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Original Article

OUTCOMES OF CORNEAL COLLAGEN CROSS LINKING IN PEDIATRIC KERATOCONUS IN UPPER EGYPT

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Abstract

***Purpose**: To assess the short term visual, refractive, and tomographic outcomes of corneal collagen cross-linking (CXL) in pediatric patients with keratoconus. **Patients and Methods:** A prospective interventional non-comparative case series study that was conducted in The Future Center for refractive surgery, Sohag, in the period from May 2017 to October 2018, All the eyes were treated with accelerated trans-epithelial corneal cross-linking under topical or general anesthesia and the following data were collected at baseline,3 months, 6 months, and 12 months postoperatively for all patients: uncorrected- and best-corrected visual acuity, sphere, spherical equivalent, cylinder, and tomographic findings. **Results:** A total of 50 eyes of 25 patients, 16 males (64%) and 9 females (36%) were included. Mean age at surgery was 15.76±1.67 years (range, 13-18). Mean uncorrected visual acuity was 0.83±0.30 logMAR at baseline and 0.74±0.33 logMAR at 12 months (P=0.009). Mean preoperative best-corrected visual acuity was 0.52±0.28 logMAR, which improved to 0.31±0.27 logMAR at 12 months (P<0.0001).Mean sphere was -3.17±3.95 at baseline and improved to -2.75± 3.55 at 12 months (P=0.01). Mean cylinder was -3.12±2.25 preoperatively and improved to -2.71± 2.56 at 12 months (P=0.052). Baseline spherical equivalent was-4.69±4.48 which improved to -4.08± 4.30 at 12 months (P=0.003). Mean baseline Kmax, Kmin, and Kmean values were 48.31±3.92, 44.48±2.73, 46.07±2.87 respectively; these values were stable at 12 months (P>0.05). There was non-significant reduction in the mean thinnest corneal area from baseline (453.36±40.50 mm) to 12 months (447.84±46.51 mm), (P=0.06). There were no significant postoperative complications. One case show progression at the 12th month as the followings were noticed; The cylinder increased from -7.00 to -10.50, The flattest K increased from 55 D to 59 D, The steepest K increased from 58 D to 61 D, the corneal thickness at thinnest location decreased from 400 µm to 381 µm. **Conclusion:** In this study CXL effectively stabilized keratometry values at 12 month, while improving uncorrected visual acuity, best corrected visual acuity, and refractive indices.*

Keywords: *Corneal collagen cross-linking, Pediatric Keratoconus, Upper Egypt*

1. Introduction

Keratoconus is characterized as a bilateral, non symmetrical and non inflammatory, progressive corneal ectasia [1]. Visual impairment results from progressive myopia, and irregular astigmatism which caused by progressive corneal thinning and protrusion. It usually starts at puberty and stabilizes in the fourth decade [2]. Pediatric keratoconus (<18 years of age) is more progressive than in adults [3].Wollensak,

et al, [4] introduced corneal collagen cross linking (CXL) in 2003 for treatment of keratoconus. In which they used riboflavin which is vitamin B2 in combination with ultraviolet A to form a new cross links on the surface of collagen fibrils, by this they can increase the strength of the cornea and halting further progression [5]. This study aimed to assess the short term visual, refractive, and tomographic outcomes of CXL in patients <18 years of age.

2. Patients and Methods

A prospective interventional case series study that was conducted in The Future Center for refractive surgery, Sohag, in the period from May 2017 to October 2018. The study included 50 eyes of 25 patients with keratoconus less than 18 years of age. The study had been approved by the Health Research Ethics Committee at Sohag Faculty of Medicine. Informed written consents were taken from the patients and their families after full explanation of this procedure for treatment of keratoconus and the nature of their disease. Diagnosis of keratoconus was based on clinical findings and corneal images generated by the (CSO, Florence, Italy). Exclusion criteria were as follows: Advanced keratoconus with keratometry values more than 60 D and thinnest corneal thickness less than 400 µ and history of previous corneal surgery. After the treatment, the patients were followed up for 12 months. At each follow-up visit, a standard examination was carried out to assess uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), refractometry, keratometry, and corneal topography. The progression of keratoconus over 12 months was defined on the basis of following changes; **1)** Change in either myopia and/or astigmatism of ≥3 D. **2)** Change in K-readings of ≥1.5 D. **3)** Corneal thickness decrease of ≥5%.

2.1. *Surgical procedure*

All the eyes were treated with accelerated trans-epithelial corneal cross-linking under topical or general anesthesia. CXL was performed under aseptic technique in the operating theatre under topical anesthesia eye drops or general anesthesia. Surgical field were prepared and eyelid speculum was inserted. Corneal epithelium was left intact. We used the KXL® System (Avedro Inc., USA) accelerated CXL protocol, riboflavin (Para Cel) dropped on the cornea every one and half minutes for 4.5 minutes. Then dropping of riboflavin (VibexXtra) every one and half minutes for 6 minutes. Followed by 5.20 minutes accelerated CXL using the pulsed mode with 45 mW / CC power. The cornea was completely rinsed with balanced salt solution. Eyelid speculum removed. Postoperatively, Patients advised to refrain from eye rubbing. Antibiotic eye drops (e.g 0.3% moxifloxacin) and lubricants Hypromellose were advised for one week. Corticosteroids (e.g 1% Prednisolone acetate) eye drops were continued for two weeks. Bandage contact lens were applied and removed on first postoperative day.

2.2. *Statistical analysis*

Data was analyzed using SPSS. Quantitative data was represented as mean, standard deviation, median and range. Comparison was made between preoperative and postoperative follow up data at 3, 6, and 12 months using RMANOVA test. Sphericity were examined using test of Sphericity. Fisher's Least Significant Difference (LSD) post hoc test to examine the difference at each time point. P value was considered significant if it was less than 0.05.

3. Results

The total number of patients included in this study was 50, with age range from 13 to 18 years old and mean age of 15.76±1.67 years.16 patients were males (64.00%) and 9 patients were females (36.00%), tab. (1).

Table (1) Patients' demographics

Total number of study eyes	50
Total number of study patients	25
Age:	
Mean ± SD	15.76±1.67
Median (Range)	16 (13-18)
Gender:	
Male	16 (64.00%)
Female	9 (36.00 %)

3.1. *Visual acuity and refractive data*

The mean uncorrected visual acuity was 0.83±0.30 log MAR at baseline and 0.74±0.33 log MAR at 12 months with significant difference (P=0.009). Mean preoperative best-corrected visual acuity was 0.52±0.28 log MAR, which improved to 0.31±0.27 log MAR at 12 months with significant difference (P<0.0001), tab. (2). The mean preoperative spherical equivalent was -4.69±4.48 and showed a decrease throughout the follow up period ending with mean value -4.08±4.30 at 12th month with significant p value (P=0.003),the sphere value had a similar course: starting from a preoperative mean of -3.17±3.95 to -2.75±3.55 at the end of follow up period with significant p value (P=0.01), the mean cylinder value was -3.12±2.25, These value was not significantly changed at 12th month (P=0.052), tab. (2).

Table (2) Visual acuity, in logarithm of the minimal angle of resolution units, spherical equivalent, Sphere and cylinder data (all reported as mean _ SD)

	Preoperative	Postoperative 3rd month	Postoperative 6th month	Postoperative 12th month	P value
UCVA	0.83±0.30	0.78±0.28	0.73±0.30	0.74±0.33	p=0.009
BCVA	0.52±0.28	0.45±0.24	0.36±0.23	0.31±0.27	p<0.0001
Sphere, D	-3.17±3.95	-2.86±3.37	-2.8±3.55	-2.75±3.55	P=0.01
Cylinder, D	-3.12±2.25	-2.97±2.15	-2.72±2.31	-2.71±2.56	P=0.052
SE,D	-4.69±4.48	-4.35±3.85	-4.16±4.24	-4.08±4.30	P=0.003

UCVA *uncorrected distance visual acuity;* ***BCVA*** *best-corrected visual acuity;* ***D*** *diopter;* ***SD*** *standard deviation;* ***SE*** *spherical equivalent*

3.2. *Tomography*

The tomographic data which was statistically analyzed in this study included the keratometry values and corneal thickness at thinnest location from preoperative to 3 months, 6 months and 12 months postoperative values. Mean baseline K_1(flattest k), K_2(steepest k) and $K_{average}$ values were 44.48±2.73 D, 48.31±3.92 D, 46.07±2.87 D, respectively. There was no significant change in their mean values at 12 month which was 44.54±3.46D (P=0.48), 48.15± 3.99D (P=0.99), 46.16±3.24D (P=0.96), respectively, tab. (3). There was no postoperative complications, such as chronic epithelial defects, haze, or infectious keratitis reported throughout the postoperative follow up period in the study population, one case show criteria of progression as at the end of the 12th month the followings were noticed: 1) The cylinder increased from -7.00 to -10.50, The flattest K increased from 55 D to 59 D, 2) The steepest K increased from 58 D to 61 D, 3) The decision was to retreat this patient again with another session of corneal collagen cross-linking.

Table (3) Tomographic measurements (mean ± SD)

	Preoperative	Postoperative 3rd month	Postoperative 6th month	P value
K1, D	44.48±2.73	44.49±3.12	44.54±3.46	P=0.48
K2, D	48.31±3.92	48.15±3.91	48.15±3.99	P=0.99
K avg, D	46.07±2.87	46.17±3.23	46.16±3.24	P=0.96
Thickness at thinnest location, µm	453.36±40.50	445.4±39.80	447.84±46.51	P=0.37

K1 *flattest k;* ***K2*** *steepest k;* ***Kavg****, average K.* ***D****, diopters;* ***SD****, standard deviation.* ***P value*** *for change from baseline to 3 months, and to 6 months.*

4. Discussion

It is known that typical onset of keratoconus is at puberty, but it does affect younger children. Léoni-Mesplié et al. conducted a large retrospective study, evaluating 216 keratoconic patients separated into various age groups and found that keratoconus in children was significantly more severe at diagnosis and progressed faster than in adults [6]. Since the progression of disease is more pronounced in young people than in elderly patients, cross-linking is particularly important for young patients. For example, the results of Vinciguerra's study suggest that the treatment effect could be more pronounced in young people than in older patients, whereby a mean reduction in maximum corneal refractive power of 1.27 dpt was observed within 2 years following cross-linking in patients under 18 years of age [7]. Different studies compared the efficacy and safety of epithelial on collagen cross linking versus epithelial off technique in children, as Buzzonetti et al. in 2012, Salman et al. in 2016, and Eraslan et al in 2017 [8-9]. All reported the safety of both procedures, as regard the efficacy they showed that despite the efficacy of Epithelium on procedures it remains less effective than Epithelium off. In this study, we evaluated short-term visual, refractive, and tomographic outcomes of CXL in pediatric patients with keratoconus. The patients had been subjected to accelerated transepithelial corneal collagen cross linking with follow up period of twelfth months. In this study vision improved in most of patients from the first month postoperative and this improvement remained stable till the twelfth month, also there was improvement in the refractive indices with stability of the keratometric readings and a non-significant decrease in the thickness at thinnest corneal location. Derakhshan, et al, [11] reported improvement in UCVA and BCVA at 6th month postoperative with significant reduction of the spherical equivalent and the keratometric readings. Tian M, et al. [12], also noticed improvement in vision after 1 year follow up with no significant difference in keratometric readings or in thinnest corneal thickness. Caporossi A, et al. [13], studied the effect of TE-CXL in progressive keratoconus in patients <26 years old for 24 months, results of the study showed that, an improvement in UDVA, although not statistically significant, was recorded at 6 months (P=0.13) and lasted until the 12th month. At the 18 month follow up, the UDVA was worse, returning to baseline values (P=0.61). The worsening continued through 24 months (P=0.61), The CDVA increased starting from the first month until the sixth month postoperatively (P=0.18), it returned to preoperative values at 24 months (P=0.57) and similar to their finding regarding UCVA and BCVA, they reported initial improvement in Keratometric readings during the early periods of follow up then deterioration occurred and returned to the preoperative values, in 5 patients younger than 18 years, vision worsened significantly and were retreated with the epi-off CXL technique. In this study there was a slight decrease in the thickness of

the thinnest location all over the follow up period, till the end of the 12th month slight increase in thickness had been noticed with insignificant P value=0.06. This result also noted by Cinar Y, et al. [14], where the thickness of the thinnest location reduced significantly at 1st month and regained its thickness at the 3rd and 6th month after CXL procedure. Decreased corneal thickness could be due to temporary increase in the pump activity of the endothelium which occurred due to hypoxic stress or UVA exposure and packing of the corneal lamellae due to formation of new cross-link [15]. No intraoperative or postoperative complications in patients were reported in the current study, indicating accelerated transepithelial (ATE-CXL) safety. Progression occurred only in one patient, Re-treatment was decided for the patient.

5. Conclusion

This study proved the efficacy and the safety of cxl in pediatric population. Limitations to this study; short period of follow up and limited number of studied population.

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