ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2019-66019

Accelerated (18 mW/cm² for 5 Minutes) Corneal Collagen Cross-Linking for Progressive Keratoconus: Two-Year Results

İlerleyici Keratokonusta Hızlandırılmış (5 Dakika 18 mW/cm²) Korneal Kollajen Çapraz Bağlama: 2 Yıllık Sonuçlar

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ABSTRACT Objective: To evaluate the long-term clinical outcomes (minimum follow-up period of 2 years) of accelerated crosslinking (CXL) at 18 mW/cm² for 5 minutes, in patients with progressive keratoconus. **Material and Methods:** Thirty five eyes of 35 patients with progressive keratoconus who underwent accelerated CXL were included. Topographical measurements were obtained using a rotating Scheimpflug camera (Sirius). Flat Keratometry (K) value (K1), steep K value (K2), average K value (avgK), topographic cylindrical value (Cyl), apical keratoscopy front (AKf or Kmax), apical keratoscopy back (AKb), symmetry index front (SIf), symmetry index back (SIb), central corneal thickness (CCT), thinnest point of the cornea (Thin), and total corneal volume (CV) were recorded from the topography data generated by the Scheimpflug system. **Results:** The uncorrected and best corrected visual acuity of the patients had begun to increase significantly after 6 months postoperatively (p=0.014 and p=0.0001, respectively) and continued to improve in the 12th and 24th months (p<0.05 for all). There was a statistically significant but temporary increase in keratometric values of K2, avgK and AKf at 1 month postoperative (p=0.0001, p=0.008, and p=0.001, respectively), but K2 and avgK did not show any statistically significant difference in the other follow-up visits (p>0.05 for all). Flat keratometry value decreased significantly at 24 months (p=0.029) and, AKf improved significantly at 12 and 24 months (p=0.029 and p=0.001, respectively). **Conclusion:** The accelerated CXL procedure (18 mW/cm² for 5 minutes) is effective in preventing keratoconus progression with increased visual acuity and stabilization in keratometric values after the 2-year follow-up.

Keywords: Corneal collagen crosslinking; corneal topography; keratoconus

ÖZET Amaç: İlerleyici keratokonus hastalarında 5 dakika 18 mW/cm² hızlandırılmış korneal kollajen çapraz bağlama (KÇB) tedavisinin uzun dönem (minimum takip süresi 2 yıl) klinik sonuçlarını değerlendirmek **Gereç ve Yöntemler:** İlerleyici keratokonus nedeniyle hızlandırılımış KÇB teadvisi yapılan 35 hastanın 35 gözü çalışmaya alındı. Topografik ölçümler dönen Scheimpflug kamera (Sirius) kullanılarak yapıldı. Düz Keratometri (K) değeri (K1), dik K değeri (K2), ortalama K değeri (avgK), topografik silindirik değer (Cyl), ön apikal keratoskopi (AKf veya Kmax), arka apikal keratoskopi (AKb), ön simetri indeksi (SIf), arka simetri indeksi (SIb), merkezi kornea kalınlığı (SKK), korneanın en ince noktası (Thin) ve toplam kornea hacmi (CV), Scheimpflug sistemi tarafından oluşturulan topografi verilerinden kaydedildi. **Bulgular:** Hastaların düzeltilmemiş ve en iyi düzeltilmiş görme keskinliği ameliyat sonrası 6 ay sonra anlamlı şekilde artmaya başlamış (sırasıyla p=0,014 ve p=0,0001), 12. ve 24. aylarda iyileşmeye devam etmiştir (hepsi için p<0,05). Ameliyat sonrası 1. ayda K2, avgK ve AKf'nin keratometrik değerlerinde istatistiksel olarak anlamlı ancak geçici bir artış vardı (sırasıyla p=0,0001, p=0,008 ve p=0,001), ancak K2 ve avgK değerlerinde diğer takiplerde istatistiksel olarak anlamlı bir fark bulunmadı (tümü için p>0,05). Düz Keratometri değeri, 24. ayda önemli ölçüde azaldı (p=0,029) ve AKf, 12. ve 24. ayda önemli ölçüde düzelme gösterdi (sırasıyla, p=0,029 ve p=0,001). **Sonuç:** Hızlandırılmış (5 dakika 18 mW/cm²) KÇB yöntemi iki yıllık takip sonunda artan görme keskinliği ve keratometrik değerlerde stabilizasyon ile keratokonusun ilerlemesinin önlenmesinde etkilidir.

Anahtar Kelimeler: Korneal kollajen çapraz bağlama; korneal topografi; keratokonus

The introduction of cross-linking (CXL) as a method of a new treatment modality in keratoconus reduced the number of patients undergoing keratoplasty.[1] By CXL treatment, the disease-causing corneal laxity is tightened by the chemical interaction of riboflavin and ultraviolet-A (UVA), the corneal stiffness increases, and the progression is halted.[2-5] In the standard protocol, first applied by Wollensak, the de-epithelialized cornea was saturated with riboflavin for 30 minutes followed by UV-A irradiation at 3

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Peer review under responsibility of Turkiye Klinikleri Journal of Ophthalmology.

Received: 13 Mar 2019 ***Accepted:*** 13 May 2019 ***Available online:*** 20 May 2019

mW/cm^2 for 30 minutes.[6] Although this method was shown to be effective in stopping the progression of the disease in numerous clinical studies, the duration of the operation which took approximately one hour was troublesome for the patient and the physician.[7-9]

The Bunsen-Roscoe law allows us to give the same total energy of 5.4 J/cm^2 with using a higher UV-A irradiance. By this way, similar photochemical effect can be reached in a shorter period of time.[10,11] From this point, different accelerated CXL protocols have begun to be tried by setting different UVA powers in a shorter exposure time to reduce the duration and improve the patient comfort.[12-14]

Recently, there are sufficient numbers of studies on the long-term effect of the conventional method in the literature, but they are limited in accelerated CXL.[5,15,16] In this study, we evaluated the long-term clinical outcomes (minimum follow-up period of 2 years) of accelerated CXL at 18 mW/cm^2 for 5 minutes in patients with progressive keratoconus.

MATERIAL AND METHODS

In this retrospective study, 35 eyes of 35 patients with progressive keratoconus who underwent accelerated CXL between June 2014 and March 2015, in Bagcilar Education and Research Hospital, Istanbul, Turkey were included. Patients who were followed up regularly for 2 years were included in this study. The study was carried out in accordance with the principles stated in the Helsinki Declaration and approved by the Clinical Research Ethics Committee of Bağcılar Education and Research Hospital with the project number: 2017.11.1.08.016. All patients gave written informed consent before any intervention.

Progressive keratoconus was described as an increase of 1.00 diopter (D) or more in the steepest keratometry (K) measurement or the loss of at least 2 lines of best-corrected distance visual acuity (BCVA) in the past 12 months. Patients were excluded if they were younger than 18 or older than 40 years of age and had a corneal thickness less than 400 µ at the thinnest point, corneas with hydops, scarring or previous surgery, pregnant or lactating women. All patients were asked to remove their contact lenses at least 3 weeks before any investigation.

The ophthalmic examination was carried out to all patients including assessment of the uncorrected distant visual acuity (UDVA) and best corrected visual acuity (BCVA), slit-lamp biomicroscopy and dilated fundoscopy. Topographical measurements were also obtained using a placido disk topography with Sheimpflug tomography of the anterior segment (Sirius, Costruzione Strumenti Oftalmici, Italy) according to the manufacturer's guideline by the same trained examiner. Corneal topographic parameters were recorded from the topography. All patients underwent these investigations in the preoperative period and at 1, 3, 6, 12, and 24 months postoperatively.

Surgıcal TECHNIQUE

Accelerated CXL was performed on all patients. The central 8.0 mm epithelium was scraped with a blunt spatula under topical anesthesia by 0.5% proparacaine (Alcaine; Alcon Laboratories, Inc.). Riboflavin with dextran (0.1% riboflavin in 20% dextran, Medicross, Germany) solution was applied topically at every 3 minutes for 30 minutes. After the installation of the riboflavin as a photosensitizer, ultra-violet-A (UV-A) 365 nm light at an irradiance of 18 mW/cm^2 (Peschke Meditrade, GmbH, Switzerland) was started. UV-A light was applied for 5 minutes and riboflavin had been instilled in every minute during this period. The procedure was finalized by washing the surface with 20 ml balanced salt solution. After the surgery, all patients had antibiotic eye drops (Moxifloxacin 0.5%, Vigamox[a]; Alcon Co., Inc.) and bandage soft contact lens was put in. Topical moxifloxacin eye drops (4 times per day for 1 week; Vigamox; Alcon Co., Inc.), dexamethasone SE 0.1% (Maxidex; Alcon Laboratories, Fort Worth, TX) four times daily for 2 weeks, and artificial tears (4 times per day for 1 month) were administered postoperatively. Dexamethasone was changed to loteprednol etabonate ophthalmic suspension 0.5% (Lotemax; Bausch & Lomb) four times daily for another 2-4 weeks.

Statıstıcal ANALYSIS

NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) program was used for statistical analyses. The normality of the data was

tested with the Kolmogorov-Smirnov test. In the evaluation of the data one-way analysis of variance (ANOVA) was used with its post hoc Newman Keuls test for normally distributed variables, Friedman Test was used for non-normal data with its post hoc Dunn's test in subgroup comparisons. A p value less than 0.05 was considered significant.

RESULTS

The study included 35 eyes (17 right and 18 left) of 35 patients (13 female, 22 male) with mean age of 23.97±5.41 years (range 18-35).

The UCVA and BCVA of the patients began to increase significantly from 6 months postoperatively (p=0.014 and p=0.0001, respectively) and continued to improve in the 12th and 24th months (p<0.05 for all) (Table 1, Figure 1). The UCVA did not change in 13 eyes (37.14%) at 24 months, but the increase in Snellen line was 1 line in 10 eyes (28.57%), 2 or more lines in 8 eyes (22.86%), and the decrease was 1 line in 3 eyes (8.57%), and 2 lines in 1 eye (2.86%). The BCVA did not change in 10 eyes (28.57%), but the increase in Snellen line was 1 line in 5 eyes (14.29%), 2 or more lines in 16 eyes (45.71%), and the decrease was 1 line in 4 eyes (11.43%), and none of the eyes decreased by 2 lines (0%).

There was a statistically significant but temporary increase in keratometric values of steep K value (K2), average K value (avgK) and, apical keratoscopy front or maximum K value (AKf) at postoperative 1 month (p=0.0001, p=0.008, and p=0.001, respectively), but K2 and avgK did not show any statistically significant difference in the other follow-up visits (p>0.05 for all). The flat K value (K1) decreased significantly at the 24th month (p= 0.029) and, AKf improved significantly at 12 and 24 months (p=0.029 and p=0.001, respectively). There was a statistically significant increase in apical keratoscopy back (AKb) from the 3rd month and in the follow-up months (p<0.05 for all). There was a statistically significant but temporary increase in topographic astigmatism value at 1 month (p=0.0001), but no significant difference was found during the follow-up visits compared to the preoperative values (p>0.05 for all) (Table 1, Figure 2).

The symmetry index front value (SIf) was statistically significantly lower at 12 and 24 months (p=0.02 and p=0.004, respectively). There was an increase in symmetry index back (SIb) up to 12 months (p=0.009), but no significant difference was found at 24 months (p=0.64) (Table 1).

The thinnest point of the cornea and the corneal volume (CV) were statistically significantly lower in all post-operative controls (p<0.05 for all). The central corneal thickness (CCT) decreased significantly after the first month postoperatively (p=0.0001), but began to increase and came closer to the baseline level at 24th month follow-up (p=0.109) (Table 1, Figure 3).

Most of our patients had pain due to corneal deepitelization for the first few days after surgery. There was a corneal haze and edema at variable degrees in the first few weeks in some of the patients that are susceptible to steroid treatment. Corneal scarring was observed in only one patient which did not cause a decrease in visual acuity and lasted only for about one year.

DISCUSSION

In this study, accelerated CXL of 18 mW/cm^2 for 5 minutes resulted in a decrease in Kmax, an improvement on UCVA and BCVA in a 24 month period as well as a stabilization in keratometric values. Although Kymionis showed that the demarcation line was significantly deeper in the patient group that had been exposed to 3 mW/cm^2 UVA for 30 min than the one exposed to 9 mW/cm^2 for 10 min (350 and 288 mμ), we know that the anterior 40% of the corneal stroma is two times stronger than the posterior corneal stroma.[17,18] Therefore, a CXL that affects the anterior portion of the cornea theoretically will provide sufficient efficacy in strengthening the loose cornea. In addition, Kohlhaas showed that CXL is effective only in the 200 μm portion of the anterior stroma because absorption of 70% of the UVA irradiation occurs in this part of the cornea.[19] These studies reveal clues to explain the effect of higher irradiation of UVA in shorter time durations as in our 5-minute practice, although it is likely to have a more superficial CXL effect.

TABLE 1: Visual and topographic outcomes in preoperative and postoperative two year period.

	Preoperative	1 Month	p¹	3 Month	p²	6 Month	p³	12 Month	p⁴	24 Month	p⁵
UCVA (Log MAR)	0.75±0.34	0.76±0.31	0.703	0.7±0.36	0.241	0.64±0.37	**0.014**	0.62±0.36	**0.002**	0.62±0.36	**0.001**
BCVA (Log MAR)	0.48±0.28	0.5±0.25	0.421	0.43±0.29	0.084	0.34±0.24	**0.0001**	0.29±0.17	**0.0001**	0.32±0.22	**0.0001**
K1 (D)	45.58±1.9	45.86±2.19	0.158	45.41±2.02	0.253	45.4±2.03	0.166	45.57±2.07	0.968	45.3±1.95	**0.029**
K2 (D)	49.21±2.61	50.02±2.88	**0.0001**	49.15±2.75	0.698	49.09±2.8	0.345	49.19±3.01	0.877	49±3.01	0.193
Avg K (D)	47.31±2.13	47.83±2.39	**0.008**	47.2±2.25	0.458	47.16±2.27	0.228	47.3±2.4	0.978	47.07±2.34	0.076
Cyl (D)	3.63±1.52	4.15±1.67	**0.0001**	3.74±1.60	0.082	3.68±1.64	0.568	3.61±1.68	0.889	3.65±1.6	0.827
AKf (D)	55.75±4.38	56.51±4.53	**0.001**	55.82±4.4	0.765	55.48±4.37	0.277	55.29±4.35	**0.029**	54.88±4.23	**0.001**
AKb (D)	79.91±9.61	80.38±9.28	0.727	81.93±10.04	**0.03**	84.4±11.47	**0.0001**	83.7±11.6	**0.0001**	83.34±11.45	**0.0001**
SIf	6.52±3.13	6.92±3.62	0.112	6.57±3.25	0.832	6.29±3.01	0.121	6.2±3.03	**0.02**	5.97±2.79	**0.004**
SIb	1.66±0.69	1.47±0.74	**0.016**	1.6±0.84	0.340	1.73±0.78	0.133	1.79±0.76	**0.009**	1.68±0.75	0.64
Thin (µm)	453.43±33.13	410.51±51.01	**0.0001**	409.26±47.4	**0.0001**	414.14±46.25	**0.0001**	423.83±47.09	**0.0001**	428.2±47.9	**0.0001**
Vol (µm³)	55.76±3.61	53.03±4.02	**0.0001**	53.86±4.08	**0.0001**	54.76±3.91	**0.0001**	54.35±3.6	**0.0001**	55.08±3.67	**0.026**
CCT (µm)	475.51±41.07	438.8±50.26	**0.0001**	435.91±51.12	**0.0001**	447.83±49.47	**0.0001**	456.37±49.17	**0.0001**	467.34±49.98	0.109

UCVA: Uncorrected visual acuity; BCVA: Best corrected visual acuity; K: Keratometry; Cyl: Cylinder; AKf: Apical keratometry front; AKb: Apical keratometry back; SIf: Symmetry index front; SIf: Symmetry index back; Thin: Thinnest point of cornea; Vol: Corneal volume; CCT: Central corneal thickness. Values in bold are statistically significant ($P<0.05$).

p¹ Comparison of preoperative and first month values, p² Comparison of preoperative and 3rd month values, p³ Comparison of preoperative and 6th month values,
p⁴ Comparison of preoperative and 12th month values, p⁵ Comparison of preoperative and 24th month values.

Nowadays, various accelerated CXL protocols are in clinical use and there are short time comparison studies with conventional method in the literature. Hashemi et al. compared the standard and accelerated (18 mW/cm^2 for 5 minutes) CXL, and reported that the decrease in Kmax and avgK with the improvement in visual acuity showed no difference between the two groups at the end of 6 months.[20] Cinar et al. showed similar results between accelerated (9 mW/cm^2,10 minutes) and standard protocol in terms of visual and refractive outcomes over a shorter time period (6 months).[21] Tomita et al. compared the conventional and accelerated (3 minutes 30 mW/cm^2) CXL, and they also achieved similar results in terms of the change in visual acuity and topographic parameters after the treatment between the two groups.[22]

In a recent 12 month follow up study, Elbaz et al. showed stabilization of keratometric values and topographic astigmatism after 9 mW/cm^2 for 10 minutes accelerated CXL.[12] In another study, Alnawaiseh et al. reported a significant reduction of Kmax and stabilization of the BCVA after accelerated CXL with an irradiance of 18 mW/cm^2 for 5 minutes, with a mean follow-up time of 21.7 months.[23] Similarly, Kurt et al. showed an increase on visual acuity, and flattening of Kflat, Ksteep and Kavg after the same UVA power setting and duration at 18 months.[14] Our study showed an improvement of UCVA and BCVA from the 6th month to the 24th month. We also found significantly reduced K1, Kmax, and SIf values which are the topographic indicators of CXL success. The decrease in the SIf value showing the difference in refractive power between the two hemispheres of the anterior cornea is very important in terms of reorganization of the keratoconic cornea. However, we found a significant increase in AKb which means steepening of the posterior cornea. Although it seems to be contradictory, we think that both AKf flattening together with AKb steep-

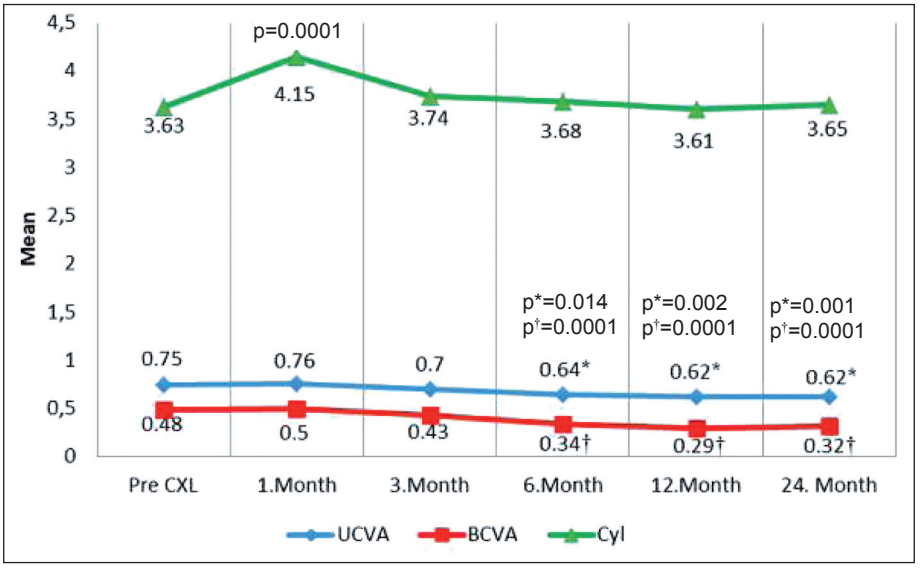

FIGURE 1: Changes in uncorrected and best corrected visual acuity and cylinderic values during follow-up period.

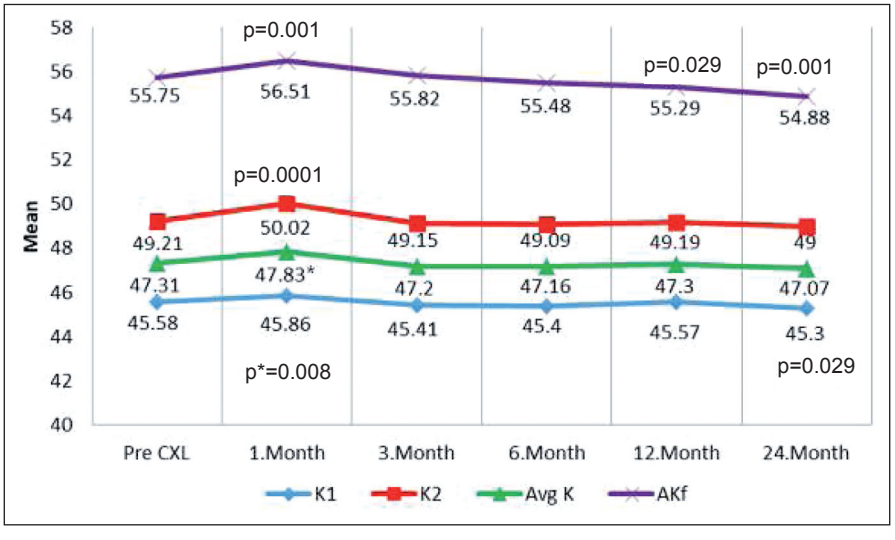

FIGURE 2: Changes in keratometry values during follow-up period.

ening may be the cause for the stabilization of keratometric values as shown in our previous study.[24]

On the other hand, there are some reports showing that accelerated crosslinking is not as effective as the standard protocol. In a study that compare the 6th month results of standard and accelerated CXL (30 mW/cm^2 for 3 min), the authors reported a smaller topographic flattening effect with accelerated CXL.[25] In another study, Toker et al. compared different CXL treatment modalities and showed that the standard and 9 mW/cm^2 (10 min) accelerated CXL protocols had more flattening effect on keratometric values than the 30 mW/cm^2 (4 min) accelerated CXL.[26] These results demonstrate that the accelerated CXL appears to be less effective in applications under 5 minutes. It is thought that the less CXL effect in accelerated protocol under a certain period of time may be associated with lower efficiency of photochemical reactions due to increased oxygen consumption at high UVA intensity.[27] Our study also included the patients with decreased vision due to the progression of keratoconus, but these were not at a level that could

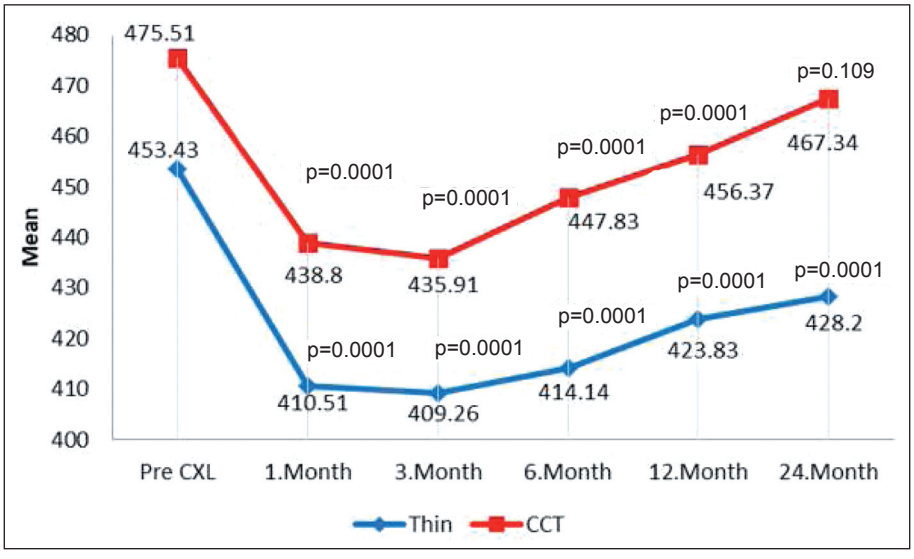

FIGURE 3: Changes in corneal thickness values during follow-up period.

adversely affect the overall statistics.

We found a decrease in CCT, Thin and CV in our study from the 1st month to the 24th month. It was shown that the causes of this reduction in corneal thickness and consequent reduction in corneal volume after CXL are keratocyte apoptosis and the changes in collagen fibrils and glycosaminoglycans in the corneal stroma.[28] The epithelial and stromal remodeling causes decreased corneal thickness to increase gradually. Although the reduction seen in CCT came closer to its preoperative level at 24 months, the CV and Thin remained significantly lower at the last visit. Similarly, Kurt et al. showed that the CCT decreased significantly in the first postoperative month and increased in the following months and came closer to the preoperative levels at 12 months.[14] Alnawaiseh et al. reported no statistically significant differences in the corneal thickness at the apex and at the thinnest point after 21 months of surgery.[23] On the other hand, Waszczykowska et al. reported a decrease in CCT at the 3rd and 12th month of accelerated CXL at 6 mW/cm^2 for 15 minutes that returned to the baseline values after the 24th month.[29] Because riboflavin with dextran is commonly used in conventional CXL procedure we also used the same riboflavin solution in this study. We think that the significant decrease in CCT, Thin and CV in our study might be related to the use of riboflavin with dextran. The use of riboflavin with hydroxypropyl methylcellulose which gives similar results with the use of riboflavin with dextran could be an alternative option.[22] Although in a study investigating conventional and accelerated CXL efficacy no significant difference was found between the use of riboflavin with or without dextran, the authors suggest the use of dextran-free riboflavin to prevent potential endothelial damage and to improve the safety profile of the procedure.[30]

In addition, it is shown that the decrease in corneal thickness is less in the conventional method than that of accelerated CXL. In a comparison study between conventional and accelerated CXL, both groups showed a significant decrease in CCT and Thin at 1 month, but the maximum decrease was shown in the accelerated CXL group at 3 months and the increase in corneal thickness was slower during postoperative period in that group.[31] In another study, Razmjoo et al. compared these two CXL methods and showed that the Thin was further reduced by accelerated CXL.[32] The use of high ultraviolet intensity may be another reason for the decrease in CCT, Thin and CV seen in our study.

The main limitation of this study is the lack of a control group and the retrospective design. It is needed to evaluate the long-term results of different accelerated CXL protocols with the conventional method.

CONCLUSION

Accelerated CXL procedure (irradiance of 18mW/cm^2 for 5 minutes) is effective in preventing keratoconus progression with increased visual acuity and stabilization in keratometric values after the 2-year follow-up. The long-term effect of this method demonstrated that it could be a safe alternative to the standard protocol in terms of reducing the duration of operation and increasing patient comfort.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ahmet Kırgız;* ***Design:*** *Ahmet Kırgız, Mehmet Orçun Akdemir;* ***Control/Supervision:*** *Ahmet Kırgız;* ***Data Collection and/or Processing:*** *Ahmet Kırgız;* ***Analysis and/or Interpretation:*** *Ahmet Kırgız, Mehmet Orçun Akdemir;* ***Literature Review:*** *Ahmet Kırgız, Mehmet Orçun Akdemir;* ***Writing the Article:*** *Ahmet Kırgız;* ***Critical Review:*** *Mehmet Orçun Akdemir.*

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