Accelerated Epi-on Versus Standard Epi-off Corneal Collagen Cross-Linking for Progressive Keratoconus in Pediatric Patients

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Purpose: To evaluate and compare the effectiveness and safety of accelerated transepithelial (A-epi-on) corneal collagen cross-linking (CXL) with standard CXL (epi-off) for children with progressive keratoconus.

Methods: Prospective, cohort study including 61 eyes of 51 patients younger than 18 years with progressive keratoconus at Oftalmosalud Instituto de Ojos, Lima, Peru. A-epi-on CXL was performed for 36 eyes using 30 minutes of impregnation (0.25% riboflavin, 1.0% phosphate hydroxypropyl methylcellulose, 0.007% benzalkonium chloride) and 5 minutes of irradiation (18 mW/cm^2). Epi-off CXL was performed for 25 eyes using 30 minutes of impregnation (riboflavin 0.1% solution plus 20% dextran 500) and 30 minutes of irradiation (3 mW/cm^2). Scheimpflug imaging parameters were evaluated preoperatively and at 6 and 12 months postoperatively.

Results: Mean uncorrected visual acuity improvement was 0.12 logarithm of the minimum angle of resolution (logMAR) for both groups (P = 0.09 for A-epi-on and P = 0.16 for Epi-off). Mean improvements in the best-corrected visual acuity were 0.09 logMAR (P = 0.05) and 0.06 logMAR (P = 0.05) at 12 months postoperatively for the A-epi-on group and the epi-off group, respectively. Mean maximum keratometry changes were +0.1 D (P = 0.62) and −0.94 D (P = 0.11) for the A-epi-on group and the epi-off group, respectively, at 12 months postoperatively. There were no significant differences between groups regarding changes in pachymetry and posterior elevation values ($P > 0.05$). Keratoconus progression was observed in 5.6% and 12% of eyes in the A-epi-on group and the epi-off group, respectively.

Conclusions: Accelerated epi-on CXL and standard epi-off CXL are safe and effective for stopping the progression of keratoconus at 12 months postoperatively.

Key Words: accelerated epi-on, standard epi-off, corneal collagen cross-linking, progressive keratoconus, pediatric patients, children

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Keratoconus is a corneal ectatic disorder characterized by bilateral conical protrusion and thinning.[1] It affects corneal stroma and leads to decreased biomechanical strength of the tissue, which is believed to be caused by diminished intrafibrillary and interfibrillary cross-links of the collagen fibers.[2] On average, it presents during the second decade of life; however, in a percentage of patients, it presents during childhood, is more aggressive, and has a higher progression risk than in older individuals.[3,4]

Corneal collagen cross-linking (CXL), which is based on the combined use of riboflavin (as a photosensitizer) and ultraviolet A (UVA) light, is the only available treatment for the underlying pathology to halt the progression of keratoconus.[5] Although CXL is a simple and relatively safe procedure, epithelial debridement involves the inherent risk of corneal infection, subepithelial haze, sterile corneal infiltrates, corneal scarring, and severe pain.[6,7] By contrast, the transepithelial technique does not require epithelial removal.[8]

Although the standard CXL (epi-off) protocol requires 30 minutes of irradiation (3 mW/cm^2), there have been changes in protocols for energy and UVA irradiation exposure time to shorten the duration of the procedure. Therefore, 10 minutes of irradiation (9 mW/cm^2) and 5 minutes of irradiation (18 mW/cm^2) have been tested with promising results.[9]

The aim of this study was to evaluate and compare the effectiveness and safety of accelerated transepithelial (A-epi-on) CXL compared with epi-off for children with progressive keratoconus.

METHODS

This prospective cohort study included patients diagnosed with progressive keratoconus who were found eligible for a CXL procedure at Instituto de Ojos, Oftalmosalud (Lima, Peru) from November 2013 to December 2014. The study complied with the Declaration of Helsinki. The ethics committee of Oftalmosalud approved the study, and written informed consent was obtained from the parents or legal representative before the procedure. If the child was able to understand the nature of the study, then written informed consent was obtained from that child as well.

Inclusion criteria were age below 18 years, a clear central cornea, minimum pachymetry of 400 μm [at the thinnest point (TP)], and documented progression defined by an increase in steep keratometry by ≥1 diopter during the

previous 6 to 12 months. Exclusion criteria were amblyopia, retinal pathology, and history of ocular infection.

Patients were examined at baseline and at 6 and 12 months after CXL. Manifest refraction, uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), slit-lamp examination, and Scheimpflug imaging analysis (Oculus Pentacam GmbH, Wetzlar, Germany) data were obtained at each follow-up time. All participants who wore contact lenses were instructed to discontinue their use at least 3 days before examinations (for scleral and soft contact lenses) or 2 weeks before examinations (for rigid permeable lenses).

Surgical Procedure

In both groups, local anesthetic eye drops containing proparacaine hydrochloride 0.5% (Alcaine; Alcon Laboratories) were administered. For epi-off, epithelial removal (9 mm) was performed using a blunt spatula (Asico AE2766). Pachymetry was confirmed using a pachymeter (Ophthasonic A-Scan/Pachometer III; Accutome, Malvern, PA). Isotonic riboflavin 0.1% solution (B2 riboflavin) plus 20% dextran 500 (Peschke, Huenenberg, Switzerland) was administered every 5 minutes for 30 minutes until complete corneal impregnation using a suction ring positioned on the cornea pooled with riboflavin. Then, the cornea was rinsed with balanced salt solution, and yellow flare was checked during the slit-lamp examination. If flare was not observed, then 10 extra minutes of impregnation was indicated until flare was observed. UVA irradiation was performed using the CCL-VARIO (Peschke Ltd, Borsigstrabe, Germany) for 30 minutes (3 mW/cm^2), and isotonic riboflavin 0.1% solution was readministered to the cornea every 5 minutes.

In the accelerated epi-on group, transepithelial riboflavin (Peschke) composed of 0.25% riboflavin, 1.0% phosphate hydroxypropyl methylcellulose, and 0.007% benzalkonium chloride was administered every 5 minutes for 30 minutes until complete corneal impregnation using a suction ring. Then, the cornea was rinsed with balanced salt solution. Yellow flare was checked during the slit-lamp examination; if flare was not observed, then 10 extra minutes of impregnation was indicated until it was observed. UVA irradiation was performed using the CCL-VARIO cross-linking system (Peschke Ltd) for 5 minutes (18 mW/cm^2).

For both groups, the post-CXL medication consisted of antibiotic eye drops [Vigamox, (moxifloxacin hydrochloride); Alcon Nederland] and nonsteroidal antiinflammatory drops [Nevanac (nepafenac) 0.1%; Alcon Nederland] for 1 week, preservative-free artificial tears for 4 weeks, and topical steroids [FML (fluorometholone) 0.1% drops; Allergan BV] 3 times per day for 3 weeks, starting 1 week after CXL. A bandage contact lens (PureVision; Bausch & Lomb) was used for the epi-off group and removed after 5 days.

Statistical Analysis

Statistical analyses were performed using SPSS version 22.0. Comparisons of mean values were performed using the Student *t* test and the nonparametric Mann–Whitney test. Data were expressed as mean and SD. For any case, $P < 0.05$ was considered statistically significant.

RESULTS

Sixty-one eyes of 51 patients were included; 31 (60.8%) males and 20 (39.2%) females were involved in the study. Thirty-six eyes in the A-epi-on group and 25 in the epi-off group were included. Mean age was 14.9 years (range, 12–15) and 13.2 years (8–16) in the A-epi-on group and the epi-off group, respectively. There was no statistically significant difference between the groups ($P = 0.12$). There was no statistically significant difference between the groups in terms of UCVA, BCVA, sphere, cylinder, and pachymetry during the preoperative evaluation ($P > 0.05$). Table 1 shows preoperative data and postoperative data (6 and 12 mo) for all parameters studied.

Visual Acuity and Refraction

For the A-epi-on group, mean UCVA improvement was 0.12 logarithm of the minimum angle of resolution (logMAR) ($P = 0.09$) at 12 months postoperatively, and mean improvement in BCVA was 0.09 logMAR ($P = 0.05$) at 12 months postoperatively. For the epi-off group, mean improvement in UCVA was 0.12 logMAR ($P = 0.16$) at 12 months postoperatively and mean improvement in BCVA was 0.06 logMAR ($P = 0.05$) at 12 months postoperatively. None of the eyes in either group lost BCVA lines.

Keratometry

Mean changes in steep keratometry were +0.23 D for the A-epi-on group and −0.33 for the epi-off group at 12 months postoperatively. There was no statistically significant difference between preoperative and postoperative values for either group ($P = 0.11$ and $P = 0.19$, respectively).

The mean maximum keratometry change was +0.1 D for the A-epi-on group at 12 months postoperatively ($P = 0.62$) and −0.94 D for the epi-off group at 12 months postoperatively ($P = 0.11$). There was no statistically significant difference between groups ($P = 0.09$).

Pachymetry

In the A-epi-on group, mean changes at the TP of the cornea were +2.99 and +1.52 μm at 6 months ($P = 0.42$) and 12 months ($P = 0.62$), respectively. For the epi-off group, mean reduction values at the TP of the cornea at 6 and 12 months postoperatively compared with preoperative values were −21.55 μm ($P = 0.03$) and −12.55 μm ($P = 0.08$), respectively. There was no difference between groups at 12 months ($P = 0.06$).

Posterior Elevation at the TP

Mean changes in the A-epi-on and epi-off groups at 12 months postoperatively were +1.86 and +2.45 μm, respectively. There was no significant difference in either group ($P = 0.62$ and $P = 0.17$, respectively).

TABLE 1. Preoperative and Postoperative Changes at 6 and 12 Months Postoperative

	Preoperative	6 Months Postoperative	12 Months Postoperative	P*	P†	P‡
A-epi-on CXL						
UCVA	0.60 (0.23)	0.51 (0.30)	0.48 (0.25)	0.24	0.09	0.91
BCVA	0.19 (0.17)	0.12 (0.11)	0.10 (0.10)	0.14	0.05	0.91
Steep keratometry	48.46 (2.91)	48.73 (3.15)	48.69 (3.15)	0.09	0.11	0.05
Maximum keratometry	52.12 (5.27)	52.48 (5.30)	52.22 (5.32)	0.11	0.62	0.09
Flat keratometry	43.55 (2.76)	43.61 (2.93)	43.55 (2.76)	0.68	1.00	0.07
Pachymetry at TP	493.01 (47.81)	496 (56.30)	494.53 (51.49)	0.42	0.62	0.06
Sphere	−0.30 (2.16)	−0.08 (1.62)	−0.25 (2.00)	0.50	0.90	0.58
Cylinder	−4.12 (1.24)	−3.35 (1.96)	−4.05 (1.93)	0.09	0.89	0.35
Asphericity	−0.81 (0.37)	−0.82 (0.43)	−0.85 (0.42)	0.68	0.26	0.26
Anterior elevation at TP	14.80 (7.77)	15.13 (8.37)	15.67 (8.30)	0.57	0.38	0.12
Posterior elevation at TP	28.47 (15.32)	29.07 (16.44)	30.33 (16.76)	0.71	0.36	0.82
Epi-off CXL						
UCVA	0.65 (0.45)	0.55 (0.39)	0.53 (0.40)	0.25	0.16	
BCVA	0.15 (0.13)	0.10 (0.10)	0.09 (0.07)	0.08	0.05	
Steep keratometry	48.70 (3.41)	48.20 (3.34)	48.37 (3.66)	0.12	0.19	
Maximum keratometry	51.31 (6.44)	50.11 (4.62)	50.37 (5.23)	0.15	0.11	
Flat keratometry	43.98 (3.43)	43.22 (3.00)	43.36 (2.99)	0.03	0.07	
Pachymetry at TP	505.11 (37.54)	483.56 (44.03)	492.56 (40.17)	0.03	0.08	
Sphere	−2.39 (2.61)	−2.14 (1.92)	−2.06 (2.04)	0.54	0.31	
Cylinder	−2.83 (2.09)	−2.03 (2.04)	−2.17 (2.02)	0.07	0.10	
Asphericity	−0.75 (−0.34)	−0.64 (0.40)	−0.66 (0.44)	0.19	0.38	
Anterior elevation at TP	14 (7.26)	12.67 (8.29)	12.56 (8.28)	0.31	0.19	
Posterior elevation TP	29.11 (15.41)	32.67 (16.59)	31.56 (17.59)	0.02	0.17	

*For preoperative changes and 6-month postoperative changes using the Student *t* test.
†For preoperative changes and 12-month postoperative changes using the Student *t* test.
‡For groups at 12-month follow-up.

CXL Failure

Five eyes experienced keratoconus progression (considered an increase of ≥1 D in maximum keratometry at 12 mo postoperatively): 5.6% (2 eyes) in the A-epi-on group and 12% (3 eyes) in the epi-off group. Table 2 shows the preoperative and postoperative data for these patients. All 5 patients had maximum keratometry values more than 52 D during preoperative evaluation. Figure 1 shows 1 case with progression and 1 case without progression in the A-epi-on group. Figure 2 shows 1 case with progression and 1 case without progression in the epi-off group.

Adverse Effects and Postoperative Complications

No intraoperative or serious postoperative complications occurred in this series of patients. One eye had stromal haze that lasted 2 months and resolved with topical corticosteroid treatment. One eye had sterile infiltrates that resolved

TABLE 2. Preoperative and 12 Month Postoperative Data for 5 Progression Cases

Group	Age	Preoperative UCVA	Preoperative BCVA	Preoperative Kmax	Preoperative Pachy TP	Postoperative UCVA	Postoperative BCVA	Postoperative Kmax	Postoperative Pachy TP
A-epi-on	10	0.69	0.10	52.5	481	0.80	0.09	60.3	415
A-epi-on	10	1.60	0.39	66.3	454	1.60	0.39	68.9	420
Epi-off	11	0.40	0.30	53.5	483	0.54	0.30	59.3	418
Epi-off	15	0.69	0.30	64.1	520	0.54	0.30	50.9	456
Epi-off	10	1.30	0.30	66.3	454	1.30	0.30	68.9	420

Kmax, maximum keratometry; Pachy TP, pachymetry at the TP.

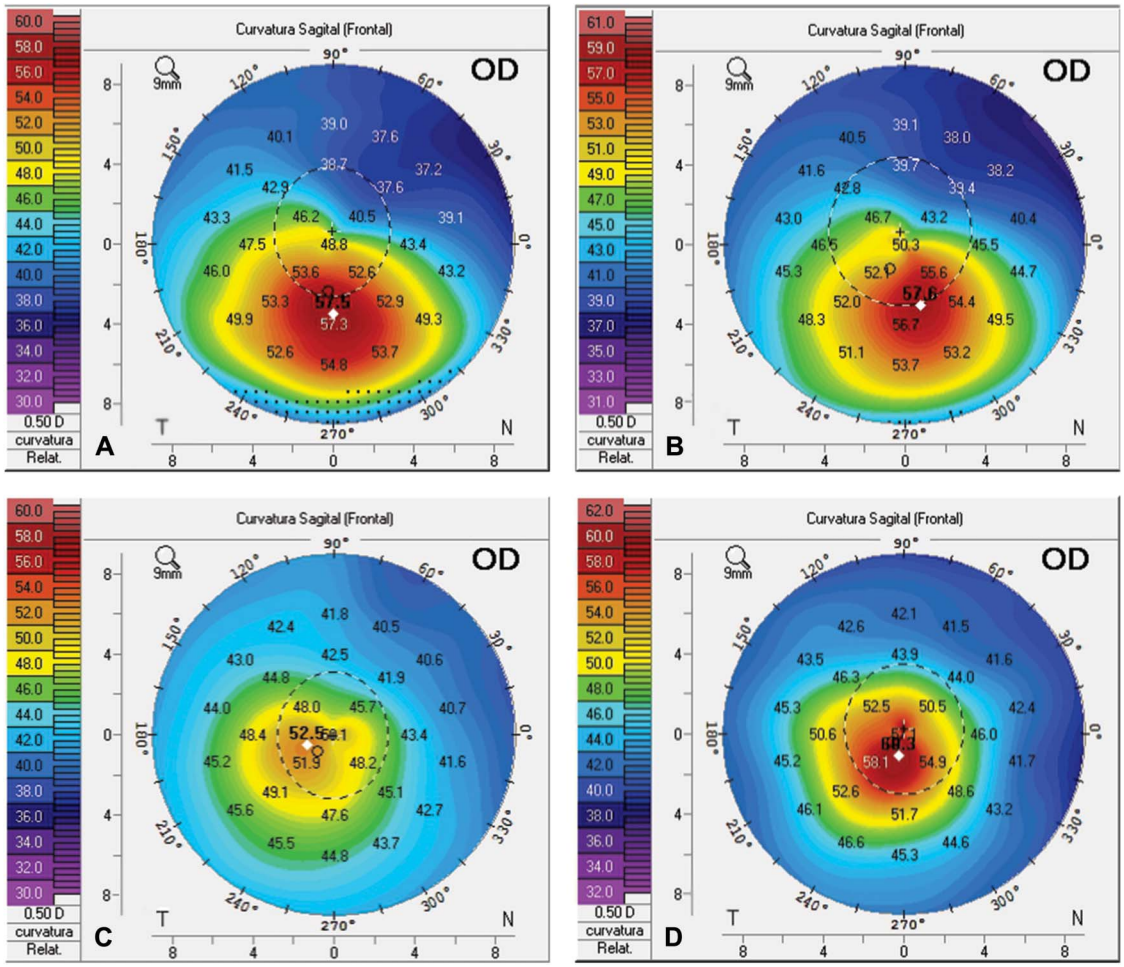

FIGURE 1. Preoperative (A) and 12 months postoperative (B) curvature map of a patient with no progression in the A-epi-on group. Preoperative (C) and 12 months postoperative (D) curvature map of a patient who experienced CXL failure in the A-epi-on group.

at postoperative day 22 using standard postoperative treatment regimens. Both eyes were from the epi-off group.

DISCUSSION

CXL is capable of halting the progression of keratoconus. This study demonstrated that both techniques, standard epi-off CXL and A-epi-on CXL, halt the progression of keratoconus in children at 1-year follow-up. Studies using standard,[9–15] accelerated,[16–19] and transepithelial[20,21] CXL for children have shown similar results in terms of effectiveness. However, to the best of our knowledge, there are no published reports comparing accelerated transepithelial and standard epi-off CXL for pediatric patients.

According to our data, similar improvements in terms of UCVA and BCVA were observed in both groups, with no statistical change at 12 months of follow-up. Different results concerning an improvement in visual acuity have been reported for children. Significant improvements in UCVA have been found from 0.12 to 0.26 logMAR for epi-off,[10–12,14] from 0.13 to 0.3 logMAR for accelerated CXL,[16–19] and 0.27 logMAR for transepithelial CXL. Some authors have indicated stable or nonsignificant changes in UCVA.[9,12,13,22] Significant improvement has been reported for BCVA from 0.1 to 0.33 logMAR for epi-off,[9,11–15,22–24] from 0.08 to 0.22 logMAR for accelerated CXL,[16–19] and 0.1 logMAR for transepithelial CXL.[20] Some authors have indicated stable or nonsignificant changes in BCVA.[12,15,18]

Pachymetry behavior after CXL was similar to that described in our previous report of adults using the standard epi-off procedure,[25] with initial thinning and posterior recovery during the follow-up period. In the epi-off group, a significant reduction of −21.55 μm was found at 6 months postoperatively; a nonsignificant reduction of −12.55 μm was found at 12 months postoperatively. The A-epi-on group showed nonsignificant increases of +2.99 and +1.52 μm at 6 and 12 months, respectively. In agreement with our results, Arora et al[11] reported a significant reduction of 53.28 μm, Soeters et al[13] reported a significant reduction of 10 μm, and Padmanabhan et al[22] reported a significant reduction of 31.1 μm using epi-off for children. We hypothesized that the greater decrease in pachymetry in the epi-off group could

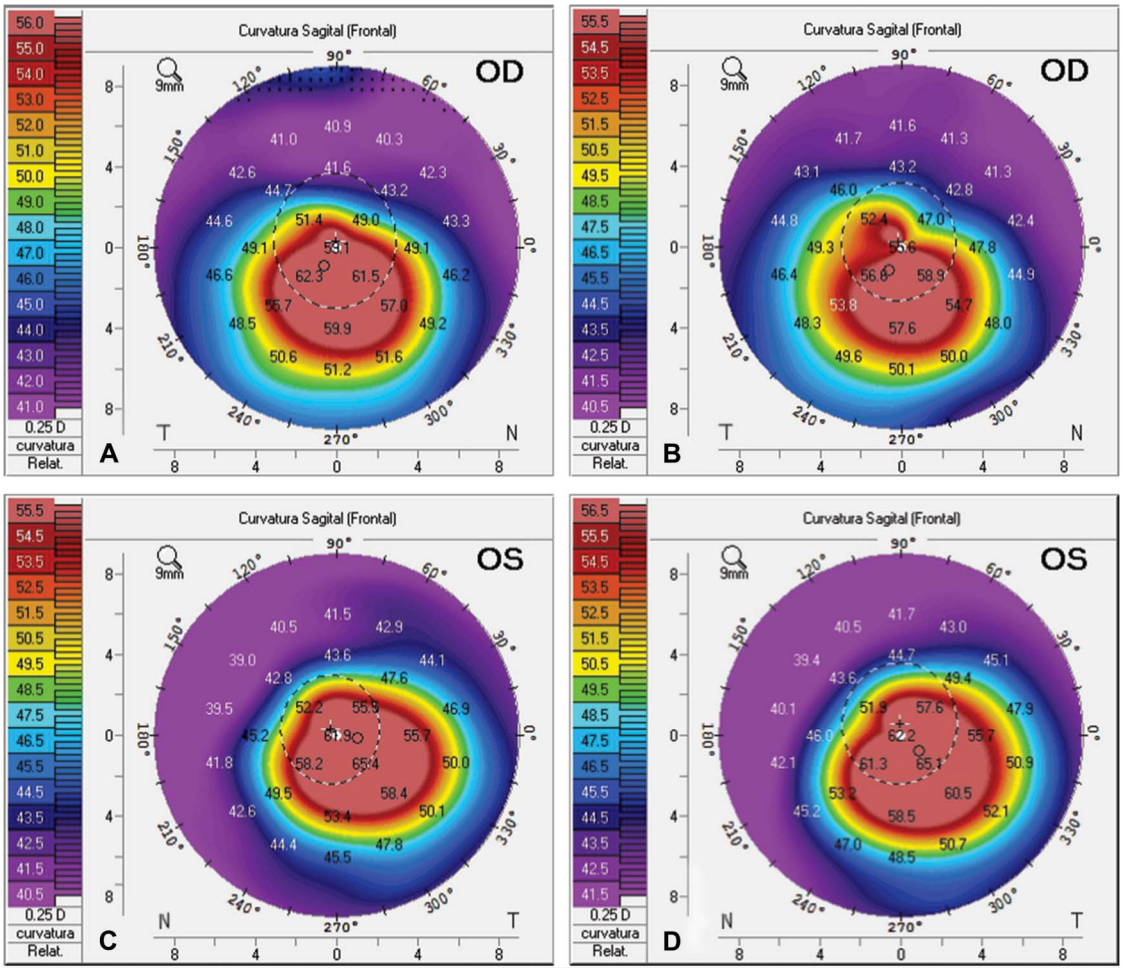

FIGURE 2. Preoperative (A) and 12 months postoperative (B) curvature map of a patient with no progression in the epi-off group. Preoperative (C) and 12 months postoperative (D) curvature map of a patient who experienced CXL failure in the epi-off group.

be attributed to the procedure itself. Demarcation lines range from 302 μm to 380 μm for conventional CXL and from 184 μm to 350 μm for accelerated CXL.[26,27] Demarcation lines are supposed to represent the effectiveness of CXL treatment due to changes in collagen fiber diameters, the stromal refractive index, and fibrillary spacing. Underestimation of corneal thickness measurements using optical methods is suspected to be a consequence of the tissue refractive index, which is expected to change in the area of the demarcation line or postoperative corneal haze[26,27] due to changes in the collagen fiber diameter and fibrillary spacing.[28] Therefore, we may assume that differences in pachymetry readings are due to different depths of the demarcation lines and the refractive index of the 2 procedures.

Despite nonsignificant differences in keratometry changes between groups, the A-epi-on group showed mean increases of +0.23 and +0.1 D for steep and maximum keratometry, respectively, at 12 months; however, the epi-off group had mean decreases of −0.33 and −0.94 D for steep and maximum keratometry, respectively. Similar to our results, Hashemi et al[9] and Vinciguerra et al[14] found no significant differences in maximum keratometry after epi-off. Buzzonetti et al[20] found no significant differences in maximum keratometry after using transepithelial CXL for children. However, most researchers found significant improvements in maximum keratometry from 0.5 to 1.24 D for epi-off,[10–13,15,22,23] from 1.0 to 2.07 D for accelerated CXL,[16–19] and from 1.14 to 2.3 D for transepithelial CXL.[12,20,21]

There were progressive cases in both groups (2 cases in the A-epi-on group and 3 cases in the epi-off group). The literature reports that progression despite CXL in children exists. Buzzonetti et al[20] found significant worsening in keratometry readings at 18 months using transepithelial CXL. Shetti et al[17] reported progression in 16.6% of cases involving accelerated epi-off CXL at 2-year follow-up. Godefrooij et al[29] reported progression of 22% of cases at 5 years. Caparrosi et al[12] reported a progression rate of 5%. Kumar Kodavor et al[10] reported a progression rate of 8.6% using the standard epi-off procedure. Because our study was not a randomized study, we cannot attribute the higher incidence of CXL failure to the epi-off procedure. Three of 5 cases that had keratoconus progression had preoperative maximum keratometry more than 54 D, and some studies suggest higher

preoperative keratometry values as a risk factor for CXL failure.[8,30,31] In fact, preoperative keratometry values more than 54 D have been associated with a failure rate up to 12% for CXL in adults. CXL failure rates observed for both procedures are in agreement with previous reports. Therefore, we cannot assume that CXL should not be performed for advanced cases because of the higher incidence of CXL failure. The effectiveness of CXL has been reported for advanced cases of keratoconus.[30] In our study, 6 eyes in the A-epi-on and 9 eyes in the epi-off group had preoperative maximum keratometry more than 54 D; among these, corneal CXL was effective for 12.

Weaknesses of the epi-off procedure included epithelial debridement with its inherent risk of corneal infection, subepithelial haze, sterile corneal infiltrates, and corneal scarring.[8] Furthermore, the A-epi-on procedure had demarcation lines that were more superficial than those of the epi-off procedure,[27] and its effects compared with those of the epi-off procedure are under debate.[13,19] Our study showed similar effects at 12 months postoperatively; however, it was reported that the effect of CXL disappears quickly in children (usually after 12 mo).[29,31] Therefore, randomized, controlled, long-term studies are necessary to determinate which procedure has better results for children over time.

In conclusion, A-epi-on CXL and epi-off CXL appear to be safe and effective for stopping the progression of keratoconus at 12 months postoperatively in pediatric patients. However, longer follow-up is necessary to assess the stability of these procedures.

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