ABSTRACT

Objective: To compare the efficacy of epi-off and epi-on collagen cross-linkage procedure in terms of visual outcomes and astigmatism during one-year period.

Study Design: Prospective study.

Place and Duration of Study: Amanat Eye Hospital from May 2014 to April 2015.

Materials and Methods: Eighty patients (102 eyes) with keratoconus were included in this study. There were forty patients (51 eyes) presented with epi-on collagen cross-linkage procedure (Group I) and forty patients (51 eyes) with epi-off collagen cross-linkage procedure (Group II). Epi-off procedure involved epithelial removal comprised of isotonic riboflavin solution 0.1% with 20% dextran, whereas epi-on procedure involved intact epithelium utilized hypotonic 0.25% riboflavin solution.

Results: In Group I, the mean age of patients was 21.83 years± 3.83 SD. There were 27 (67.5%) male and 13 (32.5%) female patients. In Group II, the mean age of patients was 20.75 years ± 4SD. There were 22 (55%) male and 18 (45%) female patients. Uncorrected visual acuity improved to 0.04 Log MAR in epi-on and 0.03 Log MAR in epi-off procedure with p-value=0.7 (statistically insignificant), whereas best corrected visual acuity improved to 0.06 Log MAR in epi-on and 0.02 LogMAR in epi-off technique with p-value=0.28 (statistically insignificant) respectively. However, mean pre-operative topographic astigmatism were (5.51± 2.58) with epi-on procedure and (3.98 ±2.30) with epi-off procedure, improvement of mean post-topographic astigmatism were improved in epi-on procedure (5.10 ±2.42) than epi-off procedure (3.96± 2.20).

Conclusion: There was insignificant difference between both cxl procedures. However, improvement of mean topographic astigmatism were observed in epi-on as compared to epi-off collagen cross linkage procedure.

Key Words: Epi-On CXL, Epi-Off CXL, Keratoconus, Riboflavin.

Introduction

Keratoconus is degenerative eye disease characterized by localized thinning and conical protrusion of the cornea, which typically develops in the inferior-temporal and central zones. It results in distorted, blurred vision, glare and photophobia. Consequently, visual acuity is reduced due to irregular astigmatism and high myopia resulting from asymmetric topographical changes in the anterior corneal surface. Keratoconus is the most prevalent form of corneal ectasia and affects all ethnicities. It is a progressive condition with a heavy burden for patients as a result of aggravation in the third decade of life.

A diagnosis of keratoconus is most commonly made through slit lamp examination, corneal topography, measurement of visual acuity and refraction. Since slit lamp examination is unable to show the signs of keratoconus in the early stages and visual acuity may not be affected, corneal topography is the only reliable criterion. Recent advances in corneal imaging and the possibility of the assessment of the corneal surface with the help of anterior or posterior elevation measurements have provided ophthalmologists with valuable information. Pentacam employs the Scheimpflug imaging technique to present the corneal topographic indices with an acceptable accuracy and repeatability. In the mildest form of keratoconus, spectacles or soft contact lenses may help. But as the disease progresses, with the thinning of the cornea and more irregularity in shape, glasses and regular soft contact lens no longer provide adequate vision correction. Corneal cross-linking has made it possible to arrest keratoconus, especially in the early stages, hence significantly reduce the need for corneal transplantation (keratoplasty). Therefore, early diagnosis is of vital importance.
Corneal collagen cross-linking (CXL) with riboflavin and ultraviolet-A is a new technique of corneal tissue strengthening by using riboflavin as a photosensitizer and UVA to increase the formation of intra and inter fibrillar covalent bonds by photosensitized oxidation. There are two procedures introduced for treating keratoconus, epi-off collagen cross-linkage (standard CXL) and epi-on collagen cross-linkage (trans-epi CXL). Epi-off CXL involved epithelium removal followed by instillation of 0.1% isotonic riboflavin drops with 20% dextran solutions. However, the epi-on CXL procedure involved intact epithelium with hypotonic riboflavin drops 0.25% solution. Long-term clinical reports showed that both these methods halted the progression of keratoconus and to some extent improves refractive and topographic parameters.

Recently introduced technique epi-on CXL that involves intact epithelium targets to reduce postoperative pain, reduced chances of infections and early visual recovery. The aim of this study was to find the efficacy of epi-off and epi-on collagen cross-linkage in terms of visual outcome and astigmatism in keratoconus patients in order to better define the validity of both techniques.

**Materials and Methods**

A prospective study conducted in the settings of Amanat Eye Hospital, Rawalpindi. Consecutive sampling technique was used to collect the sample of eighty patients (102 eyes) from May 2014 to April 2015 with age group 14-31 years. An informed consent was obtained from all the patients enrolled in the study. An approval was taken from the hospital ethical committee. There were forty patients (51 eyes) with epi-on CXL procedure (Group I) and forty patients (51 eyes) with epi-off CXL procedure (Group II). The inclusion criteria included 14-31 years of age, history of vigorous eye rubbing, intolerant to contact lenses, patients with the complaint of unstable refraction, vision deterioration, Pentacam corneal thickness 450 microns - 380 microns depending upon K-readings on the basis of mild<48D, moderate 48-54D and advanced keratoconus>54D. The exclusion criteria included systemic diseases affecting ocular conditions and corneal scarring.

Pre and post-operative testing included uncorrected distance visual acuity (UDVA), best-corrected distance visual acuity (CDVA), slit-lamp examination, corneal topography (Oculus Pentacam). UDVA and CDVA were recorded using Log MAR Early Treatment Diabetic Retinopathy Study vision chart at distance of 4m. Pentacam topography was used to evaluate pre- and postoperative corneal topography and pachymetry. Slit-lamp examination was done by an ophthalmologist. The selection criteria for CXL procedure includes high K-readings >47.0 D and corneal thickness <450 microns. Those with K-readings >49.0 D and corneal thickness < 400 microns undergo epi-on CXL procedure, as thin corneas can be best treated with epi-on technique.

Epi-off CXL technique involved epithelial debridement performed under topical anesthetic drops followed by instillation of isotonic riboflavin drops 0.1% in 20% dextran solution for 30 minutes. The cornea was exposed to UVA 370 nm light for 3 minutes at an irradiance of 30mW/cm², bandaged contact lenses were applied for 5 days after the procedure.

New intervention for the treatment of keratoconus in regards to patient comfort and safety is epi-on CXL procedure (trans-epi). Epi-on CXL involved intact epithelium followed by instillation of hypotonic riboflavin drops 0.25% solution for one hour, then cornea was subjected to UVA radiation for 3 minutes with a wavelength of 370 nm at the intensity of 30mW/cm² within a circular diameter of 9 mm which increases collagen cross-linkages and stiffens the cornea. Pre-operatively and post-operative data of visual acuity and astigmatism were measured by using Log MAR chart and corneal topography (Pentacam) at baseline, three and twelve months respectively.

The Statistical Package for Social Sciences software (SPSS, version 22) was applied to organize and tabulate the data collected. Pre and post-operative data of visual acuity and astigmatism were calculated by using independent sample t-test. All the results were evaluated at a confidence interval of 95%. p-value <0.05 considered to be statistically significant.

**Results**

Eighty patients (102 eyes) presented with mean age (in years) ± SD as 21.29 ± 4.07. There were forty patients (51 eyes) with epi-on CXL procedure (Group I) and forty patients (51 eyes) with epi-off CXL procedure (Group II). In Group I, the mean age of
patients (in years) ± SD was 21.83 ± 3.83 (range 14 to 31). There were 27 (67.5%) male and 13 (32.5%) female patients. Right eye was affected in 15 (37.5%) patients, left eye was affected in 14 (35%) patients while there were 11 (27.5%) patients with both their eyes affected. In Group II, the mean age of patients (in years) ± SD was 20.75 ± 4.27 (range 14-31). There were 22 (55%) male and 18 (45%) female patients. The right eye was affected in 17 (42.5%) patients, left eye was affected in 12 (30%) patients while there were 11 (27.5%) patients with both their eyes affected.

The Independent Sample t-test reported no significant statistical difference between epi-on cxl and epi-off cxl procedure in terms of improvement in un-corrected visual acuity after three months, twelve months and between three to twelve months of treatment, with p values > 0.05. There was also statistically insignificant difference among group 1(cxl epi-on) and group 2 (cxl epi-off) procedure on the basis of improvement in best corrected visual acuity with p-value > 0.05 (Table I and II).

After stratification of keratoconus as mild, moderate and severe, Independent Samples t-tests revealed that there were statistically insignificant difference between group 1 (epi-on cxl) and group 2 (epi-off cxl) procedure in terms of improvement in astigmatism after three months, twelve months and between three to twelve months of treatment among all three grades of keratoconus, with p values > 0.05 (Table III and IV).

Table III: Astigmatism results on the basis of grades of keratoconus after epi-on cxl procedure

<table>
<thead>
<tr>
<th>Grades of keratoconus</th>
<th>Improved</th>
<th>Stable</th>
<th>Worsened</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Moderate</td>
<td>12</td>
<td>5</td>
<td>11</td>
<td>28</td>
</tr>
<tr>
<td>Severe</td>
<td>7</td>
<td>3</td>
<td>5</td>
<td>15</td>
</tr>
</tbody>
</table>

Table IV: Astigmatism results on the basis of grades of keratoconus after epi-off cxl procedure

<table>
<thead>
<tr>
<th>Grades of keratoconus</th>
<th>Improved</th>
<th>Stable</th>
<th>Worsened</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>8</td>
<td>13</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Moderate</td>
<td>9</td>
<td>1</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
treating keratoconus. At 12 months post treatment results showed that both procedures proved to be useful and effective in halting the progression of keratoconus. Caporossi et al. and Magli et al. reported a study of 26 eyes treated by epi-on CXL, and they observed an initial, although not statistically significant, increase in UDVA and CDVA in the first 3 months. However, this study showed no statistically significant difference between both CXL procedures on the basis of uncorrected visual improvement after three months, twelve months and between three to twelve months of treatment. The person who lost 2 lines of Log MAR chart of best-corrected visual acuity (BCVA) was 18 years old female who at baseline had un-corrected distance visual acuity (UDVA) of 0.6 Log MAR, BCDVA of 0.2 Log MAR and maximum K-value of 56.70D. After 12 months she was noted to had further deterioration of vision, UCDVA was 1.0 Log MAR, BCDVA was 0.6 Log MAR and the maximum K value had increased slightly to 57.30D.

Wollensek et al. reported regression with reduction of maximum K readings by 2.01D after epithelial removal in 70% of eyes with mean follow-ups of 23.2 months. In this study we analyzed no change in mean keratometric readings in case of the steep and flat meridian with epi-off procedure. Several complications were reported in the literature, especially after epi-off CXL procedure such as corneal edema and endothelial damage. In this study we observed significantly greater postoperative pain in the epi-off CXL group compared to epi-on CXL group with no complications in both treatment groups. An overall analysis of the clinical outcomes after epi-off and epi-on CXL showed that keratoconus was relatively stable after 12 months, and no differences were observed comparing the two procedures. The main aim of the CXL procedure initially was to stabilize the keratoconic cornea. Stabilization was achieved with extra benefits like more symmetric corneas, which not only increased visual acuity but made the cornea easier to fit with contact lenses. It is reported that the cornea still tolerates contact lenses after the procedure. Some investigations indicate that keratoconus leads to keratoplasty in approximately 20% of patients. Collagen cross linkage (CXL) will significantly decrease the need for keratoplasty or at least delay the need for it.

### Table V: The descriptive statistics of keratometric readings after epi-on and epi-off CXL procedure

<table>
<thead>
<tr>
<th>K-readings</th>
<th>Procedure</th>
<th>Total</th>
<th>Mean ±SD</th>
<th>Min</th>
<th>Max</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-operative Keratometric Reading of Steep Meridian</td>
<td>On</td>
<td>51</td>
<td>52.06 ± 4.56</td>
<td>42.00</td>
<td>63.00</td>
<td>21.00</td>
</tr>
<tr>
<td></td>
<td>Off</td>
<td>51</td>
<td>48.24 ± 3.29</td>
<td>42.00</td>
<td>60.75</td>
<td>18.75</td>
</tr>
<tr>
<td>Keratometric Reading of Steep Meridian after 3 Months of Treatment</td>
<td>On</td>
<td>51</td>
<td>52.15 ± 4.63</td>
<td>42.50</td>
<td>63.50</td>
<td>21.00</td>
</tr>
<tr>
<td></td>
<td>Off</td>
<td>51</td>
<td>48.34 ± 2.95</td>
<td>43.50</td>
<td>59.75</td>
<td>16.25</td>
</tr>
<tr>
<td>Keratometric Reading of Steep Meridian after 12 Months of Treatment</td>
<td>On</td>
<td>51</td>
<td>51.91 ± 4.63</td>
<td>42.50</td>
<td>63.25</td>
<td>20.75</td>
</tr>
<tr>
<td></td>
<td>Off</td>
<td>51</td>
<td>48.40 ± 2.86</td>
<td>43.50</td>
<td>57.75</td>
<td>14.25</td>
</tr>
</tbody>
</table>

### Fig 3: Mean pre-operative topographic astigmatism after epi-on and epi-off CXL procedure

Mean pre-operative topographic astigmatism were (5.51± 2.58) with epi-on procedure and (3.98 ±2.30) with epi-off procedure, improvement of mean post-topographic astigmatism were improved in epi-on procedure (4.84 ±2.42) than epi-off procedure (3.96± 2.20) after six months as shown in figure IV.

### Fig 4: Mean post-topographic astigmatism after epi-on and epi-off CXL procedure

**Discussion**

This study analyzed comparison of CXL procedure in two homogenous groups (epi-on and epi-off CXL) for treating keratoconus. At 12 months post treatment results showed that both procedures proved to be useful and effective in halting the progression of keratoconus. Caporossi et al. and Magli et al. reported a study of 26 eyes treated by epi-on CXL, and they observed an initial, although not statistically significant, increase in UDVA and CDVA in the first 3 months. However, this study showed no statistically significant difference between both CXL procedures on the basis of uncorrected visual improvement after three months, twelve months and between three to twelve months of treatment. The person who lost 2 lines of Log MAR chart of best-corrected visual acuity (BCVA) was 18 years old female who at baseline had un-corrected distance visual acuity (UDVA) of 0.6 Log MAR, BCDVA of 0.2 Log MAR and maximum K-value of 56.70D. After 12 months she was noted to had further deterioration of vision, UCDVA was 1.0 Log MAR, BCDVA was 0.6 Log MAR and the maximum K value had increased slightly to 57.30D.

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However, limitations of this study include limited treated eyes and shorter follow-ups (12 months).

**Conclusion**

One year follow-up study showed that in terms of visual outcomes and topographic parameters, there were statistically insignificant differences between both cxl procedures. However, mean topographic astigmatism tends to improved in epi-on procedure as compared to epi-off cxl procedure. Above all, the added advantage of patient comfort reduced post-operative infection and early visual recovery gave epi-on cxl, the best treatment of choice.

**REFERENCES**