

## A Study on The Effectiveness of Accelerated Crosslinking in Managing Cases with Progressive Keratoconus in Children and Adolescents

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### ABSTRACT

**Background:** Keratoconus (KC) normally appears around adolescence, while advanced instances have been documented in youngsters as young as four years old. KC occurs at a greater rate and progresses quicker in juvenile patients than in adults. The advancement of KC may result in visual impairment in young patients, as well as ramifications for the child's social and scholastic development.

**Objective:** To study the effectiveness of accelerated collagen crosslinking (CXL) in halting the progression of keratoconus in children and adolescents for up to 3 years after treatment.

**Patients and Methods:** This was a retrospective interventional study. 15 eyes from 9 children and adolescents, who had a confirmed progressive keratoconus, underwent accelerated collagen crosslinking (CXL), and followed up for 3 years for mean keratometric reading (Km), corneal front astigmatism (Astig), pachymetry at pupillary center, Index of surface variance (ISV), and Index of vertical asymmetry (IVA)

**Results:** Mean logMAR VA significantly improved. No statistically significant change occurred in K mean values from preoperative to postoperative values at years 1-3. Main K-apex decreased significantly from preoperative  $54.34 \pm 5.31D$  to  $52.34 \pm 5.37$  at year-1 postoperatively ( $P = 0.004$ ),  $51.24 \pm 4.51$  at year-2 ( $P = 0.012$ ),  $51.13 \pm 4.87$  at year-3 ( $P = 0.007$ ). The mean topographic cylinder (Astig) values did not change significantly from preoperative to year-1 ( $P = 0.90$ ) at year-2 ( $P = 0.13$ ) at year-3 ( $P = 0.75$ ). Mean pachymetry value at the center of the cornea significantly changed from preoperative  $507.25$  to  $475.167$  at year-1 ( $P = 0.22$ ) and  $463.9$  at year-2 ( $P = 0.004$ ), but not year-3 ( $483.67$ ,  $P = 0.18$ ).

**Conclusions:** The accelerated technique of collagen cross-linking could stop the progression of keratoconus with no serious adverse effects in adolescent cases over a period of 3-years.

**Keywords:** Accelerated crosslinking, Keratoconus.

### INTRODUCTION

Keratoconus is asymmetric progressive corneal thinning, combined with collagen organization changes in cornea. It leads to irregular astigmatism and myopia, which causes moderate to severe visual impairment<sup>(1,2)</sup>. Keratoconus can affect both the adult and the pediatric age group. Keratoconus in the latter group is more progressive than keratoconus in the adult due to the dynamic environment in the young cornea with a higher risk of needing keratoplasty<sup>(3-5)</sup>. It has an estimated worldwide incidence of 1/2000<sup>(5)</sup>. There are reports that pediatric keratoconus is more prevalent than that of adults<sup>(6)</sup>. Keratoconus was diagnosed in children as early as the fourth year of life.<sup>7</sup> Keratoplasty remained the main treatment for cases with severe keratoconus cases who were intolerant to hard contact lenses till the introduction collagen crosslinking in recent years.

This study aim was to assess the effectiveness of accelerated CXL in halting the progression of keratoconus in children and adolescents up to 3 years following treatment.

### PATIENTS AND METHODS

This was a retrospective interventional study. 15 eyes from 9 children and adolescents, who had a confirmed progressive keratoconus, attended the outpatient clinic of the Ophthalmology Department at Research Institute of Ophthalmology, (Giza) from January 2014 to January 2017. Mean $\pm$ SD (range) age at surgery in years was  $14.5 \pm 3.6$  (12-17).

Keratoconus was diagnosed by clinical presentation and the use of Pentacam 70700 (Oculus Optikgeräte GmbH, Germany), which is built on the principles of Scheimpflug imaging. Progression of keratoconus was detected by Scheimpflug imaging (Pentacam), which was also used in the follow up of these cases for up to 3 years postoperatively.

A minimum pachymetry of 400  $\mu$ m, as measured by the Pentacam was a prerequisite to perform CXL in the study. Cases were evaluated preoperatively, early postoperatively (first 2 weeks for epithelial healing) and at 1, 2 and 3 years postoperatively. During the preoperative visit and at yearly postoperative visits up to year 3, best corrected visual acuity (BCVA) was assessed by Snellen charts. This was later converted to logMAR VA for statistical analysis purposes, slit-lamp examination, Goldmann applanation, and Scheimpflug imaging were performed. Km (mean keratometric reading), corneal front astigmatism (Astig), pachymetry at pupillary center, Index of surface variance (ISV), and Index of vertical asymmetry (IVA), were evaluated.

**Surgical procedure:** A central corneal zone of 8-mm was marked by an 8-mm marker. Corneal epithelium was then manually removed in this zone using a blunt hockey knife. Riboflavin ophthalmic solution 0.1% with hydroxypropyl methylcellulose (VibeX Rapid; Avedro Inc.) was instilled every 2 minutes for 10 minutes. The Avedro system was then used to irradiate the corneas with UVA. The pulsed mode delivered  $7.2 \text{ J/cm}^2$  of total energy utilising the system's nomogram (power:  $30 \text{ mW/cm}^2$ ) (one second on,

one second off). To get 4 minutes of UVA time, 8 minutes of total treatment time were required. VibeX Rapid solution was instilled during irradiation to the corneal surface every 2 minutes. The procedure was concluded by irrigating the corneas, and applying contact lenses which were left in place until re-epithelialization was complete.

**Ethical consent:**

An approval of the study was obtained from Research Institute of Ophthalmology, Giza, Academic and Ethical Committee. Every patient's gurdian signed an informed written consent for acceptance of participation in the study.

This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

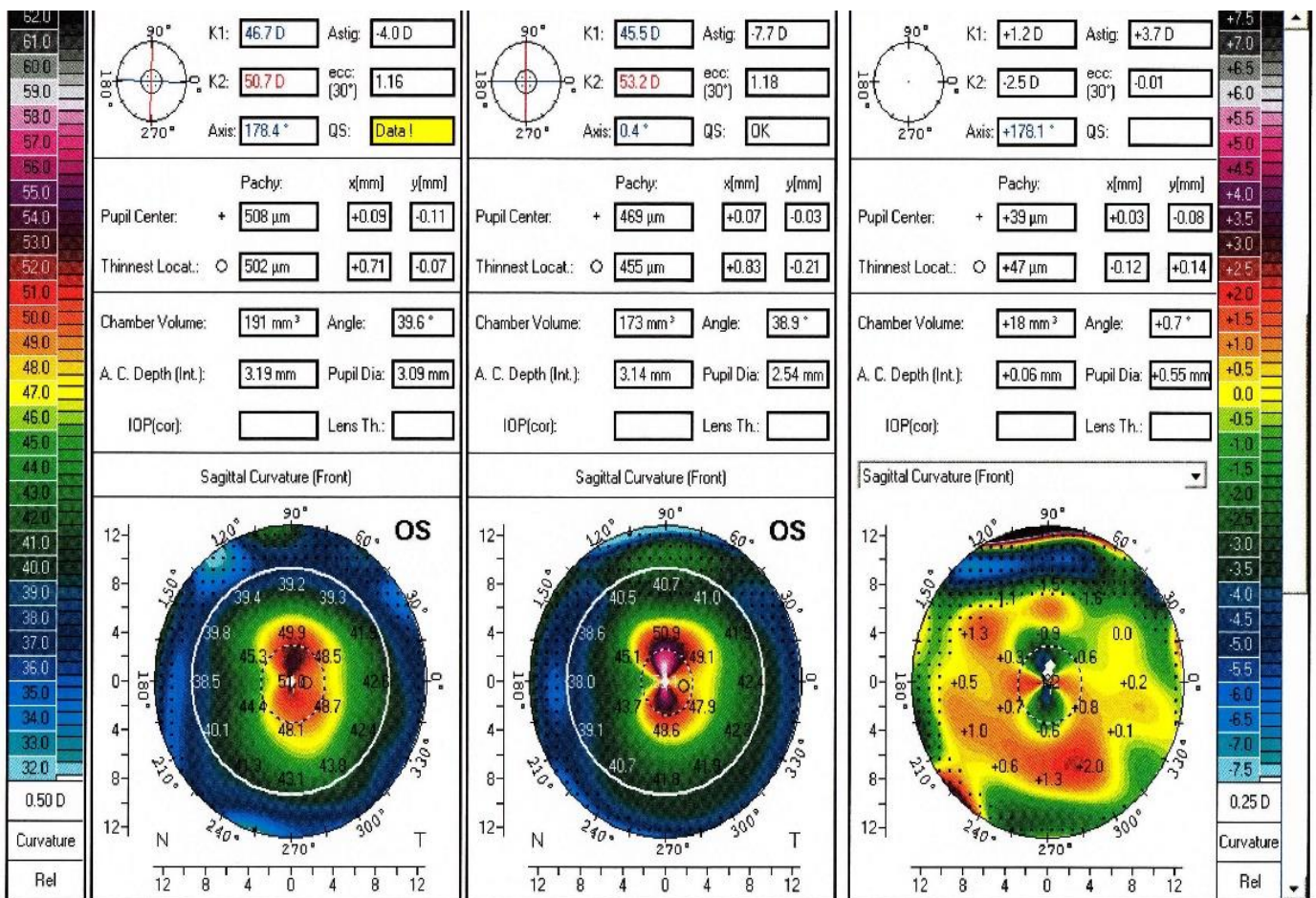
**Statistical analysis**

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA).

Data were tested for normal distribution using the Shapiro Wilk test. Quantitative data were expressed as mean ± SD (Standard deviation) and range. P value < 0.05 was considered significant.

**RESULTS**

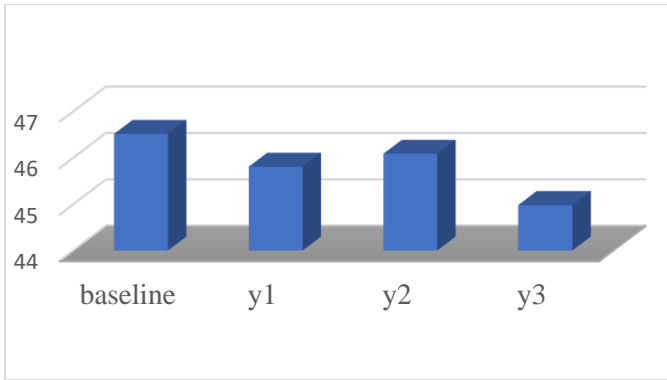
CXL was performed to 15 eyes from 9 children and adolescents, who had a confirmed progressive keratoconus between January 2014 and 2017 (Figure 1).



**Figure (1):** Progression along the course of 1 year in an eye with keratoconus, with increase of K-values and thinning of 40μm

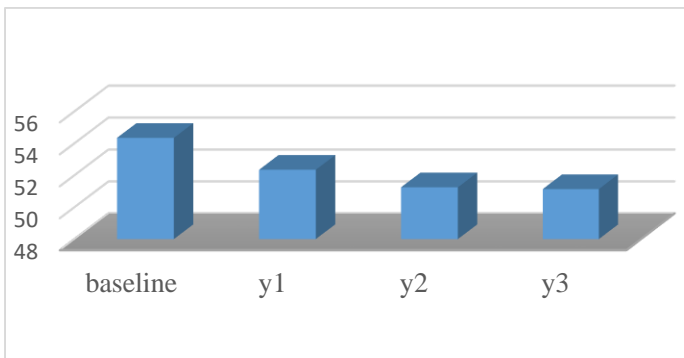
The mean logMAR VA showed significant improvement from 0.61 ± 0.30 to 0.40 ± 0.25 postoperatively (P = 0.002).

K mean values did not show a significant change from preoperative to postoperative values at years 1-3 (Figure 2).



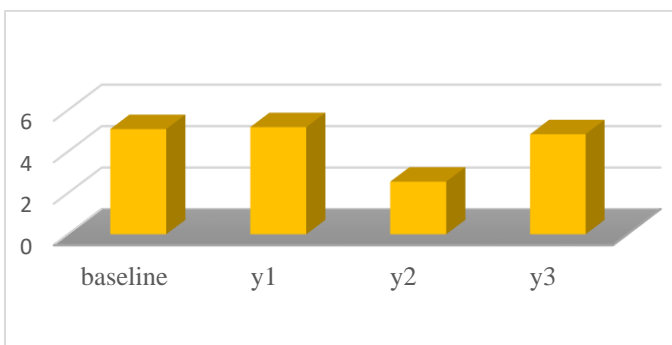
**Figure (2):** K Mean change from preoperative to postoperative years 1, 2, 3.

The mean K apex exhibited a significant reduction from preoperative value of  $54.34 \pm 5.31D$  to  $52.34 \pm 5.37$  at year-1 postoperatively ( $P = 0.004$ ),  $51.24 \pm 4.51$  at year-2 ( $P = 0.012$ ),  $51.13 \pm 4.87$  at year-3 ( $P = 0.007$ ) (Figure.3).



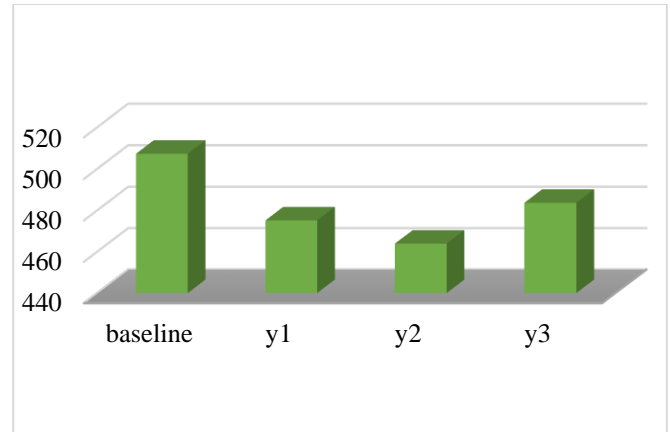
**Figure (3):** Mean K apex change from preoperative to postoperative years 1, 2, 3.

Compared to baseline values, the mean corneal front cylinder (Astig) values did not show a significant change at year-1 ( $P=0.90$ ), year-2 ( $P=0.13$ ) nor at year-3 ( $P=0.75$ ) (Figure 4).



**Figure (4):** Topographic cylinder change from preoperative to postoperative years 1, 2, 3.

Mean pachymetry value at the center of the cornea significantly changed from preoperative  $507.25$  to  $475.167$  at year-1 ( $P = 0.004$ ), but not year-3 ( $483.67$ ,  $P = 0.18$ ) (Figure 5). As regards the indices for Keratoconus Screening, the mean ISV and mean IVA values did not show a significant differences at any of the postoperative visits compared to preoperative values. ( $P > 0.5$  for all).



**Figure (5):** Central pachymetry change from preoperative to postoperative years 1, 2, 3.

There were no cases of keratitis or delayed epithelial healing. The majority of eyes experienced a mild form of corneal haze for a few days following treatment. This, however, showed spontaneous regression. 2 eyes (13.3%) showed significant haze, which developed few months after CXL and resolved slowly along a course of 10 months on topical steroids.

## DISCUSSION

This study was carried out to evaluate the effectiveness and potential complications of CXL for progressive keratoconus in children and adolescents. These cases were brought to the suspicion of keratoconus diagnosis by a rapid increase of refraction value (along months), and binocular asymmetrical astigmatism<sup>(8)</sup>. Diagnosis was confirmed afterwards by Scheimpflug imaging (Pentacam).

Pediatric KC is often more advanced at diagnosis compared to adult KC. It is also more aggressive, with visual and refractive deterioration progressing more rapidly. In addition, it was reported that pediatric KC shows a less favourable postoperative outcomes, which more often needs further interventions, like repeating the CXL or even the need for corneal transplantation. **Chatzis and Hafezi** studied the progression of KC in cases who were 18 years or younger. They found that 52 out of 59 eyes (88%) showed signs of progression within the first year postoperatively<sup>(8,9)</sup>. On the other hand, other studies have reported that progression of pediatric keratoconus could be stopped using collagen cross-linking<sup>(10,11)</sup>. In accordance with these results, the current study, mild progression was observed in 2 of 15 eyes, and was put under follow-up for the potential need of an additional procedure. Remaining 13 eyes did not show any clinical or topographical sign of progression.

Other keratometric findings ( $K_{mean}$ ,  $ICV$ ,  $IVA$ ) were without significant intergroup difference at the year-1, year-2 and year-3 visits. This is in agreement with several previous studies, which found that CXL treatment leads to stabilization of keratoconus in 76%–78% in pediatric population<sup>(5, 12)</sup>.

Transepithelial CXL was documented to be less effective than epi-off CXL as the intact epithelium is thought to hinder optimal penetration of riboflavin into

the stroma of the cornea, which reduces its effectiveness<sup>(13)</sup>. The accelerated protocol used in this study is associated with a less exposure time, which renders it better tolerated by patients. This shorter time of exposure also reduces the risk of infection<sup>(14)</sup>. **Cinar et al.**<sup>(15)</sup> detected significant improvement in visual acuity values 5 years after treatment when they used the epithelium-off accelerated CXL in the pediatric and adolescent age group.

Mild transient haze was observed in 7 of 15 eyes in this study. Significant haze was detected in 2 eyes (13.3%). Accelerated CXL was previously reported to produce less corneal haze compared to the standard Dresden protocol<sup>(16)</sup>. It was previously reported that transient anterior stromal corneal haze occurred after standard Dresden protocol CXL and was attributed to lacunar edema in the keratocytes. This was recognized as a sign of successful CXL<sup>(17)</sup>. Results of the current study showed that changes in refraction and keratometric indices and values were insignificant in this age subset. BCVA were significantly improved with mean changes of 0.21 logMAR. The improvement in VA following corneal cross-linking in this younger age group is possibly caused by improvement in higher-order aberrations of the cornea<sup>(18)</sup>.

Standard CXL is recorded to induce more reduction of the corneal thickness than that caused by CXL<sup>(19)</sup>. The mean minimum pachymetry values were found to be significantly reduced 1 month following CXL and revert to their baseline levels 6 months postoperatively<sup>(20)</sup>. This is rather similar to findings in our study in which pachymetry at the corneal center was significantly reduced at year-1 and year-2 postoperatively. The reduction was not significant at year 3.

## CONCLUSION

The outcomes of this study showed that CXL in is a safe option in the management of keratoconus in children and adolescents. It is effective in stabilizing progressive keratoconus in pediatric and adolescent population. Early management would expectedly reduce the need for keratoplasty with its mediocre success rates in children.

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**Author contribution:** Authors contributed equally in the study.

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