



ARAŞTIRMA / RESEARCH

Outcome of UVA-Riboflavin collagen cross-linking of cornea in patients with keratoconus

Keratokonus hastalarında UVA-Riboflavin korneal kollajen çapraz bağlama tedavisinin sonuçları

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Abstract

Purpose: In this study, we aimed to show changes of central corneal thickness and effects of treatment on visual acuity after corneal collagen cross-linking in keratoconus patients.

Materials and Methods: 26 eyes of 51 patients with keratoconus who undergone corneal collagen cross-linking were included in to the study. Central corneal thickness measurements and best corrected visual acuity were recorded before and after 1st and 6th month of corneal collagen cross-linking operation.

Results: Mean central corneal thickness measurements were recorded as; 435,43±44,35 µm, 376,68±66,55 µm and 392,62±64,21 µm before and after 1st and 6th month of corneal collagen cross-linking, respectively. There was a statistically significant difference between pre-op and postop 1st month, pre-op and postop 6th month and postop 1st month and post-op 6th month central corneal thickness measurements. Also, there was a statistically significant increase in best corrected visual acuity after the operation.

Conclusion: There was a statistically significant difference between pre-op, post-op 1st month and postop 6th month central corneal thickness and best corrected visual acuity measurements.

Key words: Keratoconus, Corneal collagen cross-linking, riboflavin, UVA.

Öz

Amaç: Bu çalışmada, keratokonus hastalarında korneal kollajen çapraz bağlama tedavisinin görme keskinliği ve merkezi kornea kalınlığına etkilerinin gösterilmesi amaçlanmıştır.

Gereç ve Yöntem: Korneal kollajen çapraz bağlama işlemi uygulanan 26 hastanın 51 gözü çalışmaya dahil edildi. Merkezi kornea kalınlık ölçümleri ve en iyi düzeltilmiş görme keskinlikleri işlemden önce ve sonrasında 1. ay ve 6. ayda kayıt altına alındı.

Bulgular: Ortalama merkezi kornea kalınlık ölçümleri işlem öncesi, işlem sonrası 1. ay ve işlem sonrası 6.ay olmak üzere sırasıyla 435,43±44,35µm, 376,68±66,55µm ve 392,62±64,21 µm olarak kaydedildi. İşlem öncesi ve işlem sonrası 1. ay, işlem öncesi ve işlem sonrası 6.ay ve işlem sonrası 1. ay ve işlem sonrası 6.ay merkezi kornea kalınlığı ölçümleri arasında istatistiksel olarak anlamlı fark bulundu. Aynı zamanda, işlem sonrası görme keskinliği artışı istatistiksel olarak anlamlı bulundu.

Sonuç: İşlem öncesi, işlem sonrası 1.ay ve işlem sonrası 6. ay merkezi kornea kalınlık ölçümleri ve en iyi düzeltilmiş görme keskinliği ölçümlerinde istatistiksel olarak anlamlı değişiklikler bulundu.

Anahtar kelimeler: Keratokonus, korneal kollajen çapraz bağlama, riboflavin, UVA.

INTRODUCTION

Keratoconus is a disease characterised with usually bilateral, non-inflammatory, progressive thinning

and steepening of the 2/3 central cornea¹. It usually starts at puberty and mostly one eye is affected more than the other. It is supposed that micro-trauma (atopy, eye scratching, use of rigid gas permeable contact lens), oxidative stress and genetic factors

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(familial tendency, other genetic disorders) may play a role in etiology².

Corneal thinning which is the major component of the keratoconus is caused by loss of structural elements. Corneal thinning may be explained by decrease in the number of collagen lamella, decrease in the number of collagen fibers in each lamella and/or tight packing of the fibers³⁻⁵.

The most important complaint of keratoconus is low visual acuity. Initially, low visual acuity is confused with simple refractive errors and this similarity delays early diagnosis of the disease^{6,7}. At the beginning of the disease, myopic changes are seen and use of glasses are sufficient to correct low vision. By the progression of the disease, corneal ectasia and steepening increase. At this stage, irregular astigmatism is increased and glasses are insufficient to correct visual acuity; so rigid gas permeable contact lenses are used for the treatment⁸. In about 10-20% of the patients with keratoconus, disease progresses and finally goes to keratoplasty⁹. Keratoplasty is needed in patients with advanced keratoconus whose vision can not be corrected by other methods. Although success of the surgery is higher than the other keratoplasty indications, because of invasiveness of the procedure and post-surgical complications; it should be considered as the last choice¹⁰⁻¹¹.

Recently, technological developments allowing earlier recognition of the disease has brought new methods of treatment. In this purpose, corneal cross-linking (CCL) which was reported to be effective in preventing the progression of the disease has taken place in clinical practice¹²⁻¹⁶. CCL is a new method of treatment developed with the purpose of preventing progressive thinning of the cornea caused by keratoconus¹⁷. Stimulation of riboflavin by ultraviolet-A (UVA) reveals oxygen radicals, that causes formation of new covalent bonds between amino acids of the adjacent collagen fibrils. In previous studies, it has been shown that as a consequence of these chemical reactions, corneal rigidity, elasticity and resistance to proteolytic enzymes increase. The effect of CCL is not evenly distributed on whole corneal thickness. It effects anterior 200-300 μm part of the cornea where UVA is most absorbed. Keratocyte apoptosis in the anterior stroma and demarcation line between treated and non-treated corneal areas has been shown in studies¹⁸⁻²¹.

It is a well-known fact that genetic predisposition and geographical conditions play an important role in keratoconus disease. This is a study that we think will contribute to the literature in terms of reflecting the results of the initiatives made by different physicians, on people with different genetic structure and at a different geography in our country.

MATERIALS AND METHODS

This retrospective study was carried out in Adiyaman University School of Medicine Education and Research hospital. 26 eyes of 51 patients with keratoconus who underwent CCL operation were included in to the study. All procedures followed the Declaration of Helsinki rules and written informed consent was obtained from all patients. Ethics committee approval was obtained (Adiyaman University School of Medicine, local ethics committee-approval no:2015/08-2, approval date:02.12.2015). The inclusion criteria for the study group was to have keratoconus without any systemic disorder. The exclusion criteria included the following; any previous ocular surgery, history of eye trauma, and systemic diseases.

Central corneal thickness (CCT) measurements and best corrected visual acuity (BCVA) were recorded before and after 1st and 6th month of CCL. IOP measurements were taken before and after 6th month of CCL. IOP measurements were taken by Goldmann applanation tonometer by the same examiner. When determining CCT, three consecutive measurements were obtained by Orbscan II corneal topography device (Bausch and Lomb, Rochester, NY, USA) and average of the thinnest measurements were recorded.

Corneal crosslinking protocol

CCL was performed under topical anesthesia for all patients. Before operation, 10% povidone-iodine was applied to the periocular region. After sterile draping and positioning eyelid speculum, 5% povidone-iodine was applied to the ocular surface and fornix for three minutes. Then, it is rinsed out with saline solution. By using a blunt knife, full-thickness epithelial debridement was performed on 8-9 mm of central corneal area. 0.1% iso-osmolar riboflavin solution (G. Streuli & Co. AG) was dropped on the corneal surface every 5 minutes for 30 minutes to ensure adequate penetration into the

corneal stroma. Two 370 nm UVA diode (Roithner Lasertechnik, Vienna, Austria) was applied from 1 cm from the corneal surface for 30 minutes (3 mW/cm² irradiation, 5.4 J/cm²). The calibration of irradiation was achieved by using a UVA light-meter (UV Light Meter YK- 35UV, Lutron, Taipei). During the irradiation, one drop of riboflavin solution was instilled every 5 minutes to the corneal surface.

Postoperative follow-up

After operation, topical antibiotic drops (0.3% ofloxacin) were ordered 4 times a day for a week and a bandage contact lens was applied until epithelial healing for 3-5 days. After removal of the bandage contact lens, topical corticosteroid drops (prednisolone acetate 1%) were ordered 4 times a day for 4-6 weeks. To increase ocular comfort, all patients received preservative free artificial tears 4 times a day for a month.

Statistical analysis

CCT measurements and BCVA were recorded at 1st and 6th months of the operation. Postoperative CCT measurements were compared with preoperative values. Statistical analysis was performed with Statistical Package for Social Sciences (SPSS) 21.0 for windows (SPSS Inc., Chicago, IL, USA). The normality of the distributions of quantitative variables of each parameter before and after the treatment were assessed by the Shapiro-Wilk's test. Because the distributions were significantly different from a normal distribution, non-parametric tests were used. The Wilcoxon signed rank test was used to evaluate the variables before and after treatment. A p value lower than 0.05 was considered as statistically significant.

RESULTS

Of 26 patients with the diagnosis of keratoconus, 15 were male (57.7%) and 11 were female (42.3%). The mean age of the patients were 24.57±5.28 (range, 16-40). Mean CCT measurements were recorded as; 435,43±44,35 μm, 376,68±66,55 μm and 392,62±64,21 μm before and after 1st and 6th month of corneal collagen cross-linking, respectively (Table 1).

There was statistically significant difference between pre-op and postop 1st month, pre-op and postop 6th

month and post-op 1st month and post-op 6th month central corneal thickness measurements (p<0.05) (Table 1).

Table 1. Comparison of central corneal thickness (CCT) measurements

CCT/ Mean±SD (μm)	P-value
Preoperative :435.43±44.35 - Postoperative 1st month: 376.68±66.55	p<0.001
Preoperative:435.43±44.35 - Postoperative 6th month: 392.62±64.21	p<0.001
Postoperative 1st month: 376.68±66.55- Postoperative 6th month: 392.62±64.21	p=0.050

SD: standart deviation, μm: microns, CCT: central corneal thickness

Also, there was a statistically significant increase in BCVA after the operation compared to the pre-operative measurements (p<0,05). Pre-operative and post-operative intraocular pressure (IOP) was recorded as 10.96±2.03 and 11.09±2.04, respectively (Table 2). The difference between pre-operative and post-operative intraocular pressure measurements were not statistically significant (p=0.164).

Table-2. BCVA and IOP measurements before and 6th months after operation

	Pre-op	Post-op	P-value
BCVA	0.18±0.20 (logMar)	0.40±0.34 (logMar)	p<0.001
IOP	11.09±2.04 (mmHg)	10.96±2.03 (mmHg)	P=0.164

BCVA: Best Corrected Visual Acuity, IOP:Intraocular pressure

DISCUSSION

Since the treatment of human subjects with CCL began in 2003, many studies have been shown that it prevents the progression of keratoconus by 90-98 % and increases the visual acuity^{9,15,16,22}. The increase in corneal stiffness after CCL also improves topographic findings in keratoconus patients²³⁻²⁷. CCL treatment is becoming more common because of low complication rates and easy application.

In this study, postoperative changes in corneal thickness, IOP and visual acuity after CCL were analyzed during a 6 months period. We found a statistically significant difference between pre-op and postop 1st month, pre-op and postop 6th month and post-op 1st month and post-op 6th month central corneal thickness measurements. Decrease in the corneal thickness in the early post-operative period showed a slight increase in long term period

but still did not reach pre-operative values at the end of the 6th month. In a study by Greenstein et al, 54 patients with keratoconus and 28 patients with post-LASIK keratectasia were undergone to CCL operation. Minimum corneal thickness of apex and pupil center were measured at 1,3,6 and 12 months after operation. Corneal thickness measurements at 1st and 3rd month postoperatively were statistically significantly thinner than preoperative measurements. At 6th month postoperatively, although corneal thickness was significantly lower than preoperative measurements, it was statistically significantly higher than 3rd month measurements. At 12 month postoperatively, corneal thickness measurements of apex and pupil center were lower than pre-operative values but the difference was not statistically significant. However, 12th month lowest corneal thickness measurements were statistically significantly lower than pre-operative values. In the same study, corneal thickness decreased at 1st and 3rd month postoperatively, then started to increase between 6th and 12th month and finally reached pre-operative values at 12th month postoperatively²⁸. Generally after CCL operation, a decrease in corneal thickness in patients with keratoconus and an increase in corneal thickness in patients with post-LASIK corneal ectasia was reported²⁸. Similar results were obtained in various studies^{27,29}. In contrast with the literature, Vinciguerra et al. found a decrease in pupil-center pachymetry and no change in thinnest pachymetry in eyes with keratoconus and a significant decrease in pupil-center pachymetry and thinnest pachymetry in eyes with ectasia 1 year after CXL²⁶.

In our study, at 1st month corneal thinning was significant, at 6th month CCT continued to be significantly thinner than pre-operative values but it was thicker compared to the 1st month measurements. The physiology of the initial corneal thinning after CCL is not understood yet. There are some possible explanations in the literature. Epithelial remodeling is thought to be a possible factor affecting corneal thickness. Re-epithelialization of the cornea after CCL usually takes 4-5 days³⁰. Extension of the epithelialization time may play a role in early days after surgery but decrease in CCT at 6th month can not be explained by this hypothesis. Corneal structural changes in collagen fibrillar level, changes in corneal hydration and keratocyte apoptosis may be more possible causes^{20,21,30-32}. Keratocyte apoptosis is the most likely accepted among the others. In the literature, it

was shown that CCL induces apoptosis on the affected areas. It was shown that number of keratocytes in the affected area decrease, by the time regenerate and then re-settle³³. In our study, change in CCT after CCL operation may be explained by apoptosis and re-settlement of activated keratocytes by the time.

Beside the changes in corneal thickness, regarding pre-operative and post-operative vision, a statistically significant increase in BCVA was recorded ($p < 0,05$). In a randomised controlled clinical study by Witta-Silva et al, it was shown that BCVA continues to get better during the 12 month follow-up period³⁴. In addition, it was thought that CCL operation leads to flattening of the cornea and causes slow but considerable increase in vision, especially in the first 6 months²⁶. In accordance with previous studies, we recorded an increase in vision after CCL operation. There was not a significant difference between pre-operative and post-operative IOP.

In conclusion, CCL method with riboflavine and UVA seems to be a safe and effective method to stop or slow the progression of keratoconus and other corneal ectasias. CCL reduces spherical or cylindrical refractive errors, corneal keratometric values and increases visual acuity. In this study, we found that after CCL operation, corneal thinning was significant initially and then it continued to be thinner than pre-operative values at 6th month.. However, more studies with larger series and longer follow-up period are needed to determine the long-term effects of CCL and whether they are permanent.

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