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ORIGINAL ARTICLE

Outcomes of Corneal Collagen Cross-linking for Keratoconus the Effect of Cone Location

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ABSTRACT

Aim: One-year outcome of corneal collagen cross-linking (CXL) for keratoconus with reference to topographic cone location.

Materials and methods: Clinical audit of the results of CXL were used. Three hundred and seventy-eight eyes of 225 patients with preoperative and 12-month completed follow-up were included. Cone location was defined by cone location magnitude index (CLMI) using the Keratron scout topography system. The eyes were divided into two groups–central with cone location within 3 mm zone of the topography map and paracentral with cone location between the 3 and 5 mm zones.

Results: The overall group showed a mean flattening of the CLMI of 1.67 D [preoperative 53.35 ± 5.63 D, 12 months 51.69 ± 4.67 (p = 0.095)]. The flattening in central cone group was 2.67 D [preoperative 54.01 ± 5.3819, at 12 months to 51.341± 4.588 (p = 0.016)]. In paracentral cone group the flattening was lesser at 1.73 D [preoperative apex K 52.805 ± 6.382, at 12 months 51.03 ± 4.82 (p = 0.006)]. The difference between groups was statistically significant (p < 0.001). The central cone group showed no significant shift in cone position [preoperative 1.0059 ± 0.24, at 12 months 0.986 ± 0.206 (p = 0.45)]. The paracentral cone group showed a significant mean shift of 1.05 mm in cone location [preoperative 2.224 ± 0.440, at 12 months 1.196 ± 0.529 (p = 0.001)].

Conclusion: Cone location has an impact on the results of corneal cross-linking. The paracentral cones show a significant shift toward the center of the cornea and the central cones show a larger flattening.

Keywords: Keratoconus, Cone location, Corneal topography, Cornea collagen cross-linking.

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INTRODUCTION

Keratoconus is a disease that is characterized clinically by an area of abnormally high curvature, reduced corneal thickness and progressive corneal topographic irregularity.[1] Tensile testing of cornea strips from keratoconus eyes have shown that the corneal strain-dependent elastic modulus is 50 to 60% less in keratoconus eyes compared to normal corneal tissue.[2] This supports the concept of biomechanical weakening in the area of the cone is the pathway through which the various biological factors affect the corneal shape.

Corneal collagen cross-linking (CXL) is a treatment designed to arrest progression of keratoconus and may have beneficial visual and optical effects.[3-6] In our reported results treated eyes demonstrated an –2.7 dioptre (D) flattening at the apex of the cone.[3,5] Changes in uncorrected visual acuity have been ascribed to corneal flattening and spectacle corrected visual acuity to the improved corneal symmetry. Both are produced by the stiffening and shrinkage of corneal collagen.[7] Since the effects of corneal cross-linking are believed to be biomechanical the initial corneal shape may be important for the ultimate effect of the treatment.[8] As part of our clinical audit we looked at the possibility of preoperative cone location on the outcome of CXL. To the best of our knowledge there is no study done in Indian eyes.

MATERIALS AND METHODS

Data from the clinical audit of our center completed in May 2012 was included. Data from patients who underwent corneal collagen cross-linking for progressive keratoconus and completed 12 of follow-up were included.

This clinical audit analysis included patients with the following inclusion criteria: Progressive keratoconus, corneal thickness of at least 400 µm, no slit-lamp evidence of corneal scaring. Exclusion criterion was cone location outside the 5 mm optical zone on CLMI assessment.

Progression was defined as an increase in maximum keratometry (K) of 1.00 D in 1 year, patient reports of deteriorating best corrected visual acuity (BCVA) (excluding other possible noncornea-related reasons for deterioration), or the need for new contact lens fitting more than once in 2 years.[3,5] Ultrasonic pachymetry was used with 9 points being measured in each eye (Palm Scan, Micro medical Technologies, USA).

All patients or the legal guardians (in case of patients less than 18 years of age) provided informed consent after receiving a detailed description of the nature of the treatment. Patients less than 18 years of age were also included in our study as the occurrence of keratoconus is seen at much earlier age and with rapid progression in the Indian Subcontinent.

The cross-linking was performed in the day-care facility. After topical anesthesia (proparacaine hydrochloride 0.5% eye drops) was administered, the epithelium was debrided using a blunt spatula in a 9.0 mm diameter area. This was to ensure that the riboflavin penetrated the stroma and that a high level of UVA absorption was achieved and deeper

penetration was avoided. As a photo sensitizer, 0.1% riboflavin solution was applied to the cornea every 5 minutes for 25 minutes before the irradiation to allow sufficient saturation of the stroma. Next, an 8.0 mm diameter of central cornea was irradiated with UVA light with a wavelength of 370 nm and an irradiance of 3 mW/cm^2. The CBM (Caporossi, Baiocchi, Mazzotta) X Linker (CSO, Italy), was used as the UVA radiation source. This cross-linker has five prefocused diodes with a LED divergence of 10° to provide a homogenous UVA radiation. During the 25 minutes of irradiation, drops of 0.1% riboflavin solution (Ricrolin, Sooft Italia) were applied to the cornea every 5 minutes to sustain the necessary concentration of the riboflavin.

After the treatment, the eyes were patched for 24 hours. On removal of the patches the patients were instructed to use 0.5% moxifloxacin eye drops (Alcon laboratories, India), 1% prednisolone acetate eye drops (Allergan, India) and Tears Naturale II (Alcon Laboratories, India) for a period of 1 week. All drops were recommended for use at four times daily.

Follow-up examinations were performed on days 1 and 3 or until complete re-epithelialization. Subsequent examinations were at 1, 3, 6 and 12 months and then advised annually. At each examination, refraction, uncorrected distance visual acuity (UDVA), BCVA (Snellen vision charts) with glasses or with contact lenses, corneal topography (Keratron Scout, Optikon, Italy), central corneal thickness (CCT) (Palm Scan, Micro Medical Technologies, USA), and intraocular pressure (IOP) (Goldman applanation tonometer, Haag Streit, Switzerland) were recorded.

Pre- and postoperative topography was obtained using the Keratron topography system. The apex was measured by collating the cone location magnitude index (CLMI) from the corneal topography (Keratron Scout, Optikon, Italy) maps. The CLMI calculation is offered as a default in the Keratron topography and is based on the concept of location of the center of the cone and its magnitude. We used CLMI an automated index generated by locating the steepest 2 mm region in an 8 mm search location, measuring the average curvature magnitude in this region and comparing it to a 2 mm region located at the same radial distance in the opposite quadrant. The algorithm is designed to determine the steepest 2 mm diameter circle within the central 8 mm of the topography. The area-corrected average of all points outside of the circle is subtracted from the corrected average of all the points within the circles. This is repeated for the circle 180° away. The results are compared to decide if the area is a cone. This is different from K_{max} that is derived from the simulated (SIM) K values and is a single point measurement as the CLMI is calculated as an average of all points in the 2 mm region of the greatest curvature. Preoperative cone location using the CLMI was divided into two zones – central 3 mm zone (group I) and paracentral 3 to 5 mm zone (group II) as seen in the topography maps. The zones were restricted to two as only five eyes were found to be outside the 5 mm zone. These were excluded from the analysis. Values were obtained preoperatively and 12 months postoperatively.

Statistical analysis was done using Microsoft Excel (Microsoft Office 2007, Microsoft Corporation, USA) and JMP 8 statistical analysis software. A paired two-tailed Student's t-test was used to analyze the postoperative changes compared to the baseline within the groups.

RESULTS

Three hundred and seventy-eight eyes of 225 patients with a mean age of 16.34 ± 7.46 years (range: 12-37 years) were evaluated. Five were excluded due to the cone location being outside the 5 mm optical zone on CLMI assessment. Of the 373 eyes, 257 eyes were classified in group I (central cone group) and 121 eyes were classified in group II (paracentral cone group).

Apex Keratometry (as per CLMI)

Mean preoperative CLMI K for the group overall was 53.35 ± 5.63 D. At 1 year post corneal cross-linking it was significantly decreased by 1.66 D to 51.69 ± 4.67 (p = 0.0095).

- *Group I (central cone):* Mean preoperative apex K was 54.01 ± 5.3819. At 1 year it significantly decreased by 2.67 D to 51.341 ± 4.588 (p = 0.016).
- *Group II (paracentral cone):* Mean preoperative apex K was 52.80533 ± 6.382933. At 1 year it decreased significantly by 1.73 D to 51.03 ± 4.82 (p = 0.006) (Table 1).

Table 1: Apex keratometry changes over 1 year (CLMI)

	Preoperative (D)	*At 12 months postprocedure*	*p-value*
Combined cohort	53.35 ± 5.63	51.69 ± 4.67	0.0095
Central cone	54.01 ± 5.381	51.341 ± 4.588	0.016
Paracentral cone	52.80 ± 6.38	51.03 ± 4.82	0.006

Location of the Cone (Ltmm)

Mean cone location in mm from the optical axis was also assessed for the two groups.

Mean cone location for group I (central cone group) preoperatively was 1.005976 ± 0.240085 and did not show any significant difference at 1 year 0.986344 ± 0.206703 (p = 0.45).

Mean cone location for group II (paracentral cone group) preoperatively was 2.224651 ± 0.440114 and decreased significantly by 1.05 mm to 1.196801 ± 0.529968 (p = 0.001).

Visual Acuity

Uncorrected Distance Visual Acuity

Central cone group (group I): Preoperative UDVA was 0.47 ± 0.23 (decimal notation conversion from Snellen acuity) improved to 0.53 ± 0.12 but did not reach statistical significance (p = 0.3).

Paracentral cone group (group II): Preoperative UDVA was 0.54 ± 0.22 and significantly improved to 0.68 ± 0.25 (p = 0.004).

The combined cohort showed significant improvement from 0.53 ± 0.34 to 0.61 ± 0.21 (p = 0.001).

Corrected Distance Visual Acuity

Central cone group (group I): BCVA significantly improved from preoperative mean of 0.5 ± 0.35 to 0.68 ± 0.24 (p = 0.001).

Paracentral cone group: BCVA significantly improved from preoperative mean of 0.46 ± 0.12 to 0.56 ± 0.11 (p = 0.01).

Combined group BCVA also significantly improved from a preoperative mean of 0.49 ± 0.43 to 0.61 ± 0.23 (p < 0.001).

DISCUSSION

The difference maps generated to compare the change between preoperative and 12 months maps showed two patterns. Pattern 1 revealed paracentral steepening with or without central flattening. This was associated with reductions in the spherical equivalent refractive error, and simulated K values. It was seen most often in eyes with cones within the 3 mm zone of the topographic curvature maps. Pattern 2 showed peripheral flattening with central steepening. This pattern was associated with cones in the 3 to 5 mm optical zone of the topographic curvature maps. It is thought that the corneal lamellae on one side of a meridian to the displaced cone apex have more length to shrink than fibrils on opposite side. Collagen cross-linking may thus lead to an apparent pulling up of the cone apex to the center.[9]

Three hundred to 500 corneal lamellae extend from limbus to limbus. The lamellae are more closely packed in the center.[10] Meek et al have also shown that compared to normal corneas; collagen fibrillar distribution is unevenly distributed around the presumed apex of the cone in keratoconic corneas.[11]

Collagen cross-linking is a technique that helps arrest the progression of keratoconus.[3-7] Wollensak et al reported a 3.5-fold increase in the Young's modulus of human corneas after CXL *ex vivo*.[12] The effect of this treatment is limited to the anterior 200 to 300 microns with an irradiance of 3 mW/cm^2.[12] Additionally, unexpected corneal curvature reductions and improvements in uncorrected and corrected visual acuity have been reported.[3-6]

We have previously shown that patients undergoing CXL show a mean improvement in keratometry of about 2.7 D and up to one line improvement in Snellen visual acuity at 1 year after CXL.[3] This cohort reflects a similar finding of 1.7 D decrease in the CLMI K values at 12 months post-treatment. Since the optical effect of corneal cross-linking is believed to be dependent on the location of the cone relative to the optic axis,[9] we tested the hypothesis that the initial corneal topography pattern may influence the clinical outcomes. However, in comparison to the Orbscan II used in a previous study that required manual derivation of the data with consequent limitations,[9] we used CLMI an automated index generated by locating the steepest 2 mm region in a 8 mm search location, measuring the average curvature magnitude in this region and comparing it to a 2 mm region located at the same radial distance in the opposite quadrant.

In a computational modeling of keratoconus progression using finite element model (FEM); Roy and Dupps[13] reported on the sensitivity of CXL outcome to cone location. They reported that the eccentric cone centralized slightly with the standard CXL treatment. This was reflected in our patients as the paracentral area cones showed centralization over the 12-month period. Furthermore, they also suggested that metrics of cone severity such as CLMI[14] may provide a more complete characterization of the topographic effect of treatment. This supports our use of the CLMI as the main measure to assess the outcome of our cases of CXL. It should however, noted that though CLMI can be calculated using data from various different devices, it may show significantly different results with different technologies (devices), the magnitude of the differences is not likely to be clinically relevant to study of ecstatic disorders.[15]

Visual acuity did not show significant difference between groups. This may be influenced by the fact that the central cone group had a worse visual acuity to begin with. Thus, even a significant improvement in the CLMI index compared to the paracentral group was not adequate to demonstrate a statistical difference from the paracentral group. In the paracentral group this could be due to the fact that the cone migration to the center caused an increase in myopia and thus a drop in uncorrected visual acuity.

The difference in the topographic patterns in this study can be due to the following mechanisms:

1. Treatment rendered by a nonhomogenous beam over the entire treatment zone.[16] Thus, a variable intensity of the ultraviolet light may lead to variable stiffening at the different locations and thus variable treatment patterns.
2. *Variable depth of effect:* This can be influenced by the presence and composition of the precorneal riboflavin film,[17] presence of corneal epithelium,[18] and the integrity of the epithelial tight junctions.[19] The latter two would be applicable on to cases where transepithelial cross-linking is the method adopted for cross-linking.
3. *Cosine effect:* As the angle of incidence of the ultraviolet beam with the cornea decreases toward the periphery, due to the corneal curvature, less treatment ensues per unit area of the cornea. Thus, a more peripheral cone may receive less of a cross-linking response.[20]

Thus, as corneal collagen cross-linking continues to be seen as a viable treatment option for treatment of keratoconus and keratectasia further changes are possible to refine the treatment. Our study shows that the cone location is possibly an important factor in the clinical outcome of corneal cross-linking. This can form the basis of further modification in the delivery modalities of the ultraviolet beam depending on the cone. It may be possible to think of changing the treatment pattern from standard broad-beam delivery to smaller effective treatment zone. A delivery of cone-cantered, variable intensity treatment or topography linked treatment patterns may alter the outcomes even further.[13] Among the presently available options, treatment with intracorneal rings to shift the cone toward the center may help in improving the corneal cross-linking outcomes.

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