Transepithelial versus standard corneal collagen cross-linking for treatment of grades 1–3 keratoconus

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Purpose The purpose of this article was to assess the safety and efficacy of transepithelial corneal collagen cross-linking (epithelial on) versus standard (epithelial off) technique in halting the progression of keratoconus.

Patients and methods A prospective nonrandomized interventional comparative standard technique was conducted, which divided 40 patients into two groups: in group A, 34 eyes of 24 patients were enrolled and treated by transepithelial cross-linking, and in group B, 28 keratoconus eyes of 16 patients were included and treated by the standard technique. In group A, a solution of riboflavin 0.1%, dextran T500, trometamol, and EDTA (trans-Ribo) was instilled. In group B the epithelium was removed and riboflavin 0.1 solution (10 mg of riboflavin-5-phosphate in a 20% dextran T500 10 ml solution Ricrolin was instilled. Ultraviolet A irradiation (Food and Drug Administration approval) Avedro system was used with total energy 7.2, power intensity 30 mW, induction time 10 min, ultraviolet time continuous 4 min, and ultraviolet time pulse 8 min, but in transepithelial cross-linking, the intensity was 45 mW. Preoperative and postoperative assessments were performed at baseline and 3, 6, and 12 months postoperatively.

Results Group A showed statistically highly significant differences between mean uncorrected visual acuity (UCVA) and mean UCVA at first, sixth, and 12th months postoperatively. In group B, there were statistically highly significant differences between mean UCVA preoperatively and the mean UCVA at first, sixth, and 12th months postoperatively. In group A, there were statistically significant differences between mean Km (mean k power) preoperatively and mean Km at the first and at 12th months postoperatively, whereas in group B, there were statistically significant differences between mean Km preoperatively and the mean Km at first month and statistically insignificant difference at third, sixth, and 12th months postoperatively.

Conclusion Both epithelial-on and epithelial-off techniques appeared to correct best-corrected visual acuity but epithelial-off technique was more effective in reduction of KM, astigmatism, *Q*-value and anterior elevation. Moreover, epithelial off showed to halt keratoconus progression more than epithelial-on technique.

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Introduction

Corneal collagen cross-linking (CXL) is the current treatment able to slow or halt the progression of ectatic disease [1]. According to the standard CXL protocol, the epithelium should be removed before irradiation to allow good penetration of riboflavin into the corneal stroma [2]. Riboflavin acts as a photosensitizer and enhances ultraviolet A (UVA) absorption increasing the efficacy of the CXL process while providing also increased shielding of the deeper ocular structures from excessive UVA [3]. The effect of CXL is based on the augmentation of the number of intrafibrillar and interfibrillar covalent bonds. As riboflavin cannot easily penetrate intact cornea epithelium, removal of epithelium is necessary for the classic CXL procedure (epithelial-off CXL). However, the removal of epithelium can cause severe postoperative pain and temporary visual blurring. To avoid these problems, transepithelial cross-linking (TE-CXL) has been introduced based on the use of a special riboflavin solution which can penetrate the intact epithelium [4]. The aim of this study to evaluate long-term follow-up data of TE-CXL (epithelial on) versus standard (epithelial off) technique in the management of grades 1–3 keratoconus.

Patients and methods

An informed consent was signed after explanation of the procedure. Approval was obtained from the ethical committee of the Faculty of Medicine, Al-Azhar University. In this prospective, nonrandomized, interventional comparative study, patients with bilateral keratoconus grades 1–3 were enrolled from February 2016 to March 2017, and divided into two groups (A and B). Group A (epithelial on) included 34 eyes of 24 patients and group (epithelial off) B included 28 eyes of 16 patients. The study was conducted in Nour El-Hayaha Eye Center (Cairo). Inclusion criteria for the treatment of CXL were documentation of progressive keratoconus by

an increase of at least 1.00 D in the maximum cone apex curvature or an increase of at least 1.00 D in the central corneal astigmatism over the previous 6 months and patients older than 18 years, keratoconus stages 1–3, according to the Amsler classification [5], with a completely clear cornea at slit lamp examination, central corneal thickness (CCT) greater than 400 μm to be treated with standard CXL or CCT between 370 and 400 μm to be treated by epithelial-on technique. Patients with corneal scarring, active ocular infection, autoimmune disorders, pregnancy, lactation, previous ocular diseases, or any other ocular surgery were excluded from the study. All patients underwent a complete ophthalmological examination, which included uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), and corneal topography with the Pentacam (type70700, SN 34822150, Oculus Pentacam; Optikgerate GmbH, D-35582 Wetzlar, Germany). Postoperative follow-up visits were scheduled at first day, first, third, sixth, and 12th months after surgery.

Surgical technique

Topical and systemic antibiotics were prescribed 2 days before surgery. Topical anesthesia using 0.4% benoxinate hydrochloride eye drops was applied to the eye (Benox 4%; Epico Inc., Cairo, Egypt) every 10 min for 30 min. In group A, riboflavin 0.1 solution in 15% Dextran T500 with sodium EDTA 0.01% and trometamol (trans-Ribo) was instilled with soaking time, part 1 every 1:30minute(min) for 4:30 min and part every 1:30 for 6 min. A commercially available UVA system (Avedro, FDA approved) for therapeutic treatment was used (the UV-X devices; Avedro Inc., Waltham, MA, USA), with a total energy of 7.2 J/cm^2 surface dosage and a power intensity of 45 mw. The induction time was 10 min, UV time continuous was 4 min, and UV time pulse was 8 min. Trans-Ribo was kept in the refrigerator at a +4 to +8°C and used immediately during the surgery. At the end of surgery, the eye was washed with balanced salt saline, and eye drops were applied including topical antibiotics (fourth-generation quinolone) and topical steroid (prednisolone acetate 1%), and the patients were instructed to wear sunglasses for 5–7 days. Eye lubricant was used four times daily for 2 weeks. In group B, the epithelium was mechanically removed by surgical Beaver blade within the central 8-mm diameter. An 8-mm zone marker was used to mark the corneal area to be de-epithelialized. The room lights were turned off to avoid damage of riboflavin by light. The riboflavin was instilled every 2 min for 10 min with total energy of 7.2 J/cm^2 surface dosage, power intensity of 30 mW, induction time of 10 min, UV time continuous of 4 min, and UV time pulse of 8 min. Contact lens was applied and was removed after epithelial healing, and in most cases, re-epithelialization took place at the fourth to fifth postoperative day. Moreover, topical antibiotics fourth-generation quinolone and nepafenac 0.1% (Nevanac; Alcon Inc., Fort Worth, TX, USA) were used four times daily for 1 week. The patients were instructed to wear sunglasses for 5–7 days. Eye lubricant was applied four times daily for 1 month. Corticosteroid was prescribed at the fifth day after complete epithelialization to avoid haziness. Follow-up was done after 1 day then 1 week and 1 month. UCVA, BCVA, K_{max}, CCT, and thinnest corneal thickness were recorded at 1, 3, 6, and 12 months.

Statistical analysis

The sample size was calculated according to Raosoft, and all statistical calculations were done using Statistical Package for the Social Science version 20.00; SPSS Inc., Chicago, Illinois, USA. Quantitative data with parametric distribution were done using analysis of variance *t* test. The confidence interval was set to 95%, and the margin of error accepted was set to 5%. The *P*-value was considered nonsignificant at the level of more than 0.05, significant at the level of less than 0.05 and 0.01, and highly significant at the level of less than 0.001. Pearson's linear correlation coefficient (*r*) was estimated to show the relationship between quantitative parameters [6].

Results

This study included 34 eyes of 24 patients in group A, with mean±SD age of 24.33±5.68 years (range, 18.0–30.0 years) and 28 eyes of 16 patients in group B, with mean±SD age of 26.21±4.34 years (range, 19.0–32.0 years). Tables 1 and 2 show baseline characteristics of patients regarding age, sex, and number of patients, and both groups were comparable, whereas Tables 3 and 4 show baseline characteristic of patients regarding UCVA, dioptric power, BCVA, K_1, K_2, Km (Figs 1 and 2), *Q*-value, anterior elevation, posterior elevation, and CCT. Both groups were comparable with insignificant statistical differences between both groups. Group A showed a statistically significant improvement from the baseline value (Table 5), and the mean preoperative UCVA±SD was 0.04±0.02. There were statistically highly significant differences between mean UCVA preoperatively and the mean UCVA at first, sixth, and 12 months, postoperatively (*P*? 0.001, 0.001, 0.001, and 0.001, respectively).

Table 1 Personal data of the first group

	Transepithelial (*n*=24)	*P*-value
Age (years)		
Means±SD	24.33±5.68	0.023
Range	18.0–30	
Sex [*N* (%)]		
Male	8 (33.3)	0.012
Female	16 (66.6)	

Table 2 Personal data of the studied group

	Epithelial-off group (*n*=16)	*P*-value
Age (years)		
Means±SD	26.21±4.34	0.043
Range	19.0–32.0	
Sex [*N* (%)]		
Male	4 (25)	0.016
Female	12 (75)	

Table 3 Preoperative data in the first group

Number of eyes	UCVA	refraction spherical correction	Cylinder	BCVA	K_1	K_2	KM	Astigmatism	*Q*-value	Anterior elevation	Posterior elevation	CCT
4	0.05	–6	–2.25	0.4	49.3	53.1	51.2	3.4	–1.25	52	105	395
3	0.2	–4	–1.25	0.6	48.3	52.1	50.2	2.75	–1.3	49	100	400
5	0.2	–3.5	–0.0.75	0.7	50.2	53.1	51.65	2.25	–0.90	40	103	412
4	0.1	–2.5	–2.25	0.7	48.4	52.3	50.35	3.5	–0.87	42	99	400
3	0.16	–2.5	–3.00	0.8	53.2	54.1	53.65	4.5	–1.25	43	102	410
1	0.3	–2.	–0.0.5	1.0	48.1	52.3	50.2	2.25	–1.1	25	104	402
3	0.1	–3	–2.25	0.8	50.2	54.2	52.2	3.5	–1.25	28	98	400
2	0.16	–2.25	–2.25	0.8	51.2	53.1	52.15	3.25	–1.37	36	61	407
1	0.4	–2.75	–5.25	0.6	49.2	52.4	50.8	6.25	–0.87	28	65	409
3	0.1	–5	––0.2	0.7	51.3	54.1	52.7	3.25	–0.89	30	80	433
2	0.2	–4.25	–2.0	0.8	50.1	53.6	51.85	3.00	–0.1.2	48	55	450
3	0.05	–6.5	–3.75	0.4	50.7	53.2	51.95	4.25	–1.8	45	76	420

BCVA, best-corrected visual acuity; CCT, central corneal thickness; UCVA, uncorrected visual acuity.

Table 4 Preoperative data in the second group

Number of eyes	UCVA	Refr spher	Cylinder	BCVA	K_1	K_2	KM	Astigmatism	*Q*-value	Anterior elevation	Posterior elevation	CCT
2	0.05	–5.5	–1.25	0.3	50.1	54.0	52.05	4.1	–1.05	47	97	441
3	0.16	–3.75	–1.50	0.5	48.3	49.6	50.7	2.75	–1.3	49	89	410
1	0.1	–2.5	–0.1.0	0.6	49.3	52.6	50.95	2.25	–0.90	40	99	433
3	0.16	–2.5	–1.25	0.5	50.2	53.1	51.65	3.5	–0.87	42	105	420
3	0.2	–2.5	–2.75	0.7	52.4	54.2	53.3	4.5	–1.25	43	87	415
2	0.4	–2.	–0.75	0.9	51.2	54.3	52.7	2.25	–1.1	25	67	442
2	0.1	–2.50	–1.75	0.7	52.1	54.4	53.25	3.5	–1.25	28	70	413
3	0.2	–0.75	–3.25	0.7	50.1	53.5	51.8	3.25	–1.37	36	56	417
5	0.3	–1.75	–3.25	0.4	47.4	51.2	49.3	6.25	–0.87	28	49	432
1	0.1	–4.0	–0.2	0.6	48.2	54.1	51.15	3.25	–0.89	30	80	418
1	0.3	–3.75	–2.0	0.6	49.3	52.4	50.85	3.00	–0.1.2	48	70	413
2	0.05	–5.5	–2.75	0.3	48.4	51.4	49.9	4.25	–1.8	48	69	460

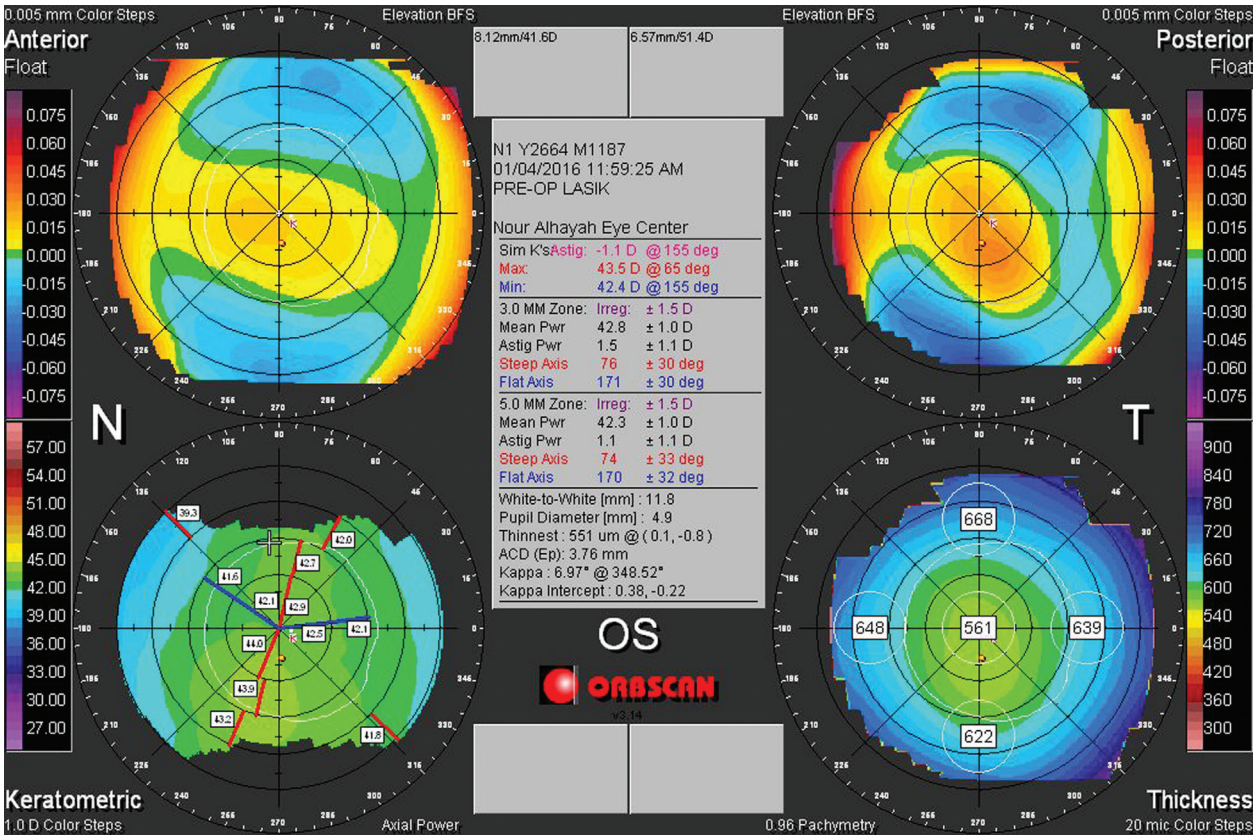
BCVA, best-corrected visual acuity; CCT, central corneal thickness; UCVA, uncorrected visual acuity.

In group B (Table 6), there were statistically highly significant differences between mean UCVA preoperatively and the mean UCVA at first, sixth, and 12th months postoperatively (*P*? 0.001, 0.000, and 0.001, respectively). The differences between mean UCVA in both groups in the follow-up periods were statistically significant at the first, third, and sixth months (*P*? 0.037, 0.002, and 0.002, respectively). The difference between both groups was highly significant at first day between the two groups (*P*? 0.000). There was more improvement in UCVA in group A than in group B (Table 7).

In group A, there were statistically significant differences between mean BCVA preoperatively and the mean BCVA at first and third months (*P*=0.002 and 0.002, respectively), and highly significant differences at sixth and 12 months postoperatively (*P*? 0.001 and 0.001, respectively) (Table 8, Fig. 3).

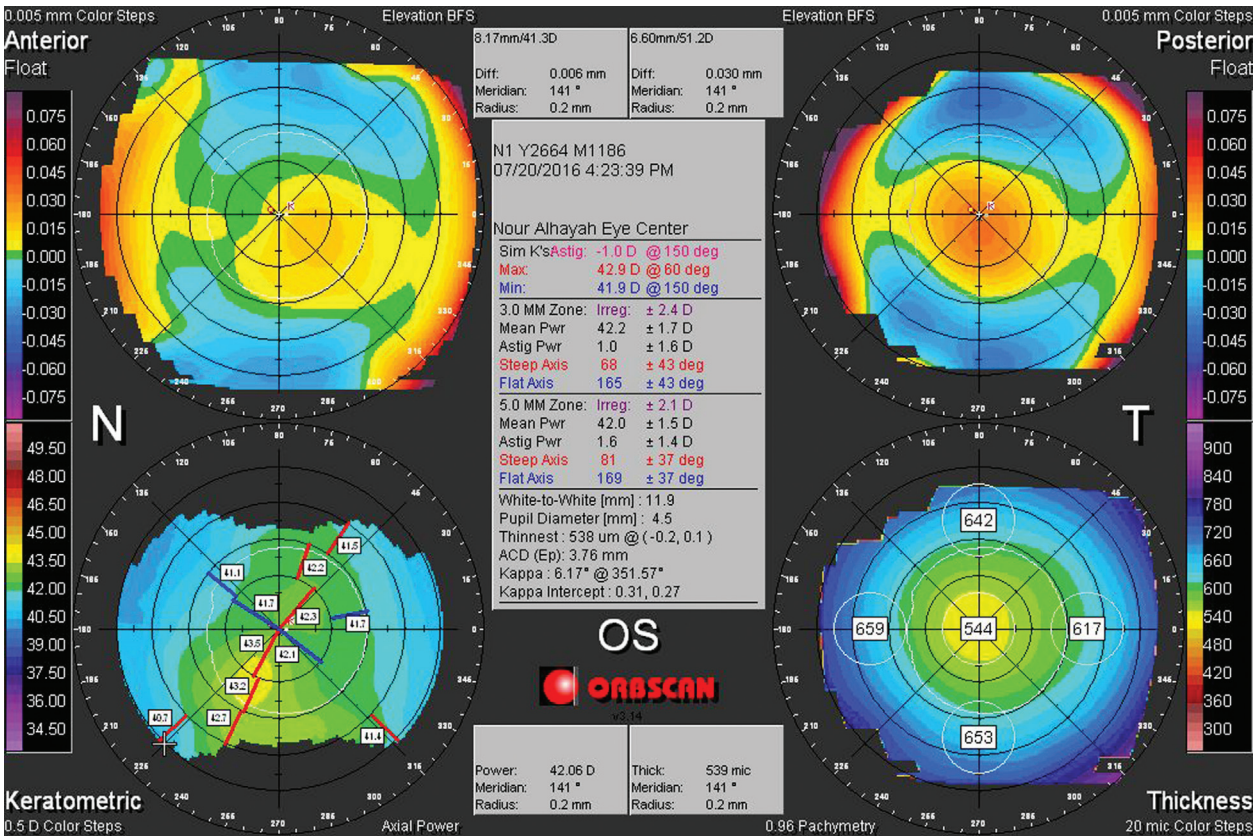
In group B, there were statistically highly significant differences between mean BCVA preoperatively and the mean BCVA at third, sixth, and 12 months postoperatively (*P*=0.001, 0.001, and 0.001, respectively). The difference between mean BCVA in both groups in the follow-up periods were

Figure 1



Preoperative.

Figure 2



Postoperative.

Table 5 Third month follow-up for group 1

Number of eyes	UCVA	Refr spher	Cylinder	BCVA	K_1	K_2	KM	Astigmatism	Q-value	Anterior elevation	Posterior elevation	CCT
3	0.4	–4.25	–0.75	0.5	49.0	50.1	49.55	2.00	–0.76	25	97	419
3	0.3	–2.25	–1.00	0.6	47.3	48.00	47.65	1.25	–1.00	30	89	400
2	0.4	–1.5	–0.1.0	0.6	46.3	47.24	46.77	1.1	–0.75	28	99	440
4	0.3	–1.5	–0.75	0.5	46.1	49.2	47.65	1.75	–0.175	30	105	426
2	0.3	–1.75	–1.75	0.7	48.1	51.2	49.65	2.00	1.75	40	87	402
3	0.4	–1.75.	–0.25	0.8	48.1	50.3	49.65	0.75	–0.86	23	67	408
3	0.2	–1.25	–1.25	0.7	49.3	50.1	49.7	1.25	–0.75	27	70	413
3	0.3	–1.25	–2.00	0.7	46.3	48.2	47.25	1.5	–0.125	30	56	426
4	0.3	–1.50	–1.75	0.5	46.4	48.1	47.25	1.25	–1.20	24	49	450
3	0.2	–2.25	–1.75	0.6	45.2	47.2	46.2	1.00	–0.0.30	28	80	430
3	0.4	–2.25	–1.50	0.6	48.2	50.1	49.15	1.00	–0.04	27	70	455
1	0.2	–4.00	–1.50	0.4	46.1	48.2	47.15	0.75	–0.190	29	69	428

BCVA, best-corrected visual acuity; CCT, central corneal thickness; UCVA, uncorrected visual acuity.

Table 6 Third month follow-up for group 2

Number of eyes	UCVA	Refr spher	Cylinder	BCVA	K_1	K_2	KM	Astigmatism	Q-value	Anterior elevation	Posterior elevation	CCT
2	0.4	–2.75	–0.75	0.5	48.2	49.0	48.6	4.1	–0.48	37	97	440
1	0.4	–2.50	–0.075	0.6	47.6	48.6	48.1	2.75	–1.0	40	89	4.7
3	0.3	–2.0	–0.75	0.6	48.5	48.6	48.55	2.25	–0.1.18	25	99	412
2	0.2	–1.75	–1.00	0.5	49.1	50.1	49.6	3.5	–0.47	24	105	400
2	0.3	–1.75	–1.25	0.6	50.1	51.0	50.55	4.5	–1.00	26	87	400
3	0.4	–1.5	–0.50	0.8	49.1	50.3	49.7	2.25	–1.0	26	67	423
1	0.2	–1.25	–1.25	0.8	50.0	52.4	51.2	3.5	–1.75	36	70	400
3	0.3	–0.75	–0.50	0.9	49.0	50.5	49.75	3.25	–1.25	30	56	415
1	0.3	–1.0..	–2.00	0.8	47.4	48.2	47.8	6.25	–0.76	25	49	4.9
3	0.2	–2.0	–0.25	0.8	47.1	48.1	47.6	3.25	–0.100	25	80	400
4	0.4	–1.25	–1.0	0.7	49.3	51.4	50.35	3.00	–0.50	28	70	399
3	0.3	–3.5	–1.75	0.8	47.4	50.1	48.75	4.25	–0.75	28	69	460

BCVA, best-corrected visual acuity; CCT, central corneal thickness; UCVA, uncorrected visual acuity.

Table 7 Uncorrected visual acuity after cross-linking in both groups

UCVA	Group 1 (mean±SD)	Group 2 (mean±SD)	*P*-value
Preoperative	0.06±0.02	0.08±0.04	0.341
First day	0.26±0.1	2.1±1.0	
P-value	0.001	1.2	0.158
First month	0.30±0.1	0.23±0.08	0.037
P-value	0.001	0.001	
Third month	0.39±0.11	0.25±0.09	0.002
P-value	0.001	0.000	
Sixth month	0.39±0.02	0.25±0.09	0.002
P-value	0.001	0.001	

UCVA, uncorrected visual acuity

statistically significant at third and sixth months (P=0.008 and 0.003, respectively). There was more improvement in BCVA in group A than in group B.

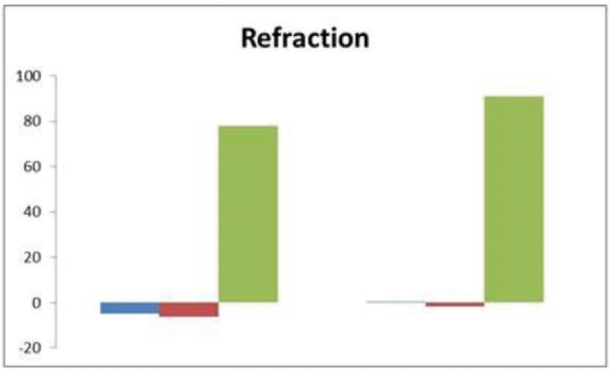
In group A, there were statistically significant differences between mean Km preoperatively and mean Km at the first and at 12 months postoperatively (P=0.003 and 0.031, respectively), whereas in group B (Figs 1 and 2), there were statistically significant differences between mean Km preoperatively and the mean Km (Tables 4 and 5) at first month (P=0.006) and statistically insignificant difference at third, sixth, and 12 months postoperatively (P=0.068, 0.061, and 0.111, respectively). There were statistically significant differences at first, third, sixth, and 12 months (P=0.032, 0.013, 0.011, and 0.009, respectively) regarding mean Km in both groups, as Km was decreased more in group B than in group A during the follow-up period. In group A, mean ±SD

Table 8 Best-corrected visual acuity after cross-linking in both groups

BCVA	Group 1 (mean±SD)	Group 2 (mean±SD)	*P*-value
Preoperative	0.34±0.15	0.08±0.04	0.341
First day	0.51±0.08	0.46±0.14	
P-value	0.002	1.3	0.158
First month	0.59±0.13	.49±0.13	0.007
P-value	0.002	0.001	
Third month	0.69±0.13	0.55±0.12	0.001
P-value	0.001	0.000	
Sixth month	0.70±0.11	0.55±0.11	0.001
P-value	0.001	0.001	

BCVA, best-corrected visual acuity.

Figure 3



Refraction postoperatively left column group (1) and right column group (2) with more improvement in group (1).

topographic astigmatism was decreased at first month (2.25± 1.25 D), at third month (2.1±1.23 D), at 6 months (1.58±1.23 D) and at 12 months (1.72±1.22 D), postoperatively. There were statistically significant differences between mean preoperative and postoperative topographic finding of astigmatism at the end follow-up period (*P*=0.025, 0.004, 0.001, and 0.001, respectively). In group B, there was a decrease in topographic astigmatism more in group B than in group A during the follow-up period. In group A, there were statistically significant differences between preoperative mean *Q*-value and the mean *Q*-value at first and third months (*P*=0.029, 0.36) and statistically insignificant differences at 6- and 12-month postoperatively (*P*=0.268, 0.125). In group B, there were statistically significant differences between preoperatively mean and postoperative mean *Q*-value at first, third, sixth, and 12th-month follow-up period (*P*=0.035, 0.000, 0.001, and 0.001). The differences between mean *Q*-value in both groups in the follow-up periods were statistically significant at first, third, and sixth months (*P*=0.036, 0.019, 0.019, and 0.019, respectively) and statistically insignificant at 12 months (*P*? 0.081). There were more decreases in *Q*-value in group B than group A during the follow-up period. In group A, there were statistically significant differences between preoperative mean anterior elevation and the mean anterior elevation at first, third, sixth, and 12 months postoperatively (*P*? 0.002, 0.0001, 0.001, and 0.0003, respectively).

In group B, there were statistically significant differences between preoperatively mean anterior elevation and the mean anterior elevation at first, third, sixth, and 12th months postoperatively (*P*=0.004, 0.0002, 0.003, and 0.0002, respectively). The difference between mean anterior elevation in both groups in the follow-up periods was statistically insignificant at first day, first, third, and sixth months (*P*=0.342, 0.315, 0.456, 0.453, respectively) with decreased in anterior elevation more in group A than group B during follow-up period. In group A, there were statistically significant differences between preoperative mean CCT and mean CCT at first month (*P*=0.000) and statistically insignificant at third, sixth, and 12th months postoperatively (*P*=0.872, 0.835, and 0.834, respectively).

In group B, there were statistically significant differences between mean CCT preoperatively and the mean CCT at first and third months, postoperatively (*P*=0.010, 0.031, respectively) and statistically insignificant at 6 and 12 months postoperatively (*P*=0.125 and 0.0.37, respectively). The differences between mean CCT in both groups in the follow-up period were statistically insignificant at first month (*P*=0.878) and statistically significant at third, sixth, and 12th months (*P*=0.002, 0.003, and 0.002, respectively). There was an increase in CCT more in group B than group A during follow-up period. No complications such as corneal haze, melting, corneal infection, or endophthalmitis were found in our study.

Mean pain postoperatively was significantly higher in the epithelium-off than epithelium-on group in the first day of surgery (4.3±1.3 vs. 1.1±1.0, respectively, *P*=0.001) with no significant differences at the following 4 days.

Discussion

CXL stiffens the cornea by 300%, increases the collagen fiber diameter by 12.2%, and induces the formation of high-molecular-weight collagen polymers, with a remarkable chemical stability [7].

Combined action of 0.1% riboflavin (photosensitizing agent) and UVA irradiation induces release of single

oxygen that photopolymerizes stromal collagen, reduces the lytic effect of collagenase, and increases corneal resistance to deformation [8].

TE-CXL was introduced with the purpose to reduce the associated complications of corneal epithelial removal in the traditional method [9]. In our study, there was a marked improvement of the visual acuity both UCVA and BCVA postoperatively. There was improvement in UCVA more in group A than in group B, but the differences between mean UCVA in both groups in the follow-up periods were statistically significant at the first, third, sixth, and 12th months, and the improvement was permanent, as seen in another study [10]. There was improvement in UCVA more in group A than group B. Moreover, Caporossi and colleagues reported a temporary increase in both UCVA and BCVA within the first 3 months only [11]. This study is in disagreement with another study reported by Magli *et al.* [8], who stated that UCVA and BCVA improved but not significantly at months 3 and 6 and decreased to baseline values at month 12. In the present study, mean *K*, *Q*-value, and central corneal astigmatism showed improvement in epithelial-off CXL than epithelial-on CXL; this study is closely related to a study conducted by Aydin and colleagues, who reported that the epithelial-off group showed statistically significant improvement regarding mean *K* and central corneal astigmatism, but is in contrary to Akbar *et al.* [12], who reported that the flattening of 1.66 D of K_{max} was attributed to high premax of 62.49 D which tends to flatten more with transepithelial corneal cross-linking in treatment of progressive keratoconus: 12-month 'clinical results'.

Mean CCT decreased at third month of CXL, but then increased gradually and reached to baseline level finally [13]. In this study, the pachymetry at thinnest point on corneal topography decreased significantly from baseline at 1-year follow-up time. This study is closely related to a study reported by Akbar *et al.* [12], who reported that the pachymetry at thinnest point on dual Scheimpflug corneal topography decreased significantly from baseline (*P*? 0.000) at 1-year follow-up visit.

These changes in corneal thickness are owing to lamellar changes and remodeling of corneal stroma after CXL. It seems that there are other parameters rather than the corneal thickness responsible for post cross-linking changes. Few studies evaluated different preoperative parameter effects on post cross-linking outcomes. It was concluded that a thinnest corneal thickness less than 450 μm significantly led to more improvement and flattening in the maximum K [14]. Many study were closely related to this study, which reported weaker or even no effect of TE-CXL in halting the progression of ecstatic cornea [15]. In our study, 35.3% in epithelial-on group showed a keratoconus progression at 12-month follow-up time; this study is closely related to conclusion reported by others [16,17]. Caporossi *et al.* reported that functional results after TE-CXL showed keratoconus instability, in particular in pediatric patients [11]. TE-CLX was significantly weaker and unstable and may be owing to minimal penetration of riboflavin, a hydrophilic molecule, through intact epithelium [18]. The postoperative pain was significantly more in the epithelium-off CXL on the first 4 days postoperative, with no significant differences noted after the fourth day postoperatively.In this study, TE-CLX was shown to be safer than epithelium-off CXL. Photophobia and transient corneal edema were observed in 35%, with almost all patients improving to normal condition in 4 weeks post operative, and this was closely related to Ameen *et al.* [19] and Magli *et al.* [8]. The limitations of this study are the relatively small number of patients and short follow-up limited to one year.

Conclusion

Epithelial on and epithelial off appeared to correct BCVA but epithelial-off technique was more effective in reduction of KM, astigmatism, *Q*-value and anterior elevation. Moreover epithelial-off technique was shown to halt keratoconus progression more than epithelial-on technique.

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Conflicts of interest

There are no conflicts of interest.

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