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Corneal Collagen Crosslinking: An Observational Study in a Tertiary Eye Hospital in Bangladesh

Collagen Crosslinking Outcome

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Abstract:-

➢ ***Aim:***

To observe the result of corneal collagen crosslinking in keratoconus patients in a tertiary eye hospital in Bangladesh.

➢ ***Material and Methods:***

Fifty-two eyes of 37 patients received collagen crosslinking therapy over a period of 2 years. Patient with keratoconus under the age of thirty, clear cornea with a thickness more than 400 micron were cross-linked with "epi-off" procedure. Corneal thickness < 400 µ, corneal scar, active VKC, history of previous herpes viral diseases were excluded. All patients were assessed by pentacam topography. Collagen cross-linking was done under topical, peribulbar block or general anesthesia depending on the age and co-operation of the patients. Central corneal epithelium measuring 8-9 mm of was detached with the help 70% ethyl alcohol. 0.1% riboflavin solution was applied over the cornea for 60 minutes with every 2 minutes interval and UV-A (370nm) irradiance last 30 minutes. Corneal surface cleaned with Hartmann's solution, bandage contact lens was applied and installed broad spectrum antibiotic and then pad and bandage. Post operatively patient was treated with topical cycloplegic, antibiotic and corticosteroid. Regular follow up at day 7, one month, 3 months and 6 months were taken. Every follow up, visual assessment, intraocular pressure measurement measurement was done by air puff tonometer. After 6 months, pentacam topography was done in treated eyes and compared with the pre-CXL topography to assess the changes. All data regarding age, gender, stage, visual acuity, K-Max, astigmatism, Q-value, CCT, CTI, thinnest pachymetry were recorded pre- and post-operatively and analyzed by using SPSS-16 software.

➢ ***Result:***

There were total 52 eyes of 37 patients and the male female ratio was 1.5: 1. Mean age was 19.73+4.30 years (range 11 to 28 years). It was observed that 96 % (n-50) patient's progression was stopped. 17% patients improve to subclinical level after CXL, which is statistically significant. Corneal diopter-power (K-Max) became reduced to a significant level. Change of astigmatism did not show statistically significant. Corneal asphericity expressed by 'Q'-value, central corneal thickness (CCT), thinnest pachymetry of cornea and corneal thickness index (CTI) all reduced to a statistically significant levels. Although the central corneal thickness reduced but looks stronger shown by reducing the curvature.

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Good visual acuity (6/6-6/18) was achieved in 58% patients, where as poor vision reduced to 2% from 21%. There was no significant complications except one patient develop rounded corneal scar along the base of the cone.

➢ ***Conclusion:***

Corneal collagen crosslinking therapy halted the progression of keratoconus effectively and improved clinical outcome.

Keywords:- *Keratoconus, Corneal Collagen Crosslinking (CXL), Riboflavin, UVA-370, Pentacam Topography.*

I. INTRODUCTION

Corneal collagen crosslinking (CXL) procedure used to treat and arrest the progressive nature of keratoconus. With advancing of age, the collagen of corneal stroma become crosslinked by oxidation. Keratoconus usually progress rapidly in teenage and due to this crosslinking of collagen corneal ectasia become stable thereafter. In the 1990s at the University of Dresden, researcher used UV light and riboflavin (vitamin B2) solution on rabbit cornea to induce collagen cross-linking. It was shown that the treated corneas were more harder and stronger to enzymatic degradation. The endothelium was not damaged in those corneas that have more than 400 microns thickness [1]. In 2003 in Dresden, pilot studies of corneal cross-linking on human cornea with the use of UV-light alone with a promising result. On April 18, 2016 FDA approved the use of UV-Light and riboflavin solution for corneal collagen cross-linking [2]. Riboflavin acts as a photosensitizer that absorb light peak with at 370 nm and thus UV-A band (365-370) light is typically used for CXL. Water-soluble riboflavin easily enters the corneal stroma after removal of epithelium when applied topically [3]. Covalent bonds are formed between collagen molecules by reactive oxygen species, which is formed from riboflavin on exposure to UV-light [4]. Thus the tensile strength and rigidity of the cornea greatly increased and prevent progression [2]. It was shown that corneal stroma absorbed nearly 95% of UV-A (370 nm) light with an irradiance of 3 mW/cm^2 and 0.1% riboflavin and thus irradiation reduced to to 0.15 mW/cm^2 at the endothelial level, which is much below the cytotoxic threshold (0.36 mW/cm^2) for endothelium [5]. Homogenous irradiation with a total surface dose of 5.4 J/cm^2 (370 nm vavelength) ensures all structures of cornea is below harmful levels [6]. According to the Bunsen Roscoe law, if the total surface irradiance is constant, the photochemical effect will be similar and thus various protocols are available with different intensity and different duration of UV-A irradiation [7].

II. MATERIAL AND METHODS

This is a prospective observational study done at Chittagong Eye Infirmary & Training Complex during the period of 2 years starting from August 2021. Fifty-two eyes of 37 patients were involved in this study. Patient with progressive keratoconus under the age of 30, clear cornea with a thickness more than 400 micron were included in this study. All patients were crossed-linked with "epi-off" procedure. Thin cornea less than 400 microns, corneal scar, active VKC, history of previous herpes viral disease were excluded. All patients were assessed by pentacam topography. Counseling regarding purpose of cross-linking were done to every patient and their legal guardian. The study was approved by the local institutional review board (IRB) and conducted according to the Declaration of Helsinki 2013.

➢ *Procedure:*

Collagen cross-linking was done under topical (0.5% proparacaine 3-times 5 minutes interval), peribulbar block (5ml bupivacaine 0.5% with 5 ml lignocaine 2% and 150 unit of hyaluronidase), or general anesthesia (sevoflurane with intubation) depending on the age and co-operation of the patients. Patients were draped with aseptic precaution. 70% ethyl alcohol placed over the cornea for 2 minutes and central 8-9 mm of corneal epithelium was scrapped with the help of crescent blade. Riboflavin 0.1% solution was applied over the corneal surface every 2 minutes for first 30 minutes. Then surgeon wore protective-goggles and start UV-A (370nm) irradiance (*CF X*-LINKER, IROMED Group, Italy) at a distance of 50 mm and focus sharp on the central 8-9 mm corneal surface. During this procedure riboflavin solution again installed every 2 minutes for next 30 minutes [figure-1]. After this treatment, thoroughly washed the corneal surface with Hartmann's solution and applied bandage contact lens and installed broad spectrum antibiotic and then pad and bandage. Post operatively patient was treated with cycloplegic-homatropine 2% eye drop 3 times daily for 7 days, moxifloxacin 0.5% 4 times daily for 7 days and dexamethasone 0.1% 4 times daily for 7 days and then tapered. After 7 days, bandage contact lens was removed and artificial tear was prescribed 4 times a day for 1 month. Regular follow up at 1 mnths , 3 months and 6 months were taken. Every follow up, visual assessment, intraocular pressure measurements were done by non contact air puff tonometer. After 6 months, pentacam topography was done in treated eyes and compared with the pre-CXL topography to assess the changes. All data regarding age, gender, stage of keratoconus, visual acuity, maximum keratometry power, astigmatism, Q-value, central corneal thickness, corneal thickness index, thinnest pachymetry were recorded pre- and post- operatively. All data were analyzed by using SPSS16 software. A *p-value <0.05* was considered significant.

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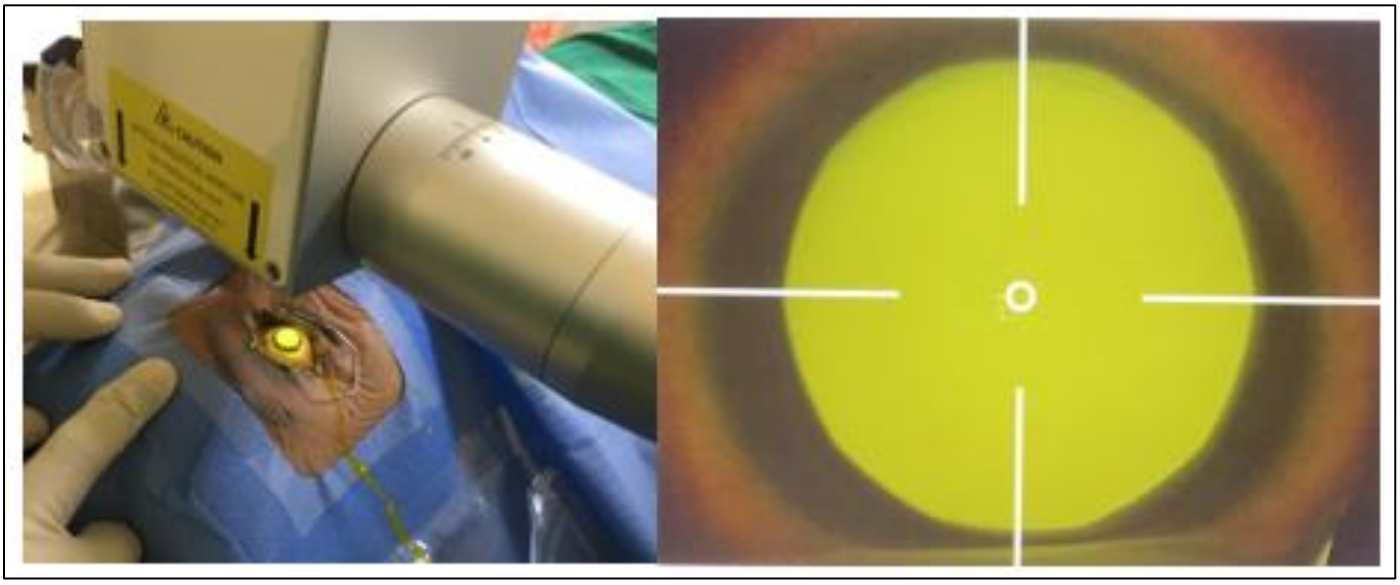

Fig 1 Cross-Linking Procedure.

III. RESULTS

There were total 52 eyes of 37 patients with a male female ratio 1.5: 1 [table-1 & 2]. Mean age was 19.73+4.30 years (range 11 to 28 years).

Table 1 Patients and Eyes

Patients	Male	Female	Total
Both eyes	9 (9x2=18)	6 (6x2=12)	15
One eye	13	9	22
Total patients	22 (9+13)	15 (6+9)	37
Total Eyes	31 (18+13)	21 (12+9)	52

Table 2 Patients and Eyes

Eyes	Frequency	Percentage
Male eyes	31	60%
Female eyes	21	40%
Total eyes	52	100%

According to well-known Amsler-Krumeich classification system, there were 1.9% (n=1) subclinical, 42.30% (n=22) mild, 44.20% (n=23) moderate and 11.50% (n=6) advanced keratoconus. Post-CXL status was 17.30% (n=9), 36.50% (n=19), 36.50% (n=19) and 9.60% (n=5) respectively. It is observed that, 17% patients improve to subclinical level after CXL which is statistically significant [table-3,4, figure-2]. The difference of pre- and post-operative TKC found statistically significant at 0.001 levels (X^2=72.434[a]; Cramer's V= 0.681; df = 9; Sig. p = <001) [table-4]. It was observed that 96% patient's progression was stopped.

Table 3 Pre- and post-CXL Keratoconus Grading

Type of keratoconus	Pre- CXL %, (n)	Post-CXL %
Subclinical	1.90% (1)	17.30% (9)
Mild	42.30% (22)	36.50% (19)
Moderate	44.20% (23)	36.50% (19)
Advanced	11.50% (6)	9.60% (5)
Total	100% (52)	100% (52)

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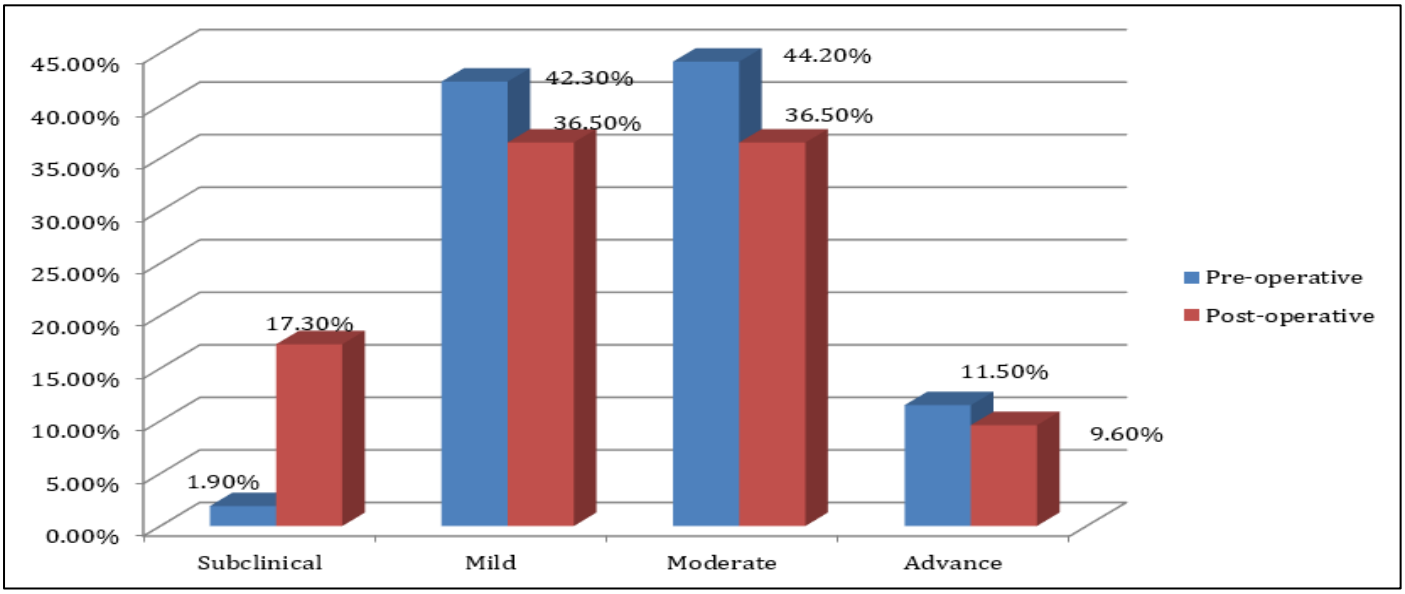

Fig 2 Pre- and Post-CXL Comparison

Table 4 Pre- and Post-CXL Comparison

	Post-CXL				
Pre-CXL	**Subclinical**	**Mild**	**Moderate**	**Advanced**	**Total**
Subclinical	1.90 %	-	-	-	1.90%
Mild	11.50%	28.80%	1.90%	-	42.30%
Moderate	3.80%	7.70%	32.70%	-	44.20%
Advanced	-	-	1.90%	9.60%	11.50%
Total	17.30%	36.50%	36.50%	9.60%	100.00 %
X2 = 72.434a; Cramer's V= 0.681; df = 9; Sig. *p* = <0.001					

Regarding keratometric power of cornea, it was observed that there is highly significant change in both flat and steep meridians. Corneal power became reduced to a significant level. Change of astigmatism did not show statistically significant. Maximum keratometric (K-Max) reading also changed significantly [table -5].

Table 5 Comparison between Flat and Steep Meridian and Astigmatism

Variable	**Mean ± SD**		***p-value***
Flat meridian K_1	Pre-	47.94 ± 3.96	0.000
	Post-	46.01 ± 4.20	
Steep meridian K_2	Pre-	52.30 ± 4.77	0.000
	Post-	50.36 ± 5.18	
Astigmatism	Pre-	4.40 ± 2.06	0.343
	Post-	4.26 ± 2.16	
K-Max	Pre-	55.40 ± 8.80	0.042
	Post-	53.66 ± 5.82	

Corneal asphericity expressed by 'Q'-value, central corneal thickness (CCT), thinnest pachymetry of cornea and corneal thickness index (CTI) all reduced to a statistically significant levels [table-6]. Although the central corneal thickness reduced but looks stronger shown by reduce the curvature.

Table 6 Different Indices

Variable	**Mean ± SD**		***p-value***
'Q'-Value	Pre-	1.26 ± 0.57	0.000
	Post-	0.98 ± 0.67	
CCT	Pre-	458.24 ± 31.19	0.000
	Post-	413.94 ± 46.09	
CTI	Pre-	1.41 ± 0.28	0.005
	Post-	1.30 ± 0.13	
Thinnest pachymetry	Pre-	445.81 ± 33.68	0.000
	Post-	397.02 ± 48.38	

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The difference of pre and post-operative posterior elevation found statistically significant at 0.001 level (X^2 = 31.202[a]; Cramer's V= 0.548; df = 4; Sig. P = <0.001). [table-7,8, figure-3]

Table 7 Posterior Elevation

Posterior elevation	Pre-CXL	Post-CXL
<17 µ	27%	21%
17-20 µ	6%	4%
>20 µ	67%	75%
Total	100%	100%

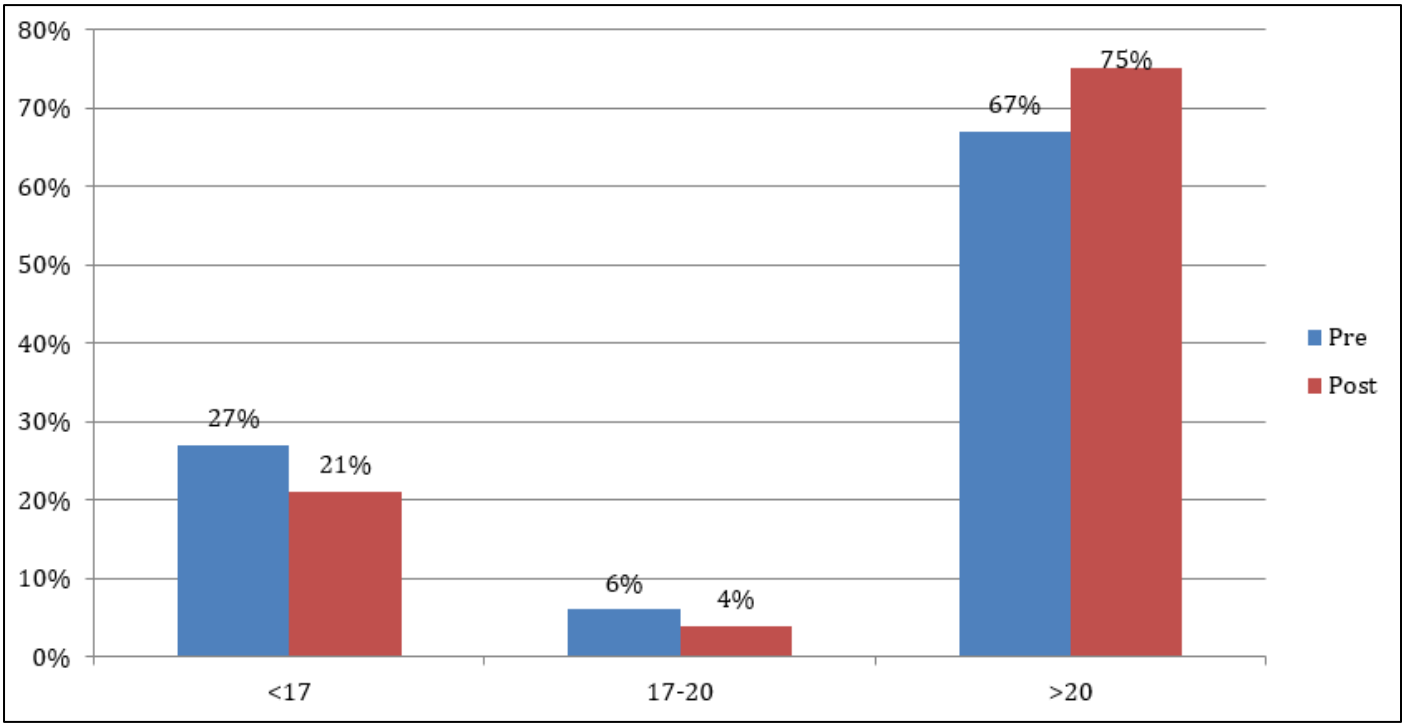

Fig 3 Pre- and Post-CXL Comparison of Posterior Elevation.

Table 8 Pre- and Post-CXL Comparison of Posterior Elevation.

Posterior elevation	Post-CXL			
Pre-CXL	<17 µ	17-20 µ	>21 µ	Total
<17 µ	9 (17.3%)	1 (1.9%)	4 (7.7%)	14 (26.9%)
17-20 µ	-	1 (1.9%)	2 (3.8%)	3 (5.8%)
>20 µ	2 (3.8%)	-	33 (63.5%)	35 (67.3%)
Total	11 (21.2%)	2 (3.8%)	39 (75.0%)	52 (100.0%)
X2 = 31.202a; Cramer's V= 0.548; df = 4; Sig. P = <0.001				

Good visual acuity (6/6-6/18) was achieved in 58% patients, where as poor vision reduced to 2% from 21%. The difference of pre and post-operative visual acuity found statistically significant at 0.001 level (X^2 = 15.704[a]; Cramer's V= 0.389; df = 4; Sig. *p*= <0.001) [table-9,10, figure-4].

Table 9 Visual Acuity Comparison

Visual Acuity	Pre-CXL	Post-CXL	
6/6 – 6/18	38.5%	58%	
6/24- 6/60	40.5%	40%	
<3/60	21%	2%	
Total	100%	100%	
Visual acuity	**Mean ± SD**		***p value***
LogMar	Pre-	0.79 ± 0.53	0.000
	Post-	0.52 ± 0.34	

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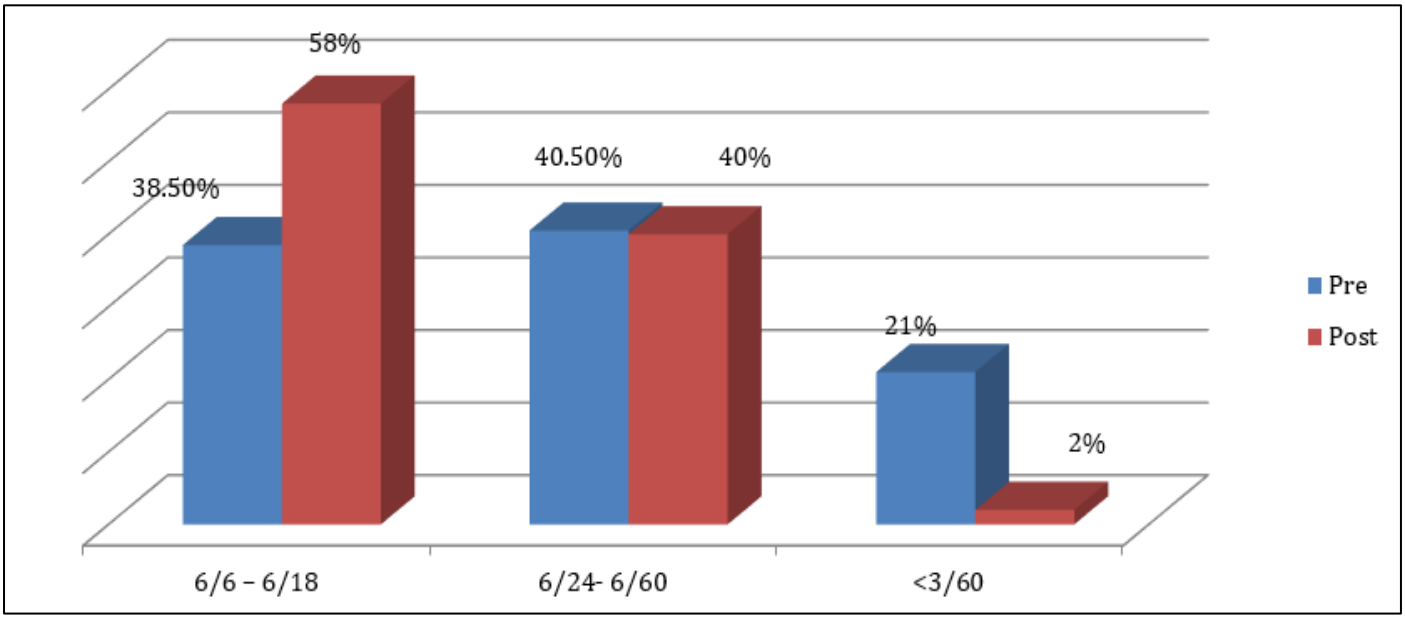

Fig 4 Visual acuity comparison

Table 10 Pre- and Post-Operative Visual Acuity

Visual acuity	6/6 - 6/18	6/24 - 6/60	<6/60	Total
6/6 – 6/18	17 (32.7%)	3 (5.8%)	-	20 (38.5%)
6/24- 6/60	11 (21.2%)	10 (19.2%)	-	21 (40.4%)
<3/60	2 (3.8%)	8 (15.4%)	1 (1.9%)	11 (21.2%)
Total	30 (57.7%)	21 (40.4%)	1 (1.9%)	52 (100.0%)
$X^2 = 15.704^a$; Cramer's V= 0.389; df = 4; Sig. *p*= <0.001				

There was no significant complications except one patient develop rounded corneal scar along the base of the cone.

IV. DISCUSSION

The keratoconus is usually diagnosed and tracked its progression with the help of pentacam topography which is based on the Scheimpflug imaging system (Oculus, Germany) by using K-max value (maximal keratometry), anterior and posterior corneal surface elevation map, and pachymetric map [8]. Four indices are suggested by Rabinowitz for screening purpose of keratoconus. K-max more than 47.2 diopters, I-S value more than 1.2 diopters, Sim-K astigmatism more than 1.5 iopters and radial axis skewing of bowtie more than 21 degree, all these indices are used for diagnosis of keratoconus as well as detect progression [9]. Amsler-Krumeich classifed the keratoconus depending on using refractive error of patient, central corneal power, central corneal thickness, and the presence or absence of corneal scarring [10]. Keratoconus is a central or paracentral noninflammatory ectatic degenerative disorder of the cornea, where numbers collagen fibrils of corneal stroma decreased, epithelial basement membrane fragmentation, Bowman's layer disintegration, degeneration of basal epithelial cells and stromal keratocytes. That's why the cornea become thin and the configuration of collagen lamellae changed in keratoconus [11]. In 1991 Klingman and Gebre showed that on chronic exposure of UV light skin collagen changed its biochemical properties and this collagen shown highly resistant to break with pepsin, which indicate the much more covalent bonds are formed by UV light. By using riboflavin and UVA irradiation, Spoerl *et al* [6] first showed crosslinking of corneal collagen. Wollensak *et al* [12] and Kohlhaas *et al* [13] were used this method and showed a remarkable positive effect of CXL on human cornea. CXL is a technique to increase corneal collagen strength by using riboflavin and UVA radiation. Riboflavin is a photo sensitizer molecule that causes cross linkage between collagen fibrils by inducing covalent inter- and intrafibrillar collagen bond thus increase in biomechanical strength of human cornea around 300%. In this procedure the maximum cross linking occurs in the anterior stromal collagen [6]. The CXL mainly used to arrest the progression of corneal ectatic disorders such as keratoconus, pellucid marginal degeneration, post-LASIK ectasia. Keratoconus of teenagers are usually progressive in nature and need to treat with CXL at the time of diagnosis and do not to wait for confirmation of progression [14]. Kymionis et al showed that although the thickness decreased due to effect of CXL but more more rigid and compact corneal stroma achieved through this procedureand they found a significant reduction of in central corneal thickness (mean 75 microns reduced) [15]. In our study the central corneal thickness reduce from 458.24 ± 31.19 to 413.94 ± 46.09 [table-6] CXL with "epi-off" can be done after epithelial removal and "epi-on" with epithelial intact. In our all cases 'epi-off' procedure was followed. The main indication of CXL is to stop the progression of ectatic condition. The progression criteria depends on change of refraction especially astigmatism, visual acuity and topographic change. According to these criteria, 96%

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corneas of our study, the progression was stopped. Different studies showed the decrease K-Max an indication of stability of corneal curvature. In our study the decreased K-Max is comparable with these studies [table-11]. Other variables such as Q-value, corneal thickness index (CTI) and central corneal thickness (CCT) also decreased significantly [table-6]. Visual acuity also improved [table-9,10, figure-4].

Table 11 Decreased Kmax in Other Studies [16]

Authors	Follow up (months)	K-max
Agrawal (2009)	12	Kmax decreased by 2.73 D
Coskunseven et al (2009)	5-12	Kmax decreased by 1.57 D
Fournie et al (2009)	3-18	Kmax decreased by 1.68 D
Witting-silva et al (2008)	3-12	Kmax decreased by 1.45D
Our study	6	Kmax decreased by 1.74D

Complications of CXL have been observed in different studies. Due to debridement of corneal epithelium there is a chance of microbial keratitis with E. coli, acanthamoeba, streptococcus, staphylococcus, pseudomonas due to poor hygiene and reactivation of herpetic keratitis- geographical ulcer and iritis have been reported [17]. There is a high risk of haze formation after CXL in advanced cases due to low corneal thickness as well as steep corneal curvature [18]. One of our advanced keratoconus developed annular corneal scar around the base of cone. The haze looks like polygonal crosslinking network. Haze causes light scattering that causes some photophobia and vision deterioration and this haze reduce some extend subsequently. Using the current recommended protocol with a thickness of central cornea more than 400µ, the irradiation (0.18mW/cm^2), which reaches to the corneal endothelium much more lower than damaging threshold of endothelium (0.35 mW/cm^2) [19]. Corneal endothelium may be damaged due to a stromal thickness less than 400m or incorrect focusing even corneal perforation if the procedure is done on a thinner cornea. No of our patient showed endothelial de-compensation presented as corneal edema or bullus keratopathy.

V. CONCLUSION

Corneal collagen cross-linking is an effective procedure in halting the progression of keratoconus and improving the clinical outcome. It is essential to evaluate the topographic criteria to select the cases especially central corneal thickness. Counseling also equally important because the primary goal of the procedure to stop the progression of the disease rather than improving the disease condition.

VI. LIMITATION

Small sample size, we did not assess the endothelial cell count before and after the CXL.

➢ *Conflict of Interest:*

- No Commercial/Financial Interest.

➢ *Funding/Financial Support:*

- No Institutional Funding.

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REFERENCES

[1]. P T Ashwin, P J McDonnell. Collagen cross-linkage: a comprehensive review and directions for future research. Br J Ophthalmol 2010;94:965e970.
[2]. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003 May;135(5):620-7.
[3]. Sorkin N, Varssano D. Corneal Collagen Crosslinking: A Systematic Review. OPH. 2014;232(1):10-27. doi:10.1159/000357979
[4]. Subasinghe SK, Ogbuehi KC, Dias GJ. Current perspectives on corneal collagen crosslinking (CXL). Graefes Arch Clin Exp Ophthalmol. 2018;256(8):1363-1384. doi:10.1007/s00417-018-3966-0
[5]. Xia Y, Chai X, Zhou C, Ren Q. Corneal nerve morphology and sensitivity changes after ultraviolet A/riboflavin treatment. Exp Eye Res. 2011;93(4):541–547.
[6]. Spörl E, Huhle M, Kasper M, Seiler T. Artificial stiffening of the cornea by induction of intrastromal cross-links. Ophthalmologe. 1997;94(12):902–906.
[7]. Randleman JB, Khandelwal SS, Hafezi F. Corneal cross-linking. Surv Ophthalmol. 2015;60(6):509-523. doi:10.1016/j.survophthal.2015.04.002.
[8]. Grisevic S, Gilevska F, Biscevic A, Ahmedbegovic-Pjano M, Bohac M, Pidro A. Keratoconus Progression Classification One Year After Performed Crosslinking Method Based on ABCD Keratoconus Grading System. Acta Inform Med. 2020 Mar;28(1):18-23.
[9]. Rabinowitz YS. Videokeratographic indices to aid in screening for keratoconus. J Refract Surg. 1995;11(5):371–379.
[10]. Rabinowitz YS. Keratoconus. Surv Ophthalmol. 1998 Jan-Feb;42(4):297-319.
[11]. Meek KM, Tuft SJ, Huang Y, Gill PS, Hayes S, Newton RH, Bron AJ. Changes in collagen orientation and distribution in keratoconus corneas. Invest Ophthalmol Vis Sci. 2005;46(6):1948–1956.

ISSN No:-2456-2165 https://doi.org/10.5281/zenodo.14598591

[12]. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin ultraviolet- A-induced cross-linking. J Cataract Refract Surg. 2003;29(9):1780–1785.
[13]. Kohlhaas M, Spoerl E, Schilde T, Unger G, Wittig C, Pillunat LE. Biomechanical evidence of the distribution of cross-links in corneas treated with riboflavin and ultraviolet A light. J Cataract Refract Surg. 2006;32(2):279–283.
[14]. Chatzis N, Hafezi F. Progression of keratoconus and efficacy of pediatric corneal collagen cross-linking in children and adolescents. J Refract Surg. 2012;28(11):753–758.
[15]. Kymionis GD, Kontadakis GA, Kounis GA, Portaliou DM, Karavitaki AE, Magarakis M, Yoo S, Pallikaris IG. Simultaneous topography-guided PRK followed by corneal collagen cross-linking for keratoconus. J Refract Surg. 2009;25(9):S807–S811.
[16]. Alhayek A, Lu PR. Corneal collagen crosslinking in keratoconus and other eye disease. Int J Ophthalmol. 2015 Apr 18;8(2):407-18. doi: 10.3980/j.issn.2222-3959.2015.02.35. PMID: 25938065; PMCID: PMC4413599.
[17]. Pollhammer M, Cursiefen C. Bacterial keratitis early after corneal crosslinking with riboflavin and ultraviolet-A. J Cataract Refract Surg. 2009;35(3):588–589.
[18]. Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. J Refract Surg. 2009;25(9):S824–S828.
[19]. Wollensak G, Spoerl E, Wilsch M, Seiler T. Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. J Cataract Refract Surg. 2003;29(9):1786–1790.