A RETROSPECTIVE STUDY OF VISUAL OUTCOME OF PATIENTS WITH PROGRESSIVE KERATOCONUS AFTER CORNEAL COLLAGEN CROSSLINKING

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Submitted: 10/3/2018; Accepted: 11/9/2018; Published 21/12/2018

ABSTRACT

Background

Corneal collagen cross-linking is a new treatment modality aimed at increasing the biomechanical stability of the cornea through the application of riboflavin and UVA-induced collagen cross-linking it seems to be possible to stop the progression of keratoconus (a progressive, non-inflammatory corneal thinning disorder).

Objectives

To assess the effectiveness of corneal collagen cross-linking in stabilizing progression of keratoconus and visual effects in patients with progressive disease.

Patients and Methods

Fifty nine eyes of thirty-five patients with progressive keratoconus (19 females and 16 males) who underwent corneal collagen crosslinking between Dec. 2013 and Sep. 2014 were included in a retrospective non-controlled experimental study. The data collected in Tooe Maleek private hospital and Shahid-Aso Eye Teaching Hospital, in which recorded pre-procedure uncorrected, and best spectacle-corrected visual acuity using Snellen acuity chart-decimal notation, autorefraction (by autorefractometer) and topography findings (CCT and mean K-reading using OCULUS-PENTACAM) were taken and patients examined after the procedure in a period between 6-12 months and then pre and post crosslinking findings were compared. The data were collected between January to July 2015.

Results

The age of all patients were under 30 years. Females more commonly affected than males. The most common association or risk factor was continuous rubbing of the eyes. After corneal cross-linking, there was a statistically significant improvement in uncorrected, best spectacle-corrected visual acuity, decreased central corneal thickness (CCT) and mean keratometric reading (K reading). While each of myopic spherical equivalent and cylinder refractive error showed no statistically significant difference before and after the procedure (Stabilized).

Conclusion

The corneal collagen crosslinking with riboflavin and UV-A irradiation was proved to be effective in halting the keratoconus progression.

Keywords: *Keratoconus, Crosslinking, Keratometric, Riboflavin, UV-A irradiation.*

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https://doi.org/10.17656/jsmc.10174

INTRODUCTION

Keratoconus (KC) is a progressive, non-inflammatory corneal thinning disorder that produces a unique spectrum of change in the surface curvature of the cornea [1]. It is usually a bilateral disease but often asymmetric. Classically the onset of the disease starts at puberty and it is progressive until the third or fourth decade of life, when it usually arrests. It has an incidence of approximately 1 per 2000 in general population [12]. It is characterized by central corneal thinning, corneal scarring, corneal protrusion and progressive irregular myopic astigmatism, contributing to mild to marked impairment in the quality of vision. It is the most common ectatic dystrophy of the cornea3 and the major reason for corneal transplantation in the developed countries [3].

Corneal collagen crosslinking (CXL) is a relatively new, minimally invasive surgical technique used for the management of ectatic disorders such as keratoconus, pellucid marginal corneal degeneration (PMCD) and post refractive-surgery corneal ectasia. The use of riboflavin, also known as vitamin B2, in conjunction with ultraviolet-A irradiation (at a frequency of 370 nm, a wavelength which is strongly absorbed by riboflavin) facilitates the formation of cross links between collagen fibrils in the corneal stroma, producing a stiffening effect capable of halting the progression of the ectasia.4

The introduction of corneal collagen cross-linking in routine clinical practice was a fact during the last decade. The possible treatment options for keratectasia prior to CXL were spectacle correction, rigid gas permeable contact lenses, intracorneal ring segment implantation and in advanced cases lamellar or penetrating keratoplasty. Corneal cross-linking has given to patients with ectatic disorders the chance to postpone or even avoid corneal transplantation by arresting the progression of the primary disorder [4].

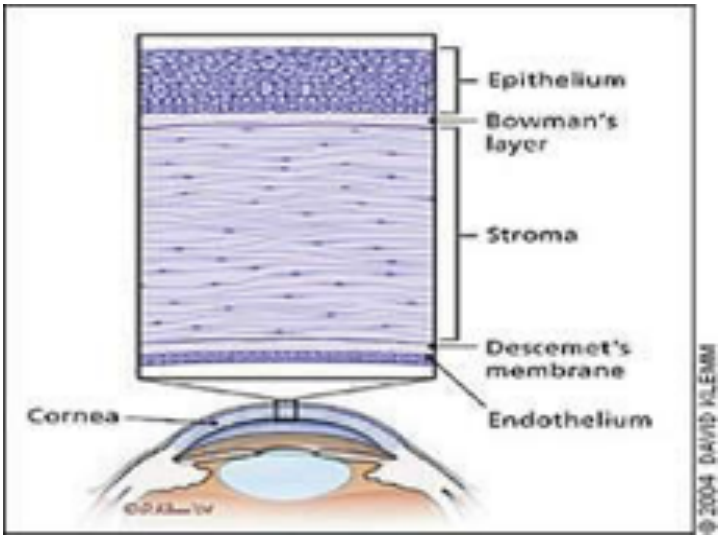

Figure 1. Structure of the cornea [1].

Assessment of keratoconus

Corneal topography

Placido-disk based corneal topography had been considered the most sensitive measurement for detecting keratoconus for many years [5] . Keratoconus is featured by a localized area of increased steepness, inferior-superior power asymmetry, and skewed steep radial axes above and below the horizontal meridian [2].

Recently, with the advent of Orbiscan slit scanning topography and the Scheimpflug imaging devices (Pentacam comprehensive eye scanner) in (Oculus Optikgera·te GmbH, Wetzlar, Germany), anterior and posterior corneal surface elevation data measurement and pachymetry map detection have become possible [6].

General guidelines for screening for keratoconus:

1. Anterior and posterior elevation maps: In the anterior elevation map differences between the best fit sphere and the corneal contour of less than +12 µm are considered normal, between +12 µm and +15 µm are considered suspicious, and more than

+15 µm are typically indicative of keratoconus. Similar numbers about 5µm higher apply to posterior elevation maps.

2. Anterior curvature map: The steepening of the cornea, irregular astigmatism, inferior steepening (I-S difference), location of steepest point and thinnest point on the cornea may help in the diagnosis of keratoconus.

3. Pachymetry and thickness distribution maps: The pachymetry map represents the thickness distribution throughout the cornea. It shows the corneas that are not only thin, but with their thinnest portion significantly displaced. At times, the pachymetry distribution may be the most sensitive or earliest indicator of an ectatic disorder and may be abnormal in spite of normal anterior corneal surface [(4)].

Contraindications of corneal collagen cross linking

1. Corneal thickness < 400 µm at thinnest location because of danger of damaging the endothelium.
2. Maximum Keratometry reading > 60 D.
3. High visual expectations of patients.
4. Corneal epithelial healing disorders.
5. Previous herpes keratitis.
6. Corneal melting disorders.
7. Pregnancy.
8. Continuous eye rubbing habits especially when associated with the following systemic conditions: Leber congenital amaurosis, Down syndrome, atopic disease, contact lens wear, floppy eyelid syndrome, and nervous habitual eye rubbing.
9. Corneal scarring.

The objecvives to this study was to To assess the effectiveness of corneal collagen crosslinking, in treating or halting keratoconus before proceeding to other more invasive and less safe techniques (lamellar or penetrating keratoplasty).

PATIENTS AND METHODS

Study design

A retrospective non-controlled observational study.

Sample size and duration of the study

Fifty nine eyes of 35 patients with progressive keratoconus (24 bilateral and 11 unilateral) of age between 14 and 30 years (16 males and 19 females) who underwent corneal collagen crosslinking between December 2013 and September 2014 were included.

Setting, data collection and the Intervention (Procedures)

Questionnaires were prepared and data collected in Tooe Maleek private hospital and Shahid-Aso Eye hospital, in which recorded pre-procedure uncorrected visual acuity (UC VA) and best spectacle-corrected visual acuity (BSCVA) using Snellen visual acuity chart(with their decimal notation), autorefraction (by TopCon Autorefractometer) and topography findings (OCULUS PENTACAM) were taken and patients examined again after the procedure in a period between 6-12 months and then pre and post crosslinking results were compared. This study conducted between January to July 2015.

The OCULUS Pentacam was used to study the corneal topography which is a rotating Scheimpflug camera. The rotational measuring procedure generates crisp Scheimpflug images in three dimensions, with the dot matrix fine meshed in the center due to rotation. It takes a maximum of 2 seconds to generate a complete image of the anterior eye segment. Any eye movement is detected by a second camera and corrected for in the process. The Pentacam calculates a three dimentional model of the anterior eye segment from as many as 25,000 true elevation points. The topography and pachymetry of the entire anterior and posterior surface of the cornea from limbus to limbus are calculated and depicted.

The corneal collagen crosslinking surgical technique done as follows; after application of topical anesthesia, it is done either by trans-epithelial (23 patients) or epithelium off technique (12 patients) in which the central 8-9 mm of the epithelium is removed. Next riboflavin (0.1% solution) is applied every 2-5 minutes for approximately 30 minutes until the stroma is completely penetrated as indicated by yellow flare in the anterior chamber. The trans-epithelial technique is similar except that the treatment is applied through the intact epithelium and the riboflavin solution is applied every minute in the first 30 minutes. The cornea is exposed to 3 mW\cm^2 surface irradiance (5j\cm^2 surface dose) of UV-A energy for a total of 30 minutes.

During treatment, riboflavin solution is applied every 2-5 minutes to ensure saturation of the tissue. After treatment, a bandage contact lens is applied until the epithelium is completely healed (for about 5-7 days), followed by application of topical corticosteroids, antibiotics and artificial tears.

Inclusion criteria

Patients with documented progression of keratoconus who underwent Corneal collagen crosslinking.

Exclusion criteria

Patients with stable disease not needed crosslinking and those with very advanced disease needed other

Statistical analysis

The Collected data were entered into SPSS-V21 (statistical package for social science-Version 21). Descriptive analysis (frequencies and percentages) was performed for the demographic, testing significance between studied variable were performed by using student t-test, a *p* value of less than 0.05 indicated statistical significance.

RESULTS

Among 35 patients 19 (54%) were female and 16 (45%) were male. Their age ranged between (14-30) years, with a mean age of 20.5 years. Regarding their occupation, (68%) were students, (20%) were unemployed, and (12%) were employed. History of ocular allergy including chronic rubbing was very common among these patients, which was positive in (44%) of them. Family history for the disease was positive in (14%) of all cases.

After treatment with collagen crosslinking (after one year of treatment), table 1 shows mean increase of un-corrected Visual acuity of (0.07±0.05) (56% have increase in their visual acuity by 1.6 Snellen line, 36% didn't lose or gain lines and 8% have lost 1 line) and of best spectacle-corrected VA of (0.10±0.04) (70% have increase in VA by 1.7 Snellen line, 22% didn't lose or gain lines and 8% have lost 1.7 line), which were statistically significant, but there was not any Statistically significant difference between the pre and post crosslinking states (became stabilized).

Regarding corneal topography findings, there were mean decreases of central corneal thickness of (12±14μm), and decrease in the mean keratometric reading of (0.81) postoperatively, these difference were statistically highly significant (P value= <0.001).

Table 1. The associations between the pre and post crosslinking states (became stabilized).

Parameters *	Studied time (mean ±S.D)		P values
	Pre operative	Post operative	
UC VA	0.27±0.16	0.33±0.22	<0.001
BSC VA	0.44±.21	0.53±.25	<0.001
SEQ	-4.97±3.27	-4.84±3.73	0.516
CYL	-3.86±1.94	-3.79±2.18	0.576
CCT	470.80±23.65	457.86±27.35	<0.001
Mean K	47.46±3.64	46.65±3.76	<0.001

* UC VA: (UnCorrected Visual Acuity), BSC VA: (BestCorrected Visual Acuity)
SEQ: (Sepherical Equivallent), CYL: (Cylinder), CCT: (Central Corneal Thickness)
Mean K: (Mean Keratometry

DISCUSSION

Results obtained after the crosslinking; there were a mean increase in un-corrected and best spectacle-corrected visual acuity of (0.07±0.05)(p<0.001), and (0.10 ±0.04) (p<0.001), respectively, which are close to results obtained by Coscunseven et al's study in Turkey [8] including thirty eight eyes of 19 patients with progressive keratoconus in a prospective comparative study. Average follow-up was 9±2 months (range: 5 to 12 months) a mean increase in un-corrected and best spectacle-corrected visual acuity of (0.06±0.05), and (0.10 ±0.14) p<0.01 respectively, which can be caused by the proximity of their sample sizes and the post-operative period at which the patients were followed up. Other studies showed different results for example in a study done by Dr. Mohammed Iqbal, Sohag University Hospital, Egypt [9] involved 58 eyes of 40 keratoconus patients, reported that the best corrected visual acuity improved by one line in 54% of the eyes, remained unchanged in 36%, and decreased by one line in 10% . in comparing to our study in which 62% have increase in VA by 1.7 line, 30% didn't lose or gain lines and 8% have lost 1 line). In another study done in Italy, it has been reported that the long-term results of 44 keratoconic eyes treated by collagen cross-linking in the first Italian open, nonrandomized clinical trial, the Siena Eye Cross Study, the mean best spectacle-corrected visual acuity improved by 1.9 Snellen lines, and the uncorrected visual acuity improved by 2.7 Snellen lines which were supported by clinical and topographic, modifications [10].

The stability achieved for spherical equivalent was (-4.97±3.27) /(4.84±3.73) p<.516, and cylindrical refractive error (3.86±1.94) /(-3.79±2.18) p<.576, this is comparable to what is done in a study conducted by Wiitig-silva C, in the Centre for Eye Research-Australia, East Melbourne in which, 66 eyes of 49 patients with documented progression of keratoconus have been enrolled and randomized, also showed no statistically significant difference and states that these results suggest stabilization of the cross-linked eyes [11], however in the first in vivo controlled clinical study by Wollensak et al. (2003), which included 23 eyes with moderate or advanced progressive keratoconus, shows that CXL is effective in halting the progression of keratoconus and that the SEQ (spherical equivallent) is reduced by an average of 1.14 D [12], this difference may be caused by the longer follow up time and the duration of the study (4 years) and the inter study variability of the stages or severity of the disease.

Regarding corneal topography results which showed a decrease in mean central corneal thickness of 12 μm, are also close to results of coscunseven's comparative study, which decreased by a mean of 11 μm (p =.065), in another study done by Sedaghat, in Mashhad, Iran [13]. Collagen cross-linking was performed on 97 eyes showing a mean decrease in corneal thickness at apex of 15 μm.

The mean Keratometric reading decreased by a mean of (0.81), like in an Iranian study done by Dr. Mehran Zarei in mashhad [14]. Ninety-two eyes of 53 subjects with progressive keratoconus were evaluated in 1-year follow-up in a retrospective, nonrandomized, single-center clinical study which estimated a mean decrease by (0.94) (P < 0.001), these results are confirmed by Agrawal's study done on 37 eyes of Indian subjects 1 year after treatment [15] in which the Keratometry value at the apex decreased by a mean of 2.73 D in 66% of the eyes, and some of these differences in topography findings may be related to various topography devices used in these studies with which the patients were examined.

Table 2 .Outcomes of corneal collagen cross-linking for keratoconus in different studies.

Authors	Type of study	nNo. of participants	follow up period	Results
Caporrosi et al [16]	Prospective, non-randomised	10 eyes of 10 patients	6 months	Increased UCVA, mean Km reduction of 2.1±0.13 D
Hoyer et al[17]	Retrospective	153 eyes of 111 patients	12 months (minimum)	Km values decreased in the third year by 4.34 D
Raisk-up wolf Et al [18]	Retrospective	480 eyes of 272 patients	6 months (minimum)	Km values decreased in the third year by 4.34 D
Jankov Et al [19]	Prospective, non-randomised	25 eyes of 20 patients	4-7 months	Km max decreased by more than 2 D
Vinciguerra Et al [20]	Prospective, non-randomised	28 eyes of 28 patients	12 months	Mean average simulated Km decreased by 6.07 D
Grewal Et al [21]	Prospective, non-randomised	102 patients	12 months	No significant change in visual acuity and corneal curvature

Limitations

- Limited number of patients available for the study because the procedure is relatively new.
- It is not performed in public hospital.
- It is coasty and lastly.
- The time limit of the study are main reasons why we did the study retrospectively rather than prospectively.

Conclusions

The corneal collagen crosslinking which is proved to be an effective procedure in halting the progression (as indicated by stabilization of the spherical equivalent refraction and cylinderic refractive error) in most cases, and even improvement in the condition (as indicated by change in the un-corrected, best-spectacle-corrected VA and decrease in the mean keratometric reading). It can be also concluded that a high percentage of these patients have history of eye rubbing (or ocular allergy) which we found to be the most common associated feature in these patients.

Recommendation

Early diagnosis of keratoconus and early corneal crosslinking is important point in effectiveness of crosslinking.More study to be done for long term effect of corneal crosslinking.

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