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Original Article / *Özgün Araştırma*

Collagen Cross-linking in Keratoconus Patients with Thin Corneas: Short-Term Results

İnce Kornealı Keratokonus Hastalarında Kollajen Çapraz Bağlama: Kısa Dönem Sonuçları

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Summary

Purpose: To study the effectiveness and safety of corneal collagen cross-linking with hypoosmolar riboflavin solution applied to keratoconus patients with thin corneas.

Material and Method: In this retrospective study, medical records of keratoconus patients planned for cross-linking surgery and having thinnest corneal thickness (TCT) less than 400 µm after corneal epithelial removal were reviewed. There were 12 patients and 16 eyes in the study cohort. After the epithelium was removed, hypoosmolar solution was applied for 30 minutes and pachymetric measurements were taken. If corneal thickness became more than 400 µm, the cross-linking procedure was started; if not, hypoosmolar solution was continued until corneal thickness reached 400 µm. Maximum keratometry values (K Max), pachymetric measurements, uncorrected distance visual acuities (UDVA), and corrected distance visual acuities (CDVA) were recorded. Comparison between preoperative measurements and measurements taken in sixth postoperative month were performed.

Results: The mean TCT was 422.75±26.98 µm preoperatively (max: 450, min: 360). The mean TCT was reduced to 373.63±22.41 µm after epithelium was removed (max: 398, min: 325). There was a statistically significant difference between preoperative K max (62.62±5.09) and postoperative K max (61.55±5.80), (p=0.03). On the other hand, the difference between preoperative-postoperative UDVA (p=0.29) and preoperative-postoperative CDVA was not significant (p=058). There were no cases with significant corneal opacity or with any other complication.

Discussion: Corneal collagen cross-linking with hypoosmolar riboflavin solution in keratoconus patients with thin corneas is an effective procedure and can be considered as safe regarding preservation of visual acuities and absence of significant corneal opacity. *(Turk J Ophthalmol 2012; 42: 316-20)*

Key Words: Corneal cross-linking, keratoconus, thin corneas

Özet

Amaç: İnce kornealı keratokonus hastalarına uygulanan hipoozmolar riboflavin solüsyonuyla kollajen çapraz bağlamanın etkinlik ve güvenilirliğinin çalışılması.

Gereç ve Yöntem: Bu retrospektif çalışmada çapraz bağlama operasyonu planlanan ve kornea epiteli kaldırıldıktan sonra en ince korneal kalınlık değeri (EKK) 400 µm olan keratokonus hastalarının medical kayıtları incelendi. Çalışma gurubunda 12 hasta ve 16 göz bulunmaktaydı. Epitel kaldırıldıktan sonra hipoozmolar solüsyon 30 dakika boyunca uygulandı ve pakimetrik ölçümler alındı. Eğer korneal kalınlık 400 µm'dan fazla olduysa çapraz bağlama prosedürüne başlandı; eğer olmadıysa korneal kalınlık 400 µm olana kadar hipoozmolar solüsyon uygulamasına devam edildi. Maksimum keratometri değerleri (K maks), pakimetrik ölçümler, düzeltilmemiş uzakta görme keskinlikleri (DGK) ve düzeltilmiş uzakta görme (DUGK) keskinlikleri kaydedildi. Preoperatif ölçümlerle postoperatif 6. aydaki ölçümler karşılaştırıldı.

Sonuçlar: Ortalama preoperatif EKK 422,75±26,98 µm idi (maks: 450, min: 360). Epitel kaldırıldıktan sonra EKK 373,63±22,41 µm'a düştü (maks: 398, min: 325). Preoperatif K maks (62,62±5,09) ve postoperative K maks (61,55±5,80) arasında istatistiki olarak anlamlı bir fark vardı (p=0,03). Diğer yandan preoperatif-postoperatif DGK (p=0,29) ve preoperatif-postoperatif DUGK (p=0,58) arasındaki fark önemli değildi. Belirgin korneal opasitesi veya diğer komplikasyonları olan hiçbir vaka yoktu.

Tartışma: İnce kornealı keratokonus hastalarında hipoosmolar riboflavin solüsyonuyla korneal kollajen çapraz bağlama etkin bir prosedürdür; ayrıca görme keskinliklerinin korunduğu ve belirgin korneal opasitelerin olmadığı göz önünde bulundurulursa güvenilir bir yöntem olduğu söylenebilir. *(Turk J Ophthalmol 2012; 42: 316-20)*

Anahtar Kelimeler: Korneal çapraz bağlama, keratokonus, ince kornealar

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Introduction

Corneal cross-linking has been introduced as a novel therapeutic method for keratoconus.[1] The aim of this treatment is to arrest progression of keratoconus by improving biomechanical properties of the cornea.[2-4]

The treatment protocol consists of administration of ultraviolet A (UVA) irradiation to riboflavin saturated cornea. The combined action of riboflavin and UVA radiation generates reactive oxygen radicals that induce formation of additional covalent bonds between or within the cornea l collagen fibers and increases the resistance of corneal collagen to enzymatic degradation.[5] These biochemical alterations lead to increased corneal rigidity by about 300%.[2] As a result, corneal cross-linking not only improves the corneal shape or visual acuity of the patient, but also changes the progression of the disease that is unique to it.

Since the introduction of cross-linking procedure, there are many studies reporting the positive effects of the procedure on patient's refractive status and visual acuity levels, hence suggesting the use of corneal cross-linking in keratoconus and many other ectatic corneal disorders.[1,6-10] However, there is limited data regarding the use of cross-linking in thin keratoconic corneas in the literature.[11-16]

The problem in thin corneas is the increased risk of induced cytotoxic damage to corneal endothelium by the procedure. The parameters of the treatment protocol were designed to achieve a cross-linking effect limited to anterior 300-350 µm of corneal stroma in order to prevent the endothelium and other deeper ocular structures. As a result, patients with corneas thinner than 400 µm were not appropriate for standard treatment protocol.[1,17] Some modified techniques of cross-linking for thin corneas were suggested.[11,14] One of these techniques is the application of hypoosmolar riboflavin solution for swelling up the cornea in order to increase the stromal thickness,[11] but series assessing the safety and efficacy of modified protocols are absent.

The purpose of the present study was to evaluate the outcomes of cross-linking treatment with UVA and hypoosmolar riboflavin solution in thin corneas.

Material and Methods

In this retrospective study, medical records of progressive keratoconus patients who underwent cross-linking surgery with thinnest corneal thickness (TCT) less than 400 µm after corneal epithelial removal were investigated. Informed consent forms were signed by all of the patients before the procedure. Progression criteria were increase in maximum keratometry of 1.0 D per year, deterioration of visual acuity, and frequent need for contact lens change. Patients having corneal scars were excluded.

In the time period from January 2008 to February 2010, cross-linking procedures were planned for 63 eyes of 43 patients. There was central corneal scarring in ten eyes of six cases, thus they were excluded. In the remaining patient group, only 16 eyes of 12 patients had central corneal thickness less than 400 micron after the epithelial removal, which were included into the evaluation.

Preoperatively, maximum keratometry values (K Max), average keratometry values (K Av) uncorrected distance visual acuities (UDVA), and corrected distance visual acuities (CDVA) were recorded. Corneal topography measurements were performed by Keratron Scout (Opticon 2000 SpA, Rome, Italy). In addition, a thorough ophthalmologic examination of the anterior and posterior segments was performed. Cross-linking procedures were performed by the same surgeon (NC) and described as follows. First, 0.5% proparacain HCL (Alcaine, Alcon Inc, Hünenberg, Switzerland) topical eye drops were administered, then epithelium was removed at a diameter of 9 mm. Pachymetry measurements (Pacline, Opticon 2000 SpA, Rome, Italy) were taken after the removal of the epithelium. If the TCT was below 320 µm, patients would not be considered for treatment. There were no such cases. Hypoosmolar riboflavin 0.1% solution was applied to the cornea of all cases every 30 seconds for 30 minutes if the pachymetry was between 320 µm and 400 µm. Pachymetry measurements were repeated after 30 minutes and hypoosmolar solution was continued to be administered until TCT exceeded 400 µm. After the intended corneal thickness was achieved, diffusion of riboflavin into the anterior chamber was checked by slit lamp biomicroscope to make sure that riboflavin had successfully penetrated through the cornea. The cornea was irradiated with a wavelength of 370 nm UVA light and an irradiance of 3mW/cm^2 for 30 minutes. During this time, hypoosmolar riboflavin solution was continued to be applied every 5 minutes. After the treatment, a silicon hydrogel contact lens (air optix, CIBA vision, Atlanta, GA, USA), was placed on the cornea and 0.3% lomefloxacin (Okacin, Novartis Ophthalmics AG, Hettlingen, Switzerland), antibiotic eye drops, were administered until the epithelium healed. Also, artificial tears and topical fluorometholone were prescribed for two weeks.

The patients were examined daily until the epithelium completely healed, and then the contact lens was removed, which was at postoperative 6th day in all patients. After then, patients were followed up at 2nd week, 1st month, 2nd month, and 6th month. On these dates, all ophthalmological examinations were repeated as performed preoperatively. Comparisons between preoperative and sixth postoperative month measurements were made.

The change in the K max values were classified as such: if the difference between preoperative and postoperative K max was between ±1 D, this change was accepted as stabilization; if the difference was more than -1D, this change was accepted as regression; if the difference was more than 1D, this change was accepted as progression.

Data were described as mean ± standard deviation (SD) for continuous variables and as individual counts and percentages for categorical variables. Differences between preoperative and postoperative measures were analyzed using a dependent

student's t test for continuous data. A p-value of less than 0.05 was considered to be statistically significant. Statistical analysis was performed using SPSS for Windows (version 15.0, SPSS Inc., Chicago, IL).

Results

There were 12 patients and 16 eyes in the study cohort. Five of these patients were male and seven of them were female. The mean age of the cases was 24.88±7.01 (min:16, max:34).

There was a wide variation in TCT measurements preoperatively. Minimum TCT was 360 µm and maximum TCT was 450 µm, although the mean preoperative TCT was 422.75±26.98 µm.

TCT values decreased further after epithelium was removed. So, the mean TCT was reduced to 373.63±22.41 µm. Minimum TCT was measured as 325 µm and maximum TCT was measured as 398 µm.

Comparison of preoperative and postoperative K max values showed that K max values decreased at 6th month. Although the difference between mean preoperative and postoperative K max values was slight, there was a statistically significant difference between preoperative K max (62.62±5.09) and postoperative K max (61.55±5.80), (p=0.03). The change of K max for each eye is depicted in Figure 1.

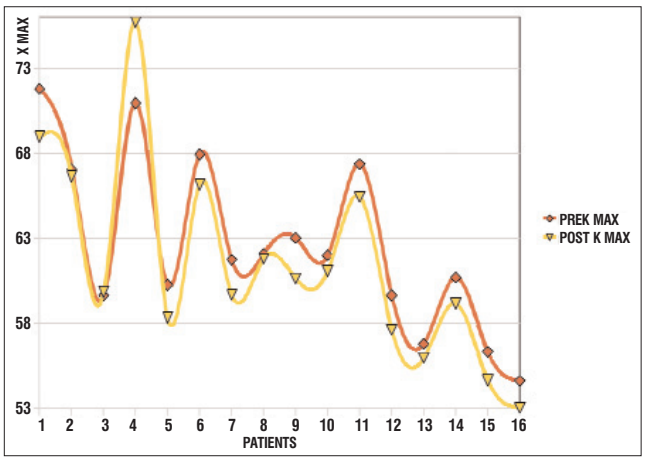

Figure 1. The change of K max for each eye following cross-linking

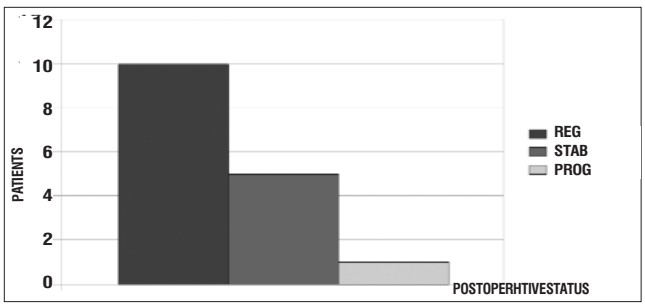

Figure 2. Regression, stabilization and progression amounts of eyes six months after cross-linking

Also, there was a reduction in K Av values at the sixth month examinations. Preoperative K Av value was 50.65±2.61, which decreased to 49.62±2.82 postoperatively. The difference of preoperative and postoperative K Av values was statistically significant (p=0.00).

When the changes in K max were evaluated by the criteria described in the methods section previously, to show stabilization or deterioration, it appeared that cross-linking treatment causes stabilization in most of the cases. At the end of sixth postoperative month, there was regression in 10 eyes, stabilization in five eyes and progression in only one eye when the K max changes were taken into consideration. These changes are represented in a bar graphic (Figure 2).

In contrast with the beneficial effects of cross-linking treatment on the K max values and stabilization of keratoconus progression, changes in visual acuity, both in UDVA and in CDVA, were not pronounced, though there was an increase in both postoperative CDVA and UDVA values in most of the cases. This result was confirmed by the statistical analyses. The difference between preoperative UDVA (0.17±0.12) and postoperative UDVA (0.2±0.09) was not significant (p=0.29). Similarly, the difference between preoperative CDVA (0.51±0.19) and postoperative CDVA (0.52±0.16) was not significant (p=0.58).

There were no peroperative complications. In the postoperative follow-up period, all cases showed a predictable clinical course and no significant corneal haze or any other complications occurred.

Discussion

The results of the present study indicate that cross-linking treatment causes a statistically significant decrease in K max values in progressive keratoconus patients. Regression was achieved in 10 eyes (62.5%), stabilization was achieved in five eyes (31%), and progression was observed in only 1 eye (6%). There was no significant decrease in visual acuity levels and both UDVA and CDVA remained stable. None of the patients developed corneal scar or corneal opacity.

Cross-linking treatment has emerged as a very promising new treatment modality for keratoconus. However, it has some important proposed limitations. One of these limitations is presence of a TCT of less than 400 µm. Corneal thickness is an important preoperative criterion for treatment decision, because cross-linking treatment might cause undesired cytotoxic effects to endothelium in thinner corneas. Accordingly, there is a general consensus that residual corneal thickness should be more than 400 µm.[17] On the other hand, such an approach will lead to exclusion of many patients with corneal thickness below 400 µm from cross-linking treatment. In fact, in such cases, stabilization of the pathobiologic mechanism may offer a chance of visual rehabilitation by contact lenses and by other options and may decrease the need for penetrating keratoplasty. Because of such a limitation, these patients lose the chance of less

invasive treatment options. Modifications of the standard treatment protocol were introduced in order to make it possible to treat keratoconus patients with thinner corneas safely.[11,14] Hafezi et al. proposed a modification of the standard treatment protocol that includes application of hypoosmolar riboflavin solution in thin corneas to reach at least 400 µm of corneal thickness and then the application of cross-linking treatment safely to cornea having stromal thickness above threshold level. They applied this protocol to 20 patients and reported stabilization of keratectasia in 12 patients and regression in eight patients. They did not report any cross-linking-associated complications.[11] Similarly, Hersh and Raiskup reported successful results with the same method.[12,15] Since there is limited data related with this modified protocol, it is not clear yet what is the minimum corneal thickness required for successful cross-linking in thin corneas. In a case report, Hafezi stated that cross-linking procedure was ineffective in a patient having extremely thin cornea and suggested that corneal thickness should be at least 330 µm for successful cross-linking treatment with hypoosmolar riboflavin solution.[16]

In the current study, the preoperative K max values of 62.62±5.09 decreased to 61.55±5.80 after cross-linking treatment. The amount of decrease in average K max value was 1.07 D and this was statistically significant (p=0.03). Wollensak et al. observed 2.01 D decrease in K max values after treatment in their pilot study including 23 eyes1, and Raiskup reported 2.57 D decrease in K max value7, while Caporossi et al. reported 2D reduction in mean K values.[10] Vinciguerra even reported a more drastic decrease in K max value, around 6 D.8 The important point here is that these results are long-term outcomes, after 12 to 36 months of follow-up period, while the results presented in the current study are early outcomes of a 6-month follow-up period. Since the effect of cross-linking treatment on corneal curvature and visual acuity shows gradual increase within years, the decline in K max values is expected to continue further.

Keratoconus is still not a curable disease. Cross-linking treatment offers stabilization for the disease process. In fact, in most cases regression could also be observed. In the present study, stabilization of keratoconus was obtained in 31% (five eyes) and regression was achieved in 62.5% (10 eyes) according to the decrease in K max readings. These results are compatible with the similar studies performed both in thinner and thicker corneas. Hafezi reported stabilization of kerectasia in 12 of 20 patients having thin corneas and regression in 8 of them.[11] Raiskup et al. also reported stabilization of K values after cross-linking procedure in thinner corneas.[15] Wollensak et al. observed regression of keratoconus in 16 eyes (70 %),[1] while Caporossi reported stability of keratoconus in all of the 44 eyes that they investigated.[10] There are increasing number of studies reporting similar results.[19,20,21] As a result, collagen cross-linking is proposed as an effective therapeutic option for progressing keratoconus.

Only one eye in the present study showed progression, hence failure rate was 6%. Hafezi reported a case of failure after cross-linking procedure for keratoconus patient having corneal thickness of 268 µm and suggested that swelling with hypoosmolar riboflavin solution should not be performed to patients having corneas thinner than 330 µm.[16] Wollensak and Caporossi reported no failure,1,6 while Raiskup-Wolf reported 1%.[7] Koller et al.[22] investigated complication and failure rates after cross-linking and observed 7.6% failure rate. They concluded that K max readings greater than 58 D is the only identified risk factor for failure and limiting the preoperative maximum K readings to 58 D or less would have reduced the failure to 2.8%. In the current study the preoperative mean K max readings were 62.62±5.09 D, so such an amount of failure rate was within expected limits.

In the present study, most of the patients had an increase in CDVA and UDVA postoperatively, but increases were minimum and failed to reach statistically significant levels. Most of the cases in our study were highly advanced cases and the prospect of an increase in visual acuities was very low. Wollensak reported a statistically significant increase in CDVA in 65% (15 eyes) of their patients.[1] Caporossi observed 1.9 Snellen line increase in CDVA. Raiskup-Wolf also reported at least one line improvement in BSCVA in 53% of 142 eyes (p<0.01) which remained stable in 29% of eyes after 3 years of treatment.[10] On the other hand, Grewal et al. reported stable CDVA postoperatively but no statistically significant improvement,[19] while Wittig-Silva et al.[21] also reported a trend toward improvement in CDVA but not a statistically significant increase.

In our study, UDVA and CDVA measurements were maintained in all patients and even a slight increase was observed. No patients experienced a decrease in visual acuity from preoperative levels. No corneal scar or opacity was observed. These results are important in evaluation of the safety of this modified procedure.

The most important difference between the present study and the previous similar studies is that a homogeneous cohort, consisting of only keratoconus patients having corneal thickness less than 400 µm were studied. Accordingly, all the patients were in an advanced stage of keratoconus and had a very high mean K max value of around 62 D.

On the other hand, this study had some important limitations such as a relatively small number of cases and a limited follow-up period. Beside this, specular microscopic examinations for evaluating endothelial cell count was not performed. Future studies with larger sample sizes and longer follow-up periods would yield more scientific evidences, robust enough to make more secure and firmer conclusions.

As conclusion, the modified cross-linking treatment protocol with application of hypoosmolar riboflavin solution in keratoconus cases with a corneal thickness less than 400 µm caused a significant decrease in K max values. Unexpected complications did not develop in any patients. Achievement of either stabilization or regression, with preservation of visual acuities, is possible in a great majority of cases.

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