Role of corneal collagen cross-linkage in the treatment of keratoconus

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Abstract

Purpose: to evaluate the efficacy and safety of corneal collagen cross linkage in treatment of mild and moderate keratoconus and its effect on the progression of the disease.

Methods: The study included 20 eyes of mild or moderate progressive keratoconus. Mild keratoconus was considered if the maximal Sim-K reading less than 48 D, while moderate keratoconus was considered if maximal Sim-K reading between 48-54 D. All patients were subjected to complete ophthalmological history, visual acuity assessment (uncorrected and best spectacle corrected) and was measured by Landolt's chart and expressed as Snellen's decimal equivalent, slit lamp examination, Corneal topography using a schiempflug-placido topographer: Sirius topography (CSO, Florence, Italy)

Results: This study was performed on 20 eyes of 13 patients (7 males and 6 females) with mean age 21.75 ± 4 years (range 17-30 years). Eleven (84.6 %) patients had bilateral keratoconus at start of the study. Both eyes of only 7 patients were eligible for the study parameters. In the other 4 patients, only one eye of each patients was included in the study and other eye was excluded either due to corneal opacity, pachymetry less than 400 micron or such eye with less severe keratoconus and patient refused surgery in that better eye. All patients wear spectacles for more than 3 years with frequent change with mean period of change 4.3±2.1 months. Eight patients wear soft contact lens and none of the patients wear hard contact lens. Only 5 patients had corneal topography 12 months or more before start of study and all showed increase in Sim-K by at least 2 diopters. Ten patients had documented reduction in BCVA by one line or more and had documented worsing of spherical equivalent by more than 2 diopters 6 months before start of the study.

Conclusion: CXL is a favorite treatment tool and first line of treatment for progressive keratoconus. Corneal collagen CXL is a safe and effective procedure to halt the progression of keratoconus.

Introduction

Keratoconus is a Greek word (kerato: cornea; konos : cone) meaning cone-shaped protrusion of the cornea.[1] It was first described in 1854.[2] Keratoconous (Kc) is asymmetric, bilateral, progressive and non inflammatory ectasia due to gradual biomechanical instability of the cornea.[3] It is a degenerative disorder characterized by stromal thining and secondary conical ectasia resulting in irregular astigmatism and visual loss.[4]

Keratoconous, classically, has its onset at puberty and is progressive until the third to fourth decades of life, when it usually arrests. It may however, commence later in life and progress or arrest at any age. Rarely, it may be congenital.[5]

Despite the intensive research activity over the last decades into the aetiology and pathogenesis of keratoconous, the cause(s) and possible mechanisms for its development remain poorly understood.[6]

Management of KC has advanced during the last few years and still in progress. As there are new modalities of treatment, it is better to say that there are traditional modalities and modern modalities of treatment rather than saying old and new. That is because the old modalities such as spectacle correction, contact lenses, penetrating keratoplasty (PKP), and conductive keratoplasty is still used although the demand upon the last two modalities has been decreased by the modern alternatives [7]

Ribofl avin/ultraviolet A (UVA) – induced collagen cross-linking of the cornea (CxL) is a novel approach that aims at increasing the mechanical and biochemical stability of the stromal tissue. Its goal is to slow down or arrest KC progression to delay or avoid recourse to keratoplasty. The purpose of this treatment is to create additional chemical bonds inside the corneal stroma by means of photopolymerization in the anterior two thirds of the stroma, while minimizing exposure to the surrounding structure of the eye.[8] This study aims to evaluate the efficacy and safety of corneal collagen cross linkage in

treatment of mild and moderate keratoconus and its effect on the progression of the disease.

Patients and methods

Study design: prospective unrandomized study

Participants:

The study included 20 eyes of mild or moderate progressive keratoconus. Mild keratoconus was considered if the maximal Sim-K reading less than 48 D, while moderate keratoconus was considered if maximal Sim-K reading between 48-54 D

Progression of keratoconus was documented by at least 2 of the following:

1- Reduction of BCVA by one line or more over a 6-month period before the intervention.
2- Worsing of the spherical equivalent by 2 diopters or more over a 6-month period.
3- Frequent change of accurate eyeglasses (twice or more in previous one year).
4- If available, increase of the Sim-K by 2 diopters or more over at least one year period before intervention.

Exclusion criteria:-

1. The corneal thickness less than 400 µm.
2. The average Sim-K more than 52 D.
3. Corneal opacification due to any cause.
4. Attack of hydropes.
5. Pregnant or nursing ladies.
6. Patients with history of corneal refractive surgery.
7. Patient refusal of surgery.

Methods:-

All patients were subjected to the following (baseline and during follow up):-

- Complete ophthalmological history.

- Visual acuity assessment (uncorrected and best spectacle corrected) and was measured by Landolt's chart and expressed as Snellen's decimal equivalent.
- Slit lamp examination.
- Corneal topography using a schiempflug-placido topographer: Sirius topography (CSO, Florence, Italy) was done baseline, 6 months and 12 months postoperatively From the printout, the following parameters were taken:
  1- Maximal Sim K reading *(Sim-K is an index that simulates the reading that would be obtained with a keratometer i.e. the mean sagittal curvature from the 4th and 8th Placido ring).*
  2- Average Sim-K
  3- Sim Astigmatism and its axis.
  4- Thinnest location pachymetry.
  5- Pachymetry at the apex of the cornea *(the steepest point in the corneal surface).*
  6- SIF (symmetry index front):
  7- SIB (symmetry index back) :
  8- BCV index (Baiocchi-Calossi-Versaci) *that allows the* Apical curvature *(the diopteric power at the apex of the cornea.*

The surgical procedure

Every patient was subjected to epithelium-off corneal collagen cross linking. Pilocarpine 2 % was instilled as one drop twice before surgery to minimize the lens and retina exposure to UV rays. Topical anesthesia was instilled in the form of benoxinate hydrochloride (Benox, Epico) as one drop every 5 minutes for 30 minutes before surgery. Skin disinfection was performed by the use of povidone iodine 10% to soak the skin.

The cross linking was done by the use of Xlink Opto, Austrilia (figure 6-1). Its parameters were T (Time): 30 minutes, D (Dose): 5.371 J/ccm, P (Power): 1.50 mW and I (Intensity): 2.984 mW/ccm .

The used riboflavin was riboflavin phosphate 0.127 g (Ricrolin , Sooft, Italy) which was equivalent to 0.1% basic riboflavin. Riboflavin

was kept in the refrigerator at +4 to + 8C0 and discarded immediately after surgery.

The epithelium in the central 8 mm of the cornea was removed with a blunt tipped spatula (figure 6-2). The lights were turned off in order not to affect the composition and efficacy of riboflavin by the room light. The riboflavin was instilled every 2-3 minutes for 30 minutes (figure 6-3) till the corneal stroma was saturated with riboflavin and this was checked by slit lamp examination to detect fluorescence of riboflavin in the anterior chamber.

Corneal irradiation with UVA was performed for 30 minutes with dropping of the riboflavin every 3 minutes (figure 6-4). Irrigation of the eye was performed. Soft Contact lens was applied on to the cornea (figure 6-5). Eye drops were instilled at the end of surgery in the form of antibiotic eye drops (Gatifloxacin 0.3%, Zymer, Allergan®), steroid eye drops (Prednisolone acetate 1 %, Predforte, Allergan®) and cyclopentolate. Lastly the eye was covered by eye patching.

Postoperative antibiotic eye drops (Gatifloxacin 0.3%, Zymer, Allergan®) was used hourly during the first 24 hours, then 4 times daily. Steroid eye drops (Prednisolone acetate 1 %, Predforte, Allergan®) was used TID from the 1st postoperative day. Topical gel was used twice daily. Systemic vitamin A and vitamin C were used twice daily. Systemic analgesic and anti-inflammatory (Ibuprufen,200 mg t.d.s) drugs also were used. The treatment usually lasted 7-10 days postoperatively.

The patient was followed up daily in the 1st week till re-epithelization of the cornea took place. During this follow up, the patient was examined by the slit lamp to detect corneal re-epithelization and haziness. Then the patient was followed up at the 1st, 3rd, 6th and 12th months postoperatively and corneal topography done at 6 and 12 months postoperatively.

In most cases, re-epithelization took place in the 1st 48 hours, then the contact lens was removed and eye patching was stopped. The patient was instructed to wear sun glasses for 2 weeks.

Statistical analysis:

Statistical analysis was done by the use of SPSS version 15.0 for windows. Statistical difference was tested by paired sample T test and statistically difference is considered significant if $P \leq 0.05$.

Results:

This study was performed on 20 eyes of 13 patients (7 males and 6 females) with mean age 21.75 ± 4 years (range 17-30 years). Eleven (84.6 %) patients had bilateral keratoconus at start of the study. Both eyes of only 7 patients were eligible for the study parameters. In the other 4 patients, only one eye of each patients was included in the study and other eye was excluded either due to corneal opacity, pachymetry less than 400 micron or such eye with less severe keratoconus and patient refused surgery in that better eye. All patients wear spectacles for more than 3 years with frequent change with mean period of change 4.3±2.1 months. Eight patients wear soft contact lens and none of the patients wear hard contact lens. Only 5 patients had corneal topography 12 months or more before start of study and all showed increase in Sim-K by at least 2 diopters. Ten patients had documented reduction in BCVA by one line or more and had documented worsing of spherical equivalent by more than 2 diopters 6 months before start of the study.

TABLE 1: Documented progression of keratoconus in the study eyes.

Parameter of progression	No of eyes
Frequent change of accurate eyeglasses (twice or more n previous one year	20 (100%)
Reduction of BCVA by one line or more over a 6-month period before the intervention	10 (50%)
Worsing of the spherical equivalent by 2 diopters	10 (50%)

or more over a 6- month period	
Increase of the Sim-K by 2 diopters or more over at least one year period before intervention	5 (25%)

During the follow up of the patients, 2 eyes of 2 patients were excluded one female patient got pregnant after 3 months of start and the other male patient traveled abroad after 6 months of the start. So that at the end of the study we considered only 18 eyes in the statistical analysis.

The preoperative values on the day of treatment were compared with postoperative values of the 12-month examination. This showed that UCVA improved at least one line in 88.9% (16/18) of eyes and decreased by only one line in 11.1 % (2\18). Figure 1 shows UCVA at the start and at the end of the study in all patients. BCVA improved at least one line in 94.4 % (17/18) of eyes and remained stable in 5.6 % (1\18). Figure 2 shows BCVA at the start and at the end of the study in all patients.

Spherical errors in all patients were statistically different at the end of the study when compared with the preoperative values (P=0.01). Figure 3 shows spherical error in all patients.

Astigmatism remained stable (within ± 0.50 D) in 72.2% (13/18) of eyes and decreased by at least of 1.00 D in 27.8 % (5/18) of eyes. Figure 4 shows astigmatism in all patients. Spherical equivalent SE showed no statistical difference between baseline and 12-month postoperative values (P > 0.05). Figure 5 shows the baseline and the postoperative SE in all patients.

Sim maximal K decreased by a least 1.00 D in 50 % (9/18) of eyes and remained stable (within ± 1.00 D D) in 50 % (9/18) of eyes. Figure 6 shows the difference between postoperative and preoperative maximal Sim-K. The average K value decreased by at least 1.00 D in 44.4 % (8/18) eyes and remained stable (within ± 1.00 D D) in 55.6% (10/18) of eyes. Figure 7 shows the difference between postoperative and preoperative average

Sim-K. Apical curvature decreased by at least 1.00 D in 61.1 %(11\18) of eyes and remained stable within ± 1.00 D in 39.9 %(7\18) of eyes. Figure 8 shows the difference between postoperative and preoperative apical corneal curvature.

Pachymetry at the thinnest corneal location remained stable (within 50 Um) in 66.7% (12\18) of the eyes and decrease by more than 5o Um in 33.3 % (6\18) of the eyes (figure 9). Similar results were obtained regarding pachymetry at corneal apex (figure 10).

Symmetry index front (SIF) remained stable within 1.00 D in 44.4 % (8\18) of eyes, decreased by more than 1.00 D in 44.4% (8\18) of eyes and increased by more than 1 D in 11.2 % (2/18) of eyes (figure 11). Symmetry index back (SIB) remained stable within 1.00 D in 83.3 % (15\18) of eyes, decreased by more than 1.00 D in 11.2% (2\18) of eyes and increased by more than one D in one patient (5.6%) (Figure 12). BCV remained stable within 1.00 Um in 72.2 % (13\18) of eyes, decreased by more than 1.00 Um in 22.2 % (4\18) of eyes and increased by 1.3 Um in 5.6 % (1/18) of eyes (Figure 7-13). Tables 2 and 3 summarize all the study results.

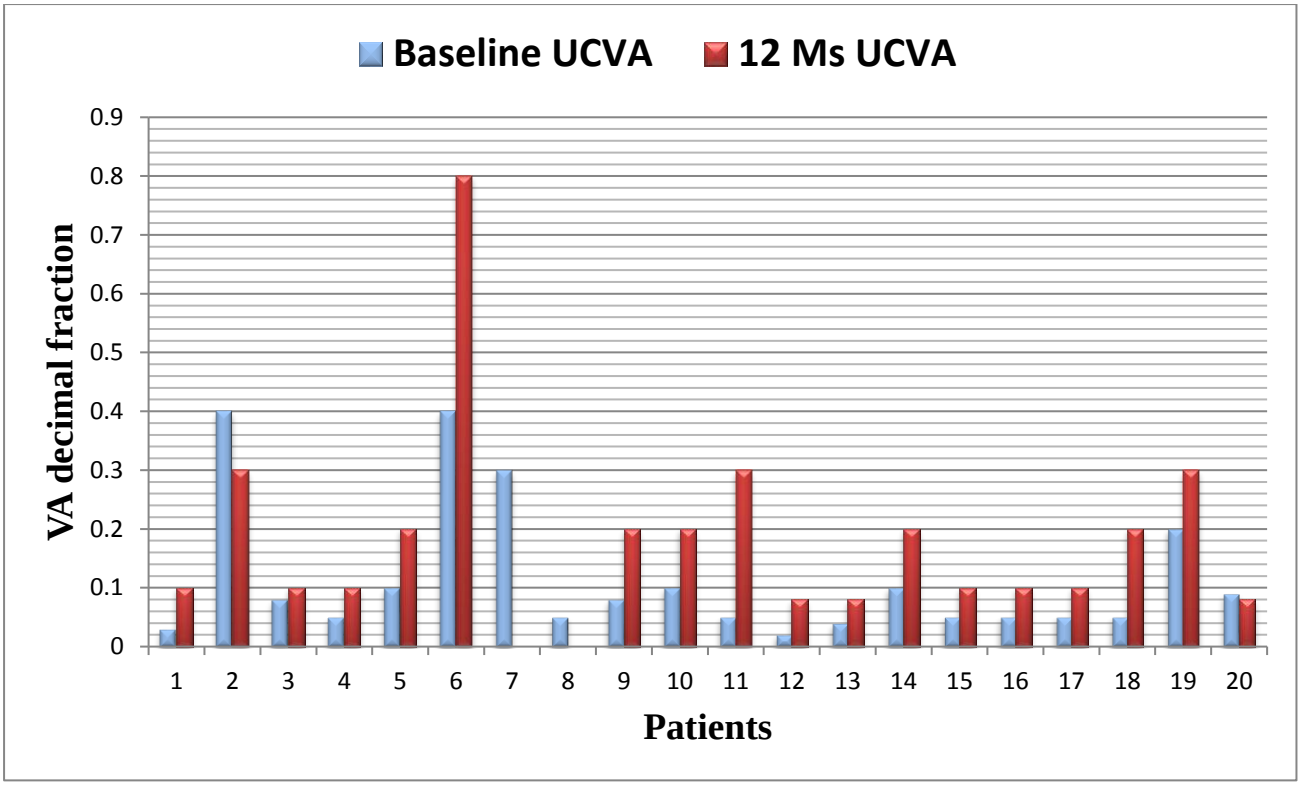


Fig 1: UCVA at the start and at the end of the study.

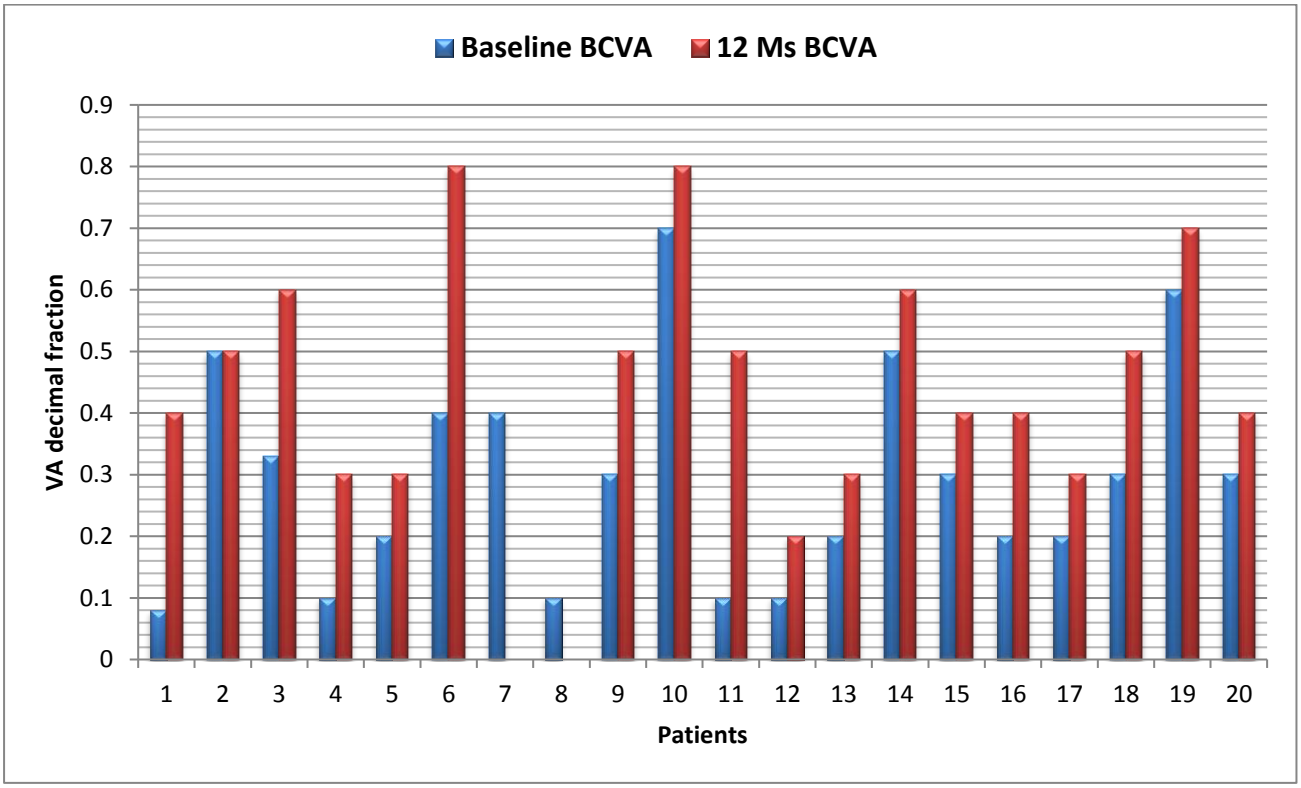


Fig 2: Show BCVA at the start and at the end of the study.

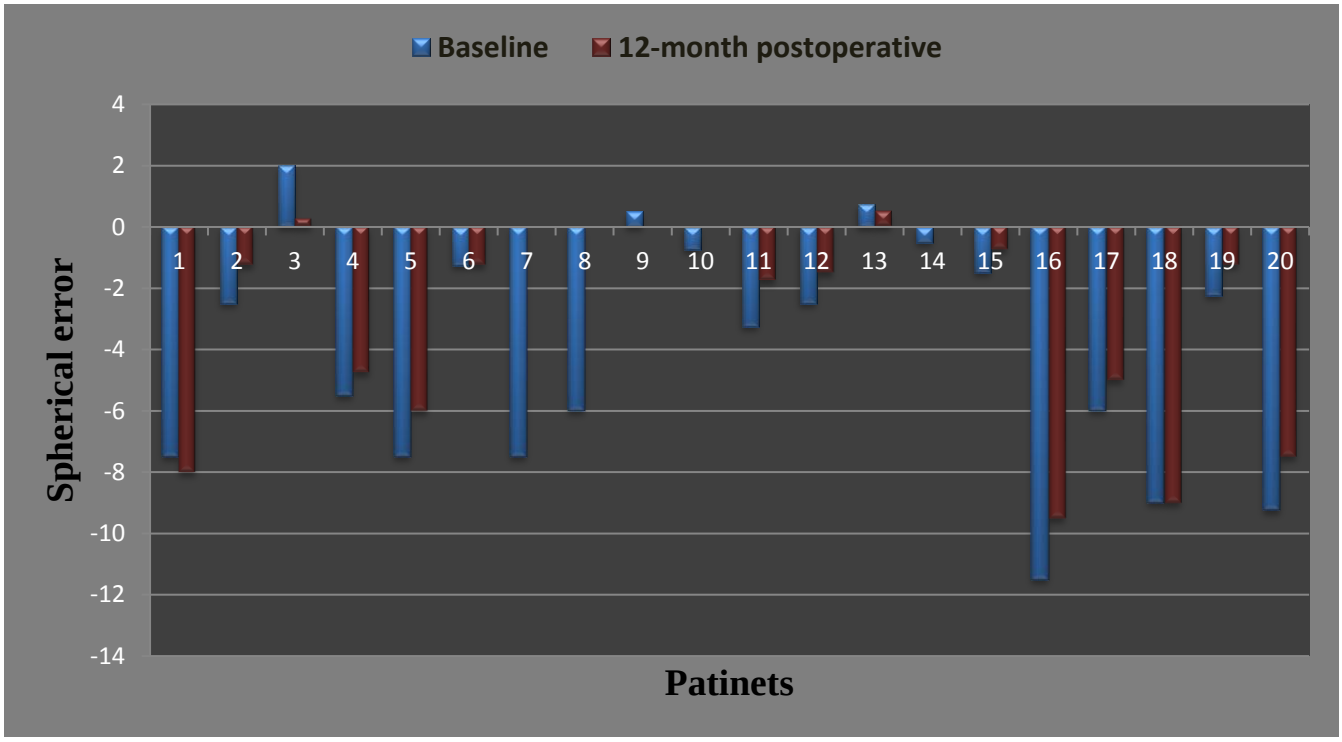


Fig 3: Baseline and 12-month postoperative spherical error in all patients.

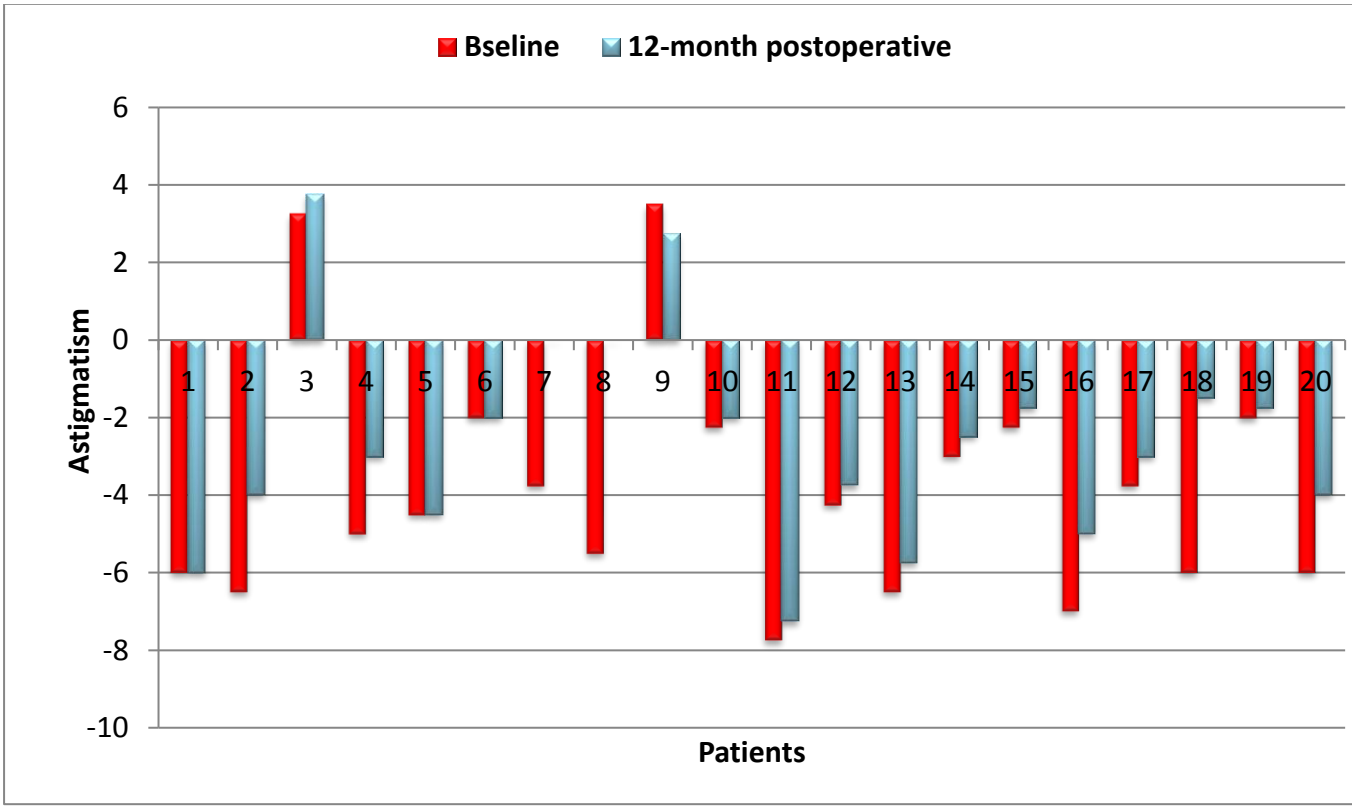


Fig 4: Baseline and 12-month postoperative astigmatism in all patients.

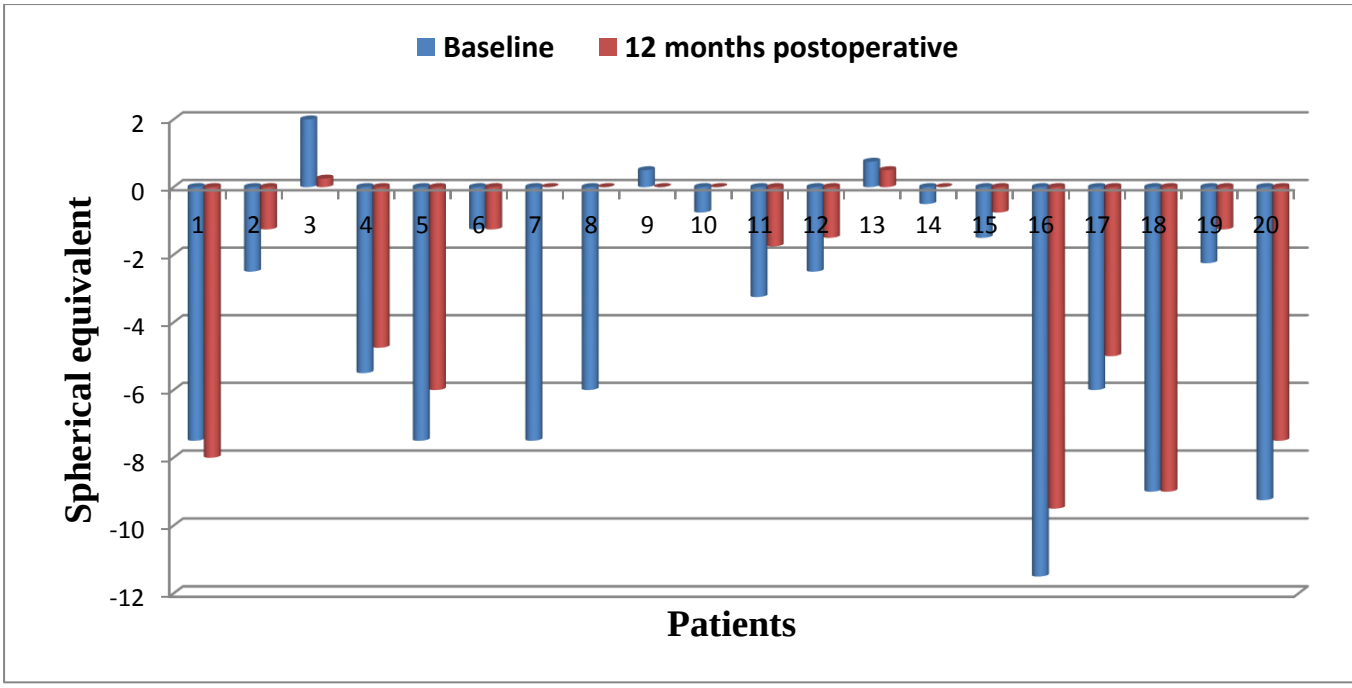


Fig 5: Baseline and 12-month postoperative spherical equivalent in all patients.

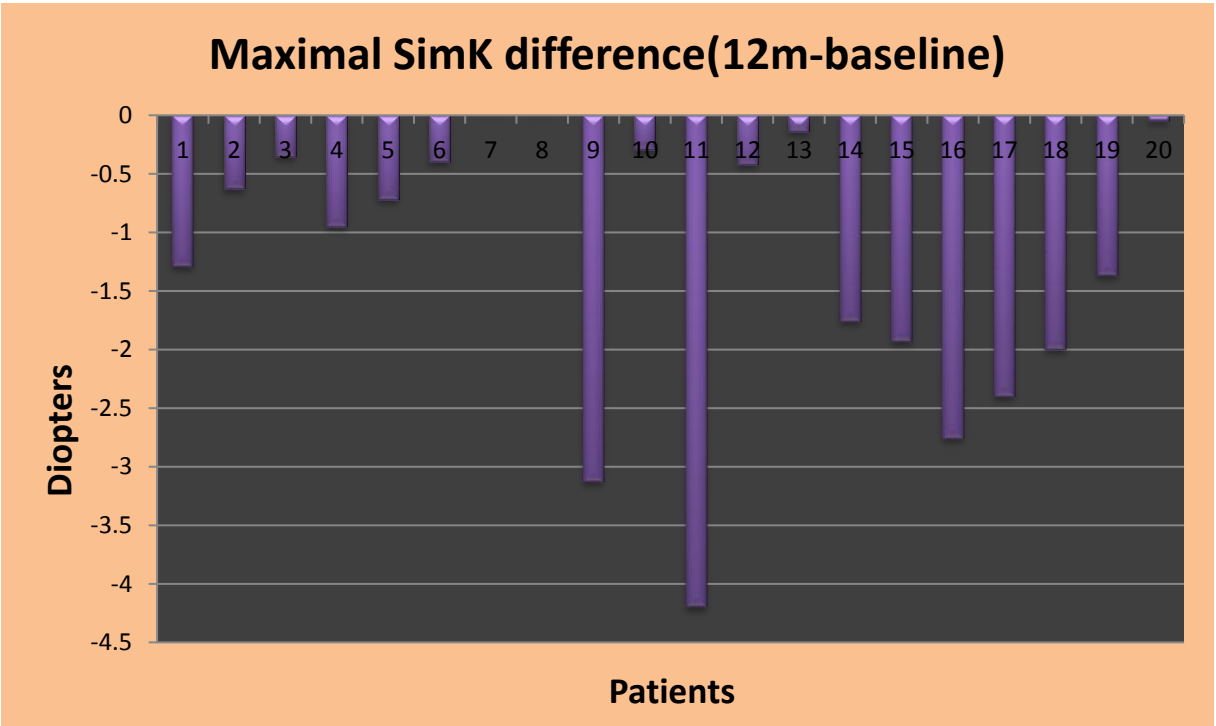


Fig 6: The difference between postoperative and preoperative Maximal Sim-K

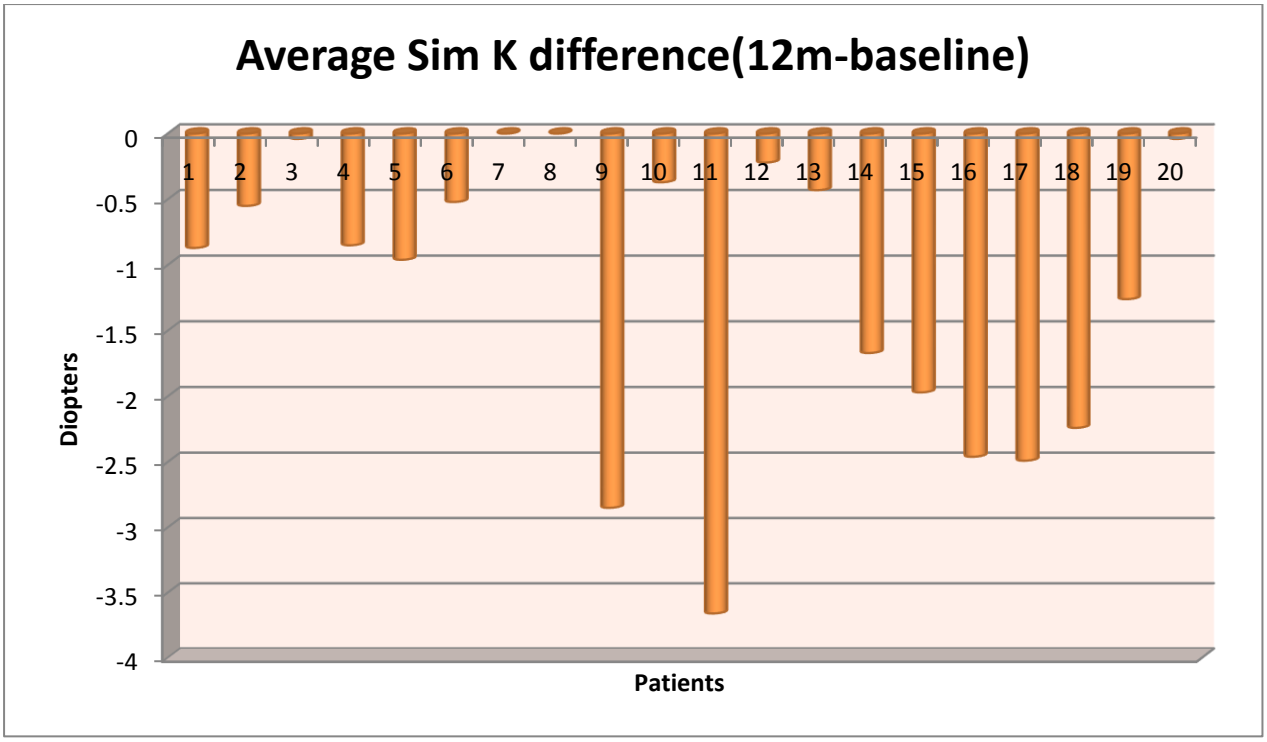


Fig 7: The difference between postoperative and preoperative average Sim-K

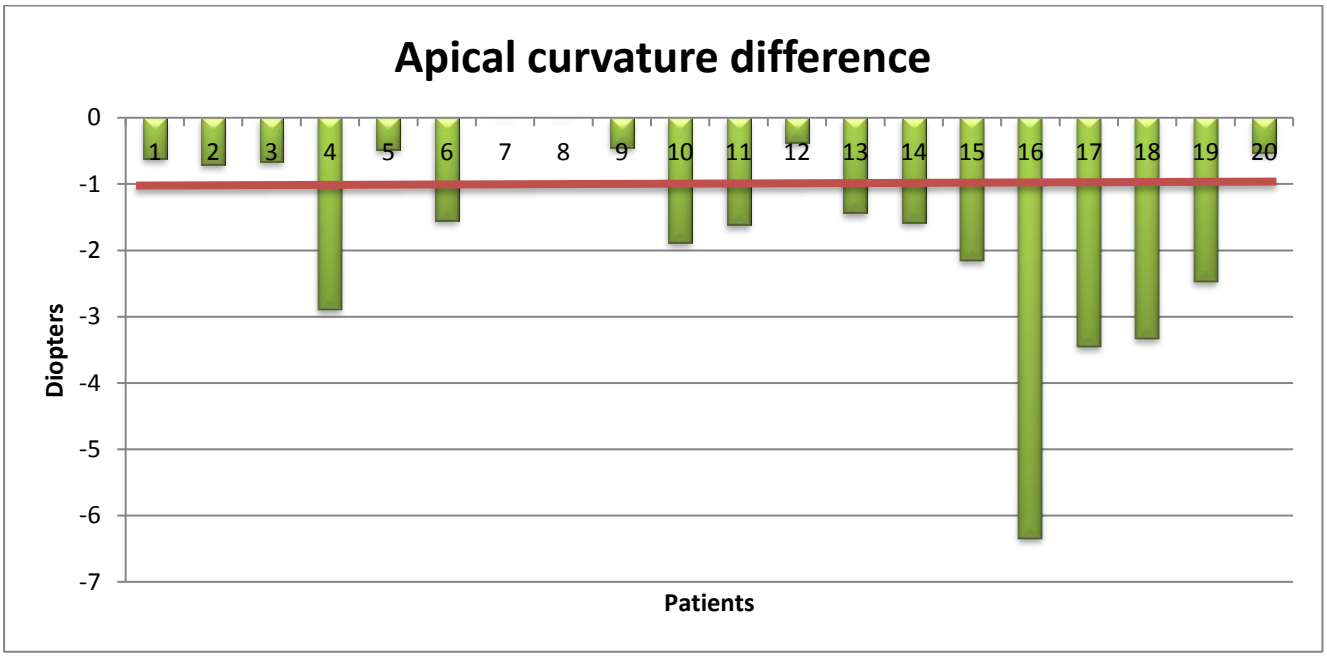


Fig 8: The difference between postoperative and preoperative corneal apical curvature.

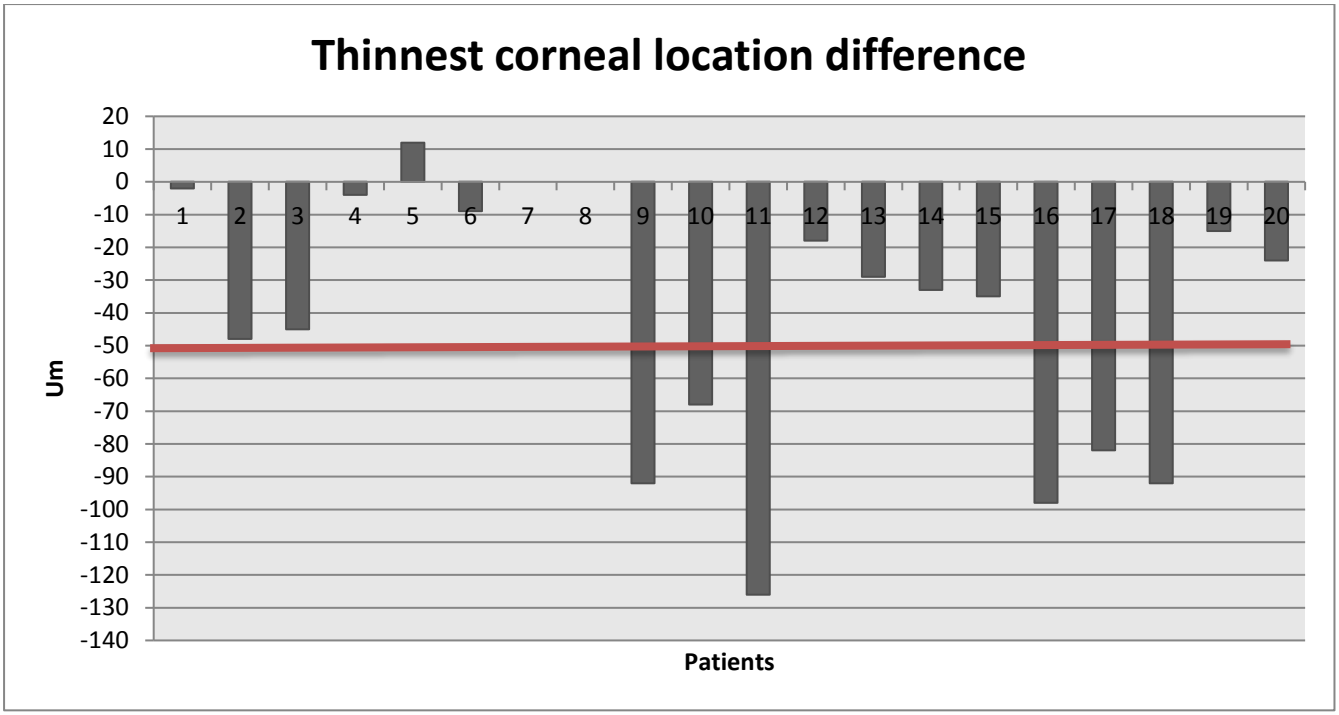


Fig 9: The difference between postoperative and preoperative pachymetry at the thinnest corneal locations.

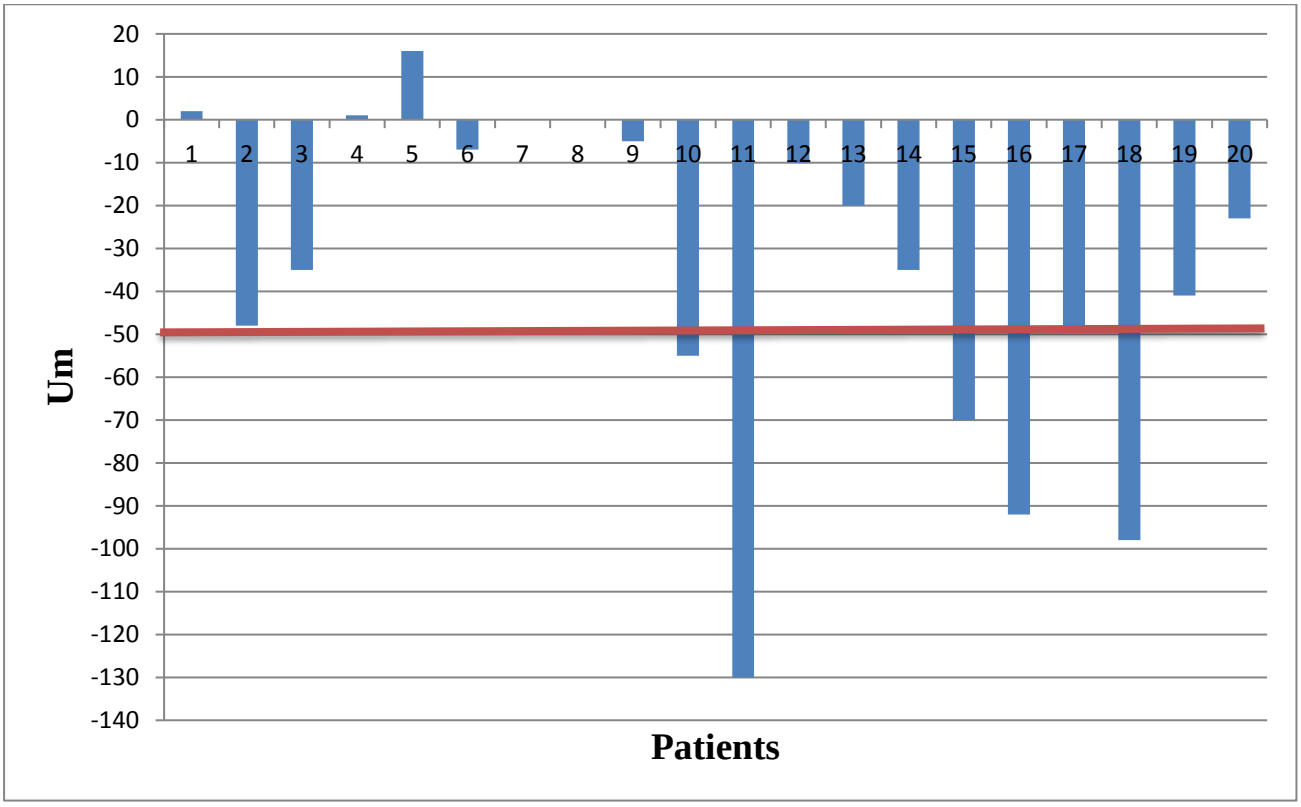


Fig 10: The difference between postoperative and preoperative Pachymetry at the corneal apex

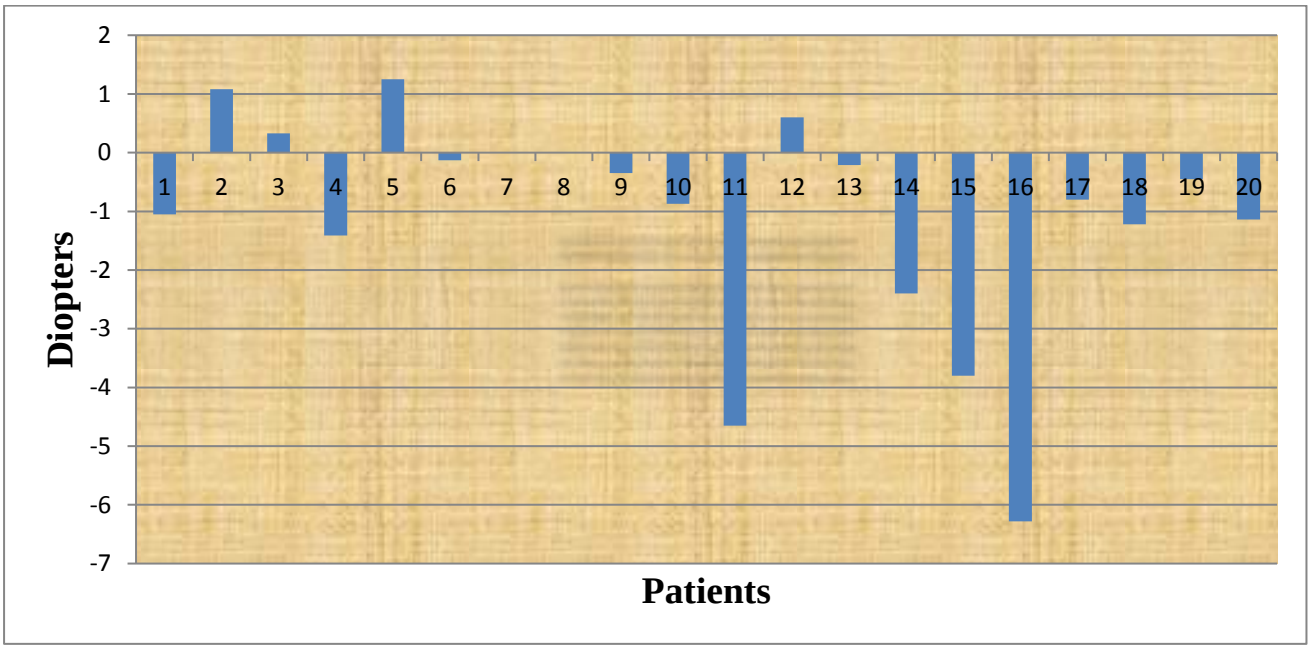


Figure 11: Postoperative and preoperative Symmtery index front SIF difference

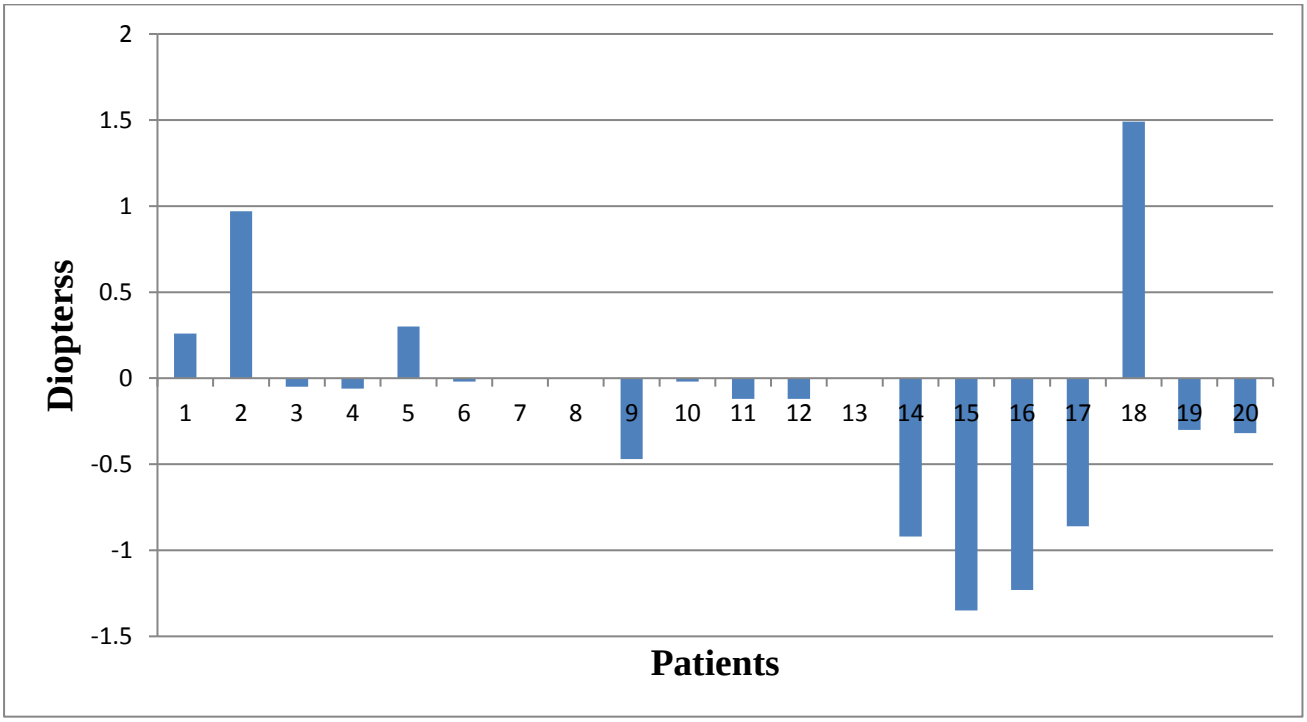


Figure 12: Post and preoperative Symmtery index back SIB difference.

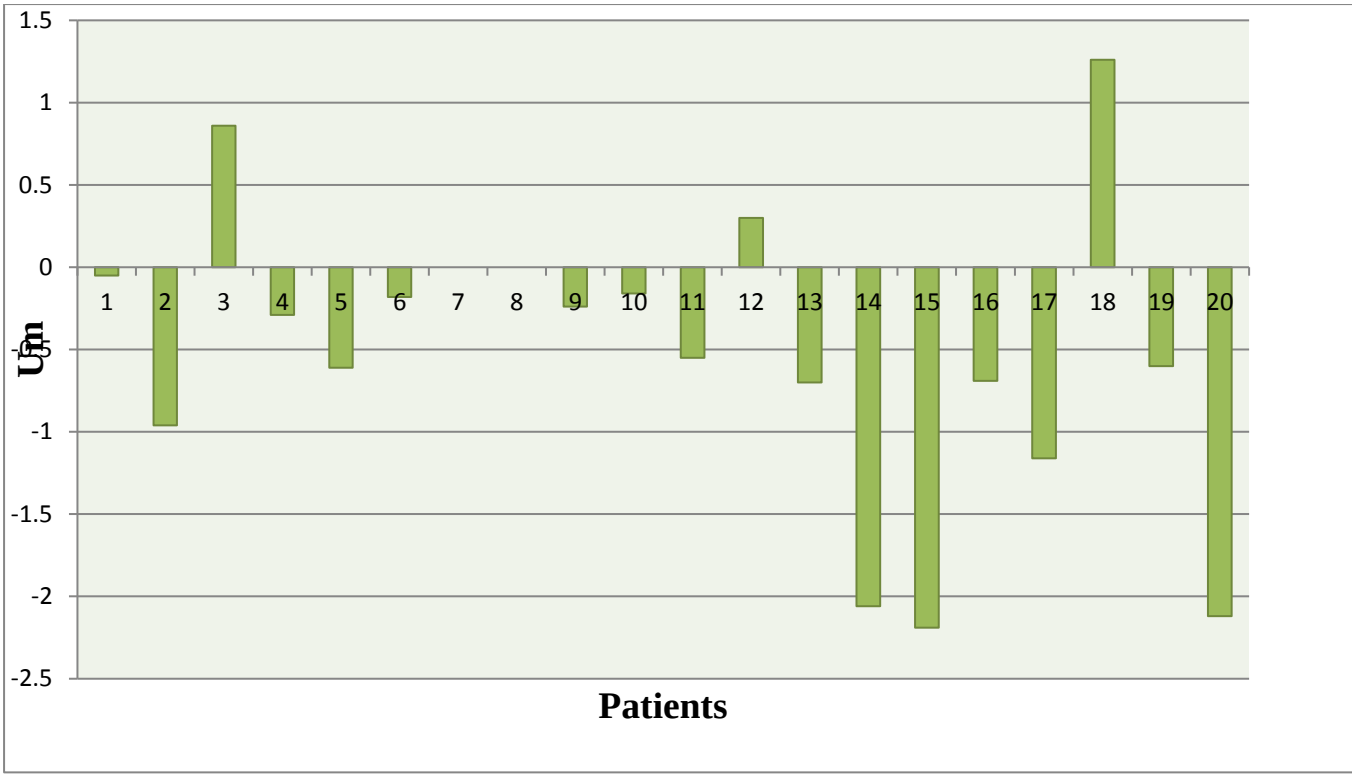


Figure 13: Differences between 12-month post and preoperative BCV.

Table 2: Summary of results of one year CXL study

Variant	Result
Age	
• Mean:	21.75 ± 4 years
• Range	17-30 years
UCVA	
• Improved at least one line	88.9% (16/18) of eyes
• Decreased by only one line	11.1 % (2\18) of eyes
BCVA	
• Improved at least one line	94.4 % (17/18) of eyes 5.6 % (1\18) of eyes
• Remained stable	

Astigmatism:	
• Stable within ± 0.50 D	72.2 % (13/18) of eyes
• Decreased by at least 1 D	27.8 % in (5/18) of eyes
Sim-Maximal K value	
• Decreased by at least 1.00 D	50 % (9/18) eyes
• Remained stable (within ± 1.00 D)	50 % (9/18) eyes
Sim- average K value	
• Decreased by a at least 1.00 D .	44.4 % (8/18) eyes
• Remained stable (within ± 1.00 D).	55.6 % (10/18) eyes
Apical K value	
• Decreased by at least 1.00 D	61.1 %(11\18) eyes
• Remained stable (within ± 1.00 D)	39.9 %(7\18) eyes
Pachymetry at corneal thinnest location	
• Stable (± 50 Um).	66.7% (12\18) eyes
• Decrease by > 5o Um.	33.3% (6\18) eyes
Pachymetry at corneal apex	
• Stable (± 50 Um).	72.2 % (13/18) of eyes
• Decrease by > 5o Um.	27.8 % in (5/18) of eyes
Symmetry index front (SIF)	
• Stable ± 1.00 D	44.4% (8\18) eyes
• Decreased by >1.00 D	44.4% (8\18) eyes
• Increased by >1.00 D	11.2 % (2/18) eyes
Symmetry index back (SIB)	
• Stable ± 1.00 D	83.3% (15\18) eyes
• Decreased by >1.00 D	11.2 % (2\18) eyes
• Increased by >1.00 D	

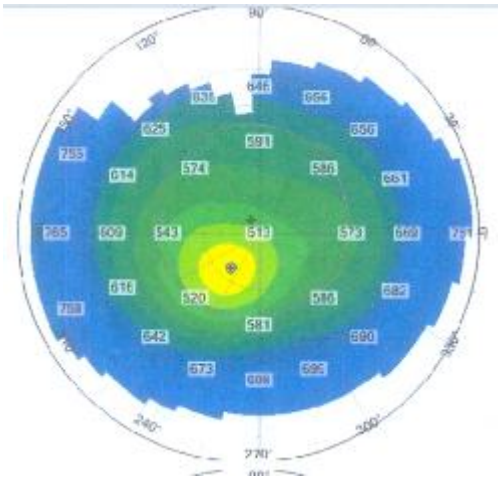
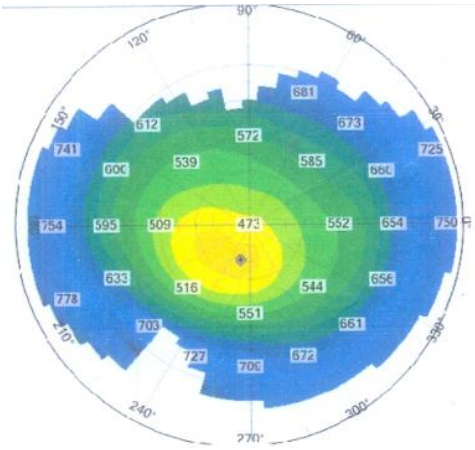
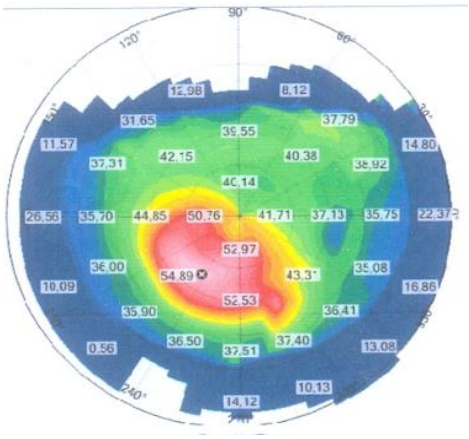
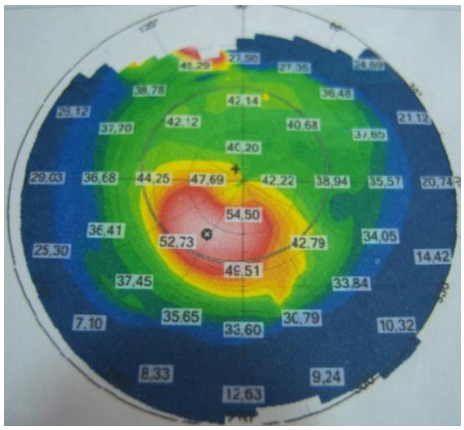
	5.6 % (1/18) eyes
BCV	
• Stable ± 1.00 Um	72.2 % (13\18) eyes
• Decreased by >1.00 Um	22.2 % (4\18) eyes
• Increased by >1.00 Um	5.6 % (1/18) eyes

Table 3: Summaries statistical differences between baseline and 12-month data.

	Baseline mean±SD	**12-month postoperative mean±SD**	**P value**
Uncorrected VA (Decimal Snellen,s fraction)	0.1145±0.12	0.1967±0.17	0.002
Best spectacle corrected VA (Decimal Snellen's fraction)	0.2955±0.18	0.47±0.17	0.000
Spherical error	-4.050±3.83	-3.15±3.4896	0.016
Cylindrical error	-3.8625±3.03	-2.847±2.758	0.005
Spherical equivalent	-4.7825±6.127	-4.569±4.212	0.846
Maximal sim-keratometry	49.10±3.24	47.56±3.20	0.000
Average sim-keratometry -	47.44±2.65	46.02±2.739	0.000
Thinnest corneal location	447.20±33.27	404.389±57.557	0.000
Apical pachymetry	466.70±44.82	435.69±57.21	0.02
symmetry index front SIF	7.56±4.597	5.75±4.42	0.014

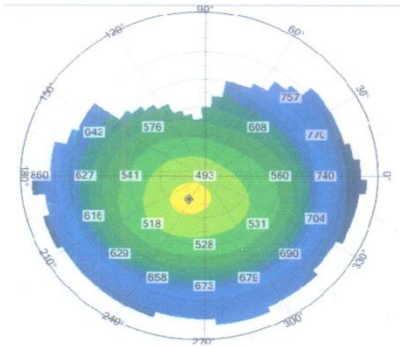
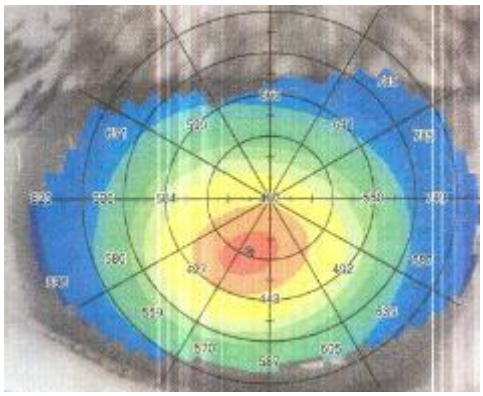
symmetry index back SIB	2.11±1.25	1.76±1.14	0.109
BCV	3.83±2.00	3.039±1.697	0.020
Apical curvature	58.72±6.24	55.81±4.74	0.000

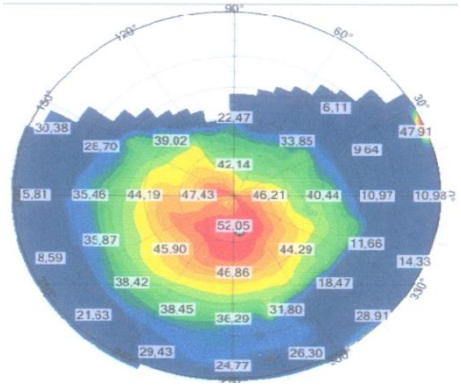
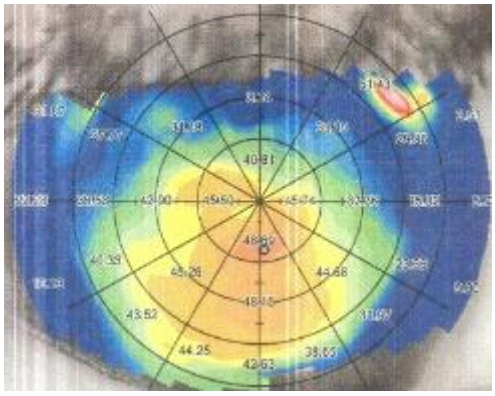
Table 4: Example of stabilization the state of KC 1-year after CXL.

Variant	**Preoperative**	**1-year Postoperative**
Pachymeteric map		
Tangential curvature map		
UCVA	0.02	0.08
BCVA	0.1	0.2
K readings	43.67 @ 53	43.62 @ 39

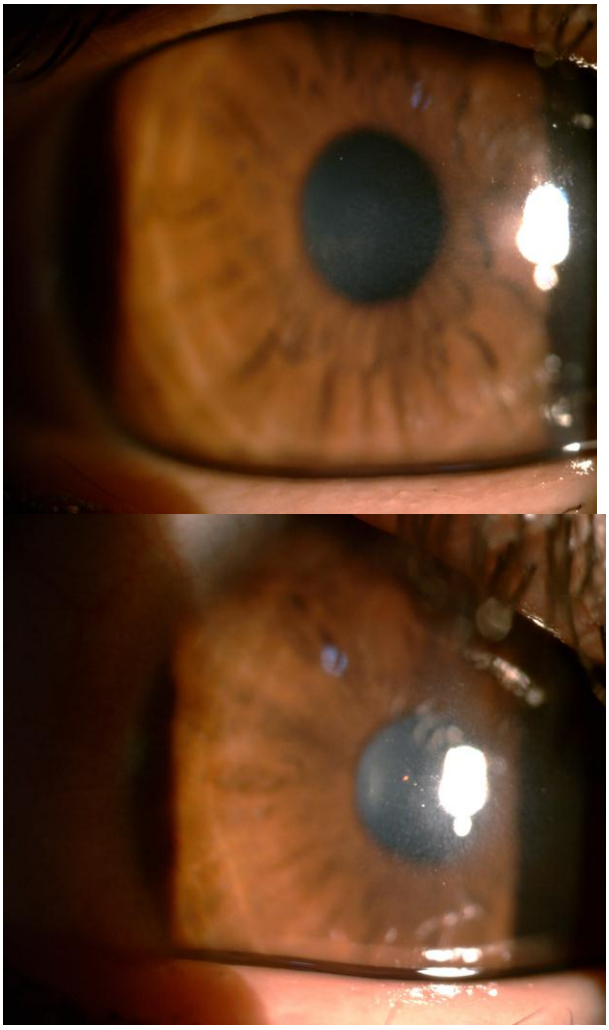
	45.68 @ 143	45.26 @ 129
K Average	44.65 D	44.43 D
Astigmatism	-2.01 D	-1.65 D
Apical curvature	61.75 D	61.37 D
Corneal thickness at the thinnest location	465 µm	447 µm
Pachyapex	480 Um	481 Um
SIF	7.51 D	8.11 D
SIB	3.00 D	2.88 D
BCV	4.73 Um	5.03 Um

Table 5: Example of regression the state of KC 1-year after CXL.

Variant	**Preoperative**	**1-year Postoperative**
Pachymeteric map		

Tangential curvature map		
UCVA	0.05	.0.2
BCVA	0.3	0.5
K readings	45.75 @ 35 48.31 @ 125	43.33 @ 52 46.31 @ 142
K Average	47.01 D	44.77 D
Astigmatism	-2.52 D	-2.98 D
Apical curvature	52.15 D	48.82 D
Corneal thickness at the thinnest location	477 µm	385 µm
Pachyapex	488 Um	390 Um
SIF	6.43 D	5.21 D
SIB	0.94 D	2.43 D
BCV	2.98 Um	4.24 Um

As regard postoperative complications, no serious complications such as infection, corneal opacifications or cataract were reported in any case. 4 eyes (4/20 i.e. 20%) (Figure 14) developed corneal haze the last minimally for one two month and maximally 4 months and treated by frequent topical steroid.



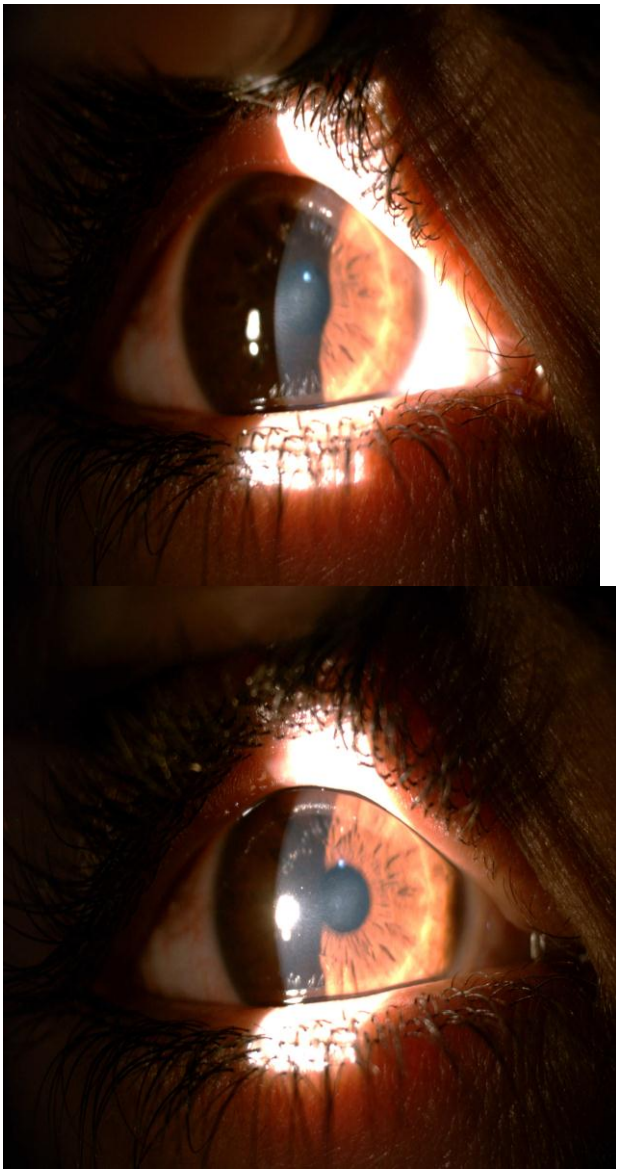


Figure 14 : Two examples of corneal haze after CXL.

Discussion

Collagen crosslinking, although developed primarily to mitigate progression of ectatic corneal processes, has also been found to improve visual acuity and corneal topography characteristics in some patients.[9-12] These effects are likely secondary to changes in the cornea's optical architecture, a result of the direct crosslinking effects and the consequent wound-healing processes.[13-15]

Early reports on the effectiveness of CXL treatment feature since 2003. Wollensak *et al.*'s nonrandomized clinical pilot study of Epi-off on 23 eyes of 22 patients with moderate or advanced progressive keratoconus (maximum K-value: 48–72 D) showed an arrest of progression of keratoconus in all treated eyes.[16]

A reduction in maximal keratometry (K) readings of 2.01 D and of the refractive error of 1.14 D over a mean follow-up period of 23 months was found in 70% of cases, with slight visual acuity improvement in 65% of cases. A subsequent report on the 3- and 5-year results of the Dresden clinical study shows that all 60 treated eyes had no progression of keratoconus, with 31 eyes also revealing a slight reversal and flattening of the keratoconus by up to 2.87 D. Best-corrected visual acuity (BCVA) had improved slightly by 1.4 lines.[17] Their results showed that the mean decrease in maximum K was 2.01 D and the mean decrease in refractive error was 1.14D. These clinical observations were later confirmed by multiple other reports. [9-12, 18-22]

A long-term retrospective study by Raiskup *et al.* of 480 eyes from 272 patients with progressive keratoconus (of which 241 eyes had a minimum follow-up of 6 months) showed corneal flattening by 2.68 D in the first year, 2.21 D in the second year and 4.84 D in the third year, with BCVA improvement by one or more lines in 53% of 142 eyes in the first year and 57% of 66 eyes in the second year.[23] Two patients had continuous progression of keratoconus and underwent repeat CXL treatment. Two patients with keratoconus progressed despite CXL and were required a repeated applications of UVA/riboflavin.[23] Another prospective, randomized controlled trial in Australia (Wittig-Silva *et al.*) on 66 eyes of 49 patients with documented progression of keratoconus showed flattening

of the steepest simulated K value (Kmax) by an average of 0.74 D at 3 months, 0.92 D at 6 months and 1.45 D at 1 year, while in the control eyes mean Kmax steepened by 0.60 D in 3 months, 0.60 D in 6 months and by 1.28 D after 1 year.[18] A trend towards improved best spectacle-corrected visual acuity was seen in the treated keratoconus eyes compared with that of the controls, which showed a progressive decrease. However, no statistically significant changes were found for spherical equivalents or endothelial cell density.

Grewal *et al.*'s study showed no significant change between mean preoperative and 1-year mean postoperative BCVA, spherical equivalent, anteriorcorneal and posterior curvature, and apex anterior and posterior corneal elevation in 102 keratoconus patients with CXL treatment.[25]

Coskunseven *et al.*'s prospective analysis of 38 eyes (19 patients) with progressive keratoconus (worse eye underwent Epi-off CXL and fellow eye served as control; mean follow-up: 9 ± 2 months) observed an average reduction of 1.03 ± 2.22 D (range: -5.25 to +3.75 D) in spherical equivalent and 1.04 ± 1.44 D (range: -2.00 to +4.00 D) in the refractive cylinder.[19] The corneal curvature decreased by 1.57 ± 1.14 D, while an increase in IOP by 2 ± 2 mmHg (statistically significant) was observed. Vinciguerra et al.[9] and Agarwal et al.[20] also noted similar results in their studies. Corneal wavefront measurements show a significant change at 12 months following treatment, although the initial 6–9 months do not show any significant change.

In our study (which concerned with 18 eyes of documented keratoconus which underwent Epi-off CXL and followed up for 12 months) the results showed improvement of UCVA in 88.9 % and stabilization in 11.1% and improvement of BCVA in 94.4 % and stabilization in 5.6 %. Sim maximal K decreased by a least 1.00 D in 50% (9/18) of eyes and remained stable (within ± 1.00 D D) in 50% (9/18) of eyes. The average K value decreased by at least 1.00 D in 44.4 % (8/18) eyes and remained stable

(within ± 1.00 D D) in 61.1% (10/18) of eyes. Apical curveature decreased by at least 1.00 D in 55.6 %(10\18) of eyes and remained stable within ± 1.00 D in 39.9 %(7\18) of eyes.

In the current study, mean refractive astigmatism reduced from -3.86 ±3.03 at start of the study to -2.85±2.76 12-month postoperatively. Jankov MR et al,[25] showed that refractive cylinder decreased less than 0.5 D (from -2.29 ± 1.77 to -1.86 ± 0.92 D), without reaching a statistically significant difference during their study on 25 eyes of keratoconus. This may be attributed to short follow up period that was 6 months only. This attribution can be enforced by another study of contributing authors [26] where they observed reduction of the refractive astigmatism with mean decrease (less myopic) 1.04 +/- 1.44 D (range: -2.00 to +4.00 D ($P < .01$). the reduction of astigmatism also observed in an Indian study which was performed on 68 eyes of 41 KC patients by Vinay B368 who observed 12 months after CXL that refractive astigmatism was reduced by a mean of 1.20 diopter (D) in 47% (17/37) of eyes (P=0.005) and remained stable (within ± 0.50 D) in 42% (15/37) of eyes.

Regarding corneal pachymetry, we found that Pachymetry at the thinnest corneal location and Pachy-apex remained stable (within 50 Um) in about two third of cases or more and decrease by more than 5o Um in at least one third of the eyes. Steven A et al,[27] found that After CXL, the cornea thins and then recovers toward baseline thickness and the cause and implications of corneal thickness changes after CXL remain to be elucidated. Vinciguerra et al.[9] found a decrease in pupil-center pachymetry and no change in thinnest pachymetry in eyes with keratoconus and a significant decrease in pupil-center pachymetry and thinnest pachymetry in eyes with ectasia 1 year after CXL.[**9**] Grewal *et al.*'s [28] study showed no significant change between mean preoperative and 1-year mean postoperative central corneal thickness (458.9 +/- 40 microm and 455.2 +/- 48.6 microm. However, Paolo V et al, [29] showed that mean 12-month baseline pupil center pachymetry and total corneal volume decreased significantly ($P = .045$). Greenstein SA et al [14] observed

that the thinnest pachymetry slightly decreased from baseline to 12 months (mean change -6.6 ± 22.4 μm; P=.01). In a long term study[30] with mean follow up period of 28.08± 8.39 months, Zotta PG et al observed that a statistically significant decline in corneal pachymetric values (at the thinnest location) when compared with preoperative values (467.65 ± 41.08 μm) was demonstrated at 12 (449.63± 83.53μm) and 24 (459.97± 47.32 μm) months after CXL ($p<0.05$).

A prospective analysis of IOP measurement by Goldman applanation tonometry before CXL and 6 and 12 months after CXL on 55 eyes of 55 patients revealed a statistically significant increase in the measured IOP 6 and 12 months after CXL, with a mean measured IOP of 9.95 ± 3.01 mmHg before CXL a 11.40 ± 2.89 mmHg at 6 months and 11.35 ± 3.38 mmHg at 12 months. This change in IOP was not found to correlate with patient age, preoperative pachymetry or preoperative K readings. The increase in corneal rigidity following CXL treatment in eyes with keratoconus results in a significant increase in IOP measured by Goldman applanation tonometry.[21] In our study we did not measure IOP pre and postoperative due to unavailability of an accurate device for IOP measurement.

The corneal haze after CXL has been found to be maximal at 1 month postoperatively, with a progressive decrease from 3 months. It is then found to significantly decrease between 3 and 12 months, and these changes in haze do not seem to correlate with postoperative clinical outcomes.[13] in the current study, 4 eyes (4/20 i.e. 20%) developed corneal haze the last minimally for one two month and maximally 4 months and treated by frequent topical steroid.

Koppen *et al.* reported four patients who developed multiple white stromal infiltrates and ciliary injection after CXL, which responded to topical and subconjunctival steroids.[31] Sterile

infiltrates that resulted in stromal melt were also observed after CXL in other studies.[32-33] Bacterial keratitis can cause complications following corneal CXL for keratoconus, and reported microorganisms include *Escherichia coli*,[34] *Acanthamoeba* [35] and *Pseudomonas*.[36] CXL treatment has been reported to induce herpetic keratitis with iritis even in patients with no history of herpetic disease.[37] In addition, in one patient with postlasik ectasia, a diffuse lamellar keratitis developed after CXL.[38] Corneal melt with perforation on topical use of diclofenac and proparacaine following CXL has also been reported in the literature.[339] **I**n our study no serious complications were reported.

Conclusion

CXL is a favorite treatment tool and first line of treatment for progressive keratoconus. Corneal collagen CXL is a safe and effective procedure to halt the progression of keratoconus. Considering the risk of progression of keratoconus and the need for keratoplasty at advanced stages of the disease, CXL may be considered in any patient diagnosed with progressive, forme fruste, or clinically significant keratoconus or similar corneal ectatic conditions. CXL is visual stabilizing and in some cases is visual improving procedure in patients with keratoconus.

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