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Research Article

Outcome of Epithelium-on Versus Epithelium-off Corneal Collagen Cross-linkin in Keratoconus

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Abstract

Purpose: To compare and measure the epithelium on versus epithelium off corneal collagen cross linking in the treatment of keratoconus.

Methods: This interventional study was conducted in the Department of Community Ophthalmology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh and Green Eye Hospital, Dhanmondi, Dhaka, from January 2020 to September 2021. Forty patients with keratoconus were randomly selected to one of the two treatment groups. Twenty patients treated with epithelium on CXL were considered Group I (n = 20), and the other 20 patients treated with epithelium off CXL were considered Group II.

Results: The mean age was 21.95 ± 4.19 years in group I and 20.9 ± 3.35 years in group II. The mean BCVA was 0.48 ± 0.42 logMAR unit in group I and 0.45 ± 0.27 logMAR unit in group II. Keratometry values remain unchanged in both groups except the mean simulated maximum keratometry readings. The simulated maximum keratometry in postoperative day-15 was 52.68 ± 4.02 diopters in group I and 56.51 ± 5.21 diopters in group II. The mean simulated maximum keratometry postoperative day-30 was 52.96 ± 4.02 diopters in group I and 56.6 ± 5.31 diopters in group II. The mean corneal thickness preoperatively was 450.5 ± 38.4 µm in group I and 445.5 ± 33.89 µm in group II. The mean postoperative corneal thickness on day-15 and 30 was 451.85+-38.22 and 451.6 ± 38.43 µm in group I and 437.9+31.38 µm and 438.5 ± 33.51 µm in group II respectively. The mean OSDI preoperative was 16.3 ± 2.23 in group I and 15.2 ± 2.07 in group II. The mean OSDI on postoperative day-1 was 17.15 ± 2.21 in group I and 15.75 ± 2.07 in group II. The mean OSDI on postoperative day-30 was 15.4 ± 2.11 in group I and 15.9 ± 2.38 in group II. The improvement was not statistically significant.

Conclusion: Both procedures can halt the progression of keratoconus. In terms of results and related complications, both treatment procedures are equivalent.

Keywords: Corneal Collagen Cross-linking; Epithelium-Off; Epithelium-on; Keratoconus

Abbreviation

CXL: Corneal Collagen Crosslinking; UDVA: Uncorrected Distance Visual Acuity; BCVA: Best Corrected Visual Acuity

Introduction

Keratoconus is usually bilateral, slowly progressive ectatic condition characterized by central and paracentral corneal stromal thinning, weakening of biomechanical bond, and steepening of the corneal curvatures leading to significant alteration of quality of vision. As a result, vision is blurry and distorted, making daily tasks like reading or driving difficulties. Diagnosis of keratoconus can be made with corneal tomography [1-3].

There are several medical and surgical approaches have been used in the treatment of keratoconus [4].

Corneal collagen crosslinking (CXL) is a minimally invasive procedure is used to arrest the progression of keratoconus. CXL induces crosslinks in the stromal collagen of the cornea. There are two types of CXL- Epithelium off and Epithelium on CXL. The objective of the CXL is to halt the progression of keratoconus by avoiding or delaying the need for corneal transplantation [5,6].

Epi-off CXL is done by debridement of corneal epithelium to enhance the stromal penetration of photoactivated riboflavin. Removal of epithelium involves the risk of corneal infection, severe post-operative paid, sub-epithelial haze,delayed healing, superficial punctatekeratopathy and herpetic activation. In epi-on CXL technique, the epithelial layer of the cornea remains intact, early painless recovery, vision is back to baseline within a day, less postoperative cell loss. But some failure rate is noted in different studies. The clinical effects of epi on CXL corneal curvature have been studied in several studies. Epi on CXL technique shows visual and tomographic changes similar to the epi-off method with superior patient comfort post-intervention. Both techniques could stop progression but many patients had improved quality of vision, reduced keratometric readings and diminished astigmatism [7]. However, our country did not have adequate data on the ophthalmological outcome of epithelial on vs. epithelial off corneal collagen crosslinking in keratoconus. The recent study has been designed to compare the effect of epithelial on vs. epithelial off corneal collagen crosslinking in keratoconus.

Materials and Methods

This interventional study was conducted in Bangabandhu Sheikh Mujib Medical University (BSMMU), Shahbagh and Green Eye Hospital, Dhanmondi, Dhaka, from January 2020 to September 2021. A total of 40 patients with keratoconus were randomly selected to one of the two treatment groups and each group contained 20 patients.

The selection was based on patients with evolving keratoconus with no evidence of corneal scarring, any opacity, central corneal thickness at least 400 μm, age between 15 to 40 years and both male and female. Patients with a history of herpetic keratitis, vernal keratoconjunctivitis, severe dry eye, concomitant autoimmune diseases, pregnancy and lactation and patients with previous intraocular surgery were excluded.

Informed written consent was taken from each patient. All patients were assessed preoperatively by detailed history and clinical examination. Uncorrected distance visual acuity (UDVA) was measured in the LogMAR chart. Best-corrected distance visual acuity (BDVA) measured in LogMAR chart. Anterior segment by Slit-lamp examination and intraocular pressure measurement by Goldmann Applanation Tonometer. Corneal pentacam tomography to detect keratoconus, irregularities on the anterior and posterior corneal surface, corneal astigmatism, and measurement of central and peripheral corneal thickness. Ocular surface disease index questionnaire is used to measure postoperative complication and improvement. Follow-up was done on the 1st, 15th and 30th postoperative days. Keratoconus progression was documented through a clinical and instrumental (tomographic or pachymetric) worsening in the previous 3 months of observation.

CXL is a minimally invasive procedure. Corneal crosslinking uses unique riboflavin eye solution and ultraviolet light from a particular machine to strengthen the collagen fibers in the cornea. Epi-off CXL technique was performed by instillation of 0.5% Proparacaine hydrochloride eye drops for topical anesthesia and to reduce the risk for ultraviolet light exposure. A 9.0 mm corneal epithelium was mechanically removed with all aseptic precautions. Riboflavin (0.1% in 20% dextran solution) was administered topically every 2 minutes for 10 minutes. Then cornea was exposed to UVA 370 nm light which was on pulsed mode for 8 minutes at an irradiance of 30 mW/cm^2 with a total energy of 7.2 J/cm^2. At the end of the

procedure, moxifloxacin 0.5% eye drops were administered and a therapeutic bandage contact lens was then applied. A combination of topical tobramycin and dexamethasone phosphate 0.1% eye drops four times daily for 2 weeks and 0.3% hypromellose eye drop was prescribed. After three days, the therapeutic contact lens was removed. Lubricating eye drops were advised for the next three months. In the epi-on CXL group, corneal epithelial remained intact. Instilling 0.5% proparacaine hydrochloride eye drop corneal imbibition was obtained with two types of riboflavin concentrated solution for soaking. ParaCel-1 (0.25% riboflavin, 0.85% HPMC, 0.02% BAC was applied for 4 minutes then ParaCel-2 (0.22% riboflavin,0.85% HPMC, 0.02% BAC) was applied for next 6 minute. Then cornea was exposed to UVA 370 nm light for 5 minute 20 second. Postoperatively, topical moxifloxacin 0.5% eye drop and 0.3% hypromellose eye drop was prescribed four times daily for 1 week. All patients were operated by the same surgeons with same machine. Follow-up was done on days 1, 15, and then after 1month.

Results

A total 40 eyes of 40 patients with keratoconus were included in this study. The mean age was 21.95 ± 4.19 years, from 15 -30 years in group I and 20.9 ± 3.35 years from 15 - 29 years in group II. The mean age difference was almost similar between the two groups; no statistically significant ($p > 0.05$) difference was observed between the two groups. Figure 1 is showing the distribution of the patients of both groups by age.

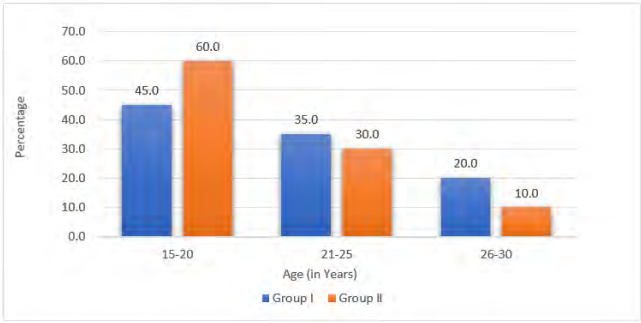

Figure 1: Bar diagram shows the distribution of the study patients by age (Group I is epithelium on and group II is epithelium off).

Table 1 is showing the difference of pre and postoperative BCVA between 2 groups. The mean BCVA preoperative was 0.53 ± 0.4 logMAR unit in group I and 0.4 ± 0.27 logMAR unit in group II. The mean BCVA postoperative day-1 was 0.52 ± 0.41 logMAR unit in group I and 0.45 ± 0.27 logMAR unit in group II. The mean BCVA postoperative day-15was 0.49 ± 0.43 logMAR unit in group I and 0.45 ± 0.27 logMAR unit in group II. The mean BCVA postoperative day-30 was 0.48 ± 0.42 logMAR unit in group I and 0.45 ± 0.27 logMAR unit in group II. The difference was statistically not significant ($p > 0.05$) between the two groups.

BCVA	Group I (n = 20)	Group II (n = 20)	p value
	Mean ± SD (logMAR)	Mean ± SD (logMAR)	
Preoperative	0.53 ± 0.4	0.4 ± 0.27	$^{a}0.236^{ns}$
Range (min,max)	0.2,2	0,1	
Postoperative day-1	0.52 ± 0.41	0.45 ± 0.27	$^{a}0.527^{ns}$
Range (min,max)	0.2,2	0,1	
Postoperative day-15	0.49 ± 0.43	0.45 ± 0.27	$^{a}0.726^{ns}$
Range (min,max)	0,2	0,1	
Postoperative day-30	0.48 ± 0.42	0.45 ± 0.27	$^{a}0.789^{ns}$
Range (min,max)	0,2	0,1	
p value	$^{b}0.086^{ns}$	$^{b}0.212^{ns}$	

Table 1: Distribution of the study patients by BCVA in logMAR units (n = 40).

ns= Not Significant, [a]p value reached from Unpaired t-test, [b]p value reached from Paired test.

The pre and postoperative difference of simulated maximum keratometry between 2 groups is shown in table 2. The mean simulated maximum keratometry preoperative was 53.82 ± 4.12 diopters in group I and 56.49 ± 5.3 diopters in group II. The mean simulated maximum keratometry postoperative day-1 was 53.89 ± 4.16 diopters in group I and 56.49 ± 5.3 diopters in group II. The mean simulated maximum keratometry postoperative day-15 was 52.68 ± 4.02 diopters in group I and 56.51 ± 5.21 diopters in group II. The mean simulated maximum keratometry postoperative day-30 was 52.96 ± 4.02 diopters in group I and 56.6 ± 5.31 diopters in group II. The difference between postoperative day-15 and postoperative day-30 was statistically significant ($p < 0.05$) between the two groups.

Simulated maximum keratometry	Group I (n = 20)	Group II (n = 20)	p value
	Mean ± SD (diopters)	Mean ± SD (diopter)	
Preoperative	53.82 ± 4.12	56.49 ± 5.3	[a]0.083[ns]
Range (min,max)	45.1,60	45,66	
Postoperative day-1	53.89 ± 4.16	56.49 ± 5.3	[a]0.092[ns]
Range (min,max)	45.1,60	45,66	
Postoperative day-15	52.68 ± 4.02	56.51 ± 5.21	[a]0.013[s]
Range (min,max)	45.4,60.1	46.1,65.8	
Postoperative day-30	52.96 ± 4.02	56.6 ± 5.31	[a]0.019[s]
Range (min,max)	45.4,60.1	46.1,65.8	
p value	[b]0.061[ns]	[b]0.468[ns]	

Table 2: Distribution of the study patients by simulated maximum keratometry (n = 40).

s= Significant, ns= Not Significant, ap value reached from Un-paired t-test, bp value from Paired test.

The mean corneal thickness preoperative was 450.5 ± 38.4 µm in group I and 445.5 ± 33.89 µm in group II. The mean corneal thickness postoperative day-1 was 450.5 ± 38.4 µm in group I and 445.5 ± 33.89 µm in group II. The mean corneal thickness postoperative day-15 was 451.85 ± 38.22 µm in group I and 437.9 ± 31.38 µm in group II. The mean corneal thickness postoperative day-30 was 451.6 ± 38.43 µm in group I and 438.5 ± 33.51 µm in group II. The difference was statistically not significant ($p > 0.05$) between the two groups. Figure 2 is showing that there was reduction of corneal thickness postoperatively after epithelium off CXL group.

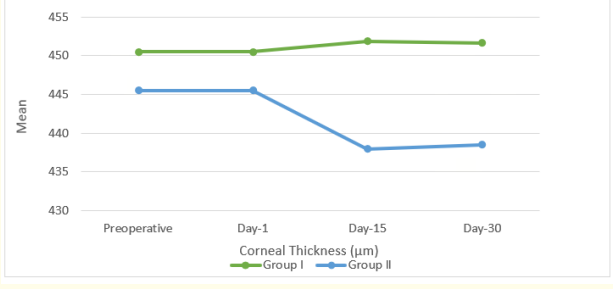

Figure 2: Line chart shows the distribution of the study patients by corneal thickness (Group I is epithelium on and group II is epithelium off).

The mean OSDI score preoperatively was 16.3 ± 2.23 in group I and 15.2 ± 2.07 in group II. The mean OSDI on postoperative day-1 was 17.15 ± 2.21 in group I and 15.75 ± 2.07 in group II. The mean OSDI on postoperative day-15 was 15.7 ± 1.75 in group I and 16.1 ± 1.68 in group II. The mean OSDI postoperative day-30 was 15.4 ± 2.11 in group I and 15.9 ± 2.38 in group II. The difference of postoperative day-1 was statistically significant ($p < 0.05$) between the two groups. Figure 3 is showing, the mean OSDI score increased in patients after epithelium off CXL.

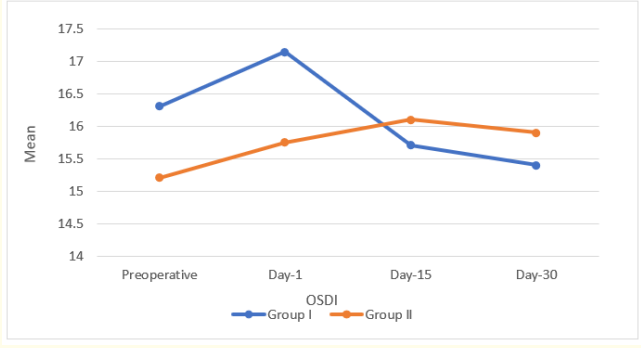

Figure 3: Line chart shows the distribution of the study patients by corneal OSDI (Group I is epithelium on and group II is epithelium off).

Discussion

This study was carried out to measure and compare preoperative and postoperative best-corrected visual acuity (BCVA), central corneal thickness, simulated maximum keratometry in keratoconus patients of both groups. This study also measured and compared preoperative and postoperative Ocular Surface Disease Index (OSDI), preoperative and postoperative complication.

Age is an essential factor that needs to be taken into account with this pathology. In this present study, it was observed that 45.0% of patients belonged to age 15-20 years in group I and 60.0% in group II. The mean age was 21.95 ± 4.19 years, from 15 -30 years in group I and 20.9 ± 3.35 years from 15 - 29 years in group II. The mean age difference was almost similar between the two groups.

Yuksel., *et al.* (2020) observed that the mean age was 20.3 ± 4.6 years in group I and 20.3 ± 4.6 years in group II, which supports the present study [3]. In this current study, it was observed that male predominant, were 100.0% of patients were male in group I and 70.0% in group II. The difference was statistically significant ($p < 0.05$) between the two groups [3,8-10].

In this present study, it was observed that the mean BCVA preoperative was 0.53 ± 0.4 logMAR unit in group I and 0.4 ± 0.27 logMAR unit in group II. The mean BCVA postoperative day-1 was 0.52 ± 0.41 logMAR unit in group I and 0.45 ± 0.27 logMAR unit in group II. The mean BCVA postoperative day-15was 0.49 ± 0.43 logMAR unit in group I and 0.45 ± 0.27 logMAR unit in group II. The mean BCVA postoperative day-30 was 0.48 ± 0.42 logMAR unit in group I and 0.45 ± 0.27 logMAR unit in group II. The mean BCVA was almost similar between the two groups and within the group in all follow-ups; no statistically significant ($p > 0.05$) difference was observed between the two groups.

In a study, it was observed that BCVA showed a significant ($p < 0.05$) improvement between preoperative and 3 and 12-month visits decreasing from 0.17 logMAR preoperatively to 0.12 logMAR at 12 months.

A study found a significant increase in BCVA compared to the baseline was recorded in both groups ($p < 0.05$). The epi-on group exhibits a better outcome compared to the epi-off group at the end of the follow-up ($p < 0.05$). Previous randomized clinical trials were found similar consistent results, which reveal a more vital recovery of BCVA in the comparison of both groups in many studies [11-13]. However, it has been shown that, for progressive keratoconus patients, the standard crosslinking stop the disease's progression in the long term [15].

In this present study, it was observed that the mean simulated maximum keratometry preoperative was 53.82 ± 4.12 diopters in group I and 56.49 ± 5.3 diopters in group II. The mean simulated maximum keratometry postoperative day-1 was 53.89 ± 4.16 diopters in group I and 56.49 ± 5.3 diopters in group II. The mean simulated maximum keratometry postoperative day-15 was 52.68 ± 4.02 diopters in group I and 56.51 ± 5.21 diopters in group II. The mean simulated maximum keratometry postoperative day-30 was 52.96 ± 4.02 diopters in group I and 56.6 ± 5.31 diopters in group II. The mean simulated maximum keratometry was at day-15 and postoperative day-30 showed significantly ($p < 0.05$) higher in group II. Akbar., *et al*. (2017) study observed that the simulated K showed significant reduction with both transepithelial CXL and epithelium off CXL, significantly higher in epithelium off the CXL group, which support the present study.

Kmax usually increases in the first few months after epithelium-off CXL (Hersh., *et al*. 2017) then decreases, and that reduction in Kmax can continue past the first year [15]. Longer follow-up also is essential because the rate of progression of keratoconus is not constant over time. The K-max is one of the main indicators of the biomechanical stability of the keratoconus after CXL.

In this current study, it was observed that the mean corneal astigmatism preoperative was 4.36 ± 1.94 diopters in group I and 5.67 ± 3.09 diopters in group II. The mean corneal astigmatism postoperative day-1 was 4.36 ± 1.94 diopters in group I and 5.67 ± 3.09 diopters in group II. The mean corneal astigmatism postoperative day-15 was 4.26 ± 1.62 diopters in group I and 5.7 ± 3.04 diopters in group II. The mean corneal astigmatism postoperative day-30 was 6.12 ± 8.76 diopters in group I and 5.7 ± 2.98 diopters in group II. The mean corneal astigmatism was almost similar between the two groups and within the group in all follow-ups; no statistically significant ($p > 0.05$) difference was observed between the two groups.

In this current study, it was observed that the mean corneal thickness preoperative was 450.5 ± 38.4 µm in group I and 445.5 ± 33.89 µm in group II. The mean corneal thickness postoperative day-1 was 450.5 ± 38.4 µm in group I and 445.5 ± 33.89 µm in group II. The mean corneal thickness postoperative day-15 was 451.85 ± 38.22 µm in group I and 437.9 ± 31.38 µm in group II. The mean corneal thickness postoperative day-30 was 451.6 ± 38.43 µm in group I and 438.5 ± 33.51 µm in group II. In all follow-ups, the mean corneal thickness was almost similar between the two groups and within the group; no statistically significant ($p > 0.05$) difference was observed between the groups. Similarly, Beckman, (2021) study showed no statistically significant difference in refractive outcomes for minimum corneal thickness. Arance-Gil., *et al*. (2021) obtained in their study that corneal thickness is reduced following epi-off CXL [16].

In this present study, it was observed that mean preoperative OSDI score was 16.3 ± 2.23 in group I and 15.2 ± 2.07 in group II. The mean OSDI score postoperative day-1 was 17.15 ± 2.21 in group I and 15.75 ± 2.07 in group II. The mean OSDI postoperative day-15 was 15.7 ± 1.75 in group I and 16.1 ± 1.68 in group II. The mean OSDI postoperative day-30 was 15.4 ± 2.11 in group I and 15.9 ± 2.38 in group II. The mean OSDI was significantly ($p < 0.05$)

higher in group I but on day 15 and preoperative day 30 was almost similar between the two groups, no statistically significant ($p > 0.05$) difference was observed between two groups. Cifariello., *et al*. (2018) study findings report for the first time Ocular Surface Disease Index (OSDI) difference in patients who underwent CXL and showed the score was significantly ($p < 0.05$) lower in patients of Group II, which support the present study. At the baseline, the score was 4.85 ± 1.18 and 4.98 ± 1.32 OSDI, respectively. After treatment, the score increased to 13.56 ± 2.15 OSDI in group I and 11.26 ± 2.12 OSDI in group II.

Conclusion

Corneal CXL treatment is a relatively new, revolutionary, minimally invasive procedure aiming to stabilize keratoconus. This study was undertaken to compare the epithelium-on versus epithelium-off corneal collagen crosslinking. It was done by creating new chemical bonds between collagen fibrils at the corneal stroma in the treatment of keratoconus. Both techniques seem an equally safe, easy procedure, well-tolerated, effective in treatment with good visual and refractive outcomes.

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