Accelerated Epi-On Versus Standard Epi-Off Corneal Collagen Cross-Linking for Progressive Keratoconus in Pediatric Patients: Five Years of Follow-Up

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Purpose: The purpose of this study was to evaluate and compare the 5-year efficacy and safety of accelerated transepithelial (A-epi-on) corneal collagen cross-linking (CXL) with standard CXL (epi-off) in children with progressive keratoconus (KC).

Methods: This prospective cohort study included 78 eyes of patients aged 18 years old or younger with progressive KC who underwent CXL at the Oftalmosalud Institute of Eyes, Lima, Peru. A-epi-on CXL was performed in 32 eyes (30′ of impregnation/5′ of irradiation at 18 mW/cm2) and epi-off CXL was performed in 46 eyes (30′of impregnation/30′ minutes of irradiation at 3 mW/cm2). Visual acuity, refraction, and the Scheimpflug imaging parameters were evaluated preoperatively and postoperatively at 1 and 5 years.

Results: The best corrected visual acuity improved to 0.06 logarithm of the minimum angle of resolution (SD: 0.19, $P = 0.03$) and 0.09 logarithm of the minimum angle of resolution (SD: 0.13, $P < 0.001$) in the A-epi-on and epi-off groups, respectively. The mean flattening in the mean keratometry was 0.09 diopters (D) (SD: 0.68, $P = 0.33$) and 3.18 D (SD: 5.17, $P < 0.001$) in the A-epi-on CXL and Epi-off groups at the 5-year follow-up. Significant differences were found in the change at 1 and 5 years between the groups for cylinder reduction, flat and mean K, and pachymetry (all $P < 0.05$). The KC progression rate was 9.37% (3/32) in the A-epi-on CXL; no progression was found in the epi-off CXL group at the 5-year follow-up.

Conclusions: Both procedures halted the progression of KC at the 5-year follow-up; however, epi-off CXL was safer and more effective when compared with A-epi-on CXL.

Key Words: pediatric patients, children, corneal collagen cross-linking, accelerate CXL, epi-on CXL, epi-off CXL, transepithelial CXL

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Keratoconus is a progressive ectatic corneal disorder characterized by bilateral conical protrusion and thinning. It affects the corneal stroma and leads to decreased biomechanical tissue strength, which is believed to be caused by diminished intrafibrillary and interfibrillary cross-links of the collagen fibers.[1] Keratoconus (KC) is more severe in children; 30% present with stage IV KC,[2–5] advanced cases that are more severe and rapidly progressing[2–6] and in younger patients progress more aggressively.[6]

Corneal cross-linking (CXL) is the only Food and Drug Administration-approved treatment available to halt the progression of KC. Long-term studies have proved its efficacy and safety in adults.[7,8] Although CXL is a relatively safe procedure, debriding the corneal epithelium can cause a risk of microbial infection, subepithelial haze, sterile corneal infiltrates, and corneal scarring.[9] By contrast, the transepithelial technique does not require epithelial removal, and considering that children can benefit from this procedure, studies comparing these techniques are necessary.

Despite several publications regarding CXL in children,[5,10–17] there is limited information on long-term studies after 5 years[6,18–20] and special and different treatment modalities. The aim of this study was to evaluate and compare the efficacy and safety of accelerated transepithelial corneal CXL with standard epi-off CXL in children with progressive KC at the 5-year follow-up.

METHODS

This prospective cohort study included all consecutive pediatric patients in whom the standard epi-on CXL procedure or accelerated epi-off CXL for progressive KC was performed from September 2008 through September 2014 and were 18 years old or younger at the time of CXL the at Oftalmosalud Institute of Eyes, Lima, Peru. The study complied with the tenets of the Declaration of Helsinki. The ethics committee of Oftalmosalud approved the study, and written informed consent was obtained from the parents or their legal representatives before the procedure. If the child was able to understand the nature of the study, then written informed consent was obtained from the child as well.

The inclusion criteria were age below 18 years (range 8–17), a clear central cornea, minimum pachymetry of 400 μm at the thinnest point, and documented progression defined by an increase in steep keratometry (K) of 1 D or greater assessed

between 2 tests with at least 2 months apart. The exclusion criteria were amblyopia, retinal pathology, and a history of ocular infection.

The present study shows the postoperatory results at 12 and 60 months; nevertheless, the standard follow-up protocol for patients after CXL is at day 1, 7, and 30 postoperatory days; every 3 months during the first year; every 6 months during the second year; and afterward, 1 visit per year. 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 of the 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). In addition, keratoconus eyes were also classified into center or decenter cones for some statistical analysis. Central cones were defined if the steepest meridian on topographic map was positioned within the central 3 mm and paracentral cones if the steepest meridian was located out the central 3-mm zone.[21,22]

Surgical Procedure

Local anesthetic eye drops containing proparacaine hydrochloride 0.5% (Alcaine; Alcon Laboratories) were administered to the patients in both groups. 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 pooled with riboflavin positioned on the cornea.

Then, the cornea was rinsed with balanced salt solution, and the presence of a yellow flare was checked during the slit-lamp examination. If a flare was not observed, then 10 extra minutes of impregnation was indicated until a flare was observed. UVA irradiation was performed using the CCL-VARIO cross-linking system (Peschke Ltd, Borsigstrasse, Germany) for 30 minutes (3 mW/cm2), and isotonic riboflavin 0.1% solution was readministered to the cornea every 5 minutes.

In the accelerated epi-on group, transepithelial riboflavin (Peschke) composed 0.25% riboflavin, 1.0% phosphate hydroxypropyl methylcellulose, and 0.007% benzalkonium chloride was administered using a suction ring every 5 minutes for 30 minutes until complete corneal impregnation was achieved. Then, the cornea was rinsed with balanced salt solution. The presence of a yellow flare was checked during the slit-lamp examination; if a 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) for 5 minutes (18 mW/cm2).

For both groups, post-CXL medication consisted of antibiotic eye drops (Vigamox, moxifloxacin hydrochloride; Alcon Nederland, Gorinchem, Netherlands) and nonsteroidal anti-inflammatory 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 analysis was performed using R version 3.6.1, a free statistical software under the terms of the Free Software Foundation's general public license (https://www.r-project.org/). Changes within each group (epi-off and A-epi-on) regarding time were evaluated using the Quade test. Post hoc testing using adjusted P values for multiple comparisons (the false discovery rate method) was performed when the Quade test indicated statistically significant differences. For comparisons between the 2 methods, permutation tests for analysis of variance (ANOVA) designs were performed to establish whether the differences were statistically significant. Post-ANOVA comparisons were conducted using the Wilcoxon rank-sum test. All of the tests were performed with a type I error equal to 0.05.

RESULTS

A total of 78 eyes of 65 patients were included; 36 (55.38%) male and 29 (44.62%) female patients were involved in this study. There were 32 eyes in the A-epi-on group and 46 in the epi-off group. The mean patient age was 13.2 ± 2.6 years (range 8–16) and 14.6 ± 2.1 years (range 10–17) in the A-epi-on and epi-off groups, respectively (P = 0.12). There was no statistically significant difference between the groups in UCVA, BCVA, sphere, cylinder, K, and pachymetry during the preoperative evaluations ($P > 0.05$). In the epi-off group all 46 eyes were evaluated at pre-op, 1, and 5 years of follow-up. In the A-epi-on group, 32/32 were evaluated at pre-op and 1 year of follow up and 31/32 at 5 years of follow-up. Table 1 and 2 shows both groups' preoperative and postoperative operative data and mean changes in each group, respectively.

Visual Acuity

For the epi-off and A-epi-on groups, there were not significant changes in the UCVA neither at 12 months nor at 60 months of follow-up.

For the epi-off group, mean BCVA improvement was 0.03 ± 0.13 and 0.09 ± 0.13 logarithm of the minimum angle of resolution at 12 and 60 months postoperatively (P = 0.097 and $P < 0.001$, respectively), whereas in the A-epi-on group, mean improvement was 0.09 ± 0.17 and 0.06 ± 0.19 at 12 and 60 months postoperatively, and it was statistical significant at both follow-up periods (P = 0.042 and P = 0.037, respectively).

In the epi-off group, there was no loss of BCVA lines; however, in the A-epi-on group, there was a loss of BCVA lines in 3 of the 3 eyes that progressed (1 patient had a loss of one line of BCVA and 2 patients had a loss of 2 lines of BCVA); there was no loss of line vision on BCVA in the rest of the patients who did not progress.

TABLE 1. Mean Values of Each Parameter at 12 and 60 months Postoperative

Parameter	Preop Mean ± SD	12 mo Mean ± SD	60 mo Mean ± SD	*P**	*P*†	*P*‡
Epi-off CXL						
UCVA (LogMar)	0.61 ± 0.40	0.58 ± 0.42	0.61 ± 0.32	0.987	0.987	0.987
BCVA (LogMar)	0.19 ± 0.15	0.16 ± 0.14	0.10 ± 0.10	**0.002**	0.097	**<0.001**
Sphere (D)	−1.20 ± 1.53	−1.07 ± 1.27	−1.60 ± 1.57	0.129	0.129	0.129
Cylinder (D)	−3.43 ± 2.17	−2.77 ± 1.75	−2.56 ± 1.92	**0.042**	**0.043**	**0.043**
Flat K (D)	44.91 ± 2.56	44.58 ± 2.31	44.19 ± 2.35	**0.002**	0.070	**0.001**
Steep K (D)	49.60 ± 3.84	49.63 ± 3.60	48.58 ± 3.26	**0.014**	0.800	**0.023**
Mean K (D)	49.35 ± 6.77	46.90 ± 2.58	46.24 ± 2.48	**<0.001**	**0.011**	**<0.001**
Corneal astigmatism (D)	4.54 ± 3.01	5.01 ± 2.74	4.39 ± 2.59	0.377	0.377	0.377
Maximum K (D)	54.37 ± 5.69	54.07 ± 5.70	52.74 ± 4.73	**<0.001**	0.087	**<0.001**
Pachymetry TP (μm)	490.36 ± 36.57	465.96 ± 44.47	473.50 ± 43.18	**<0.001**	**<0.001**	**<0.001**
Asphericity	−0.85 ± 0.39	−0.80 ± 0.41	−0.70 ± 0.40	**0.023**	0.401	**0.022**
Anterior elevation (μm)	17.44 ± 9.71	15.80 ± 9.49	13.25 ± 8.98	**<0.001**	0.196	**<0.001**
Posterior elevation (μm)	33.03±20.47	36.68±21.98	34.67±20.13	0.157	0.157	0.157
A-epi-on CXL						
UCVA (LogMar)	0.60±0.23	0.48±0.25	0.56±0.34	0.100	0.100	0.100
BCVA (LogMar)	0.19±0.17	0.10±0.10	0.13±0.14	0.055	**0.042**	**0.037**
Sphere (D)	0.07±2.33	−0.25±2.00	−0.52±2.40	0.838	0.838	0.838
Cylinder (D)	−5.12±1.24	−4.78±1.40	−4.87±1.45	0.608	0.608	0.608
Flat K (D)	43.51±2.82	43.55±2.76	43.67±3.02	0.764	0.764	0.764
Steep K (D)	49.48±2.89	49.65±3.11	49.50±3.22	0.266	0.266	0.266
Mean K (D)	47.32±2.78	47.41±2.88	47.41±3.08	0.338	0.338	0.338
Corneal astigmatism (D)	5.90±1.17	6.14±1.33	5.87±1.38	0.087	0.087	0.087
Maximum K (D)	52.11±5.29	52.22±5.32	51.83±4.83	0.252	0.252	0.252
Pachymetry TP (μm)	483.00 ± 47.81	484.53 ± 51.49	490.33 ± 52.19	**0.030**	0.735	**0.044**
Asphericity	−0.81 ± 0.37	−0.85 ± 0.42	−0.72 ± 0.29	**0.005**	0.581	**0.014**
Anterior elevation (μm)	14.80 ± 7.77	15.67 ± 8.30	13.73 ± 7.81	0.183	0.183	0.183
Posterior elevation (μm)	28.47 ± 15.32	30.33 ± 16.76	28.87 ± 15.31	0.735	0.735	0.735

Bold indicates statistically significant difference.

**P* value= *P* value for multiple comparisons using the Quade test.

†*P* = *P* value between preoperative and 1 year postoperative (using the Wilcoxon rank-sum test with continuity correction, only performed for those values with statistical significance on *P**).

‡*P* = *P* value between preoperative and 5 years postoperative (using the Wilcoxon rank-sum test with continuity correction only performed for those values with statistical significance on *P**).

TP, thinnest point.

Refraction

For the epi-off group, cylinder had a significant decrease of 0.66 ± 1.37 D and 0.89 ± 2.39 D at 12 and 60 months postoperatively ($P = 0.04$ both); sphere did not have significant changes neither at 12 months nor at 60 months postoperatively.

For the A-epi-on group, sphere and cylinder did not have significant changes neither at 12 nor at 60 months postoperatively.

Keratometry

For the epi-off group, flat, steep, and maximum K did not have significant changes at 12 months postoperatively; however, at 60 months, all of them reached significant flattening of 0.77 ± 1.41 , 1.02 ± 1.85 D, and 1.67 ± 2.22 D, respectively ($P < 0.001$, $P = 0.023$, and $P < 0.001$, respectively); the mean K reached significant flattening of 2.45 ± 5.22 D and 3.18 ± 5.17 D at 12 and 60 months, respectively ($P = 0.01$ and $P < 0.001$, respectively). For the A-epi-on group, flat, steep, maximum, and mean K did not have significant changes neither at 12 nor 60 months postoperatively. Figures 1 and 2 show the preoperative and postoperative mean K and maximum K readings in both groups.

A total of 9.37% (3/32) of patients in the A-epi-on group experienced Kmax progression greater than 1 D, the progression was evidenced at the 12-month follow-up visit for the 3 cases, whereas none of the patients in the epi-off group experienced Kmax progression greater than 1 D at 5 years.

The rate of patients with flattening in the Kmax greater than or equal to 2 D at 5 years postoperative was 43.47% (20/46) in the epi-off group and 12.5% (4/32) in the A-epi-on group. Stabilization in the maximum K (between ± 1 D) at 5 years of follow-up was achieved in 52.18% of the cases in the epi-off group and 59.38% of the cases in the A-epi-on group. 8.68% (4/46) in the epi-off group and 18.75% (6/32) of the eyes in the A-epi-on group showed flattening of one meridian with steepening of the orthogonal meridian (coupling effect). Overall, 43.47% (20/46) in the epi-off group and 18.75% (6/32) of the eyes in the A-epi-on group showed flattening of both meridians.

TABLE 2. Mean Absolute Change in Each Parameter at 1 and 5 years of Follow-Up in the A-Epi-on and Epi-off Groups

	Epi-off CXL		A-Epi-on CXL		*P* Between Procedures		
Parameter	At 1 year Mean ± SD	At 5 years Mean ± SD	At 1 year Mean ± SD	At 5 years Mean ± SD	*P**	*P*†	*P*†
UCVA (LogMar)	0.03 ± 0.28	0.01 ± 0.35	0.12 ± 0.24	0.04 ± 0.37	0.232	0.232	0.232
BCVA (LogMar)	0.03 ± 0.13	0.09 ± 0.13	0.09 ± 0.17	0.06 ± 0.19	0.117	0.117	0.117
Sphere (D)	0.13 ± 1.28	0.26 ± 1.60	0.32 ± 2.15	0.59 ± 1.93	0.345	0.345	0.345
Cylinder (D)	0.66 ± 1.37	0.89 ± 2.39	0.33 ± 1.33	0.25 ± 1.01	**0.045**	**0.032**	**0.041**
Flat K (D)	0.32 ± 1.39	0.77 ± 1.41	0.05 ± 0.37	0.17 ± 0.70	**0.033**	**0.05**	**0.021**
Steep K (D)	0.02 ± 1.40	1.02 ± 1.85	0.17 ± 0.40	0.02 ± 0.77	0.055	0.055	0.055
Mean K (D)	2.45 ± 5.22	3.18 ± 5.17	0.09 ± 0.29	0.09 ± 0.68	**0.010**	**0.045**	**0.001**
Maximum K (D)	0.30 ± 1.86	1.67 ± 2.22	0.11 ± 0.79	0.27 ± 1.23	**0.035**	0.146	0.116
Pachymetry TP (μm)	24.40 ± 28.87	16.67 ± 26.20	1.53 ± 11.73	7.33 ± 11.78	**0.001**	**<0.001**	**<0.001**
Asphericity	0.05 ± 0.21	0.15 ± 0.0.24	−0.03 ± 0.10	0.09 ± 0.15	0.404	0.404	0.404
Anterior elevation (μm)	1.64 ± 3.22	4.42 ± 5.42	0.87 ± 3.68	1.07 ± 4.08	0.063	0.063	0.063
Posterior elevation (um)	3.65 ± 7.17	1.22 ± 12.53	1.87 ± 7.74	0.40 ± 8.99	0.911	0.911	0.911

Bold indicates statistically significant difference.
*P = Test for multiple comparisons (using the Quade test).
†P = P value between procedures for the change at 1 year of follow-up (using the Wilcoxon rank-sum test with continuity correction, only performed for those values with statistical significance on P*).
‡P = P value between procedures for the change at 5 years of follow-up (using the Wilcoxon rank-sum test with continuity correction, only performed for those values with statistical significance on P*).
TP, thinnest point.

Pachymetry

For the epi-off group, there was a significant decrease in pachymetry of 24.40 ± 28.87 μm and 16.67 ± 26.20 μm at 12 and 60 months postoperatively ($P < 0.001$ both).

For the A-epi-on group, pachymetry at the thinnest point had no significant changes at the 12-month follow-up; however, at 60 months of follow-up, a significant increase of 7.33 ± 11.78 μm was found ($P = 0.044$).

Corneal Elevation Values

For anterior elevation values, no significant changes were found at the 12-month follow-up in the epi-off group; however at the 60-month follow-up, a significant decrease of 4.42 ± 5.42 μm ($P < 0.001$) was found. For the A-epi-on group, no significant changes were found neither at 12 nor 60 months of follow-up.

For posterior elevation values, no significant changes were found neither at 12 neither nor 60 months of follow-up in both groups.

Cone Morphology

There were 29 and 17 centered and decentered cones in the epi-off group and 16 and 16 in the A-epi-on group. There was no statistically significant difference between the groups in the amount of decentered and center cones ($P = 0.179$ using the Fisher exact test). In addition to this, when analyzing the flattening effect at 60 months of follow-up between center and decentered cones, there was not statistical significant differences on mean, flattest, and steeper K when epi-off CXL neither A-epi-on CXL was performed (P = 0.116, 0.303, 0.109, and 0.141, respectively, using permutation tests for ANOVA).

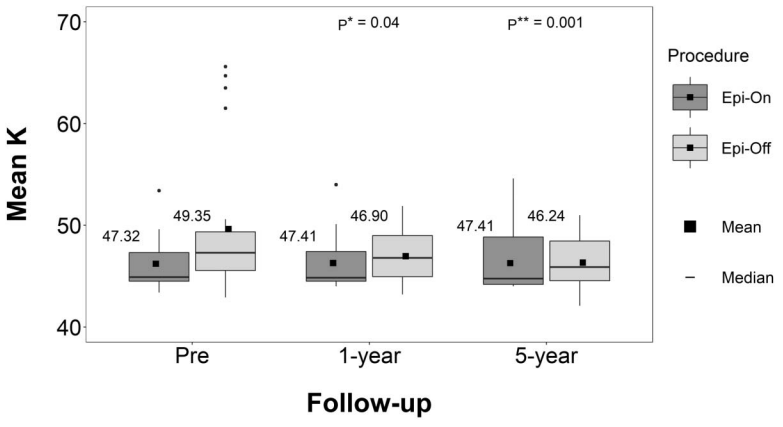

FIGURE 1. Preoperative and postoperative mean K for epi-off and A-epi-on CXL (*P and **P = P value for the change on mean K epi-off CXL/A-epi-on CXL comparison at 1 and 5 years, respectively).

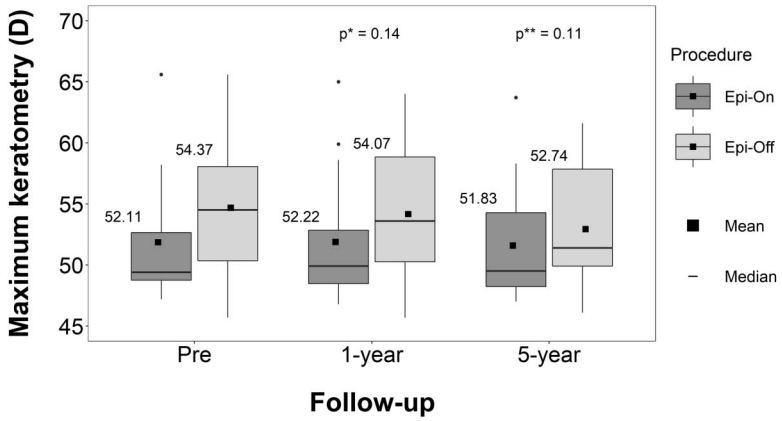

FIGURE 2. Preoperative and postoperative maximum K for epi-off and A-epi-on CXL (*P and **P = P value for the change on maximum K epi-off CXL/A-epi-on CXL comparison at 1 and 5 years, respectively).

KC Progression after CXL

Three patients experienced progression, all of them after A-epi-on CXL:

Patient 1: Maximum K were 50.8 , 52.4 and 53.8 D at pre, 1, and 5 years of follow-up, respectively. Thinnest pachymetry were 432, 425, and 420 μm at pre, 1, and 5 years of follow-up, respectively. BCVA was 20/20, 20/25, and 20/30 at pre, 1, and 5 years of follow-up, respectively. Epi-off procedure was indicated after the 1-year follow-up visit; however, the patient did not perform it and had loss of follow-up; at the 5-year follow-up visit, corneal parameters, worsening so, deep anterior lamellar keratoplasty was indicated and performed; 10 months after deep anterior lamellar keratoplasty procedure, UCVA and BCVA was 20/60 and 20/40, respectively.

Patient 2: Maximum K were 46.8, 47.9 and 48.1 D at pre, 1, and 5 years of follow-up. Thinnest pachymetry were 509, 497, and 490 μm at pre, 1, and 5 years of follow-up, respectively. UCVA was 20/30 at preoperative and 20/40 at 1 and 5 years of follow-up. BCVA was 20/20 at preoperative and 1 year postoperative and 20/25 at 5 years of follow-up, respectively. Epi-off procedure was indicated at the 5-year follow-up visit (not performed yet).

Patient 3: Preoperative Maximum K was 50.0 and 52.1 D at the 1-year follow-up. Thinnest pachymetry were 495 and 473 μm at pre and 1 year of follow-up. BCVA was 20/20 and 20/30 at pre and 1 year of follow-up, respectively. Epi-off procedure was indicated after the 1-year follow-up visit; however, the patients did not perform the procedure and was lost to follow up.

DISCUSSION

This comparative study shows that although both procedures halted the progression of KC at 5 years of follow-up, epi-off CXL did so to a significantly higher degree and with a higher flattening effect than A-epi-on the procedure.

The long-term effects of these procedures on the pediatric population remains unknown because there is limited information, mainly regarding epi-on CXL and accelerated CXL; for epi-on and accelerated CXL, there is only available data for 36 months. For standard epi-off CXL, only 2 studies reported follow-up periods longer than 5 years. Patdmanabham et al[18] showed results of 194 eyes of patients between 8 and 18 years old, with a mean follow-up time of 3.5 years (range 2–6.7 years). Maximum K demonstrated a mean flattening of 1.2 D, and no complications were reported; however, there was a trend toward steepening of the cornea in 24% of patients at long-term follow-up. Mazzota et al[6] in a prospective longitudinal cohort study of 62 eyes of pediatric patients who underwent epi-off CXL reported efficacy and safety of the procedure up to 10 years of follow-up and found statistically significant changes at 5 years in UCVA, BCVA, and maximum K. To the best of our knowledge, no studies with 5 years of follow-up are available on the accelerated or epi-on procedures in children.

Comparison studies are also limited in children; to date, there are no randomized studies in children comparing both procedures, and we are aware that this represents one of the limitations of this study. Our group presented results comparing epi-off versus accelerated epi-on CXL at 1 year of follow-up and found no significant differences between groups at 1 year of follow-up in visual acuity, refraction, and K flattening.[23] Recently, Buzzonetti et al[24] presented the results in a comparative study and found that CXL halted KC progression in 75% of eyes, whereas iontophoresis iontophoretic transepithelial CXL seemed to slow down KC progression in 50% of eyes, with no significant improvement in the K readings at 36 months of follow-up in neither group.

Our current study shows that epi-off CXL was more effective than A-epi-on CXL. Epi-off CXL halted the progression of KC in 100% of the cases, whereas A-epi-on CXL in 90.63% of the cases. Kmax stabilization between ± 1 D at 5 years of follow-up was achieved in 59.38% of the cases in the A-epi-on group versus 52.18% of the cases in the epi-off group. The intense flattening effect was higher in the epi-off group, 43.47% (20/46) in the epi-off group and 12.5% (4/32) in the A-epi-on group, and had a flattening effect in the Kmax greater than 2 D at 60 months of follow-up.

In addition, the long-term behavior of the different corneal parameters was different in both groups. Thus, A-epi-on procedure shows significant changes on BCVA at 12 and 60 months of follow-up and significant improvement on asphericity at 60 months of follow-up. Aversely, epi-off procedure shows significant changes at 12 and 60 months of follow-up in cylinder, Km, and pachymetry but also shows

several significant changes at 60 months of follow-up that were not significant at 12 months in maximum K, Ks, Kf, anterior elevation, asphericity, and BCVA, suggesting that the long-term effect on the cornea of the epi-off procedure is different than the epi-on procedure. This was confirmed by the significant differences found between groups at 60 months of follow-up in cylinder, Kf, Km, and pachymetry. Similar to our results, Mazzota et al[6] found statistically significant changes at 5 years in UCVA, BCVA, and maximum K.

Safety was also higher in the epi-off group. In the epi-off group, there was no loss of BCVA lines; however, in the A-epi-on group, there was a loss of BCVA lines in 3 of the 3 eyes that progressed (1 patient had a loss of one line of BCVA and 2 patients had a loss of 2 lines of BCVA); there was no BCVA loss of line vision in the rest of the patients who did not progress.

Although epi-off procedure seems to be more effective than A-epi-on procedure, it is important to remember that KC progression in children occurs approximately in 80% of the cases 5, and in both procedures, the progression was halted in more than 90% of the cases; in addition, there are some cases where corneal debridement is a challenge in a pediatric patient, for example, younger children and those with developmental delays or when general anesthesia is not available. We need randomized studies that can prove our results; however, it seems that epi-off CXL is more aggressive in flattening K readings when compared with A-epi on procedure, and maybe, this fact should be taken into account when thinking on the desirable effect on the cornea and the risk of progression in each patient, for example, cases with high K readings that would benefit from higher flattening effects and patients with mild KC where stabilization of the K readings or lower flattening effects are desired.

In conclusion, our results show that epi-off CXL was safer and more effective in halting the progression of KC in children at 5 years of follow-up when compared with A-Epi-on CXL.

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