All authors read and approved the final manuscript.

References

1. -Belin MW, Khachikian SS, Ambrosio R Jr (2011) The use of intracorneal rings for pellucid marginal degeneration. *Am J Ophthalmol* 151(3):558–559; author reply 559

2. -Sridhar MS, Mahesh S, Bansal AK, Nutheti R, Rao GN (2004) Pellucid marginal corneal degeneration. *Ophthalmology* 111(6):1102–1107
3. -Mounir A, Radwan G, Farouk MM, Mostafa EM (2018) Femtosecond-assisted intracorneal ring segment complications in keratoconus: from novelty to expertise. *Clinic Ophthalmol* 12:957–964
4. -Saib N, Bonnel S, Fenolland JR, Abrieu M, Rambaud C, Berguiga M, Froussart-Maille F, Rigal-Sastourne JC (2015) Intrastromal corneal rings and corneal collagen crosslinking for progressive keratoconus: comparison of two sequences. *Eye (Lond)* 29(2):294–295
5. -Kymionis GD, Bouzoukis DI, Portaliou DM, Pallikaris IG (2010) New INTACS SK implantation in patients with post-laser in situ keratomileusis corneal ectasia. *Cornea* 29(2):214–216
6. -Pinero DP, Alio JL, El Kady B, Coskunseven E, Morbelli H, Uceda-Montanes A, Maldonado MJ, Cuevas D, Pascual I (2009) Refractive and aberrometric outcomes of intracorneal ring segments for keratoconus: mechanical versus femtosecond-assisted procedures. *Ophthalmology* 116(9):1675–1687
7. -Alio JL, Artola A, Hassanein A, Haroun H, Galal A (2005) One or 2 Intacs segments for the correction of keratoconus. *J Cataract Refract Surg* 31(5):943–953
8. -Chan CC, Sharma M, Wachler BS (2007) Effect of inferior–segment Intacs with and without C3–R on keratoconus. *J Cataract Refract Surg* 33:75–80
9. -Sharma M, Boxer Wachler BS (2006) Comparison of single–segment and double–segment Intacs for keratoconus and post–LASIK ectasia. *Am J Ophthalmol* 141:891–895
10. -Alio JL, Artola A, Ruiz-Moreno JM, Hassanein A, Galal A, Awadalla MA (2004) Changes in keratoconic corneas after intracorneal ring segment explantation and reimplantation. *Ophthalmology* 111(4):747–751
11. -Daxer A (2010) Adjustable intracorneal ring in a lamellar pocket for keratoconus. *J Refract Surg* 26(3):217–221
12. -Bedi R, Touboul D, Pinsard L, Colin J (2012) Refractive and topographic stability of Intacs in eyes with progressive keratoconus: five-year follow-up. *J Refract Surg* 28(6):392–396
13. -Shetty R, Kurian M, Anand D, Mhaske P, Narayana KM, Shetty BK (2008) Intacs in advanced keratoconus. *Cornea* 27(9):1022–1029
14. -Jabbarvand M, Hashemian H, Khodaparast M, Bazvand F, Beheshtnejad A (2015) Outcome of complete intrastromal ring implantation using femtosecond laser in pellucid marginal degeneration. *Eye* 29:783–790
15. -Hashemian SJ, Farshchian N, ForoutamJazi A, Jafari ME, Hashemian MS, Hashemian SM (2018) Visual and refractive outcomes and tomographic changes after femtosecond laserassisted intrastromal corneal ring segment implantation in patients with keratoconus. *J Ophthalmic Vis Res* 13:376–382
16. -Abad JC, Arango J, Tobon C (2011) Comparison of astigmatism correction using shorter arc length 90 degrees /120 degrees asymmetric intacs severe keratoconus versus 150 degrees single-segment intacs severe keratoconus in asymmetric keratoconus. *Cornea* 30(11):1201–1206
17. -Amanzadeh K, Elham R, Jafarzadehpur E (2017) Effects of single-segment Intacs implantation on visual acuity and corneal topographic indices of keratoconus. *J Curr Ophthalmol* 29(3):189–183
18. -Fahd DC, Alameddine RM, Nasser M, Awwad ST (2015) Refractive and topographic effects of single-segment intrastromal corneal ring segments in eyes with moderate to severe keratoconus and inferior cones. *J Cataract Refract Surg* 41(7):1434–1440
19. -Fahd DC, Jabbur NS, Awwad ST (2012) Intrastromal corneal ring segment SK for moderate to severe keratoconus: A case series. *J Refract Surg* 2012;28:701-5
20. -Kubaloglu A, Sari ES, Cinar Y, Koytak A, Kurnaz E, Piñero DP, Ozerturk Y (2010) A single 210-degree arc length intrastromal corneal ring implantation for the management of pellucid marginal corneal degeneration. *Am J Ophthalmol* 150(2):185–192

21. -Ertan A, Bahadır M (2006) Intrastromal ring segment insertion using a femtosecond laser to correct pellucid marginal corneal degeneration. *J Cataract Refract Surg* 32:1710–1716
22. -Pinero DP, Alio JL, Morbelli H, Uceda-Montanes A, El Kady B, Coskunseven E, Pascual I (2009) Refractive and corneal aberrometric changes after intracorneal ring implantation in corneas with pellucid marginal degeneration. *Ophthalmology* 116(9):1656–1664
23. -Kymionis GD, Aslanides IM, Siganos CS, Pallikaris IG (2004) Intacs for early pellucid marginal degeneration. *J Cataract Refract Surg* 30(1):230–233
24. -Coskunseven E, Kymionis GD, Tsiklis NS, Atun S, Arslan E, Jankov MR, Pallikaris IG (2008) One-year results of intrastromal corneal ring segment implantation (Keraring) using femtosecond laser in patients with keratoconus. *Am J Ophthalmol* 145(5):40–45
25. -Ertan A, Kamburoglu G (2008) Intacs implantation using femtosecond laser for management of keratoconus: comparison of 306 cases in different stages. *J Cataract Refract Surg* 34(9):1521–1526
26. -Boxer Wachler BS, Christie JP, Chandra NS, Chou B, Korn T, Nepomuceno R (2003) Intacs for keratoconus. *Ophthalmology* 110:1031–1041
27. -Wild CL, Naylor SG, Varga Z, Morrell A, Ball JL (2017) Keraring implantation using the Zeiss Visumax femtosecond laser in the management of patients with keratoconus. *Eye* 31:916–923