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Effect of Collagen Cross-Linking on Corneal Thickness in Children with Progressive Keratoconus

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ABSTRACT

CXL tends to alter the collagen of the cornea via alteration of biochemical properties in Keratoconus using assisted riboflavin and UVA. This causes an increase in rigidity of the cornea and slows the progression of the disease. **Objectives:** To analyze the mean changes in corneal thickness after Corneal Collagen Cross-Linking (CXL) among children aged 8 to 15 years diagnosed with Keratoconus. **Methods:** This quasi-experimental study was conducted at the Department of Cornea, Al-Ibrahim Eye Hospital, Karachi, from March–September 2022. A sample size of 34 was calculated using G Power software with 80% power and a 95% confidence level. Non-probability consecutive sampling was used. Pediatric patients (8–15 years) with progressive keratoconus were included, while those with other ectatic disorders, active ocular disease, or prior anti-glaucoma medication were excluded. Ethical approval and informed consent were obtained. Clinical assessments were done before and after CXL, with follow-ups at weeks 4 and 12. Data were analyzed using SPSS version 23.0, applying appropriate statistical tests. **Results:** The study observed a mild reduction in keratometric values (K1, K2, Kmax) and central corneal thickness following collagen cross-linking in 34 children with progressive keratoconus over three months. Although Kmax decreased from 56.3 ± 10.3 to 53.4 ± 8.9 and corneal thickness from 487.88 ± 31.66 µm to 485.73 ± 31.90 µm, these changes were not statistically significant, indicating early stabilization without significant structural alteration. **Conclusions:** Collagen cross-linking in children with progressive keratoconus appears to stabilize corneal curvature with minimal impact on central corneal thickness over a short-term period, though changes are not statistically significant.

INTRODUCTION

Keratoconus is defined as a progressive, asymmetric, bilateral corneal ectasia of a non-inflammatory variety. Instability in the corneal collagen fibers causes thinning and a progressive increase in the curvature of the cornea [1]. This leads to loss of visual acuity with irregular astigmatism. Typically, Keratoconus presents during puberty, which tends to stabilize by the fourth decade of life [2]. In children <15 years of age, Keratoconus is seldom advanced at the time of diagnosis and might rapidly progress in children as compared to adults [3]. In treating Keratoconus, collagen cross-linking (CXL) causes strengthening of collagen bonds in the corneal stroma coupled with ultraviolet A (UVA) that is activated using riboflavin [4]. Initially, CXL was introduced by Wollensak and colleagues, while now it is regarded as the first line of treatment in patients having progressive Keratoconus [5]. Even the ability to halt progression of Keratoconus amongst adults has been established well in the published literature. Treating pediatric Keratoconus using CXL is an area of research that is limited [6, 7]. In the pediatric population with Keratoconus, progression has been reported in as high as 88 % of patients over a period of one year [8]. The requirement for penetrating keratoplasty among children is observed to be 7 times higher than in adults because of the disease's aggressive nature (especially in children below the age of 18 years) [9]. To

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avoid penetrating keratoplasty, it has become a necessity to halt or slow down Keratoconus progression using a more rapid and effective technique [10]. CXL tends to alter the collagen of the cornea via alteration of biochemical properties in Keratoconus using assisted riboflavin and UVA [11]. This causes an increase in rigidity of the cornea and slows the progression of the disease. In the procedure of standard epithelium-off CXL (SCXL) procedure, 5.4 J/cm2 of energy is delivered using 3 mW/cm2 intensity over the next 30 minutes (using the Dresden protocol) [12]. With the use of the standard protocol, visual stabilization coupled with decreasing keratometric values and reduced progression of KCN were observed in studies done on pediatric populations [13]. The etiology of KCN is unknown. Various associations are identified, including contact lens wear (rigid gas permeable, RGP), Down syndrome, Leber congenital amaurosis, chronic eye rubbing, and atopic disease/s [14]. A positive family history of KCN is found in around 6 to 8 % of patients, demonstrating possible familial transmission [15].

Even though CXL is a well-known treatment for halting Keratoconus progression, the majority of the researches have studies adult patients. With regards to corneal thickness specifically in the pediatric population, limited data persists, especially in patients exhibiting a more aggressive progression of disease. Moreover, local studies from developing populations also remain scarce. Progressive keratoconus amongst the pediatric age group causes rapid thinning of the cornea, resulting in deterioration of vision, substantially affecting quality of life. Whilst CXL is rising among children, its exact effect on the thickness of the cornea is not well established in the literature. This creates uncertainty in making clinical decisions and in devising management strategies in the long term. This study aimed to evaluate the effect (mean change) of corneal CXL on the thickness of the cornea in a pediatric population aged 8 to 15 years, diagnosed with Keratoconus.

METHODS

This was quasi-experimental research (pre and post-interventional study) carried out at the Department of Cornea, Al-Ibrahim Eye Hospital, Karachi, from March 2022 to September 2022. After ethical approval from the ERC (Ethical Review Committee) (Ref: ATMC/IERC/12(2021) dated 22 March 2021) of Al-Ibrahim Eye Hospital, data collection commenced. Using the freely available G*Power software for sample size calculation, the sample size was calculated as follows: with 80% power, 95% confidence level, a 5% margin of error, and mean pre-CXL of 486.9 ± 26.5 and post-CXL of 474.8 ± 28.6 [16]. The sample size came out to be 34. The sampling technique used for this research was a non-probability consecutive sampling technique. All eligible patients attending the department during the study period were selected to minimize selection bias. Pediatric population of either gender aged between 8 and 15 years, diagnosed with progressive Keratoconus with frequent changes in refractive error within the last three months, either before or after presenting in OPD, were included in the research. Patients with corneal progressive ectatic disorders apart from Keratoconus, such as pellucid marginal degeneration and Keratoglobus, were excluded from the study. In addition, patients having a history of active ocular disease such as allergy, inflammation, and infection, with severe corneal opacification or scarring on slip lamp examination, were also excluded. Patients with a history of anti-glaucoma drugs (Prostaglandin analogues) were also excluded from the research. All patients underwent standard epithelium-off collagen CXL (Dresden protocol), which was performed by an experienced ophthalmologist under aseptic measures. This ensured consistency of the procedure across all cases. Baseline ophthalmic examination was performed for all participants, including uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), slit lamp examination, fundoscopy, and refraction assessment. Patients attending the cornea clinic of the hospital were included as per the inclusion and exclusion criteria. A self-designed questionnaire was utilized for analysis of data. A thorough clinical examination was carried out along with history taking before and after CXL (which was carried out by an experienced Ophthalmologist). Informed consent was obtained from each patient before inclusion in the study. Baseline corneal thickness (central corneal thickness and thinnest corneal thickness) was measured before collagen cross-linking using pachymetry or Scheimpflug imaging. Progressive keratoconus was identified based on an increase in keratometric readings, reduction in corneal thickness, deterioration of visual acuity, or increase in refractive error over time.

Data analysis was carried out using SPSS version 23.0. Demographical information of patients included age, gender, and duration of KCN. Follow-up of patients was done at the 4th and 12th week post-CXL. The primary outcome measure was the change in thickness of the cornea. The secondary outcome measure was the change in keratometric parameters such as K1, K2, and Kmax, which were measured at baseline, 4 weeks, and at 12 weeks post-CXL. Continuous variables such as age, thinnest corneal thickness, K1, K2, Kmax, best corrected and uncorrected visual acuity were represented as mean and standard deviation (if normally distributed), while median and interquartile range (if data were skewed). Normality of data was tested using the Shapiro-Wilk test. Categorical data were recorded as frequency and percentage for

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gender. Stratification was done for confounders/effect modifiers such as gender, age, K1, K2, best and uncorrected visual acuity. Post-stratification, independent t-test was applied. From baseline, week four, and week twelve, comparison of mean differences of central corneal thickness was carried out using repeated measures ANOVA, keeping $p<0.05$ statistically significant.

RESULTS

The baseline demographics of patients included in the study are presented. The mean age of patients was 10.3 ± 3.15 years, with 19 (55.88 %) males and 15 (44.12 %) females. The mean duration of Keratoconus was 8.3 ± 2.9 months (Table 1).

Table 1: Baseline Demographics of Patients Included (n=34)

Variables	Frequency (%) / Mean ± SD
Age (years)	10.3 ± 3.15
Male	19 (55.88 %)
Female	15 (44.12 %)
Mean Duration of Keratoconus (months)	8.3 ± 2.9

The study illustrates the graphical comparison of keratometric values K1, K2, and Kmax before and after collagen cross-linking (CXL) in 34 children with progressive keratoconus. The mean K1 value decreased from 46.7 ± 4.5 diopters pre-operatively to 46.1 ± 4.4 at one month and 45.8 ± 3.9 at three months post-operatively. Similarly, the mean K2 value reduced from 50.2 ± 5.1 to 49.8 ± 4.8 at one month and further to 49.1 ± 4.6 at three months. The steepest keratometric value, Kmax, showed a decrease from 56.3 ± 10.3 pre-operatively to 55.7 ± 9.8 after one month and 53.4 ± 8.9 at the third month. All three keratometric indices demonstrated a consistent downward trend, indicative of corneal flattening following CXL (Table 2).

Table 2: Comparison of Mean K1, K2 And Kmax at Baseline, One Month Post-Op and Third Month Post-Op (n=34)

Variables	Mean ± SD	p-value
K1 Pre-Operative	46.7 ± 4.5	0.32
K1 Post-Operative 1 Month	46.1 ± 4.4	
K1 Post-Operative 3 Months	45.8 ± 3.9	
K2 Pre-Operative	50.2 ± 5.1	0.25
K2 Post-Operative 1 Month	49.8 ± 4.8	
K2 Post-Operative 3 Months	49.1 ± 4.6	
Kmax Pre-Operative	56.3 ± 10.3	0.25
Kmax Post-Operative 1 Month	55.7 ± 9.8	
Kmax Post-Operative 3 Months	53.4 ± 8.9	

The results provide a statistical comparison of mean central corneal thickness measured at baseline, one month, and three months after CXL. The mean corneal thickness at baseline was 487.88 ± 31.66 µm, followed by 486.73 ± 31.90 µm at one month and 485.73 ± 31.90 µm at three months. The ANOVA analysis yielded a mean square value of 39.35, an F statistic of 0.04, and a p-value of 0.96, indicating no statistically significant difference in corneal thickness over the study period. The 95% confidence intervals further support the consistency of the measurements: 476.83–498.92 at baseline, 475.60–497.86 at one month, and 474.60–496.86 at three months post-operatively (Table 3).

Table 3: Comparison of Mean Central Corneal Thickness Differences Between Baseline, One Month Post-Op and Third Month Post-Op (n=34)

Time Period of Measurement	Mean ± SD	Mean Square	F Statistics	95 % Confidence Interval	p-value
Baseline	487.88 ± 31.66	39.35	0.04	476.83- 498.92	0.96
Post-Op One Month	486.73 ± 31.90			475.60- 497.86	
Post-Op Third Month	485.73 ± 31.90			474.60-496.86	

DISCUSSION

In this study involving 34 children with progressive keratoconus, collagen cross-linking (CXL) resulted in a mild but consistent reduction in keratometric values and central corneal thickness over three months. The mean K1 decreased from 46.7 ± 4.5 to 45.8 ± 3.9 diopters, K2 from 50.2 ± 5.1 to 49.1 ± 4.6, and Kmax from 56.3 ± 10.3 to 53.4 ± 8.9, indicating a trend toward corneal flattening; however, these changes were not statistically significant ($p > 0.05$). Similarly, central corneal thickness showed a slight decrease from 487.88 ± 31.66 µm at baseline to 485.73 ± 31.90 µm at three months, with no significant difference over time ($p=0.96$). Similar results have been observed in other research as well [17]. Literature supports the use of CXL in pediatric Keratoconus [18]. The researchers reported CXL to be both safer and efficacious compared with other modalities for improving uncorrected distance visual acuity as well as corrected distance visual acuity among < 18-year-olds [19]. In current research, the mean age of the pediatric population was 11.3 ± 2.2 years. Similarly, another study also observed similar results, with a mean age of 12 ± 2.02 years in the study [16]. A study by Ng et al. observed the mean age of patients with Keratoconus to be 15.7 ± 2.1 years [20]. Likewise, the current study observed a reduction in mean corneal thickness from pre-operative to post-operative three months, even though insignificant, was also reported by a study from Egypt, where pre-operative mean corneal thickness was reduced from 486.9 ± 26.5 um to 474.8 ± 28.6 um and 470.2 ± 28.3 um at third and sixth month, respectively [16]. Ng *et al.* in their study found a reduction of mean corneal thickness from 469.6 ± 19.1 um to 467.7 ± 21.4 um post-operatively [20].

Although our study evaluated the mean change in corneal thickness pre-operatively and post-operatively at 1st and 3rd month, the study was not free from limitations. The sample size of the study was very limited since this was single-centered research. Even though the study made use

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of consecutive sampling, which is best suited for the study design used in the research. The findings of this study suggest that while CXL may help stabilize keratometric parameters in pediatric patients, its short-term effect on corneal thickness and curvature is not statistically significant. Larger long-term multicenter studies with larger paediatric populations and longer follow-up (>12 months) are required to confirm long-term stability of corneal thickness and keratometric parameters in children with progressive keratoconus after CXL.

CONCLUSIONS

Collagen cross-linking in children with progressive keratoconus appears to stabilize corneal curvature with minimal impact on central corneal thickness over a short-term period, though changes are not statistically significant.

Authors' Contribution

Conceptualization: NK
Methodology: NK, ST
Formal analysis: NK
Writing and Drafting: AF, AS, IA, MSF
Review and Editing: NK, AF, ST, AS, IA, MSF

All authors approved the final manuscript and take responsibility for the integrity of the work

Conflicts of Interest

All the authors declare no conflict of interest.

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