COMPARISON OF RAPID AND CONVENTIONAL CORNEAL COLLAGEN CROSS LINKING IN PATIENTS HAVING KERATOCONUS

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ABSTRACT

Objective: To compare the effect of rapid and conventional methods of corneal collagen cross linking (CXL) on visual acuity (VA) and corneal parameters in Keratoconus.

Study Design: Randomized control trial.

Place and Duration of Study: Armed Forces Institute of Ophthalmology, Feb 2012 to Apr 2013.

Patients and Method: Thirty patients, fifteen in each group, were randomized by non probability consecutive sampling to rapid or conventional CXL group. Pre and post operative (6 months) best corrected visual acuity (BCVA), anterior and posterior keratometric (K) values and pachymetry were recorded. Intra and inter group comparison of all these parameters were statistically analyzed.

Results: All thirty patients showed either stabilization or improvement in BCVA. Both groups showed comparable results in terms of improvement BCVA (p = 0.682), reduction in the corneal thickness at thinnest point (p = 0.062), anterior flat and steep K (p = 0.633, p = 0.443 respectively) and posterior flat and steep K values (p = 0.130, p = 0.068) at six months duration.

Conclusion: Conventional and rapid methods of CXL are comparable in terms of their effect on VA and corneal parameters.

Keywords: Astigmatism, Corneal topography, Keratoconus.

INTRODUCTION

Corneal collagen cross linking is an established procedure for halting the progression of eccentric and Keratoconus. Ever since its advent, this modality has been at the height of its exploration by researchers. In Keratoconus collagen lamellae with lattice arrangement in corneal stroma have reduced number, irregular arrangement and separation between bundles. CXL produces extra bonds between the collagen fibrils in stroma by photopolymerization leading to biomechanical effects on cornea. Finally it causes stiffening of the ectatic cornea. Standard protocol for CXL includes removal of epithelium, however transepithelial techniques are also employed. As per the conventional method, (the Dresden protocol)4 after removing epithelium, cornea is exposed to dextran based 0.1% Riboflavin solution for 30 minutes. Corneas having thickness less than 450 microns are pre treated with dextran free 0.1% Riboflavin. Once a strong yellow flare is identified in the anterior chamber, the cornea is irradiated with Ultra Violet A (UVa) rays (365-370 nm), light source 5 cm away from the eye, having luminance of 3 mW/cm² for thirty minutes. The total radiant exposure is 5.4 J/cm². The rapid or accelerated modality (9 mW/cm² for ten minutes) employs the Bunsen Roscoe law, which suggests that keeping the radiant exposure at constant and increasing the fluence, we can reduce the duration of exposure thus achieving the same corneal biomechanical effects as with conventional technique. The rapid, high fluence method can be utilized in the interest of both patients and the surgeons. The aim of this study is to compare the effect of rapid with conventional CXL in terms of BCVA,
pachymetry, anterior and posterior flat and steep K values.

PATIENT AND METHODS

A total of thirty patients were enrolled after approval from the hospital ethical committee and informed consent of the patients. Fifteen patients were randomized to each group that is the conventional and rapid group. Diagnosed patients of Keratoconus, more than 18 years of age, having more than 1 Dioptre (D) change in refraction, more than 1.5 D change in anterior steep K and more than 1D change in posterior steep K over past one year were included. Patients having history of systemic and other ocular disorders, corneal scarring, thinnest point pachymetry less than 400 microns and steep K values more than 58 D were excluded. Patients were worked up for their uncorrected and best corrected visual acuity (Snellen’s chart). Corneal topography on Galilei G4-Dual Scheimpflug Analyzer V 6.0.3, was performed and corneal thickness at the thinnest point, anterior and posterior steep and flat keratometry (K) values were recorded at baseline. The values were recorded on a predesigned proforma. In the conventional group, epithelium was removed with Kimura Spatula under topical anesthesia. Stromal bed was exposed to isotonic Riboflavin drops (vitamin B2 > 0.1%, HPMC 1.1%, MedioCROSS-MR) every two minutes for 30 minutes. In case of corneal thickness less than 450 microns, cornea was pretreated with hypotonic Riboflavin drops (vitamin B2 > 0.1%, MedioCROSS-HR) for ten minutes. Per operative pachymetry was performed and once corneal thickness reached to 400 microns only then rest of the procedure with isotonic Riboflavin drops was undertaken, otherwise the hypotonic Riboflavin was again administered for ten minutes duration. After confirming flare in anterior chamber, cornea was irradiated with UVA of 3 mW/cm² luminance for 30 minutes. Same procedure was carried out in the accelerated group, but with high fluence and lesser time; 9 mW/cm² for ten minutes. At the end of the procedure soft bandage contact lens was applied, topical drops including 1% Cyclopentolate and 0.5% Moxifloxacin eye drops were prescribed every 8 hours for two weeks along with tablet Diclofenac 50 mg twice a day for initial three days. All patients underwent routine follow up in OPD on first post op day, one week and later after one and six months of procedure. Patients’ post operative assessment of corrected visual acuity and other corneal biomechanical properties already mentioned recorded at six months visit were taken as final outcome measure.

Statistical analysis was performed by SPSS version 20.0. Results were expressed as mean ± standard deviation or median ± Inter quartile range (IQR), where appropriate, for all continuous variables. For categorical data frequency and percentage were calculated. t-test and Mann Whitney U test (where applicable) were applied according to the type of data and distribution of variables. p-value < 0.05 was considered statistically significant.

RESULTS

There were 7 (46.7%) males and 8 (53.3%) females in conventional group and 8 (53.3%) males and 7 (46.7%) females in the rapid group. Mean age in the conventional and rapid groups was 24.3 ± 2.3 and 23.7 ± 2.5 years respectively. Both the groups were comparable in terms of gender and age (p > 0.05).

Visual acuity was graded as better (improvement of > one line), same or worse (deterioration > one line). In the conventional group 10 (66.7%) while in rapid group 12 (80%) patients had better vision. No patient in either group showed worse post operative vision at six months as shown in the Fig-1. Results of the two groups were found to be comparable (p = 0.682).

Thinnest point pachymetry was taken as the reference point for all patients. The reduction in corneal thickness at the end of six months was statistically significant in each group (p < 0.001). Both the groups were found to be comparable in terms of the change in corneal thickness post operatively (p = 0.062).
Anterior keratometric readings, both flat and steep K values were reduced significantly at six months in both the groups (Table-1) and on comparison both the groups showed no statistical significant difference (p = 0.633, p = 0.443 for flat and steep K values respectively).

Conventional group caused significant decrease in posterior flat and steep K values, whereas the rapid group showed statistically insignificant change in posterior K values at six months (Table-1). But on inter group comparison the two groups were again comparable with insignificant p value of 0.130 and 0.068 for posterior flat and steep K values respectively. Here it is noteworthy that the effect of rapid CXL technique on posterior flat and steep K values was statistically insignificant. Both the groups were found to be comparable in all parameters under consideration including best corrected visual acuity, pachymetry, anterior flat and steep K values and posterior flat and steep K values at six months.

**DISCUSSION**

CXL has been a focus of corneal surgeons and researchers over the past one decade.

**Table-1: Effect of conventional and rapid corneal collagen cross linking (CXL) on corneal parameters.**

<table>
<thead>
<tr>
<th>Corneal parameters</th>
<th>Pre operative</th>
<th>Post operative</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pachymetry (microns) (Conventional )</td>
<td>468.93+25.92</td>
<td>439.67+27.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pachymetry (microns) (Rapid)</td>
<td>428.13+50.11</td>
<td>410.80+51.58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior flat K(D) (Conventional)</td>
<td>44.56+1.14</td>
<td>43.66+1.56</td>
<td>0.005</td>
</tr>
<tr>
<td>Anterior flat K(D) (Rapid)</td>
<td>47.08+4.78</td>
<td>45.45+3.32</td>
<td>0.029</td>
</tr>
<tr>
<td>Anterior steep K(D) (Conventional)</td>
<td>47.83+2.03</td>
<td>46.56+1.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anterior steep K(D) (Rapid)</td>
<td>50.29+5.38</td>
<td>48.38+3.38</td>
<td>0.024</td>
</tr>
<tr>
<td>Posterior flat K(D) (Conventional)</td>
<td>-7.20+0.65</td>
<td>-6.89+0.90</td>
<td>0.038</td>
</tr>
<tr>
<td>Posterior flat K(D) (Rapid)</td>
<td>-7.26+0.93</td>
<td>-7.25+1.26</td>
<td>0.964</td>
</tr>
<tr>
<td>Posterior steep K(D) (Conventional)</td>
<td>-8.01+0.70</td>
<td>-7.59+0.97</td>
<td>0.007</td>
</tr>
<tr>
<td>Posterior steep K(D) (Rapid)</td>
<td>-7.99+1.10</td>
<td>-8.00+1.22</td>
<td>0.945</td>
</tr>
</tbody>
</table>

**Table-2: Comparison of conventional and rapid corneal collagen cross linking (CXL) group**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Difference observed at six months</th>
<th>Comparison between two groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional Median+IQR</td>
<td>Rapid Median+IQR</td>
</tr>
<tr>
<td>Anterior flat K(D)</td>
<td>0.90+1.46</td>
<td>0.94+1.64</td>
</tr>
<tr>
<td>Anterior steep K(D)</td>
<td>1.10+1.26</td>
<td>1.92+2.92</td>
</tr>
<tr>
<td>Posterior flat K(D)</td>
<td>-0.29+0.67</td>
<td>-0.07+0.64</td>
</tr>
<tr>
<td>Posterior steep K(D)</td>
<td>-0.37+0.80</td>
<td>0.02+0.69</td>
</tr>
</tbody>
</table>

**Figure-1: Effect of corneal collagen cross linking (CXL) on Best corrected visual acuity at six months.**

Incidence of corneal transplant in Keratoconic eyes has greatly reduced ever since CXL has been adopted as a regular method of halting
progression of Keratoconus. Visual improvement has shown to occur after three months. Many studies have concluded that CXL (conventional method) has a clinically significant effect on keratometry readings and vision. Raisskupf Wolf et al concluded that steep K values decreased by 2.68 D and visual acuity improved by more than or equal to one line in 53% patients by the end of first year. Our results showed change in anterior steep K values of 1.10 D and improvement in vision in 66.7% of the patients in conventional group, main difference between the two studies was shorter duration of our study. Both, best corrected visual acuity and K values showed statistically significant improvement in Melbourne study carried out on 49 patients at 12 months duration. Long term stabilization of corneal parameters up to 48 months has been shown by Caporossi A and colleagues. Rapid CXL with high fluence UVA irradiation has been studied by Gatziofus Z and co researchers who found out that at the end of six months, accelerated method although safe did not show significant change in keratometric values and uncorrected visual acuity. They adopted 5 minutes protocol (18 mW/cm²) and only seven eyes were included whereas our study had 15 patients who underwent 10 min (9mW/cm²) protocol. Dan Gore and Bruce Allan of Moorefield Eye Hospital who worked on rapid CXL of 4 minutes protocol with 30mW/cm2 luminance with follow up duration six months, observed that the decrease in mean pachymetry (11 microns) was statistically significant (p = 0.02). This results was similar to our study in which the decrease in pachymetry was statistically significant (p < 0.001). The same study carried out at Moorefield Eye Hospital, observed an insignificant decrease in posterior steep K value (p = 0.96), insignificant increase in anterior steep K value (p = 0.20) and a significant increase in anterior flat K (p = 0.001). All these results are contrary to our observation where anterior flat and steep K values were significantly decreased (p = 0.029 and p = 0.024 respectively) and posterior steep K was insignificantly increased (p = 0.945). This study was different from our study in the respect that it used 4 minutes protocol with 30 mW/cm² luminance and all patients of ectasias were included unlike our study which included only Keratoconus patients. Another recent study by Cinay et al did not reveal any statistically significant difference between accelerated and conventional methods of CXL at six months. We can understand from these studies that rapid method is comparable to the conventional method in treatment of Keratoconus, however randomized controlled trials of larger sample size and longer duration are required to establish the effect of rapid technique.

CONCLUSION

Rapid or accelerated method of CXL is comparable to the conventional method in terms of visual acuity, pachymetry, anterior and posterior K readings in Keratoconus patients. Replacing the rapid method with the conventional one can be beneficial and convenient both for the patient as well as the surgeon.

Conflict of Interest: This study has no conflict of interest to declare by any author.

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