Tomographic and Biomechanical Properties Changes Following Transepithelial (Epi-on) Corneal Crosslinking in Keratoconus

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Abstract

This is a prospective, interventional and non-controlled case series study; performed on 20 eyes having keratoconus.

The aim of this study is to evaluate effect of transepithelial (epi-on) Corneal Collagen Crosslinking (CXL), in the management of keratoconus, regarding changes in vision, tomographic and biomechanical properties of the cornea, for 1 year.

All patients underwent transepithelial (epi-on) corneal collagen crosslinking, and evaluation was done preoperatively and postoperatively at 3, 6 and 12 months, regarding Changes in Best Corrected Visual Acuity (BSCVA), maximum corneal curvature (Kmax), Central Corneal Thickness (CCT), Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF).

Results of the study showed that BSCVA decreased significantly after 1 year, associated with insignificant flattening of the cornea (Kmax insignificant decrease after 1 year). Results also showed statistically significant decrease in Central Corneal Thickness (CCT) after 1 year. Biomechanical properties of the cornea did not improve after 1 year, with the decrease in Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF). No corneal haze occurred postoperatively in all patients.

Key Words: Corneal collagen crosslinking – Keratoconus – Transepithelial (epi-on) – Biomechanical properties of cornea.

Introduction

KERATOCONUS is a common noninflammatory, degenerative disorder of the cornea, characterized by stromal thinning and conical ectasia that results in irregular astigmatism and associated visual loss [1].

In 2003, Wollensak et al., [2] introduced Corneal Collagen Crosslinking (CXL) using riboflavin and Ultraviolet-A (UVA) for the treatment of progressive keratoconus. The technique was shown to arrest the progression of keratoconus after crosslinking due to the increase in the biomechanical strength of the human cornea.

Riboflavin and Ultraviolet-A (UVA) increases the biomechanical stability of the corneal stroma and the resistance to enzymatic digestion by inducing crosslinkage between the stromal collagen molecules [3].

Aim of work: The aim of this study is to evaluate effect of transepithelial (epi-on) Corneal Collagen Crosslinking (CXL), in the management of keratoconus, regarding changes in vision, tomographic and biomechanical properties of the cornea, for 1 year.

Patients and Methods

This study conducted in Ophthalmology Department, Faculty of Medicine, Cairo University from 2013-2015. This is a prospective, interventional and non-controlled study; performed on 20 eyes having keratoconus.

Patient selection:

Inclusion criteria:

- Keratoconus patients with corneal thickness greater than 400um.
- Age group: 18- 40 years old.
- Patients should be ophthalmologically free apart from having keratoconus.

Exclusion criteria:

- Keratoconus patients with history of previous corneal surgeries or previous crosslinking.
- History of herptic keratitis, any corneal infection and severe dry eye.
- Corneal thickness less than 400 microns at any point.
Diabetes mellitus, concomitant autoimmune diseases.

Pregnant or lactating females.

Corneal scarring, central or paracentral opacities, or other anterior segment pathology.

**Patient counseling and consent:**

All patients received a thorough explanation of the study procedure. Study participants gave informed consent before initiation of any study related procedures; elaborating expected results and any possible complications.

**Pre-operative assessment:**

All patients were evaluated by full medical history, full review of their ophthalmic history and full ophthalmologic examination, including the objective refraction, uncorrected and best spectacle corrected Snellen visual acuity (UCVA and BSCVA), slit lamp examination, posterior segment examination, and intraocular pressure measurement. Evaluation of corneal tomographic data included CCT and Kmax, and corneal biomechanical data included CH and CRF.

**Surgical technique:**

Topical anesthesia Benoxinate eye drops was administered before surgery. Standard preoperative preparation with 5% povidone iodine was performed. The eyelids and eyelashes were covered with a sterile drape. A special riboflavin solution was used; Medio-Cross TE (Peschke Meditrade GmbH, Germany), composed of 0.25% riboflavin-5-phosphate hydroxypropyl methylcellulose, benzalkonium chloride and NaCl, was instilled topically every 2 minutes for 30 minutes. The cornea was exposed to UVA light of 366-374nm at an irradiance of 3,0mW/cm² for 30 minutes (UV-X, Zurich, Switzerland). Meanwhile riboflavin instillation was continued every 2 minutes. At the end of the procedure, antibiotic drops were administered. Antibiotic tears, artificial tears and corticosteroid drops were used with gradually tapering of steroids over 3-4 weeks, and stopped after one month. Artificial tears were also continued for the same period.

**Postoperative evaluation:**

Postoperative follow-up visits were scheduled at the 1st, 4th, 6th, 30th day and the 3rd, 6th, 12th month after surgery. Best corrected visual acuity is measured, slit lamp examination; and assessment of epithelial healing. Corneal tomographic data was evaluated using Ocular Response Analyzer (ORA) (Reichert Ophthalmic Instruments, New York, USA).

**Results**

**Patients demographics:**

20 keratoconic eyes, 6 of which were for male patients (30%) and 14 were for female patients (70%). The mean age of the patients is 25.25±2.99 years, ranging from 20 to 31 years.

**Outcomes:**

1- **BSCVA:**

VA has been measured in Snellen decimal value. The mean postoperative BSCVA at three month was 0.3±0.19 ranging from 0.1 to 0.87, decreasing insignificantly by a mean of 0.063±0.217 Snellen’s lines with \( p \)-value 0.021. At 6 months the mean BSCVA was 0.37±0.21 ranging from 0.08 to 0.78 thus improving significantly by a mean of 0.006±0.289 Snellen’s lines compared to preoperative BSCVA with \( p \)-value 0.009. Finally at 12 month BSCVA decreased to 0.33±0.21 ranging from 0.1 to 0.8, decreasing significantly by a mean of 0.032±0.226 Snellen’s line compared to preoperative BSCVA with \( p \)-value 0.001, as shown in Fig. (1) and (Table 1).

![Fig. (1): Graph comparing both preoperative and postoperative mean BSCVA at 3, 6 and 12 months.](image)

**Table (1):** Changes in BSCVA throughout this study group and its significance using the paired \( t \)-test.

<table>
<thead>
<tr>
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<th>Mean preoperative BSCVA</th>
<th>Mean postoperative BSCVA at 3 month</th>
<th>Mean postoperative BSCVA at 6 months</th>
<th>Mean postoperative BSCVA at 12 months</th>
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<tr>
<td></td>
<td>0.365±0.18</td>
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2- Pentacam findings:
• K-readings:
   The topographic analysis done by the Pentacam revealed a mean preoperative Kmax of 50.605±4.54 D ranging from 45.1 D to 59.3 D. The mean postoperative Kmax at three months was 49.78±3.51 D ranging from 45.95 D to 56.4 D with a decrease of 0.822±0.527 D which was statistically insignificant (p-value=0.514). The mean postoperative Kmax at 6 months was 49.5±1.8 D ranging from 46.6 D to 52.5 D, thus showing a mean reduction of 1.105 D±1.8 D compared to preoperative Kmax which was statistically insignificant (p-value=0.342). The mean postoperative Kmax at 12 months was 50.27±3.13 D ranging from 46 D to 56.2 D, thus showing a mean reduction of 0.340 D±3.13 D compared to preoperative Kmax which is statistically significant (p-value=0.002). All data are shown in Fig. (2) and (Table 2).

3- Corneal biomechanics (ORA results):
• Corneal hysteresis and corneal resistance factor:
   The mean preoperative Corneal Hysteresis (CH) was 8.025±0.85 mmHg ranging from 6.2 to 9 mmHg. The mean CH after 3 months was 7.92±0.43 mmHg ranging from 7.25 to 8.55 mmHg; with a decrease of 0.11±0.51 mmHg which is statistically insignificant (p-value=0.632). At 6 months, CH decreased to 7.64±0.53 mmHg ranging from 7 to 8.4 mmHg; with a decrease of 0.38±1.03 mmHg from preoperative values, which is also statistically insignificant (p-value=0.083). And lastly at 12 months, CH decreased to 7.62±0.55 mmHg ranging from 7.1 to 8.7 mmHg; that is less than preoperative values by 0.38±1.03 mmHg, which is statistically significant (p-value=0.009).

   The mean preoperative Corneal Resistance Factor (CRF) was 7.05±1.04 mmHg ranging from 6 to 8.8 mmHg. Mean CRF values at 3 months was 6.73±0.59 mmHg, ranging from 5.8 to 7.5, thus the mean CRF decreased significantly by 0.32±1.06 mmHg at 3 month with p-value=0.002. At 6 months
mean CRF decreased to 6.75±0.57mmHg ranging from 6 to 7.5mmHg; thus decreasing significantly by 0.303± 1.017mmHg at \( p \)-value=0.001. On the last visit after 12 months, CRF reached 6.68±0.49mmHg ranging from 6.1 to 7.5mmHg, less than preoperative values by 0.37±1.062mmHg which is statistically insignificant at \( p \)-value=0.778.

All figures and values of Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF) are shown in Figs. (4,5) and (Table 4).

Discussion

An intact corneal epithelium absorbs 30-33% of UVA irradiation, and with additional effect of riboflavin in the epithelium, this blockage rate reaches to approximately 85%. In addition to UVA blockage, an intact corneal epithelium avoids the riboflavin infiltration to corneal stroma, because of its hydrophilic macromolecular structure. It has been reported that some substances such as benzalkonium chloride, EDTA, and trometamol may enhance the epithelial penetrance of hydrophilic macromolecules. Based on these findings, transepithelial CXL has been defined for the treatment of progressive keratoconus without debridement of corneal epithelium [4].

There are controversial reports about the efficacy of TE-CXL. Koppen et al. [4], analyzed the efficacy of TE-CXL in 53 eyes of 38 patients with progressive keratoconus. They reported that TE-CXL was less effective than standard CXL in stabilizing progressive disease. However, Filipello et al. [5], reported that TE-CXL appeared to stop keratoconus progression with a significant improvement in visual and topographic parameters in a patient group of 20 keratoconus cases.

Regarding Best Spectacle Corrected Visual Acuity (BSCVA), our study showed there was significant reduction of BSCVA after 1 year, decreasing significantly by a mean of 0.032±0.226 Snellen's lines with \( p \)-value 0.001. In their study, Kocak et al. [6], showed no statistically significant change in BSCVA after 1 year. Fileppelo et al. [8], conducted a study in 2012 on 20 patients with bilateral keratoconus; treating the worse eye with transepithelial CXL. They found statistically significant improvement of BSCVA after 1 year. In their study, a ring shaped silicon container was used to increase corneal contact time with riboflavin during CXL. And this may have played a role in increasing effectiveness of the transepithelial CXL procedure, thus explaining the improvement of vision.

Regarding corneal topography, Kmax, our study showed that there was a statistically insignificant flattening of Kmax after 1 year. The mean preoperative Kmax was 50.60±4.54D, and the mean postoperative Kmax after 1 year was 50.27±3.13D, showing a mean reduction of 0.34D±5.32D with \( p \)-value 0.77. Kocak et al. [6], reported that in transepithelial (epi-on) CXL, Kmax showed statistically significant steepening (worsening) after 1 year. In their study concerning transepithelial (epi-on) CXL in 2012; Fileppelo M et al. [8], found
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statistically significant improvement (flattening) in Kmax after 1 year.

Regarding corneal pachymetry, CCT measurements showed the mean preoperative Central Corneal Thickness (CCT) was 441.85±23.07µm, and after 1 year the CCT decreased to 419.12±13.57µm, with a decrease by 22.7±27.87µm which is statistically significant difference (thinning) \((p\text{-value}=0.002)\). Our results also concur with results of the comparative study carried out by Kocak I et al. [6], in 2014; where they showed statistically significant decrease (thinning) after 1 year (approximately 5% thinning).

Regarding corneal biomechanical properties as measured by Ocular Response Analyzer (ORA), our study showed that Corneal Hysteresis (CH) decreased significantly after 1 year, decreasing by 5.05%. And as for Corneal Resistance Factor (CRF), there was also a decrease in CRF after 1 year (which was insignificant). Preoperative CH was 8.025±0.85mmHg and CRF was 7.05±1.04 mmHg, and after 1 year they decreased to 7.62±0.55 mmHg and 6.68±0.49mmHg respectively.

Regarding postoperative complications after Transepithelial CXL, there was no postoperative haze in all cases.

References


الملخص العربي

تم تصميم الانتباه الكولاجيني عبر الخلايا الطلائية لتجنب الألم المبكر بعد العملية الجراحية والتدورة المؤقتة الرؤية، وهو ما كان يحدث مع تقنية الإنتباه الكولاجيني التقليدية، وذلك عن طريق تجنب ازالة الخلايا الطلائية. وقد أظهرت نتائج الدراسة أنه بالرغم من عدم وجود علامة بالقرنية بعد الجراحة أو ألم، إلا أن التقييم لم يظهر تحسينًا في حالة القرنية. وعلى الرغم من التسلط الضئيل في القرنية بعد سنة (انخفاض Kmax) فوق كبير بعد سنة. أيضاً لم تظهر الخصائص الميكانيكية الحيوية للقرنية تحسنا بعد سنة. وظهر ذلك في احتفاظ مقاومة CCT المركزية (Kmax) فوق كبير بعد سنة. أيضا، لم تظهر الخصائص الميكانيكية الحيوية للقرنية تحسنا بعد سنة. وظهر ذلك في احتفاظ مقاومة CRF. وعامل صلابة القرنية (CH) القرنية.