Original Research Article

Corneal Collagen Cross-linking (CXL): Effectiveness and Safety in Progressive Keratoconus in Pediatric Patients with Adequate Corneal Thickness

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Abstract

Background: This study was undertaken to evaluate the outcomes of corneal collagen cross-linking for treatment of progressive keratoconus in pediatric patients who had adequate corneal thickness. **Material and Methods:** About 50 eyes of pediatric age group (<18years) with progressive keratoconus having corneal thickness more than 450 microns were subjected to accelerated corneal collagen cross-linking(CXL). Pre-op parameters were compared with1month, 6 months, 12 months post CXL. Scheimpflug Imaging was used to assess the Maximum keratometry (Kmax), Pachymetry (thinnest), Total corneal irregular astigmatism (RMS).Best Corrected Visual Acuity(BCVA), Spherical Equivalent and Corneal endothelial counts were also assessed. **Results:** At6 and 12monthsKmaxreduced from pre-op 57.26±4.69D to 57.73±5.06D and 56.34±4.90D (Pvalue<0.05); Pachymetry changed from 466.96±19.59µm to451.44±19.41µmand 449.28±20.75µm(P value <0.05); BCVA was improved from 0.598±0.318 to 0.530 ± 0.292 at 6 months andto 0.488 ± 0.283 at 12 months(P value <0.05). RMS reduced from 1.005±0.473 to 1.04±0.477 and 0.90±0.478 (P value <0.05) at 6 months and 12 months respectively. There was no significant change in spherical equivalent and endothelial count at 1 year of follow up. **Conclusion:** Corneal Collagen Cross-linking is a safe and effective procedureto freeze keratoconus progression in pediatric eyes.

Keywords: Keratoconus, Corneal Collagen Cross-linking, Corneal thickness, Best Corrected Visual Acuity, Maximum keratometry Kmax, Pediatric, Total Corneal Irrgeular Astigmatism RMS

Introduction

Keratoconus,the most common primary corneal ectasia, is progressive non- inflammatory disease thathas shown to result in severe visual distortion, especially in pediatric age group with considerable influence on their social and educational development. The reported incidence of Keratoconus ranges from 50 – 230 per 100,000 with an estimated prevalence of per 100,000[1]. In India incidence is 2300 per 100,000(0.0003-2.3%)[2]. The number of pediatric cases presenting as keratoconus are being observed with increasing incidence of allergic eye disease and eye rubbing.

Natural progression of the disease may lead to vision threatening sequelae including hydrops, corneal scarring, surgical intervention as end stage of the progression. The keratoplasty has shown to be effectivebut requires lifelong follow up, management of the rejection and post keratoplasty astigmatism. Collagen cross-linking with riboflavin (Vitamin B2) and UV-A (370nm) is one such modality for halting the progression of thinning and ectasia[3]. It is a minimally invasive procedure in which photopolymerization of corneal collagen is done by combined use of Riboflavin and Ultraviolet-A ray mediated by reactive oxygen species. Prevention of the progression of keratoconus can be done by CXL procedure by increasing rigidity of corneal collagen due to the formation of covalent bonds between collagen fibrils[4].

As many studies have shown positive effects of CXL so it could potentially reduce the need for corneal grafting in patients with keratoconus which is generally the young population. For preventing disease progression, the CXL effects are convincing in adults, and so CXL has gained popularity as the treatment of choice for progressive keratoconus in adults[5,6,7]. To date several cohort studies on cross-linking in pediatric populations have been published making CXL a treatment of choice for preventing the progression of keratoconus.

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Material and methods

This hospital based before and after interventional study was conducted in ophthalmology department of SMS Medical College and Attached group of hospitals Jaipur, Rajasthan, in pediatric patients attending the Ophthalmology OPD of SMS hospital starting from December 2016 for a period of 12 months till the sample size was achieved. A total of 50 eyes with progressive keratoconus undergoing corneal collagen cross-linking treatment were included.

The study included the patients less than 18 years of age with progressive keratoconus fulfilling Rabinowitz criteria and Corneal thickness of >450 µm. Exclusion of patients with corneal scar, hydrops, history of any previous corneal surgery such as corneal ring insertion or corneal transplant, herpetic keratitis, severe dry eye, concurrent corneal infection, concomitant immune diseases and DM and poor compliance.A detailed history including ocular, medical and family history was obtained. All the patients were subjected for detailed ocular examination including Best Corrected Visual Acuity (BCVA), automated refraction, retinoscopic examination, slit lamp examination, corneal topography using Scheimpflug imaging system and specular microscopy for measuring endothelial cell count.

All surgeries were done by same experienced surgeon under topical anaesthesia with proparacain 0.5% and xylocaine 4% eye drops every 5 minutes for 30 minutesin cooperative children. General anaesthesia backup was ready for uncooperative patients. After removal of 8-9mm of central corneal epithelium by blunt spatula,isotonic riboflavin dye 0.1% with 20% dextran (D500)was instilled every 3 minutes for 30 minutes following which UV A (370 nm) was irradiated

at30mW/cm^{2}for 3minutes (Figure 1) and after putting Bandage Contact Lens (BCL) into treated eye, bandage was done.

Post-operatively patients were given topical antibiotics, steroids, and lubricants and followed up at 1 week, 1 month, 3 months and 6 months after surgery. BCL was removed on 7th post operative day. All the examinations were performed by a single observer in order to avoid bias both pre and postoperatively. Each follow up included assessment of BCVA, Spherical equivalent,Scheimpflug imaging (Pentacam, Kmax, Corneal thickness, RMS) and specular microscopy.

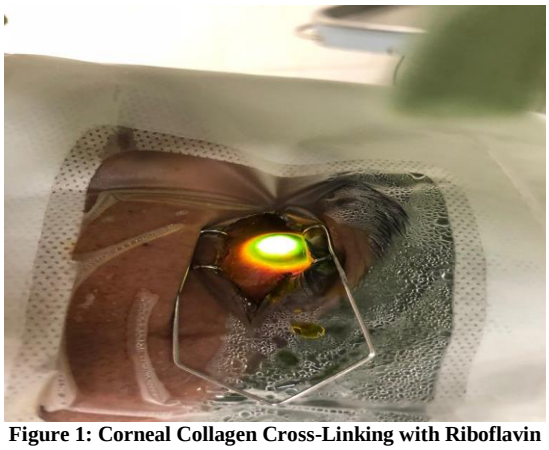

Figure 1: Corneal Collagen Cross-Linking with Riboflavin

Statistical analysis

The data thus obtained was compiled and analysed using statistical package for social services.(SPSS vs 20, SPSS Inc, Chicago, IL,USA). For Qualitative data percentage and proportion was used and Mean and Standard Deviation were used for Quantitative data. Difference in pre and post operative values was analysed by using paired 't' test. P <0.05 was considered as significant for measured variables.

Results

This study included 50 eyes of 39 patients and had reported outcomes of pediatric CXL, following standard Dresden Protocol followed for one year at upgraded department of Ophthalmology, SMS Hospital, Jaipur, Rajasthan. BCVA, Spherical Equivalent, Kmax, Endothelial cell count, Corneal thickness, RMS values were evaluated before and after the procedure.

Our Study includes the patients of less than 18yrs of age with corneal thickness more than 450 microns.The mean age of the patients with Keratoconus was 14.87 years. Majority of the cases were aged 15 – 18 years and were males. (Table 1)

Table 1: Distribution of the study group according to demographic characteristics

	Demographic characteristics	Frequency	Percent
Age (in years)	**8 – 14 years**	17	43.6
	15 – 18 years	22	56.4
Sex	**Male**	26	66.7
	Female	13	33.3

We have compared reports of pre and post CXL treatment on the study group and found that BCVA waschanged from 0.598±0.318 pre-op to 0.530±0.292 at 6 months and to 0.488±0.283(P<0.05) at 12 months follow up.Thus, mean pre operative log MAR was improved significantly in1 year follow up.

Table 2: Best Corrected Visual Acuity (BCVA) at different follow up intervals

	Mean (log MAR)	Std. Dev.	Std. Error	P value
Pre-Op.	0.598	0.318	0.045	-
1 month follow up	0.578	0.312	0.044	0.242 (NS)
6 months follow up	0.530	0.292	0.041	0.007 (Sig)
1 year follow up	0.488	0.283	0.040	0.0003 (Sig)

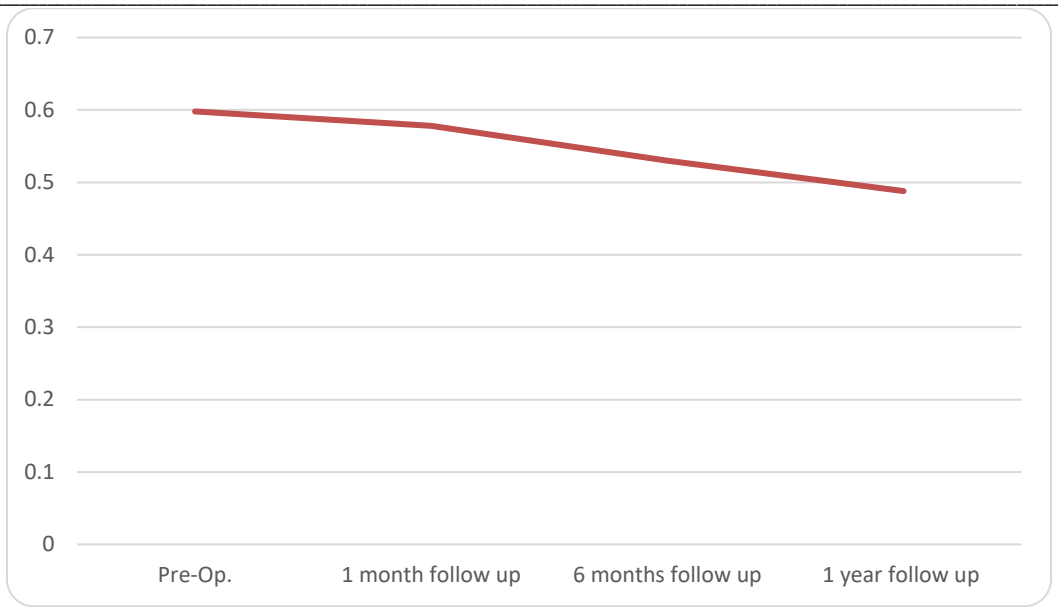

Figure 2: Best Corrected Visual Acuity (BCVA) at different follow up intervals

The changes in Spherical Equivalent from baseline pre operative value 6.22±2.54D increased to 6.30±2.41Dand 6.39±2.35D at 1 month and 6 months follow up respectively but decreased after one year to 6.14±2.41D (P>0.05). (Table 3, Figure 3) So overall non-significant changes were observed in patients.

Table 3: Spherical Equivalent (SE) at different follow up intervals

	Mean (Dioptre)	Std. Dev.	Std. Error	P value
Pre-Op.	6.22	2.54	0.360	-
1 month follow up	6.30	2.41	0.341	0.115 (NS)
6 months follow up	6.39	2.35	0.333	0.113 (NS)
1 year follow up	6.14	2.41	0.341	0.260 (NS)

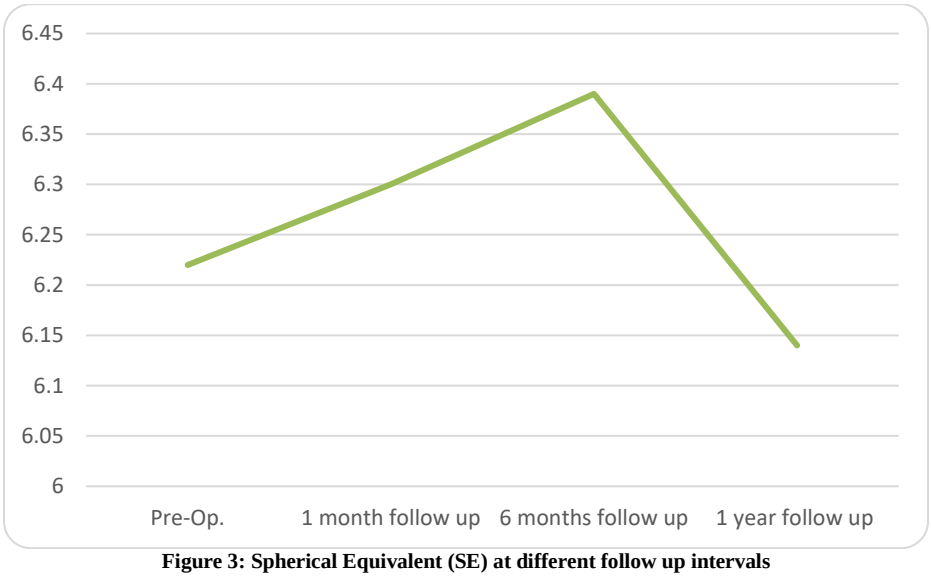

Figure 3: Spherical Equivalent (SE) at different follow up intervals

Comparing the Keratometry,Kmaxbefore and after treatment at different follow up intervals, pre-op 57.26±4.69Dvalue changed to 58.21±4.69D (P<0.05)at 1month and reduced to 57.73±5.06D at 6 months and 56.34±4.90D at 12months follow up.This difference was statistically significant (P=0.0002) showing halting of keratoconus progression.(Table4, Figure4)

Table 4: Kmaxat different follow up intervals

	Mean (Diopter)	Std. Dev.	Std. Error	P value
Pre-Op.	57.26	4.69	0.664	-

1 month follow up	58.21	4.59	0.65	0.0002 (Sig)
6 months follow up	57.73	5.06	0.717	0.021 (Sig)
1 year follow up	56.34	4.90	0.693	0.0002 (Sig)

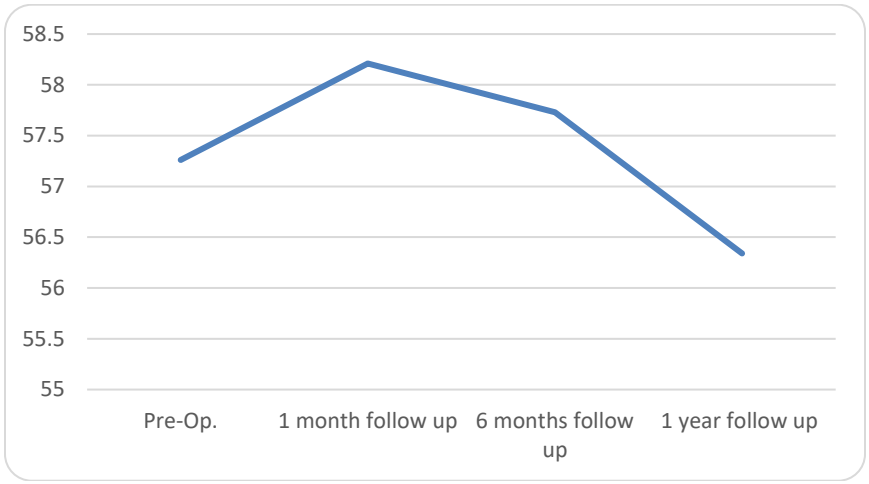

Figure 4: Kmaxat different follow up intervals

Talking about pachymetry, in this study we have found that meancentral corneal thickness changes significantly from baseline 466.96±19.59µm to 451.44 ±19.41µm at 6 monthsand 449.28±20.75µm (P<0.05) at 12months follow up. (Table 5, Figure 5)

Table 5: Corneal Thickness at different follow up intervals

	Mean (micronµm)	**Std. Dev.**	**Std. Error**	**P value**
Pre-Op.	466.96	19.59	2.77	-
1 month follow up	450.94	19.82	2.80	0.0002 (Sig)
6 months follow up	451.44	19.41	2.74	0.0002 (Sig)
1 year follow up	449.28	20.75	2.93	0.0002 (Sig)

Figure 5: Corneal Thicknessat different follow up intervals

We assessed the endothelial cell count, post-operatively at intervals of 1month, 6 months and 12 months and noted that ,pre-op values in (cells/mm^2) 3038.53±203.49 declined to 2979.46±437.87at 6months and at 12 months follow up increased again to 3030.19±267.47 (P >0.05). Although the mean endothelial cell count decreased as compared to baseline but it was statistically non-significant. (Table 6, Figure 6)

Table 6: Endothelial cell count (cell/mm^2) at different follow up intervals

	Mean(cell/mm^2)	**Std. Dev.**	**Std. Error**	**P value**
Pre-Op.	3038.53	203.49	28.78	-
1 month follow up	3039.05	201.76	28.53	0.952 (NS)
6 months follow up	2979.46	437.87	61.92	0.265(NS)
1 year follow up	3030.19	267.47	37.83	0.775(NS)

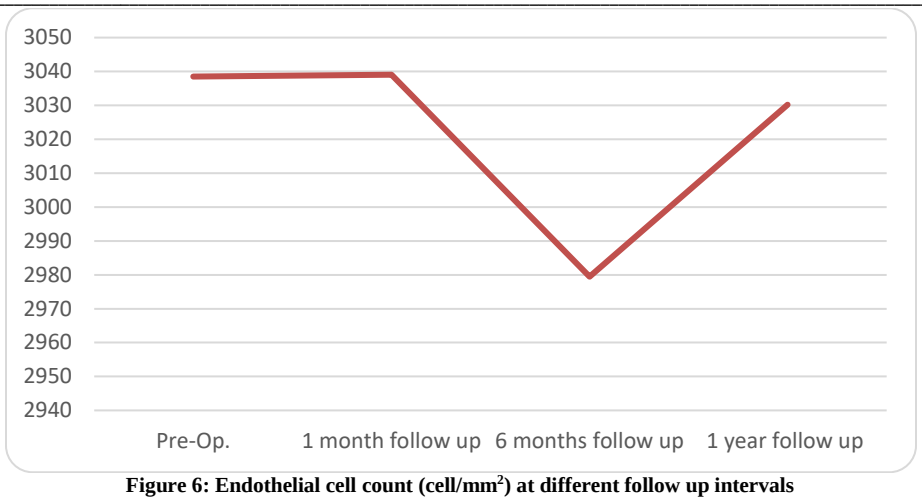

Figure 6: Endothelial cell count (cell/mm^2) at different follow up intervals

We observed that Total corneal irregular astigmatism RMS values changed non significantly from pre-operative 1.005±0.473 to 1.04±0.477 at 6 months, but at 1year follow up significantly declined to 0.90±0.478 (P=0.0003). (Table 7, Figure 7)

Table 7: RMSat different follow up intervals

	Mean	Std. Dev.	Std. Error	P value
Pre-Op.	1.005	0.473	0.066	-
1 month follow up	1.14	0.448	0.063	0.0003 (Sig)
6 months follow up	1.04	0.477	0.067	0.200 (NS)
1 year follow up	0.90	0.478	0.025	0.0003 (Sig)

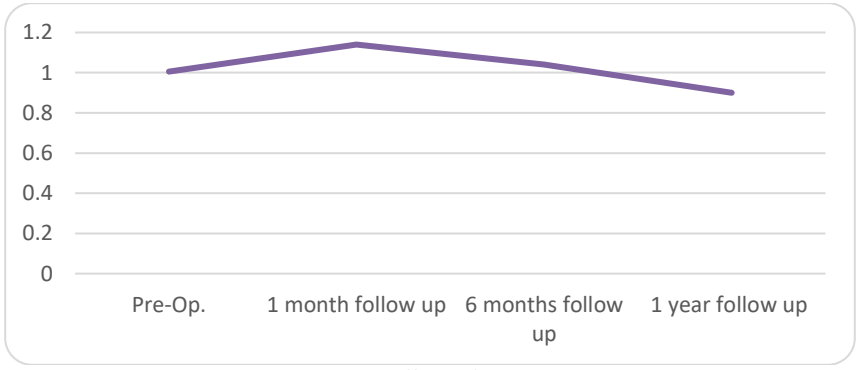

Figure 7: RMS at different follow up intervals

Discussion

This study was mainly under taken to study the effect of CXL treatment on the pediatric age group. The study included 50 eyes of 39 patients undergoing CXL followed for one year at upgraded department of Ophthalmology, SMS Hospital, Jaipur, Rajasthan.

Our study had found that the BCVA was significantly improved at 6 months and 1 year of follow up, as a result visual acuity enhancement in pediatric patients was seen. A two years study by Vinciguerra et al noted that, there was a significant improvement in the young age group's BCVA throughout the follow up[8]. A prospective study report from Caporrossi et al (Siena CXL Pediatrics trial) involving 152 eyes of 77 patients (10 to 18 years) remains the largest series with 3 years follow up.The study demonstrated after CXL, keratoconus stabilized and demonstrated rapid significant visual function improvement in these pediatric patients[9]. A study on pediatric age group by Shetty et al had shown a significant improvement of best corrected visual acuity over 24months[10]. Another study by Badawi et al, proved therefractive errors statistically significantly less than the preoperative values in one year of follow up[11].

One of the most important aspects of this study, maximum keratometry (Kmax), showed significant reduction from baseline values at 6 months and 12 months follow up(P=0.0002). This establishes the stabilisation of keratoconus after treatment. A study by Soeters et al reported that the pediatric corneas flattened 1 years after CXL by a mean of 1.8 diopters (D)[12]. Another study by Zotta et al had studied eight pediatric eyes for a period of three years and demonstrated stabilisation of K1 and K2 in all the cases[13]. Similar study by Wollensak et al in Dresden at a follow-up ranging from 3 to 47 months, progression of keratoconus was stopped in all 23 treated eyes. A mean reduction of 2.01 diopters in maximal keratometry and 1.14 diopters in refractive error wasobserved in the 16 eyes that showed regression[14].

The spherical equivalentshowed non-significant changesafter the procedure throughout the follow ups till 1 year of study. Kodavoor et al had also shown a non-significant change at the end of one year follow up after CXL[15]. A two years study by Shetty et al had observed an improvement in spherical equivalent (from −4.70±3.86D to −3.75±3.49D; *P* = 0.15)[10].

Endothelial cell count assessment post operatively at intervals of 1 month, 6 months and 1 year revealed that, the mean endothelial cell count decreased but it was non-significant. In a study by Narsollahi et al, had shown a non-significant change in corneal endothelial count[16]. Vinciguerra et al studied endothelial cell count for 12 months in treated eyes and found that cell counts did not changed significantly (P=0.13)[17].

Evaluation of the corneal thickness in our study has shown statisticallysignificant changes in 6 months and 1 year follow up with reduction of the values from baseline parameters.

Bamahfouz et al studied corneal parameters for 18months after CXL and there was a decline in central corneal thickness in majority of cases[18]. GreensteinA et al evaluated corneal thickness after CXL revealed that pachymentry declines during first 3months but remained close to baseline at 6months and 1 yr follow up[19]. Sharma N et al, found in 6months of a study that the central corneal thickness decreased by mean 22.7 ± 10.3 μm[20].

The RMS changed non-significantly from pre-operative values at 6 months but at 12 months significant changes were noted.Since the total aberrations keep on changing, this cannot be considered as reliable indicator. In a study by Alireza et al had shown that, CXL improves corneal topographic and refractive values in patients with keratoconus less than 18 years of age[21].

As compared to adult cornea, in the pediatric age, corneal collagen remodeling occurs at a higher rate[22]. Thus, studies with longer follow-up periods are necessary for young age to assess the progression of disease. Keratoconus in children, specially those suffering from vernal kera to conjuctivitis and having history of eye rubbing tends to be more vulnerable than adults so frequent follow-up is required as they progressively worsen[22].

Conclusion

This study on pediatric population progressive keratoconus had shown improvement in BCVA and stabilization of Kmax in 1 year of follow up. Non significant changes were noted in spherical equivalent, endothelial cell count and total corneal irregular astigmatism RMS and there was slightreduction ofcorneal thickness. This study concludes that, CXL is a safe and effective procedure to freeze keratoconus progression in pediatric eyes.

Our study has shown CXL in pediatric patients is as effective as in adult population without any deleterious effect in endothelial cell count.Since our study is one of the largest studies of pediatric CXL in 50eyes which also shows effectiveness and safety of the procedure, it can be concluded that many eyes can be saved from blindness using corneal collagen cross-linking.

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