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ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2017, 6(9): 45-49

Long-Term Outcome of Corneal Cross-Linking for the Treatment of Progressive Keratoconus

Ladan Saffarian Toosi[1*], Hamid Khakshour[2], Habibollah Esmaily[3] and Ramin Daneshvar[2]

[1]Department of Ophthalmology, Mashhad Branch, Islamic Azad University, Mashhad, Iran

[2]Eye Research Center, Mashhad University of Medical Sciences, Mashhad, Iran

[3]Faculty of Health, Mashhad University of Medical Sciences, Mashhad, Iran

**Corresponding e-mail: alijavadi401@gmail.com*

ABSTRACT

Purpose: *Corneal collagen cross-linking (CXL) is a promising method in the treatment of keratoconus (KCN); however, long-term results of this treatment modality are under-represented in the literature. In this article, we describe outcome of CXL in a cohort of patients after 4 years of follow-up.* ***Materials and methods:*** *CXL with corneal epithelium removal was done in patients with progressive clinical keratoconus. Full set of ophthalmic examination and scanning slit corneal topography were done for patients before intervention and on regular postoperative follow-up examinations.* ***Results:*** *One hundred thirty-two eyes of 66 consecutive subjects were enrolled in the study with a mean follow-up period of 48 months. Uncorrected distant visual acuity improved from preoperative value of 0.26 ± 0.21 to 0.36 ± 0.23 Snellen acuity in last follow-up exam (p=0.0008). Mean keratometry decreased from 46.18 ± 2.36 D before CXL to 45.6 ± 2.37D in last follow-up (p=0.0480). Similarly, maximum keratometric value were 49.05 ± 3.75 and 47.93 ± 4.14, in preoperative exam and at last postoperative visit, respectively (p=0.0226).* ***Conclusion:*** *CXL results in reduction of keratoconus progression and improvement of visual acuity in long-term follow-up.*

Keywords: Keratoconus, Corneal collagen cross-linking

INTRODUCTION

Keratoconus (KCN) is a usually bilateral, non-inflammatory, progressive corneal ectasia that results in corneal protrusion, irregular astigmatism and decreased vision [1,2]. Keratoconus is the most common indication for corneal transplantation surgery [3]; however, cornel collagen cross linking (CXL) is the procedure that may halt the progression of keratoconus [4] and other corneal ectasia [5] and could potentially reduce the demand for corneal transplants. It was first introduced by Spoerl and colleagues in 1998 [6]. In conventional method, riboflavin administered topically to de-epithelialized cornea serves as a photosensitizer that is activated by ultraviolet A (UVA) light and through a set of chemical reactions results in increased corneal stiffness [6].

Several studies support the role of CXL in the management of keratoconus; however, there is a paucity of long term data. According to some studies long term efficacy and safety of CXL are uncertain [7]; indeed, there are few publications with more than 5 years of follow up.

In these study, we present results of corneal collagen cross-linking in 132 eyes of 66 patients with progressive, clinical keratoconus and with a mean follow-up period of more than 4 years.

MATERIAL AND METHODS

This was a prospective clinical study in 132 eyes of 66 subjects with progressive KCN conducted at an eye center in north eastern part of Iran.

Written informed consents were obtained from all participants and the study adhered to the tenets of Declaration of Helsinki. The definition of progressive keratoconus was made as an increase in the maximum cone apex curvature of more than one diopter (D) or increase in corneal astigmatism of more than one diopter within a year and subjective deterioration of vision.

Exclusion criteria were central or paracentral corneal scars, corneal thickness less than 400 micron, active ophthalmic inflammation or infection, previous refractive or other corneal surgery, pregnancy, breast feeding and sever dry eye.

The following assessments at baseline and postoperative visits were performed: uncorrected visual acuity (UCVA; expressed in logarithm of the minimum angle of resolution (log MAR) units), best corrected visual acuity (BCVA; expressed in log MAR), dry and cycloplegic refraction (after instillation of cyclopentolate 1%), slit lamp and fundoscopic examination, intraocular pressure (IOP) measurement with Goldmann applanation tonometry (Haag-Streit AG, Koeniz, Switzerland), and corneal topographic and pachymetry values, derived from Orbscan-II (Bauch and Lomb, Rochester, NY, USA).

All of the surgeries were performed by a single surgeon with the same technique. Topical anaesthetic drop (tetracaine 0.5%) was instilled twice. Mechanical epithelium removal of central 8 mm area of the cornea was performed using a no. 57 Beaver blade under sterile condition.

Riboflavin 0.1% solution (10 mg riboflavin in 10 ml dextran 20% solution) was instilled every 2 min for 24 minutes. Adequate penetration of riboflavin was confirmed by slit lamp examination and riboflavin application was continued every four minutes during ultraviolet A exposure.

A calibrated UV-X device (UV-X 1000 IROC, Zurich, Switzerland) was used to deliver UV-A irradiation. The instrument was set at a safe working distance of 5 cm from the corneal surface with medium size UV rays aperture at the wave length of 370 nm and a surface irradiance of 3 mw/cm^2. The instrument was calibrated with UV-A meter, provided by the manufacturer, to control the desired levels of irradiance before each treatment.

After treatment, the eyes were rinsed with sterile saline solution. One drop of chloramphenicol 0.5% was instilled and a bandage contact lens was inserted (CIBA Vision, Duluth, GA, USA).

After surgery chloramphenicol 0.5% and betamethasone 0.1% eye drops were continued four times a day for one week. Subsequently betamethasone was replaced with fluorometholone acetate 0.1% (Flarex, Alcon laboratories, France) given four times daily for one week then tapered on a weekly-basis over the next 4 weeks.

Postoperative examinations were carried out at day one, 7th day and one month, 3, 6, and 12 months and then every 6 months after surgery.

We used one sample Kolmogorov – Smirnov test for investigating the normality of data distribution. Mean and standard deviation were used to describe the data. Paired sample t-test was used to look for statistical significance of observed changes in the study parameters. Statistical significance level (p value) was set at 0.05 level. The study had a pre-calculated power of 80%. All statistical analysis was done using the SPSS version 12 software (SPSS Science Inc, Chicago, IL).

RESULTS

This article represents the results of 132 eyes of 66 patients with a mean follow up of 4 years.

The mean age of included subjects was 22.58 ± 4.20 years (range from 14 years to 36 years). Thirty-four (51.5%) subjects were female.

The UCVA improved in 55 (41.6%) eye. Twenty-one (15.9%) eyes gained two or more lines of UCVA.

The mean UCVA improved 12 months after surgery from 0.26 (Snellen equivalent, decimal unit) to 0.36 (Snellen equivalent, decimal unit) ($p<0.0001$) and UCVA improved from 0.26 (Snellen equivalent, decimal unit) to 0.36 (Snellen equivalent, decimal unit) after mean follow up period of 48 months ($p<0.0001$).

The mean BCVA increased from 0.89 preoperatively to 0.90 (Snellen equivalent, decimal unit) postoperatively after one year ($p=0.358$) and 0.90 after mean follow up of 4 years; the difference was not statistically significant.

The mean preoperative spherical refractive error was -1.45 ± 2.30 diopters, the mean cylinder was -3.68 ± 1.80 diopters and mean spherical equivalent (SE) was -3.27 ± 2.43 diopters. Postoperatively the mean sphere was -1.34 ± 2.22 diopters, the mean cylinder was -3.12 ± 1.83 diopters and the mean SE was -2.89 ± 2.41 diopters (Table 1).

Table 1 Comparison of baseline and last follow-up clinical characteristics of 132 keratoconic eyes after corneal collagen cross-linking (CXL) with a follow-up period of 48 months

Parameter	Before CXL Mean ± SD	Last follow-up after CXL Mean ± SD	p-value
UCVA	0.26 ± 0.21	0.36 ± 0.23	0.0008
BCVA	0.89 ± 0.15	0.90 ± 0.15	0.35
K_{min}	44.81 ± 2.61	44.18 ± 2.51	0.046
K_{max}	49.05 ± 3.75	47.93 ± 4.14	0.0226
K_{mean}	46.18 ± 2.36	45.6 ± 2.37	0.048
Sphere	-1.45 ± 2.30	-1.34 ± 2.22	0.7203
Cylinder	-3.68 ± 1.80	-3.12 ± 1.83	0.0144
CCT	468.89 ± 42.61	450.87 ± 52.87	0.0025
SE	-3.27 ± 2.43	-2.89 ± 2.41	0.2217

BCVA: Best Spectacle Corrected Visual Acuity; CCT: Central Corneal Thickness; Cylinder: Cylindrical Refractive Error; K_{max}: Maximum Keratometric Value; K_{mean}: Mean Keratometric Value; K_{min}: Minimum Keratometric Value; SE: Spherical Equivalent; UCVA: Uncorrected Visual Acuity

K_{max} improved 1.18 diopters on a mean follow up period of 48 months (p=0.0226). Twenty-one eyes improved at least 2 diopters between baseline and 48th month.

Dividing the patients into 3 groups according the baseline K_{max} (Group A, K_{max} < 50.00 D, Group B, K_{max} = 50.00 – 54.00D and Group C, K_{max} > 54.00) showed that more changes occurred in group A.

Mean baseline corneal pachymetry was 468.89 ± 42.61 (range 400 to 554) microns. One year postoperatively, the mean corneal thickness was 450.87 ± 52.87 microns (Table 1).

Slight transient corneal haze was seen in 53 eyes (40.1%); however, no significant complication including corneal endothelial cell loss, limbal vasculature changes, lens or retinal problems was seen.

DISCUSSION

CXL seems to have an important role in halting the progression of keratoconus. Despite increasing popularity of CXL in recent years in different parts of the world, long term studies are still limited [7,8].

Our study is important regarding to two points: the large number of patients and the long period of follow up. There are few published studies with such long-term results [9,10]. The short-term results of current cohort of subjects were first published in 2010 in which we reported a 0.94 ± 0.71 diopter decrease in mean K, a 0.18 ± 0.79 decrease in spherical power and a 0.78 ± 1.40 diopters decrease in cylindrical power (p<0.001) [8].

O' Brart, et al. reported an improvement in Sim K values by -0.62 D after 18 months in treated group (p<0.001) [7,9-11]. Raiskup, et al. documented a decrease in K max by an average of -2.57 D in their cohort of patients [12].

Wittig-Silva, et al. reported significant improvement of -0.15 Log MAR in BSCVA at 36 months [10]. They did not detect any change in spherical equivalent or cylindrical component of the subjective refraction. They also reported an improvement in K_{max} by a mean of -0.74D after 12 months in cross linked group and progression by a mean of +1.28D.

In our study, we noticed improvements in topographic parameters and visual outcomes at 4 years follow up. The UCVA and BCVA improved after this period from 0.26 to 0.36, which could be explained by corneal shape improvement and stabilization. Moreover, we found a statistically highly significant decline in mean K (-1.21 ± 0.61), spherical power (0.18 ± 1.14) and cylindrical power (0.50 ± 1.13) after 4 years. Forty-eight eyes (36.36%) demonstrated a decrease of more than 1 diopter in sim K and K_{max} parameters.

Following CXL, reduction of efficacy of proteinase enzymes followed by reducing collagenase activity and extracellular matrix (ECM) digestion [7,13], results in improvement in corneal shape and increase resistance of cross linked corneal tissue [6,14].

Our results showed that CXL is effective in halting the progression of keratoconus for at least 4 years. However, as KCN can recur after many years [15], long-term studies are highly warranted.

Coparossi, et al. [16], Raiskup-Wolf, et al. [17], and Vincogurra, et al. [18] reported their results to halt the KCN with follow up of more than 36 months.

We noticed correlation between preoperative parameters and the degree of postoperative corneal flattening. Our results showed UCVA on average improved 2 Snellen lines at 48 months. Hence, CXL could help to improve the patients' quality of vision, too.

In our study, corneal thickness showed significant change over the study period. We used two devices to assess corneal thickness. But the thickness measurements with Pentacam were less repeatable and reproducible in contrast to Orb scan II and the average pachymetry by the former device was lower. The observed decreased in corneal thickness following CXL could still be an artefact and must be confirmed by ultrasonic pachymetry; however, the data of the later was not available in our study. It is similar to the results of Caporassi, et al. [16]. This underestimation of corneal thickness measurements may be due to the effect of corneal haze after CXL on light transmission [16].

Most common adverse effect after CXL is transient corneal oedema. Nearly 80% of our patients had a transient corneal oedema after the procedure. We noticed mild degree of corneal haze in 40% of cases; in Wittig-Silva and colleagues' study the corneal haze resolved in all cases with time [10].

There was no evidence of endothelial cell damage in our study after 4 years of follow up, but other authors have published such damages associated with CXL [19-21].

No adverse effect on lens and limbal vascular pattern and retina were seen after 4 years in our study.

CONCLUSION

Overall, our study showed that CXL could be considered as a promising first line treatment for most patients with progressive KCN, especially considering our encouraging long-term results. In any case, long term follow-up is needed because of the nature of KCN.

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