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Original Article

A Study of the Effect of Corneal Collagen Crosslinking in Pediatric Patients with Keratoconus

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Abstract

Collagen cross linking (CXL) is a proved treatment for patients with progressing keratoconus and has been shown to delay or even stop the progression of corneal ectasia, thus reducing the need of keratoplasty. CXL has been utilized for over 20 years in adult patients and based on the evidence of its efficacy and safety; this treatment has been recently introduced in the management of pediatric keratoconus as well. Pediatric keratoconus differs in many ways from adult keratoconus and hence needs to be managed differently. In our study we have tried to evaluate the efficacy and safety of CXL in pediatric patients.

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Keywords: *Keratoconus, Collagen-Cross-Linking, Specular Microscopy, Topography, Pediatric*

Introduction

Keratoconus is a progressive, asymmetric, non-inflammatory corneal thinning characterized by changes in the structure and organization of corneal collagen.[1,2,3,4] The disease usually develops in the second decade of life. The cornea becomes increasingly conical due to its biomechanical instability leading to irregular astigmatism and progressive decrease in visual acuity.

Management of pediatric keratoconus is different than in adults in many ways:

1) Under diagnosis of the condition
2) Poor compliance of patients.
3) Accelerated progression of the disease
4) Need for associated management of vernal keratoconjunctivitis.
5) Modifications in treatment modalities
6) Visual impairment in pediatric patients may significantly affect their social and educational development and overall have an impact on their quality of life.

The treatment options for adults and pediatric keratoconus have been similar in the form of spectacle correction, contact lens, keratoplasty since many years. However current treatment modalities lead to improved visual acuity and also prevent progression of the disease.

Corneal Collagen Cross linking (CXL) is a relatively new treatment method developed to increase the mechanical and biochemical strength of the stromal tissue via exposure of the ectatic cornea to Riboflavin ultraviolet-A (UVA) light. It involves a photopolymerization reaction which induces biochemical and microstructural changes within the corneal stroma. This stimulates the generation of stiffer collagen fibrils and a rearrangement of the corneal lamellae. These structural and biomechanical alterations result in a regression of the corneal curvature and improved shape there-by stabilising keratoconus and preventing its progression.

This procedure is the only currently available semi surgical therapeutic approach for patients with progressing keratoconus and has been shown to delay or halt the progression of corneal ectasia, thus reducing the need of keratoplasty.

CXL has been utilized for over a 20-year period in adult patients and based on the evidence of efficacy and safety; this treatment has been recently introduced for the management of pediatric keratoconus.

A prospective, interventional study was carried out at our centre, a tertiary care referral hospital, to study the efficacy and safety of corneal collagen cross linking in patients below 18 years of age and diagnosed to have keratoconus.

Aim of the Study

1) To assess the short-term efficacy of Corneal Collagen Cross linking by comparing visual acuity and various topographic parameters at 6 months .
2) To assess the safety of corneal Collagen Cross-linking (CXL) in pediatric patients.
3) To study the effectiveness of Collagen-Crosslinking in preventing the progression of Kera-toconus (KCN).

Material and Method

Study design: A prospective interventional study.

Study site: Tertiary care centre.

Study period: The study period was from January 2015 to January 2017.

Number of patients: 30 eyes of 30 patients were included for the study. In case of bilateral KCN, the more severe eye was considered for the study.

Criteria for case selection:

Inclusion criteria:

- Children below 18 years of age diagnosed to have keratoconus.
- Corneal thickness >400 microns at the thinnest location.
- Patients for whom consent could be obtained from parents as legally acceptable representatives.

Exclusion Criteria

- Patients wearing contact lens.
- Post surgical ectasia.
- Corneal scarring in either eye.
- Previous eye surgery.
- Ocular surface or tear disorders.
- Coexistence of ocular pathology other than KCN.
- Eyes with corneal thickness <400 microns at the thinnest point
- Concurrent corneal infections.
- Patient or parents refusing the treatment.

All ethical considerations were taken care of. After the informed consent process, a detailed history was elicited from the parents of the patients. Preliminary data of age, sex, residential address and registration number was recorded. Elaborative data was noted in form of Best Corrected Visual Acuity (BCVA), cycloplegic refraction, slit lamp examination, fundus examination and keratometry (K1- flat keratometry and K2 – steep keratometry). Corneal topography with Scheimpflug Imaging (The Pentacam, Oculus) was done. Corneal astigmatism, pachymetry at the center (Pachy center) and pachymetry readings at the thinnest location (Pachy thinnest) were noted.

The standard Dresden cross-linking protocol was carried out by a single surgeon and it consisted of the following:

- An area 5 -9 mm in diameter of the corneal epithelium was debrided depending on the position of cone under general anesthesia or local anesthesia depending on child cooperation.
- A 0.1 % Riboflavin solution was applied every 5 minutes for 30 minutes.
- The UV-A diode of 365-370nm wavelength was applied for 30 minutes at a distance of 1 cm from the cornea providing irradiance of 5.4 J/sq cm.
- Riboflavin was applied every 5 minutes during radiation.
- After completion of treatment proper eye wash was done followed by instillation of Moxifloxacin eyedrops and application of a bandage contact lens. Post operatively, Moxifloxacin eyedrops were continued alongwith lubricant eyedrops, both 4 times a day for three weeks.

All clinical examination was repeated at Day 1, 1 week, 1 month, 3 months and 6 months after the treatment. Pentacam examination was done at 3 months and 6 months after collagen cross linking.

The changes in simulated keratometry values in the flattest meridian (K1) and the steepest meridian (K2), topometric astigmatism, manifest refraction, and BCVA were analysed to evaluate the effect of crosslinking treatment. Post-procedure data was available for all 30 eyes. The paired t-test was used to evaluate the differences in the different parameters between pre- and post-procedure values and a p-value of ≤ 0.05 was considered to be statistically significant.

Results & Observations

The surgery and the postoperative period were uneventful in all patients. The cornea re-epithelialized by one week after treatment. In the early postoperative period, all eyes had minimal anterior stromal corneal haze that resolved approximately 3 months postoperative.

Gender wise distribution:

Table 1: Gender distribution

	Number (n=30)	Percentage
Girls	16	53.3%
Boys	14	46.6%

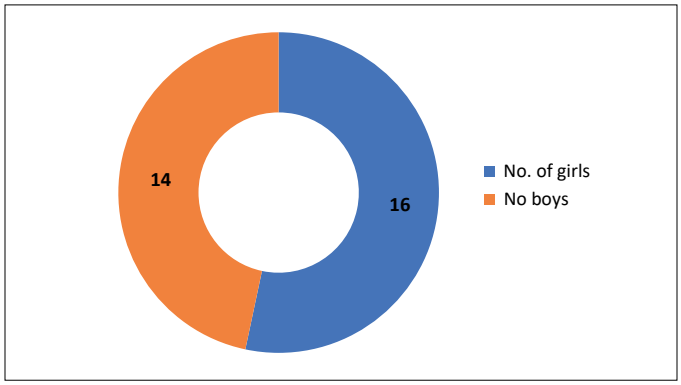

Figure 1: *Gender distribution*

Age predilection:

The mean age of the patients was 14.6 years (range, 0-18) years.

Table 2: Age distribution

Age (yrs)	Number of children (n=30)	Percentage
0-3	0	0%
3-6	0	0%
6-9	0	0%
9-12	4	13.33%
12-15	15	50%
15-18	11	36.66%

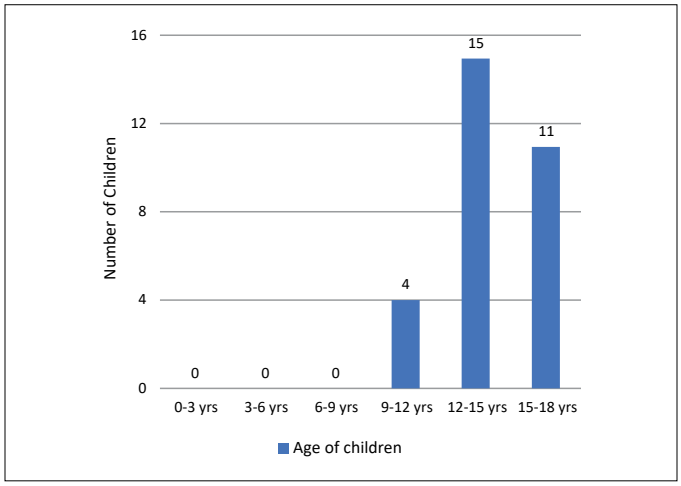

Figure 2: *Age distribution*

Visual Acuity:
Preoperative Best-Corrected Visual Acuity (BCVA) was 0.41 ± 0.179 (range, 0.0-1.0) LogMAR. Postoperatively, at 1 week it was 0.42 ± 0.156 and at 1 month postoperative follow up, the values were 0.33±0.146 LogMAR. At 3 months postoperative follow up, the mean vision was 0.32±0.144 and at 6 months follow up it was 0.225±0.15 . P value was less than 0.0001 indicating it to be extremely statistically significant.
Best corrected visual acuity:

Table 3 : Changes in visual acuity

Vision improvement	1 week	1 Month	3 months	6 months
No improvement	12	25	14	6
1 line improvement	4	1	12	17
2 line improvement	1	0	1	6
3 line improvement	0	1	1	1
Deterioration of vision	13	3	2	0

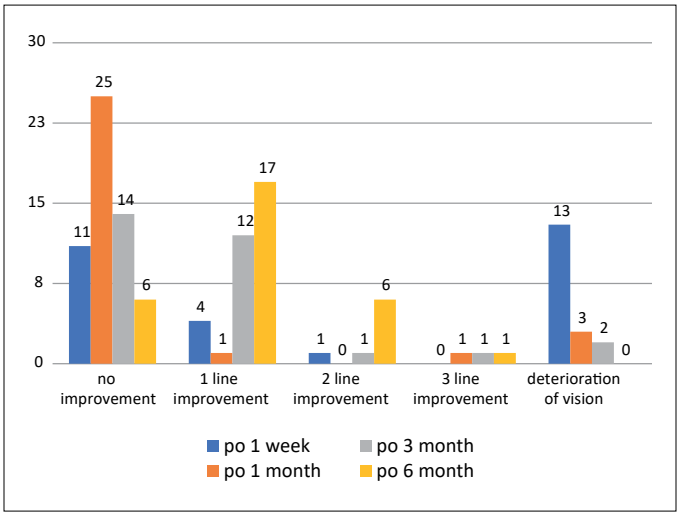

Figure 3: *Changes in visual acuity*

One week after the collagen cross linking, 13 (43.33 %) eyes showed decrease in vision by one line, 12 (40.0%) eyes showed no change, 4 (13.3%) eyes showed 1 line improvement and 1 (3.33%) eye showed 2 lines improvement on Snellen' s chart . It was noticed that vision started to improve after 3 months of CXL. At 6 months post-operative, 17 (56.66%) eyes showed 1 line improvement, 6 (20%) eyes had 2 line improvement in vision, 1 (3.33%) eye had 3 lines of improvement in visual acuity. Six (20%) eyes showed no improvement in vision, but none showed deterioration of vision.

Refractive outcome:

Table 4: Refractive spherical component:

	Mean ± SD (D)
Pre-operative	-3.01 ± 2.73
Post op 1 week	-3.30 ± 2.68
Post op 1 month	-3.30 ±2.64
Post op 3 month	-3.14 ± 3.01
Post op 6 months	-2.98 ± 2.69

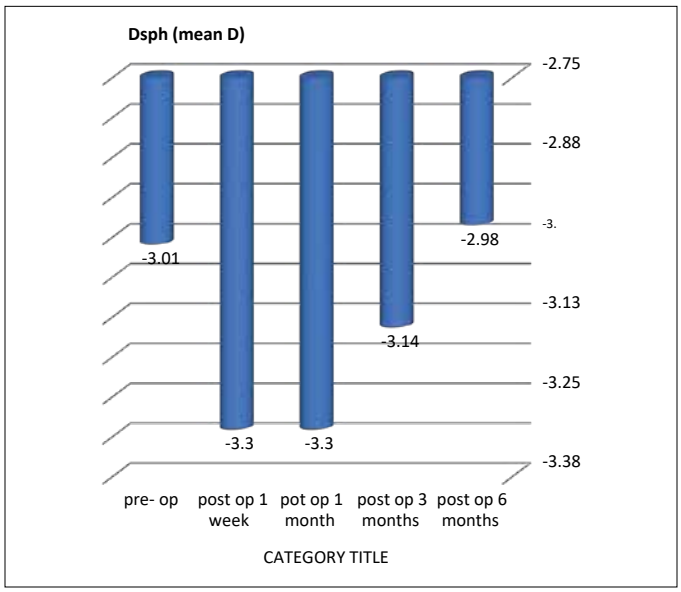

Figure 4: *Refractive spherical component:*

The mean spherical component being -3.01 ± 2.73 (mean ± SD) pre-operatively, it was seen to increase till post operative 1 month to almost -3.3 ± 2.64. It then gradually reduced after 3rd month of CXL to -3.14 ± 3.01 and at 6 months to -2.98±2.69 as seen in the graph. Hence the difference of 0.03 D at 6 months was seen. P value being 0.96 was not statistically significant.

Table 5: Refractive cylindrical component

	Mean ± sd
Pre-op	-4.43 ± 1.61
Po 1 week	-4.33 ± 1.57
Po 1 month	-4.29 ± 1.58
Po 3 months	-3.88 ± 1.54
Po 6 months	-3.69 ± 1.48

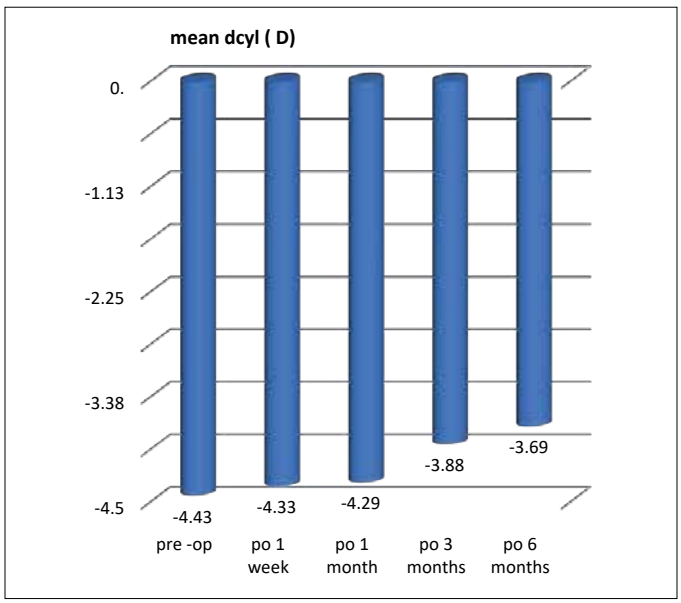

Figure 5: *Refractive cylindrical component :*

As per the above mentioned data, gradual decrease in mean refractive cylindrical component was seen from first week post procedure itself. At 6 months, mean cylindrical component reduced to -3.69±1.48 from -4.33±1.61 (pre-op mean cylindrical value ± SD). Hence, the difference of 0.74 D was seen with a p value of 0.03969, being significant.

Keratometry:

Table 6: Mean K1 readings

	MEAN K1	SD
Pre- op	47.63	2.82
Post op 6 months	46.90	3.00
Difference	0.73	

Table 7: Mean K2 readings

	MEAN K2	SD
Pre- op	49.51	4.75
Post op 6 months	48.62	5.05
Difference	0.89	

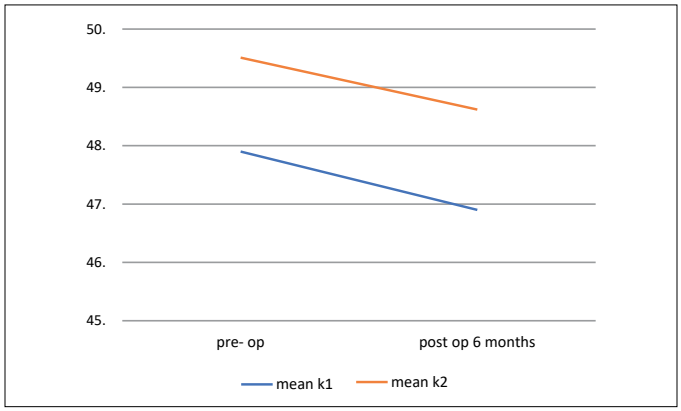

Figure 6: *Mean K1 and K2 readings*

Table 6 and 7 show the results obtained from Scheimpflug topography (Pentacam). Anterior surface keratometry in steep and flat axes decreased after 6 months. Mean K1 pre operatively was 47.63 D ± 2.82 which reduced to 46.90D ± 3.00 making a difference of 0.73 D, p-value being 0.178 and not significant.

Pre operatively mean K2 was 49.51D ± 4.75 which reduced to 48.62 D ± 5.05 at 6 months making a difference of 0.89 D, p-value of 0.75 not being significant.

Pachymetry:

Table 8: Pachymetry- thinnest point (µm)

	Mean Pachy (µm)	SD
Pre-op	447.10	37.91
Post op 6 months	443.67	36.88

Table 9: Pachymetry- central corneal thickness (µm)

	Mean pachy central (µm)	SD
Pre –op	468.73	37.80
Post op 6 months	458.07	36.84

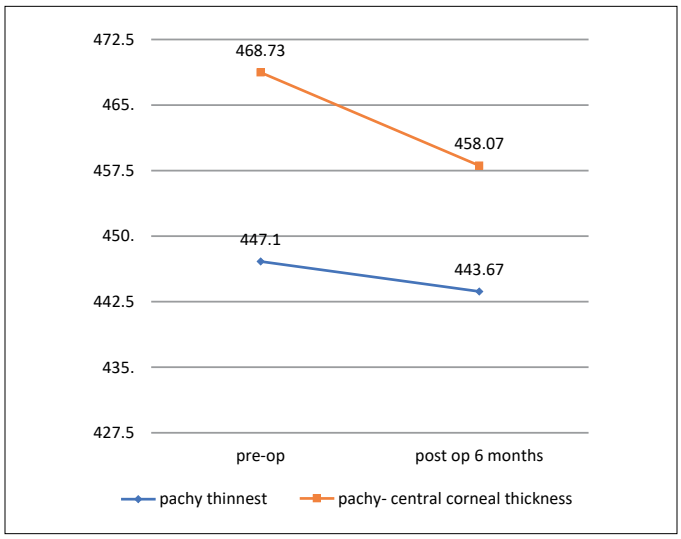

Figure 7: *Changes in pachymetry*

Corneal thickness at the central, paracentral and at the thinnest point was measured prior to the operation and at final follow-up. No significant difference was observed in any of these measurements.

Topographic astigmatism

Table 10: Changes in mean corneal astigmatism

	Mean (D)	SD
Pre-op	3.82	1.97
Post –op 6 months	3.34	1.85
Difference	0.48	

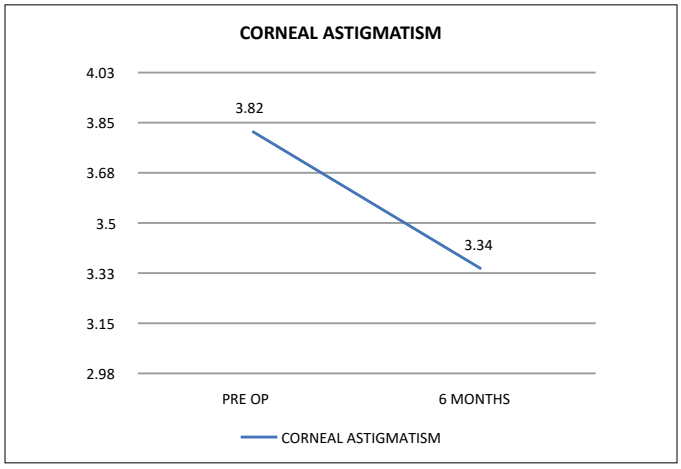

Figure 8: *Changes in mean corneal astigmatism*

Corneal astigmatism preoperative and at follow-up post procedure at 6 months showed a difference of 0.48 D. The value was not significant at $p < 0.05$ (p value 0.22).

Discussion

Corneal CXL is a new technique for the treatment of progressive pediatric keratoconus. In our study we studied its efficacy in halting the progression of the disease and improvement of vision in the pediatric age group.

In our study, the preoperative mean sphere was -3.01 ± 2.73 D and decreased to −2.98 ± 2.69 D (P = 0.96). This data very well coincides with the study performed by Mohammadreza et al done in 2008. The preoperative mean cylinder changed significantly from −4.43 ± 1.61 D to −3.69 ± 1.48 D (P = 0.039). Our study showed postoperative BCVA improvement that was statistically significant (P <0.0001). Twenty four eyes (80%) gained one or more lines of preoperative BCVA. It seems that increasing in postoperative BCVA is associated with improvement of postoperative refractive errors. Similar results were found by other previous studies. Vinciguerra et al. reported significant improvement in UDVA and CDVA most likely by significantly reducing corneal asymmetry and total abrasions. In a study done by Caporossi et al, a reduction of about 2.50 D was showed in the mean spherical equivalent postoperatively. Our results are similar to the research of Saffarian et al., that was done on an Iranian population in 2010. This study showed a statistically significant decreasing of cylindrical power (P < 0.001) and decline of −0.18 ± 0.79 diopter (D) in spherical power (P > 0.05). In 2008, Raiskup-Wolf et al. described what remains the largest published series comprising 241-eyes followed in Dresden for up to 6 years after cross-linking. This uncontrolled, retrospective study confirmed earlier findings with statistically significant improvements in astigmatism, best corrected visual acuity, and maximum simulated keratometry values (Kmax) at 12 months. Flattening was noted in 54% of eyes with a mean change in Kmax of −1.91 D (P < 0.01). In our evaluation, there was no statistically significant difference between pre- and post-operative K values (K1 and K2) (P > 0.05 for all comparisons) and corneal thickness values (P = 0.343). Different previous studies have shown that keratometry reading have decreased significantly after cross linking while in our study keratometry of our patients did not change significantly post-operatively. Despite this fact, refraction and visual acuity parameters improved significantly. This results are not clear and need to be investigated. Previous studies demonstrated an improvement of visual acuity alongwith an improvement of K reading. One explanation may be the improvement of optical aberrations which were not measured in our study.

Vinciguerra et al , Raiskup wolf et al , Capprrosi et al , Soeter's et al, Zotta et al and Chatzi and Hafizi et al showed corneal flattening post CXL in keratoconus. All of these studies were carried out for a different time span minimum of which was of 6 months and the longest was that of 3 years. Most studies reported a Kmax reduction of 1–2 dioptre (D) after 1-year post-CXL. Hen-riquez et al. reported a 2.66 D reduction in Kmax based on their randomized prospective comparative study of 10 eyes. Hersh et al. reported a reduction of 1.70 D based on their randomized control trial of 48 eyes. In Australia, Wittig-Silva et al. reported a mean reduction of 1.45 D at 12 months post-CXL based on their RCT of 49 eyes. Individually, Kmax value decreases of 2.0D or more were reported in 22 eyes (31%) in Hersh's study, in 13 eyes (21.3%) in Asri's study, and in 14 eyes (50%) in Ivarsen's study. Ivarsen also reported the most pronounced decrease in the Kmax value (7.4 D). However, the corneal topography results from long-term follow-up varied between different studies. Raiskup-Wolf et al. reported that Kmax decreased significantly, by 2.21 D in the second year and by 4.84 D in the third year. Hashemi et al. reported that Kmax and Kave decreased slightly (by 0.16 D and 0.1 D, respectively) at 5 years after the procedure.

Conclusion

1) 50% of the cases were between 12-15 years of age group.
2) Mean preoperative Best-Corrected Visual Acuity (BCVA) was 0.41 ± 0.179 (range, 0.0-1.0) LogMAR. Postoperatively, at 6 months follow up it was 0.225±0.156 .p value is less than 0.0001 indicating it to be extremely statistically significant.
3) Immediately after the collagen cross linking, 43.33 % eyes showed deterioration of the vision, 40.0% eyes showed no improvement, 13.3% eyes showed 1 line improvement and 3.33% eye showed 2 lines improvement on snellen' s chart .
4) At 6 months post- operative 56.66% eyes showed 1 line improvement on snellen's chart, 20% eyes had 2 line improvement in vision, 3.33% eye had 3 lines improvement in visual acuity. Whereas 20% eyes showed no improvement in vision, but none showed deterioration of vision.
5) The mean spherical component being -3.01 ± 2.73 (mean ± SD) D pre-operatively, it is seen to increase till post operative 1 month to almost -3.3 ± 2.64D. It then gradually reduces after 3rd month of CXL to -3.14 ± 3.01D and at 6 months to -2.98±2.69 D. Hence the difference is of 0.03 D at 6 months is seen. P value being 0.96 is not statistically significant.
6) As per the above mentioned data, gradual decrease in mean refractive cylindrical component is seen from first week post procedure itself. At 6 months of post op, mean cylindrical component reduced to -3.69± 1.48 from -4.33±1.61 (pre-op mean cylindrical value ± SD). Hence, the difference of 0.74 D was seen (p value = 0.03969 i.e p-value< 0.05)
7) At 6 months of post op, mean cylindrical component reduced to -3.69± 1.48 from -4.33±1.61 (pre-op mean cylindrical value. Hence a significant difference of 0.74 D was seen (p value =0.03969 i.e p-value< 0.05).
8) Pre-operatively mean K1 47.63 D ± 2.82 which reduced to 46.90D ± 3.00 making a difference of 0.73 D (P value being 0.178) not being significant.
9) Pre-operatively mean K2 was 49.51D ± 4.75 which reduced to 48.62 D ± 5.05 at 6 months making a difference of 0.89 D (p value being 0.75) not being significant.
10) Central corneal thickness, corneal thickness at the thinnest point and corneal astigmatism showed no significant difference at 6 month follow up post operatively.

This study has few limitations. The study subjects in our study are limited. A larger multicentric study will be needed to derive stronger conclusions. The time span of the study was short. A long term follow-up is required to get down

to some more reliable results and to look for progression or regression in long term. At present, keratoconus is not curable. However, crosslinking was able to stop its progression in our series of cases.

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