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**ORIGINAL ARTICLE**

# Role of Corneal Collagen Cross Linking in Halting the Progression of Keratoconus: A Contralateral Eye Study

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## ABSTRACT

**Objective:** To assess the efficacy of Corneal Collagen Cross-Linking in preventing the progression of Keratoconus by comparing changes in Maximum Simulated Keratometry (K-max) in treated and untreated eye of the same patient.

**Methodology:** All the cases, that met the inclusion/exclusion criteria (with complete pre-operative examinations), were enrolled in the study. Patients gave informed permission. In each patient, a computerized random number table was used to pick one eye for treatment and the other as a control. Patients were told to stop wearing hard contact lenses 3 weeks before the treatment and soft lenses 1 week before. After pre-op assessment, the selected eye underwent CXL. To control bias, only one experienced surgeon carried out the procedure and a thorough examination was done at 1st post-op day, 01 week, 01, 03 and 4 months after CXL. Main outcome measure during follow up was K-max as measured by Corneal Topography using Galilei G4. One experienced person performed corneal topography for all eyes to control bias.

**Results:** In our study, mean age was 20.55+6.27 years, 60.61%(n=20) were male while 39.39%(n=13) were females. Comparison of the efficacy of corneal collagen cross-linking in preventing the progression of keratoconus by comparing changes in maximum simulated keratometry (K-max) in treated and untreated eyes of the same patient shows that 96.97%(n=32) in CXL and 3.03%(n=1) in control group showed efficacy whereas remaining 3.03%(n=1) in CXL and 96.97%(n=32) in control group had no efficacy, p value was 0.000.

**Conclusion:** We concluded that Corneal Collagen Cross Linking is significantly effective in preventing increase in K-max when compared with the control group.

**Keywords:** Keratoconus, Maximum Simulated Keratometry, Corneal Collagen Cross-Linking, Efficacy

## INTRODUCTION

Keratoconus is a corneal ectatic disorder, non-inflammatory and degenerative in nature, main feature of which is progression of corneal stromal thinning throughout the course of disease[1] ultimately leading to high irregular astigmatism and corneal scarring[2] thus decreasing visual quality.[3] The reported incidence of this disease is about 1 in 2000.[3] This disease is bilateral but signs and symptoms vary in intensity in the two eyes.[3] Keratoconus is diagnosed early in life (usually 2nd or 3rd decade), thus its effect on the quality of life is significant.[4]

Treatment modalities usually employed to combat Keratoconus include spectacles, soft and hard contact lenses, intracorneal ring segment implants and lamellar/penetrating keratoplasty for advanced cases.[1-5] Although none of these modalities target the progression of the disease.[3]

Corneal Collagen Cross-Linking (CXL) is the latest technique to halt the progression of Keratoconus.[6] First performed by Wollensak in 2003, this new popular technique abolishes the requirement for corneal transplant in most cases.[6] A photosensitizing agent (Riboflavin/Vitamin B2) and UV-A radiation when used in combination lead to photopolymerisation of collagen fibrils of corneal stroma thus increasing its tensile strength.[6] It cause release of free oxygen radicals thus ensuring covalent cross linking among neighboring collagen molecules.[3] The documented failure rate is approximately 3% and complication rate is less than 1%.[5]

A study[3] was conducted in Noor Eye Hospital, Tehran Iran to check how effective CXL is in stopping the progression of Keratoconus. In treated eyes, mean decrease in K-max was 0.22 dioptre at the end of one year and in control group it was increased by 0.41 dioptre, (P<0.001). In about one third of the treated eyes, they noticed a decline of >0.5 dioptre in K-max and most of untreated/control eyes had an increase in K-max and more progression of disease. In 88% of treated eyes, there was no progression of disease while in 61.5% of untreated eyes, there was progression of disease. Another study[7] assessed the effectiveness of CXL by looking at results of 3-year follow-up. In 95.8% of cases, progression of disease was arrested. But it was a case series without controls and just looked at the long-term effects of CXL on vision and some other variables.

Worldwide, only two or three prospective randomized controlled trials have been reported[3,8] that prove efficacy of CXL in progressive Keratoconus. Only one study[3] was found that compared two eyes of the same patient. No such studies have ever been conducted in Pakistan. We intend to generate data on the effect of CXL on progressive Keratoconus by comparing both eyes of the same patient (untreated eye will serve as control for treated eye) with a randomized case (eye) selection hence eliminating the confusing effect of different rates of progression so that CXL becomes a widely used procedure thus ensuring control of this potentially blinding condition at a stage where a person can still function effectively in day-to-day life.

## METHODOLOGY

This study included 66 eyes in cases between 10-30 years of age with confirmed bilateral Keratoconus (based on clinical and topography findings), bilateral minimum corneal thickness of more than 400 micrometers (as measured by Galilei G4) and K-max <60 dioptres in each eye (based on Galilei G4), whereas all those with corneal scarring in either eye, history of previous eye surgery, any ocular surface or tear problem or coexistence of ocular pathology other than Keratoconus and pregnancy were excluded from the study. After the formal and informed consent, the patients were proceeded for the procedure. A proforma (enclosed in the end) was used to collect patient information from all the patients. In each patient, a computerized random number table was used to pick one eye for treatment and the other as a control. Patients were told to stop wearing hard contact lenses 3 weeks before the treatment and soft lenses 1 week before. The selected eye underwent CXL after preliminary pre-op examination. To control bias, only one experienced surgeon carried out the procedure. The procedure was performed under aseptic conditions. Topical anesthetic drops (Proparacaine Hydrochloride 0.5%) were instilled, epithelium was removed from central 7-8 mm of cornea by beaver knife and riboflavin 0.1% (without Dextran) was instilled once every two minutes for the first 20 minutes. Patients were examined on the slit lamp to observe presence of riboflavin in anterior chamber. UV-A irradiation was done for the next 10 minutes while continuing instillation of riboflavin 0.1% (1 drop/2 minutes) and pachymetry was performed before epithelium removal, after epithelium removal, after 20 minutes of riboflavin administration and after UV-A exposure to check corneal thickness at every step of the procedure. Cornea was irrigated with sterile Balanced Salt Solution (BSS) and Bandage Contact Lens (BCL) was applied followed by

the application of the eye pad. Antibiotic and steroid drops were started from the next day (Tobramycin+Dexamethasone 0.1% was given for the first month and replaced by Fluorometholone 0.1% in the next month along with artificial tears for two months). BCL was removed on 5th post-op day.

All eyes underwent complete examinations at the 1st post-op day, 01 week, 01, 03 and 04 months after CXL. Main outcome measure during follow-up was K-max as measured by Corneal Topography using Galilei G4. One experienced person performed corneal topography for all eyes to control bias. Using SPSS 22nd version, Mean+SD were calculated for age and K-max whereas demographics like gender and efficacy were presented in percentage.

## RESULTS

Mean+SD was computed as 20.55+6.27 years (for patients ages 10-20 (n=15) and 21-30 (n=18)). 60.61%(n=20) of patients were male and 39.39%(n=13) were female.

Comparison of mean pre-operative K-max in CXL and control group shows 54.18+3.64 and 53.77+3.48 respectively; p value was 0.635. Comparison of mean post-operative (4 months) K-max in CXL and control group shows 53.53+3.48 and 55.57+3.56 respectively; p value was 0.23. (Table 1)

Comparison of efficacy of Corneal Collagen Cross-linking in preventing the progression of keratoconus by comparing changes in maximum simulated keratometry (K-max) in treated and untreated eyes of the same patient shows that 96.97%(n=32) in CXL and 3.03%(n=1) in control group showed efficacy whereas remaining 3.03%(n=1) in CXL and 96.97%(n=32) in control group had no efficacy, p value was 0.000. (Table 2)

Table 1: Comparison Of Mean Pre-Operative And Post-Operative K-Max In Cxl And Control Groups (n=33 and 66 eyes)

| | CXL Group (n=33) | | Control Group (n=33) | | P value |
|---|---|---|---|---|---|
| Pre-operative | Mean | SD | Mean | SD | |
| | 54.18 | 3.64 | 53.77 | 3.48 | 0.635 |
| Post-operative | 53.53 | 3.48 | 54.57 | 3.56 | 0.23 |

Table 2: Comparison Of Efficacy In Both Groups (n=33 and 66 eyes)

| Efficacy | CXL Group (n=33) | | Control Group (n=33) | |
|---|---|---|---|---|
| | No. of patients | % | No. of patients | % |
| Yes | 32 | 96.97 | 1 | 3.03 |
| No | 1 | 3.03 | 32 | 96.97 |
| Total | 33 | 100 | 33 | 100 |

P value=0.000

## DISCUSSION

This study was done with the view to generate data on the effect of CXL on progressive Keratoconus by comparing both eyes of the same patient (untreated eye will serve as control for the treated eye) with a randomized case (eye) selection hence eliminating the confusing effect of different rates of progression so that CXL becomes a widely used procedure thus ensuring control of this potentially blinding condition at a stage where a person can still function effectively in day-to-day life.

In our study, mean age was 20.55+6.27 years. 60.61%(n=20) were male while 39.39%(n=13) were females. Comparison of efficacy of Corneal Collagen Cross-linking in preventing the progression of keratoconus by comparing changes in maximum simulated keratometry (K-max) in treated and untreated eyes of the same patient shows that 96.97%(n=32) in CXL and 3.03%(n=1) in control group showed efficacy whereas remaining 3.03%(n=1) in CXL and 96.97%(n=32) in control group had no efficacy; p value was 0.000.

We compared our results with a study[3] conducted at Noor Eye Hospital, Tehran, Iran to check how effective CXL is in stopping the progression of Keratoconus. In treated eyes, mean decrease in K-max was 0.22 dioptres at the end of one year and in control group it was increased by 0.41 dioptres,(P<0.001). In about one third of treated eyes, they noticed a decline of >0.5 dioptres in K-max and most of untreated/control eyes had an increase in K-max and more progression of disease. In 88% of treated eyes, there was no progression of the disease while in 61.5% of untreated eyes, there was progression of the disease. Another study[7] assessed the effectiveness of CXL by looking at the results of 3-year follow-up. In 95.8% of cases, progression of the disease was arrested. But it was a case series without controls and just looked at the long-term effects of CXL on vision and some other variables. The findings of our study are correlated with the above studies, where the efficacy of CXL is higher, while we also added a control group and the limitation of previous study at Al-Shifa hospital was overcame by adding control group.

The short-term efficacy and safety of CXL in halting the progression of KCN was evaluated by Mohammad A. Seyedian et al.[9] They found that, one year after surgery, the mean K-max values decreased by 0.22 D in the treated eyes, while they increased by 0.41 D in the control group. The significance level for this difference was extremely high (P 0.001). The average best-sight corrected visual acuity (BSCVAA) increased by 0.13 LogMAR and dropped by 0.13 LogMAR in the control group (a 0.01 LogMAR increase),(P =0.014). In the eyes that were given CXL, no vision impairment due to problems occurred. Three (12%) of the eyes treated showed an increase in keratometry of more than 0.50 D at 1 year, indicating failure. Preliminary and 1-year results suggest CXL can effectively prevent the course of KCN without generating major problems, they concluded. These results corroborate our own.

Three-year outcomes were reported by Hoyer et al[10] for 153 eyes, showing a mean decrease in K-max of 4.0 D and a 2% treatment failure rate (3 eyes). Findings parallel to those in Italy,[11] France,[12] and India,[13] have been reported. 13 All these reports address case series without controls.

These results give us reason to hope that CXL could one day be included in the conventional therapy for progressive KCN, and therefore we encourage more prospective controlled trials to test this hypothesis. This type of research is uncommon at the moment.[14] Till yet, the longest follow-up period that has been documented is 6 years.[15] More comprehensive trials with longer follow-ups are required, however this study gives information on the effectiveness of this novel therapy option.

## CONCLUSION

We concluded that Corneal Collagen Cross Linking is significantly effective in preventing increase in K-max when compared with control group.

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