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ORIGINAL ARTICLE

Visual and topographical outcomes following accelerated corneal crosslinking in progressive keratoconus

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Abstract

Purpose: The purpose of the study was to evaluate changes in vision and the optical performance of the cornea in patients with keratoconus following treatment with accelerated corneal crosslinking (CXL).

Methods: Sixty-two eyes of 40 keratoconus patients with 12-month follow-up of after accelerated CXL (9 mw, 10 min) were included in the study. Best-corrected visual acuities (BCVAs), follow-up time, simulated keratometry values, spherical equivalent (SE), manifest astigmatic correction (MAC), total root mean square (RMS), low order aberrations (LOA)-RMS, high-order aberrations (HOAs)-RMS, horizontal coma, vertical coma, horizontal trefoil, vertical trefoil, spherical aberration, thinnest pachymetry (thin), and central corneal thickness values before and after the treatment were reviewed retrospectively. The patients were divided into two groups as those with maximum keratometry values below 51 D (Group 1) and above 51 D (Group 2).

Results: In Group 1, the improvement in BCVA was not significant (p=0.09) but the improvement in Kmax (p=0.001) and SE (p=0.001) was significant. In Group 2, mean BCVA showed improvement of three lines from 0.78±0.5 to 0.48±0.48 logMAR (p=0.016). In addition, the mean Kmax flattened by 0.52 D (p=0.016). SE decreased up (p=0.001) and the improvement in RMS HOA was significant (p=0.005) in Group 2. In Group 1, change in BCVA was correlated with change in SE and spherical aberration (p<0.05, for all). In Group 2, the change in BCVA has significant association with the change in MAC, total RMS HOA, vertical coma, vertical trefoil, and spherical aberrations (p<0.05, for all).

Conclusion: Accelerated CXL leads to visual, refractive, topographic, and HOAs improvement, particularly in severe keratoconus.

Keywords: Cross linking; ectasia; high-order aberration; keratoconus; low-order aberration.

Keratoconus is an ectatic corneal disease characterized by continuous loss of stroma resulting astigmatism and deteriorated quality of sight.[1] Corneal crosslinking (CXL) has been demonstrated to be effective in vast majority of patients in suspending the ectatic process with progressive keratoconus and post-LASIK ectasia.[2–4] The conventional CXL therapy is applied through UVA light that includes 3.0 mW/cm^2 radiation for 30 min, with a total energy dose of

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5.4 J/cm^2.[5] Since the standard treatment duration is long, accelerated CXL has gained popularity recently. The reciprocity law, also called Bunsen–Roscoe law, demonstrates that total surface dose is critical and same biological effect of 30 min of UVA light at 3.0 mW/cm^2 could be provided with 10 min of UVA light at 9.0 mW/cm^2.[6] Accelerated CXL has been shown to induce similar biomechanical change on cornea as those induced by standard treatment.[7,8]

Keratoconus, leading to irregular astigmatism, myopia, higher order aberrations (HOAs), and finally scar tissue on cornea, could raise to a prominent decrease in visual quality.[1,9] Some recent reports demonstrated that CXL results in aberrational and visual quality changes by corneal reshaping as well as ceases the progression of disease.[10,11] Even rehabilitation of vision supplied by CXL is restricted, it is remarkable to evaluate whether reduced HOAs and improved visual quality can be achieved post-CXL.

In this study, we aimed to evaluate changes in vision and aberrations of the cornea in patients with progressive keratoconus 12 months after accelerated CXL.

Materials and Methods

This study involved 62 eyes of 40 patients with progressive keratoconus. All of the eyes had accelerated CXL procedure and the minimum follow-up period was 12 months, according to chart review. This study was generated in compliance with the rules of the Declaration of Helsinki and was confirmed by local ethics committee (E-19.014). Patients or their legal representative gave informed consent for this study.

These criteria were taken for inclusion the patients: A progression of maximum keratometry (Kmax) of more than 1.00 diopter (D) within 12 months and corneal thickness (at the thinnest point) of >400 mm. The criteria of exclusion involved lactation, apical cornel scarring, previous corneal surgery, pregnancy, presence of ocular infection, and connective tissue disease. The effect of treatment was evaluated at the 12-month follow-up visit. Patients underwent complete ophthalmologic examination with measurement of uncorrected visual acuity and best-corrected visual acuity (BCVA), biomicroscopic examination, fundus assessment, and corneal tomography with a rotating Scheimpflug corneal tomography (Pentacam HR; Oculus Optikgeräte GmbH, Wetzlar, Germany). The BCVA was evaluated as logMAR.

Patients using contact lenses (CLs) were advised to stop wearing at least 1 week before examination. Optical aberrations of cornea were evaluated at every visit by Pentacam, which examines the elevations of anterior and posterior cornea over the central 6.0 mm and computes HOAs from these data of elevation. Aberrations at anterior, posterior, and total cornea are calculated by the software program. Total corneal lower order aberrations (LOAs) and total corneal HOAs are given as subdivision by the software in Scheimpflug tomography system. Software program of the device changes the elevations into Zernike polynomials expressed in corneal wavefront, which involves eighth-order aberrations. Total root mean square (RMS), HOA-RMS, horizontal coma Z (3, 1), vertical coma Z (3, 1), horizontal trefoil Z (3, 3), vertical trefoil Z (3, 3), and spherical aberration Z (4, 0) values were the aberrations that were analyzed. Simulated keratometry values, Kmax, thinnest pachymetry, and pachymetry apex values were also recorded from tomographical analyses. Following CXL, all measurements were renewed at 1, 3, 6, and 12 months.

Patients were divided into two subgroups: Those with a Kmax value of <51.0 D (mild-to-moderate keratoconus) defined as Group 1 (36 patients, 19 males–17 females) and Kmax of ≥51.0 D (severe keratoconus) as Group 2 (26 patients, 13 males–13 females) according to the baseline Kmax in both groups. Mean age of Group 1 and Group 2 was 24.58±5.35 (19–42) and 24.54±6.48 (19–43). There were 20 males and 16 females.

Surgical Procedure

Proparacaine hydrochloride (0.5%) (Alcaine) was used before procedure of CXL. Central corneal epithelium debridement with 8.5 mm diameter with a crescent knife using alcohol with 20% concentration. Alcohol was applied for 30 s. Afterward, surface was cleaned with 0.9% NaCl solution. Isotonic riboflavin solution without dextran (MedioCROSS® H, Avedro Inc., USA) was applied with 2 min interval immediately after removal of the epithelium for 30 min. An ultrasound probe (SP-2000, Tomey, Inc.) was used for measuring the pachymetry preoperatively and every 10 min after removing epithelium of the cornea. If the cornea was thinner than 400 μm, hypotonic riboflavin was applied. Corneal thickness was swollen to at least 400 μm by this method. Riboflavin was applied at 2 min intervals beside the course of a 10 min exposure to 9 mW/cm^2 UV-A (Cross-K, NIDEK, Italy). At last step, a therapeutic contact lens (Air Optics; Alcon, Inc.) was applied. Postoperatively, both eyes were treated with diclofenac (Acular LS®) (4 times a day) and netilmicin (Netira®) (4 times a day), loteprednol (Lotemax®, Bausch and Lomb Inc.) (3 times a day), and artificial tears (6 times a day). Patients were followed up on a daily basis until complete reepithelization was observed. Topical netilmicin was used for 1 week, loteprednol was used with a tapering

schedule for 3 months, and artificial tear was continued for 6 months. We did not experience corneal scar or epithelial healing problem following CXL.

Statistical Analyses

Statistical analyses were conducted with the SPSS program (v. 20.0, IBM Corporation, USA). Kolmogorov–Smirnov test was used for distribution of sample means. Continuous variables are given as mean±SD, while categorical variables are given as numbers and percentages. Comparison of the categorical variables was done using the χ^2 test. The Student's t-test was applied for comparing the groups. Significance of differences between means and medians between pre- and post-operative clinical measurements was calculated with paired samples t-test. Spearman's rank correlation test was performed for correlation between continuous variables. P<0.05 was regarded as statistically significant.

Results

Mean age of Group 1 and Group 2 was 24.58±5.35 (19–42) and 24.54±6.48 (19–43) years, respectively (p>0.05). The sex distribution was similar in both groups (p>0.05). Mean follow-up time was 334.25±287.36 (12–994) months.

In Group 1, the increase in BCVA was not significant (p=0.09) but the improvement in Kmax (p=0.001) and SE (p=0.001) was significant. In Group 2, mean BCVA showed improvement of three lines from 0.78±0.5 (0.00–2) to 0.48±0.48 (0.00–1.7) logMAR (p=0.016). In addition, the mean Kmax flattened by 0.52 D (p=0.016) (Table 1). SE decreased (p=0.001) and the improvement in RMS HOA was remarkable (p=0.0047) (Table 2). Post-operative RMS LOA difference was not significant in both groups (p>0.05).

After CXL, differences in mean RMS values of horizontal coma, vertical coma, horizontal trefoil, and vertical tre-

Table 1. Visual acuities and corneal topographic findings of patients at baseline and 12 months after corneal crosslinking

Parameters	Group 1 (mean, min–max)	Group 2 (mean, min–max)	p-value
BCVA (logMAR)			
Pre-operative	0.36±0.34 (0.00–1.7)	0.78±0.5 (0.00–2)	0.001
12-month post-operative	0.32±0.42 (0.00–1.7)	0.48±0.48 (0.00–1.7)	0.063
Mean change	0.04±0.32	0.31±0.46	0.001
p-value*	0.09	0.016	
Spherical equivalent			
Pre-operative	–3.84±2.43 (–7.25, –2.75)	–6.01±3.32 (–12, –2.25)	0.001
12-month post-operative	–3.44±2.26 (–7.25, –2.50)	–5.39±3.01 (–10.5, –2.00)	0.002
Mean change	–0.4±1.23	–0.62±0.79	0.008
p-value*	0.001	0.001	
Manifest astigmatic (D)			
Pre-operative	3.15±1.72 (1.25–5.75)	3.81±2.21 (1.5–7.75)	0.001
12-month post-operative	2.85±1.67 (1.25–5.50)	3.17±2.17 (1.5–7.75)	0.001
Mean change	–0.32±0.59	–0.64±0.65	0.001
p-value*	0.04	0.009	
Thin (mμ)			
Pre-operative	449.41±29.45 (420–527)	431±33.18 (384–483)	0.025
12-month post-operative	435.97±36.32 (407–509)	412.65±63.12 (378–472)	0.059
Mean change	13.44±20.67	18.35±25.65	0.081
p-value*	0.001	0.001	
CCT (mμ)			
Pre-operative	462.22±32.61 (431–530)	444.96±32.74 (401–491)	0.025
12-month post-operative	448.58±36.02 (418–517)	428.46±60.85 (384–477)	0.082
Mean change	13.64±11.36	16.5±14.79	0.129
p-value*	0.109	0.097	
Kmax (D)			
Pre-operative	47.81±2.60 (45.30–50.4)	55.55±3.11 (51.1–60.7)	0.001
12-month post-operative	47.3±2.62 (45.2–50.2)	55.03±3.57 (50.7–59.5)	0.001
Mean change	0.51±0.74	0.52±0.93	0.436
p-value*	0.001	0.016	

Data were shown as mean±SD, BCVA: Best-corrected visual acuity; Cyl: Topographic cylindrical value; Thin: Thinnest point of cornea; CCT: Central corneal thickness; D: Diopters; Kmax: Maximum keratometry value. P: Paired t-test, p*: Student's t-test, p<0.05 is statistically significant.

Table 2. Pre-operative and 12-month post-operative corneal optical aberrations

Parameters	Group 1 (mean, min–max)	Group 2 (mean, min–max)	p-value
Total corneal aberrations			
Pre-operative	9.85±4.11 (5.70–14.90)	15.07±5.30 (9.30–22.50)	0.001
12-month post-operative	9.63±3.91 (5.60–14.50)	14.77±5.63 (9.20–22.10)	0.001
Mean change	0.22±0.76	0.30±1.23	0.167
p-value*	0.172	0.920	
Corneal LOAs			
Pre-operative	9.53±3.99 (5.50–14.30)	14.47±5.23 (8.70–20.50)	0.001
12-month post-operative	9.31±3.78 (5.50–13.10)	14.24±5.52 (8.70–19.80)	0.001
Mean change	0.32±0.94	0.23±1.32	0.092
p-value*	0.158	0.989	
Corneal HOAs			
Pre-operative	2.46±1.07 (0.70–4.10)	4.03±1.57 (2.30–8.80)	0.001
12-month post-operative	2.37±1.04 (0.60–4.10)	3.80±1.51 (1.70–7.70)	0.001
Mean change	0.09±0.46	0.23±1.02	0.032
p-value*	0.156	0.047	
Horizontal coma			
Pre-operative	–0.37±0.84 (–1.10–0.5)	0.02±0.37 (–0.40–0.50)	0.001
12-month post-operative	–0.33±0.71 (–1–0.4)	0.01±0.25 (–0.3–0.3)	0.001
Mean change	–0.04±0.27	0.01±0.22	0.057
p-value*	0.467	0.159	
Vertical coma			
Pre-operative	–0.35±0.92 (–1.30–1.40)	3.29±1.42 (1.20–4.80)	0.001
12-month post-operative	–0.31±0.84 (–1.10–1.20)	2.87±1.27 (1.60–4.50)	0.001
Mean change	–0.04±0.36	0.42±0.19	0.001
p-value*	0.315	0.02	
Horizontal trefoil			
Pre-operative	0.12±0.17 (–0.10–0.40)	0.27±0.18 (0–0.50)	0.032
12-month post-operative	0.11±0.14 (–0.10–0.30)	0.26±0.16 (0–0.40)	0.033
Mean change	0.01±0.06	0.01±0.07	0.767
p-value*	0.568	0.374	
Vertical trefoil			
Pre-operative	0.02±0.16 (–0.20–0.20)	0.57±0.34 (0.10–1.10)	0.001
12-month post-operative	–0.01±0.17 (–0.20–0.20)	0.41±0.37 (0–0.90)	0.001
Mean change	0.03±0.12	0.16±0.12	0.03
p-value*	0.467	0.02	
Spherical aberration			
Pre-operative	–0.85±0.69 (–1.50–1.60)	–0.56±0.44 (–1–0.20)	0.04
12-month post-operative	–0.32±0.96 (–0.70–0.80)	–0.41±0.12 (–0.4–-0.1)	0.07
Mean change	–0.53±0.24	–0.15±0.16	0.001
p-value*	0.001	0.03	

RMS: Root mean square; LOAs: Lower order aberrations; HOAs: Higher order aberrations. P: Paired t-test; p*: Student's t-test, $p<0.05$ is statistically significant.

foil aberrations were not significant in Group 1 ($p>0.05$, for all). However, spherical aberration value significantly increased 12 months after the procedure in Group 1 ($p=0.001$). In Group 2, vertical coma and vertical trefoil values decrease significantly after CXL ($p=0.02$, for both). In addition, spherical aberration was higher than pre-operative value significantly ($p=0.03$). Thinnest pachymetry values have decreased considerably at 12 months in both groups ($p=0.001$, for both). There was no significant change in central corneal thickness (CCT) value in both groups ($p>0.05$). Table 3 shows the association between BCVA and topographic outcomes. In Group 1, change in BCVA was correlated with change in SE and spherical aberration ($p=0.023$ and $p=0.014$, respectively). In Group 2, the change in BCVA has a significant association with the change in manifest astigmatic correction, total RMS HOA, vertical coma, vertical trefoil, and spherical aberrations ($p<0.05$, for all).

Table 3. Correlation between the changes in best-corrected visual acuity and the changes in clinical and topographic parameters 12 months after crosslinking

Parameters	ΔBCVA			
	Group 1		Group 2	
	r	p	r	p
ΔSpherical equivalent	0.336	0.023	0.361	0.036
ΔManifest astigmatic (D)	−0.195	0.247	0.305	0.047
ΔThin (mμ)	−0.047	0.687	−0.124	0.213
ΔKmax (D)	−0.069	0.567	−0.058	0.456
ΔTotal corneal aberrations	−0.031	0.429	0.032	0.439
ΔCorneal LOAs	−0.071	0.341	−0.315	0.058
ΔCorneal HOAs	0.011	0.475	−0.396	0.022
ΔHorizontal coma	0.065	0.565	0.145	0.136
ΔVertical coma	−0.061	0.543	−0.415	0.017
ΔHorizontal trefoil	0.045	0.513	−0.241	0.267
ΔVertical trefoil	−0.070	0.741	−0.161	0.042
ΔSpherical aberration	−0.251	0.014	−0.179	0.036

BCVA: Best-corrected visual acuities; LOAs: Lower order aberrations; HOAs: Higher order aberrations.

Discussion

CXL is a potent modality for stopping the keratoconus progression by improving interfibrillar linkages through photopolymerization of riboflavin.[12] Standard CXL has been shown to stabilize keratometric values in large published clinical trials.[13–15] Since duration of standard CXL is long, accelerated CXL has been preferred in clinical practice by some clinicians.[16–20] CXL has been reported to have effect on optical quality in keratoconus eyes.[10,11,21] We assumed that the effect of CXL could be variable in different degrees of keratoconus. Hence, we divided the patients into two groups in accordance with Kmax value. Patients with Kmax <51 D were considered as Group 1, and those with Kmax ≥51 D were considered as Group 2. In this study, reporting the changes in optical performance and visual acuity of progressive keratoconus patients 12 months following accelerated CXL was aimed. Keratoconus was assessed as progressive if decreased visual acuity accompanied at least one of the following criteria over the preceding 6 months: An increase of at least 1.0 diopter in the steepest simulated keratometric value derived from corneal topography, an increase in astigmatism as determined by manifest subjective refraction at least 1.0 diopter, or ≥0.1 mm decrease in the back optic zone radius of the best fitting contact lens.

In addition, we intended to show the changes in HOAs and other topographical parameters if they were associated with changes in BCVA. We demonstrated improvements in spherical equivalent (SE), manifest astigmatic correction and spherical aberrations in both groups, in addition, Group 2 showed significant improvements in BCVA and most corneal HOAs 12 months following accelerated CXL. Furthermore, when change in BCVA was correlated with change in SE and spherical aberration in Group 1, Group 2 also demonstrated association with change in BCVA and manifests astigmatic correction, total RMS HOA, vertical coma, vertical trefoil, and spherical aberrations.

Aberrational analysis of cornea is crucial in describing optic quality of the eye. Since cornea composes the most refractive component of optical system of the eye and takes first place among the other refractive components. Although CXL is applied on the anterior corneal surface, it indirectly influences HOAs of posterior cornea.[10,21] Assessment of corneal aberrations is quite important during refractive surgery planning and trial of CL for rehabilitation of vision in eyes with keratoconus. A significant decrease was shown in spherical aberration, total HOA, vertical coma, and vertical trefoil and in more advanced stage of keratoconus 12 months following CXL compared to pre-operative values. Similarly, Uysal et al.[22] showed a remarkable reduction in vertical coma, vertical trefoil, and in the total HOA 1 year after CXL. Kosekahya et al.[23] also reported a significant decrease in corneal HOAs, vertical coma, and spherical aberration values 12 months after CXL. In another study, Wisse et al.[24] did not find a change in total HOAs, coma, and trefoil values; they found significant decrease in spherical aberration 12 months after CXL. However, in these studies, keratoconus stage was not considered. In this study, low-grade and high-grade keratoconus were evaluated separately and found that the change in HOAs is more remarkable in severe stage. CXL results increase in intrastromal covalent

bonds and leads to biomechanical stabilization of the cornea. Effective depth of CXL is investigated in several studies and anterior 300 µm is assumed to be the effective depth.[25,26] The effective depth could be reached better in severe group which leads to remarkable change in HOAs. However, future studies are needed for being proved. Whether this difference is specific to accelerated CXL is not known. There is a meta-analysis comparing the effects of standard and accelerated CXL.[27] They showed that standard CXL reduces Kmax more than accelerated CXL, however, accelerated CXL reduces CCT and endothelial cell density less. Despite this finding, further randomized controlled trials are indicated.

Visual quality in keratoconus may be limited by increased corneal aberrations, particularly with coma.[28] Hence, improvement in corneal HOAs may lead to improvement in BCVA after CXL. In this study, reduced vertical trefoil, vertical coma, and spherical aberration values were found to be correlated with BCVA in severe keratoconic eyes. In addition, mild-to-moderate keratoconus group showed correlation between spherical aberration and BCVA. Vinciguerra et al.[21] reported remarkable deterioration in total HOAs, astigmatism, and coma values, and improvement of BCVA following CXL. Wisse et al.[24] assessed HOAs 12 months following CXL in keratoconic eyes and visual acuity effect. They did not find a change in total HOAs, coma, and trefoil values, while a decrease in spherical aberration value was found, 12 months following CXL. The study showed variations in HOAs had no effect on BCVA except horizontal coma which has correlation with uncorrected visual acuity. Greenstein et al.[10] found that trefoil, coma, and spherical aberration values decreased after CXL, whereas variations in HOAs did not correlate with visual acuity recovery.

In current study, Kmax value flattened about 0.5 D in both groups. However, this improvement in keratometry was not correlated with BCVA. Improvement of keratometry values has been reported in some recent studies.[23,29,30] Greenstein et al.[31] demonstrated reduced topography indices in patients with keratoconus 12 months after CXL. Whereas, they did not find an association with visual acuity. In addition, Ghanem et al.[11] revealed that CXL has a potential role in recovery of visual acuity, improvement of topographic parameters, and corneal HOAs after 2 years. In this study, Kmax was found to correlate with BCVA. In addition, CCT and thin values decreased in this study following CXL. Thin value deterioration was significant in both groups, however, these parameters were not correlated with BCVA. Greenstein et al.[32] explained this reduction with keratocyte apoptosis and changes in collagen fibrils and glycosaminoglycans in the corneal stroma after CXL. The epithelial and stromal remodeling probably leads to decreased corneal thickness gradually. In addition, they found that the reduction in CCT approached to pre-operative level at 24 months but thin remained lower significantly.

This study has some limitations. Conventional CXL was not evaluated, the study had relative small sample size and a short follow-up period. Another limitation was using Pentacam device for calculating corneal aberrations rather than a wavefront device. Hence, we could not report the whole HOAs of the eye.

Conclusion

Accelerated CXL provides visual, refractive, topographic, and HOAs improvement, particularly in severe keratoconus patients. These improvements after CXL may imply that CXL attempts to approach keratoconic eyes toward normal values. Management of corneal aberrations besides refractive correction may lead to better visual outcomes in keratoconus patients.

Ethics Committee Approval: This study was approved by Ankara City Hospital Ethics Committee (date: July 04, 2019; number: 014).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: E.E.K., O.E.K.; Design: E.E.K., O.E.K.; Supervision: O.E.K.; Resource: D.O.; Materials: D.O., F.S.A.A., G.C.; Data Collection and/or Processing: F.S.A.A., G.C.; Analysis and/or Interpretation: F.S.A.A., G.C.; Literature Search: E.E.K., D.O.; Writing: E.E.K.; Critical Reviews: O.E.K.

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