Evaluation of the Role of Corneal Collagen Cross-Linking in Stoppage of Progression of Keratoconus

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Abstract

Hypothesis: Collagen cross-linking is a new, minimally invasive method, aims to strengthen the stroma by inducing cross links between neighboring collagen fibers in cases of keratoconus. Few studies have examined the effectiveness of collagen cross-linking in treating keratoconus and improving visual acuity.

Aim: Is to assess the effectiveness of corneal collagen cross-linking in stoppage of the progression of keratoconus through comparing visual acuity and pentacam diagnostic criteria before corneal collagen cross-linking and 6 months to one year after corneal collagen cross-linking.

Participants: Fifty patients undergoing CXL in single eye.

Study Design: A Prospective, interventional, single center study.

Intervention: Riboflavin-ultraviolet X (UV-X) induced CXL included instillation of 0.1% riboflavin and follow-up UAVA, BCVA and pentacam assessment at baseline, 1,3,6,12 months after the procedure.

Results: The mean age of 23.32±3.99 years. Twenty nine patients were males (58%) and 21 were females (42%). There were 50% of patients that had CXL for the right eye keratoconus and 50% for the left side. There was a significant improvement of UAVA, BCVA and decrease in K1, K2 at 12 months of follow-up compared to baseline with unchanged corneal thickness. Minimal and transient complications were recorded.

Conclusion: CXL is a safe minimally invasive procedure that showed improvement in UAVA and BCVA in keratoconus along 1 year follow-up. CXL stopped the progression of keratoconus along 1 year follow up with unchanged corneal thickness. CXL is a safe with infrequent and unsustained complications for treatment of keratoconus.

Key Words: Crosslinking – Keratoconus – Pentacam.

Introduction

KERATOCONUS has an incidence of 1 in 2000 in the general population but is being detected in 5% of myopes who present for refractive surgery evaluation. Prior to the introduction of methods to assess corneal topography, the diagnosis was based on history and the presence of clinical signs.

Posterior and anterior elevation, pachymetric, and keratometric parameters measured by the Pentacam camera can effectively discriminate keratoconus from normal corneas serving as a useful diagnostic tool for disease staging.

Treatment options include conservative approaches, aimed at improving visual acuity, such as rigid contact lenses placed to straighten corneal aberrations [1]. Alternatively, more invasive methods are applied using intrastromal corneal implants [2], performing anterior lamellar keratoplasty, and penetrating keratoplasty in extreme cases [3,4]. However, these therapies only address the refractive consequences of the disease and not the underlying pathology, namely a stromal instability stemming from collagen abnormalities [5], and with the exception of corneal transplantation do not halt the progression of the disease.

Collagen cross-linking, a new, minimally invasive method, aims to strengthen the stroma by inducing cross links between neighboring collagen fibers. This method results in an increase in corneal tensile strength, with no medium term adverse effects on its normal architecture. Clinically, treated patients display improvement in both visual acuity and keratometric readings. This method may provide clinicians with easily accessible tools to stop the progression, and even correct visual deterioration due to corneal ectasia [6].
Inducing cross links between neighboring collagen fibers is achieved by combining the photosensitizer riboflavin with an initiating UVA beam [7]. The wavelength of 370nm is used to achieve maximal absorption by the riboflavin, while remaining below harmful DNA and retinal radiation levels.

Few studies have examined the effectiveness of collagen cross-linking in treating keratoconus and improving visual acuity. Though this method appears to offer an improvement to patients suffering from corneal ectasia, it must be noted that its safety and long-term effects have not been extensively studied [6].

The turnover rate of collagen fibers in the cornea is several years [8] and it remains unclear whether the changes noted in corneal stability will last or whether its effects are limited. Furthermore, the effect of corneal thickness on endothelial and ocular damage remains a safety concern. Future studies are needed to explore these long-term effects as well as other aspects of ocular safety [6].

**Aim of the work:**

The objective of this study is to assess the effectiveness of corneal collagen cross-linking in stoppage of the progression of keratoconus through comparing visual acuity and pentacam diagnostic criteria before corneal collagen cross-linking and 6 months to one year after corneal collagen cross-linking.

**Subjects and Methods**

Patients were selected outpatient clinic, Cairo University and Beni-Swif University from 2010-2011.

The study is a prospective study that was done in (El-Rowade Corrective Center) after approval of the ethic committee and a written informed consent was taken from the subjects aged >18 years. Our study enrolled 50 patients with keratoconus with the following inclusion criteria:

1. Age not exceeding 30 years old.
2. Pachymetry is not less than 400 µm.
3. Steepest corneal curvature not more than 65D.
4. Visual acuity improves with correction, with BCVA not less than 6/36.

All of the subjects will be subjected to the following:

1. Visual acuity measurement and BCVA.
2. Pentacam (Wavelight Oculyzer Allegro) study for measurement of:
   - Flat corneal curvature (K1).
   - Steep corneal curvature (K2).
   - Corneal astigmatism.
   - Corneal thickness (thinnest location).
   - Posterior surface elevation (central point and highest point in the central 5mm).
3. Corneal collagen cross-linking (removal of epithelium then riboflavin B2 for 30 minutes drop/2 minutes then UV with riboflavin for another 30 minutes then wash and antibiotic drops and contact lens). Cross linking between neighboring collagen fibers is achieved by combining the photosensitizer riboflavin with an initiating UVA beam by UV-X device. Exposing riboflavin to UVA light promotes its photomediator properties and extends the effects of the irradiation to the surrounding tissue. Following exposure, riboflavin is excited into a triplet state thereby generating reactive oxygen species; singlet oxygen and superoxide anions, These then act to induce the formation of new covalent bonds between the aminoacids of neighboring collagen fibers.

The wave length of 370nm is used to achieve maximal absorption by the riboflavin, while remaining below harmful DNA and retinal radiation levels Error! Bookmark not defined. The procedure is constant and does not cause thermal damage [9].

The treatment was conducted following local anesthesia of the eye. An abrasion of a central corneal circle is created by mechanical removal of the epithelium for better riboflavin diffusion into the stroma. This is made at a size of between 5.9mm according to the desired treatment area [10,11,12].

A 0.1% riboflavin solution in 20% dextran is applied manually every 2 minutes, starting 30 minutes before UVA exposure to allow stromal saturation. The irradiation is performed from a distance of 1cm for 30 minutes. A UVA diode at a wave length of 365-370nm is used to deliver an irradiance of 3mW/cm² (a total dose of 5.4J/cm² of the cornea) [13,14].

Repeated applications of topical anesthesia to the cornea are performed every 15 minutes. Corneal temperature during the procedure is constant and does not cause thermal damage [9].

Following the treatment a contact lens is fitted until re-epitelization and local antibiotics and steroids are applied for a duration of up to several weeks [11,13]. Error! Bookmark not defined.
Follow-up after 3 days (after complete epithelial healing) then removal of contact lens and give topical steroids for 1 month. Follow-up by penta-cam and visual acuity after 1, 3, 6 months and one year later.

Statistical analysis:
Statistical analysis was done using SPSS program for windows version 13. Continuous variables are presented as a mean and standard deviation while categorical variables are presented as frequencies and percentages. Paired \( t \)-test is used to compare continuous variables of same population. Chi square test is used to compare between nominal variables. \( p \)-value less than 0.05 is considered significant in all tests.

Results
The total number of subjects was 50 patients with keratoconus and mean age of 23.32 ± 3.99 years that ranged between 15 to 29 years. Twenty nine patients were males (58%) and 21 were females (42%). There were 50% of patients that had CXL for the right eye keratoconus and 50% for the left side. Values of visual acuity assessment and penta-cam were recorded at 0, 1, 3, 6 and 12 months after the procedure as shown in Table (1).

By comparing the means of the above mentioned values at the baseline to that at 0, 1, 3, 6 and 12 months by paired sample \( t \)-test the results were as follows:

- The UAVA showed insignificant difference at 1 month compared to baseline and inadequately significant decrease at 3 rd month. It was markedly and significantly improved on the 6 th and 12 th month compared to baseline as shown in Fig. (1).
- BCVA showed a significant decrease compared to baseline at 1.3 months and a significant improvement at the 6 th and 12 th month as shown in Fig. (2).
- K2 showed a non significant decrease at 1.3 months but the decrease was significant at 6 th and 12 th month. On the other hand K1 decreased significantly starting from the 1 st month as shown in Table (2) and Fig. (3).
- The astigmatism showed insignificant increase at the 1 st and 3 rd months and a significant decrease at 6 th and 12 th months as shown in Fig. (4).
- The posterior surface elevation (C) decreased significantly by the 3 rd month on the other hand (H) showed a significant decrease only after 6 month as shown in Fig. (5).
- There was insignificant decrease in the corneal thickness at the thinnest corneal location as shown in Table (3) and Fig. (6).

Regarding complications; there were no complications in 33/50 cases (66%) and 26% suffered from haze during the 1 st month, 4% dryness and 4% had decentememembrane folds.

Table (1): Visual acuity and penta-cam parameters at baseline and during follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Before CXL</th>
<th>1 month</th>
<th>3 month</th>
<th>6 month</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>UAVA</td>
<td>0.17±0.14</td>
<td>0.16±0.13</td>
<td>0.16±0.13</td>
<td>0.19±0.18</td>
<td>0.25±0.19</td>
</tr>
<tr>
<td>BCVA</td>
<td>0.58±0.17</td>
<td>0.49±0.17</td>
<td>0.50±0.17</td>
<td>0.65±0.19</td>
<td>0.71±0.19</td>
</tr>
<tr>
<td>K1</td>
<td>47.09±3.5</td>
<td>46.84±3.11</td>
<td>46.78±3.12</td>
<td>46.24±3.06</td>
<td>43.19±3.06</td>
</tr>
<tr>
<td>K2</td>
<td>51.59±4.67</td>
<td>51.5±4.26</td>
<td>51.46±4.4</td>
<td>50±3.9</td>
<td>46.39±3.98</td>
</tr>
<tr>
<td>CCT</td>
<td>462.82±34.73</td>
<td>462.7±34.3</td>
<td>462.24±34.34</td>
<td>462.2±34.6</td>
<td>460.42±37.56</td>
</tr>
<tr>
<td>ASTIGMATISM</td>
<td>4.52±2.06</td>
<td>4.65±2.01</td>
<td>4.55±2.05</td>
<td>3.58±1.62</td>
<td>3.24±1.59</td>
</tr>
<tr>
<td>POST-C</td>
<td>32.28±9.24</td>
<td>32.14±9.44</td>
<td>31.7±9.08</td>
<td>30.08±8.62</td>
<td>27.9±8.6</td>
</tr>
<tr>
<td>POST-H</td>
<td>41.1±12.09</td>
<td>41.3±12.68</td>
<td>40.88±12.48</td>
<td>38.7±11.85</td>
<td>36.28±11.96</td>
</tr>
</tbody>
</table>

Fig. (1): UAVA improvement after CXL.

Fig. (2): BCVA improvement after CXL.
Keratoconus is a corneal degeneration characterized by stromal thinning and conical ectasia. Unfortunately, because of the young age of onset, keratoconus often has a significant negative effect on quality of life. The course of the disease varies from slight irregular astigmatism to severe visual impairment resulting from increasing protrusion.
and subepithelial scarring, and corneal degeneration remains one of the most common indications for corneal transplantation [15].

In concordance to our study there is mounting evidence of the efficacy and safety of corneal collagen crosslinking treatment [15,16] (using the photosensitizer riboflavin and ultraviolet-A (UVA) light with a wavelength of 370nm in halting the progression of keratoconus [17,18]), (and post-refractive surgery corneal ectasia [19] with minimal toxicity and adequate safety [20]. Riboflavin, administered topically to de-epithelialized corneas, serves as a photosensitizer that is activated by UVA light. The light induced production of oxygen radicals leads to the development of strong chemical bonds between collagen fibrils, thereby stiffening the cornea.

As introduced by Wollensak et al., the crosslinking procedure significantly increases the biomechanical strength of the human cornea by up to 330%, similar to UV-induced hardening of filling materials in dentistry [13,20].

With crosslinking, additional covalent binding between collagen molecules is achieved. This stabilizes the corneal collagen scaffold and alters several tissue properties, with the stiffening effect concentrated in the anterior 200 to 300mm of the cornea due to the high absorption of UV light in this area [21].

Corneal collagen crosslinking with riboflavin and UVA has been shown to be a safe and effective treatment for keratoconus. However, the safety parameters must be strictly adhered to because UVA light can damage the cornea [22]. In our study there was no recorded complications in 66% of population and nil recorded major complications or reactivation of herpetic keratitis. Corneal haze has been recorded in 26% of cases and improved within 1 month after the procedure.

By comparing visual acuity changes in our study during follow-up to baseline values; the visual acuity in our study was found to improve across the period of follow-up but on the other hand it was fixed and showed no further deterioration in Dilarj study in 2009 as BCVA (0.22 ±0.10 and 0.20±0.10 and p-value 0.89) [15]. Also there was improvement in astigmatism in our study in front of non significant improvement in Dilarj study.

In concordance to our improved visual acuity, Paolo et al conducted a study on 28 keratoconic patients and found that mean baseline UCVA and BSCVA were 0.17±0.09 and 0.52±0.17, respectively; 12-month mean UCVA and BSCVA were 0.27±0.08 and 0.72±0.16, a statistically significant difference (p=0.05) Error! Bookmark not defined.

In our study K1 and K2 showed a significant decrease during 1 year follow-up Paolo found that Mean baseline simulated keratometry (SIM K) flattest and steepest meridians and SIM K average were 46.10, 50.37, and 48.08 D, respectively; at 12 months, 40.22, 44.21, and 42.01 D, respectively, were recorded, a difference that was significant for all 3 indices (p<0.05) Error! Bookmark not defined.

In concordance to other studies the corneal thickness in our study showed insignificant change across 1 year follow-up as that was concluded by Dilarj study that was no significant difference in mean measurements between preoperatively and 1 year postoperatively, respectively, for central corneal thickness (458.9±40nm & 455.2±48.6mm) [15].

Also there was insignificant differences in Dilarj study between baseline and follow-up measurements of the anterior corneal curvature (50.6±7.4 D and 51.5±3.6 D), posterior corneal curvature (7.7±1.2 D and 7.4±1.1 D), apex anterior (p=0.9), posterior corneal elevation (p=0.7) and he concluded that the corneal thickness and corneal volume after crosslinking remained stable until the 1-year follow-up, suggesting that crosslinking did not induce significant edema.

Also Paolo found that total (whole eye) aberrations showed a significant reduction in astigmatism and spherical aberrations. However, corneal surface aberrometric analysis did not show an improvement in coma, indicating that there is a significant change in the posterior surface of the cornea, which was masked by the total aberration status Error! Bookmark not defined.

In our study there as a significant improvement of the posterior point elevation but Dilarj did not observe a significant change in anterior or posterior corneal elevation values, that provides additional evidence of the stability of the corneal surface. However, the anterior and posterior elevation data before and after crosslinking did show a very large standard deviation in his study.

Future therapies may be optimized by combining the crosslinking procedure with intracorneal rings [23] and topography-guided photorefractive keratectomy [24] and might even provide the possibility of reversing the ectasia.
Conclusion:

CXL is a safe minimally invasive procedure that showed improvement in UAVA and BCVA in keratoconus along 1 year follow-up. CXL stopped the progression of keratoconus along 1 year follow-up with unchanged corneal thickness. CXL is a safe with infrequent and unsustained complications for treatment of keratoconus.

References


