ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/ophthal.2020-78105

Accelerated Corneal Cross-linking Treatment in Keratoconus Patients: Three-Years Results

Keratokonus Hastalarında Hızlandırılmış Kornea Çapraz Bağlama Tedavisi: Üç Yıllık Sonuçlar

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ABSTRACT Objective: To evaluate the three-year results of accelerated corneal collagen crosslinking treatment in keratoconus patients. **Material and Methods:** Fifty eyes of 50 keratoconus patients were retrospectively reviewed. An accelerated corneal crosslinking treatment procedure was performed on the patients who exposed 9 mW/cm^2 irradiance ultraviolet-A with riboflavin for 10 minutes. All cases were evaluated with best corrected visual acuity (BCVA), topographic, tomographic, and topometric parameters, along with corneal densitometry, using the Scheimpflug imaging system (Pentacam® HR, Oculus Inc., Wetzlar, Germany) preoperatively and postoperatively at the sixth month and first, second, and third years. **Results:** The mean age of the patients was 21.7±5.1 years. BCVA was statistically significantly improved at the sixth month and first, second, and third years when compared to preoperative values (p<0.001, for all). Anterior K_{max} values decreased statistically significantly at the postoperative first, second, and third years (p<0.001, for all). The thinnest corneal thickness decreased statistically significantly at the sixth month and first, second, and third years when compared to preoperative values (p<0.001, for all). Anterior elevation values decreased statistically significantly at the sixth month and first, second, and third years when compared to preoperative values (p<0.001, for all). No significant corneal densitometric change was found on the 10-12 mm zone at all layers (p>0.05, for all). The mean vertical coma, spherical aberration, high-order aberration, and total corneal aberration values were significantly decreased at the first, second, and third years when compared to preoperative values (p<0.05, for all). **Conclusion:** Accelerated corneal crosslinking treatment reduces the risk of keratoconus progression and provides visual, topographic, and aberrometric improvement in some patients. Therefore, accelerated corneal crosslinking treatment is an effective treatment method to prevent progression in progressive keratoconus patients.

Keywords: Keratoconus; corneal topography; riboflavin

ÖZET Amaç: Keratokonus hastalarında hızlandırılmış korneal kollajen çapraz bağlama (KKÇB) tedavisinin 3 yıllık sonuçlarının değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Progresif keratokonusu olan 50 hastanın 50 gözü retrospektif olarak incelendi. Hastalara 10 dk 9 mW/cm^2 ultraviyole-A ile hızlandırılmış KKÇB tedavisi uygulandı. Tüm olguların operayon öncesi ve sonrası 6. ay, 1. yıl, 2. yıl, 3. yıldaki, en iyi düzeltilmiş görme keskinliği (EİDGK), topografik, tomografik, topometrik ve dansitometrik parametreleri (Pentacam® HR, Oculus Inc., Wetzlar, Almanya) değerlendirildi. **Bulgular:** Çalışmaya katılan hastaların yaş ortalaması 21,7±5,1 yıl idi. Operasyon sonrası 6. ay, 1, 2 ve 3. yıldaki EİDGK değerinde operasyon öncesine göre istatistiksel olarak anlamlı artış saptandı (sırasıyla; p=0,001; p<0,001; p<0,001; p<0,001). Operasyon sonrası 1, 2 ve 3. yıldaki anterior maksimum keratometri değerinde istatistiksel olarak anlamlı azalma saptandı (sırasıyla p<0,001; p<0,001; p<0,001). Tüm takiplerde en ince kornea kalınlığında, operasyon öncesine göre istatistiksel olarak anlamlı azalma olduğu saptandı (sırasıyla p<0,001; p<0,001; p<0,001; p<0,001). Operasyon sonrası 6. ay, 1, 2 ve 3. yıldaki ön elevasyon değerlerinde istatistiksel olarak anlamlı azalma olduğu saptandı (sırasıyla p<0,001; p<0,001; p<0,001; p<0.001). Tüm tabakalarda 10-12 mm zonda korneal dansitometride tedavi sonrası anlamlı değişiklik saptanmadı (Tüm takipler için p>0,05). Ortalama vertikal koma, sferik aberasyon, yüksek sıralı aberasyon, total aberasyon değerlerinde 1, 2 ve 3. yılda istatistiksel olarak anlamlı azalma saptandı (Tüm takipler için p<0,05). **Sonuç:** Hızlandırılmış KKÇB tedavisi keratokonus progresyonunu durdurmakta ve bazı hastalarda görsel, topografik ve aberometrik düzelme sağlamaktadır. Bu nedenle hızlandırılmış KKÇB, ilerleyici keratokonus hastalarında ilerlemeyi önlemek amacıyla uygulanabilecek etkin bir tedavi yöntemidir.

Anahtar Kelimeler: Keratokonus; kornea topografisi; riboflavin

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Peer review under responsibility of Turkiye Klinikleri Journal of Ophthalmology.

Received: 15 Jul 2020 ***Received in revised form:*** 24 Aug 2020 ***Accepted:*** 31 Aug 2020 ***Available online:*** 31 Dec 2020

Keratoconus is a degenerative disease that leads to irregular astigmatism and decreased visual acuity as a result of progressive thinning in the cornea.[1,2] Current treatments have two goals: stopping the disease and increasing the vision.[3] Treatments such as glasses and contact lenses, which are used to correct refractive errors, cannot prevent progression, and eventually corneal transplantation in keratoconus patients may be necessary.[4]

Corneal collagen crosslinking (CXL) treatment, first defined by Wollensak et al., can stop the progression of keratoconus using ultraviolet-A (UV-A) light and riboflavin.[5] Through this treatment, not only are new covalent bonds created among the collagen molecules biochemically but also the cornea is made more stable. With this treatment, corneal rigidity has been shown to increase, and the cornea becomes more resistant to enzymatic destruction.[6,7] Clinical trials support these findings.[8,9]

The conventional CXL protocol is an application of iso-osmolar 0.1% riboflavin solution to the cornea with the epithelium extracted for 30 minutes. This is followed by the application of 365-nm UV-A at a density of 3 mW/cm^2 lasting 30 minutes. Elimination of the corneal epithelium facilitates riboflavin passing adequately through the corneal stroma. Riboflavin is a photosensitizing agent that visualizes free radicals. The duration of treatment in the conventional method lasts one hour-lengthy for both the patient and the physician. According to the Bunsen-Roscoe rule, when the total energy level remains constant, changing the energy and radiation duration does not alter the photochemical reaction.[10] According to this rule, the application of high-intensity energy for a shorter time and the application of lower-intensity energy for a longer time should have the same effect.

Our study aimed to evaluate the long-term effects of accelerated (9 mW/cm^2) CXL treatment in patients with progressive keratoconus.

MATERIAL AND METHODS

This retrospective cross-sectional clinical study included 50 eyes of 50 patients with at least 3-year follow-up of accelerated CXL with the diagnosis of progressive keratoconus in our hospital eye clinic. A consent form was signed after the patients or their parents had been informed about the treatment before the procedure. Ethical approval for the study was obtained from the Numune Training and Research Hospital Ethics Committee. The study was performed in line with the Declaration of Helsinki.

PATIENT POPULATION

The study included patients aged between 9 and 50 years with clinically and topographically-proven progressive keratoconus, transparent cornea, and no other ocular or systemic disease. A rise in maximum keratometry (K_{max}) of more than 1 D in successive measurements in the last 6 months was acknowledged as a progression criterion. Previous corneal surgery, apical scar, active ocular infection, history of herpetic keratitis, severe dry eye, pregnancy and lactation, and connective tissue disease were specified as exclusion criteria.

FOLLOW-UP AND EVALUATION PARAMETERS

Patients with a follow-up of at least 36 months who regularly attended their follow-ups were included. Before and after CXL treatment, all patients were examined at 6 months, 1 year, 2 years, and 3 years. Before and after the control examinations, a Huvitz HRK-7000A (Huvitz Co. Ltd., Korea) auto-refractometer was used for the measurements. Spherical and cylindrical values of the patients were recorded. The best corrected visual acuity (BCVA) of the patients was measured with a Snellen chart and converted to logMAR for statistical analysis. Intraocular pressure measurements were performed using a Goldman applanation tonometer (Haag Streit, Inc., USA) and recorded.

Corneal topography examination was performed with a Pentacam HR (Oculus Inc., Wetzlar, Germany). Measurements were carried out by the same technician using 3D scanning in 25 images/1 sec mode. Parameters obtained from Pentacam HR measurements were: K_{max} (steepest keratometry on the anterior surface of the cornea), corneal astigmatism values, anterior surface elevation, posterior surface elevation, thinnest corneal thickness, anterior and posterior elevation values at the thinnest corneal point, flat K (K1) and vertical K (K2) for central 3.0

mm, and corneal asphericity (Q value) on the sagittal curvature map; surface variance index, vertical asymmetry index, keratoconus index, central keratoconus index, elevation asymmetry index, and elevation decentralization index on the topometric map; and trefoil, coma, spherical aberration, high-order aberration (HOA), and total corneal aberration in Zernike analysis. Total corneal aberrations were calculated using Pentacam software with the pupil center in a 6.0-mm diameter central area.

In the densitometry measurements, the entire cornea was separated into four concentric areas. The first region comprised a 2-mm diameter circular area at the center of the cornea. The second region was located in the 2-6 mm annular area around the first region. The third region was situated in the 6-10 mm annular area around the second region, and the fourth region was located in the 10-12 mm annular area around the third region. This analysis also demonstrated values of the cornea at three different depths. The anterior layer possesses a surface area of 120 µm, and the back layer covers an area of 60 µm from the back of the cornea. The central corneal layer is between these two layers. The corneal densitometry values are expressed as the pixel luminance per unit volume in the Scheimpflug image and they were expressed in grayscale units. According to the degree of backscattering light from the cornea, the measurements ranged from 0 (maximum transparency) to 100 (completely opaque cornea).

TREATMENT PROTOCOL AND SURGICAL METHOD

Accelerated CXL treatment was performed on all patients by two experienced surgeons. An Apollo M17KKDL (Meram Medicine, Turkey) crosslinking apparatus was used as the UV device. The treatment was performed in the operating room under sterile conditions. Proparacaine HCl 0.5% ophthalmic solution (Alcaine®, Alcon, Fort Worth, TX, USA) was used for topical anesthesia. Then, the eye and surrounding area were cleaned with 10% povidone-iodine and covered with a sterile drape. The eyelids were opened using a speculum. In the central cornea, the epithelium was extracted via a blunt tip spatula in the 8 mm diameter area. Every 2 minutes, iso-osmolar riboflavin was instilled to the patients whose corneal thickness was over 400 µm (MERRIBO, Meram Medical, Turkey). After 30 minutes, the corneal thickness was again measured through ultrasonic pachymetry. Hypo-osmolar riboflavin solution (0.1% riboflavin-5-phosphate in NaCl) was dropped to patients with corneal thickness below 400 until they reached 400 µm. Radiation therapy was then initialized with UV-A (370 nm). The laser probe was calibrated at a distance of 5 cm from the corneal apex and UV-A was applied for 10 minutes at 9 mW/cm² irradiance. Throughout the UV-A treatment, the riboflavin solution was dropped every 2 minutes. At the end of the CXL process, the patient's eye was irrigated with sodium chloride 0.9%, and a drop of 5% moxifloxacin (Vigamox®, Alcon Laboratories, Inc., USA) was instilled before a soft contact lens was placed (Bausch & Lomb PureVision™, Rochester, NY, USA). Following the CXL treatment, patients received 5% moxifloxacin (Vigamox®, Alcon Laboratories, Inc., USA) four times a day for 1 week and 0.5% loteprednol etabonate (Lotemax®, Bausch & Lomb, Rochester, NY, USA) four times a day for 1 week. After 4 weeks, this was reduced to one drop once a week. After the CXL treatment, the patients were invited for a follow-up visit on the first day. On the fifth day, contact lenses were removed following epithelial healing.

STATISTICAL ANALYSIS

SPSS 24.0 (IBM Corp., NY, USA) was used for statistical analysis. All data are presented as mean±standard deviation. The normal distribution of the data was evaluated using visual (histogram and probability groups) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk) tests. In the comparison of the measurements obtained preoperatively and at the sixth month, first year, second year, and third year postoperatively, Student's t-test was used in dependent groups and the Wilcoxon test if non-parametric conditions were met. A p-value of <0.05 was considered statistically significant.

RESULTS

Fifty eyes of 50 patients were included in the study. The average age of the patients was 21.7±5.1 years; 19 (38.0%) were female and 31 (62.0%) were male.

Table 1 displays the preoperative and follow-up BCVA, keratometry, elevation, and corneal aspherity values and their comparison. While there was a statistically significant increase in BCVA values at the sixth month, first year, second year, and third year after treatment (p=0.001, p<0.001, p<0.001, p<0.001, respectively), there was no considerable difference following the first year in BCVA levels when we compared the first and second years and the first and third years (p=0.164, p=0.146, respectively).

When the keratometry values of the patients were examined (K1, K2), a statistically significant decrease was found in sixth-month postoperative values compared to the pretreatment levels (p=0.006, p=0.004, respectively). Compared to the pretreatment period, there was a statistically significant decrease in K_{max} values in the first year, second year, and third year following the treatment (p<0.001, for all). In the third year after treatment, K_{max} values decreased by 2.70 D compared to pretreatment.

There was a statistically significant decrease in thinnest corneal thickness values at the 6th month, 1st year, 2nd year and 3rd year after the treatment (p<0.00, for all). In the third year following the treatment, a decrease of 26.9 µm was observed compared to pretreatment thickness. A statistically significant decrease occurred in anterior elevation values at 6 months, 1 year, 2 years, and 3 years following treatment (p<0.001, for all). In the third year following the treatment, the anterior elevation value decreased by 6.5 µm compared to the pretreatment level. Compared to pretreatment, the Q value in the third year after treatment decreased by an average of 0.20.

Table 2 displays the preoperative and follow-up corneal densitometry values of the patients and their comparison. Compared to pretreatment, corneal densitometry values were considerably increased in the anterior layer of the cornea in the 0-2 mm zone at the sixth month, first year, and second years; in the 2-6 mm zone at the sixth month and first year; and in the 6-10 mm zone at the first, second, and third years (p<0.05, for all). Corneal densitometry values were significantly increased in the central layer of the cornea in the 0-2 mm zone at the sixth month and first year; in the 2-6 mm zone at the sixth month and second and third years; and in the 6-10 mm zone at the first, second, and third years compared to pretreatment. Corneal densitometry values were significantly increased in the posterior layer of the cornea in the 0-2 mm zone at sixth months; in the 2-6 mm zone at the sixth month and second year; and in the 6-10 mm zone at the second and third years compared to pretreatment (p=0.002, p=0.014, p=0.044, p<0.001, p=0.006, respectively). Corneal densitometry values were significantly increased in the total layer of the cornea in the 0-2 mm zone at the sixth month and first year; in the 2-6 mm zone at the sixth month; and in the 6-10 mm zone at the first, second, and third years

TABLE 1: The preoperative and follow-up BCVA, keratometry, elevation and corneal aspherity values and their comparison.

Year, y	Pre-op	6th month	1st year	2nd y	3rd y	Pre-op-6th month	6th month-1st y	1st year-2nd y	2nd year-3rd y	Pre-op-3rd y
BCVA (logMAR)	0.45±0.20	0.28±0.17	0.18±0.14	0.16±0.14	0.15±0.14	**p=0.001**	**p=0.005**	p=0.164	p=0.950	**p<0.001**
K_1, (D)	45.84±2.94	45.23±3.03	44.62±2.79	44.36±2.75	44.23±2.78	**p=0.006**	p=0.125	p=0.118	p=0.338	**p<0.001**
K_2, (D)	50.33±3.70	49.74±3.57	49.23±3.19	48.79±3.22	48.63±3.16	**p=0.004**	p=0.898	p=0.136	p=0.482	**p<0.001**
K_{max}, (D)	56.17±5.42	55.31±5.11	54.21±4.68	53.71±4.48	53.41±4.81	p=0.072	p=0.269	p=0.155	p=0.343	**p<0.001**
Thinnest, µm	459±45.60	431.83±52.18	430±55.70	433.77±56.36	432.16±58.65	**p<0.001**	p=0.507	p=0.206	p=0.728	**p<0.001**
AE, µm	21.55±8.22	17.63±8.66	17.18±9.31	15.17±8.50	15.08±8.10	**p<0.001**	p=0.752	p=0.297	p=0.343	**p<0.001**
PE, µm	45.95±15.88	47.12±18.36	50.12±17.96	49.61±17.17	49.24±17.18	p=0.635	p=0.398	p=0.635	p=0.901	p=0.398
Q value	0.89±0.33	0.82±0.34	0.74±0.32	0.70±0.32	0.69±0.32	p=0.125	p=0.210	p=0.467	p=0.548	**p<0.001**

BCVA: Best corrected visual acuity; AE: Anterior elevation; PE: Posterior elevation; D: Dioptri; µm: Micron.Bold values indicates p<0.05.

TABLE 2: Preoperative and follow-up corneal densitometry values of the patients and their comparison.

Year, y GSU	Pre-op	6th month	1st year	2nd year (µm)	3rd year (µm)	Pre-op-6th month	6th month-1st year	1st year-2nd year	2nd year-3rd year	Pre-op-3rd year
0-2 mm										
Anterior	22.70±3.59	32.52±6.45	31.52±11.11	28.41±10.23	27.10±9.40	**p<0.001**	p=0.107	p=0.072	p=0.217	p=0.666
Central	14.21±1.61	17.78±3.35	16.50±3.80	15.00±4.09	14.67±4.73	**p<0.001**	p=0.291	**p=0.003**	p=0.107	p=0.666
Posterior	8.47±1.29	9.88±1.70	9.33±2.14	8.46±1.60	8.95±2.66	**p=0.002**	p=0.312	**p=0.002**	p=0.297	p=0.950
Total	15.13±1.94	20.06±3.40	19.11±5.29	17.28±5.11	17.04±5.13	**p<0.001**	p=0.463	**p=0.009**	p=0.429	p=0.229
2-6 mm										
Anterior	19.16±2.26	24.12±3.58	21.91±5.47	19.78±4.22	19.06±3.03	**p<0.001**	**p=0.011**	**p=0.003**	p=0.411	p=0.282
Central	12.13±1.13	13.56±1.54	12.34±1.99	11.31±1.44	10.98±1.21	**p=0.001**	**p<0.001**	**p=0.002**	p=0.107	**p<0.001**
Posterior	8.66±1.49	9.46±1.19	8.95±1.14	9.19±5.97	8.59±1.05	**p=0.014**	p=0.104	**p=0.005**	p=0.121	p=0.195
Total	13.39±1.33	15.71±1.87	14.40±2.70	13.16±2.10	12.88±1.61	**p<0.001**	**p=0.001**	**p=0.004**	p=0.376	p=0.177
6-10 mm										
Anterior	16.54±3.09	16.41±3.31	15.65±3.57	15.18±3.61	14.84±3.01	p=0.874	**p=0.004**	p=0.937	p=0.255	**p<0.001**
Central	11.09±1.45	10.89±1.73	10.55±1.87	10.11±1.61	10.00±1.65	p=0.635	**p=0.030**	p=0.193	p=0.343	**p<0.001**
Posterior	8.81±1.09	8.79±1.35	8.53±1.26	8.21±1.20	8.39±1.36	p=0.312	p=0.376	p=0.125	p=0.343	**p=0.006**
Total	12.15±1.77	12.03±2.02	11.57±2.11	11.13±2.01	11.09±1.91	p=0.825	**p=0.004**	p=0.398	p=0.658	**p<0.001**
10-12mm										
Anterior	29.60±10.94	28.45±11.48	25.97±9.40	27.74±8.18	27.44±9.59	p=0.191	p=0.191	p=0.191	p=0.191	p=0.191
Central	17.20±5.54	16.61±5.87	15.19±3.82	15.74±3.78	15.91±4.68	p=0.297	p=0.398	p=0.137	p=0.312	p=0.087
Posterior	12.66±3.06	12.52±3.56	11.86±2.82	11.95±2.71	12.25±3.03	p=0.147	p=0.147	p=0.147	p=0.147	p=0.147
Total	19.82±5.92	19.40±6.61	17.67±4.91	18.49±4.40	18.54±5.35	p=0.183	p=0.442	p=0.354	p=0.277	p=0.197
Total										
Anterior	20.51±2.79	23.57±3.46	22.04±5.04	20.93±4.17	20.41±3.27	**p<0.001**	**p=0.011**	p=0.080	p=0.749	p=0.587
Central	12.93±1.33	13.84±1.71	12.87±1.90	12.24±1.77	12.07±1.72	p=0.011	**p=0.001**	p=0.066	p=0.237	**p<0.001**
Posterior	9.38±1.04	9.78±1.26	9.33±1.19	8.92±1.18	9.18±1.33	p=0.275	p=0.080	p=0.106	p=0.125	p=0.142
Total	14.28±1.57	15.74±1.96	14.75±2.56	14.03±2.25	13.89±1.98	**p<0.001**	**p=0.001**	p=0.116	p=0.443	p=0.323

GSU: Grayscale units; mm: Milimeter. Bold values indicates p<0.05.

compared to pretreatment (p<0.001, p<0.001, p<0.001, p=0.002, p<0.001, p<0.001, respectively).

Table 3 displays the corneal topometrics and aberration values and their comparison before and after treatment. Excluding IHA in the third year, a statistically significant decrease occurred in corneal topometric values (ISV, IVA, KI, CKI, IHD; p<0.001, for all). Compared to pretreatment, a statistically significant decrease was observed in vertical coma, spherical aberration, HOA, and total corneal aberration values at the first, second, and third years after treatment (p<0.05, for all).

TABLE 3: Corneal topometrics and aberration values of patients before and after treatment and their comparison.

Year, y	Pre-op	6th month	1st y	2nd y	3rd y	Pre-op-6th Month	6th month-1st y	1st y-2nd y	2nd y-3rd y	Pre-op-3rd y
ISV	82.08±26.33	81.77±29.74	75.48±23.31	73.65±22.18	71.95±23.16	p=0.937	p=0.054	p=0.255	p=0.312	**p<0.001**
IVA	0.80±0.35	0.82±0.33	0.77±0.32	0.76±0.31	0.72±0.34	p=0.229	p=0.242	p=0.206	p=0.591	**p<0.001**
KI	1.21 ±0.09	1.20±0.11	1.19±0.08	1.18±0.09	1.17±0.09	p=0.398	p=0.430	p=0.242	p=0.282	**p<0.001**
CKI	1.06±0.03	1.06±0.04	1.04±0.04	1.04±0.03	1.04±0.04	p=0.184	p=0.621	p=0.107	p=0.825	**p<0.001**
IHA	37.84±25.41	36.82±20.64	36.36±22.09	31.31±21.81	32.09±19.66	p=0.144	p=0.144	p=0.144	p=0.144	p=0.144
IHD	0.117±0.05	0.113±0.04	0.105±0.04	0.09±0.04	0.09±0.04	p=0.100	p=0.206	p=0.054	p=0.975	**p<0.001**
Vertical koma (µm)	1.88±0.89	1.78±0.82	1.63±0.87	1.51±0.89	1.47±0.93	**p=0.004**	p=0.129	p=0.136	p=0.448	**p<0.001**
Trefoil (µm)	0.18±0.35	0.19±0.39	0.09±0.35	0.17±0.32	0.17±0.35	p=0.570	p=0.570	p=0.570	p=0.570	p=0.570
Spherical aberration (µm)	0.53±0.53	0.47±0.77	0.22±0.60	0.12±0.57	0.09±0.61	p=0.100	p=0.149	p=0.184	p=0.924	**p<0.001**
HOA	2.60±1.06	2.58±1.13	2.38±0.91	2.26±0.88	2.25±0.94	p=0.229	p=0.499	p=0.030	p=0.411	**p<0.001**
Total corneal aberration (µm)	10.86±4.18	10.67±3.73	9.92±3.40	9.58±3.40	9.36±3.55	p=0.255	p=0.248	p=0.877	p=0.752	**p<0.001**

ISV: IVA: KI: CKI: IHA: IHD: HOA: High order aberrations; µm: Micron. Bold values indicates p<0.05.

DISCUSSION

CXL treatment was first defined by Wollensak et al. in 2003. Its objective is to increase the cross-links in the collagen to provide hardening of the cornea and stop the progression of ectatic illnesses. CXL treatment is the sole proven treatment option to diminish the risk of progression of ectasia.[5,11] Current studies have stated that treatments performed for 10 minutes with 9 mW/cm^2 radiation and 5 minutes with 18 mW/cm^2 radiation are safe, decrease the risk of progression of keratoconus, and have clinical results similar to the standard Dresden Protocol.[12,13]

Our study used an accelerated CXL method, with 9 mW/cm^2 radiation for 10 minutes, where the epithelium was extracted. The goal of CXL treatment is to reduce the risk of progression of keratoconus. Enhancing visual acuity is not a preliminary goal of treatment. Patients should be informed about this.

VISUAL ACUITY

In our study, BCVA increased from 0.45±0.20 logMAR preoperatively to 0.15±0.14 logMAR at 3 years. Despite the significant increase in BCVA up to the first year, the significance fell at the second and third years in comparison with the first year. We assume that the increase in visual acuity is because of the flattening effect of the anterior keratometry and decrease in corneal aberrations following the treatment. Given these results, accelerated CXL treatment has positive results in visual acuity in keratoconus patients. Many other studies have shown that BCVA may increase after treatment.[14-16] Çınar et al. observed a significant increase in BCVA (0.15 logMAR) at 6 months with accelerated CXL treatment (9 mW/cm^2, 10 min).[15] Shetty et al. found a significant decrease of 0.12 logMAR in BCVA at 2 years of fol-

low-up after accelerated CXL treatment (9 mW/cm^2, 10 min) in 30 children under the age of 14 years.[17] Kanellopoulos found an increase in BCVA in their study using an accelerated procedure (7 mW/cm^2, 15 min).[18]

Çınar et al. compared the accelerated method with the standard procedure and found that BCVA increased in both groups, but this increase was significant only in the accelerated group.[14] No significant difference was observed among the two groups. Chow et al. compared the standard procedure with an accelerated CXL procedure (18 mW/cm^2, 5 min), and found no considerable difference in BCVA.[16] Madeira et al. also compared the accelerated (6 mW/cm^2, 15 min) and standard protocols and found a significant increase in BCVA in the first year, but no difference in BCVA was seen between the two groups.[19] Another study also compared the accelerated CXL procedure (9 mW/cm^2, 10 min) and the standard procedure, finding significant improvements in BCVA and corneal flattening in the standard procedure but not in the accelerated procedure. In this study, the change of BCVA in the accelerated and standard groups was 0.021 logMAR and -0.126 logMAR, respectively.[20]

TOPOGRAPHIC RESULTS

In our study, K_{max} was 56.17±5.42 preoperatively and 53.41±4.81 at the third year. Following the treatment, a considerable decrease was seen in the K_{max} value at the first, second, and third years in comparison to the pretreatment levels. At the third year, an average flattening of 2.7 D was detected. Accelerated CXL treatment can thus be considered to provide a partial regression as well as to reduce the risk of progression.

Similarly, Çınar et al. found a decrease of 1.4 D in K_{max} at the 6-month follow-up of treatment with accelerated CXL (9 mW/cm^2, 10 min).[15] Following 2 years of follow-up after accelerated CXL (9 mW/cm^2, 10 min) in 30 children below 14 years old, Shetty et al. found a 2 D decrease in keratometry values (K1, K2).[17] The study of Elbaz et al. (9 mW/cm^2, 10 min) showed that the progression of the disease stopped, although there was no regression in the topographic parameters.[21] Tomita et al. indicated a decrease of 0.62 D in K_{max} at the 1-year follow-up of an accelerated CXL procedure (30 mW/cm^2, 3 min).[22] Conversely, Mazzotta et al. detected a progression in the second and third years in 19% of pediatric keratoconus patients who had undergone accelerated CXL treatment.[23] The study of Ozer et al. followed 35 pediatric eyes for an average of 56 months.[24] Despite the treatment, progression of keratometry values and central corneal thickness were seen in %20 of the patients.[24] This was affected by the patient population having pediatric keratoconus, which is attributed to environmental factors such as atopy, allergy, and scratching.

Other studies have compared topographic results of the standard and accelerated procedure. For instance, Çınar et al. compared accelerated CXL (9 mW/cm^2, 10 min) with the standard procedure.[14] The decrease in K_{max} in both groups was significant, and no significant difference was seen between the two groups. In another study comparing accelerated CXL (9 mW/cm^2, 10 min) with the standard procedure, corneal flattening was significant in the standard treatment (1.8 D), but no significant change was seen between the two groups (0.3 D).[20] This difference may be because the formation of covalent bonds between collagen molecules is oxygen-dependent, so the accelerated procedure has less effect than the standard procedure. This was also shown in an ex vivo study.[25]

Our study showed that the minimum corneal thickness declined considerably in comparison with the preoperative value at 6 months and remained stable until 3 years of follow-up. Taking into account the duration of our study, this thinning of the cornea may also be an indicator of progress, and these patients should be monitored at close range, including other parameters. In three studies using accelerated protocols, no significant change was found in the minimum corneal thickness at 12 months after treatment.[12,16,26] Mazzotta et al. notified that the minimum corneal thickness declined considerably after 1 and 3 months following accelerated CXL, but reached baseline again at 6 months and remained stagnant for 10 years.[23] Corneal thinning after CXL treatment was reported to result from dehydration, epithelial thinning, and keratocyte apoptosis. However, studies have reported that this thinning is not

permanent and that the corneal thickness has reached pretreatment level at roughly 12 months.[16,26]

TOPOMETRIC RESULTS

In our study, a decrease was seen in anterior elevation after treatment, and a considerable increase was observed in posterior elevation. We assume that the decrease in anterior elevation was because of the flattening of the anterior surface of the cornea and epithelial remodeling. There are differing opinions in the literature on this, with many studies finding different results. Taheri et al. reported no change in anterior or posterior elevation, as did Steinberg et al.[27,28] Koç et al. found a decrease in anterior elevation but no significant change in posterior elevation at 6 months with an accelerated procedure (9 mW/cm^2, 10 min).[29]

DENSITOMETRY RESULTS

Corneal densitometry is a measure of light transmittance and the transparency of the cornea. Corneal densitometry may vary due to the factors such as edema, haze, scarring, active inflammation, infiltrate, and deposited material in storage diseases. In a study that reported changes in corneal densitometry in keratoconus, this change was shown to be greater in the central cornea and epithelial and anterior stromal layers, possibly due to impaired collagen sequencing.[30] Corneal densitometry may change due to the epithelial healing process, temporary haze caused by keratocyte damage, and demarcation lines after CXL treatment.

In our study, corneal densitometry reached the highest value at 6 months in all layers in the 0-2 mm zone after treatment. This value decreased until 3 years of follow-up but did not return to preoperative values. In the 2-6 mm zone, corneal densitometry increased in all layers, reaching the highest value at the sixth month. This value decreased to the preoperative value by 2 years and fell below the basal value in the third year. In general, we found no change in corneal densitometry after treatment in the 6-10 mm and 10-12 mm zones. Consistent with the area where the epithelium was removed, we found that the treatment had no effect on the peripheral corneal densitometry but affected the central corneal densitometry. The increase in corneal densitometry was evident in the superficial layers of the cornea, affecting the central cornea where the treatment was applied and decreasing over time, suggesting that this is not a treatment-related complication and may be a part of the healing process. We believe that the change in corneal densitometry can be used as a parameter showing treatment efficacy, and comparative studies could be done with anterior segment optical coherence tomography.

Alnawaiseh et al. reported no significant change in the densitometry values in all layers and zones 22 months after accelerated CXL treatment.[12] Alnawaiseh et al. found a significant increase in all corneal densitometry between 1 and 3 months after treatment and a decrease between 24 and 36 months in another study with a 36-month follow-up period.[31] Corneal densitometry was found to be highest in the first month after treatment. In the same study, they reported that corneal densitometry regressed to preoperative values at 1 year and decreased to preoperative values after 2 years.[31] Koç et al. found that corneal densitometry values were significantly higher than preoperative values even 1 year after accelerated CXL.[32]

ABERRATION RESULTS

In our study, vertical coma, spherical aberration, HOA, and total corneal aberration were decreased; trefoil value did not change. The decrease in vertical coma and spherical aberration may have contributed to the increase in BCVA. Studies have shown that HOA, total corneal aberration, vertical coma, and trefoil values have decreased after CXL treatment, whereas spherical aberration values have not changed.[33,34] When Ozulken et al. compared the values of patients in two groups (10 min, 9 mW/cm^2 and 5 min, 18 mW/cm^2) before and after CXL, significant decreases were observed in only coma and total HOA.[35] Kirgiz et al. evaluated anterior corneal HOAs and compared their changes in the 6-mm zone. All anterior corneal aberrations demonstrated a significant reduction in both groups (5 min, 18 mW/cm^2 and 10 min, 9 mW/cm^2).[36]

A limitation of our study is the lack of endothelial count. Therefore, we could not observe the effects of accelerated CXL treatment on endothelium. No corneal endothelial complications were reported in the cornea where corneal thickness was above 400 μm. Another limitation was that we could not investigate the de-

marcation line in patients with anterior segment optical coherence tomography. One parameter showing the effectiveness of CXL treatment is the depth of the demarcation line. The most important disadvantage is the retrospective design of our study. Despite these limiting factors, our study is important in terms of showing the 3-year results of accelerated CXL efficacy.

CONCLUSION

Accelerated CXL treatment may reduce the risk of progression of keratoconus and provides visual, topographic, and aberrometric improvement. Therefore, accelerated CXL is an effective treatment method to prevent progression in patients with progressive keratoconus.

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: *Emre Aydemir, Mustafa Koç;* ***Design:*** *Emre Aydemir, Hasan Kızıltoprak;* ***Control/Supervision:*** *Gözde Aksoy Aydemir, Kemal Tekin;* ***Data Collection and/or Processing:*** *Emre Aydemir, Hacı Hasan Özkan;* ***Analysis and/or Interpretation:*** *Emre Aydemir, Hasan Kızıltoprak;* ***Literature Review:*** *Gözde Aksoy Aydemir;* ***Writing the Article:*** *Emre Aydemir, Mustafa Koç;* ***Critical Review:*** *Gözde Aksoy Aydemir, Kemal Tekin, Hasan Kızıltoprak;* ***References and Fundings:*** *Hacı Hasan Özkan;* ***Materials:*** *Hasan Kızıltoprak.*

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