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Original Research Article

Visual improvement after corneal collagen cross-linking in keratoconus

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ABSTRACT

Purpose: This study was carried out to evaluate the effect of corneal collagen cross-linking on visual acuity, astigmatism and topographic readings (K1, K2, Kapex).

Materials and Methods: A nonrandomized noncontrolled clinical study was conducted in two tertiary eye centres in Bangladesh from July 2017 to June 2019. All attending patients diagnosed with Keratoconus were included in this study according to selection criteria. Patients with a corneal thickness of fewer than 400 microns, previous viral infection, cornea scarring, corneal opacification, severe ocular surface disease, history of immune disorders, pregnancy, and breastfeeding were excluded from the study. All selected patients underwent collagen cross-linking with Riboflavin and Ultraviolet A, followed up five days, one and six months following the procedure. Visual acuity, topographic readings (K1, K2, Kapex) and cylindrical values were assessed on every visit. The mean value of visual acuity was compared statistically with the baseline value.

Results: A total of 30 eyes of 30 patients were studied in this study. The male-to-female ratio was 2:1. The Mean age (± SD) of the study subjects was 22.7±7.10. Before CXL, the Mean uncorrected visual acuity (UCVA) ±SD was 0.86±.35. In post-CXL follow-up time, the mean UCVA±SD was 0.46±.23 after six months of CXL. Before CXL, the Mean BCVA±SD was 0.35±.22. In post CXL era, the Mean ± SD BCVA was 0.14±.13 after six months of CXL. The Mean K1±SD was 45.66±3.43 before CXL, and the result changed after CXL. The Mean K1±SD was 43.29±3.29 after six months of CXL. The Mean K2±SD was 50.22±5.93 before CXL, and the result differed after six months of CXL. The Mean Kapex ±SD was 54.50±7.38 before CXL, and that was 51.32±6.93 after six months of CXL.

Conclusion: Keratoconus is a bilateral non-inflammatory disorder progressively leading to vision-threatening ocular morbidity. Collagen cross-linking improves visual and topographic findings– K1, K2, and Kapex and reduces astigmatism. Early diagnosis of Keratoconus and prompt treatment will help achieve better vision.

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1. Introduction

Keratoconus is a bilateral, non-inflammatory and progressive disorder. It consists of thinning and forward protrusion of cornea, progressive myopia and irregular astigmatism.[1] In Keratoconus, the structural integrity of the collagen matrix was compromised. Patients commonly complain about dimness of vision, increased light sensitivity, severe headache, and difficulty reading, writing, and driving. Corneal Topography is one of the most reliable tools for diagnosis. Previously, spectacles, contact lenses, and corneal transplantation were the choices of treatment.[2] In 2003, Wollensak et al. published a seminal article on corneal collagen cross-linking (CXL) with evidence of using CXL to prevent the progression of Keratoconus. That study stated a case series of patients with progressing Keratoconus who had undergone CXL with riboflavin and ultraviolet A (UVA).[3] Corneal collagen cross-linking (CXL) means the photopolymerization of the stromal fibrillar tissue through the dual action of the photosensitizing substance riboflavin (Vitamin B2) performed with an illuminator in a solid state of UVA with the irradiation of the UV light.[4] Photo oxidation between UVA light (370 nm) and riboflavin (B2 vitamin) is the leading process. UVA light activates riboflavin into a triplet, producing reactive oxygen species (ROS), including singlet oxygen. ROS reacts with collagen fibril molecules in the corneal stroma. It enhances the mechanical strength of the cornea by forming new chemical bonds between amino acids and groups of collagen fibril molecules. CXL is giving excellent results by slowing down or arresting the progression of Keratoconus. Many patients had improved uncorrected and best corrected visual acuity, reduced keratometry readings, and diminished astigmatism.

Keratoconus may finally progress to acute hydrops, corneal scarring etc. and later blindness. Before CXL, keratoplasty was the last destination for Keratoconus. But it was a far cry due to less availability of donor cornea, high cost and other complications. On the other hand, CXL is non-invasive, relatively safer, less time-consuming and free from infections.[5]

Usually keratoconus appears at puberty. Delayed diagnosis leads to rapid progression in paediatric patients.[6–8] CXL is nominated as gold standard for all ages for keratoconous.[9–11]

Corneal collagen cross-linking was introduced in Bangladesh in 2011 in private hospitals. In 2019, it was also started in the Government hospital National Institute of Ophthalmology. The procedure was performed under the direct supervision of expert cornea specialists. It improves the patient's vision after 4 to 5 months of the procedure. Improved refractive status has become the critical point of a patient's improved lifestyle. We attempt to evaluate the outcomes of corneal collagen cross-linking on visual acuity, Astigmatism and Topographic readings (K1, K2, Kapex).

2. Methodology

This nonrandomized, noncontrolled clinical study was conducted by the Ophthalmology department of BIRDEM Hospital and Harun Eye Foundation and Hospital, Dhaka, from July 2017 to June 2019. Patients of Keratoconus eligible for collagen cross-linking are taken as the study population irrespective of age, gender, and occupation. Primary outcome variables include a) Uncorrected Visual Acuity before corneal collagen cross-linking and after corneal collagen cross-linking (after five days, one month, six months), b) Best Corrected Visual Acuity before corneal collagen cross-linking and after corneal collagen cross-linking (after one month, six months), c) Flat keratometry, K1 before corneal collagen cross-linking and after corneal collagen cross-linking (6 months), d) Steep keratometry, K2 before corneal collagen cross-linking and after corneal collagen cross-linking (6 months), e) Steepest keratometry, Kapex before cross-linking and after cross-linking (6 months) f) Astigmatism before cross-linking and six months after cross-linking. A total of 30 cases were included in the study. They were selected purposively. For those who had progressive Keratoconus, an increase in K max of 1 diopter (D) in 1 year, a change in either myopia or astigmatism ≥3 D in 6 months, or a mean central K-reading change ≥1.5 D was observed in three consecutive topographies in 6 months, a mean central corneal thickness decrease ≥5% in three consecutive periods in the previous six months, clear cornea, most negligible corneal thickness is more than 400 microns were included in the study. Those who had corneal scarring, other ocular pathology affecting visual acuity, pregnancy, lactation, systemic collagen or autoimmune diseases, most negligible corneal thickness less than 400 microns, prior ocular surgery, allergic to riboflavin, history of viral infection, corneal opacity, history of poor epithelial wound healing, severe ocular surface diseases were excluded.

Patients were selected according to clinical features. Written informed consent was obtained from all patients. A detailed history was taken. A clinical examination was performed and adequately recorded. Proper ocular examinations were done first by torchlight and then under the Slit lamp. Snellen's and Log MAR charts measured pre-CXL visual acuity (uncorrected and best corrected). Goldmann Applanation Tonometer evaluated intraocular pressure, Ophthalmoscopy was performed to exclude other pathology. Corneal topography was done, and findings were recorded. Post CXL visual acuity (uncorrected and best corrected) was measured after five days, one month and six months. Post-CXL topographic findings would have been recorded after six months. All collected Data were recorded correctly. A proforma was prepared to record

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the data on particulars of the patients and pre-CXL and post-CXL assessments of the patients. CXL induced by riboflavin and ultraviolet A radiation was performed under sterile conditions. Riboflavin, 0.1% solution, was instilled every 10 minutes for 2 hours. Topical anaesthesia was provided by oxybuprocaine 0.4% eye drops preserved instilled every 5 minutes for 15 minutes. One drop of pilocarpine 1% was then instilled to constrict the pupil and reduce ultraviolet A irradiation to the lens and retina. An eyelid speculum was inserted, and riboflavin was instilled over the cornea every 3 minutes for 15 minutes. Ultraviolet A irradiation was delivered using a light link collagen cross-linking machine. Ultraviolet a irradiation was applied to the central 9 mm cornea for 30 minutes, and the riboflavin solution was instilled every 5 minutes. At the ending stage, the eye was rinsed with a balanced salt solution, and a therapeutic bandage soft contact lens was applied. A bandage contact lens was continued for five days. Post-operative Dexamethasone, Moxifloxacin, Artificial tear, and Fluorometholone eye drops were given. Follow-ups were done in the first week, after two weeks, after one month, after three months, after six months and later every six months if there were no complications.

3. Results

A total number of 30 eyes of 30 patients with Keratoconus were evaluated in the study. The Mean age ±SD of the study subjects was 22.7±7.10 (SD) years. The minimum to maximum age was 10 to 35 years. The mean age was 22.7±7.10. Among them, 20 (66.7%) were male and 10 (33.3%) female patients, the male to female ratio was 2:1.

Before collagen cross-linking (CXL), the mean Uncorrected visual acuity (UCVA) was 0.86 (0.86±0.35). The mean UCVA after 5 days of CXL was 0.98 (0.98±0.33), and that was 0.46 (0.46±0.23). The p-value was 0.001 and statistically highly significant (Table 1). Less than, which indicates significant changes after 5 days, 1 month and 6 months.

Before collagen cross-linking (CXL), the Best corrected visual acuity (BCVA) was 0.35 (0.35±0.22). After one month of CXL, it was 0.27 (0.27±0.17), after six months, it was 0.14 (0.14±0.13). The p-value was 0.001 that was statistically highly significant (Table 2).

K1(flat keratomtry) value was 45.66±3.43 diopter before CXL and 43.29±3.29 diopter 6 months after CXL (Table 3). K2 (steep keratometry) reading was 50.22±5.93 diopter before CXL and 47.23±5.75 diopter 6 months after CXL. Kapex (steepest keratometry) reading was 54.50±7.38 diopter before CXL and 51.32±6.93 diopter 6 months after CXL. Cylindrical value was reduced from 4.79±3.35 diopter to 2.55±2.19 diopter. Central Corneal Thickness which was reduced from 467.53±37 micro meter to 425.03±35.82 micrometer.

4. Discussion

Keratoconus is a non-inflammatory acquired condition where cone-like forward protrusion of the cornea occurs, which later leads to corneal distortion, apical thinning and scarring.[12] Corneal collagen cross-linking changes the natural course of Keratoconus by ceasing its progression. Cross-linking is performed by using UVA at 370 nm and the photosensitizer riboflavin that stabilize the collagen matrix of the cornea.[13]

This study's minimum to maximum age was from 10 to 35 years. Maximum patients ranged from 18 to 35 years (73.33%). The mean age was 22.7±7.10. Siddiqui MR et al. study had the same result; the mean age was 21 years.[13] According to Ercüment Bozkurt et al. study, the mean age was 23.87±5.07 years; the age range was 18–34 years.[14] In a study by Sibel Ahmet, the mean age was 26±5 years (min: 18 years; max: 39 years).[15] These studies had a nearer result with this study.

In this study, male patients were 66.67%, and females were 33.33%. In one study, Mauro C. Tiveron et al. had the same result with 66.6% males and 33.4% females.[16] Sibel Ahmet et al. study had 65.0% male and 35.0% female.[15] These studies had a similar result with this study.

According to this study, patients' UCVA was diminished after five days of CXL. But after one month Post CXL follow-up, patients' UCVA showed gradual improvement. After six months, the improvement in UCVA was excellent.

S Rossi et al. study had the same pre-CXL Uncorrected Visual acuity of 0.88±0.19 in Logmar chart.[17] In a study by Sibel Ahmet et al., UCVA was 0.77±0.40 before CXL.[15] According to Siamak et al. study, pre-CXL UCVA was 0.72±0.02.[18] UCVA was reduced in the first week of post-CXL.[19] This study resembles a picture of UCVA after five days of CXL in my study, where UCVA was diminished in the first week. According to Siamak et al., UCVA was improved one month after CXL. In that study, UCVA was improved from 0.72±0.02 to 0.63±0.023 after one month of CXL.[18] This result resembles my study in which UCVA was improved after one month of CXL. According to Sibel Ahmet et al., UCVA was improved from 0.77 ± 0.40 to 0.55 ± 0.31.[15] A study reported that UCVA significantly improved after one month of CXL.[19] According to Guzel Bikbova et al. study, UCVA was improved after one-month post-CXL from 0.61 ± 0.44 to 0.48 ± 0.38.[20] All these studies had improved UCVA after one month of CXL. Sibel Ahmet et al. study had the same results as mine, where UCVA improved from 0.77 ± 0.40 to 0.48 ± 0.28 after six months of CXL.[15] Some other studies had similar results; UCVA was improved six months after CXL from 0.52±0.19 to 0.42±0.2;[19] in Siamak et al. study, UCVA was improved six months after CXL from 0.72±0.02 to 0.54±0.03;[18] in Guzzle Bikbova et al. study, UCVA has improved after six-month posts CXL from 0.61 ± 0.44 to 0.49 ± 0.31;[20] in Ercüment Bozkurt et al. study, UCVA has improved after

Table 1: Distribution of uncorrected visual acuity (UCVA) in different periods

Assessment schedule	Visual acuity (Log MAR)	p-value
Baseline	0.86±0.35	————-
Five days post-CXL	0.98±0.33	<0.001^s
1-month post-CXL	0.70±0.27	<0.001^s
6-month post-CXL	0.46±0.23	<0.001^s

s=significant, p-value obtained by paired t-test

Table 2: Distribution of best-corrected visual acuity (BCVA) in different periods

Assessment schedule	Visual acuity (Log MAR)	p-value
Baseline	0.35±0.22	————-
1-month post-CXL	0.27±0.17	<0.001^s
6-month post-CXL	0.14±0.13	<0.001^s

s=significant, p-value obtained by paired t-test

Table 3: Distribution of topographic readings (K1 = Flat Keratometry, K2 = Steep Keratometry, Kapex = Steepest Keratometry), Cylindrical value, and corneal thickness before CXL and after six months post-CXL

Variables	Before CXL	6 Months After CXL	Results (Paired t-test)
Mean K1 Diopter (D) Mean K1±SD Diopter (D)	45.66 45.66±3.43	43.29 43.29±3.29	P-Value <0.001^s
Mean K2 Diopter (D) Mean K2±SD Diopter (D)	50.22 50.22±5.93	47.23 47.23±5.75	P-Value <0.001^s
Mean Kapex Diopter (D) Mean Kapex±SD Diopter (D)	54.5 54.50±7.38	51.32 51.32±6.93	P-Value <0.001^s
Astigmatism (Cylindrical Value): Mean Cylindrical Value (D) Mean Cylindrical Value ±SD (D)	4.79 4.79±3.35	2.55 2.55±2.19	P-Value <0.001^s
Corneal Thickness: Mean CCT Micrometer Mean CCT±SD	467.53 467.53±37	425.03 425.03±35.82	P-Value <0.001^s

K1= Flat Keratometry, K2= Steep Keratometry, Kapex= Steepest Keratometry S=significant, D- Diopter, p-value obtained by paired t-test

six-month posts CXL from 0.56 ± 0.38 to 0.50 ± 0.29.[14]

In this study, patients' BCVA improved after one month and six months of CXL. This study also showed significant improvement of BCVA after CXL, which is necessary for a better lifestyle for a patient. Siamak et al. study had similarities with my study, which showed marked improvement in vision one month and six months after CXL. In that study, BCVA before CXL was 0.26±0.029, after one month of CXL, it was 0.23±0.015, and after six months of CXL was 0.17±0.015.[18] In a study, the transepithelial CXL group provided more improvement in BCVA.[19] It was also similar to the present study. In Guzzle Bikbova et al. study, BCVA was 0.34 ± 0.29 before CXL; 0.30±0.3, one month after CXL; 0.28 ± 0.28, 6 months after CXL.[20] According to Sibel Ahmet et al., BCVA was also improved one month and six months after CXL; BCVA was 0.36 ± 0.23 before CXL, 0.27 ± 0.24 1 month after CXL and 0.26 ± 0.23 6 months after CXL.[15]

The study showed improved K1 readings after CXL. Less K1 value indicates a more improved condition of Keratoconus. Many studies had similarities with this study. In Guzel Bikbova et al. study, K1 was 44.6 ± 1.12 diopter before CXL and 42.38 ± 1.75 diopters after six months of CXL.[20] Sibel Ahmet et al. study showed diminished K1 readings after CXL. In that study, K1 was 45.50 ± 2.84 before CXL and diminished to 43.32 ± 2.25 6 months after CXL.[15] In Filippello M et al. study, K1 was 45.13 ± 0.97 diopter before CXL and 44.57 ± 1.11 diopter after six months of CXL.[21]

K2 (steep keratometry) reading after six months indicated diminished corneal convexity after CXL. Massimo et al. study had a similar result to my study.[21] In that study, K2 was 51.02±1.10 diopter before CXL and 47.82 ± 0.78 diopters after six months of CXL.[21] Guzel Bikbova et al. showed reduced K2 from 47.80 ± 2.23 diopter to 45.78 ± 2.01 diopter.[20] The Sibel Ahmet et al. study also showed diminished K2 readings after six months of CXL from 48.72 ± 3.08 diopter to 46.81 ± 3.00 diopter.[15]

Kapex (steepest keratometry) was also reduced after six months after CXL. Diminished Kapex is the marker of the arrest of progression of Keratoconus and further improvement of the corneal stroma. Sibel Ahmet et al. study had similarities with this study. It showed diminished Kapex readings after six months of CXL from 54.90 ± 4.81 diopters to 51.98 ± 5.00 diopter.[15] Tian et al.[22] and Mauro C et al.[16] ten studies have the same results that showed a reduction of Kapex readings six months after CXL.

From corneal topographic readings, astigmatism is measured as a cylindrical value. Reduced Cylindrical value signifies improved visual perception and reduced visual morbidity. Guzel Bikbova et al. showed reduced astigmatism from 3.44 ± 0.48 diopter to 2.87 ± 0.67 diopter.[20] Massimo et al. study had a similar result to this study. In that study, astigmatism was 5.89 diopters before CXL and 3.25 diopters after six months of CXL.[21] Mona El Sayed et al. showed reduced astigmatism from 3.44 ± 0.48 diopter to 2.87 ± 0.67 diopter.[23]

In this study, Topographic readings include Central Corneal Thickness which was reduced due to CXL. Sibel Ahmet et al. study had similarities with this study. It showed diminished corneal thickness after six months of CXL from 470 ± 32 micrometres to 404 ± 47.11 diopter.[15] S Rossi et al.[17] had a similar result where the corneal thickness was reduced six months after CXL.

Corneal collagen cross-linking forms new covalent bonds between collagen fibers, which increase the strengthens and the rigidity of the cornea by more than 300%.[24] Excellent outcomes are possible if early diagnosis and rapid interventions were performed.[25]

5. Limitations

This study has limitations. It represents the results at a single Centre only. The results were based on six months follow-up period. So, further evaluation and long-term follow-up are necessary.

6. Conclusion

Corneal collagen cross-linking was helpful in Bangladesh in preventing visual morbidity caused by Keratoconus. Long-term effects of Collagen cross-linking should be studied for detection of future progression. The multi-centre study is necessary to evaluate the outcome. Collagen cross-linking machine, corneal topography and other diagnostic procedures, investigation facilities necessary for CXL and skilled human resources should be available in at least secondary level eye care service centres.

7. Data Availability

Data used to support the findings of this study were included in this article.

8. Ethical Aspect

Patient confidentiality was ensured.

9. Source of Funding

None.

10. Conflict of Interest

None.

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