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Prospective, randomized contralateral eye study of accelerated and conventional corneal cross-linking in pediatric keratoconus

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Abstract

Purpose To compare the outcomes of two different cross-linking (CXL) protocols, in pediatric keratoconus eyes.

Materials and methods In this prospective randomized contralateral eye interventional study, 68 eyes of 34 patients, 9–16 years old, underwent CXL and enrolled between October 2011 and October 2013. Group A represents conventional riboflavin–ultraviolet A (UVA)-induced CXL with 30 min of exposure to UVA irradiation of 3 mW/cm^2. Group B represents accelerated cross-linking with 5 min of continuous UVA irradiation of 18 mW/cm^2. In either group, total energy delivered was adjusted to 5.4 J/cm^2. Follow-up of all patients was accomplished throughout the postoperative 3 years, and the data from the preoperative, 12, 24, and 36 months visits were analyzed and compared in both groups. Uncorrected visual acuity, corrected distance visual acuity, steepest keratometry (K_{max}), corneal astigmatism (simulated K), total wavefront aberrations, central corneal thickness (CCT), corneal densitometry, manifest refraction spherical equivalent, and endothelial cell density (ECD) were evaluated at baseline, 12, 24, and 36 months post-CXL.

Results At 1-year assessment, the mean value of UCVA, CDVA, and K_{max} showed a statistically significant difference between both groups, without any documented change in the variables throughout the remaining follow-up (1–3-year) period. Twelve months postoperatively, mean LogMAR UCVA and CDVA were (0.11 ± 1.60) and (0.03 ± 1.60), respectively, in accelerated CXL group, compared to conventional CXL group values of (0.20 ± 1.00) and (0.06 ± 1.22), showing a statistically significant difference ($P < 0.05$). Mean K_{max} in accelerated CXL group (45.47 ± 0.44) showed a statistically significant difference ($P < 0.05$) compared to conventional CXL group (46.41 ± 1.59) at 12 months post-CXL. On the other hand, wavefront aberrations, simulated K, corneal densitometry, ECD, and CCT changes showed nonstatistically significant difference in conventional CXL group, compared to accelerated CXL group ($P > 0.05$) throughout the follow-up course.

Conclusions Both conventional and accelerated CXL improved UCVA and CDVA, attenuated disease progression, and reduced corneal steepness and wavefront aberrations at 1, 2, and 3 years postoperatively. In no case did keratoconus progress over the 36-month follow-up.

Keywords Accelerated · Conventional · Cross-linking · Pediatric · Keratoconus

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Introduction

Keratoconus in pediatric population has a known progressive course. All eyes with progressive keratoconus should be considered for treatment with CXL with the goal of mitigating the disease progression [1]. Several studies proved the efficacy of CXL in increasing the biomechanical stability of the cornea and the ability to arrest the progression of keratoconus [2–5].

The less rigid pediatric cornea with higher probability of accelerated progression necessitates the prompt keratoconus management with cross-linking. Chatzis et al. [6] concluded that it is not necessary to confirm keratoconus progression in pediatric patients and that CXL treatment may proceed immediately after initial diagnosis.

Early treatment of pediatric mild keratoconus could be of greater benefit than waiting until severe stage evolves with inevitable corneal transplantation. In children, keratoplasty carries a poorer prognosis than in adults [7]. CXL is a safe and effective choice in halting the progression of pediatric keratoconus.

Photochemical cross-linking of the separate stromal collagen bundles results in significant stiffening of the corneal stroma [8]. The CXL procedure that was first performed in Germany in the 1990s at Dresden University aims to halt disease progression by increasing the rigidity and stiffness of the corneal stroma [1, 8]. Regression in disease severity can be concluded by the improvement in the post-CXL visual acuity and keratometry readings compared with baseline values [2, 9]. Failure to interrupt the progressive course of pediatric keratoconus will end up with an advanced stage that ultimately requires a corneal graft procedure in 10–20% of cases. [10].

The basic clinical outcomes of CXL follow a reproducible time course following the procedure. In general, visual acuity and corneal steepness worsen at the 1-month time point. Resolution to baseline usually occurs by approximately 3 months, with improvement thereafter [9]. This is almost similar to the clinical time course of CXL-associated corneal haze, which is greatest at 1 month, plateaus at 3 months, and significantly declines between 3 and 12 months postoperatively [11].

Stromal and epithelial healing responses to CXL appear to continue over months, which explains the changes in clinical outcomes [9]. During the early post-CXL period, initial keratoconus progression may arise owing to epithelial debridement, followed by slow continuous improvement of keratoconus indices, first because of re-epithelialization and then because of the cross-linking effect on the cornea [12].

Age, baseline CDVA, and preoperative thinnest corneal pachymetry appear to influence the early and late outcomes of CXL treatment. A worse preoperative corrected visual acuity is related with better visual improvement, whereas age (> 30) and baseline thinnest corneal pachymetry (< 450 μ) are usually associated with more flattening of maximum keratometry (K_{max}) [13].

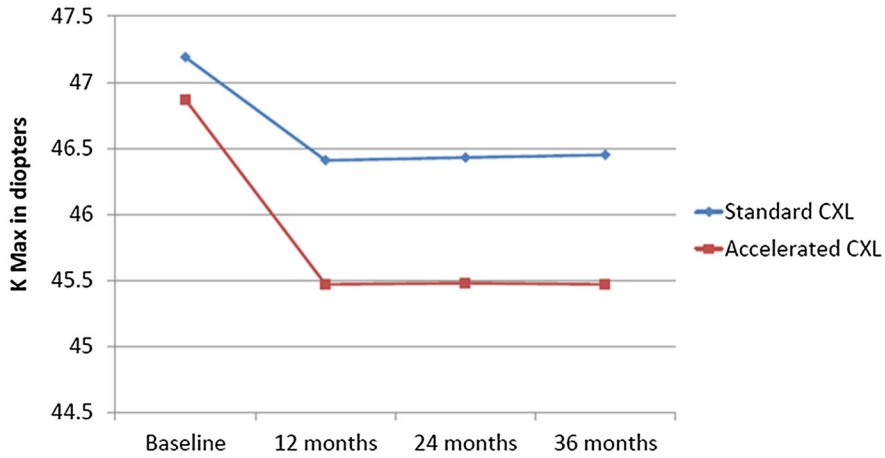

Fig. 1 K_{max} in group A vs group B, at baseline and postoperatively (12, 24 and 36 months)

In progressive keratoconus, eyes with worse CDVA and higher *K* readings are more likely to have an improvement after CXL [1].

Subjective improvement in visual symptoms like diplopia, glare, halo, starbursts, and foreign-body sensation usually improve 1 year after CXL, which authenticates the objective findings of improved quantitative visual, optical, and topographic metrics after CXL [2].

Witting-Silva et al. [14] randomized 100 eyes with progressive keratoconus into CXL treatment or control groups and reported a sustained improvement in K_{max}, UCVA, and CDVA after CXL, whereas eyes in the control group demonstrated further progression.

On the other hand, Greenstein et al. [15] did not correlate the post-CXL improvement in the Pentacam corneal indices like index of vertical asymmetry, index of surface variance, and keratoconus index, and the decrease in corneal and ocular high-order aberrations (HOAs) with changes in corrected or uncorrected distance visual acuity.

Accelerated CXL protocols using higher power and shorter exposure times have been established, aiming to reduce patient treatment time. The safe and effective use of accelerated CXL is based on the Bunsen–Roscoe law of reciprocity [16] that predicts that the same subthreshold total cytotoxic corneal endothelial UV dosage can be administered by increasing UV fluence while simultaneously reducing exposure time.

The present study prospectively compared two cross-linking protocols in management of pediatric keratoconus; conventional versus accelerated CXL. Each eye was randomly assigned to one of the two CXL techniques, into group A for conventional CXL, and group B for accelerated CXL.

The randomized contralateral eye study design gives the advantage of accurate assessment of the efficacy of accelerated CXL in pediatric keratoconus eyes with potentially progressive nature.

Corneal thickness, *K* readings, and uncorrected visual acuity were the variables compared to assess efficacy in both groups.

Patients and methods

This prospective randomized contralateral eye interventional study included 34 patients, aged 9–16 years, with keratoconus, of stage I–II according to Amsler–Krumeich grading system [17]. The 68 eyes were randomly divided into group A for conventional CXL and group B for accelerated CXL. This was a single-center, contralateral eye study of two eyes per patient; one eye was assigned to conventional CXL and the other eye to accelerated CXL. The research was done in the period between October 2011 and December 2012 at Magrabi Aseer Specialized Eye Hospital (MEH) in the Kingdom of Saudi Arabia (KSA).

The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committee of MEH (Protocol Number: PRO111002). Before the surgery, comprehensive discussion with the patients' parents was carried out, during which the details, benefits, and possible complications of each procedure were explained. A written informed consent was obtained from all parents. The conventional cross-linking procedure for group A patients and the accelerated cross-linking procedure for group B cases were done by the first (S.E.) and second (A.Y.) authors.

The inclusion criteria were age less than 16 years, corneal thickness of 400 μm or more at the thinnest location, and clear cornea with documented diagnosis of bilateral keratoconus indicated for CXL in both eyes. An abnormal topography pattern on the sagittal map (crab claw pattern or asymmetric bowtie with a skewed radial axes) and corneal thickness less than 470 μ were the criteria essential for a diagnosis of keratoconus by corneal tomography (Pentacam, Oculus Optikgeräte GmbH, Wetzlar, Germany) [18–20].

Topographic evidence of keratoconus progression is usually defined by an increase of 1.0 D or more in the steepest keratometry (K); an increase of 1.0 D or more in the manifest cylinder; or an increase of 0.5 D or more in the manifest refraction spherical equivalent over two successive follow-ups. However, the authors considered that keratoconus in children is inevitably progressive and was treated once initially diagnosed. The exclusion criteria were: corneal thickness of less than 400 μm, K_{max} above 53 D, and CDVA worse than 0.50.

Besides, children with documented unilateral keratoconus were managed by cross-linking of the potentially progressing eye only and were excluded from the study.

Follow-up visits for all patients were scheduled at 5 days, 3 weeks, and 2, 6, 9, 12, 18, 24, 30, and

Table 1 A comparison of all variables between both groups is demonstrated at all time points

		Baseline (mean ± SD)	*P* value	12 months (mean ± SD)	*P* value	24 months (mean ± SD)	*P* value	36 months (mean ± SD)	*P* value
LogMAR UCVA	Group A	0.21 ± 1.10	0.12	0.20 ± 1.00	< 0.05	0.20 ± 0.92	< 0.05	0.20 ± 1.0	< 0.05
	Group B	0.18 ± 1.40		0.11 ± 1.60		0.11 ± 1.52		0.11 ± 1.60	
LogMAR CDVA	Group A	0.10 ± 1.22	0.321	0.06 ± 1.22	<0.05	0.06 ± 1.40	< 0.05	0.06 ± 1.3	< 0.05
	Group B	0.08 ± 1.22		0.03 ± 1.60		0.03 ± 1.40		0.03 ± 1.52	
MRSE in diopters	Group A	−3.65 ± 0.80	0.026	−3.24 ± 0.64	0.025	−3.24 ± 0.65	0.025	−3.57 ± 0.53	0.025
	Group B	−4.09 ± 0.73		−3.57 ± 0.52		−3.57 ± 0.54		−3.57 ± 0.53	
CCT in microns	Group A	460.72 ± 22.17	0.097	454.66 ± 22.43	0.126	455.01 ± 22.13	0.13	455.01 ± 22.11	0.13
	Group B	467.30 ± 3.39		460.78 ± 3.37		459.99 ± 3.03		459.99 ± 3.02	
Sim-K in Diopters	Group A	3.92 ± 1.41	0.81	4.24 ± 2.95	0.76	4.19 ± 2.85	0.74	3.76 ± 2.26	0.94
	Group B	4.01 ± 1.52		4.16 ± 2.54		4.09 ± 2.53		3.74 ± 2.28	
K_{max} in Diopters	Group A	47.19 ± 1.62	0.308	46.41 ± 1.59	< 0.05	46.43 ± 1.43	< 0.05	46.45 ± 1.43	< 0.05
	Group B	46.87 ± 0.77		45.47 ± 0.44		45.48 ± 0.44		45.47 ± 0.54	
Total wavefront in RMS	Group A	6.82 ± 3.20	0.433	5.59 ± 2.85	0.191	5.59 ± 2.89	0.192	5.59 ± 2.85	0.191
	Group B	7.29 ± 1.12		6.29 ± 1.16		6.29 ± 1.19		6.29 ± 1.16	
ECD (cells/mm^2)	Group A	2945.2 ± 138.5	0.13	2838.9 ± 134.07	0.15	2810 ± 129	0.14	2790 ± 121	0.15
	Group B	2964.4 ± 114.5		2860.5 ± 111.10		2845 ± 104		2839 ± 103	
Densitometry (GSU)	Group A	18.18 ± 0.68	0.07	18.62 ± 1.24	0.086	18.61 ± 1.24	0.086	18.62 ± 1.24	0.086
	Group B	18.34 ± 0.72		19.15 ± 1.21		19.15 ± 1.21		19.14 ± 1.21	

Group A conventional cross-linking, *Group B* accelerated cross-linking, *UCVA* uncorrected distance visual acuity in LogMAR, *CDVA* corrected distance visual acuity in LogMAR, *MRSE* manifest refractive spherical equivalent, *CCT* central corneal thickness in microns, *Sim-K* simulated keratometry, K_{max} steepest *K* in diopters, *ECD* endothelial cell density in cells/mm^2

P value compares between the absolute baseline, 12, 24, and 36 month post-CXL values between both groups

36 months post-CXL; no patient missed the planned follow-up visits.

The present study compared the two cross-linking protocols in the management of pediatric progressive keratoconus eyes by analyzing the outcomes at baseline and at 12, 24, and 36 months post-CXL. Regarding the primary outcome variables, Pentacam HR was used for evaluation of corneal densitometry, K_{max}, and the CCT on a pachymetry map (Oculus Inc., WA, USA). In Scheimpflug-based corneal densitometry, the backward light scatter was measured in GSU for anterior, middle, and posterior corneal stroma, in three concentric zones. LogMAR charts (Keeler, Weymouth, UK) were used for UCVA and spectacle CDVA assessment.

The other data extracted were the MRSE, total and corneal wavefront aberrations (OPD-Scan II; Nidek, Japan), and endothelial cell count based on noncontact endothelial specular microscopy (SP 500; Seed Co., Tokyo, Japan).

In both groups, Merocel® sponge soaked in 50% alcohol (Medtronic Xomed, Inc., FL, USA) was applied for 20 s to loosen the epithelium from the stroma; the epithelium was then easily peeled off and removed from the 9-mm treatment zone by using Merocel® sponge. This was followed by instillation of 0.1% riboflavin–20% dextran solution (Vibex®, Avedro, Inc., MA, USA) for 30 min. The cornea was exposed to ultraviolet light with a flat beam profile at a wavelength of 365 nm (KXL®, Avedro, Inc., MA, USA). In the conventional CXL group, exposure to UV irradiation was adjusted to a fluence of 3 mW/cm^2 for 30 min, with riboflavin instillation every 5 min during the 30-min irradiation period. In the epithelium—off accelerated cross-linking group, riboflavin was applied twice under a UVA fluence of 18 mW/cm^2 for 5 min to deliver a total energy of 5.4 J/cm^2.

In both methods, after the application of riboflavin, the corneal surface was washed thoroughly with a balanced salt solution. Ultrasound (US) pachymetry was then carried out. If the cornea was thinner than 400 μm, hypotonic riboflavin solution was applied, after which another US pachymetry was done to determine whether the stroma had swollen to more than 400 μm. This was followed by the UV irradiation treatment. In both groups, a bandage contact lens was applied at the end of the procedure; the contact lens was removed after 4–5 days. Postoperatively, moxifloxacin 0.5% (Vigamox®, Alcon Laboratories, Inc., TX, USA) and prednisolone acetate 1% (Pred Forte®, Allergan, Inc., CA, USA) were prescribed six times daily for 2 weeks. This was replaced with fluorometholone 0.1% (FML®, Allergan, Inc., CA, USA) four times daily for 2 more weeks and then twice daily for 15 days. After 6 weeks, no medication was used.

All cases in this double-blinded study were operated on under general anesthesia (GA), given by a certified anesthesiologist.

This prospective, randomized contralateral eye study, was conducted on 68 eyes of 34 patients, randomly recruited one eye of each patient for conventional CXL and the other for accelerated CXL. Each patient underwent both procedures sequentially on the same day: conventional CXL on one eye and accelerated CXL on the contralateral eye. Covariate adaptive randomization was carried out at the coordinating office of the cornea and refractive unit, recorded in a log, and applied using computer-generated program (GraphPad Software, Inc., CA, USA). The unit of randomization was one eye. Regardless of the relative disease severity, each keratoconus eye was randomly assigned to one of the two CXL techniques and to either of the two surgeons who participated in the study. However, the range of disease severity in both groups did match preoperatively. All baseline variables (as shown in Table 1) did not show a statistically significant difference between both groups, including K_{max} range of (44.98–49.65 D) and (45.77–47.89 D), in group A and B, respectively.

The patients (under GA), surgeons, and independent postoperative examiners remained masked at all times during the assigned treatment.

Due to lack of any reports for the south Saudi population, sample size (32 eyes for each group) was calculated using MedCalc 10.2.0.0, by referring to success rates from the literature. Statistical analysis was performed using SPSS 15 software. All normally distributed continuous data were presented as means and standard deviations. A paired two-tailed Student t test was used to analyze the postoperative outcomes from baseline. An independent t test was used to compare postoperative outcomes in the two groups: accelerated and conventional CXL eyes. A P value of < 0.05 was considered significant.

Results

The study enrolled 68 eyes of 34 patients of mean age 12.3 ± 2.4 years (range: 9–16 years). The two randomized groups were analyzed together and individually by an independent postoperative examiner and followed for up to 3 years. The studied variables include UCVA, CDVA, MRSE, CCT, Sim-K, K_{max}, wavefront aberrations, ECD, densitometry, and age, without any statistically significant difference at baseline values between both groups preoperatively. A comparison of all variables between both groups is demonstrated at all time points in Table 1.

Mean baseline, 12, 24, and 36-month LogMAR UCVA and CDVA of conventional and accelerated CXL group eyes are shown in Table 1. Both postoperative UCVA and CDVA in accelerated CXL group showed a statistically significant difference ($P < 0.05$), compared to the conventional CXL group, at all time points (Fig. 1). The nonstatistically significant difference in baseline UCVA and CDVA

between both groups made them comparable at all time points postoperatively.

Mean value for accelerated CXL group steepest K after 12 months, showed a reduction of 1.4 D compared to baseline value, a statistically significant ($P = 0.002$) difference, while conventional CXL group showed a nonstatistically significant reduction in steepest K by 0.78 D. A statistically significant difference was found between both groups ($P < 0.05$). In both groups, mean K_{max} after 1 year showed the same value at 2, and 3 years post-CXL (Fig. 1). The nonstatistically significant difference in baseline K_{max} between both groups made them comparable at all time points postoperatively.

In accelerated CXL group, the mean preoperative MRSE was -4.09 ± 0.73 (range -3.25 to -5.25 D). At 1 year, the mean MRSE decreased by 0.52 D, compared to the conventional CXL group that showed a mean baseline MRSE of -3.65 ± 0.80(range -2.75 to -6.00 D), and a mean reduction of 0.41 D. In both groups, mean MRSE showed the same value at 1, 2, and 3 years post-CXL. Despite the superior MRSE reduction in the accelerated CXL group at 1 year, the statistically significant difference ($P = 0.026$) in baseline MRSE between both groups made them noncomparable at all time points postoperatively.

In the conventional CXL group, mean baseline densitometry was 18.18 ± 0.68 GSU (range 16–19.9) that increased to 21.87 ± 0.95 (GSU) and 21.39 ± 0.76 (GSU) after 1 and 3 months, respectively. Mean preoperative densitometry in the accelerated CXL group was 18.34 ± 0.72 GSU (range 15.98–19.9) that increased to 22.25 ± 0.35 (GSU) and 22.16 ± 0.29 (GSU) after 1 and 3 months, respectively. Both groups showed a statistically significant increase ($P < 0.05$) in corneal densitometry at 1 month post-CXL. However, densitometry reached near-baseline values at 12 months postoperatively that persisted unchanged at 24 and 36 months post-CXL, showing a nonstatistically significant difference compared to baseline values. No statistically significant difference in corneal densitometry between both groups ($P > 0.05$) was found at any time point.

Baseline total wavefront aberrations in conventional CXL group (6.82 ± 3.20, range 3.89–11.87) and in accelerated CXL group (7.29 ± 1.12, range 3.98–10.51), for a 3-mm pupil, showed a nonstatistically significant reduction ($P > 0.05$) in whole eye (total) aberrations at 12, 24, and 36 months post-CXL.

Mean baseline thinnest pachymetry point was 450 ± 09 μ in conventional CXL group versus 429 ± 12 μ in accelerated CXL group. Central corneal thickness (460.78 ± 13.37) in conventional CXL group at 12 months post-CXL, showed a decrease by 6.52 μ from baseline values and showed a nonstatistically significant change ($P = 0.126$), compared to accelerated CXL group, in which 12-month CCT (454.66 ± 12.43) showed a decrease by 6.06 μ.

Baseline endothelial cell density (2945.2 ± 138.5), range 2765–3111 cells/mm^2 in conventional CXL group, and (2964.4 ± 114.5), range 2789–3123 cells/mm^2 in the accelerated CXL group, showed nonstatistically significant reduction ($P > 0.05$) throughout the follow-up time points, in both groups.

There were no significant differences between both groups in changes of simulated keratometry ($P = 0.94$) 12 months after CXL.

No eye developed an infection, delayed re-epithelialization, or corneal scarring throughout the follow-up period.

Discussion

Since its introduction by Wollensak et al. in 2003, corneal collagen cross-linking has been used as a treatment modality aimed at strengthening the cornea in keratoconus and post-LASIK ectasia cases. The safety and efficacy of cross-linking in the management of progressive keratoconus has been reported in many studies.

The purpose of this prospective randomized contralateral eye interventional study was to assess the safety and efficacy of cross-linking in its accelerated and conventional protocols at different time points after CXL.

Compared to Dresden protocol, ACXL in children carries the advantages of shorter duration of exposure to general anesthesia (GA), thus reducing the risks of GA. Besides, better cooperation of children may be achieved when topical anesthesia is used. Children with Down syndrome and keratoconus, which is a common association, would benefit from the

advantage of short exposure to GA, especially if cardiac and chest problems exist.

In the present study, both postoperative UCVA and CDVA in accelerated CXL group showed a statistically significant difference ($P < 0.05$), compared to group A, at all time points. Both groups showed a nonstatistically significant reduction in MRSE, and total wavefront aberrations.

Both groups showed a statistically significant increase ($P < 0.05$) in corneal densitometry at 1 month post-CXL, with no statistically significant difference in corneal densitometry between conventional CXL group and accelerated CXL group ($P > 0.05$) at any time point.

Whereas the accelerated CXL group showed a statistically significant reduction in steepest K after 12 months, the conventional CXL group showed a nonstatistically significant reduction in K_{max}. A statistically significant difference was found between both groups ($P < 0.05$).

Central corneal thickness and endothelial cell density in both groups showed a nonstatistically significant change, without significant intergroup difference.

Minoru et al. [21] compared the outcomes of accelerated corneal collagen CXL and conventional corneal CXL in 48 eyes of 39 patients; 30 eyes underwent accelerated CXL, and 18 eyes had conventional CXL. However, the study included only adult patients between 20 and 45 years old. No statistically significant differences in the postoperative changes in uncorrected or corrected distance visual acuity or in the MRSE were found between the two procedures. There were also no statistically significant differences in the postoperative changes in the keratometry readings from the Pentacam Scheimpflug device.

Visual acuity is one of the most important parameters indicating the efficacy of the CXL treatment. Dalal et al. [22] included 142 eyes in a study on CXL in progressive keratoconus. The results showed that at 6 months, the CDVA had stabilized in 53 eyes (48.1%), improved in 36 eyes (32.7%), and declined in 18 eyes (16.3%). After 1 year, the CDVA had stabilized in 31 eyes (47.6%), improved in 26 eyes (40.0%), and declined in 8 eyes (12%).

In the present study, both CXL techniques resulted in improved CDVA and UCVA, reduced corneal steepness, and decreased high-order aberrations (HOAs).

No statistically significant loss of corneal endothelium density or change in the morphology was noted in either group between the baseline and the 12-month assessment. This finding agrees with the results of other studies [21, 22].

The maximum K value is a key topographic indicator of the success of CXL because it measures, to some extent, the severity of the ectatic change. Previous studies have reported decreases in the maximum K value of 6.16 D [21] in adult keratoconic eyes and 2.3 ± 1.4 D in pediatric keratoconic eyes [23] after conventional CXL.

In our study, the Pentacam-measured K_{max} during the last follow-up visit at 36 months post-CXL indicated a statistically significant difference ($P < 0.05$) between the two groups (Table 1), with a statistically significant reduction in steepest K in the accelerated CXL group. This may be attributed to the statistically significant difference in baseline thinnest corneal pachymetry between both groups.

Minoru et al. [21] reported nonstatistically significant differences in the K_{max} readings between accelerated and conventional CXL. The regression in the K_{max} value obtained with the conventional Scheimpflug differential analysis system was found 1 year after both procedures. The baseline K_{max} was higher than in the current study, with the accelerated CXL group showing a decrease of 0.95 D in the mean K_{max} of 50.45 ± 5.28, compared with a decrease of 1.49 D in the mean K_{max} of 48.82 ± 4.56 in the conventional CXL group. However, that retrospective study enrolled adult patients only (20–45 years old) and had a larger accelerated CXL group (30 eyes) than the conventional CXL group (18 eyes). Besides, the accelerated CXL procedure was adjusted to 3 min at 30 mW/cm^2.

In another retrospective study, Ng et al. [24] reported a statistically significant decrease of 1.8 ± 1.8 D in the mean K_{max} of 53.5 ± 6.3 D in the conventional CXL group and a nonstatistically significant decrease of 0.30 ± 0.9 D in the accelerated CXL group, with a preoperative steepest K of 51.6 ± 4.00 D. The authors used the UV-X 2000 system (IROC, Switzerland) at 9 mW/cm^2 for 10 min in the accelerated CXL procedure on adult patients (32.6 ± 6.6 years) and the Avedro KXL system at 18 mW/cm^2 for 5 min on pediatric patients.

The heterogeneity of the population size and patient age; the different ultraviolet A machines, riboflavin preparations, and CXL protocols used; the variable total energy of irradiation; and the varying disease severities made the comparison of outcomes between some of the aforementioned studies and the current study impracticable.

The safety, efficacy, and induced refractive changes of conventional CXL in children with keratoconus were studied by Abdelrahman in 2013. The author compared the results of transepithelial CXL in 22 eyes with those of conservative treatment in control eyes of the same patients. In the transepithelial CXL eyes, the UCVA after 12 months showed a statistically significant ($P < 0.05$) improvement by a mean of 0.27 LogMAR. No patient showed loss of lines of preoperative UCVA. All eyes achieved a CDVA of 20/50 or better. On the other hand, the control group showed a worsening of the UCVA (worse than 20/200) in 6 eyes (27%); 9 eyes (40.90%) lost 1 line of preoperative CDVA. [23].

In the current study, the corneal thickness decreased at 12, 24, and 36 months postoperatively but was close to the baseline value at the last follow-up visit. Our results agree with Abdelrahman, [21] who reported a nonstatistically significant change in the 12-month CCT (467.7 ± 21.4) compared with the preoperative values (469.6 ± 19.1) in the pachymetry map.

The degree of post-CXL haze was found to be correlated with poorer preoperative UCVA and CDVA, thinner pachymetry, and higher K_{max} [11]. Greenstein et al. studied the corneal haze after conventional cross-linking in adult keratoconus patients. They reported a statistically significant increase in the mean densitometry values between the baseline and at 1 month post-CXL ($P < 0.001$). There was no significant change between the post-CXL values at 1 month and at 3 months, nor between those at 3 months and at 6 months. A statistically significant decrease was found between the mean densitometry values at 6 months and at 12 months. Although the mean densitometry values decreased at 6 and 12 months post-CXL, these remained higher than the baseline values ($P < 0.001$) [25].

In our study, both groups showed a statistically significant increase ($P < 0.05$) in corneal densitometry at 1 month post-CXL. However, the densitometry measurements decreased to near-baseline values at 12 months postoperatively; these remained unchanged at 24 and 36 months post-CXL, indicating a nonstatistically significant difference compared with the baseline values. No statistically significant difference in corneal densitometry was found at any time point between conventional and accelerated CXL group ($P > 0.05$).

In contrast to cross-linking in adults, the type of anesthesia is a crucial issue in pediatric keratoconus, especially when there is a correlation with Down syndrome. The relatively short period of exposure of children to GA in accelerated cross-linking, as in the accelerated CXL group cases in our study, is considered a clear advantage over the 60-min GA exposure in conventional cross-linking.

One of the advantages of this study is its prospective double-masked randomized design, with a long postoperative follow-up period of 3 years. To our knowledge, this the first study to compare conventional and accelerated cross-linking in pediatric progressive keratoconus. Future research with a larger data set and a longer follow-up period is recommended to evaluate and compare the long-term results of both techniques in a pediatric population.

One limitation of the present study was the lack of slit lamp grading of the post-CXL corneal haze and the demarcation line depth for the purpose of correlation with the Scheimpflug densitometry and visual acuity at different time points.

In conclusion, this study proved that cross-linking is a safe and efficient treatment in progressive keratoconus in children. Accelerated CXL was comparable with conventional CXL at all time points and showed significantly better outcomes regarding post-CXL visual acuity and reduction in corneal steepness.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study adhered to the tenets of Declaration of Helsinki, and IRB approval was obtained from an ethical committee—Magrabi Aseer Hospital.

Informed consent An informed consent was obtained from all parents.

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