Riboflavin-UVA-Induced Corneal Collagen Cross-linking in Pediatric Patients

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Purpose: Evaluation of stability and functional response after riboflavin-UVA–induced cross-linking in a population of patients younger than 18 years with progressive keratoconus after 36 months of follow-up.

Methods: Prospective nonrandomized phase II open trial conducted at the Department of Ophthalmology, Siena University, Italy. The "Siena CXL Pediatrics" trial involved 152 patients aged 18 years or younger (10–18 years) with clinical and instrumental evidence of keratoconus progression. The population was divided into 2 groups according to corneal thickness (>450 and <450 μm) at the time of enrollment. The riboflavin-UVA–induced corneal cross-linking was performed in all patients according to the standard epi-off protocol. Parameters recorded preoperatively and postoperatively were as follows: uncorrected visual acuity, best spectacle–corrected visual acuity, corneal topography and surface aberrometry (CSO Eye Top topographer; Florence, Italy), optical pachometry (Visante OCT; Zeiss Meditec, Jena, Germany), and HRT II confocal microscopy (Rostock Cornea Module, Heidelberg, Germany).

Results: Functional data at 36 months showed an increase of +0.18 and +0.16 Snellen lines for uncorrected visual acuity and best spectacle-corrected visual acuity, respectively, in the thicker group (corneal thickness >450 μm) and +0.14 and +0.15 Snellen lines, respectively, in the thinner group (corneal thickness <450 μm). Patients in the latter group already showed a better and faster functional recovery than the thicker group at 3-month follow-up. Topographic results showed statistically significant improvement in K readings and asymmetry index values. Coma reduction was also statistically significant.

Conclusions: The study demonstrated significant and rapid functional improvement in pediatric patients younger than 18 years with progressive keratoconus, undergoing riboflavin-UVA–induced cross-linking. In pediatric age, a good functional response and keratoconus stability was obtained after corneal cross-linking in a 36-month follow-up.

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Diagnosis of keratoconus before adulthood is a negative prognostic factor for progression, increasing the probability of the need for corneal transplant.[1] Younger patients are a population particularly at risk for faster progression of the disease.[1,2]

Medium- to long-term results reported in the literature[3–5] have demonstrated the capacity of riboflavin-UVA–induced cross-linking to slow the progression of keratoconus through photopolymerization of collagen mediated by reactive oxygen species, increasing the biomechanical rigidity and biochemical resistance of the cornea.[6–8] The effects of cross-linking against progression of the ectasia are not limited to the instantaneous formation of covalent bonds (cross-links) within and between collagen fibrils and to the inhibition of collagenase,[9,10] but the long-term stabilizing effect is sustained by synthesis of new collagen, having different structure[11,12] and resistance,[13] capable of imparting variable lamellar compaction to the corneal stroma.[14] This compaction is responsible for functional changes recorded after treatment and improvement of functional results, as reported in a recent study by our group.[14] Long-term international results[3–5] suggest that corneal cross-linking should now be the elective therapy for young patients with progressive keratoconus. The aim of this study was the evaluation of stability and functional response after riboflavin-UVA–induced cross-linking in a population of patients younger than 18 years with progressive keratoconus.

PATIENTS AND METHODS

More than 500 patients have been treated in Siena since 2004. The study "Siena CXL Pediatrics" involved analysis of a sample of 152 keratoconus patients aged 18 years or younger (range, 10–18 years) with clinical and instrumental evidence of progression; 94 eyes (61%) had 12 months of follow-up, and 81 eyes (53%) were at 24 months of follow-up and 77 eyes (51%) at 36 months of follow-up. The male:female (M:F) ratio was 4:1. The population was divided into 2 groups according to corneal thickness at the time of enrollment in the treatment protocol. The thicker group included 56 eyes with corneal thickness >450 μm, namely, stages I and II. The thinner group included 21 eyes with corneal thickness <450 μm, namely, stages II and III.

Inclusion Criteria

The patients were enrolled between September 2006 and September 2009. Patients 18 years and under (range 10–18 years) with clinically and instrumentally documented keratoconus progression in the last 3 months were enrolled in the treatment protocol. The parameters taken to indicate that keratoconus was progressive were at least 2 of the following: uncorrected visual acuity (UCVA)/best spectacle-corrected visual acuity (BSCVA) deterioration ≥1 Snellen line, Sph/Cyl increase >0.50 diopters (D), Kave (average) increase >0.50 D, topographic surface asymmetry index (SAI)/symmetry index (SI) increase >0.50 D, reduction in corneal thickness (thinnest point) ≥10 μm, biomicroscopic and confocal microscopic evidence of clear cornea (absence of scar and Vogt striae), and clinical refractive instability that could not be corrected optically by spectacles or contact lenses.

Surgical Technique

The surgical procedure of corneal cross-linking induced by riboflavin and UVA was performed in all pediatric patients according to our protocol[3]: premedication with 2% pilocarpine in the eye to be treated 30 minutes before the operation, topical anesthesia with 4% lidocaine 15 minutes before the operation, verification of the energy of the solid-state UVA source (Caporossi, Baiocchi, Mazzotta VEGA X-linker; Costruzione Strumenti Oftalmici, Florence, Italy) at 3 mW/cm^2 (range, 2.7–3.2 mW/cm^2 on power meter), placing the patient under the operating microscope and inserting a lid speculum with closed valves, opening a disposable 0.1% riboflavin–20% dextran solution (Ricrolin; Sooft, Montegiorgio, Italy), marking the epithelium with a Thornton marker in the area to treat (diameter, 9 mm) and removing the epithelium with a blunt metal spatula, 10 minutes corneal soaking in 0.1% riboflavin–20% dextran solution before the start of UVA irradiation, irradiation of the 8-mm corneal area 6 times for 5 minutes each time (total 30 minutes), instillation of riboflavin–dextran solution after each 5-minute irradiation and every 2 to 3 minutes during UVA irradiation, washing the eye surface with balanced saline solution and instillation of 2 to 4 drops of ofloxacin and cyclopentolate at the end of the procedure, and dressing the eye with a therapeutic soft corneal lens for 4 days. No adjunctive sedation was required before the procedure, and all children were able to tolerate the treatment. Sometimes, the presence of a parent (generally the mother) was needed in the operating room to effectively reduce the patient's anxiety.

Follow-up and Assessment Criteria

Follow-up of patients varied from a minimum of 3 months to a maximum of 48 months. Seventy-seven eyes (51%) or 152 had a follow-up of more than 36 months. Data were acquired at various stages of follow-up: preoperative assessment (treatment day), assessment on the fourth day on removal of the therapeutic contact lens, and clinical and instrumental assessment 1 month and 3, 6, 12, 24, and 36 months after the operation. The following parameters were recorded: UCVA, BSCVA, topographic indices of symmetry, such as SAI and SI by CSO Eye Top topographer (CSO, Florence, Italy), aberrometric surface indices (coma value) by CSO Eye Top topographer, optical pachometry by Visante OCT (Zeiss Meditec, Jena, Germany), and confocal microscopy (HRT II) by Rostock Cornea Module (Heidelberg, Germany).

RESULTS

Regarding the incidence of keratoconus in patients younger than 18 years in our series, we found an M:F ratio of 4:1, which differs from epidemiological findings in the literature of 2:1 M:F ratio.[15,16] We did not find any statistically significant differences in incidence of the pathology between the right eye and left eye.

In the thicker group patients (corneal thickness >450 μm), the UCVA collected at 12, 24, and 36 postoperative months showed an increase of +0.22 (P = 0.0018), +0.2 (P = 0.0021) and +0.18 (P = 0.002) Snellen lines, respectively. BSCVA showed a gain of +0.19 (P = 0.0018), +0.17 (P = 0.0029), and +0.16 (P = 0.0045) Snellen lines after 12, 24, and 36 months, respectively (Fig. 1A).

In the thinner group patients (corneal thickness <450 μm), the UCVA showed an increase of +0.16 (P = 0.0021), +0.13 (P = 0.0019), and +0.14 (P = 0.0023) Snellen lines at 12, 24, and 36 months of follow-up, respectively. BSCVA showed a gain of +0.17 (P = 0.0031), +0.17 (P = 0.0033), and +0.15 (P = 0.0051) Snellen lines after 12, 24, and 36 months, respectively (Fig. 1B).

Patients in the thinner group already showed a significantly faster functional recovery than the thicker group at the 3-month follow-up (+0.05 Snellen lines on average) (Fig. 2) The thicker group (patients aged 18 years or younger with corneal thickness >450 μm, stages I–II) showed a statistically significant reduction in Kmin value of –0.49 D (P = 0.0041), –0.38 D (P = 0.0031), and –0.42 D (P = 0.0023) at 12, 24, and 36 months of follow-up, respectively; a statistically significant reduction in Kmax value was recorded during the follow-up by a mean of –0.43 D (P = 0.0068), –0.84 D (P = 0.0052), and –0.76 D (P = 0.0071) at 12, 24, and 36 months, respectively; Kave reduction was also statistically significant by a mean of –0.46 D (P = 0.0051), –0.60 D (P = 0.0046), and –0.58 D (P = 0.0038) at 12, 24, and 36 months after treatment (Fig. 3A).

The thinner group (patients with corneal thickness <450 μm, stages II–III) showed a statistically significant reduction in Kmin values by a mean of –0.49 (P = 0.008), –0.61 D (P = 0.0054), and –0.58 D (P = 0.0079) at 12, 24, and 36 months of follow-up, respectively; Kmax value showed a statistically significant reduction by a mean of −0.41 D (P = 0.0022) at 12 months, –0.71 D (P = 0.0059) at 24 months, and –0.61 D (P = 0.0048) at 36 months. Kave values at 12, 24, and 36 months of follow-up were also statistically significant and reduced by a mean of –0.45 D (P = 0.0048), –0.66 D (P = 0.0069), and –0.60 D (P = 0.0051), respectively (Fig. 3B).

In the thicker group, the SAI was significantly improved by a mean of –0.70 D (P = 0.0048), –0.73 D (P = 0.0043), and –0.72 D (P = 0.0041) at 12, 24, and 36 months, respectively; topographic SI showed a statistically nonsignificant reduction by a mean of –0.04 D (P = 0.09), –0.17 D (P = 0.07), and –0.13 (P = 0.018) at 12, 24, and 36 months, respectively (Fig. 4A).

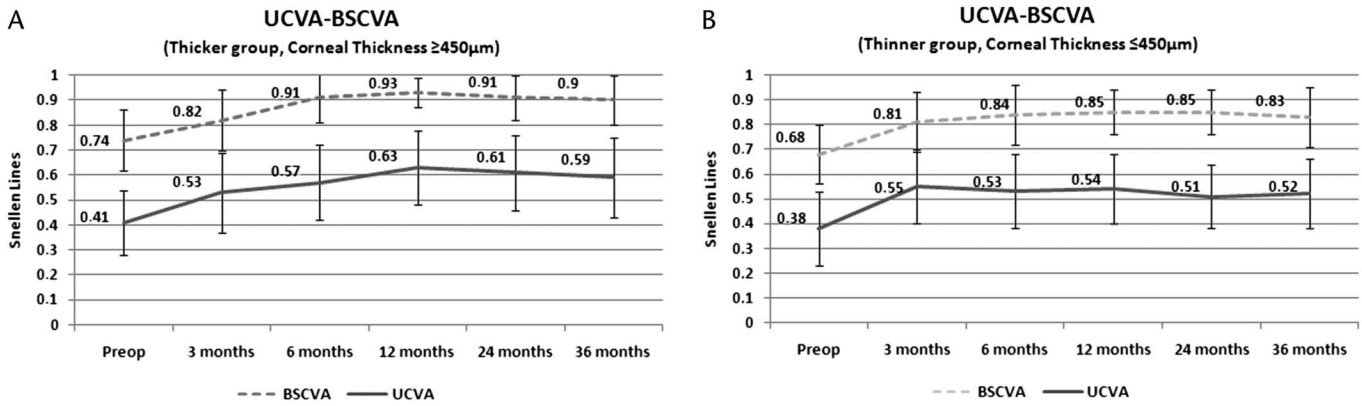

FIGURE 1. In the thicker group, UCVA (A, continuous line) and BSCVA (A, dotted line) gained a mean of +0.18 and +0.16 Snellen lines, respectively, after 36 months of follow-up. In the thinner group, UCVA (B, continuous line) and BSCVA (B, dotted line) improved by a mean of +0.14 and +0.15 Snellen lines at 36 months of follow-up, respectively. Irrespective of preoperative corneal thickness, functional improvement was statistically significant in both groups without significant differences in gained lines. Final visual acuity was better in the thicker group because of the earlier stage of keratoconus at the time of enrollment in the treatment protocol.

he thinner group showed a statistically significant reduction in the SAI by a mean of –0.74 D (P = 0.0039), –0.76 D (P = 0.0044), and –0.69 D (P = 0.0089) at 12, 24, and 36 months after treatment, respectively. Topographic SI showed a statistically nonsignificant reduction by a mean of –0.11 D (P = 0.070), –0.13 D (P = 0.059), and –0.06 D (P = 0.065) at 12, 24, and 36 months of follow-up, respectively (Fig. 4B). Coma values showed a statistically significant reduction since the first postoperative 3 months in both groups, from 1.63 to 1.08 µm (P = 0.0048) at 36 months in the thicker group (Fig. 5A) and from 1.74 to 1.29 µm (P = 0.0071) at 36 months in the thinner group (Fig. 5B).

CONCLUSIONS

The results of the Siena CXL Pediatrics study demonstrated significant and rapid functional improvement (average, +0.15 Snellen lines) in patients younger than 18 years with progressive keratoconus undergoing riboflavin-UVA–induced cross-linking. No adverse events (infections or scars) were recorded in this pediatric series. Transient corneal edema with glare disability in the first postoperative 4 to 6 weeks was present in 55% of patients (without a statistically significant visual loss) and was well managed with topical preservative-free steroids (fluorometholone drops, tapered 3 times a day for 4–6 weeks). A slight to moderate haze (stromal hyperdensity)[12] occurred in 9.8% of patients without negatively influencing visual acuity. Analysis of the 2 groups showed that at 3-month follow-up, functional recovery was already faster, by an average of +0.5 Snellen lines in UCVA and BSCVA, in patients with corneal thickness <450 µm (thinner group) than in those with corneal thickness >450 µm (thicker group). At the third month of follow-up, indeed, the reduction of coma values was double in the thinner group patients than that in the thicker group patients, becoming superimposable along the follow-up. At 36 months of follow-up, there was not a statistically significant difference in coma value improvement between the 2 groups.

The faster functional response in patients with lower corneal thickness seems to be reasonably explained by early coma value improvements, probably because of the relatively higher percentage of cross-linked tissue. Patients with greater corneal thickness improved slower but at 36 months of follow-up, the gain of functional data was a mean of +1.5 Snellen lines in BSCVA and +1.6 Snellen lines in UCVA without statistically significant differences between the 2 groups. Final visual acuity (UCVA and BSCVA) was better in the thicker group because of the earlier stage of keratoconus at the time of enrollment. However, the poorer final visual acuity in the thinner group patients was well explained by their more advanced stage of keratoconus at the time of inclusion in the treatment protocol.

As demonstrated in the literature,[14] it is impossible to predict the exact distribution of cross-links in the cornea and the geometric redistribution of newly formed collagen.[12] The recovery process is therefore variable and random whatever the

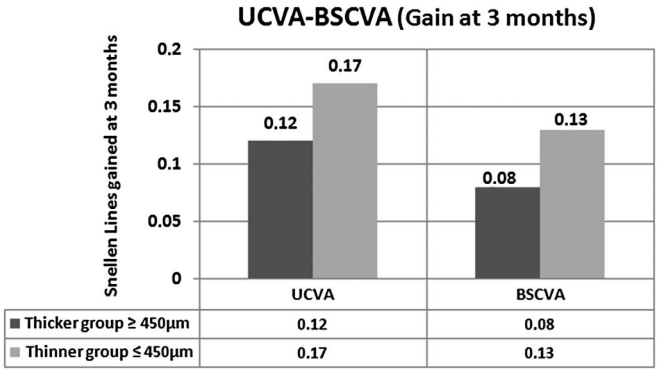

FIGURE 2. Comparative refractive results of UCVA (left) and BSCVA (right) between the 2 groups [thicker (>450 µm) and thinner (<450 µm)] recorded at the third postoperative month showed a faster recovery (+0.5 Snellen lines on average) in the thinner group likely related to the relatively increased cross-linking percentage with faster coma value improvements.

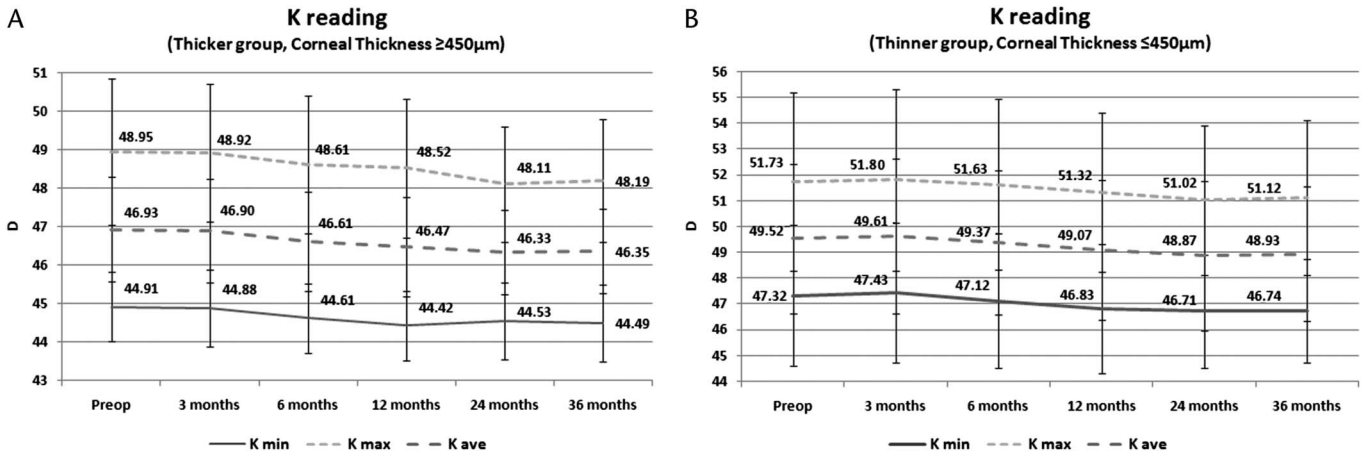

FIGURE 3. Topographic results after cross-linking in pediatric patients. Patients younger than 18 years with corneal thickness >450 µm (thicker group) (A) and patients with corneal thickness <450 µm (thinner group) (B) showed a statistically significant reduction in all K reading values at 36 months of follow-up. Kmin (inferior continuous line) was reduced by a mean of –0.42 D and –0.69 D, respectively; Kmax (superior dotted line) by a mean of –0.58 and –0.69 D, respectively; Kave (intermediate large dotted line) by a mean of –0.76 and –0.68 D at 36 months of follow-up, without statistically significant differences between the 2 groups.

initial corneal thickness or age of the patient. With regard to functional results, the response in terms of visual improvement in these young patients was statistically significant in the whole population and in the 2 groups. As a consequence of corneal flattening and lamellar compaction after cross-linking,[14] mean variations in K readings and topographic SIs were also statistically significant in our series. The improvement in topographic indices reflects improved corneal symmetry because of recentering of the corneal apex (push-up effect), as recently demonstrated in the literature.[14] Topographic indices recorded in the 2 groups showed a statistically significant mean reduction of maximum K reading and corneal surface asymmetry values.

This study demonstrates the effective capacity of corneal cross-linking to slow the progression of keratoconus in pediatric patients aged 18 years or younger, improving functional performance in 80% of patients 3 years after the operation, irrespective of preoperative corneal thickness. In a small percentage of pediatric cases (4.6%), a worsening of functional and instrumental (topographic and pachometric) data was observed during the follow-up, reasonably explained by the higher aggressiveness and progressiveness of keratoconus in pediatric patients because of genetic and other environmental factors.[1,15]

The results of this study suggest that riboflavin-UVA–induced cross-linking stabilized the progression of keratoconus in all cases and led to functional improvement in UCVA, BSCVA, SAI, and coma values in 80% of cases, with statistically significant results. These outcomes lead us to the preliminary conclusion that corneal cross-linking should

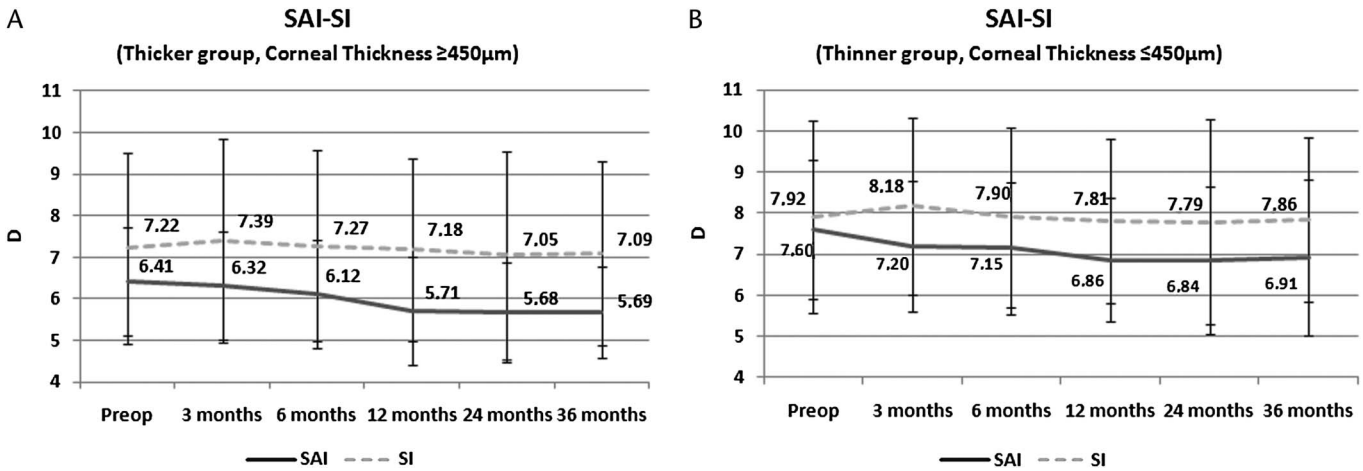

FIGURE 4. Topographic SI modifications after cross-linking in pediatric patients. Surface anterior index (SAI, continuous line) in the thicker group (A, continuous line) was significantly improved at 36 months of follow-up by a mean of –0.72 D and in the thinner group (B, continuous line) by a mean of –0.69 D; topographic SI reduction showed a statistically nonsignificant reduction in both groups 36 months after treatment, respectively, by a mean of –0.13 D (A, dotted line) and –0.32 D (B, dotted line).

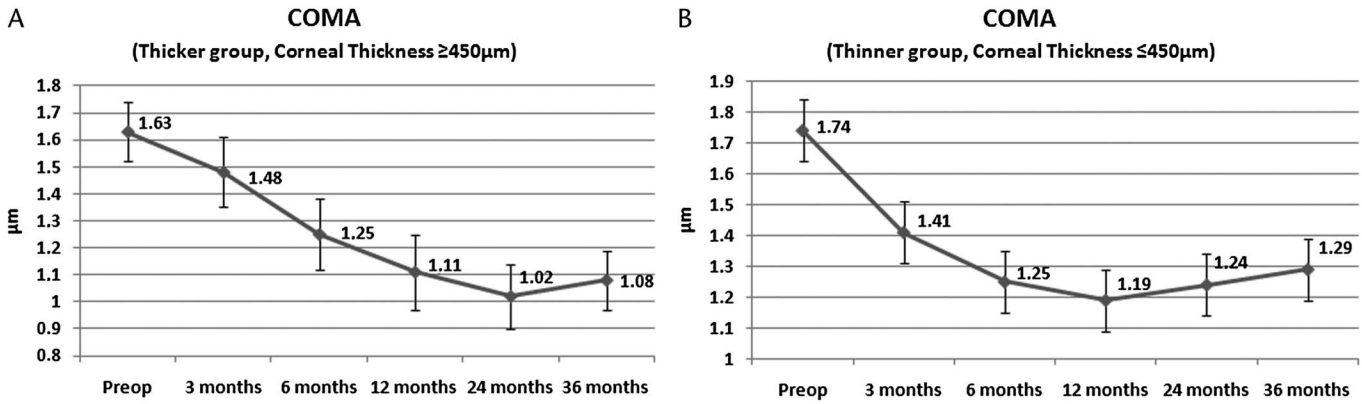

FIGURE 5. Postoperative coma changes after corneal cross-linking in pediatric patients. Coma values at 36 months showed a statistically significant reduction since the first postoperative 3 months in both groups, from 1.63 to 1.08 μm at 36 months in the thicker group (A) and from 1.74 to 1.29 μm in the thinner group (B). Coma improvement at the third month was lower in the thicker group (–15 μm) than in the thinner group (–0.33 μm), explaining the faster improvement of visual acuity in this group. At 36 months of follow-up, there was not a statistically significant difference in coma values improvement between the 2 groups (–0.55 and –045 μm, respectively).

currently be the elective treatment for progressive keratoconus in pediatric patients younger than 18 years. Particularly in this age group, the disease is more aggressive,[1,16] but a good functional response and keratoconus stability are obtained.

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