# Accelerated Corneal Cross-linking in Pediatric Patients With Keratoconus: 24-Month Outcomes

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## ABSTRACT

**PURPOSE:** To compare the efficiency and safety of accelerated corneal cross-linking in pediatric patients with progressive keratoconus.

**METHODS:** In this retrospective interventional case series, 44 eyes of 38 pediatric patients with progressive keratoconus were enrolled. All consecutive patients underwent accelerated corneal cross-linking with settings of 30 mW/cm$^2$ for 4 minutes, corresponding to a total dose of 7.2 J. The efficacy and safety of the procedure were assessed over a 24-month follow-up period.

**RESULTS:** Mean ± standard deviation age of 10 girls and 28 boys was 15.3 ± 2.1 years (range: 9 to 18 years). Uncorrected distance visual acuity improved significantly from 0.52 ± 0.36 to 0.39 ± 0.26 logMAR ($P$ = .002), and corrected distance visual acuity improved significantly from 0.38 ± 0.24 to 0.30 ± 0.20 logMAR ($P$ < .001). Mean spherical and cylindrical refraction were not significantly altered ($P$ > .001 for both). At the last follow-up visit, the flat keratometry value decreased from baseline from 46.4 ± 3.0 to 46.0 ± 2.9 diopters and the steep keratometry value decreased from 50.6 ± 4.2 to 50.1 ± 4.0 diopters ($P$ < .001 for both). The total higher-order aberrations, coma, and astigmatism II values were also significantly decreased at 24 months after treatment ($P$ < .05 for all). No serious complications were recorded during the follow-up.

**CONCLUSIONS:** The findings revealed that accelerated corneal cross-linking halted the keratoconus progression without relevant side effects in pediatric patients over a 24-month follow-up period. Visual acuity, keratometric values, and corneal aberrations also improved.


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Early diagnosis of keratoconus in children is crucial due to the likelihood of halting the progression of the disease with new therapeutic modalities such as corneal collagen cross-linking (CXL). The standard CXL treatment is an epithelium-off procedure and uses UVA light with a 3 mW/cm$^2$ radiation for a duration of 30 minutes, corresponding to a total energy dose of 5.4 J/cm$^2$.[1] Recently, the use of a higher-irradiance UVA light source has been proposed to deliver the same total UVA energy in a shorter time period according to the Bunson–Roscoe law of reciprocity in a procedure termed "accelerated CXL."[2] Preliminary clinical studies[3-5] in adults and experimental data[6] have shown encouraging results for accelerated CXL. Previous clinical studies[7-13] have shown that standard CXL in pediatric patients is an effective and safe procedure for halting the disease and provides improvement in visual and topographic outcomes; however, limited outcomes have been reported on accelerated CXL treatment in pediatric keratoconus. This study evaluated the results of accelerated corneal CXL in pediatric patients with keratoconus and analyzed various outcome parameters during 24 months of follow-up.

## PATIENTS AND METHODS

### Study Design

This retrospective interventional case series included pediatric patients with progressive keratoconus who received CXL treatment in the Beyoglu Eye Research and Education Hospital. The patients' parents were informed about the risks and benefits of all procedures and provided written informed consent. The study followed the tenets of the Declaration of

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Helsinki and was approved by the ethics committee of the Beyoglu Eye Research and Education Hospital.

### Patient Population

Patients younger than 18 years and observed for at least 24 months were included in this study. Diagnosis of keratoconus was based on the presence of at least one keratoconus sign (corneal stromal thinning, Vogt striae, Fleischer ring, scissoring of the red reflex, or oil droplet sign identified by retinoscopy) and the presence of at least one topographic finding (an increased area of corneal power surrounded by concentric areas of decreasing power, inferior-superior power asymmetry, an inferior-superior dioptric asymmetry difference of 1.9 diopters [D] or more, or skewing of the steepest radial axes above and below the horizontal meridian). Keratoconus progression was defined as maximum keratometry (Kmax) increase of 1 D or more, corneal astigmatism increase of 1 D or more, and increase in manifest refraction spherical equivalent of 0.50 D or more verified by consecutive examination with a 3-month interval.

Exclusion criteria included patients with a history of ocular surgery, thinnest corneal thickness (with epithelium) less than 400 mm, a Kmax value greater than 65 D, central corneal opacity, a history of herpetic keratitis, coexisting ocular pathology, a history of contact lens wearing for at least 1 month, and a history of systemic disease or systemic medication use that was likely to affect corneal wound healing.

### Examination Protocol and Study Measurement

Preoperative and postoperative comprehensive examinations at 1, 6, 12, and 24 months were performed in all cases, including uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), manifest refraction, slit-lamp biomicroscopy, Goldmann tonometry, and fundus evaluation. All patients underwent corneal topographic and anterior aberrometric analysis (at the 3-mm zone) with the Sirius system (Costruzioni Strumenti Oftalmici, Florence, Italy). Endothelial cell density with specular microscopy was also measured at baseline and 1 month postoperatively.

### Surgical Procedure

After topical anesthesia with proparacaine HCl (Alcaine; Alcon Co., Inc., Mississauga, ON, Canada), corneal epithelium was removed with a blunt spatula (9-mm diameter). After epithelial removal, 0.1% riboflavin eye drops were applied to the corneal bed for 15 minutes with a frequency of one drop every 2 minutes. After the completion of the 15-minute riboflavin application procedure, accelerated CXL was performed using 4 minutes of continuous UVA 365-µm light (KXL System; Avedro, Inc., Waltham, MA) at an irradiance of 30 mW/cm$^2$ (7.2 J/cm$^2$) over a 9.0-mm diameter circular spot centered on the cornea based on the manufacturer's recommendation. At the end of the procedure, a bandage contact lens (PureVison; Bausch & Lomb, Inc., Rochester, NY) was placed and the eyelid speculum was removed from the eye. Prescriptions were given for moxifloxacin 0.5% (Vigamox; Alcon Laboratories, Inc., Fort Worth, TX) eye drops four times per day for 1 week, artificial tears four times per day for 1 month, and Flarex (0.1% florometalon asetate; Alcon Co., Inc., Couvreur NV, Puurs, Belgium) eye drops four times per day (1 month after epithelial healing).

### Mean Outcome Measures

The following data were used for analysis: (1) visual and refractive values; (2) simulated keratometric values (flat keratometry [K1], steep keratometry [K2], mean keratometry [Kmean], and apex keratometry [Kapex]); (3) corneal thickness; (4) keratoconus screening indices, which include the highest point of ectasia on the anterior corneal surface (keratoconus vertex$_{FRONT}$) and highest point of ectasia on the posterior corneal surface (keratoconus vertex$_{BACK}$), the symmetry index of the anterior curvature (symmetry index$_{FRONT}$), the symmetry index of the posterior curvature (symmetry index$_{BACK}$), and the Baiocchi Calossi Versaci Index front and back; (5) corneal wavefront aberrations; (6) endothelial cell density; (7) the efficacy index, defined as UDVA postoperatively/CDVA preoperatively; and (8) the safety index defined as CDVA postoperatively/CDVA preoperatively.

### Statistical Analysis

Data analyses were performed using SPSS version 16.0 (SPSS, Inc., Chicago, IL) for Windows. Normality of all data samples was assessed using the Kolmogorov–Smirnov test. A paired *t* test was used to compare the postoperative changes from the preoperative values. A *P* value less than .05 was considered statistically significant.

## RESULTS

### Demographic Results

A total of 61 eyes of 50 patients were examined. Three patients (5 eyes) did not come to control visits after 6 months and 9 patients (12 eyes) did not complete the 24 months of follow-up. The study enrolled 44 eyes of 38 patients. The mean ± standard deviation age of the 10 girls and 28 boys was 15.3 ± 2.1 years (range: 9 to 18 years).

TABLE 1

**Visual and Refractive Outcomes After Accelerated Cross-linking in Pediatric Keratoconus**

| Parameter | Mean ± SD (Range) Baseline | 1 Month | *P* | 6 Months | *P*[b] | 12 Months | *P*[b] | 24 Months | *P*[b] |
|---|---|---|---|---|---|---|---|---|---|
| UDVA logMAR | 0.52 ± 0.36 (0.03 to 1.30) | 0.48 ± 0.32 (0.10 to 1.30) | .092 | 0.42 ± 0.28[a] (0.05 to 1.00) | **.001** | 0.41 ± 0.26[a] (0.05 to 1.00) | **.004** | 0.39 ± 0.26[a] (0.00 to 1.00) | **.002** |
| CDVA logMAR | 0.38 ± 0.24 (0.00 to 0.80) | 0.44 ± 0.25 (0.10 to 0.80) | .127 | 0.37 ± 0.25 (0.05 to 0.90) | .621 | 0.31 ± 0.20[a] (0.00 to 0.80) | **< .001** | 0.30 ± 0.20[a] (0.00 to 0.80) | **< .001** |
| Sphere (D) | -3.42 ± 2.43 (-14.50 to 0.00) | -3.36 ± 2.42 (-14.50 to 0.00) | .605 | -3.36 ± 2.38 (-14.50 to 0.00) | .160 | -3.32 ± 2.44 (-14.00 to 0.00) | .498 | -3.31 ± 2.38 (-13.50 to 0.00) | .463 |
| Cylinder (D) | -4.07 ± 1.62 (-7.00 to 0.50) | -4.17 ± 1.67 (-7.50 to -0.50) | .268 | -4.05 ± 1.61 (-7.50 to -0.50) | .865 | -3.94 ± 1.57 (-7.00 to -0.50) | .226 | -3.90 ± 1.53 (-7.00 to -0.50) | .124 |
| SE (D) | -5.45 ± 2.99 (-16.88 to -0.75) | -5.44 ± 3.02 (-16.88 to -0.75) | .774 | -5.39 ± 3.08 (-16.38 to -0.50) | .233 | -5.30 ± 2.98 (-16.38 to -0.50) | .281 | 5.27 ± 2.91 (-15.88 to -0.50) | .205 |

*SD = standard deviation; UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; D = diopters; SE = spherical equivalent*
[a]*Statistically significant increased values (P < .05).*
[b]*Values in bold are statistically significant.*

## Visual Acuity

The baseline and postoperative visual acuity values are shown in **Table 1**. The mean logMAR UDVA was not significantly different at the 1-month visit ($P = .092$) but was significantly better at the 6-, 12-, and 24-month visits ($P < .05$ for all). The logMAR CDVA was not significantly different at the 1- and 6-month visits ($P > .05$ for both) but was significantly better at the 12- and 24-month visits ($P < .05$ for both). At the last visit (24 months), UDVA improved (gain of one line or more) in 31 eyes, remained stable in 10 eyes, and decreased (loss one line or more) in 3 eyes. CDVA improved in 27 eyes and remained stable in 17 eyes. No eyes showed deterioration (loss of more than one line of CDVA) (**Figure 1**). The efficacy and safety indices were 1.04 ± 0.26 and 1.24 ± 0.26, respectively.

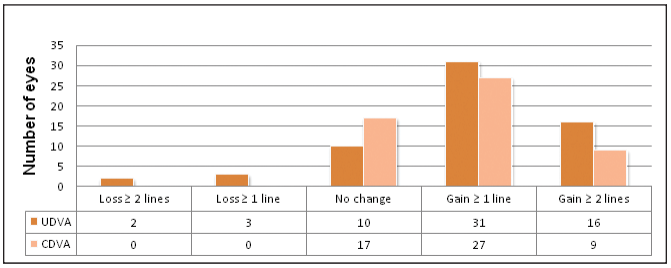


**Figure 1.** Change in uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) in Snellen lines between baseline and last visit postoperatively.

## Refractive Outcomes

The mean spherical refraction, cylindrical refraction, and spherical equivalent refraction were not significantly changed at each visit after CXL compared to baseline values ($P > .05$ for all visits) (**Table 1**). At the last visit, spherical refraction decreased (decrease of 1 D or more) in 4 eyes, remained stable (change of less than 1 D) in 36 eyes, and increased (increase of 1 D or more) in 4 eyes. Cylindrical refraction decreased in 5 eyes, remained stable in 38 eyes, and increased in 1 eye (**Figure A**, available in the online version of this article).

## Topographic Outcomes

The mean keratometric (K1, K2, Kmean, and Kapex) and corneal astigmatism values are summarized in **Table 2**. The mean K1, K2, and Kmean values were not significantly different at the 1- and 6-month visits ($P > .05$ for all) and were significantly lower at the 12- and 24-month visits ($P < .05$ for all). The mean Kapex was significantly lower at the 6-, 12-, and 24-month visits ($P < .05$ for all). At the last visit, K1 values decreased (decrease of 1 D or more) in 5 eyes and remained stable in 39 eyes. K2 values decreased in 4 eyes and remained stable in 40 eyes. Kapex values decreased in 18 eyes and remained stable in 26 eyes. No eyes showed deterioration (lost 1 D or more) in topographic parameters (**Figure B**, available in the online version of this article).

## Keratoconus Screening Indices

Keratoconus screening indices measured by Sirius system are shown in **Table A** (available in the online version of this article). The main keratoconus $\text{vertex}_{\text{FRONT}}$ value was significantly lower at the 24-month visit compared to the mean baseline value ($P = .003$). The main symmetry $\text{index}_{\text{FRONT}}$, symmetry $\text{index}_{\text{BACK}}$, keratoconus $\text{vertex}_{\text{BACK}}$, Baiocchi Calossi Versaci Index front, and Baiocchi Calossi Versaci Index back values were not significantly different at all postoperative visits when compared to baseline values ($P > .05$ for all).

TABLE 2

**Topographic Outcomes After Accelerated Cross-linking in Pediatric Keratoconus**

| | Mean ± SD (Range) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Baseline** | **1 Month** | ***P*** | **6 Months** | ***P*[b]** | **12 Months** | ***P*[b]** | **24 Months** | ***P*[b]** |
| K1 | 46.4 ± 3.0 (41.3 to 55.1) | 46.3 ± 3.1 (41.4 to 55.1) | .645 | 46.20 ± 3.08 (41.4 to 55.9) | .082 | 45.9 ± 3.0[a] (41.4 to 56.0) | **< .001** | 46.0 ± 2.9[a] (40.8 to 55.8) | **< .001** |
| K2 | 50.6 ± 4.2 (43.8 to 61.2) | 50.7 ± 4.4 (43.9 to 61.8) | .492 | 50.5 ± 4.3 (44.0 to 60.9) | .530 | 50.2 ± 4.0[a] (44.0 to 60.9) | **< .001** | 50.1 ± 4.0[a] (43.7 to 60.5) | **< .001** |
| Kmean | 48.3 ± 3.4 (42.5 to 56.9) | 48.4 ± 3.5 (42.7 to 57.0) | .790 | 48.2 ± 3.5 (42.7 to 57.4) | .332 | 47.9 ± 3.3[a] (42.7 to 57.3) | **< .001** | 47.9 ± 3.2[a] (42.2 to 56.8) | **< .001** |
| Kapex | 57.1 ± 5.5 (46.7 to 64.1) | 57.2 ± 5.5 (47.0 to 65.6) | .585 | 56.5 ± 5.2[a] (46.2 to 65.8) | **.004** | 56.0 ± 5.0[a] (46.6 to 64.2) | **< .001** | 56.1 ± 5.1[a] (47.1 to 64.6) | **< .001** |
| Corneal astigmastim | 4.3 ± 2.3 (0.4 to 11.8) | 4.4 ± 2.4 (0.4 to 11.5) | .206 | 4.3 ± 2.4 (0.5 to 11.5) | .474 | 4.2 ± 2.3 (0.5 to 11.4) | .429 | 4.2 ± 2.4 (0.5 to 10.9) | .703 |

*SD = standard deviation; K = keratometry; K1 = flat keratometry; K2 = steep keratometry; Kmean = mean keratometry; Kapex = apex keratometry*
[a]*Statistically significant increased values (P < .05).*
[b]*Values in bold are statistically significant.*

### Wavefront Aberrations

**Table B** (available in the online version of this article) shows corneal aberration changes. The total higher-order aberration (HOA), $Z^3$ coma, and $Z^4$ astigmatism II values decreased significantly at 6, 12, and 24 months after treatment ($P < .05$ for all). Wavefront error decreased significantly at the 24-month visit ($P = .036$). The mean $Z^2$ astigmatism, $Z^3$ trefoil, $Z^4$ quatrefoil, and $Z^4$ spherical aberration values did not change significantly at all postoperative visits when compared to baseline values ($P > .05$ for all).

### Corneal Thickness and Endothelial Cell Density

Corneal thickness changes are shown in **Table C** (available in the online version of this article). Corneal thickness showed a significant decrease at the 1-month visit, but returned to baseline values at the 6-month visit, and remained stable afterward. The mean preoperative endothelial cell density was 2,651 ± 244 cells/mm$^2$ (range: 2,195 to 3,245 cells/mm$^2$) and decreased to 2,629 ± 232 cells/mm$^2$ (range: 2,179 to 3,171 cells/mm$^2$) at the 1-month visit ($P = .065$).

### Complications

Thirty-four patients reported minor to moderate postoperative ocular pain, which was relieved to some extent over the first 2 to 3 days postoperatively. No postoperative complication, such as corneal haze or infection, was observed.

## DISCUSSION

CXL is the most promising treatment modality in the progression of keratoconus. Because keratoconus progression is more aggressive in the pediatric population,[14] CXL should be primarily considered for these patients to halt disease progression, prevent visual impairment, and obtain satisfactory correction with spectacles or contact lenses.

Accelerated CXL uses a greater UVA irradiance intensity with lower total exposure time when compared to standard protocol.[3-5,15] The clinical benefits of increasing the intensity and reducing the treatment time are not exactly clear. The Bunson–Roscoe law describes the photo response of a material to a certain energy dose. It concludes that all photochemical reaction processes depend only on the total absorbed energy that is determined by radiant intensity and exposure time. A recent ex vivo study evaluated the response of porcine eyes to irradiances between 3 and 90 mW/cm$^2$ with illumination times between 30 seconds and 1 minute. This study showed that irradiation levels up to 45 mW/cm$^2$ produced significantly stiffer corneas, whereas levels of 50 mW/cm$^2$ and above did not show significantly greater stiffness.[15]

Previous studies have shown promising results for conventional CXL treatment in pediatric patients and for accelerated CXL treatment in adults.[3-5,8-13] Recent studies on accelerated CXL have used two treatment modalities with settings of 30 mW/cm$^2$ for 3 minutes or 9 mW/cm$^2$ for 10 minutes, which were corresponding to a total dose of 5.4 J.[4,16] This study assessed the outcomes of accelerated CXL (30 mW/cm$^2$ for 4 minutes, a total dose of 7.2 J) for progressive keratoconus in a cohort of pediatric patients. To our knowledge, this is the first reported evaluation of accelerated CXL with a total dose of 7.2 J in pediatric patients with progressive keratoconus. According to our data, accelerated CXL seemed to halt the progression of pediatric

keratoconus in all treated eyes for the 24-month CXL follow-up. Our study also found that none of the keratoconus screening indices that may represent morphological changes in keratoconic cornea worsened during follow-up.

The corneal flattening effect of conventional CXL has been previously reported in patients younger than 18 years. However, the results are controversial. Previous studies[8,17,18] have reported a significant improvement in both K1 and K2 values with a follow-up ranging from 12 to 36 months. Vinciguerra et al.[19] reported that although K1 was significantly flattened, K2 was insignificantly changed 12 months after conventional CXL treatment. Soeters et al.[10] and Arora et al.[13] found that no significant changes were noted in both K1 and K2 at 12 months after CXL. The study found that all mean keratometric values including K1, K2, Kmean, and Kapex were significantly flattened 24 months after accelerated CXL. Chatzis and Hafezi[11] and Kumar Kodavoor et al.[18] reported promising results with 87% to 91.4% of eyes showing regression or stabilization in Kmax after conventional CXL. In our study, all keratometric values decreased (decrease of 1 D or more) or remained stable (change of less than 1 D) in all eyes (100%) after accelerated CXL. On the other hand, two previously published studies evaluated the transepithelial CXL in pediatric keratoconus. One of them compared outcomes of epithelium-off and epithelium-on corneal CXL and found similar effectiveness with significant improvement in minimum keratometry, Kmax, and Kmean values 12 months after surgery.[8] Conversely, Buzzonetti and Petrocelli[7] reported that all keratometric parameters including minimum keratometry, Kmax, and Kmean showed significant worsening 18 months after transepithelial CXL in pediatric patients with progressive keratoconus.

Corneal wavefront aberrations data allow for the detailed description of the optical quality of the cornea. It is a reliable tool for the detection of keratoconus and to follow up the progression of the disease.[20] In the current study, we evaluated the behavior of the anterior corneal HOA after accelerated CXL and found that corneal wavefront aberrations analyses showed an improvement in total higher-order root mean square, $Z^3$ coma, and $Z^4$ astigmatism II. Vinciguerra et al.[19] evaluated the total and corneal aberrations after conventional CXL in pediatric keratoconus. They found that total aberrations showed a significant reduction in astigmatism, coma, and spherical aberrations. Although corneal HOAs were statistically decreased, no statistically significant changes were observed in corneal coma and corneal spherical aberration. On the other hand, Buzzonetti and Petrocelli[7] found that the corneal HOAs showed no change in coma and spherical aberration, whereas HOAs showed significant worsening 18 months after transepithelial CXL in the pediatric cohort.

Several studies have reported a significant improvement in UDVA and CDVA after conventional CXL for pediatric keratoconus.[7,8,13,19] Chatzis and Hafezi[11] reported that CDVA improved or remained unchanged in 22 of 23 (96%) eyes at 24 months postoperatively and in 21 of 21 (100%) eyes at 36 months postoperatively. Kumar Kodavoor et al.[18] found that at the end of 1 year, there was improvement or stabilization in CDVA in 30 of 35 eyes (85.7%). This study found that UDVA and CDVA improved or remained stable in 41 (93.1%) eyes and 44 (100%) eyes, respectively, 24 months after accelerated CXL, with a mean improvement of 0.13 and 0.08 logMAR, respectively. In this study, a significant improvement in visual acuities (UDVA and CDVA) despite minimal changes in refractive and keratometric values. An explanation for the visual acuity improvement in pediatric patients could be the improvement of corneal aberrations including total HOA, coma, and astigmatism. Similarly, Vinciguerra et al.[21] and Caporossi et al.[22] described this improvement of coma in pediatric patients after CXL and suggested that improvement in visual acuity is the result of the improvement of refraction and keratometric values and the improvement of corneal aberrations.

Corneal thinning is commonly seen early after CXL. It has been associated with treatment-related effects from stromal compaction, postoperative dehydration, and alterations in epithelial healing and distribution.[10,14,23] Corneal thickness gradually increases over the first 6 months following CXL and returns to baseline values after standard CXL by 1 year.[13,19,23,24] In our study, the corneal thickness significantly decreased 1 month postoperatively and returned to the baseline value at 6 months. A recent study[25] showed that corneal thickness returned to baseline value at 3 months after accelerated CXL procedure in adult patients, which was earlier than previous published studies.

Corneal haze has commonly been shown after CXL treatment. In the pediatric population, the rate of corneal haze after conventional CXL treatment was reported as 13% by Arora et al.,[13] 6.9% by Vinciguerra et al.,[19] and 23% by Kumar Kodavoor et al.[18] On the other hand, Magli et al.[8] and Soeters et al.[10] did not find corneal haze after conventional CXL, as was the case in our study. In adults, Elbaz et al.[16] reported corneal haze in 12.5% of eyes after accelerated CXL (irradiance of 9 $mW/cm^2$; 10 minutes). Also, Mita et al.[5] found that 5.1% of eyes developed corneal haze after accelerated CXL (irradiance of 30 $mW/cm^2$; 3 minutes). The reason

no eyes developed corneal haze after CXL in our study may be associated with the baseline characteristics of our cases. Although we did not classify the severity of ectasia, most of our patients had mild or moderate cases. The mean K2 value (50.6 D) was lower in our study than it was in previous studies. The K2 value was 52.0 D or lower in 33 of 44 eyes, and the CDVA was 20/40 or better in 25 eyes. Raiskup et al.[26] showed a greater tendency toward stromal haze in patients with more advanced cases. Greenstein et al.[27] reported that the degree of haze was correlated with poorer visual acuity, thinner corneal thickness, and higher Kmax and Kmean values. They also stated that the corneal haze seemed to be worse with thinner corneas and that it resolved as the cornea got thicker. In our study, during follow-up, corneal thickness decreased to a mean of 433 mm at 1 month, which was the lowest mean corneal thickness value during the follow-up. Moreover, accerated CXL time, which was the shortest when compared to previous studies, may be associated with haze formation in pediatric patients. However, future studies are required for better understanding the association between CXL time and haze formation.

The previous studies using anterior segment imaging techniques such as anterior segment optical coherence tomography or confocal microscopy have shown a demarcation line between the cross-linked and untreated cornea. This demarcation line has been reported at a depth of approximately 300 mm after conventional CXL treatment.[28,29] Two recent studies by Kymionis et al. reported that demarcation depths were 288 and 322 mm after accelerated CXL.[30,31] It has also been shown that accelerated CXL did not change endothelial cell density.[5,25,30-32] Similarly, a recent study by Mazzotta et al.[33] and our study found that accelerated CXL with a total dose of 7.2 J did not cause any endothelial damage. This indicates that the increased intensity of the UVA irradiance did not adversely affect the endothelial cell layer.

Results of CXL in children with keratoconus in the current study are encouraging, without disease progression or significant complication during 24 months of follow-up. Accelerated CXL also offers less surgical time than standard treatment. This is a big advantage because children show low compliance to prolonged treatment and may also need general anesthesia. However, our study has a few limitations. First, due to the fact that progression of keratoconus is more aggressive in pediatric patients than adults, a longer follow-up is required. Second, the study has a retrospective design and does not include a control group. A randomized prospective study is required to compare the efficacy and safety of accelerated CXL with standard CXL. Moreover, pediatric corneas have different biomechanical properties from adult corneas. It remains unknown whether pediatric corneas allow possible retreatments.

The findings of this study demonstrated that corneal accelerated CXL appears to stabilize the progression of pediatric keratoconus without apparent complication for 24 months of follow-up. It also appears to improve visual acuity, keratometric values, and corneal aberrations.

### AUTHOR CONTRIBUTIONS

*Study concept and design (EBO, NK, KIC); data collection (EBO, KIC, TK); analysis and interpretation of data (EBO, NK, AD); drafting of the manuscript (EBO, NK, KIC, TK); critical revision of the manuscript (EBO, NK, AD); statistical expertise (NK)*

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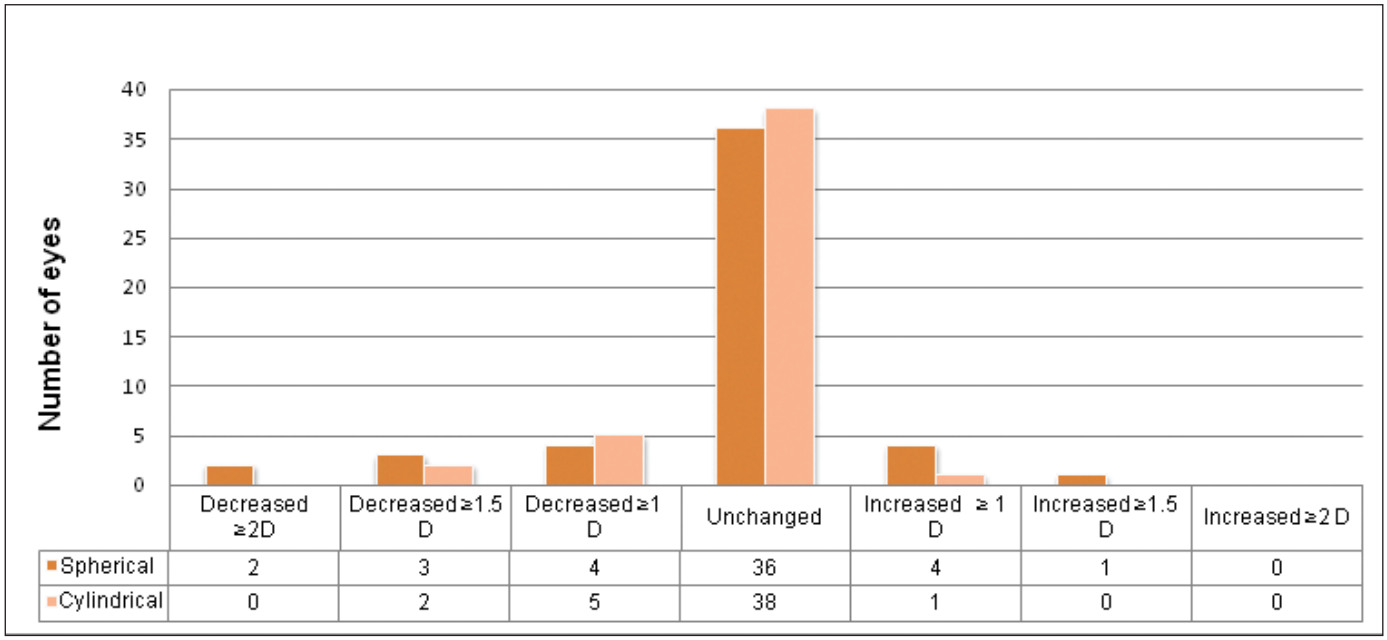


**Figure A.** Change in refraction between baseline and last visit postoperatively. D = diopters

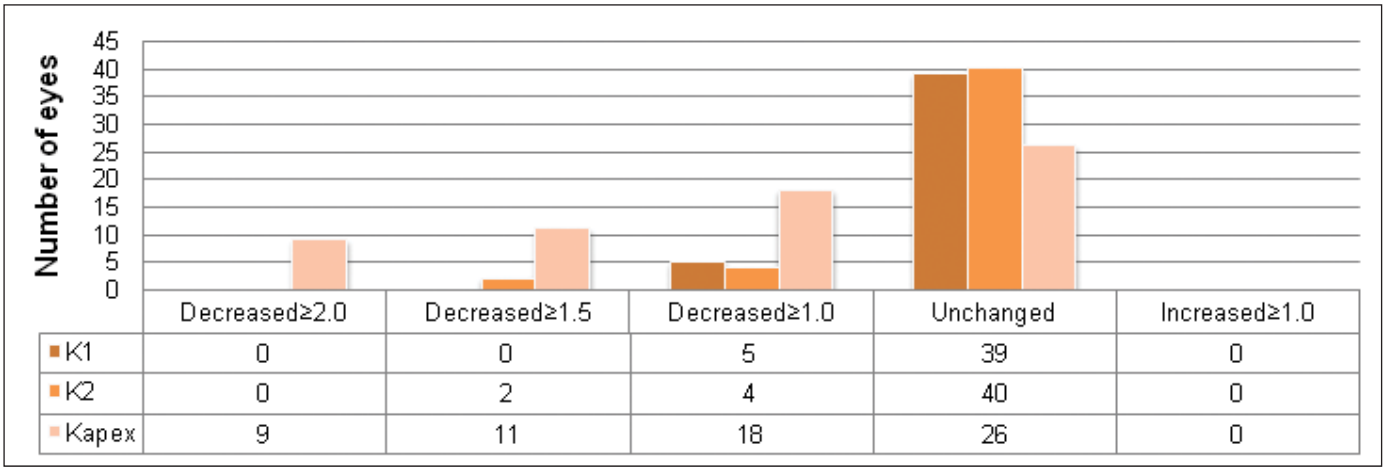


**Figure B.** Change in keratometry values between baseline and last visit postoperatively. K1 = flat keratometry; K2 = steep keratometry; Kapex = apex keratometry

TABLE A

## Changes in Keratoconus Screening Indices After Accelerated Cross-linking in Pediatric Keratoconus

| | Mean ± SD (Range) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Baseline** | **1 Month** | ***P*** | **6 Months** | ***P*** | **12 Months** | ***P*** | **24 Months** | ***P*[b]** |
| Sif | 5.9 ± 3.7 (0.07 to 12.9) | 6.1 ± 3.7 (0.42 to 14.90) | .381 | 5.8 ± 3.6 (0.42 to 13.4) | .516 | 5.7 ± 3.8 (0.05 to 13.40) | .243 | 5.7 ± 3.5 (0.23 to 12.3) | .104 |
| Sib | 1.35 ± 0.78 (0.04 to 3.15) | 1.34 ± 0.76 (0.05 to 3.15) | .766 | 1.37 ± 0.77 (0.06 to 3.23) | .506 | 1.34 ± 0.73 (0.05 to 2.89) | .702 | 1.34 ± 0.75 (0.01 to 1.34) | .633 |
| KVf | 33.4 ± 14.1 (7 to 57) | 34.2 ± 14.3 (8 to 58) | .121 | 33.0 ± 13.7 (8 to 59) | .410 | 32.4 ± 13.5 (7 to 56) | .100 | 31.8 ± 13.3[a] (6 to 59) | **.003** |
| KVb | 67.5 ± 29.9 (8 to 129) | 69.0 ± 29.3 (18 to 132) | .246 | 69.1 ± 29.6 (19 to 128) | .118 | 68.4 ± 28.3 (18 to 122) | .353 | 67.3 ± 27.3 (10 to 114) | .765 |
| BCVf | 3.38 ± 1.87 (0.29 to 7.03) | 3.49 ± 1.89 (0.44 to 7.26) | .130 | 3.40 ± 1.81 (0.46 to 7.05) | .726 | 3.25 ± 1.85 (0.00 to 6.45) | .051 | 3.27 ± 1.75 (0.21 to 6.62) | .074 |
| BCVb | 3.09 ± 1.78 (0.10 to 6.92) | 3.11 ± 1.73 (0.00 to 7.12) | .808 | 3.18 ± 1.72 (0.17 to 6.76) | .115 | 3.09 ± 1.69 (0.00 to 6.68) | .991 | 3.08 ± 1.64 (0.01 to 6.17) | .839 |

*SD = standard deviation; Sif = symmetry index$_{FRONT}$; Sib = symmetry index$_{BACK}$; KVf = keratoconus vertex$_{FRONT}$; KVb = keratoconus vertex$_{BACK}$; BCVf = Baiocchi Calossi Versaci index front; BCVb = Baiocchi Calossi Versaci index back*
*[a]Statistically significant increased values (P < .05).*
*[b]Values in bold are statistically significant.*

TABLE B

## Corneal Wavefront Aberrations After Accelerated Cross-linking in Pediatric Keratoconus

| | Mean ± SD (Range) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Baseline** | **1 Month** | ***P*** | **6 Months** | ***P*[b]** | **12 Months** | ***P*[b]** | **24 Months** | ***P*[b]** |
| Total WFE | 1.51 ± 0.67 (0.26 to 3.17) | 1.56 ± 0.69 (0.26 to 3.37) | .174 | 1.50 ± 0.57 (0.35 to 3.14) | .628 | 1.46 ± 0.64 (0.32 to 3.36) | .153 | 1.45 ± 0.60 (0.34 to 3.02) | .056 |
| Total HOA | 0.55 ± 0.26 (0.10 to 0.96) | 0.54 ± 0.25 (0.09 to 1.02) | .542 | 0.52 ± 0.25[a] (0.11 to 1.02) | **.006** | 0.49 ± 0.24[a] (0.09 to 0.99) | **< .001** | 0.47 ± 0.23[a] (0.12 to 0.95) | **< .001** |
| $Z^2$ astigmatism | 1.38 ± 0.68 (0.08 to 3.16) | 1.44 ± 0.69 (0.08 to 3.21) | .099 | 1.38 ± 0.67 (0.25 to 3.12) | .965 | 1.34 ± 0.66 (0.10 to 3.35) | .355 | 1.34 ± 0.61 (0.31 to 3.01) | .260 |
| $Z^3$ trefoil | 0.20 ± 0.13 (0.02 to 0.57) | 0.20 ± 0.10 (0.04 to 0.47) | .679 | 0.20 ± 0.10 (0.04 to 0.44) | .965 | 0.19 ± 0.09 (0.01 to 0.45) | .490 | 0.18 ± 0.11 (0.03 to 0.49) | .107 |
| $Z^3$ coma | 0.46 ± 0.25 (0.03 to 0.87) | 0.44 ± 0.24 (0.03 to 0.86) | .338 | 0.42 ± 0.25[a] (0.06 to 0.95) | **.009** | 0.40 ± 0.24[a] (0.04 to 0.94) | **< .001** | 0.38 ± 0.24[a] (0.04 to 0.89) | **< .001** |
| $Z^4$ quatrefoil | 0.07 ± 0.05 (0.01 to 0.27) | 0.08 ± 0.06 (0.01 to 0.27) | .339 | 0.07 ± 0.05 (0.02 to 0.27) | .730 | 0.06 ± 0.04 (0.01 to 0.27) | .264 | 0.06 ± 0.03 (0.01 to 0.16) | .265 |
| $Z^4$ astigmatism II | 0.08 ± 0.05 (0.00 to 0.23) | 0.08 ± 0.05 (0.01 to 0.23) | .919 | 0.07 ± 0.04[a] (0.02 to 0.25) | **.046** | 0.06 ± 0.04[a] (0.00 to 0.19) | **.005** | 0.06 ± 0.03[a] (0.00 to 0.17) | **.001** |
| $Z^4$ spherical aberration | 0.08 ± 0.06 (0.00 to 0.26) | 0.08 ± 0.07 (0.00 to 0.36) | .506 | 0.07 ± 0.06 (0.00 to 0.36) | .715 | 0.06 ± 0.05 (0.00 to 0.20) | .032 | 0.06 ± 0.05 (0.00 to 0.20) | .059 |

*SD = standard deviation; WFE: wavefront error; HOA = higher-order aberrations*
*[a]Statistically significant increased values (P < .05).*
*[b]Values in bold are statistically significant.*

TABLE C

## Corneal Thickness Changes After Accelerated Cross-linking in Pediatric Keratoconus

| | Mean ± SD (Range) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Parameter** | **Baseline** | **1 Month** | ***P*[b]** | **6 Months** | ***P*** | **12 Months** | ***P*** | **24 Months** | ***P*** |
| CCT | 462 ± 35 (415 to 566) | 449 ± 34[a] (395 to 554) | **<.001** | 461 ± 36 (399 to 573) | .541 | 464 ± 36 (418 to 577) | .122 | 466 ± 35 (424 to 587) | .099 |
| TCT | 447 ± 40 (402 to 547) | 433 ± 40[a] (379 to 540) | **<.001** | 445 ± 44 (392 to 561) | .317 | 449 ± 42 (401 to 566) | .365 | 452 ± 41 (415 to 574) | .156 |

*SD = standard deviation; CCT = central corneal thickness; TCT = thinnest corneal thickness*
*[a]Statistically significant increased values (P < .05).*
*[b]Values in bold are statistically significant.*