

# Collagen Cross-Linking and Keratoconus in Pediatric Patients

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## ABSTRACT

**Purpose:** To evaluate the efficacy of corneal cross-linking on keratoconic eyes in the pediatric age group.

**Setting:** Private laser center, Haifa, Israel, affiliated to Hadassah Hospital, Jerusalem.

**Methods:** This is a retrospective study of 29 eyes of 20 children treated with corneal cross-linking with aim to arrest the progression of keratoconus. We performed collagen corneal cross-linking using riboflavin 0.1% and UVA irradiation. Follow-up ranged between 6 and 46 months (mean 25.5 months). Evaluation included uncorrected visual acuity, best spectacle corrected visual acuity, manifest refraction, slit lamp examination and corneal topography. Ocular response analyzer was used to assess the corneal resistance factor, corneal hysteresis and cornea compensated intraocular pressure.

**Results:** The results show improvement in uncorrected visual acuity and best spectacle-corrected visual acuity and reduction in astigmatism. There was no statistically significant change in sphere, keratometry, corneal resistance factor, corneal hysteresis or cornea compensated intraocular pressure.

**Conclusion:** Corneal cross-linking demonstrates efficacy in arresting the progression of keratoconus as well as improving uncorrected and best corrected visual acuity and reducing astigmatism.

**Keywords:** Keratoconus, Keratoconus in children, CXL, Collagen corneal cross-linking, Pediatric keratoconus.

**How to cite this article:** Barbara R, Pikkell J, Garzozi H, Barbara A. Collagen Cross-Linking and Keratoconus in Pediatric Patients. *Int J Keratoco Ectatic Corneal Dis* 2012;1(1):57-60.

**Source of support:** Nil

**Conflict of interest:** None declared

## INTRODUCTION

Corneal cross-linking (CXL) is gaining popularity as a treatment in arresting the progression of keratoconus. It is a relatively new therapy using ultraviolet A (UVA) with a photosensitizer riboflavin to increase corneal stiffness. It has been shown that CXL is effective in arresting the progression of keratoconus.<sup>1</sup> The technique is widely used in Europe and is in advanced phases of FDA study for approval in the USA.<sup>2</sup> Many series were published dealing with the results of CXL in ectatic corneal diseases of patients older than 18-year-old,<sup>3-15</sup> nevertheless, only two reports were published with regard to patients under 18 years of age.<sup>16</sup> CXL has been shown to improve uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA), reduce K maximum (Kmax), astigmatism and

myopia in addition to arresting the progression of KC.<sup>3-15</sup> The purpose of this study is to evaluate the results of CXL in pediatric age group.

## PATIENTS AND METHODS

This is a retrospective study of the treatment of Keratoconus with CXL in the pediatric age group. Twenty-nine eyes of 20 patients between the ages of 12.5 to 18-year-old underwent CXL for the treatment of KC. Mean age was 16 years. They were all males. Nine patients had bilateral treatment.

The indications for treatment were progression of KC. The criteria for progression (refer to changes in refraction or visual acuity in the last year) were at least one of the following (these criteria in part were chosen by the FDA for their clinical trial on keratoconus): (1) Serial corneal topographies showing increase in Kmax of 1 diopter (D) or more, (2) documented increase of astigmatism of more than 1D (clinics own records and optician records) (3) loss of BSCVA of two lines or more, (4) subjective decrease in visual acuity (VA), (5) subjective increase of glare and (6) frequent change of spectacles.

Visual acuity assessment was done using the Snellen chart. The refraction was meticulously evaluated by the same surgeon using the Snellen chart and the patients were asked to read the whole line of letters like in amblyopia testing. Computerized Corneal Topography KR7000P (Topcon) was used to evaluate and monitor the keratometric readings. Intraocular pressure was measured using the ocular response analyzer (ORA) (Reichert, USA) as well as corneal hysteresis (CH), corneal resistance factors (CRF) and cornea compensated intraocular pressure (IOPcc). Orbascan II (Bausch & Lomb) topography was used as a diagnostic tool.

Not all parameters were measurable for all patients. The ORA was only available since 2008 and was performed in only 23 eyes.

## SURGICAL TECHNIQUE

We used previously described surgical technique (the Dresden protocol). The surgical procedure was performed by one surgeon (AB) under topical anesthesia. Standard prepping and draping were performed. Till September 2008 scratches were made in the epithelium and following this date an 8 mm radius central corneal epithelium was removed. The patient was seated and riboflavin 0.1% combined with

dextran 20% was instilled every 5 minutes for 30 minutes in corneas thicker than 400  $\mu\text{m}$ . Riboflavin without dextran (hypotonic solution) was used in cases where corneal thickness was less than 400  $\mu\text{m}$ . Four eyes had corneal thickness less than 400  $\mu\text{m}$  (range was 364-398  $\mu\text{m}$  with the epithelium) and hypotonic riboflavine 0.1% without dextran 20% was used till achievement of corneal thickness of more than 350  $\mu\text{m}$  without the epithelium as measured by ultrasonic pachymetry. The maximal thickness was 525  $\mu\text{m}$ . The exposure of the cornea to UVA was done only after the appearance of a strong yellow flare in anterior chamber. Speculum was inserted and the patient was asked to look into UVA (365-370 nm) light source 5 cm from the eye (UVX, Peschke Ltd, Germany) with a light intensity of 3  $\text{mW}/\text{cm}^2$ . During treatment riboflavin was instilled every 5 minutes onto the eye and BSS every 3 minutes for further 30 minutes riboflavin with and without dextran 20% were used as given pre-CXL treatment in accordance to corneal thickness. Following the procedure contact lens (CL) was applied and oflox 0.3% (ofloxacin) antibiotics were prescribed for 3 days till full epithelization. FML 0.1% (fluorometholone) was added for 2 weeks only following epithelial healing which occurred after 3 days.

## STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS software (version 16, SPSS Inc). All measured parameters were analyzed pre- and postoperatively. The data was analyzed using the pair t-test for each parameter. Data is expressed as mean differences between pre and post for each parameter (p-value of less than 0.05 was chosen to be statistically significant).

## RESULTS

The follow-up time was between 6 and 46 months (mean 25.5 months). None of the patients in the study had progression of the KC during the follow-up time.

Results are shown in Table 1.

There were no intraoperative complications. There was one case of postoperative keratitis which was treated successfully with Vigamox (moxifloxacin 0.5%) antibiotics till complete resolution leaving no residual scarring or loss of UCVA or BSCVA, on the contrary there was improvement in UCVA and BSCVA. Most of the treated eyes developed a transient haze which did not affect the BSCVA.

### Visual Acuity

There was statistically significant improvement in the UCVA and BSCVA. The mean preoperative UCVA was 0.29. The mean postoperative UCVA was 0.51, a statistically

**Table 1:** Preoperative and postoperative mean values for the 10 parameters, compared with standard t-test. p-values are demonstrated

Characteristics	Mean		Difference of means (Pre-post)	p-value
	Pre	Post		
UCVA	0.29	0.51	-0.22	0.001
BSCVA	0.6	0.8	-0.2	0.001
SPH	-0.84	-0.7	-0.14	0.606
CYL	-4.15	-3.3	-0.86	0.002
Kmax	49.6	49.5	0.1	0.776
Kmin	45.9	45.7	0.18	0.338
Kavg	47.7	47.5	0.22	0.340
CH	9.13	9.35	-0.23	0.393
CRF	7.1	7.1	0.004	0.988
IOPcc	12.4	12.9	-0.47	0.532

UCVA: Uncorrected visual acuity; BSCVA: Best spectacle corrected visual acuity; SPH: Sphere; CYL: Cylinder; CH: Corneal hysteresis; CRF: Corneal resistance factor; IOPcc: Intraocular pressure corneal compensated

significant improvement ( $p = 0.001$ ). The mean preoperative BSCVA was 0.60. The mean postoperative BSCVA was 0.80, a statistically significant improvement ( $p = 0.001$ ).

### Spherical and Cylindrical Change

The mean sphere was reduced by 0.14D (from 0.84D to 0.70D) which was not statistically significant ( $p = 0.606$ ), nevertheless, there was a statistically significant reduction in astigmatism by 0.86D (from -4.15 D to -3.3 D) ( $p = 0.002$ ).

### Keratometry

There was no statistically significant change in the K min, K max or K average ( $p = 0.338, 0.776, 0.340$  respectively).

### CRF and CH

No statistically significant change in CRF, CH or IOPcc ( $p = 0.988, 0.393, 0.532$  respectively).

## DISCUSSION

Various studies demonstrated the efficacy of CXL in arresting the progression of KC in the adult age group. Beyond this primary effect, CXL was shown to improve UCVA, BSCVA, reduce K readings, astigmatism and high order aberrations (HOA) as well as improve keratoconus indexes.<sup>3-15</sup> Pediatric age at the time of the diagnosis of keratoconus is a negative prognostic factor for the progression of the disease and increases the probability for the need of corneal transplant.<sup>17</sup>

The FDA in its trial on the effectiveness of CXL is recruiting patients from the age of 12-year-old.<sup>2</sup>

Caporossi et al reported on 152 eyes of 105 patients under 18 years old with a mean follow-up of 12 months in

91 eyes, 24 months in 74 eyes, 36 months in 25 eyes and 48 months in seven eyes, the treatment was performed according to the Dresden protocol.

The study demonstrated a gain in UCVA and BSCVA, a reduction in K max, surface asymmetry index (SAI) and coma values.<sup>16</sup>

In this retrospective study, we evaluated UCVA, BSCVA, refraction, K readings, CH, CRF and IOPcc preoperatively and postoperatively. On one hand, our study confirms the other published results on arresting the progression of the disease, improving UCVA, BSCVA and reducing astigmatism (clear statistical significance). On the other hand our data did not show a significant change in K readings. Corneal biomechanical properties as measured by the ORA did not change significantly either.

In keratoconus CH and CRF are lower than normal as detected by ORA.<sup>18-20</sup> Although this instrument has the sensitivity to detect low values of CH and CRF, it lacks the specificity to detect the increased corneal biomechanics which was proved to increase following CXL treatment.<sup>1</sup> This correlates with published data of Zadok et al which demonstrated no change in corneal biomechanical properties as measured by the ORA.<sup>21</sup> The new software of the ocular response analyzer elaborates more data from the waveform of the tested eye and may be more sensitive in demonstrating the biomechanical changes in the cornea after CXL.

The IOPcc is supposed to reflect the 'real' intraocular pressure of the eye taking into consideration the biomechanical characteristics of the cornea, it is calculated from the ORA measurements. In our study, the mean IOPcc increased by 0.5 mm Hg but did not reach statistical significance.

## CONCLUSION

CXL is a safe and effective method in halting the progression of KC in patient under the age of 18 years. It appears to possess similar results to the adult population in terms of improvement in UCVA, BSCVA and reduction in astigmatism; however, further studies are needed to evaluate the long-term efficacy of CXL in this age group.

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