OUTCOMES OF CORNEA COLLAGEN CROSS-LINKING IN THE MANAGEMENT OF KERATOCONUS

KERATOKONUSTA UYGULANAN KORNEA KOLLAJEN ÇAPRAZ BAĞ TEDAVİSİ SONUÇLARIMIZ

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ABSTRACT

PURPOSE: To evaluate the results of cornea collagen cross-linking (CXL) in the management of keratoconus (KC).

PATIENTS AND METHODS: The data of 30 eyes of 23 patients who underwent CXL for the management of KC between May and October 2012 were reviewed retrospectively. Preoperative and postoperative first, third and sixth month uncorrected and best corrected visual acuities, corneal topographies by Pentacam, and corneal endothelial cell counts by specular microscopy were evaluated.

RESULTS: The median age of 12 male and 11 female patients was 18 (12-31). Uncorrected visual acuity was increased at 3 and 6 months of follow-up but the difference was not statistically significant (P =0.738). The best corrected visual acuity was decreased one month after the procedure and increased to the preoperative values at 3 and 6 months of follow up (P =0.528). Corneal densitometry value was increased significantly at 1, 3 and 6 months of follow up compared to the preoperative value (P <0.001, <0.001 and 0.028 respectively). The median corneal thickness at the thinnest location was decreased significantly at 1 month postoperatively (P <0.001) and then increased to the levels that was very close to the preoperative values. No significant difference was found in corneal endothelial cell count between preoperative and postoperative values (P =0.119). K1, K2, Kmax and Kapex values were increased slightly one month after CXL and then gradually decreased at 3 months and 6 months postoperatively but these differences did not reach statistical significance (P = 0.809, 0.408, 0.131, and 0.624, respectively). No significant change was found in corneal asphericity value (Q value, P =0.597). No complication and no signs of progression in KC were detected in any of the eyes.

CONCLUSIONS: Our results are compatible with the studies in the literature. CXL is a cheap and safe method to halt the progression of KC. Although the number of cases and follow up time are limited, this study is valuable to show our clinical CXL application is safe, effective and compatible with previous reports.

Keywords: *Keratoconus, corneal collagen cross-linking, Scheimpflug imaging.*

ÖZET

AMAÇ: Kliniğimizde keratokonus (KK) tanılı hastalarda uygulanan kornea kollajen çapraz bağ (KÇB) tedavisinin sonuçlarının değerlendirilmesi.

HASTALAR VE YÖNTEM: Mayıs ve Ekim 2012 tarihleri arasında KK tanısı ile KÇB tedavisi uygulanmış 23 hastanın 30 gözü geriye dönük olarak incelendi. Tedavi öncesi ve tedavi sonrası 1, 3 ve 6. aylardaki düzeltilmemiş ve en iyi düzeltilmiş görme keskinlikleri, Pentacam ile elde edilen kornea topografileri, speküler mikroskopi ile elde edilen kornea endotel hücre sayıları incelendi.

BULGULAR: On ikisi erkek, 11'i kadın hastanın yaşlarının ortanca değeri 18 (12-31) yıl idi. Düzeltilmemiş görme keskinliklerinde takiplerde işlem öncesine göre özellikle 3. ve 6. ayda artış olmasına rağmen fark anlamlı bulunmadı (P =0.738). Düzeltilmiş görme keskinliğinde 1. ayda düşüş görülmesine rağmen 3. ve 6. aydaki değerler işlem öncesi ile aynı düzeyde saptandı (P =0.528). Kornea dansitometre değerlerinde işlem öncesine kıyasla 1, 3 ve 6. aylarda anlamlı artış görüldü (sırasıyla P <0.001, <0.001 ve 0.028). İşlem sonrası 1. ayda en ince kornea kalınlığı değerlerinde anlamlı düşüş (P <0.001) ve bu düşüşü takiben 3. ve 6. aylarda başlangıç değerlerine yakın artış görüldü. Endotel hücre sayımlarında işlem öncesi ve takipler arasında anlamlı fark bulunmadı (P =0.119). K1, K2, Kmax ve Kapex değerlerinde 1. ayda hafif bir artış görülse de 3. ve 6. ay değerlerinde düşüş görüldü. Ancak bu düşüş işlem öncesi değerlere göre anlamlı bulunmadı (sırasıyla P =0.809, 0.408, 0.131, 0.624). Kornea asferisite değeri (Q değeri) açısından işlem öncesi ve takip değerleri arasında anlamlı fark görülmedi (P =0.597). Tedavi uygulanan hiçbir olguda komplikasyon gelişmedi ve keratokonus ilerleme bulgusuna rastlanmadı.

SONUÇ: Çalışmamızda elde edilen bulgular genel olarak literatürdeki diğer çalışmalarla paralellik göstermektedir. KÇB tedavisi KK ilerlemesinin durdurulmasında ucuz ve etkili bir yöntemdir. Olgu sayısı ve takip süresi kısıtlı olsa da bu çalışma kliniğimizde uygulanan KÇB tedavisinin etkin, güvenli ve literatür ile uyumlu olduğunu bildiren ilk çalışma olması açısından önem arz etmektedir.

Anahtar kelimeler: *Keratokonus, kornea kollajen çapraz bağ tedavisi, Scheimpflug görüntüleme*

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INTRODUCTION

Keratoconus (KC) is a corneal ectasia characterized by non-inflammatory, progressive thinning and cone-shaped protrusion of the cornea (1; 2). KC is generally asymmetric bilateral disease (2). It is a relatively common disease with a prevalence ranging from 50-230 per 100.000 (1). The etiology of KC is unknown (possibly multifactorial) and a strong association with eye rubbing has been reported (1, 2). A positive family history is present in a small number of patients (1, 2). Patients usually present in their second or third decade of life with progressive visual blur and distortion secondary to progressive high myopia and astigmatism (1). Corneal topography is a very useful tool in the diagnosis and tracking of the disease (1, 2).

Spectacles, soft, rigid or hybrid contact lenses, intrastromal corneal ring segments, and phakic intraocular lenses are several methods for the management of refractive outcomes of KC but none of these procedures can halt the progression of disease (1). Corneal collagen cross-linking (CXL) technique uses riboflavin and ultraviolet-A (UV-A) light to create additional covalent bonds between collagen molecules and thus increases corneal stiffness and corneal resistance against proteolytic enzymes (1, 3). CXL is the only method developed so far that halts the progression of the disease (1).

The aim of this study was to present our preliminary clinical results of CXL treatment in KC and to compare the safety and effectiveness of our CXL application with previous studies.

PATIENTS AND METHODS

Before the study, institutional review board approval was obtained and the study is adhered to the principles of Helsinki Declaration. Between May and October 2012, data of the patients who underwent CXL treatment for the management of KC were reviewed retrospectively from patient charts. A written informed consent was obtained from each patient before the CXL procedure. Postoperative first, third and sixth months uncorrected and best corrected visual acuities were recorded by Snellen charts. Corneal topography and Scheimpflug imaging were assessed using Pentacam (Oculus Inc., Wetzlar, Germany), and corneal specular microscopy was performed using Konan Specular Microscope (Konan Medical Inc., Hyogo, Japan) at each follow up time. Keratometry (K) values, such as K1, K2, Kmax (central maximum keratometry value) and Kapex (the steepest keratometry value of the cone), corneal thickness, and corneal anterior and posterior surface elevation values were evaluated using Pentacam. Corneal density measured by Pentacam Scheimpflug system.

Corneal cross-linking procedure

CXL is performed under sterile conditions in the operating room and under topical anesthesia. Central corneal epithelium (in an 8.0 mm diameter area) was mechanically removed. Then, 0.1% riboflavin, 20% dextran solution (MedioCross, Peschke Meditrade GmbH, Nürnberg, Germany) was instilled on the cornea every 3 minutes during the next 30 minutes. Before ultraviolet-A (UV-A) light application, ultrasonic corneal pachymetry (PacScan 300AP, Sonomed Escalon, New York, NY, USA) was performed to confirm the corneal thickness was above 400 μm. Then, 370 nm UV-A light with an irradiance of 3 mW/cm^2 (Opto XLink Corneal Cross- linking System, Opto Electronica S/A, Sao Paulo, Brazil) was applied to the 8 mm diameter central corneal surface from 5-6 cm distance for an additional 30 minutes. Riboflavin solution was instilled at every 5 minutes during UV-A irradiation. After the procedure, the cornea was washed with balanced salt solution and a bandage contact lens (Air Optix, Ciba Vision, Duluth, GA, USA) was placed on the cornea. During follow up, 0.3% ofloxacin (Exocin, Abdi Ibrahim Ilac, Istanbul, Turkey) 4 times daily and sodium hyaluronate included artificial tear drops (Eyestil, Teka Ilac, Istanbul, Turkey) 8 times daily were prescribed to the patients. When corneal re-epithelialization was completed, contact lens was removed and 0.1% fluorometolon eye drop (FML, Abdi Ibrahim Ilac, Istanbul, Turkey) 4 times daily was added to the treatment. The medications were tapered and stopped according to patient's clinical status.

Statistical Analyses

Statistical analyses were performed using SPSS program for Windows (version 17, SPSS, Chicago, IL, USA). Median values (minimum-maximum) were used for continuous variables, and numbers and percentages were used to show categorical data. Wilcoxon signed-rank test was used to compare two dependent continues variables and Friedman test was used to compare more than 2 dependent continuous variables. Visual acuities are shown in decimal notation. P values below 0.05 were considered as statistically significant.

RESULTS

The study included 30 eyes of 23 patients (12 male and 11 female). Median age was 18 (12-31) years. None of the patient was pregnant or breastfeeding at the time of the treatment and none of them had ocular pathology other than KC and previous refractive or corneal surgery. During follow up, although uncorrected visual acuities were increased, the difference did not reach statistical significance **(Table 1).** The best corrected visual acuity was decreased one month after the procedure and increased to the preoperative values at 3 and 6 months of follow up **(Table 1).**

Median corneal densitometry value in Scheimpflug imaging were increased significantly at 1, 3 and 6 months of follow up periods compared to the median preoperative value (P <0.001, <0.001 and 0.028 respectively, **Figure 1A and 2)**. Corneal thickness at the thinnest location was decreased significantly at 1 month postoperatively (P <0.001) and then increased to the levels that were very close to the preoperative

values **(Figure 1B).** All keratometric values (K1, K2, Kmax and Kapex) were increased slightly one month after CXL and then gradually decreased at 3 months and 6 months postoperatively but these differences did not reach statistical significance (P = 0.809, 0.408, 0.131, and 0.624, respectively, **Figure 1C**). Changes in corneal anterior and posterior elevation values in topographic analyses are shown in **Figure 1D.** No statistically significant difference was found in these changes (P = 0.114 and 0.706 consecutively).

According to specular microscopy analyses there was a decrease in endothelial cell count postoperatively but the difference was not statistically significant (P =0.119, Table 1). In topographical analyses no significant change was found in Q values (corneal asphericity value, Table 1). No intraoperative or postoperative complication and no signs of progression in KC were detected in any of the eyes during follow-up.

DISCUSSION

In 2003, Wollensak et al. (4) have shown significant benefits of CXL treatment in patients with KC for the first time in a clinical, prospective and non-randomized study. After then, several studies have shown stabilizing effects in the progression of KC, increase in visual acuity, decrease in keratometric values, flattening in corneal curvatures, and decrease in refraction after CXL without significant adverse events (5-12).

Several studies with up to 3 years of follow up have shown up to 6 D reduction in K values after CXL treatment for KC (4-12). Raiskup-Wolf et al. (6) and Wittig-Silva et al. (7) have shown that the decrease in K values continues in long term after CXL. As reported by Hersh et al. (11), in our study the K values were increased slightly at 1 month postoperatively and then started to decrease thereafter **(Figure 1C).**

Improvement in visual acuity was reported in up to 90% of eyes after CXL (4, 6, 10-12). Increases in uncorrected visual acuity by 4 Snellen lines and best corrected visual acuity by 2 lines were reported (5, 6, 8, 10). In our study the median uncorrected visual acuity was also increased at 3 and 6 months of follow up but the difference did not reach statistical significance when compared with preoperative values **(Table 1)**. Unlike uncorrected visual acuity the median best corrected visual acuity was dropped at 1 month of follow up and then increased to preoperative values at 3 and 6 months of follow up **(Table 1).**

Vinciguerra et al. (8) reported no significant change in anterior and posterior elevation after CXL. Arbalaez et al. (10) reported significant reduction in anterior elevation at 6 month postoperatively but no significant change at 1 year. They also did not report any significant change in the posterior elevation during follow-up. In the current study, a slight increase in anterior elevation and decrease in posterior elevation were found at 1 month postoperatively and they returned close to preoperative values at 6 month postoperatively **(Figure 1D).**

Changes in corneal thickness after CXL are controversial in the literature (5-7). Caporossi et al. (5) reported small increase in the early postoperative period and then corneal thickness decreased close to the preoperative values. Raiskup-Wolf et al. (6) reported decrease in the thickness in the first year and then increase after the second year. Wittig-Silva et al. (7) also reported marked decrease in thickness in the early postoperative period but the corneal thinning reversed over the follow up period. Vinciguerra et al. (8) reported significant decrease at 1 year follow-up compared to baseline. Coskunseven et al. (9) reported no significant change in corneal thickness. Arbalaez et al. (10) reported transient decrease at 3 months postoperatively and then gradual increase during 1 year follow-up. In compatible with this study, in our study the median corneal thickness at the thinnest location was decreased significantly at the first month and then started to increase **(Figure 1B)**. The decrease in corneal thickness was attributed to reduced keratinocyte numbers due to apopitosis in the early postoperative period and following increase in thickness was attributed to keratinocyte regeneration (13, 14).

Our study also described increased light scatter and corneal densitometry values after CXL by Scheimpflug imaging **(Figure 1A and 2).** Scheimpflug imaging analysis may also be used in the assessment of the treatment effect.

Damage to the limbal stem cells, corneal endothelial cells and intraocular lens, persistent corneal epithelial defects, infectious keratitis, and corneal haze, infiltrates and scarring are major concerns after CXL (4, 7, 8). No statistically significant change in endothelial cell density was reported (4, 5, 7, 8). Although endothelial cell counts were slightly decreased during follow up after CXL in our study, the difference did not reach statistical significance **(Table 1).** No signs of corneal limbal stem cell or intraocular lens damage were observed and no patient developed persistent epithelial defects, corneal scarring or keratitis during follow up.

In conclusion, most of the findings in our study are compatible with the literature. CXL is a cheap and safe method to halt the progression of KC. Our study has some limitations due to limited number of patients, short follow-up time, retrospective and non-comparative design. However, this is the first report from our clinic to show our preliminary results of CXL in the management of KC and it is valuable to show our clinical CXL application is safe, effective and compatible with previous reports.

Table 1. Changes in uncorrected and best corrected visual acuities, and corneal endothelial cell counts.

	Uncorrected visual acuity	Best corrected visual acuity	Endothelial cell count	Q value
Follow up	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**	**Median (min-max)**
Preoperative	0.3 (0.01-0.9)	0.7 (0.03-1)	2778 (1883-3497)	-0.875 (-2.16-0.16)
1 month	0.3 (0.03-0.8)	0.4 (0.1-1)	2471 (2041-3030)	-0.995 (-2.26-0.25)
3 months	0.4 (0.1-0.8)	0.7 (0.2-1)	2454 (2053-2833)	-0.820 (-1.52-0.21)
6 months	0.5 (0.03-0.8)	0.7 (0.3-0.8)	2577 (1965-2786)	-0.810 (-1.29-0.19)
P value	0.738	0.528	0.119	0.597

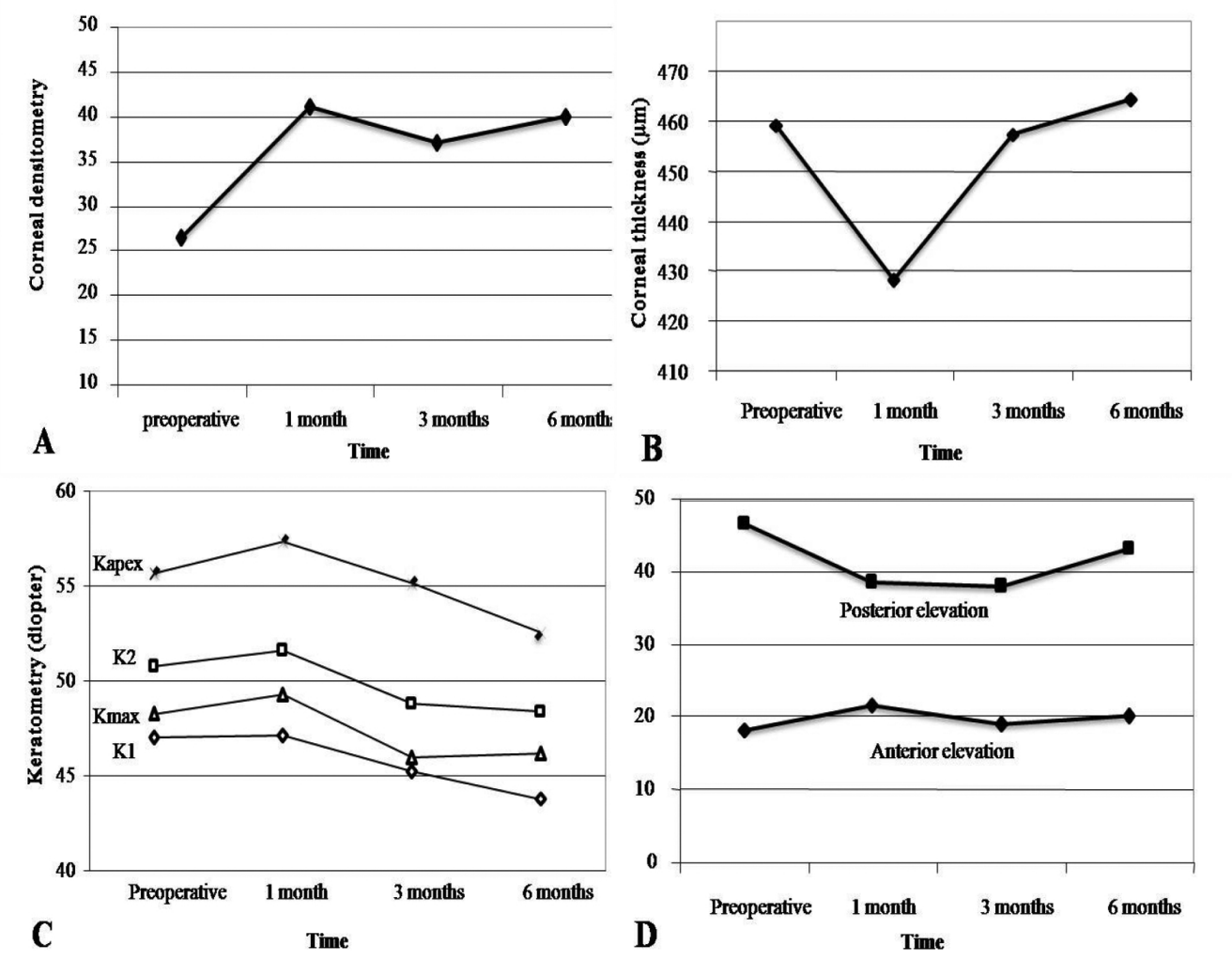

Figure 1. Changes in corneal densitometry (A), corneal thickness at the thinnest location (B), keratometric values (C), and anterior and posterior elevation values (D) during follow-up measured by Pentacam.

Figure 2. Preoperative (A) and postoperative 6th month (B) Scheimpflug images of a patient. Light scatter was increased from anterior corneal stroma at 6 months of postoperative follow up compared to preoperative image (red rectangles). Corneal density measured by Pentacam Scheimpflug system was also increased (green arrows) at 6th month.

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