Comparison of epithelium-off and transepithelial corneal collagen cross-linking for the treatment of keratoconus

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Objective
The aim of the study was to assess the safety and efficacy of epithelium-off corneal cross-linking versus epithelium-on cross-linking in the treatment of keratoconus.

Patients and methods
This study was performed on 42 eyes of 22 patients who were divided into two groups. The first group was the epithelium-off cross-linking (CXL) group that included 23 eyes of 12 patients, whereas the second group was the epithelium-on cross-linking group (the TECXL group) that included 19 eyes of 10 patients.

Results
On comparing the effect of epi-off and epi-on we found that epithelium-on CXL is superior to epithelium-off CXL regarding pain, complications, early patient convalescence as we found significant difference between epi-on and epi-off groups in postoperative complications. In epithelium-on CXL regarding eight (42%) eyes had pain, 0 eye had delayed reepithelization, one (5.26%) eye had stromal haze, and six (31.57%) eyes had treatment failure. However, epithelium-off CXL is superior to epithelium-on CXL regarding the efficacy in visual stabilization and improvement as we found a significant improvement in anterior elevation and K_{max} with P = 0.04 and 0.02, respectively. Epithelium-off CXL had significant reduction in K_{max} with P = 0.03, anterior elevation had significant reduction with P = 0.04 epithelium-on CXL having nonsignificant change in K_{max} and anterior elevation.

Conclusion
Actually, in this study, it was found that TECXL was the procedure of choice for patient comfortability, safety, and convalescence. However, the results of the study confirmed that epithelium-off CXL was the procedure of choice for the patient benefit and guaranteed visual stabilization and additional visual improvement convalescence.

Keywords:
collagen cross-linking, epithelium-off, epithelium-on ultraviolet-A, keratoconus

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Introduction

Keratoconus (KC) is known to be a progressive degenerative corneal disorder that is noninflammatory and mostly a bilateral one. Simply, this disorder is a cone-shaped bulge of the axial cornea, usually displaced inferiorly and characterized by corneal distortion, thin stroma at the conical apex with scarring, and irregular astigmatism [1–3] KC has a prevalence of 1/2000 people every year worldwide with many variations between different studies [4,5].

The specific etiology cannot be defined clearly till now, but KC is widely thought to be a result of genetics, environmental factors, chronic epithelial injury, or irritation [6–8]. These factors may cause keratocytes to slowly decrease by apoptosis leading finally to thin stroma [9].

KC has a specific clinical picture and characteristic slit-lamp appearance, but this requires KC to be in the classic or typical form. Otherwise KC will need other examinations and investigations to be correctly diagnosed specially in the early stages [10]. KC shows corneal thinning of the cone that could be up to 25% of the original normal dimensions. Endothelial reflex at the center of the cone and vertical lines in the deep layers of stroma could be seen. Nerves become more visible appearing as gray lines with small dots, a specific line goes around the cone base known as Fleischer's ring, and ruptures in Descemet's membrane and Bowman's layer [11,12].

Many treatment modalities were used for the management of KC such as spectacles, rigid contact lenses, intracorneal ring segments, corneal collagen cross-linking (CXL), and keratoplasty [5–7]. Corneal collagen CXL has become a widely used procedure [13].

As regarding the outcomes of many management procedures, corneal collagen CXL may be the only known management making it possible to arrest the progression of deformity [13]. CXL initiates photopolymerization of the corneal collagen, initiating further covalent bonds within collagen fibrils and the quaternary structure of the collagen with consequent corneal stiffening along with preserving structural integrity and corneal transparency and maintaining corneal and ocular anatomical and histological structures [14]. CXL is carried out through using ultraviolet A (UV-A) and the photosensitizer riboflavin [15,16].

Patients and methods

This study was a randomized, prospective, comparative double-blinded trial. Forty-two eyes of 22 patients were divided into two groups. The first group was the epithelium-off CXL group that included 23 eyes of 12 patients with mean age of 21.08 ± 5.58 years, whereas the second group was the epithelium-on cross-linking group (the TECXL group) that included 19 eyes of 10 patients with a mean age of 23.1 ± 9.33 years.

The study was conducted between February 2016 and September 2017 at Al-Forsan Eye Center, Assiut, Egypt.

Inclusion criteria were as follows: (a) KC with clear cornea and thinnest location of at least 450 μm in epi-off group and at least 400 μm in epi-on group. (b) Progressive KC that could be documented by subjective deterioration of vision, increase in spherical equivalent of at least −0.75 D over the past 6 months, or increase in steep *K* by at least 1 D over the past 6 months.

Exclusion criteria were as follows: (a) central corneal opacities, (b) history of herpetic keratitis, (c) severe dry eye, (d) concurrent corneal infections, (e) previous intraocular surgery, (f) abnormality in lens or retina on biomicroscopic examination, (g) pregnant and lactating women.

All eyes were subjected to the same preoperative examinations and measurements.

The following preoperative and 6-month postoperative examinations were done and the collected data were documented:

(1) Slit-lamp examination of the anterior and posterior segment
(2) Corneal topography using Pentacam (Oculus Optikgera, Wetzalar, Germany).

Early postoperative follow-up was done by slit-lamp biomicroscopy every other day for 1 week, after 2 weeks, then monthly for 6 months for the evaluation of pain, epithelial healing, and any other complications.

Pilocarpine hydrochloride 1% (Isoptocarpine; Alcon, Sharqueyyah, Egypt) eye drop was given every 10 min for three times to minimize the lens and retina exposure to UV rays. Topical anesthesia was given as benoxinate hydrochloride (one drop every 5 min for four times) (Benox; EPICO, 10th of Ramadan City, Sharqeyyah, Egypt). Skin disinfection was performed by povidone-iodine 10%. Sterile draping was then applied.

The device used was Vega CBM X-Linker (CSO, Florence, Italy). The parameters used were T (time) 9 min, D (dose) 5.4 J/cm^3, and *P* (power) 10 mW.

In the epi-off collagen cross-linking group the type of riboflavin was riboflavin Medio CROSS-M, which is equivalent to 0.1% basic riboflavin in 1.1% HPMC. Riboflavin was kept in a refrigerator at +4 to +8°C and discarded immediately after the surgery.

In the epi-off collagen cross-linking group the type of riboflavin was Medico CROSS-TE riboflavin, which is equivalent to 0.25% basic riboflavin in 1.2% HPMC and enhancers (EDTA) were added to facilitate absorption of riboflavin into the corneal stroma.

Operative procedure was the same in both groups except a corneal area of 8 mm was scraped using a blunt-tipped spatula to remove the epithelium in the epi-off group.

The room lights were decreased in order not to affect the composition and efficacy of riboflavin.

The riboflavin was instilled every 2 min for 30 min. Corneal irradiation with UV-A was performed for 9 min with instillation of the riboflavin every 2 min. Irrigation of the eye by saline was performed. A bandage soft contact lens was applied onto the cornea in the epi-off group. At the end of surgery, eye drops were applied including topical antibiotic moxifloxacin 0.5% (Vigamox; Alcon), topical steroid/antibiotic eye drops: tobramycin 0.3% plus Dexamethasone 0.1% (Tobradex; Alcon), and mydriatic (Mydriacyl; Alcon) followed by eye patching.

All eyes were subjected to the same postoperative treatment. Treatment usually lasted for 2–4 weeks including the following. (a) Antibiotic eye drops: moxifloxacin 0.5% (vigamox; Alcon) hourly at daytime during the first 24 h and then four times daily. (b) Steroi/antibiotic eye drops: Tobramycin 0.3% plus

Dexamethasone 0.1% (Tobradex; Alcon) twice daily from the first postoperative day. (c) Preservative-free tear substitute, carboxymethylcellulose sodium 0.5% (Refresh Plus, Allergan), five times daily. (d) Systemic vitamin A and vitamin C twice daily. (e) Systemic (oral) analgesic and anti-inflammatory three times/day to relief pain until reepithelization, for example, Ibuprofen (Brufen; Abbott) 400 mg three times/day for adults or 200 mg three times/day for children below 18 years. The patient was advised to use sun glasses for 2 weeks.

Early postoperative follow-up was done by slit-lamp biomicroscopy every other day for 1 week, after 2 weeks, then every month for 6 months for the evaluation of pain, epithelial healing, and any other complications.

Data were collected and analyzed using SPSS (the statistical package for the social sciences, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD, while nominal data was expressed in the form of frequency (percentage). Preoperative and postoperative data of each group was compared using the paired *t*-test while postoperative data of both groups was compared using the Student's *t*-test.

Ethical consideration

Informed consent was obtained from each patient approved by the Faculty of Medicine Research Ethics committee.

Results

This study was a randomized, prospective, comparative trial that included 42 eyes of 22 patients. The cases were divided into two groups. The first group was the epithelium off CXL group that included 23 eyes of 12 patients, while the second group was the epithelial on group that included 19 eyes of 10 patients.

The mean age of the epithelial off group was 21.08 ± 5.58 years with a range of between 12 and 33 years and seven (58.3%) patients were men while the other were women. In the case of the epithelial on group, the mean age was 23.1 ± 9.33 years with a range of between 16 and 35 years and six (60%) patients were men while the others were women.

It was noticed that there were no significant differences between both groups regarding age and sex with a *P* value of 0.09 and 0.33, respectively (Table 1).

The severity of our cases according to the keratometric classification

In the collaborative longitudinal evaluation of keratoconus (CLEK) study, keratometry value of the steepest meridian was used to classify KC [17].

There were three eyes in the mild stage (two of epi-off group and one of epi-on group), 25 eyes in the moderate stage (17 of the epi-off group and eight of the epi-on group), four eyes in the advanced stage (four of the epi-off group and eight of the epi-on group), and three eyes in the severe stage (one of the epi-off group and two of the epi-on group).

Preoperative and 6 months postoperative data of the epithelial off group

It was noticed that there was:

(1) Significant improvement ($P < 0.05$) in anterior elevation and K_{max} with $P = 0.04$ and 0.03, respectively
(2) Nonsignificant improvement ($P > 0.05$) in corneal astigmatism, K_1, K_2, K_m, back elevation, and progression index
(3) Significant worsening ($P < 0.05$) in the central corneal thickness and the thinnest location with $P = 0.01$ and 0.02, respectively (Table 2).

Comparison between preoperative and postoperative data of the epithelial on group.

Table 1 Demographic characteristics of both groups

Variables	Epithelial off group	Epithelial on group	*P*
Age (years)			0.09
Mean±SD	21.08±5.58	23.1±9.33	
Range	12-33	16-35	
Sex [*n* (%)]			0.33
Male	7 (58.3)	6 (60)	
Female	5 (41.7)	4 (40)	

P value was significant if <0.05.

Table 2 Preoperative and 6 months postoperative data of the epithelial off group

Variables	Before	After 6 months	*P*
Corneal astigmatism	3.11±1.68	2.91±1.29	0.46
K_1	46.62±3.8	46.21±3.64	0.09
K_2	49.65±4.16	49.52±4.19	0.94
K_m	48.03±5.75	47.61±3.97	0.31
K_{max}	54.55±6.21	52.71±6.39	0.03
Thinnest location	450.01±30.15	442.32±29.4	0.02
Central corneal thickness	461.19±30.03	452.782±24.97	0.01
Distance from the apex to TL	0.91±0.45	0.79±0.349	0.33
Anterior elevation	21.61±10.69	19.1 3±9.097	0.04
Back elevation	40.12±21.98	39.32±17.56	0.36
Progression index	1.88±0.475	0.91±0.555	0.12
Postoperative complications ±time of onset, offset [*n* (%)]			
Pain	17 (75)		
Delayed reepithelization	3 (13)		
Stromal haze	11 (47.8)		
Treatment failure	2 (8.6)		

Data were expressed in form of mean±SD. *P* value was significant if <0.05.

It was noticed that there was unremarkable changes between preoperative and postoperative data of epithelial on group.

(1) Nonignificant improvement ($P > 0.05$) in corneal astigmatism, K_1, K_2, K_m, anterior elevation, back elevation
(2) Nonsignificant worsening K_{max}, central corneal thickness, thinnest location, and the progression index (Table 3).

Changes between preoperative and postoperative data in both groups.

Keratometry: mean changes in steep keratometry were +0.07 D for the A-epi-on group and +0.41 for the epi-off group at 6 months postoperatively. There was no statistically significant difference between preoperative and postoperative values for either group ($P = 0.93$ and 0.09, respectively). The mean maximum keratometry change was +0.1 D for the A-epi-on group at 6 months postoperatively ($P = 0.62$) and +1.84 D for the epi-off group at 6 months postoperatively ($P = 0.03$).

Pachymetry: in the A-epi-on group, mean changes at the TP of the cornea was +1.37 at 6 months ($P = 0.84$). For the epi-off group, the mean reduction values at the TP of the cornea at 6 postoperatively compared with preoperative values were +7.69 mm ($P = 0.02$).

Posterior elevation at the TP: mean changes in the A-epi-on and epi-off groups at 6 months postoperatively were +1.05 and +0.8 mm, respectively. There was no significant difference in either group (P = 0.35and 0.36, respectively).

CXL failure: eight eyes experienced KC progression (considered an increase of 1 D in maximum keratometry at 6 months postoperatively): 31.57% (six eyes) in the A-epi-on group and 8.6% (two eyes) in the epi-off group.

Table 3 Preoperative and 6 months postoperative data of epithelial on group

Variables	Before	After 6 months	*P*
Corneal astigmatism	4.01±1.94	3.96±1.94	0.23
K_1	46.98±4.57	46.91±4.59	0.93
K_2	50.95±4.82	50.91±4.73	0.88
K_m	48.86±4.59	48.81±4.53	0.92
K_{max}	54.81±6.26	55.53±5.84	0.54
Thinnest location	425.63±50.7	424.26±52.31	0.84
Central corneal thickness	440.73±50.47	440.05±51.13	0.62
Distance from the apex to TL	0.863±0.368	0.843±0.463	0.54
Anterior elevation	22.15±9.805	21.05±10.35	0.51
Back elevation	59.52±21.14	58.47±23.32	0.35
Progression index	2.53±1.007	2.75±1.17	0.78
Postoperative complications ±time of onset, offset [*n* (%)]			
Pain	8 (42)		
Delayed reepithelization	0		
Stromal haze	1 (5.26)		
Treatment failure	6 (31.57)		

Discussion

In the epithelial off group, corneal astigmatism showed statistically nonsignificant improvement at a 6-month visit, which was consistent with the results of Elbaz *et al*. [18] and Ozgurhan *et al.* [19].

The results of Badawi [20] found significant improvement of corneal astigmatism at a 6-month visit. This may be due to her usage of a different riboflavin solution.

In the epithelial on group, there was nonsignificant improvement in corneal astigmatism at the 6-month visit, which was consistent with the results of Zhang *et al.* [21].

In the epithelial off group, K_1, K_2, K_m showed statistically nonsignificant improvement at the 6-month visit which was consistent with the results reported by Elbaz *et al.* [18] and Ozgurhan *et al.* [19]. On the contrary, Badawi [20] found significant improvement of K_1 at the 6-month visit, which may be explained by her use of a different riboflavin solution than ours.

In the epithelial on group, there was nonsignificant improvement in K_1, K_2, K_m at a 6-month visit.

In the epithelial off group, K_{max} showed progressive statistically significant improvement at the 6-month visit which was consistent with the results of Badawi [20] and Ozgurhan *et al.* [19]. On the contrary, Elbaz *et al.* [18] and Sherif [22] found a nonsignificant change at the 6-month visit.

In the epithelial on group, K_{max} showed nonsignificant worsening at the 6-month visit which was consistent with the results of Gatzioufas *et al.* [23] and Zhang *et al.* [21].

In the epithelial off group, the thinnest corneal location showed statistically significant thinning at the 6-month visit which was consistent with the results of Badawi [20].

In the epithelial on group, there was a statistically nonsignificant thinning at the 6-month visit, which was consistent with the results of Zhang *et al.* [21].

In the epithelial off group, the thinnest corneal location showed a statistically significant thinning at CCT at the 6-month visit which was consistent with

the results of Sherif [22] and Sadoughi *et al.* [24]. Also, Waszczykowska and Jurowski [25] found a statistically significant thinning at the CCT at all of their postoperative visits.

On the other hand, Ozgurhan *et al.* [19] found a nonsignificant change of CCT at postoperative visits.

In the epithelial on group, the thinnest corneal location showed statistically nonsignificant thinning at CCT at the 6-month visit, consistent with the results of Gatzioufas *et al.* [23].

In the epithelial off group, front elevation showed a statistically significant improvement at the 6-month visit which was consistent with the results of Badawi [20].

This was unlike the results of Chan *et al.* [26] who found nonsignificant change of front elevation at all of their postoperative visits.

In the epithelial on group, front elevation showed a statistically nonsignificant improvement at the 6-month visit, which means stabilization of the anterior corneal surface.

In the epithelial off group, back elevation showed a statistically nonsignificant improvement at the 6-month visit which means stabilization of the posterior corneal surface. On the other hand, Badawi [20] found nonsignificant worsening of back elevation at both postoperative visits.

In the epithelial on group, there was nonsignificant improvement in back elevation at the 6-month visit which was consistent with the results of Zhang *et al.* [21].

In the epithelial off group, the progression index showed statistically nonsignificant improvement at the 6-month visit, ulike the result of Badawi [20] who found significant improvement of average thickness increase.

In the epithelial on group, the progression index showed a statistically nonsignificant worsening at the 6-month visit.

In the epithelial off group, three (13%) eyes out of 23 eyes included in this group had delayed reepithelialization beyond 5 days. This was consistent with the rate of delayed epithelial healing (17.4%) reported by Waszczykowska and Jurowski [25].

In the epithelial on group, immediate postoperative epithelial edema and punctate epitheliopathy were found in all eyes included in this group. These epithelial changes disappeared by the third postoperative day. This finding was a common finding in epi-on studies. Immediate postoperative epithelial changes can range from simple punctate epitheliopathy [27] to even frank epithelial defect as reported by Gatzioufas *et al.* [23].

In the epithelial off group, the anterior stromal haze, of grade 1, was found in 13 (56.5%) eyes out of 23 eyes included in this group. In 10 eyes, the haze cleared at the 6-month visit while the remaining three eyes cleared from haze by the 12th month. This rate of stromal haze was more favorable than the rate of haze reported by Sherif [22] who found anterior stromal haze in 10 out of 14 eyes (71%).

In the epithelial off group, the anterior stromal haze was transient and found in one (5.26%) eye out of 19 eyes included in this group.

In the epithelial off group, the treatment failure was two out of 23 eyes treated in this group giving a rate of 8.6% which was consistent with the failure rate in a previous work by Shetty *et al.* [28] who reported three eyes out of 30 (10%) eyes.

On the other hand, Ng *et al.* [29] found progressive KC after CXL in one eye out of 12 (8.3%) eyes and Waszczykowska and Jurowski [25] found one eye out of 16 (6.25%).

In the epithelial on group, the treatment failure was six out of 19 eyes treated in this group giving a failure rate of 31.57%, whereas Gatzioufas *et al.* [23] reported a relatively higher failure rate of about 46%, where 12 out of 26 eyes showed progressive KC.

Conclusion

Actually, the results of the study confirmed that epithelium-off CXL was the procedure of choice for the patient benefit and guaranteed visual stabilization and additional visual improvement convalescence.

However, it was found that TECXL was the procedure of choice for patient comfortability, safety, and convalescence, but the results concerning visual stabilization improvement is less than that obtained from epithelium-off CXL (high failure rate).

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Conflicts of interest
There are no conflicts of interest.

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