Efficacy of UVA-Riboflavin Corneal Collagen Cross-Linking Therapy in Keratoconus Patients

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ABSTRACT

Purpose: The aim of this study was to assess the efficacy of corneal collagen cross-linking (CXL) with riboflavin using ultraviolet-A (UV-A) light on cornea parameters in patients with progressive keratoconus.

Materials and Methods: This is a retrospective study included 53 eyes of 28 patients aged between 16 and 40 years with keratoconus who underwent corneal riboflavin induced UV-A CXL. Slit-lamp examination, visual acuity tests in a decimal scale converted to logMAR data, central corneal thickness (CCT), and intraocular pressure (IOP) measurements were performed. Corneal topography was used to examine the maximum K value of the apex (Kmax), the minimum K value of the apex (Kmin), Sim K, anterior chamber depth (ACD), Kappa angle, mean power and astigmatic power in the 3.0 mm and 5.0 mm central corneal zone at 1th, 6th and 12th months.

Results: The mean age of the patients was 24.26 ± 5.06 years (range of 16-40 years). Follow-up period was 1 year. There was a reduction in the Kmax value at the end of 1 year by 1.15 D ($p < 0.001$). There was a decrease in the CCT in 1th month 445.69 µm to 391.09 µm and then to 404.47µm in postoperative 12th month ($p < 0.001$). The mean ACD was 3.26±0.23 mm preoperative and increased to 3.31±0.23 mm at 1th month, 3.30±0,25mm at 6th month and 3.29±0.24 mm at 12th months ($p<0.001$, $p=0.021$, respectively). There was no difference in kappa angle between the follow-up times.

Conclusion: CXL is a safe and effective technique to prevent the progression of keratoconus and also effective in delaying or reducing the need of the surgery.

Keywords: Corneal Cross linking, Keratoconus, Riboflavin A, Kmax, Anterior chamber depht.

INTRODUCTION

Keratoconus is a degenerative non-inflammatory eye condition where the cornea loses stability gradually.[1] The loss of stability leads to an increase in stromal thinning.

Mostly, keratoconus occurs bilaterally in adolescent years. It results in corneal thinning, protrusing, progressive myopia and irreguler astigmatism.[2]

Corneal collagen cross-linking (CXL) was first introduced by Wollensak et al as a technique to slow or stop the progressive of keratoconus.[3] The cross-linking procedure, significantly increases the biomechanical strength of the human cornea by up to 330% from that time CXL is an internationally accepted practice for the treatment of progressive keratoconus.[4] This procedure can delay or stop the progression of keratoconus and reduce the need for further surgical interventions.

In CXL, a riboflavin (vitamin B2) solution, reacts photochemically in the presence of ultraviolet-A (UV-A) light in the corneal stroma, forming free oxygen radicals. The photochemical reaction causes to form additional covalent connections between collagen fibers, which improves stability of the cornea.

There are many studies supporting that CXL therapy using photosensitizer riboflavin and UV-A light is effective for stopping the progression of keratoconus and post-refractive surgical corneal ectasia.[5-10]

The aim of our study was to evaluate the change in refractive and corneal parameters using Orbscan imaging

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during 1-year follow-up after CXL, performed according to the classic Dresden protocol.

MATERIALS AND METHODS

In this retrospective study, we enrolled 53 eyes of 28 patients with keratoconus who underwent corneal riboflavin induced UV-A cross-linking.

All procedures followed the Declaration of Helsinki rules and written informed consent was obtained from all patients. Ethics committee approval was obtained from Adana City Training and Research Hospital (local ethics committee-approval no:912, approval date: 03.06.2020). The inclusion criteria for the study group was to have keratoconus without any systemic disorder. The exclusion criteria included the following; any previous ocular surgery, history of eye trauma, intracorneal ring implants, or a history of delayed wound healing and systemic diseases.

Slit-lamp examination, visual acuity tests in a decimal scale converted to logMAR data, central corneal thickness (CCT), and intraocular pressure (IOP) measurements were performed; in order to identify numerical data, corneal topography (Orbscan II (Bausch and Lomb, Rochester, NY, USA)) was used. The maximum K value of the apex (Kmax), the minimum K value of the apex (Kmin), Sim K, anterior chamber depht (ACD), Kappa angle, mean power and astigmatic power in the 3.0 mm and 5.0 mm central corneal zone were recorded.

Corneal topographic measurements were performed after a comprehensive ophthalmologic examination, before CXL, and at 1, 6, and 12 months after CXL.

Corneal crosslinking protocol

The procedure was performed under topical anesthesia. Sterilization of the periocular region and ocular area with povidone-iodine was achieved before surgery. Full thickness epithelial debridement was performed in the central corneal region of 8-9 mm using a blunt blade. 0.1% in 20.0% dextran (500 000 Da) iso-osmolar riboflavin solution (G. Streuli & Co. AG) was applied to the corneal surface at intervals of 5 minutes for 30 minutes to ensure sufficient penetration into the corneal stroma. During the procedure, UVA light of 370 nm was irradiated with a radiant energy of 3 mW/cm² (5.4 J/cm2) for 30 minutes. The calibration of irradiation was achieved by using a UVA light-meter (UV Light Meter YK- 35UV, Lutron, Taipei). During the UVA exposure, one drop of riboflavin solution was instilled every 5 minutes to the corneal surface.

After the procedure, a bandage contact lens was attached. Topical antibiotic drops were recommended 4 times a day for a week, and after the corneal epithelium healed, the bandage contact lens was removed and topical corticosteroid drops (1% prednisolone acetate) were recommended 4 times a day for 4-6 weeks. To increase ocular comfort, all patients received protective free artificial tears 4 times a day for a month.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences software version 20.0 (IBM Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the appropriateness of calculations to normal distribution. The Wilcoxon signed rank test was used for variables with no normal distribution. A 5% level of significance were adopted; therefore, results with a p value <0.05 were considered significant.

RESULTS

A total of 53 eyes of 28 patients were analyzed; the mean age of the patients was 24.26 ± 5.06 years (range of 16-40 years). 17 were male (60.7%) and 11 were female (39.3%). The CXL was performed unilaterally in 3 patients and bilaterally in 25 patients.

Table 1 shows the best corrected visual acuity (BCVA), CCT, corneal topograhy findings before and after CXL.

There was statistically significant difference in parameters of BCVA, Kmax, Kmin, CCT, mean power of 3.0 mm and 5.0 mm central zone between the pre-op and postop 1st month, pre-op and postop 1st year ($p<0.05$) (Table 1).

There was no difference in kappa angle between the repeated measurements.

There was a reduction in the Kmax value at the end of 1 year by 1.15 D, which was statistically significant ($p <0.001$).

There was a decrease in the CCT (445.69 µm preoperative and 404.47µm postoperative first year, $p< 0.001$), which was statistically significant. No complications such as corneal haze that would affect the corneal thickness were encountered in any of the patients during the follow-ups.

The mean ACD was 3.26±0.23 mm preoperatively, at first month it was 3.31±0.23 mm, at 6th month 3.30±0,25mm and after 12 months it was 3.29±0.24 mm. The difference was statistically significant ($p<0.001$, $p=0.021$, respectively).

DISCUSSION

Keratoconus is a progressif disease, which is exactly unknown etiology, accused of genetic and environmental factors. Conical shape that happens in the cornea in keratoconus, gives rise to change of the topographic and

Table 1: *Clinical and topographic ophthalmologic measurements compared before and 1 and 12 months after surgery*

Parameters	Before Surgery (mean±SD)	1 months after surgery (mean±SD)	P	12 months after surgery (mean±SD)	P
BCVA (logMAR)	0.30±0.05	0.22±0.04	0.332	0.10±0.06	<0.001*
Kmax (D)	49.76±4.51	49.47±4.54	0.110	48.61±4.21	<0.001*
Kmin (D)	45.26±3.21	45.00±3.40	0.006*	44.64±3.25	<0.001*
Sim K	4.49±2.73	4.46±2.49	0.858	4.27±2.53	0.118
Mean power 3.0 mm zone (D)	46.61±2.87	46.31±3.07	0.007*	46.03±2.90	<0.001*
Astigmatic power 3.0 mm zone (D)	3.66±2.25	3.64±2.19	0.828	3.62±2.18	0.901
Mean power 5.0 mm zone (D)	44.71±2.05	44.43±2.19	<0.001*	44.46±2.12	0.002*
Astigmatic power 5.0 mm zone (D)	2.11±1.28	1.91±1.01	0.378	2.17±1.06	0.384
CCT	445.69±44.40	391.09±68.58	<0.001*	404.47±64.43	<0.001*
Kappa Angle	5.72±1.19	5.74±1.43	0.313	5.72±1.40	0.636
ACD	3.26±0.23	3.31±0.23	<0.001*	3.29±0.24	0.021*

BCVA: best corrected visual acuity, CCT: Central corneal thickness, ACD: Anterior chamber depht

refractive values of the cornea. In 26.8% of keratoconus patiens have advanced progression which needs to corneal transplantation.[11] Nowadays keratoconus is still the first indication of corneal transplantations.[12] CXL is a procedure that firstly described by Wollensak et al and then developed by other researchers according to the basic principals, accepted to prevent or slow down progression in keratoconus.

Actually, progression factors for keratoconus is variable. The general opinion is that progression is more aggressive and rapid in young patients. Many factors that may affect keratoconus progression have been investigated in studies; more than 1 diopter increase of corneal refractive power, more than 3 diopter increase of the myopia, or 1.5 diopter increase of the astigmatism, more than 1.5 diopter increase of the corneal refractive power, and thining of cornea more than 5%.[13] But there is no standard guideline for disease progression.

Visual acuity loss is not accepted as a progression index, because it is subjective data and visual acuity test results of keratoconus patients shows unstability in every visits.[14]

Seyeden et al applied CXL on one eye of 26 patients in 2015, and concluded that Kmax value decreased significantly in a year compared to control group.[15] Hersh et al compared 102 patients applied on CXL with 103 sham treated patients and reports that significant difference in Kmax value at the end of the 12 months follow up.[16] Henriquez et al reported, mean difference of Kmax value was 2.21 diopter in 12 months, when compared patients with control group in their study.[17]

In accordance with the literature, in this study significant improvement of the Kmax and best corrected visual acuity at the end of 12 months was determined. Also Kmin value and mean refractive power of 3 and 5 mm zone were decreased significantly. On the other hand, there is no statistically significant difference in astigmatic power of 3 and 5 mm zone. According to these results; CXL stops progression or even makes regression. Witting-Silva et al, in their study with 100 patiens followed up for 3 years, reported that 1.75±0.38 diopter increase of maximum corneal refractive power in patients with progressive keratoconus and, -1.03± 0.19 diopter decrease in patiens applied CXL.[18]

Vinciquerra et al, reported that significant decrease of CCT at the end of 12 months.[19] Greenstein et al, in randomised controlled study, reported the decrease of pachymetric measurements in the first month, reversed to the preoperative value at the end of 1 year.[20] In our study, we also found statistically significant decrease of CCT at the end of the first month, but we still found statistically significant lower measurements compared to the preoperative measurements at the end of the 1 year. Nevertheless, there were thicker CCT measurements at the end of the 12 months, according to the first month. This findings was commented on, as shown in 3 years of follow up in literature, CCT return to preoperative measurements in time.

Sheehan et al reported 7 years follow up results in 34 eyes of 24 CXL applied patients, they reported that there were no statistically significany difference between

the preoperative and postoperative ACD.[21] Toprak et al also reported no significant change in anterior chamber parameters.[22]

Polat et al. reported that this increase in ACD became apparent postoperative 6. month and was maintained till 1st year. They claimed that due to the corneal stiffness after CXL, which results of the flattening of the peripheric cornea and indirectly increasing pressure on iris-lens diagram, increase of the ACD in cases with early keratoconus.[23] Similar to this study, we determined statistically significant increase in ACD in the first month and also 12 months follow up in our study. We thought that this results due to lower Kmax value and stable cornea in our patients.

One of the limitation of our study is that there is no control group and we have not compared them with the cases who get other treatment options or get no treatment. The other limitation is short follow up time. Studies have shown that keratocyte regeneration starts at the 3rd month after the procedure and is completed in the 6th month, that the lost subepithelial and stromal nerves are revived in the 12th month and corneal sensitivity reappears.[24] It is reported that corneal epithelium is more thin and more homogenized after CXL.[25] It has been found that cornea is return back to it's original volume in 24 months.[26]

It is known that keratoconus shows more rapid progression in young patients. Most important mechanism of CXL is improvement of cornea stiffness by remodeling of the stromal collagen bound.[27] Age factor must consider when compare the effectivity, as one of the most important factor that affect corneal stiffness is age. The strong side of the study is that study group is homogene and consist of young patients.

In conclusion, CXL is seen as effective in preventing the progression of keratoconus, delaying or reducing the need of the surgery. However, randomized prospective studies, in large series and with long follow up, will show us corneal changing period and effectivity of CXL.

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