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Schirmer test type I evaluation before and after collagen cross linking for treatment of keratoconus

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Abstract

Keratoconus (KC) is a bilateral, progressive, asymmetric, non-inflammatory corneal ectasia. The cornea presumes a conical form due to its biomechanical instability leading to irregular astigmatism and reduction in visual quality. To compare Schirmer test results before and after collagen cross linking for treatment of keratoconus conditions using isotonic Riboflavin and Ultraviolet-A light. This comparative study included 60 patients suffering from keratoconus. All patients were randomly selected from the outpatient clinic of memorial institute of ophthalmology and Helwan university hospital and all tested for Schirmer test before and after collagen cross linking 1 week, 1 month, 3-month, 6 months post operative between May 2022 and May 2023. There was positive significant correlation between results of schirmer test after 6 months, age and IOP p= (0.013, 0.010) respectively. There was negative in significant correlation between results of schirmer test after 6 months, UCVA, BCVA, K1, K2, k max, Astigmatism and Thickness (u) p= (0.204, 0.114, 0.491, 0.309, 0.211, 0.390, 0.936) respectively. There are improvements in Schirmer test results after 6 months of CXL for treatment of keratoconus. There is correlation between Schirmer test results with age, UCVA, BCVA, IOP, K reading, Astigmatism and thickness at 1 month postoperative but after 6 months post operative there is only correlation between Schirmer test results and IOP.

Keywords: Schirmer Test, Collagen Cross Linking, Keratoconus.

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1. Introduction

Keratoconus (KC) is a bilateral, progressive, asymmetric, non-inflammatory corneal ectasia. The cornea presumes a conical form due to its biomechanical instability leading to irregular astigmatism and reduction in visual quality. It is almost always bilateral disease, although the clinical features are frequently asymmetrical. The rate of progression varies between individuals and between the two eyes. The severity of the disease can range from mild irregular astigmatism to sever thinning, scaring, and ectasia [1]. The Epithelium keeps the corneal surface smooth and provides a barrier against external biologic agents and chemical damage. The stroma provides structural strength, shape, and stability. It has a natural tendency to absorb fluid from the anterior chamber. The innermost layer of the cornea is the endothelium, a monolayer of hexagonal cells [2]. Corneal collagen cross-linking (CXL) has acquired nowadays popularity for the treatment of progressive corneal ectasia. This technique stabilizing the progression of keratoconus and decreases the chance of corneal transplantation through an increase of the corneal biomechanical strength [3]. Corneal cross-linking leads to apoptosis of keratocytes in the anterior stroma at the early stage after CXL as evident by a stromal demarcation line appearing at a depth of ~300 μm of cornea when viewed under confocal microscopy, which may represent a boundary between cross-linked and non-cross-linked areas [4]. The aim of this study was to compare Schirmer test results before and after collagen cross linking for treatment of keratoconus conditions using isotonic Riboflavin and Ultraviolet-A light.

2. Patients and methods

This comparative study included 60 patients suffering from keratoconus. All patients were randomly selected from the outpatient clinic of memorial institute of ophthalmology and Helwan university hospital and all tested for Schirmer test before and after collagen cross linking 1 week, 1 month, 3-month, 6 months post operative between May 2022 and May 2023.

2.1. Inclusion criteria

Keratoconus in cases below 40 years of age, Pachymetric reading > 400μm at the thinnest point of the

cornea as measured by Pentacam and Steep keratometry (Km) reading under 55.0D as measured by Pentacam.

2.2. Exclusion criteria

Patients did not fulfil the inclusion criteria above, any other previous surgical interference or previous collagen cross-linking, corneal opacity of any kind, nursing or pregnant patients, age above 40 years old, background systemic disease such as Diabetes Mellitus (D.M.) or collagen vascular disease and Patients who refuse to sign the consent.

2. 3. Methods

All patients were subjected to the following:

Detailed medical and ophthalmic history, a complete ophthalmic examination was performed including Uncorrected and best corrected visual acuity, anterior segment examination by slit lamp, posterior segment examination a+ 90 diopters lens for slit lamp fundus biomicroscopy, IOP measurement by the Goldmann applanation tonometer and Schirmer test (figure 2).

All patients were assessed for corneal curvature and astigmatism by: Refraction: Uncorrected visual acuity and Subjective best corrected visual acuity and **Pentacam:** Pentacam was used to assess patients' corneal topography, keratometry and pachymetry. The value of K1, K2 and KMAX were determined together with the size, site and centralization of the corneal cone. The amount of corneal astigmatism was measured. The corneal thickness was measured, as well as the thickest and thinnest locations were determined (figure 1).

2. 3.1. Operative Procedure

All our patients were tested for Schirmer test before the procedure. Schirmer's test uses paper strips inserted into the eye for several minutes to measure the production of tears. Both eyes are tested at the same time. Most often, this test consists of placing a small strip of filter paper inside the lower eyelid (inferior fornix). The paper was then removed, and the amount of moisture was measured. After five minutes, the patient was asked to open both eyes and look upward so the test strips may be removed. The Schirmer test score was determined by the length of the moistened area of the strips (using the scale packaged with the strips). All results were recorded then all cases underwent photo-oxidative corneal collagen cross-linking using riboflavin and UV-A light after epithelial debridement of the central 8-9 mm of the cornea.

2. 3.1.1. Anesthesia

All cases were conducted under topical anesthesia (Benoxinate HCL drops) instilled twice for 2 minutes before the procedure.

2. 3.1.2. Operative details

After applying the eyelid speculum, an 8-mm diameter marker was used to mark the corneal epithelium in a central circle. Epithelium was removed in the central 8-9 mm with a blunt metal spatula. De-epithelialization was followed by instillation of riboflavin (AVEDRO ™ Vibex Rapid). Every 2 minutes for 20-30 minutes until the stroma was filled with riboflavin. After confirming the presence of riboflavin in the corneal tissue and anterior chamber by (slit-lamp biomicroscopy), UVA irradiation was applied. The UVA irradiation was performed using an optical system at nearly 5 cm distance and exposed to UVA 365 nm light for 30 minutes at an irradiance of 3.0 mW/cm2.

2. 3.2. Postoperative medication

The postoperative treatment was as follows:

Topical combined both steroid and antibiotic drop were administrated in all patients 5 times daily for 4 weeks with monitoring intra-ocular pressure (IOP) then, will be tapered to 4 times / day for the next week then 2 times / day for the next 2 weeks. Lacrimal substitutes (preservative-free artificial tears) were administered 4 times daily for 4 to 6 weeks.

2.4. Ethical consideration

The informed consent form, and all written information were reviewed and approved by the Ethics Committee of Helwan University. The nature of the study was explained to each patient prior to surgery including its purpose, the procedure, the benefits, the expected duration, the potential risks involved, any discomfort may be caused and possible complications.

3. Results and Discussion

Regarding demographic data, mean age of the study population was 25.15 ± 4.74, number of females and males were 25 and 35 respectively. Percent of affected eye was 57.3% for right eye and 42.7% for left eye (Table 1). There was highly statistically significant improvement in UCVA and schirmer test within 6 months after treatment among the studied patients P <0.001 (Table 2). There was highly statistically significant change in K1, and K max and Astigmatism results within 6 months after treatment among the studied patients p<0.001, but there was no significant change in BCVA, IOP, K2 and thickness (0.586, 0.160, 0.323, 0.253) respectively. (Table 3). The previous table show that there were highly statistically significant changes in schiemr test results and IOP, K1, K2 and Kmax at 1 month post operative p= (0.023, 0.005, 0.008, 0.027) (Table 4). There was positive significant correlation between Result of schirmer test after 6 months, age and IOP p= (0.013, 0.010) respectively. There was negative in significant correlation between result of schirmer test after 6 months, UCVA, BCVA, K1, K2, k max, Astigmatism and Thickness (u) p= (0.204, 0.114, 0.491, 0.309, 0.211, 0.390, 0.936) respectively (Table 5). The thinning of the cornea in KC may be due to tissue degradation that involves the remodeling of the extracellular matrix as a result of collagen deficiency and increases in the levels of proinflammatory cytokines, cell adhesion molecules, and matrix metalloproteinases (MMPs) [7,8]. The main results of our study were as following: In the current study there is statistically decrease in Schirmer test results then followed by significant improvement in the results within 6 months after treatment among the studied patients. These results are in accordance with the previous study done by, Taneri et al. where he used other tests such as staining with fluorescein, RB and TBTT to examine the impact of CXL on the ocular surface and there was not a statistically significant effect after 3 and 6 months [9]. The findings suggest that potential limbal stem cell injury during the CXL procedure has no significant effect resulting in postoperative dry eye.

Figure 1: Pentacam topography (OCULUS Pentacam) [5]

Table 1: Demographic data and characteristics of the studied patients

		Total no. of patients = 60
Sex	Female	25 (41.7%)
	Male	35 (58.3%)
Age (years)	Mean ± SD	25.15 ± 4.74
	Range	17 – 30
Eye	OD	43 (57.3%)
	OS	32 (42.7%)

OD: (oculus dexter) (right eye) OS: left eye (Oculus sinister)

Table 2: Follow-up for UCVA and schirmer test among the studied patients

		Pre-operative	After 1 week	After 1 month	After 3 months	After 6 months	Test value	P-value	Sig.
UCVA	Mean ± SD	0.27 ± 0.45	0.07 ± 0.25	0.19 ± 0.39	0.26 ± 0.44	0.24 ± 0.43	27.926≠	<0.001	HS
	Range	0 – 1	0 – 1	0 – 1	0 – 1	0 – 1			
Result of schirmer test (ml)	Mean ± SD	13.03 ± 2.50	11.49 ± 1.80	12.93 ± 2.08	13.41 ± 1.90	14.01 ± 1.66	50.821•	<0.001	HS
	Range	8 – 18	8 – 16	9 – 18	9 – 18	9 – 17			

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Repeated Measures ANOVA test; ≠: Friedman test

Table 3: Follow-up for BCVA, IOP, K1, K2, K max, astigmatism and thickness among the studied patients

		Pre-operative	After 1 month	After 3 months	After 6 months	Test value	P-value	Sig.
BCVA	Mean ± SD	0.73 ± 0.45	0.72 ± 0.45	0.69 ± 0.46	0.68 ± 0.47	1.935≠	0.586	NS
	Range	0 – 1	0 – 1	0 – 1	0 – 1			
IOP	Mean ± SD	11.21 ± 2.47	11.16 ± 2.44	10.68 ± 1.60	10.87 ± 1.56	1.822•	0.160	NS
	Range	7 – 17	6 – 19	8 – 15	8 – 14			
K1	Mean ± SD	44.57 ± 3.00	43.99 ± 2.18	43.88 ± 1.95	43.88 ± 1.98	5.169•	0.020	S
	Range	40 – 64	39 – 49	40 – 49	40 – 49			
K2	Mean ± SD	47.13 ± 2.76	51.80 ± 45.05	46.39 ± 2.48	46.37 ± 2.49	0.991•	0.323	NS
	Range	42 – 53	41 – 436	42 – 53	42 – 53			
K max	Mean ± SD	50.55 ± 3.71	50.03 ± 3.67	49.91 ± 3.45	49.85 ± 3.41	9.230•	<0.001	HS
	Range	43 – 57	42 – 57	42 – 57	42 – 56			
Astigmatism	Mean ± SD	-1.76 ± 2.79	-1.28 ± 2.78	-1.21 ± 2.52	-0.92 ± 2.56	17.461≠	0.001	HS
	Range	-6 – 6	-6 – 4	-5 – 4	-5 – 4			
Thickness (µ)	Mean ± SD	459.75 ± 35.07	458.45 ± 35.49	457.47 ± 34.00	457.53 ± 33.54	1.389•	0.253	NS
	Range	400 – 538	393 – 530	395 – 525	400 – 525			

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
•: Repeated Measures ANOVA test; ≠: Friedman test

Table 4: Correlation for schirmer test with age, UCVA, BCVA, IOP, K reading, Astigmatism and thickness at 1 month postoperative

	Result of schirmer test after 1 month	
	r	**P-value**
Age (years)	-0.043	0.713
After 1 month		
UCVA	0.118	0.315
BCVA	0.035	0.767
IOP	**0.262***	**0.023**
K1	**-0.320****	**0.005**
K2	**-0.305****	**0.008**
K max	**-0.256***	**0.027**
Astigmatism	-0.159	0.174
Thickness (u)	**0.265***	**0.022**

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
Spearman correlation coefficient

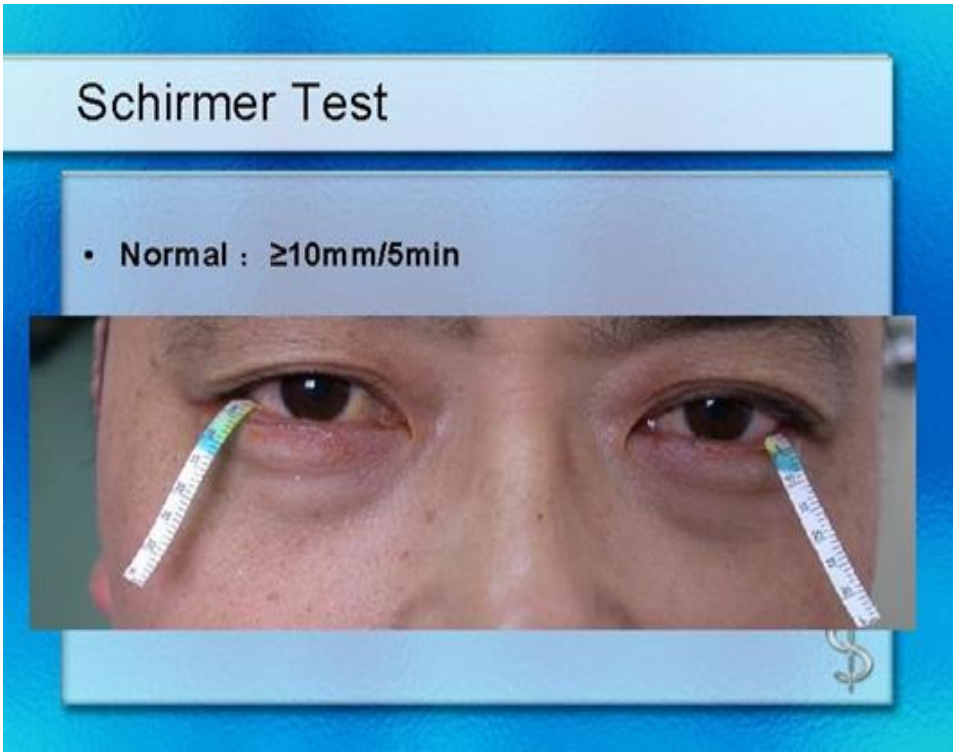

Figure 2: Schirmer test [6

Table 5: Correlation for schirmer test with age, UCVA, BCVA, IOP, K reading, Astigmatism and thickness 6 months postoperative

	Result of schirmer test after 6 months	
	r	**P-value**
Age (years)	**0.286***	**0.013**
After 6 months		
UCVA	-0.148	0.204
BCVA	-0.184	0.114
IOP	**0.295***	**0.010**
(K1	-0.081	0.491
K2	-0.119	0.309
k max	-0.146	0.211
Astigmatism	0.101	0.390
Thickness (u)	-0.009	0.936

P-value > 0.05: Non-significant; P-value < 0.05: Significant; P-value < 0.01: Highly significant
Spearman correlation coefficient

Additionally, a potential damage to corneal nerves during the CXL procedure does not appear to affect the surface lubrication after 3 months [9]. Another study done by Wang et al. where he enrolled 34 keratoconic patients and he used both techniques of CXL (EPI-ON or EPI-OFF). He reported that the changes in ocular surface disease index (OSDI), average Noninvasive Keratograph breakup time (NIKBUT), and bulbar redness were more obvious in the EPI-OFF group preoperatively and at 12 months postoperatively [10]. In the current study there is a statistically significant change in IOP results within 6 months after treatment among the studied patients and these results are in accordance with the reclad study. The current study shows a statistically significant improvement in UCVA within 6 months after treatment and these results are in accordance with Rosa, Rosa study sample consisted of 20 eyes where he used either EPI-OFF or EPI-ON technique unlike the current study only EPI-OFF CXL where used [11]. In the current study there is correlation between Schirmer test results with age, UCVA, BCVA, IOP, K reading, Astigmatism and thickness at 1 month postoperative but after 6 months post operative there is only correlation between Schirmer test results and IOP. In the current study there are statistically significant changes in IOP, K1, K2 and Kmax after 6 months post operative and these results are in accordance with many studies like (Rosa, 2015). The study reported that all topographic parameters (Kmin, Kmax, and mean K) showed a statistically significant improvement after 12 months post-surgery. Another study done by Spadea & Mencucci reported that there was a small reduction in (Kmax values) and in keratometric astigmatism in all patients. In spadea study there was a small mean reduction in the curvature values (reduced up to 4.3 D) and in of apical ectasia (Kmax keratometry astigmatism (reduced up to 5.3) in all patients. All these results were in accordance with results of the current that shows significant change in kmax values after 6 months of treatment [12]. In this study there are no statistically significant changes in BCVA 6 months after treatment unlike other study done by Cifariello et al. that showed a significant increase in BCVA compared to the baseline [3]. In cifariello study he used both techniques (EPI-ON or EPI -OFF) on 40 patients unlike the current study only EPI-OFF technique was used. He mentioned that despite the different stromal penetration between the two techniques, the clinical outcomes after CXL showed that keratoconus was relatively stable after 24 months, and no differences were observed comparing the two procedures. In the current study patients didn't report history of atopy or allergic conditions unlike Cunha et al., that reported that Twenty-five patients had a documented history of atopy (allergic asthma, atopic dermatitis, allergic rhinitis) or eye rubbing [13]. Also, there is no significant change in the corneal thickness after 6 months of CXL and these results are in accordance with the previous study done by Spadea & Mencucci [12]. The study reported that the central corneal thickness remained stable to ±10 µm in all patients. Unlike another study done by Cifariello et al that reported after 2 years follow up there was

a significant change in the mean corneal thickness after the CXL procedure [3]. Finally, the cornea is one of the most densely innervated tissues in the human body. Removal of the corneal epithelium and UVA exposure during CXL can cause damage to the subepithelial nerve plexus, which can cause decreased corneal sensitivity and adversely affect blinking and basic tear secretion. But after the epithelium starts to grow the symmetry of the corneal surface will occur which will lead to a smoother corneal surface. A healthier corneal epithelium formed after CXL, will result in better quality and a higher quantity of tear film [9].

4. Conclusion

There are improvements in Schirmer test results after 6 months of CXL for treatment of keratoconus, suggesting repair of corneal nerves and improvement in corneal sensitivity postoperatively. Also, the improvement in corneal topographic parameters after 6 months suggests an overall improvement in the corneal shape. There is correlation between Schirmer test results with age, UCVA, BCVA, IOP, K reading, Astigmatism and thickness at 1 month postoperative but after 6 months post operative there is only correlation between Schirmer test results and IOP.

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