Corneal Collagen Cross-Linking Before Ferrara Intrastromal Corneal Ring Implantation for the Treatment of Progressive Keratoconus

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Purpose: To evaluate the safety, efficacy, and stability of sequential corneal collagen cross-linking (CXL) and Ferrara intrastromal corneal ring segment (FR) implantation in selected patients with progressive keratoconus.

Methods: This prospective study involved 9 eyes with progressive keratoconus and a preoperative cylinder value equal to or greater than 5 diopters (D) diagnosed between June 2007 and October 2008. Preoperative and postoperative (6 months after the CXL procedure and 6 months after the FR implantation) biomicroscopy examinations, distance uncorrected and best-corrected visual acuities, refractive error, and topographic maps were evaluated and compared.

Results: Mean uncorrected visual acuity was 1.11 logarithm of the minimal angle of resolution (logMAR) preoperatively and 0.75 logMAR at 6 months after CXL ($P = 0.03$) and 0.23 logMAR at 6 months after FR implantation ($P < 0.001$). Mean best-corrected visual acuity was 0.26 logMAR preoperatively and 0.24 logMAR at 6 months after CXL ($P = 0.87$) and 0.12 logMAR at 6 months after FR ($P = 0.05$). Statistically significant reductions in the mean spherical equivalent (4.38 D; $P < 0.001$) and mean maximum (5.58 D; $P < 0.001$) and minimum (4.17 D; $P < 0.001$) keratometry values were present at 6 months after FR.

Conclusions: FR implantation after CXL is a safe and efficacious treatment option for managing selected patients with progressive keratoconus. Good results in terms of visual acuity, postoperative residual refractive error, and keratometry values were obtained. Longer follow-up would be valuable to confirm the stability of these results.

Key Words: corneal collagen cross-linking, keratoconus, Ferrara intrastromal corneal rings

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Keratoconus is a progressive, noninflammatory, and usually bilateral corneal ectasia, typically inferior to the center of the cornea and characterized by corneal thinning, induced myopia, and irregular astigmatism.[1,2] Currently available management options are rigid gas-permeable contact lenses,[3–5] intrastromal corneal rings, corneal collagen cross-linking (CXL),[6–11] phakic intraocular lenses, deep anterior lamellar keratoplasty, and penetrating keratoplasty.[12] Improvement in the postoperative spherical equivalent (SE), uncorrected and best-corrected visual acuities (UCVA and BCVA, respectively), and mean keratometry readings is common; however, the ability to stop or slow the progression of the cone area was only found with the CXL procedure.

The primary aim of this prospective study was to combine 2 different types of treatment for keratoconus, corneal CXL to halt the progression of the keratoconus and implantation of intrastromal corneal ring segments for refractive correction. Safety, efficacy, and visual outcomes after 12 months were evaluated.

PATIENTS AND METHODS

Patients

This prospective single-center study comprised 9 keratoconic eyes of 9 patients who met inclusion criteria with progressive keratoconus diagnosed at the Oftalmosalud Instituto de Ojos in Lima, Peru, between June 2007 and October 2008 (8 men and 1 woman) and who received CXL by UVA/riboflavin in the eye with keratoconus. Six months after the CXL procedure, the corneal intrastromal Ferrara ring (FR) was implanted.

Progression was defined by an increase in maximum keratometry (K1) of 1.00 diopter (D) or more in 1 year assessed by computerized videokeratography and patient complaints of deteriorating visual acuity (excluding possible non–cornea-related reasons for deterioration) or the need for new contact lens fitting more than once in the previous 2 years.

Inclusion criteria were the diagnosis of keratoconus (keratoconus grade I, II, and III according to the Amsler–Krumeich

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classification[13]), no corneal opacities or scarring on slit-lamp examination, central corneal thickness greater than 450 μm (measured by ultrasonic pachymetry), low quality of vision and contact lens intolerance (defined as a comfortable wear time <8 h/d), preoperative cylinder value equal to or greater than 5 D, and proof of keratoconus evolution. Exclusion criteria were any other previous or current treatments for keratoconus except contact lenses and the inability to understand the nature of the study or provide informed consent for any reason.

The UCVA, BCVA, manifest refraction, maximum and minimum simulated keratometry measurements (Keratron Scout Topographer; Optikon), and central corneal thickness (ultrasound pachymetry and Accutome pachymeter) were obtained at 6 months after the CXL procedure and 6 months after the FR implantation.

The study was approved by the ethics committee of Oftalmosalud Instituto de Ojos under the principles of the Declaration of Helsinki. Informed consent was obtained from all study participants.

Statistical analyses were performed with the SPSS (version 12) program. Comparisons of means were performed using the Student *t* test. Normality of the data distribution was evaluated using the Kolmogorov–Smirnov test. The χ^2 test was used to evaluate proportional differences between follow-up examinations.

Preparation of Riboflavin 0.1%/Dextran 20% Solution

The vitamin B_2–riboflavin-5-phosphate 0.5% (G. Streuli & Co, Uznach, Switzerland) was diluted with balanced salt solution to 0.1%, and then dextran T500 (Roth AG, Karlsruhe, Germany) was added to get a 20% dextran content. The solution was protected from light and used within 24 hours.

CXL Procedure

Topical anesthesia was achieved by instilling proparacaine hydrochloride 0.5% (Alcaine; Alcon Laboratories, Fort Worth, TX) into the eye every 5 minutes for 3 doses immediately before the procedure. After the patient was positioned under the operating microscope, a lid speculum was inserted, and the central 9 mm of corneal epithelium was removed with a blunt spatula (AE2766; Asico, Westmont, IL). The riboflavin solution was instilled every 5 minutes or sooner if the corneal surface appeared visibly dry for 30 minutes until the riboflavin had penetrated the cornea. The required irradiation of 3.0 mW/cm^2 from the UV lamp (UV-X illumination system, version 1000-0000-00; IROC AG, Zurich, Switzerland) was checked using a UV light meter (UV-Detector: Lutron YK-34UV; IROC AG). The UV radiation was then focused on the apex of the cornea at a distance of 5 cm for a total of 30 minutes, providing radiant energy of 3.0 ± 0.3 mW/cm^2. During the UVA administration, riboflavin solution was also applied to the cornea every 5 minutes or sooner if the corneal surface appeared visibly dry.

After the treatment, the eye surface was washed with 5 mL of balanced salt solution. Two drops of ofloxacin (Oflox; Allergan Laboratories, Irvine, CA) were instilled, followed by the placement of a bandage soft contact lens (SofLens 59 + 0.5 S; Bausch & Lomb. Rochester, NY). Postoperatively, patients received 500 mg of acetaminophen twice daily for 3 days, 1 drop of ofloxacin 6 times a day for 7 days, and 1 drop of ketorolac tromethamine 0.5% (Acular; Allergan Laboratories) 4 times a day for 5 days, followed by fluorometholone (Allergan Laboratories) twice daily for 5 weeks starting at day 5 postoperatively. The bandage contact lens was removed on day 4 postoperatively, at which point slit-lamp biomicroscopy examination was performed to confirm the presence of complete corneal reepithelialization. Routine visits were made at 6 and 12 months postoperatively.

Ferrara Rings

The Ferrara intrastromal corneal rings are made of polymethyl methacrylate, with an external diameter of 6.2 mm, a triangular section, and a 600-μm base. In each eye 2 segments were used. The segments are available in 5 thickness: 150, 200, 250, 300, and 350 μm. Selection of the appropriate rings was based on the Bicalho nomogram (Fig. 1) that uses the topographic distribution of the area of ectasia and the SE value.

FR Implantation

The entire procedure was performed under topical anesthesia with proparacaine hydrochloride 0.5% (Alcaine; Alcon Laboratories) by the same experienced surgeon (L.I.). A circular Ferrara marker centered on the reflex of the microscope light on the cone area was used to create 2 concentric circles on the cornea. The difference in the ratio of the 2 circles was equal to the width of the FRs, and, therefore, the area between them corresponded to the desired position of the ring's insertion channels. The corneal thickness at 6 sequential points of this area was measured with an ultrasonic pachymeter (Accutome pachymeter).

Using a diamond knife, set to 80% of the minimum corneal thickness, 1 radial corneal incision (1 mm) was created on its steep axis. A modified suction ring (designed by L.I.) was placed on the corneal surface with centration over the pupil; the vacuum was started on the low setting, and a double metallic arcuate guide (Ferrara spatula) was used along with

BICALHO'S NOMOGRAM

Topography distribution of the ectasia area

Spherical equivalent	0% / 100%	25% / 75%	33% / 66%	50% / 50%
After -10 D	25/35	25/35	30/35	35/35
-8 to -10 D	20/30	20/30	25/30	30/30
-6 to -8 D	15/25	15/25	20/25	25/25
-2 to -6 D	0/20	0/20	15/20	20/20
Until -2 D	0/15	0/15	15/15	15/15

FIGURE 1. Bicalho nomogram.

TABLE 1. Visual Acuity, Refractive Error, and Keratometry Values Over Time for Each Eye Included in the Study

Patient	1	2	3	4	5	6	7	8	9
UCVA Preop	1.30	1.30	1.30	0.60	0.54	1.30	1.30	1.30	1.10
UCVA Post CXL 6m	1.00	1.00	1.00	0.30	0.30	1.00	0.48	1.00	0.70
UCVA Post FR 6m	0.48	0.18	0.18	0.10	0.10	0.10	0.40	0.18	0.40
BCVA Preop	0.60	0.10	0.10	0.10	0.18	0.54	0.10	0.18	0.48
BCVA Post CXL 6m	0.60	0.10	0.10	0.10	0.18	0.4	0.10	0.18	0.48
BCVA Post FR 6m	0.48	0.10	0.00	0.10	0.10	0.00	0.10	0.10	0.10
K1 Preop	54.85	48.56	51.53	45.39	45.15	55.24	50.68	52.1	53.15
K1 Post CXL 6m	55.43	47.98	51.23	44.72	44.97	54.93	48.09	51.6	52.50
K1 Post FR 6m	46.10	46.41	48.36	42.95	41.44	46.06	41.47	47.10	46.50
K2 Preop	47.40	42.67	44.29	40.28	40.01	39.01	43.49	44.98	47.07
K2 Post CXL 6m	46.35	41.8	43.99	40.00	40.10	40.18	42.97	44.13	46.40
K2 Post FR 6m	39.54	39.35	39.84	37.26	38.13	38.87	35.23	41.01	42.44
Sph Preop	−11.5	−2.25	−3.00	0.50	0.25	−1.00	−3.50	−3.00	−5.00
Sph Post CXL 6m	−11.00	−1.00	−1.00	0.00	0.00	−1.00	−1.75	−3.00	−3.00
Sph Post FR 6m	−3.00	0.25	0.00	0.50	0.00	0.00	−1.00	−2.00	−1.75
Cyl Preop	−6.00	−6.00	−6.00	−6.00	−6.75	−5.00	−6.25	−5.00	−5.50
Cyl Post CXL 6m	−5.00	−5.00	−5.50	−2.75	−2.50	−5.00	−4.00	−4.00	−3.00
Cyl Post FR 6m	−1.25	−4.50	−3.75	−1.75	−2.00	−0.50	0.00	−1.00	−2.00

Cyl, cylinder value; K1, maximum keratometry value; K2, minimum keratometry value; m, months; Post, postoperative; Preop, preoperative; Sph, spherical value.

the procedure marker, which carefully elevated the cornea and simultaneously dissected 2 intrastromal channels around the cone area. Then the vacuum was turned off, and the 2 polymethyl methacrylate segments were implanted around the center of the cone in the clockwise and counterclockwise tunnels. The stromal edges of the wound were approximated, and the wounds were closed using hydration. A therapeutic soft contact lens was applied for 24 hours. Postoperative medication included a topical antibiotic–steroid combination, tobramycin plus dexamethasone (Trazidex Ofteno; Sophia Laboratories), 4 times a day for 2 weeks and artificial tears (Systane; Alcon Laboratories) 4 times a day for 2 weeks.

RESULTS

Demographics

The mean patient age was 21 years (SD = 2.12; range, 18–24 years). Keratoconus was considered as stage I in 1 patient (11.1%), stage II in 7 patients (77.7%), and stage III in 1 patient (11.1%).

Visual Acuity

The mean preoperative UCVA was 1.11 logarithm of the minimal angle of resolution (logMAR) (SD = 0.31). Postoperative UCVA at 6 months after the CXL procedure was 0.75 logMAR (SD = 0.31) and at 6 months after FR implantation UCVA was 0.23 logMAR (SD = 0.14), showing a statistically significant reduction between the preoperative and postoperative follow-up ($P = 0.03$ and $P < 0.001$, respectively). Compared with the preoperative UCVA, the postoperative UCVA at 6 months after FR showed a gain of 3 or more lines of vision in all 9 eyes. All eyes achieved visual acuity of 20/60 or better 6 months after the latest treatment. The mean preoperative BCVA was 0.26 logMAR (SD = 0.21); at 6 months after the CXL procedure, BCVA was 0.24 logMAR (SD = 0.19), and at 6 months after the FR implantation, it was 0.12 logMAR (SD = 0.14). The differences between preoperative and postoperative BCVA values were not significant ($P = 0.87$ and $P = 0.05$ at 6 months after CXL and 6 months after the FR implantation, respectively). BCVA was unchanged or improved in all eyes compared with the preoperative levels. Table 1 lists preoperative and postoperative UCVA and BCVA for each of the study eyes, and Figure 2 shows mean UCVA and BCVA at 6 months after CXL and FR.

Simulated Keratometry

The mean maximum (K1) and minimum (K2) simulated keratometry measurements, compared with preoperative levels, were reduced by 0.57 and 0.36 D, respectively, with no statistically significant difference ($P = 0.57$ for K1; $P = 0.36$ for K2) at 6 months after the CXL procedure. However, at

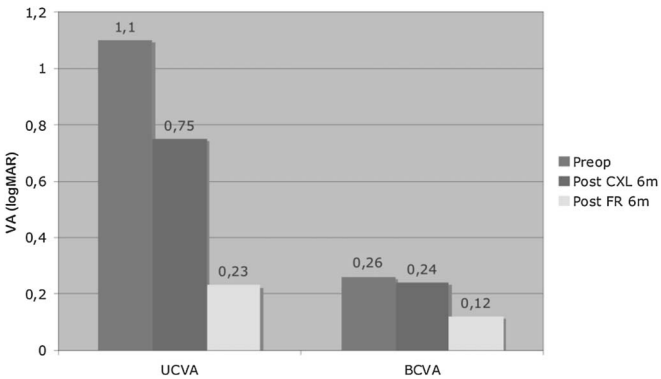

FIGURE 2. Pre- and postoperative UCVA and BCVA. m, months; Post, postoperative; Preop, preoperative; VA, visual acuity.

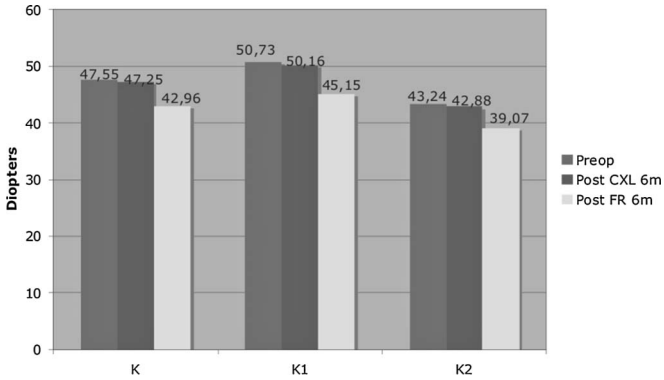

FIGURE 3. Keratometry values at pre- and postoperative follow-up. K, central keratometry value; K1, maximum keratometry value; K2, minimum keratometry value; m, months; Post, postoperative; Preop, preoperative.

6 months after FR implantation, reductions of 5.58 D in K1 and 4.17 D in K2 were observed, a statistically significant difference ($P < 0.001$ for both). Table 1 lists preoperative and postoperative keratometry measurements for each of the study eyes; Figure 3 shows mean central K, K1, and K2 at 6 months after CXL and FR, and Figures 4 and 5 show the topographic maps of 2 patients.

Refractive Outcomes

For the CXL procedure, the mean spherical value decreased by 0.53 D between the preoperative and 6-month postoperative examinations, with a nonsignificant difference ($P = 0.75$); in contrast for the cylinder value, a reduction of 1.75 D was observed, showing significant difference ($P < 0.001$). At 6 months after FR implantation, mean refractive spherical and cylinder values had decreased significantly by 2.39 D ($P = 0.02$) and 3.97 D ($P < 0.001$) compared with preoperative levels. Table 1 lists preoperative and postoperative refractive errors for each of the study eyes, and Figure 6 shows the mean preoperative and postoperative refractive errors.

Ferrara Rings

The thickness of the FRs was 0.20 mm (200 μm) in 5 patients (55.5%), 0.15 mm (150 μm) in 3 patients (33.3%), and 0.25 mm (250 μm) in 1 patient (11.1%). FR segments were successfully implanted in all eyes without intraoperative complications. Subsequent removal was not required in any patient.

DISCUSSION

The results from this study demonstrate improved refractive outcomes compared with preoperative values for patients with progressive keratoconus undergoing riboflavin/UVA CXL treatment plus FR implantation with a reduction of 4.38 D in the mean SE at 12 months postoperatively. Refractive results after CXL have demonstrated a decrease in the mean SE value from 0.93 to 1.42 D.[7,8,14,15] In terms of corneal curvature, studies described a postoperative reduction of mean keratometry from 0.92 to 2.1 D after 6 months[6] and between 1.45 and 2.68 D after 1 year.[6,7,14,15]

Previous studies of corneal ring implantation for keratoconus showed that the mean central corneal curvatures were reduced by 5.59 D[16] at 12 months and 6.1 D[17] at 13 months postoperatively with Ferrara intracorneal rings and 3.7 D[4] at 12 months and 3.59 D[3] at 6 months postoperatively with Intacs. In this combined procedure (CXL + FR), we found similar results with a mean reduction of 5.58 and 4.17 D in the maximum and minimum simulated keratometry values 6 months after the FR implantation and 12 months after the CXL procedure, showing that a stiffer cornea that has been treated by CXL can be

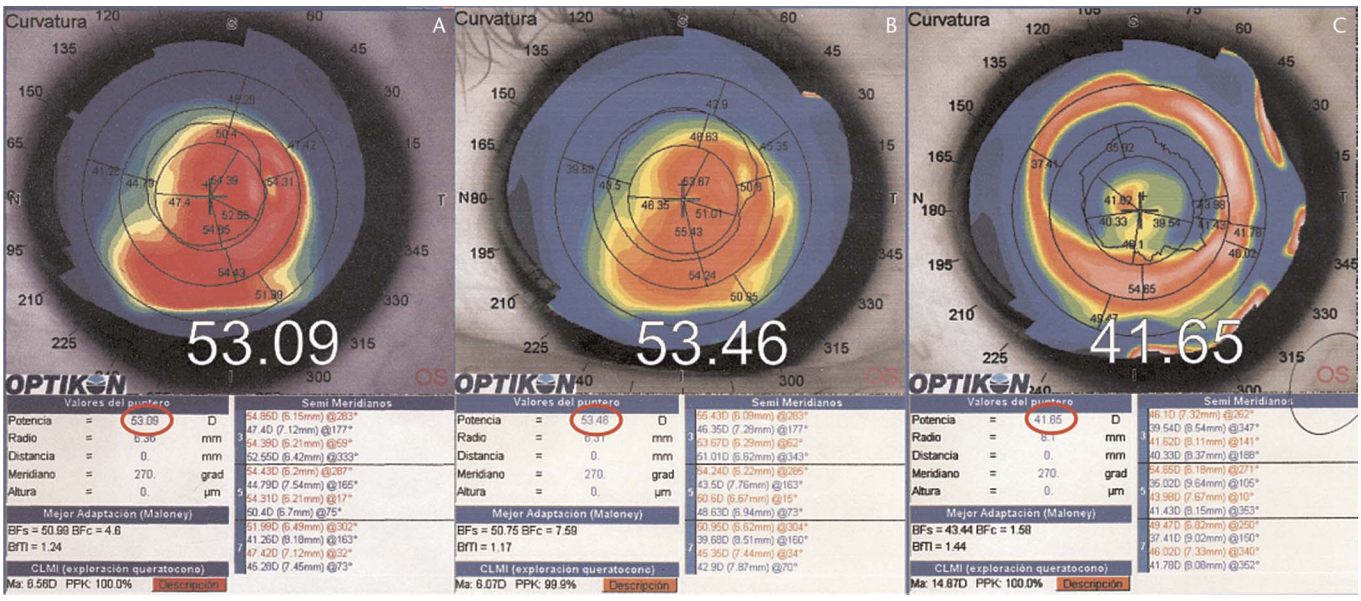

FIGURE 4. Pre- and postoperative topographic maps of 1 patient showing the evolution of the keratometry values. A, Preoperative. B, 6 months after the CXL procedure. C, 6 months after the FR implantation.

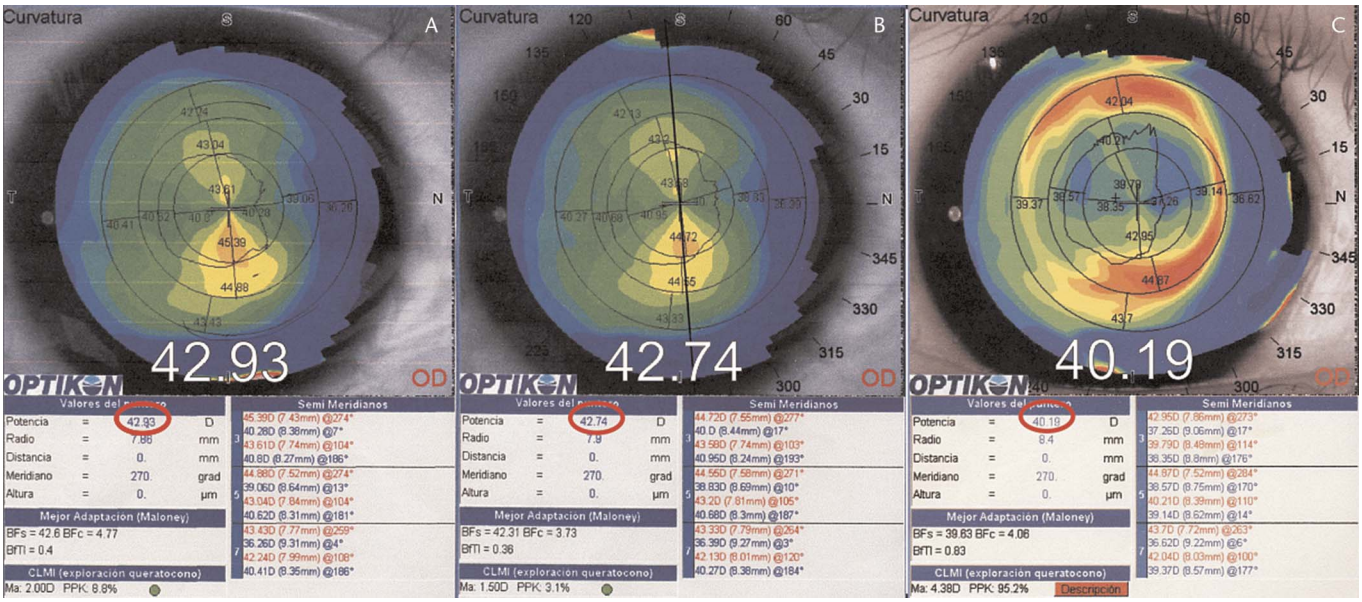

FIGURE 5. Pre- and postoperative topographic maps of another patient showing the evolution of the keratometry values. A, Preoperative. B, 6 months after the CXL procedure. C, 6 months after the FR implantation.

reshaped by the intracorneal ring, producing an acceptable flattening effect. A case report[18] of this combined procedure for ectasia after laser in situ keratomileusis showed reduction in the mean keratometry value of 9 and 6.5 D in each eye.

We decided to combine the procedures to improve the 2 principal problems in the patient with keratoconus: the refractive error using the FR and the progression of the disease using the CXL procedure. In our study at 12 months postoperatively, no patients had progression of the cone and all of them had improvement in visual acuity and refractive error. However, a longer follow-up is necessary to confirm the stability of these results.

We performed corneal collagen CXL first because FR implantation requires a corneal incision, and in our experience, patients with a history of previous incisional surgery, such as radial or astigmatic keratotomy, can develop moderate to severe haze after CXL, and because the literature[6,14] has shown that CXL produces statistically significant reductions in keratometry values and refractive errors with time, we wait 6 months before the FR implantation to consider the changes produced by the CXL procedure on the SE to calculate the thickness of the implanted ring according to the Bicalho nomogram. Although it is true that a longer period could show a greater change in this parameter, our patients usually do not like to wait a long time for a final result. In other hands, and in our practice, some patients who were scheduled to have this combined procedure have a dramatic improvement in visual acuity or keratometry values after the CXL procedure, and, thus, we decide to not implant the FR. The advantage of performing the CXL first is that we stop or slow the progression of the keratoconus and then we can treat the residual refractive error by the best alternative that can fit the patient, such as intracorneal rings or phakic intraocular lens, for example, or by a nonsurgical approach such as glasses or a contact lens. In conclusion, this combined procedure of CXL plus FR implantation appears safe and efficacious for the treatment of selected patients with progressive keratoconus, with significant improvements in visual acuity, keratometry values, and refractive error.

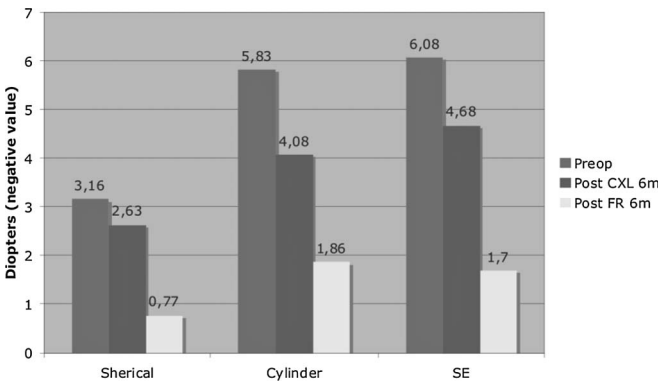

FIGURE 6. Refractive error values at pre- and postoperative follow-up. m, months; Post, postoperative; Preop, preoperative.

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