· Clinical Research ·

Evaluation of a new nomogram for Ferrara ring segment implantation in keratoconus

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Abstract
● **AIM:** To evaluate the short-term clinical outcomes of Ferrara rings in keratoconus using an optimized nomogram developed after several years of research and retrospective analysis of clinical data.

● **METHODS:** This prospective longitudinal non-comparative clinical trial evaluated 88 eyes of 88 patients (age 18-62y) with keratoconus diagnosis from two Spanish centers. Ferrara ring segment (AJL Ophthalmic) implantation was performed in all cases, using the mechanical procedure in 25 eyes (28.4%) and a femtosecond laser-assisted procedure in 63 eyes (71.6%). The ring segments implanted in each case were selected using a new optimized nomogram that considered variables such as anterior corneal asphericity and astigmatism or the discrepancy among astigmatism and coma orientations. Visual, refractive, corneal topographic, aberrometric, and pachymetric changes after surgery were evaluated during a 3-month follow-up.

● **RESULTS:** The implants induced a significant refractive change as well as an improvement in uncorrected (UDVA) and corrected distance visual acuity (CDVA; $P<0.001$). Postoperative CDVA of 0.10 logMAR or better was achieved in 28.4% and 46.5% of eyes, respectively. Two eyes (2.3%) lost two or more lines of CDVA whereas a total of 53.5% of eyes gained lines of CDVA. A significant central anterior and posterior corneal flattening was induced ($P\leq0.003$), with a significant reduction of anterior ($P<0.001$) and posterior corneal astigmatisms ($P=0.048$), and a change in anterior asphericity ($P<0.001$). Total primary coma (6 mm pupil) change was also statistically significant (preoperative 3.66±3.04 µm *vs* postoperative 2.33±2.26 µm, $P<0.001$). No significant differences were found in the effect of ring segments between cases implanted using the mechanical and femtosecond techniques ($P\geq0.101$).

● **CONCLUSION:** The implantation of Ferrara rings based on the nomogram evaluated is safe and effective for promoting a visual rehabilitation in keratoconus, with a relevant control of primary coma aberration.

● **KEYWORDS:** intracorneal ring segment; Ferrara ring segment; femtosecond; keratoconus; coma aberration
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INTRODUCTION

Keratoconus is a corneal ectatic disorder that results in progressive thinning of the cornea, increase of corneal irregularity and consequently poor visual quality leading to a reduction of the quality of life[1]. The debut of this condition in pediatric population is usually in a moderate to advanced stage, particularly in female patients[1]. Concerning the management of keratoconus, corneal collagen crosslinking (CXL) is an effective option to control its progression, with an increased risk of evolution of the disease associated to a higher economic burden if this surgical option is delayed when signs of progression are evident[2]. Intracorneal ring segments (ICRS) have been also investigated during many years as a therapeutic option for the management of keratoconus and other corneal ectatic diseases[3-6]. ICRS implantation in keratoconus significantly reduces the level of corneal high order aberrations and irregularity, leading to an improvement in visual quality[3-6]. However, there is also a great variability between studies, with some of them showing discrepant findings[3-6]. One of the main factors accounting for this variability is that most of studies are not controlled or have non-consistent designs, with no randomized comparative clinical trials performed to this date[3]. Another important factor also accounting for the variability among studies, even using the same type of ring segments, is the great variability in the nomogram or implantation criteria used. Many attempts have been done by means of simulation models of predicting the potential effect of ICRS, leading to some trends that have been found to be consistent with clinical data, such as the influence of ring thickness and diameter on the level of central flattening induced as well as the influence of the depth of implantation[7-9]. However, many of the nomograms that are being used in last years are based on empirical data or personal approximations or experiences[10-11]. There is currently a need for the development of new optimized nomograms overcoming the limitation of previous experiences and leading to higher levels of predictability. It should be considered that although ICRS implantation is safe, suboptimal results are still present in some cases, requiring adjustments and even the explantation of the ring segment[12-13]. Ferrara-type ring segments have been investigated during many years and demonstrated to be a safe option to manage corneal irregularities in a great variety of corneal conditions, including keratoconus[14-24]. It has been even confirmed the histological reversibility of the cornea when the ring segments are explanted[25]. Initially, most of case series evaluating the outcomes with this type of implants were empirical, using refraction and keratometry as key factors for the selection of the ring segments to implant in each case[26-28]. These nomograms were significantly optimized considering the peculiarities of the topographic pattern[15,17]. These optimizations were the basis for the development of a highly optimized nomogram in which the topographic pattern is considered when selecting the ring segments to implant, including factors such as asphericity, alignment of astigmatic and comatic axes. The aim of the current study was to evaluate the short-term clinical outcomes obtained with the implantation of Ferrara ring segments using this optimized nomogram which is the result of several years of research.

SUBJECTS AND METHODS

Ethical Approval The study was evaluated and approved by the Ethics Committee of these two institutions, being performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Before recruitment, the characteristics and risks of the study were carefully explained to each patient. Only those providing written informed consent and accepting the conditions of the study were enrolled.

Subjects A total of 88 eyes with the diagnosis of keratoconus of 88 patients was included in this prospective multicenter longitudinal non-comparative clinical trial (QC-CHT-2017, 46/2017). Implantation of Ferrara ring segments (AJL Ophthalmic, Vitoria-Gasteiz, Spain) was performed in all cases. The recruitment and follow-up of patients was performed in 2 different Spanish ophthalmological centers following the same protocols and guidelines: Hospital Torrecárdenas (Almería) and FISABIO-Oftalmología Médica (FOM) (Valencia).

Inclusion criteria for the study were age of 18y or more and presence of keratoconus according to the standard criteria of diagnosis of this condition consisting of asymmetric topographic pattern and at least one of the following clinical signs on slit-lamp: stromal thinning, conical protrusion of the cornea at the apex, Fleischer ring or Vogt striae[29]. Only one eye per patient was selected randomly to avoid the potential bias introduced by the inter-eye correlation that is present when including data from both eyes of each subject. The presence of severe (grade IV, Amsler-Krumeich)[30] or progressive keratoconus (increase of 1.50 D or greater per year)[31], previous ocular surgeries, active systemic or ocular diseases, ocular media opacity, and pregnancy were considered as exclusion criteria for the study. No contact lens fitting was performed in any case during the follow-up of this study.

Clinical Protocol All eyes underwent a complete eye examination before surgery that included anamnesis, measurement of uncorrected (UDVA) and corrected distance visual acuity (CDVA) using Snellen charts, manifest and cycloplegic refraction, slit-lamp anterior segment examination, infrared pupillometry, corneal topographic, aberrometric and pachymetric analysis with the Pentacam HR system (Oculus Optikgeräte GmbH, Wetzlar, Germany), and fundus evaluation under pupil dilation. An eye examination was performed in all patients the day after surgery, including measurement of UDVA and analysis of the integrity of the cornea by slit lamp. Likewise, patients were revised at 1 and 3mo after surgery, performing in all cases the following tests: slit lamp biomicroscopy, corneal topography and aberrometry, pachymetry, measurement of UDVA and CDVA, and manifest refraction. Total corneal aberrations considering the contribution of the combination of both anterior and posterior corneal surfaces were considered for the statistical analysis.

Ring Segments and Nomogram Intracorneal Ferrara rings consists of semicircular segments with an arc of multiple lengths (90º, 120º, 140º, 150º, 160º, 180º, 210º, and 320º) and a fixed triangular section: AFR (0.60 mm base, 5.0 mm optical zone) and AFR6 (0.80 mm base, 6.0 mm optical zone). They are made of polymethyl methacrylate (PMMA) with natural blue light filter. Each segment has an orifice of 0.20 mm at each end to facilitate its implantation. Furthermore, different

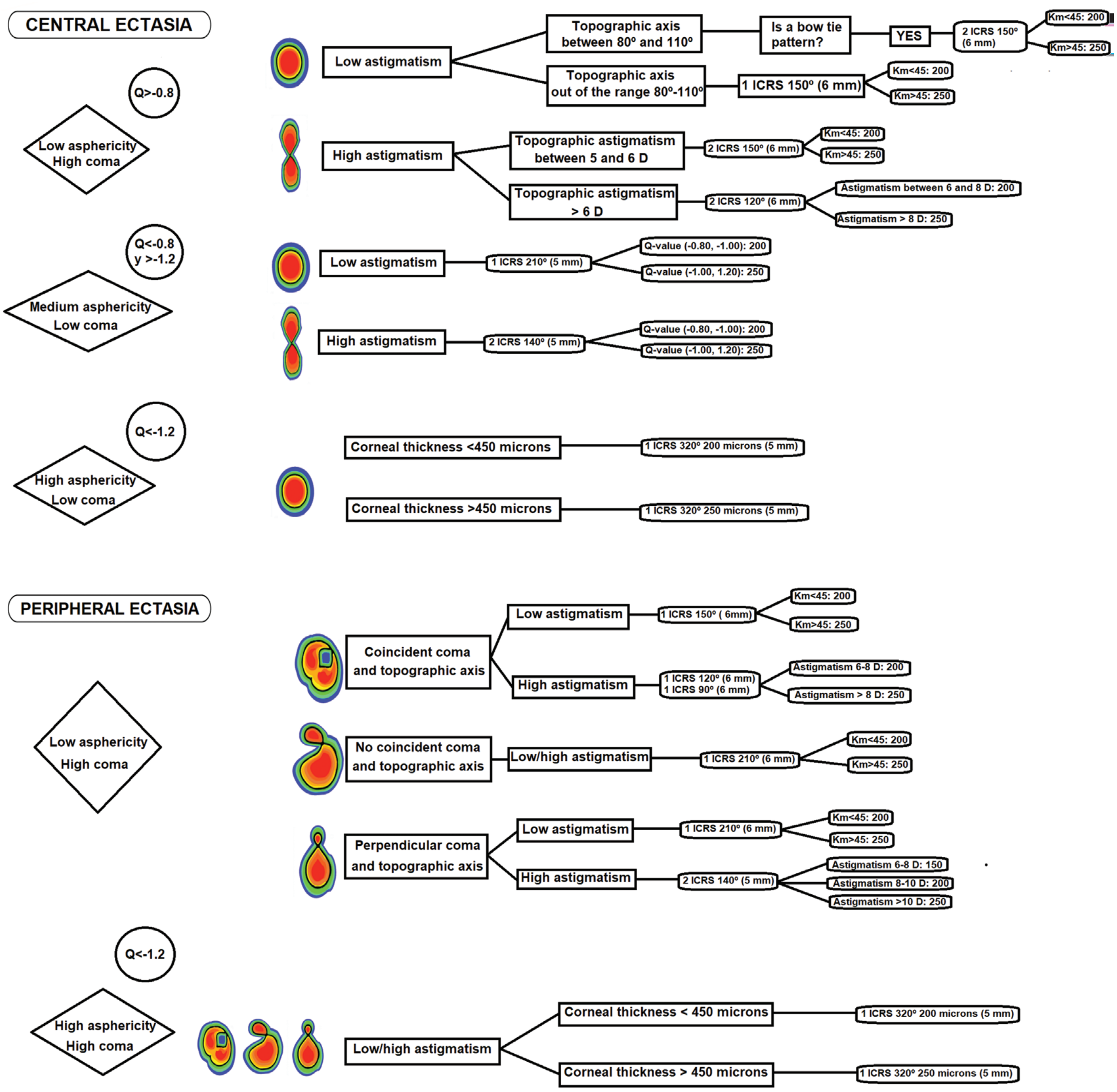

Figure 1 Personalized nomogram developed for Ferrara ring segments, showing how each case is classified for the selection of the most suitable ring segment to implant First, corneal asphericity and the primary coma level on the anterior corneal surface (left column) are considered. After this, the relative position of the axes of coma and corneal astigmatism (central column) is evaluated. Finally, the magnitude of astigmatism (right column) is considered, thus defining a total of 16 different phenotypes or corneal topographic patterns.

thicknesses are available (0.15, 0.20, 0.25, 0.30, and 0.35 mm) for each type of segment.

For a more optimized selection of the ring segments to implant in each case, a new nomogram has been developed due to several years of research[15,17]. The research group has conducted some investigations about how to proceed with Ferrara ring segment selection in paracentral keratoconus, confirming the benefit of different combinations of ring segments depending on the differences between the axes of refractive cylinder and the corneal flattest meridian and the comatic aberration map[15,17]. According to all this previous experience, the manufacturer established a new optimized nomogram considering the asphericity of the anterior corneal surface, the magnitude of astigmatism of such surface and the level of discrepancy among astigmatism and coma orientations to define the most adequate combination of ring segments to implant in each case. Specifically, each cornea was classified according to 16 different corneal patterns or phenotypes (Figure 1), which were associated to the recommendation of the implantation of a specific ring segment or combination of segments.

Surgical Procedures All surgical procedures were performed by one of two expert surgeons under topical anesthesia (application of 2 drops of proparacaine 10min before surgery). These procedures were initiated in all cases with the creation of corneal incisions on the steepest meridian according to the topographic map. In FISABIO-Oftalmología Médica Centre, the Intralase® femtosecond laser (Johnson and Johnson Surgical

Vision, Groningen, the Netherlands) was used to generate the corneal tunnels for the insertion of ring segments. The first steps for the creation of the tunnels were to mark the center of the pupil reflex on the slit-lamp and afterwards the positioning of the vacuum suction ring onto the eye. Then, the disposable glass lens of the femtosecond laser system was applanated to the cornea to fixate the eye. After this, the femtosecond laser initiated the photodisruption process, creating a continuous circular stromal tunnel at approximately 80% of corneal depth.

In Torrecárdenas Hospital, the technique of mechanical dissection was used for the creation of the tunnels as femtosecond technology was not available in this institution. The creation of a mark to be used as a reference point for centration (pupil reflex) was the first step of the surgical procedure, followed by the generation of a radial incision of approximately 1.8 mm in length. After this, a calibrated diamond knife was set at approximately 80% of the corneal thickness where the initial incision was made. Pocketing hooks (Suarez spreader) were then used to create corneal pockets on each side of the incision, attempting to maintain a constant depth. A semiautomated suction ring (KV-2000 vacuum pump, adapted for Ferrara ICRS by AJL Ophthalmic) was placed around the limbus and two semicircular dissectors were then placed sequentially into the lamellar pocket created to be steadily advanced by a rotational movement (counterclockwise and clockwise directions).

After the mechanical or femtosecond-guided laser creation of the tunnels, Ferrara rings were inserted throughout the incision into such tunnels, with their corresponding centration afterwards with the help of a Sinskey hook. A postoperative prophylactic treatment was prescribed consisting of the application of tobramycin-dexamethasone eyedrops every 6h for 1wk and the use of a topical lubricant containing polyethylene glycol 0.4% and propylene glycol 0.3% every 6h for 1mo.

Statistical Analysis Before initiating patient recruitment, sample size estimation was performed using the Dupont-Plummer approach in order to optimize the design of the study[32]. For paired tests, a total of 83 eyes were found to be necessary to detect differences of 0.10 logMAR in visual acuity measurements between consecutive visits, assuming a statistical power of 90%, a standard deviation (SD) of differences of 0.25 logMAR according to previous research[6,11], a drop-out rate of 20%, and an alpha error of 0.05.

The commercially available software package SPSS Version 22.0 (IBM Corporation, Armonk, NY, USA) was used for performing the statistical analysis of the data obtained. The normality of data samples was evaluated by means of the Kolmogorov-Smirnov test. The paired Student's *t*-test was used to assess the significance of differences between consecutive visits of normally distributed variables, including correction for multiple pairwise comparisons. The Wilcoxon test was used for non-normally distributed data instead. The Pearson or Spearman correlation coefficients were calculated for normally and non-normally distributed data, respectively, to evaluate the relationship between different clinical variables evaluated. Likewise, the comparison between mechanical and femtosecond laser-assisted tunnelization groups was performed using the unpaired Student's *t* and Mann-Whitney *U* tests for normally and non-normally distributed variables, respectively. Regarding the analysis of refractive changes, all spherocylindrical refractions obtained were converted to vectorial notation using the power vector method described by Thibos and Horner[33]. A *P*-value of less than 0.05 was considered as statistically significant for all statistical tests.

RESULTS

The sample included a total of 88 eyes that met the inclusion criteria of a total of 88 patients with a mean age of 36.4y (SD: 12.1; median: 35.5; range: 18 to 62y). Likewise, the sample included a total of 49 men (55.7%) and 39 women (44.3%), as well as a total of 42 right eyes (47.7%) and 46 left eyes (52.2%). The contribution of each participating center was as follows: Torrecárdenas Hospital Complex (25 eyes, 28.4%) and FISABIO (63 eyes, 71.6%). The average depth of implantation of the segments was 376.5 μm (SD: 49.9; median: 364.0; range: 280 to 495 μm).

The implantation was performed using mechanical tunneling in a total of 25 eyes (28.4%) and femtosecond laser-assisted tunneling in 63 eyes (71.6%). In the current study, a total of 106 ring segments were implanted, with 18 eyes being implanted with two ring segments according to the nomogram recommendations. The most implanted ring segment in the sample was 250 μm thick and 150º arc length (23 eyes, 21.7%), followed by 250 μm thick and 210º arc length (20 eyes, 18.9%). The 5-mm optical zone segments were implanted in a total of 33 eyes (37.5%), while the 6-mm optical zone segments were implanted in 55 eyes (62.5%).

Visual and Refractive Changes Table 1 summarizes the visual and refractive data obtained in the evaluated sample during the follow-up. One month after surgery, there were statistically significant changes in UDVA, the magnitude of the refractive cylinder, the spherical equivalent, the overall blur strength and CDVA ($P<0.001$), with no significant additional changes occurring during the rest of the follow-up ($P\geq 0.630$). Therefore, the ring segments induced a significant refractive change, with an improvement in UDVA and CDVA associated. The percentage of eyes with UDVA of 0.30 logMAR or better changed from a preoperative value of 12.5% to a 3-month postoperative value of 33.3% (Figure 2). Concerning CDVA, a total of 28.4% and 46.5% of eyes had a preoperative and 3-month postoperative value of 0.10 logMAR or better,

Table 1 Visual and refractive changes occurring in the sample evaluated mean±SD, median (range)

Parameters	Preop.	1mo postop.	3mo postop.	P
UDVA logMAR	0.80±0.36 0.80 (0.05 to 2.00)	0.64±0.40 0.70 (0.05 to 2.00)	0.59±0.33 0.52 (0.05 to 1.30)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
Sphere (D)	-1.46±3.44 -0.63 (-11.00 to 9.00)	-0.64±2.77 0 (-10.00 to 8.50)	-0.69±3.04 0 (-10.00 to 8.50)	0.194
Cylinder (D)	-3.68±1.78 -3.50 (-9.00 to 0.00)	-2.72±1.72 -2.50 (-6.00 to 0.00)	-2.86±1.69 -2.75 (-7.00 to 0.00)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.630 Preop. *vs* 3mo <0.001
Spherical equivalent (D)	-3.24±3.51 -2.75 (-15.50 to 7.75)	-2.00±2.96 -1.13 (-12.25 to 7.25)	-2.12±3.11 -1.50 (-12.25 to 7.25)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
J_0 (D)	-0.45±1.32 -0.63 (-2.82 to 3.90)	-0.46±1.03 -0.38 (-2.95 to 2.11)	-0.53±1.00 -0.50 (-3.29 to 1.61)	0.593
J_{45} (D)	-0.06±1.51 0 (-3.05 to 3.03)	0.04±1.16 0 (-2.50 to 2.60)	0.05±1.22 0 (-2.50 to 2.60)	0.258
B (D)	4.30±2.91 3.62 (0 to 16.14)	2.94±2.58 2.00 (0 to 12.45)	3.23±2.53 2.69 (0 to 12.45)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
CDVA logMAR	0.36±0.24 0.30 (0 to 1.00)	0.26±0.18 0.22 (0 to 0.82)	0.25±0.20 0.20 (-0.08 to 0.82)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.768 Preop. *vs* 3mo <0.001

D: Diopters; UDVA: Uncorrected distance visual acuity; CDVA: Corrected distance visual acuity; J_0, J_{45}: Power vector components of astigmatism; B: Overall blur strength.

respectively (Figure 2). At 3mo after surgery, only 2 eyes (2.3%) lost 2 or more lines of CDVA and a total of 53.5% of eyes gained lines of CDVA (Figure 3).

Corneal Topographic Changes Table 2 summarizes the corneal topographic data obtained in the evaluated sample during the follow-up. Significant decreases in the corneal power corresponding to the flattest (K1) and steepest (K2) meridians of the anterior and posterior surfaces as well as in the mean corneal power (KM) values were detected at 1mo after surgery (P≤0.003), with no additional significant changes occurring during the rest of the follow-up (P=0.999). Likewise, a significant reduction of the magnitude of anterior corneal astigmatism (ACA) was observed at 1mo postoperatively (P<0.001), without no additional significant changes afterwards (P=0.999). Furthermore, a significant reduction of the magnitude of posterior corneal astigmatism (PCA) was found at 3mo after surgery (P=0.048). Finally, only the asphericity of the anterior corneal surface (Qant) showed a significant change at 1mo postoperatively (P<0.001), with no significant changes afterwards (P=0.999). This change consisted of a decrease in prolaticity, which is consistent with the central corneal flattening observed. Indeed, a statistically significant correlation of the change in anterior KM was found with the change with surgery in Qant (r=-0.819, P<0.001) as well as with the change in posterior KM (r=-0.702, P<0.001). Likewise, a poorer but statistically significant correlation was found between the change in ACA and PCA (r=-0.476, P<0.001). Furthermore, the correlation between the change with surgery in the magnitude of ACA and the change in manifest cylinder was limited although statistically significant (r=-0.389, P<0.001).

Corneal Aberrometric Changes Table 3 summarizes the corneal aberrometric data obtained in the evaluated sample during the follow-up. A large and statistically significant reduction in primary coma RMS was observed at 1mo after surgery (P<0.001), with a non-significant reduction during the remaining follow-up (P=0.432). No significant changes with surgery were detected in the rest of corneal aberrometric data evaluated (P≥0.432).

Pachymetric Changes Figure 4 shows changes in central (CCT) and minimum corneal thickness (MCT) occurring during the follow-up in the sample evaluated. Statistically significant changes were found in both pachymetric parameters (P<0.001), with a significant increase at 1mo postoperatively (P<0.001) and no significant changes during the rest of follow-up (P≥0.699). Additionally, there was a trend to a minimal

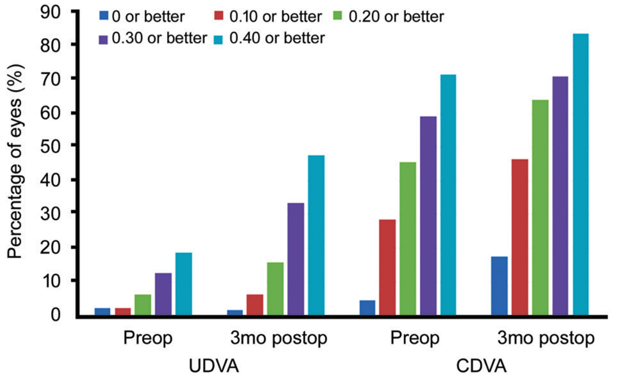

Figure 2 Distribution of preoperative and postoperative UDVA and CDVA in the sample evaluated.

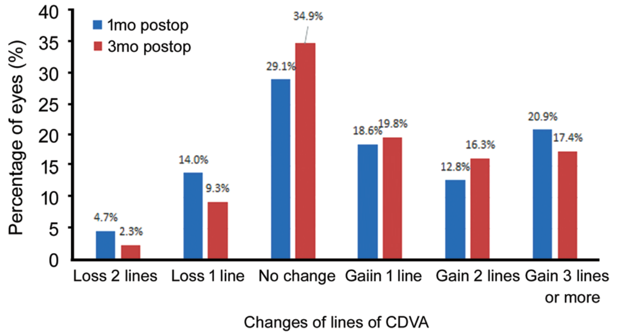

Figure 3 Distribution of changes in lines of CDVA at the end of the follow-up in the sample evaluated.

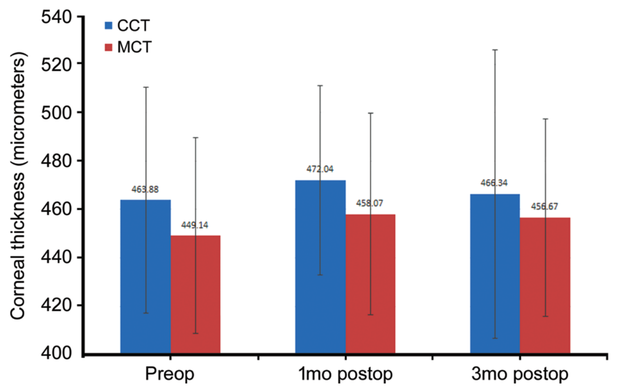

Figure 4 Pachymetric changes in the sample evaluated during the follow-up MCT: Minimum corneal thickness; CCT: Central corneal thickness.

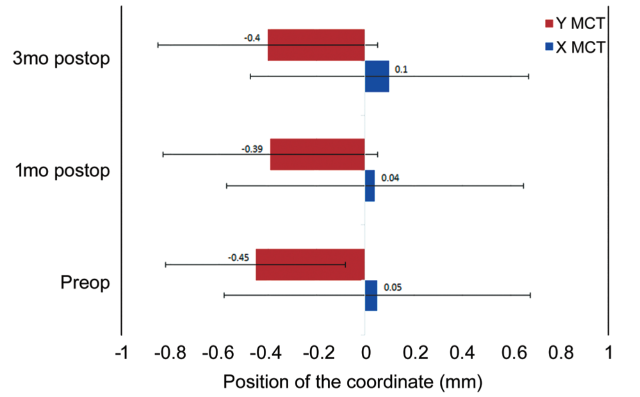

Figure 5 Changes in the X and Y coordinates of the position of the point of minimum corneal thickness (MCT) in the sample evaluated during the follow-up.

change in the position of the corneal point corresponding to the MCT, but the modifications of the X (P=0.621) and Y coordinates (P=0.295) of such position after surgery did not reach statistical significance (Figure 5).

Comparison of Mechanical and Femtosecond Laser-Assisted Implantation of ICRS Preoperatively, only significant differences between mechanical and femtosecond groups were found in J_0 (0.06±1.54 *vs* -0.65±1.17 D, P=0.036), CDVA (0.44±0.26 *vs* 0.32±0.22 logMAR, P=0.042), corneal spherical aberration (-0.24±0.54 *vs* -1.66±0.48 μm, P=0.045). At 1mo after surgery, differences in J_0 (-0.07±0.98 *vs* -0.62±1.02 D, P=0.014), CDVA (0.34±0.20 *vs* 0.23±0.16 logMAR, P=0.010), and posterior K2 (-7.13±0.55 *vs* -7.53±0.80 D, P=0.030) and KM (-6.73±0.44 *vs* -7.18±0.75 D, P=0.003) were maintained. However, no significant differences were found between mechanical and femtosecond groups in corneal spherical aberration (P=0.194). Additionally, significant differences between groups were found in anterior keratometric readings (P≤0.040), coma RMS (P=0.031) and posterior K1 (P=0.002). At 3mo after surgery, besides the significant differences among groups in J_0 (P=0.021), and posterior K2 (P=0.029) and KM (P=0.006), significant differences were found in anterior KM (P=0.041), posterior K1 (P=0.006), and manifest cylinder (P=0.017). However, changes in these parameters from the preoperative status did not differ significantly between groups (DKM anterior: -2.56±1.88 *vs* -2.50±2.00 D, P=0.835; DK1 posterior: 0.18±0.43 *vs* 0.08±0.45 D, P=0.336; Dcylinder: 1.34±2.12 *vs* 0.50±1.71 D, P=0.075). Likewise, no significant differences between mechanical and femtosecond groups were detected in the change observed at 3mo after surgery in the rest of clinical variables evaluated (P≥0.101).

Complications No serious complications occurred in the sample evaluated during the follow-up.

DISCUSSION

The implantation of Ferrara rings has been significantly optimized from the development and use of empirical nomograms several years ago to select the ring segment to implant in each specific case[26-28] to more complex nomograms considering the topographic pattern, corneal aberrations and tomographic data[15,17,34]. The aim of the current study was to evaluate the results obtained with the implantation of Ferrara rings using a new nomogram which is the result of several years of research and clinical experience of different authors[15,17,19-22,35-38]. This optimized nomogram considers the level of anterior corneal astigmatism, primary coma and asphericity as well as the level of misalignment between topographic and coma axes for the selection of the ring segment thickness and arc length to implant. It has been

Table 2 Corneal topographic changes in the sample evaluated mean±SD, median (range)

Parameters	Preop.	1mo postop.	3mo postop.	*P*
Anterior surface				
K1 (D)	46.08±3.79 46.25 (35.90 to 56.20)	44.26±3.21 44.15 (33.60 to 51.70)	44.19±3.10 44.20 (33.80 to 52.10)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
K2 (D)	50.44±4.12 50.40 (42.30 to 59.80)	47.27±3.41 46.75 (38.90 to 55.20)	47.31±3.61 46.80 (38.80 to 59.50)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
KM (D)	48.23±3.80 48.45 (39.10 to 58.00)	45.74±3.15 45.40 (36.25 to 53.45)	45.71±3.20 45.25 (36.30 to 53.85)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
Astigmatism (D)	4.36±2.25 4.25 (0 to 12.10)	3.08±1.93 2.85 (0.20 to 8.90)	3.13±2.06 2.95 (0 to 11.30)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
Kmax (D)	57.26±5.63 56.70 (46.60 to 73.90)	54.22±5.11 53.85 (45.80 to 77.60)	54.07±5.39 53.00 (45.70 to 81.50)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.171 Preop. *vs* 3mo <0.001
Q	-0.79±0.49 -0.79 (-2.46 to 0.57)	-0.38±0.50 -0.39 (-1.50 to 1.31)	-0.40±0.50 -0.41 (-1.40 to 1.44)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
Posterior surface				
K1 (D)	-6.80±0.79 -6.80 (-8.90 to -4.40)	-6.69±0.71 -6.70 (-9.40 to -5.00)	-6.69±0.66 -6.70 (-8.20 to -4.90)	0.003 Preop. *vs* 1mo 0.006 1mo *vs* 3mo 0.999 Preop. *vs* 3mo 0.018
K2 (D)	-7.64±0.77 -7.65 (-9.80 to -5.90)	-7.42±0.76 -7.40 (-10.00 to -5.70)	-7.42±0.74 -7.40 (-9.40 to -5.70)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
KM (D)	-7.21±0.75 -7.28 (-9.25 to -5.15)	-7.05±0.71 -7.03 (-9.70 to -5.50)	-7.05±0.67 -6.98 (-8.80 to -5.70)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.999 Preop. *vs* 3mo <0.001
Astigmatism (D)	0.84±0.47 0.80 (0 to 2.20)	0.73±0.42 0.70 (0 to 2.00)	0.73±0.45 0.60 (0 to 2.00)	0.004 Preop. *vs* 1mo 0.189 1mo *vs* 3mo 0.999 Preop. *vs* 3mo 0.048
Q	-0.87±0.55 -0.92 (-1.94 to 0.86)	-0.86±0.53 -0.89 (-2.38 to 0.92)	-0.87±0.53 -0.89 (-2.41 to 0.43)	0.441

D: Diopters; K1: Corneal power in the flattest meridian; K2: Corneal power in the steepest meridian; KM: Mean corneal power; Kmax: Maximum corneal power; Q: Asphericity.

demonstrated that the 320º and 210º ring segments induce more reduction in mean keratometry and asphericity than 160º rings, being a more adequate option in patients with central hyperprolate keratoconus[36-38]. Likewise, one Ferrara-type ICRS of 150º of arc length with a thickness of 150, 200 or 250 µm implanted inferiorly has been shown to be the most adequate option to reduce both astigmatism and corneal coma-like aberrations in keratoconus eyes with no coincident topographic and comatic axes[35]. In the case of keratoconus cases with coincident topographic and coma axis, the use of one Ferrara-type segment with 150º of arc implanted inferiorly for low corneal astigmatism, the use of 1 segment with 90º of arc superiorly and 1 with 150º of arc inferiorly for moderate astigmatism, and the use of 1 with 90º of arc superiorly and 1 with 120º of arc inferiorly for high astigmatism were found to provide good visual and refractive outcomes[17]. Furthermore,

Table 3 Total corneal aberrometric changes in the sample evaluated mean±SD, median (range)

Parameters	Preop.	1mo postop.	3mo postop.	*P*
High order RMS (μm)	6.68±5.89 4.43 (0.57 to 25.22)	6.01±7.36 3.84 (1.29 to 35.32)	6.67±5.39 4.86 (1.10 to 20.04)	0.846
Primary coma RMS (μm)	3.66±3.04 2.81 (0 to 17.90)	2.42±2.38 1.76 (0.03 to 12.18)	2.33±2.26 1.74 (0.24 to 12.79)	<0.001 Preop. *vs* 1mo <0.001 1mo *vs* 3mo 0.183 Preop.*vs* 3mo <0.001
Zernike coefficient for primary spherical aberration (μm)	-0.39±0.69 -0.34 (-2.01 to 0.83)	-0.07±0.71 -0.11 (-1.41 to 1.76)	0.06±0.64 0 (-1.06 to 1.64)	0.595
Trefoil RMS (μm)	0.39±0.34 0.27 (0.03 to 1.41)	0.46±0.34 0.50 (0.03 to 1.41)	0.51±0.42 0.37 (0 to 1.76)	0.432

RMS: Root mean square.

the use of two symmetrical segments have been recommended in the presence of regular astigmatism[38-39]. For this reason, the optimized nomogram evaluated considers the level of anterior corneal astigmatism, primary coma and asphericity as well as the level of misalignment between topographic and coma axes. The study was conducted in two different centers using a different method of creation of tunnels for the insertion of the ring segments to evaluate all potential factors that may influence on the outcome achievable with this new nomogram. Table 4 summarizes the main clinical outcomes obtained with Ferrara ring segments by previous authors using different types of nomograms and the outcomes of the current series.

In our sample, the implantation of Ferrara rings based on the optimized nomogram led to a significant improvement in UDVA (mean improvement of 2 lines logMAR) and CDVA (mean improvement of 1 line logMAR), which is consistent with previous series evaluating the effect of Ferrara ring implantation in keratoconus based on the use of previous nomograms and also observing a visual improvement after surgery[19-20,23,26-28,40-44]. Hamdi[19] reported in a sample of moderate to severe keratoconus cases treated with Ferrara rings using a previous nomogram of implantation an improvement of CDVA in 64% of eyes. In our series, the percentage of eyes improving CDVA at 3mo postoperatively was 53.5%, but it should be considered that cases of all types of topographic patterns were included, combining corneas with aligned and misaligned topographic and comatic axes. In any case, in our sample, a total of 88.4% of eyes improved or maintained the CDVA after surgery. It has been demonstrated that Ferrara rings provide a more efficient effect in eyes with moderately advanced asymmetric keratoconus with an initial visual acuity worse than 0.4 logMAR[41]. Alfonso *et al*[35] found that a total of 48.78% of cases from a sample of paracentral keratoconus eyes with no coincident topographic and coma axes improved CDVA after Ferrara-type ring segment implantation. The same research group reported in another study evaluating the effect of Ferrara-type ring segments in keratoconus eyes with coincident corneal keratometric, comatic and refractive axes that 84.5% of cases maintained or improved their CDVA at 5y after surgery[45]. One additional remarkable finding in our series is that 33.7% of cases gained 2 lines of CDVA or even more, which is a better result than those reported by previous authors using previous nomogram approaches for Ferrara-type ring segment implantation (26.83% keratoconus with no coincident topographic and coma axis, Alfonso *et al*[35], 25.7% keratoconus with coincident topographic and coma axis of more than 30 years old, Fernández-Vega Cueto *et al*[45]). For this reason, a safety index (ratio of postoperative CDVA to preoperative CDVA) of 1.36 was obtained in the current series, which reflects the positive overall trend to gain of lines of CDVA. Slight lower safety indices have been reported by other authors using other nomograms (Piñero *et al*[11], 1.29; Ameerth *et al*[43], 1.22). However, other authors have reported higher values of safety index using other nomograms (around 1.6)[28,40], but not indicating the percentage of the sample with cases with significant discrepancies between comatic and topographic axes and high levels of primary coma. In our sample, almost all cases presented a relevant level of discrepancy between these two axes. Regarding the comparison in terms of the efficacy index (ratio of postoperative UDVA to preoperative CDVA, a variability between 0.42 and 0.86 have been reported in previous studies using a great variety of nomograms[11,23,28,40,43]. A value of 0.52 was obtained in the current study. Future randomized comparative studies between this optimized nomogram and previous nomograms should confirm the real benefit in terms of spherocylindrical correction of the nomogram preliminarily evaluated in the current study.

Concerning refraction, a significant change in the magnitude of manifest cylinder and spherical equivalent was found after Ferrara ring segment implantation based on the optimized nomogram evaluated. This is the main factor contributing to the significant improvement in UDVA observed after surgery. Previous series have also reported significant changes in refraction after Ferrara ring segment implantation

Table 4 Summary of the main clinical outcomes of Ferrara ring segment implantation in keratoconus reported by other authors using other types of nomograms

Author (y)	*n* (age range)	Ring segments (surgical technique)	Nomogram	Change in logMAR CDVA	Change in SE (D)	Change in refractive cylinder (D)	Follow-up (mo)
Siganos *et al* (2002)[28]	26 KC	Ferrara (mechanical)	2 segments 160º; 150 μm SE<-4 D 200 μm -4.25 to -6 D; 250 μm -6.25 to -8 D 300 μm -8.25 to -10 D; 350 μm SE>-10 D	Preop. 0.37±0.25 Postop. 0.60±0.17 (decimal) Efficacy index 0.81 Safety index 1.62	Reduced SE in most of cases	-	6
Miranda *et al* (2003)[27]	36 severe KC	Ferrara (mechanical)	2 segments 160º 200 μm cone stage I; 250 μm cone stage II 300 μm cone stage III; 350 μm cone stage IV	CDVA improved in 80.56%	Preop. -7.29±3.12 Postop. -4.80±3.04	-	12
Kwitko & Severo (2004)[26]	51 KC	Ferrara (mechanical)	2 segments 160º 200 μm cone stage I; 250 μm cone stage II 300 μm cone stage III; 350 μm cone stage IV	CDVA improved in 86.4% did not change 1.9% worsened 11.7%	Preop. -6.08±5.01 Postop. -4.55±5.71	Preop. -3.82±2.13 Postop. -2.16±2.07	13.0±8.7
Torquetti *et al* (2009)[23]	28 KC	Ferrara (mechanical)	Nomogram based on position of the conus on the cornea, topographic astigmatism and pachymetric map	Preop.0.41±0.25 Postop.0.59±0.19 (decimal) Efficacy index 0.76 Safety index 1.44	-	-	5-12y
Ferrara & Torquetti (2009)[22]	80 KC and post-LASIK ectasia	Ferrara (mechanical)	210º arc length ring segment up to 2 D: 150 μm 2.25 to 4 D: 200 μm; 4.25 to 6 D: 250 μm >6.25 D: 300 μm	Preop.20/125 to postop. 20/55	Preop. -5.22 to postop. -2.26 D	Preop. 3.65 to postop. 2.69 D (keratom astig)	6.65±7.73
Piñero *et al* (2010)[11]	72 KC (15-68y)	KeraRing (FS)	Manufacturer's nomogram	Preop.0.36±0.27 Postop.0.27±0.23 Efficacy index 0.42 Safety index 1.29	Preop. -5.64±5.00 Postop. -3.99±4.50	Preop. -4.07±2.40 Postop. -2.86±1.91	3
Hamdi (2011)[19]	100 KC (16-39y)	Ferrara (mechanical)	Manufacturer's nomogram	CDVA improved 1-6 lines in 64% Unchanged 27% lost 1-2 lines 9%	Preop. -3.60±3.10 Postop. -2.52±3.10	Preop. -5.18±2.10 Postop. -2.90±2.50	6
Ferrara *et al* (2012)[39]	972 KC (oval or bow tie) (17-59y) 101 KC (nipple-type) (14-64y)	Ferrara (mechanical)	160º arc length: oval bow tie 210º arc length: nipple-type	Preop.20/100 to postop.20/40 Preop. 20/110 to postop. 20/60	Preop. -3.99±4.22 Postop. -2.26±3.09 Preop. -8.52±5.63 Postop. -4.14±4.37	-	23.8±12.2 22.9±15.1
Ameerh *et al* (2012)[43]	79 KC (13-44y)	Ferrara (mechanical)	Manufacturer's nomogram	Preop. 0.51±0.17 Postop. 0.62±0.20 (decimal) Efficacy index 0.86 Safety index 1.22	Preop. -2.32±2.75 Postop. -2.04±1.92	Preop. -3.05±1.70 Postop. -2.87±1.67	6
Torquetti *et al* (2018)[37]	138 KC (10-63y)	Ferrara (mechanical/FS)	320º arc length. Manufacturer's nomogram	Preop. 20/100 to postop. 20/40	Preop. -7.02±4.80 Postop. -3.29±3.80	Preop. 4.62±2.87 Postop. 2.74±2.07 (topo astig)	6.2±3.3
Sanders *et al* (2018)[40]	58 KC (33.3±13.2y)	Ferrara (FS)	140º arc length. Asymmetric KC <4 D: 1 seg 150 μm; >4 D and <8 D: 1 seg 200 μm >8 D: 1 seg 250 μm symmetric KC <6 D: 2 seg 150 μm; >6 D and <10D: 2 seg 200 μm >10 D: 2 seg 250 μm	Preop. 0.50±0.20 Postop. 0.30±0.21 Safety index 1.67	-	Preop. -8.00±3.45 Postop. -4.53±2.52 (topo astig)	16.81±10.8
Fernández *et al* (2021; current)	88 KC (18-62y)	Ferrara (mechanical/FS)	Optimized nomogram considering variables such as anterior corneal asphericity and astigmatism or the discrepancy among astigmatism and coma orientations	Preop. 0.36±0.24; Postop. 0.25±0.20 Efficacy index 0.52; Safety index 1.36	Preop. -3.24±3.51 Postop. -2.12±3.11	Preop. -3.68±1.78 Postop. -2.86±1.69	3

KC: Keratoconus; CDVA: Corrected distance visual acuity; SE: Spherical equivalent; D: Diopters.

using different type of nomograms and for different types of topographic patterns[15,17,35-36,38,40-41,43], with poorer results especially with the first developed nomograms[26-28]. In our series, a reduction of the spherical equivalent by more than 50% was observed in 41.5% of eyes, changing from a mean preoperative value of -3.24±3.51 D to a mean 3-month postoperative value of -2.12±3.11 D. Hamdi[19] reported a reduction in spherical equivalent after Ferrara ring implantation in keratoconus eyes based on a not fully optimized nomogram from a mean preoperative value of -3.60±3.10 D to a mean 3-month postoperative value of -2.52±3.10 D, not reaching statistical significance (P=0.209).

The myopic correction induced with the implantation of the Ferrara ring segments in the current study could be consistently explained by the significant reduction generated in the central curvature of the anterior corneal surface. This central corneal flattening is consistent with the results of all previous series evaluating the outcomes of Ferrara rings in ke ratoconus[15-17,19-20,23,26-28,35-38,41,43-45]. This significant flattening of the anterior corneal surface was observed in the steepest and flattest meridians, with an additional reduction of the magnitude of anterior corneal astigmatism and maximum keratometric reading associated. The change in manifest cylinder was explained in part by this reduction of anterior corneal astigmatism, but it was not the only factor. Indeed, a poor although statistically significant correlation was found between changes in manifest cylinder and ACA. Additionally, no significant changes with surgery were found in the power vector components of manifest astigmatism. The relevant contribution of PCA to refractive cylinder in keratoconus[46] as well as changes in specific types of high order aberrations with the potential of interfering with astigmatism may have accounted for this. It should be considered that the implantation of Ferrara rings also induced significant changes in the magnitude of PCA. Likewise, significant changes were observed in posterior central curvature, confirming that Ferrara rings induce a modeling of the global corneal structure, not only of the anterior corneal shape. This is consistent with the results of previous series showing the induction of significant modifications of the shape of the posterior corneal surface after the implantation of Ferrara rings[47-48]. The impact of these changes in the predictability of astigmatic correction should be investigated further. This may be an area for future optimizations of next nomograms of implantation of ring segment.

Besides curvature changes, a significant modification was also observed after Ferrara ring implantation in the asphericity of the anterior corneal surface, changing to a less prolate value. This modification was consistent with the significant central flattening induced, with a strong and statistically significant correlation between changes in mean keratometry and anterior corneal asphericity. However, no significant changes were detected with the implantation of the ring segments in the asphericity of the posterior corneal surface. This is consistent with previous studies reporting significant changes in anterior and posterior central corneal curvature as well as in anterior asphericity after the implantation of Ferrara rings[37,39-40,47]. This significant change of anterior asphericity with Ferrara rings was found to be especially large in magnitude when 320º arc length segments are used[37].

The significant change in anterior shape was associated with a change towards less negative value of total corneal spherical aberration, although this trend did not reach statistical significance in our series. In contrast, the change in total primary coma was statistically significant and with a mean magnitude of 1.33 μm (preoperative 3.66±3.04 μm *vs* postoperative 2.33±2.26 μm, 6-mm pupil). Previous series on Ferrara rings outcomes using other nomograms have also reported significant changes in primary coma and coma-like aberrations, but of less magnitude[15,35-36,45,49]. Alfonso *et al*[35] reported a change in corneal coma-like RMS from 0.80±0.53 μm before surgery to 0.61±0.59 μm (4.5 mm pupil) in a sample of keratoconus eyes with no coincident topographic and coma axis implanted with Ferrara-type ring segments. The same research group reported a change after Ferrara-type ring segment implantation in another sample of 409 paracentral keratoconic eyes a significant change in coma-like RMS (4.5 mm pupil) from a mean preoperative value of 1.32±1.01 μm to a mean postoperative value of 1.06±0.85 μm[15]. Therefore, the control of corneal primary coma seems to be one of the most relevant benefits of the use of this optimized nomogram. This is consistent with the significant improvement in CDVA observed in our series, with 37.4% of eyes gaining 2 logMAR lines of CDVA or more. It should be considered that the primary coma aberration is the high order aberration degrading most the visual quality in keratoconus[29-30]. Esaka *et al*[50] found by means of stepwise multiple regression analysis that CDVA in keratoconus could be predicted considering the RMS of anterior corneal elevation and total coma aberration (adjusted R=0.546).

No severe adverse events occurred during the follow-up in the current study, confirming the safety of the implant. Likewise, no corneal structural alterations were detected, although significant changes in minimum and central corneal thicknesses were found during the follow-up. Specifically, a significant increase of around 10 μm of the pachymetric parameters were found during the 3mo of follow-up postoperatively. This contrasts with previous series reporting decreases of pachymetry after Ferrara ring implantation but in a longer term[42]. Several factors may account for the pachymetric increase found in our series including a potential redistribution of corneal tissue due to the ring implantation or the level of intrasession repeatability of Pentacam pachymetric measurements. Indeed, de Luis Eguileor *et al*[51] have recently confirmed that the repeatability limits for the thinnest corneal thickness measurements obtained with the Pentacam system is 10 μm.

Finally, we have analyzed the potential effect on the outcomes of the use of the mechanical or femtosecond-laser assisted technique for the implantation of the ring segments as a more precise dissection plane depth has been demonstrated to be achieved using the femtosecond technology[52]. Although some differences were found between eyes implanted with both techniques in terms of the corneal flattening and aberrometric change induced as well as in some postoperative data, the magnitude of such differences did not reach statistically significance at 3 mo after surgery. This is consistent with the results of Monteiro *et al*[49] that also found comparable visual, refractive and aberrometric outcomes when comparing the results of Ferrara-type ring segments implanted mechanically or with femtosecond laser. Future studies should be conducted to analyze the impact of inter-surgeon variability using the mechanical implantation method on the incidence of complications, considering that previous series have reported more complications with the mechanical dissection[49] and even poorer aberrometric correction[49,53]. Likewise, differences in the initial postoperative period between mechanical and femtosecond laser assisted-assisted procedures should be investigated further as they may be the consequence of the less precise dissection plane achieved with the mechanical procedure or even of a more relevant structural or inflammatory modifications with such procedure.

There are several limitations that should be acknowledged. The main limitation was the non-comparative nature of the study, not including a control group operated on using a classical nomogram to evaluate the real improvement of our nomogram over previous approaches. Once demonstrated the safety and efficacy of the implantation of Ferrara rings with this nomogram, future comparative clinical trials should be conducted to analyze the real benefit of this new proposal of nomogram over conventional or previously developed nomograms. In any case, some discussions comparing with the results of previous nomograms have been included in the current article but taking care of extracting definitive conclusions as a direct clinical comparison (with or without randomized assignment) has not been done. Another limitation was not including the analysis of ocular wavefront aberrations as with this information a more exhaustive analysis of astigmatism could have been performed, including the analysis of discrepant astigmatism (DA), which is the discrepancy between refractive astigmatism and the sum of total corneal astigmatism and lenticular astigmatism (derived from ocular wavefront aberrometric analysis)[51]. It should be considered that DA is normally negligible in eyes with normal optics but can become significant when coma-like high order aberrations refract as astigmatism[54]. The effect of considering DA in this nomogram should be investigated further. In addition, the inclusion of eyes implanted with Ferrara rings using two different types of corneal dissection may be considered as a limitation and a potential source of bias. However, this potential bias introduced by this factor seems to be limited. No significant differences were found in the changes occurring in a great variety of parameters at 3mo postoperatively between eyes operated on using the mechanical and femtosecond-guided procedures in the current series.

In conclusion, the implantation of Ferrara rings based on a new optimized nomogram considering the level of anterior corneal asphericity, astigmatism and primary coma aberration as well as the level of misalignment between topographic and coma axes is safe and effective for promoting a visual rehabilitation in keratoconus. Using these ring segments, a significant central anterior and posterior corneal flattening is induced, leading to a refractive change and a significant reduction of the prolate shape and irregularity, and consequently to a corrected-distance visual improvement. The main advantage of this new nomogram seems to a better aberrometric control, although this should be investigated in future comparative clinical trials.

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