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Topographic Changes in Keratoconic Patients after Transepithelial (Epi-On) Collagen Cross-Linking

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ABSTRACT

Objectives: To evaluate corneal changes as measured by Pentacam before and after transepithelial corneal collagen cross-linking in cases of Keratoconus.

Study design: A prospective consecutive case series study carried out at a private lasik centre

Patients and Methods: 74 eyes of 50 patients with progressive keratoconus underwent transepithelial (Epi-on) CXL using both ParaCel™ and vibeX-Xtra. **Baseline examination included:** full ocular examination, uncorrected visual acuity (UCVA), best corrected visual acuity (BCVA), corneal topography using Pentacam™ to determine; flat corneal curvature (K1), steep corneal curvature (K2), mean corneal curvature (Km), corneal astigmatism, corneal thickness at the thinnest location and posterior surface elevation at the highest point in the central 5 mm. The follow-up visits were scheduled on 3 and 6 months after treatment by checking the BCVA, Pentacam™.

Results: Our results showed an improvements in BCVA at the end of the 6th month post operative that showed an increase from 0.48 to 0.54 and this was statistically significant (P value 0.007) (<0.01), Pentacam topographic changes were found to be decreased postoperatively and were found to be statistically insignificant.

Conclusion: In this study, with a follow-up for 6 months, we found the transepithelial corneal collagen cross-linking is beneficial and safe for patients with keratoconus. Transepithelial CXL treatment appeared to halt keratoconus progression, with a statistically significant improvement in visual acuity by stabilizing or partially reversing the keratectasia process.

Keywords: Cornea**,** KC, CXL, Pantacam

INTRODUCTION

Keratoconus is a usually bilateral non inflammatory progressive corneal thinning that is often of unknown etiology and is characterized by steepening and paracentral reduction of biomechanical strength of cornea and stromal thinning which results in irregular astigmatism and progressive myopia and this eventually leads to a decrease in visual acuity [(1)].

Its incidence in the general population is reported to be approximately one in 2000 [(2)].

Current mainstream therapy is the use of spectacles and rigid contact lenses, intrastromal corneal rings, with penetrating keratoplasty (PKP) reserved for advanced cases or contact lens intolerance [(3)]. Seeking for a way to halt this progressive disease seems to be of crucial importance, corneal collagen cross-linking (CXL, X-linking)) is a recently introduced treatment for addressing progressive keratoconus. Cross-linking is a low-invasive procedure designed to strengthen the corneal structure and stop the progression of keratoconus [(4)].

Two methods for the cross-linking are used; the ”epi-off” technique which involves removal of the central 7mm diameter area of the corneal epithelium followed by application of riboflavin 0.1% solution for a total of 30 minutes.

The other method is the “epi-on” or the transepithelial technique which involves application of two of riboflavin formulations on the surface of the cornea followed by exposing the eye to the UV light for 10 minutes.

Transepithelial crosslinking in which the epithelium is not removed has been proposed to offer a number of advantages over traditional crosslinking including an increased safety profile by reducing the risk for infection as no epithelial barrier will be broken, faster visual recovery and improved patient comfort in the early postoperative healing period.

Recently, evidences had shown that collagen cross-linking (CXL) with riboflavin drops increases the biomechanical strength and stability of the cornea [(5)].

Pentacam imaging is considered among the most prevalent modalities in the diagnosis, staging, and follow-up of keratoconus patients. It is based on a rotating camera and a monochromatic slit-light source, which rotate together. In addition to pachymetry and topographic imaging, pentacam devices provide elevation maps of the anterior and the posterior corneal surfaces [(6)].

Our aim of this study is to evaluate corneal changes as measured by Pentacam before and after

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transepithelial corneal collagen cross-linking in cases of Keratoconus.

PATIENTS AND METHODS

In this prospective consecutive case series study 74 eyes of 50 patients with keratoconus underwent transepithelial (Epi-on) CXL.

The study was approved by the Ethics Board of Al-Azhar University.

➢ **Inclusion criteria:**

1. Age > 15 years old of both sexes with progressive keratoconus documented in the past 12 months with:
- Increase in keratometry reading of greater than 1.00D.
- Increase in spherical refractive error by 0.50D.
- Increase in astigmatism by 1.00D.
2. Maximum K reading ≤ 60 D.
3. Corneal thickness > 400 um at the thinnest location .

➢ **Exclusion Criteria:**

1. Eyes classified as either normal, atypical or keratoconus suspect on the severity-grading scheme as explained in the study.
2. Patients with K-max more than 60 D.
3. Corneal thickness less than 400 um at the thinnest location.
4. Patients with corneal opacity, clinically significant corneal scarring in the CXL treatment zone or any corneal pathology.
5. Patients with history of any previous ocular surgery.
6. Pregnancy or lactation during the course of study.
7. A known sensitivity to study medications.

➢ **Baseline examination included:**

- Full ocular examination.
- Uncorrected visual acuity (UCVA).
- Best corrected visual acuity (BCVA).
- Corneal topography using Pentacam™ (Oculus Inc., Lynnwood, WA), to determine:
  - Flat corneal curvature (K1).
  - Steep corneal curvature (K2).
  - Mean corneal curvature (Km)
  - Corneal astigmatism.
  - Corneal thickness at the thinnest location.
  - Posterior surface elevation at the highest point in the central 5 mm.

Preoperative written informed consent was obtained from the patients. Written informed consent to publish the data of this paper was also obtained from the patients. This study was carried out at a private Lasik centre

➢ **The surgical procedure included:**

1. Topical anesthetic (Benoxinate hydrochloride 0.4%) to the cornea was applied twice, every 5 minutes before the instillation of riboflavin.
2. Lid speculum was inserted
3. Four drops of *Paracel*™ (0.25% Riboflavin, hydroxypropyl methylcellulose [HPMC], NaCl, EDTA, Tris, and BAC) were applied to coat the cornea every 90 seconds, for a total soak of 4 minute. *Paracel*™ allows riboflavin diffusion through an intact corneal epithelium.
4. The cornea was completely rinsed with *VibeX-Xtra*™ (riboflavin phosphate 2.8 mg/ml with sodium chloride). *VibeX-Xtra*™ is used to flush the *ParaCel*™ from the eye and to allow soaking for the remainder of the induction period. Sufficient *VibeX-Xtra*™ was applied to coat the cornea and this procedure was repeated every 90 seconds for a total of 6 minutes.
5. The UV treatment using the CCL Vario device was conducted. Accelerated CXL was for 10 minutes with 9 mW/Cm2 with a total dose of 5400 mJ. The beam was focused on the clear cornea away from limbus to protect the limbal stem cells. The system has a continuously adjustable aperture from 7 mm to 11.3 mm.
6. One to two drops of balanced salt solution (BSS) were applied as needed during irradiation.
7. After the end of treatment, the cornea was rinsed completely with BSS.
8. The eye speculum was removed and postoperative treatment was applied.

Postoperative care:

Antibiotic eye drops (tobramycin 0.3%) and topical steroids eye drops (fluorometholone 0.1%) were given 5 times daily for 2 weeks with tapering of corticosteroid eye drops over another 2 weeks. Artificial eye drops were given for 3 months.

At 5 days and 2 weeks, post operative the operated eye was examined to evaluate corneal haze, oedema and any epithelial abrasions. Re-examination was performed again after 3 and 6 months to evaluate BCVA and record topographic measurements using Pentacam.

RESULTS

The total numbers of subjects was 74 eyes of 50 patients with keratoconus were enrolled in this clinical study. Their age ranged from 15 to 43 years with a mean age of 27.28 (± 6.30) years. Thirty nine patients were females (52.7%) and 35 were males (47.3%).

Table (1): Distribution of demographic data

No. patients		**50**	
No. eyes		**74**	
		No.	**%**
Sex	Female	39	52.7%
	Male	35	47.3%
Age	Mean ±SD	27.28 ± 6.30	
	Range	15 – 43	

Table (2): Comparison between pre-operative and post-operative (3months and 6 months) as regards BCVA

	Pre-operative (N0.=74)	**Post-operative (3 months) (N0.=74)**	**Post-operative (6 months) (N0.=74)**	**One way ANOVA**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**P-value**
BCVA	0.48 ± 0.12	0.51 ± 0.12	0.54 ± 0.14	3.666	0.027
Pot hoc test					
	Pre-operative VS Post 3 months	**Pre-operative VS Post 6 months**	**Post -perative 3 months VS Post 6 months**		
BCVA	**0.199**	**0.007**	**0.158**		

Table (3): Comparison between pre-operative and post-operative (3months and 6 months) as regards k1

	Pre-operative (N0.=74)	**Post-operative (3 months) (N0.=74)**	**Post-operative (6 months) (N0.=74)**	**One way ANOVA**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**P-value**
K1	46.86 ± 3.69	46.70 ± 3.54	46.47 ± 3.83	0.21	0.811
Post hoc test					
	Pre-operative VS Post 3 months	**Pre-operative VS Post 6 months**	**Post-operative 3 months VS Post 6 months**		
K1	0.791	0.52	0.705		

Table (4): Comparison between pre-operative and post-operative (3months and 6 months) as regards K2

	Pre-operative (N0.=74)	**Post-operative (3 months) (N0.=74)**	**Post-operative (6 months) (N0.=74)**	**One way ANOVA**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**P-value**
K2	50.37 ± 4.06	50.26 ± 3.91	50.10 ± 4.09	0.086	0.917
Pot hoc test					
	Pre-operative VS Post 3 months	**Pre-operative VS Post 6 months**	**Post-operative 3 months VS Post 6 months**		
K2	0.866	0.687	0.808		

Table (5): Comparison between pre-operative and post-operative (3months and 6 months) as regards Km

	Pre-operative (N0.=74)	**Post-operative (3 months) (N0.=74)**	**Post-operative (6 months) (N0.=74)**	**One way ANOVA**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**P-value**
Km	48.58 ± 3.77	48.42 ± 3.58	48.37 ± 3.82	0.066	0.936
Pot hoc test					
	Pre-operative VS Post 3 months	**Pre-operative VS Post 6 months**	**Post-operative 3 months VS Post 6 months**		
Km	0.791	0.736	0.934		

Table (6): Comparison between pre-operative and post-operative (3months and 6 months) as regards degree of astigmatism

	Pre-operative (N0.=74)	**Post-operative (3 months) (N0.=74)**	**Post-operative (6 months) (N0.=74)**	**One way ANOVA**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**P-value**
Degree of Astigmatism (diopters)	3.71 ± 1.62	3.57 ± 1.66	3.71 ± 1.65	0.185	0.831
Pot hoc test					
	Pre-operative VS Post 3 months	**Pre-operative VS Post 6 months**	**Post-operative 3 months VS Post 6 months**		
Degree of Astigmatism (diopters)	0.6	0.996	0.597		

Table (7): Comparison between pre-operative and post-operative (3months and 6 months) as corneal thickness at the thinnest location

	Pre-operative (N0.=74)	**Post-operative (3 months) (N0.=74)**	**Post-operative (6 months) (N0.=74)**	**One way ANOVA**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**P-value**
Thinnest location (microns)	451.07 ± 32.20	454.28 ± 33.69	452.99 ± 32.63	0.18	0.836
Pot hoc test					
	Pre-operative VS Post 3 months	**Pre-operative VS Post 6 months**	**Post-operative 3 months VS Post 6 months**		
Thinnest location (microns)	0.552	0.723	0.81		

Table (8): Comparison between pre-operative and post-operative (3months and 6 months) as posterior elevation at the highest point

	Pre-operative (N0.=74)	**Post-operative (3 months) (N0.=74)**	**Post-operative (6 months) (N0.=74)**	**One way ANOVA**	
	Mean ± SD	**Mean ± SD**	**Mean ± SD**	**F**	**P-value**
Posterior elevation at the highest point	41.1 ± 12.09	40.88 ± 12.48	38.7 ± 11.85	0.883	0.415
Pot hoc test					
	Pre-operative VS Post 3 months	**Pre-operative VS Post 6 months**	**Post-operative 3 months VS Post 6 months**		
Posterior elevation at the the highest point	0.913	0.224	0.277		

Table (9): Incidence of complications

Type of complication	Number of eyes	Number of complicated eyes	Percentage
Failure	74	2	2.7%
Haze:	74		
Mild		13	17.5%
Moderate		2	2.7%
Severe		0	0%
Pain	74	35	47.2%
Microbial infection	74	0	0%

DISCUSSION

In this study 74 eyes of 50 patients with keratoconus were included. The age of patients was between 15 to 43 years with a mean age of 27.28 years. Previous studies on keratoconus had a mean age comparable to the mean age in our study [7, 8,9,10].

The study included male and female patients. However, sex was not evaluated as it is known that males and females are equally affected [11].

An epithelium-on accelerated cross linking (CXL) technique was the procedure chosen in our study. It is easy, safe, less painful and has a short recovery period. Some of the published studies had shown similar efficacy of this method to standard epithelium–off techniques [12, 13]. We preferred to do the accelerated cross linking technique (9mW/cm^2 for 10 minutes) instead of the conventional technique (3mW/cm^2 for 30 minutes) aiming to reduce patient discomfort; to achieve more effective time management; and to avoid excessive dehydration and thinning that may occur during 30 minutes period and that may lead to deeper penetration and endothelial toxicity during CXL.

Previous studies had shown that accelerated CXL has comparable results with conventional CXL in arresting the progression of Keratoconu[8,9,10].

BCVA and corneal topographic Pentacam™ parameters were evaluated at baseline repeated and recorded 3 and 6 month after performing CXL.

Our results showed an improvements in BCVA at the end of the 6th month post operative that showed an increase from 0.48 to 0.54 and this was statistically significant (P value 0.007) (<0.01). This may be explained by the flattening of topographic keratometry. However we did not record any significant changes in the degree of astigmatism at any stage of this study.

Caporossi et al. [14] reported no statistically significant increase in BCVA in the first 3 months in cases of keratoconus that were treated with TE-CXL, while ***Koppen et al.*** [15] reported a statistically significant improvement in BCVA at 6 and 12 months in the TE-CLX group.

Bernardo et al. [16] showed significant increase in BCVA in 36 eyes with progressive keratoconus that were treated with TE-CLX after 6 months of follow-up.

The pentacam™ parameters recorded before and after CXL were K_1 ,k_2, K_m, corneal astigmatism, corneal thickness at the thinnest location and posterior surface elevation at the highest point in the central 5mm.

K_1 recorded baseline mean value was 46.86 D and 3 months following CXL the mean K1 was reduced to 46.70 D. Six months postoperatively, the K1 was reduced to 46.47 D. These results were statistically insignificant.

K_2 preoperative mean value was 50.37 D. Three months postoperative K_2 was reduced to 50.26 D. Six months postoperative, the K_2 was reduced to 50.10 D. These results were statistically insignificant.

K_m showed a statistically insignificant decrease by (0.75D). The decrease in K_m is less than the results reported by ***Greenstein and Hersh,*** [17] that was (1.7D).

This statistically insignificant decrease in K_m may account for improvements in BCVA at the end of the 6th month postoperative.

Stojanovic et al. [18] reported significant decrease in the K maximum without changes in the mean K, while ***Soeters et al.*** [19] reported increase of K maximum more than 1 D after 1 year (range 1.3–5.4 D) in 23% of TE group.

Regarding posterior surface elevation, the preoperative mean was 41.1um. Three months postoperative, the mean posterior surface elevation decreased to 40.88um. Six months post operative, the mean posterior surface elevation was 38.7um, this showed a statistically insignificant decrease.

This was consistent with the results obtained by ***Arbelaez et al.*** [20] They studied collagen cross-linking with riboflavin and ultraviolet-A light in keratoconus: One-year results. They found that the mean posterior elevation at the thinnest location was 54.35 ± 29.98 pre-operatively, and decreased to

49.95 ± 28.87 and 50.45 ± 30.45 6 and 12 months respectively. However, they did not find any significant difference in the posterior elevation at the thinnest location and at the apex from pre-operative value, at 6 months and at 1 year post-treatment.

Regarding changes in the corneal thickness at the thinnest location, the results in this study showed that they were statistically insignificant. In other words we can conclude that the corneal thickness had not changed during 6 month after CXL.

Bernardo et al. [(16)] did not report statistically significant changes in the mean corneal thickness at the thinnest point, while another study reported statistically significant reduction of corneal thickness at the thinnest point [(21)].

In ***2014 Razmjoo et al.*** [(22)] studied Pentacam topographic changes after collagen cross-linking in patients with keratoconus and found that most of the parameters and indices had not changed during 1 year after CXL. They concluded that the procedure seems to be effective in stopping the disease progression at least for 12 months after surgery.

Regarding adverse effects of CXL encountered in this study, none of the treated cases had infectious keratitis, sterile infiltrates, endothelial failure, nor progressive ectasia.

Corneal haze occurred in the majority of eyes. Mild haze (grade 1) was observed in 17.5% of eyes within the first 2 weeks. Moderate haze (grade2) was observed in 2.7% of eyes within the first month postoperatively. No eyes with severe haze was seen. The low incidence of haze seen in our study may be explained by using the epithelial on procedure.

The advantages of transepithelial CXL lie in the absence of pain and complications and to early return to contact lens use and daily activities. Its drawbacks include the reduced effect on topographic parameters, which on the contrary, can be improved by conventional CXL.

The role of transepithelial CXL in clinical practice requires further assessment, patients should be informed that improvement of BCVA is a positive effect of the procedure, but the aim is a stable corneal curvature, a parameter that was maintained but not improved in this study.

The main drawbacks of our study are lack of control group and the need of longer follow-up of patients.

CONCLUSION

- In this study, with a follow-up for 6 months, we found the transepithelial corneal collagen cross-linking is beneficial and safe for patients with keratoconus. Transepithelial CXL treatment appeared to halt keratoconus progression, with a statistically significant improvement in visual acuity by stabilizing or partially reversing the keratectasia process.
- The treatment was safe and well tolerated. Its noninvasive nature makes it potentially useful in cases in which epithelial debridement is ideally avoided, such as pediatric cases, uncooperative patients, and thin corneas with thicknesses greater than 400 microns at the thinnest point.
- This clinical and topographic improvement was only partial and did not reach the normal corneal shape or the best visual acuity.
- As proved by our study, visual acuity and corneal shape did not reach normal standards, so it is recommended to use this tool in the battle against keratoconus with other tools as PRK topolinked, INTACS, Stromal CXL with Lasik according to need.

However, more studies with larger sample size and longer follow-up period for years to evaluate long term results of CXL are needed.

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