

# Accelerated Corneal Crosslinking Results with Respect to Age Groups

## Yaş Gruplarına Göre Hızlandırılmış Korneal Çapraz Bağlama Tedavisinin Sonuçları

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**ABSTRACT Objective:** To evaluate the results of accelerated (9 mW/cm<sup>2</sup>) corneal crosslinking (CXL) in progressive keratoconus according to age groups. **Material and Methods:** Patients undergoing accelerated corneal CXL with hypo-osmolar riboflavin solution were included in the study. The patients were divided into two groups: Group 1 (<18 years, 41 eyes of 37 patients) and Group 2 (≥18 years, 47 eyes of 44 patients). Uncorrected and corrected distance visual acuity (UDVA, CDVA), refraction, topographic values and higher-order aberrations were evaluated in the preoperative period and postoperatively at months 1, 3 and 6. **Results:** In Group 1, a significant increase was detected in UDVA [0.25 logarithm of minimum angle of resolution (logMAR), p=0.035] and CDVA (0.19 logMAR, p=0.029), whereas there was no significant increase in Group 2 [UDVA (0.08 logMAR, p=0.375) and CDVA (0.12 logMAR, p=0.087)]. The maximum keratometry (Kmax) reduction was not significant [1.33 Diopter (D), p=0.141] in Group 1, whereas it was significant in Group 2 (1.48 D, p=0.002). The Kmax change between the two groups was similar (p=0.728). In both groups, refraction, elevations, astigmatism, spherical aberration (except Group 1), and trefoil reduction were insignificant and similar (p>0.05). Significant coma reduction was detected in the groups (p<0.05). However, the reduction in Group 2 was more apparent (p=0.025). Higher-Order Root Mean Square (HO-RMS) and total RMS reduction were significant and similar in both groups (p<0.05). **Conclusion:** VA improvement is better in the pediatric group than the adult group, while refraction, topographic and aberration (except coma) changes are similar after accelerated corneal CXL.

**Keywords:** Keratoconus; riboflavin; age groups

**ÖZET Amaç:** İlerleyici keratokonus hastalarında hızlandırılmış (9 mW/cm<sup>2</sup>) korneal çapraz bağlama (KÇB) tedavisinin etkinliğini yaş gruplarına göre değerlendirmektir. **Gereç ve Yöntemler:** Çalışmaya hipoozmolar riboflavin solüsyonu ile hızlandırılmış KÇB tedavisi uygulanan hastalar dahil edildi. Hastalar Grup 1 (<18 yaş, 37 hastanın 41 gözü) ve Grup 2 (≥18 yaş, 44 hastanın 47 gözü) olarak 2 gruba ayrıldı. Preoperatif ve postoperatif 1., 3. ve 6. aylarda düzeltilmemiş ve en iyi düzeltilmiş görme keskinlikleri (DGK, EİDGK), refraktif kusurları ve Pentacam HR ile (Wetzler, Almanya), topografik ve yüksek sıralı aberasyon değerleri ölçüldü. **Bulgular:** Grup 1'de DGK'da 0,25 logMAR, (p=0,035), EİDGK'da 0,19 logMAR (p=0,029) artış tespit edildi. Grup 2'de ise DGK'de 0,08 logMAR, EİDGK'da 0,12 logMAR artış tespit edilmiş olup bu artışlar anlamlı değildi (p=0,375, p=0,087 sırasıyla). Grup 1'de maksimum keratometri (Kmaks) değerindeki düşüş anlamlı değilken [1,33 Dioptri (D), p=0,141] Grup 2'de bu düşüş anlamlıydı (1,48 D, p=0,002). Kmaks'taki değişim iki grupta benzerdi (p=0,728). İki grupta da refraksiyon, elevasyon, astigmatizm, ve trefoildeki düşüşleri benzer olup düşüş miktarı anlamlı değildi. Koma değerlerindeki düşüş iki grupta da anlamlı olup (p<0,05), Grup 2'deki düşüş daha belirgindi (p=0,025). Yüksek sıralı RMS (root mean square) ve toplam RMS değerlerindeki düşüş iki grupta da benzer olup anlamlıydı (p<0,05). **Sonuç:** Hızlandırılmış KÇB tedavisi ile görme keskinliği pediatrik grupta yetişkin gruba göre daha fazla artış göstermiştir. Refraktif, topografik ve aberasyon (koma hariç) değişimleri ise iki grupta da benzerdir.

**Anahtar Kelimeler:** Keratokonus; riboflavin; yaş grupları

**K**eratoconus is a progressive, non-inflammatory, ectatic corneal disease which is the major cause of keratoplasty in Europe.<sup>1</sup> Although keratoconus is most frequently diagnosed in adolescence or childhood, corneal ectasia starts at a much younger age. Since keratoconus demonstrates a higher rate and speed of progression in pediatric patients, the age of diagnosis is a negative prognostic factor for increased risk of keratoplasty.<sup>2,3</sup> Corneal crosslinking (CXL) is the only treatment that can halt progression of keratoconus and reduce the need for keratoplasty. Currently, it is performed effectively and reliably in adult and pediatric patients.<sup>4-6</sup> In this procedure, riboflavin undergoes a photooxidative reaction in the presence of ultraviolet-A (UVA). This photooxidative reaction induces formation of additional covalent bonds between the collagen fibers and thereby increases biomechanical stability of the cornea.<sup>4</sup>

In the most frequently used corneal CXL protocol (conventional CXL protocol), UVA at an intensity of 3 mW/cm<sup>2</sup> is used with iso-osmolar riboflavin solution. In this protocol the treatment time is 1 hour and the cumulative UVA dosage is 5.4 J/cm<sup>2</sup>.<sup>7</sup> The illumination intensity may be increased in order to reduce the treatment time (accelerated CXL protocol). According to the Bunsen-Roscoe law of reciprocity, the effects of the photochemical reaction are similar if illumination intensity and time are changed while the total energy is maintained.<sup>8</sup> Both experimental and clinical evidence support biomechanical equivalence and safety profile of the accelerated UV protocol compared with the conventional protocol.<sup>9,10</sup>

To perform corneal CXL reliably, the corneal thickness without epithelium must be at least 400 µm.<sup>11</sup> However, studies conducted in recent years have determined that during standard corneal CXL procedures, the corneal thickness is reduced by about 20% due to the use of iso-osmolar riboflavin solutions and the corneal thickness may be reduced below 400 µm.<sup>12,13</sup> This is because even though the iso-osmolar riboflavin solution is iso-osmolar in relation to stroma, it is actually hyperoncotic, and therefore causes liquid leakage from the corneal stroma.<sup>12</sup> To prevent thinning, current discussions

focus on the use of an iso-osmolar riboflavin solution without dextran (with hydroxypropylmethylcellulose) and hypo-osmolar riboflavin solution for thick corneas.<sup>14,15</sup> Therefore, the use of hypo-osmolar riboflavin solution has become a standard in our clinic.

The aim of this retrospective study was to evaluate the short-term outcome of accelerated corneal CXL (9 mW/cm<sup>2</sup>) according to age group in patients with progressive keratoconus.

## MATERIAL AND METHODS

Patients with progressive keratoconus were included in the current, retrospective, and non-randomized study. The patients were divided into two groups, as Group 1 (<18 age) and Group 2 (≥18 age). Progression was defined as an increase of 1.0 diopter (D) in the maximum keratometry ( $K_{max}$ ) value in the past 6 months in adults and in the past 3 months in children.<sup>6</sup> Since keratoconus progresses more aggressively in children, more frequent examinations were conducted in order to detect early progression.<sup>16</sup> Our study was conducted in accordance with the Helsinki Declaration. Ethical committee approval was not obtained since it was a retrospective study. Before performing corneal CXL, informed written consent was obtained from adults or the parents of children. Patients who had previous anterior segment surgery, ocular surface problems, corneal scars or repeated corneal CXL were excluded. The refraction measurements, uncorrected and corrected distance visual acuity (UDVA, CDVA), biomicroscopic findings, topographic findings and corneal higher-order aberration (HOAs) data (Pentacam HR, Oculus Optikgeräte GmbH) were evaluated preoperatively and 1, 3 and 6 months postoperatively. The Pentacam HR is a non-contact device using a rotating Scheimpflug camera that could image the anterior eye segment in precise three dimensions. Moreover, it has a second camera (pupil camera) to detect and correct for eye movement. Pentacam HR is more advanced than previous Scheimpflug equipments, because it provides optical distortion corrected data of the posterior cornea. In this study, the Pentacam's 50-picture 3-dimensional scan

measurement mode was used. After image capture, the instrument analyzes the Scheimpflug images of the anterior eye and allows export of corneal curvature (front and back surfaces), elevation (front and back corneal surfaces), and pachymetry maps. The measurement of each volunteer was evaluated by one experienced examiner using the Pentacam HR with automatic-release mode, in which the image capture started when corrected alignment with the corneal apex and focus was achieved. During testing, any scan that failed to obtain an 'OK' reading was repeated. Both UDVA and CDVA were recorded using Snellen's chart and later converted to logarithm of minimum angle of resolution (logMAR) values. Aberrations were evaluated in the central 6.0 mm zone. trefoil ( $Z_3^3, Z_3^{-3}$ ), coma ( $Z_3^1, Z_3^{-1}$ ), spherical aberration, higher order root mean square (HO-RMS), and total root mean square (RMS) in the Zernike analysis.

#### SURGICAL TECHNIQUE

Corneal CXL was performed in the operating room under topical anesthesia using 0.5% proparacaine hydrochloride eye drops. First, the epithelium was removed from the 8.0 mm treatment zone using a smooth spatula under sterile conditions. The hypo-osmolar riboflavin solution (without dextran, 300 mOsmol/L) was then administered for 30 min. Because the breakdown time of the hypo-osmolar riboflavin solution is low, riboflavin solution drops were administered as the corneal surface dried (q. ~1 min). Ultrasound pachymetry was then performed at the end of 30 min to confirm that the corneal thickness was more than 400  $\mu\text{m}$ . After this, the cornea was exposed to 370 nm UVA light with the CXL system for 10 minutes at an irradiance level of 9 mW/cm<sup>2</sup>. During UVA irradiation, riboflavin solution was applied to maintain corneal riboflavin saturation. At the end of the procedure bandage contact lens was inserted to minimize pain.

Postoperative treatment included 0.5% moxifloxacin hydrochloride eye drops 4 times a day for 1 week, 5% fluorometholone eye drops in tapering doses for 4 weeks and topical artificial tear supplements 4 times a day for 1 month.

#### STATISTICAL ANALYSIS

A Shapiro-Wilk test was used to analyze data normality. As normality was not valid for all data, the Wilcoxon signed-rank test was used to compare the preoperative values and the mean change in postoperative follow-ups within the groups. Mann-Whitney U test was used to compare the preoperative values and the mean change in postoperative month 6 between the two groups. Statistical analysis was performed using SPSS software, version 20 (IBM, Armonk, New York, USA). All values were expressed as mean values  $\pm$  standard deviation. A *p* value less than 0.05 was considered significant.

#### RESULTS

Eighty-eight eyes of 81 patients (51 males, 30 females) were included in the study. In Group 1, there were 41 eyes of 37 patients and in Group 2, there were 47 eyes of 44 patients. The mean age in Group 1 was 15.4 $\pm$ 1.4 (range 9-17) years, whereas it was 24.1 $\pm$ 2.4 years (range 18-33) in Group 2.

#### VISUAL ACUITY AND REFRACTION RESULTS

Table 1 shows the preoperative and postoperative VA and refraction values of the groups. In Group 1, no statistically significant difference was detected in UDVA and CDVA at month 1 (UDVA; *p*=0.821, CDVA; *p*=0.850), and month 3 (UDVA; *p*=0.736, CDVA; *p*=0.682) versus the preoperative values, whereas they significantly improved at month 6 (UDVA; *p*=0.035, CDVA; *p*=0.029). In all postoperative follow-ups, the refraction values were similar to preoperative values (spherical; *p*=0.572, *p*=0.724, *p*=0.161 cylindrical *p*=0.552, *p*=0.778, *p*=0.290 respectively). In Group 2, no statistically significant difference was detected in UDVA and CDVA at month 1 (UDVA; *p*=0.719, CDVA; *p*=0.743), month 3 (UDVA; *p*=0.596, CDVA; *p*=0.402) and month 6 (UDVA; *p*=0.375, CDVA; *p*=0.087) versus the preoperative values. Similarly, no significant differences were observed in refractions in the follow-up period (spherical; *p*=0.572, *p*=0.873, *p*=0.141, cylindrical; *p*=0.481, *p*=0.519, *p*=0.287 respectively).

**TABLE 1:** Preoperative and postoperative visual acuity and refraction values of the groups.

Parameter (Range)	Group 1 (Age < 18 years)				Group 2 (Age ≥ 18 years)			
	Preoperative (n=41)	1 <sup>st</sup> Month (n=41)	3 <sup>rd</sup> Month (n=41)	6 <sup>th</sup> Month (n=41)	Preoperative (n=47)	1 <sup>st</sup> Month (n=47)	3 <sup>rd</sup> Month (n=47)	6 <sup>th</sup> Month (n=47)
UDVA,	0.72±0.31	0.67±0.28	0.64±0.29	0.47±0.27*	0.79±0.39	0.84±0.48	0.72±0.39	0.75±0.41
logMAR	(0.88-0.16)	(0.91-0.26)	(0.81-0.22)	(0.79-0.12)	(0.91-0.22)	(0.88-0.26)	(0.81-0.24)	(0.79-0.22)
CDVA,	0.42±0.28	0.39±0.30	0.35±0.26	0.23±0.18*	0.58±0.32	0.61±0.36	0.51±0.31	0.46±0.30
logMAR	(0.88-0.0)	(0.88-0.08)	(0.82-0.08)	(0.72-0.0)	(0.91-0.24)	(0.93-0.24)	(0.86-0.24)	(0.82-0.18)
Spherical, D	-4.13±3.0 (+1.50/-8.0)	-4.54±2.70 (+2.0/-8.0)	-4.24±2.69 (+2.0/-7.50)	-3.82±2.45 (+1.75/-7.50)	-4.73±3.94 (0.0/-13.0)	-5.08±2.73 (0.0/-13.50)	-4.84±2.37 (0.50/-12.50)	-4.24±2.42 (+0.75/-12.50)
Cylindrical, D	-3.82±1.91 (-0.75/-7.0)	-4.23±2.72 (-0.75/-6.0)	-4.02±2.53 (-0.75/-6.25)	-3.54±2.02 (-0.75/-6.25)	-5.25±3.71 (-2.25/-8.50)	-5.62±3.02 (-2.75/-8.50)	-5.04±2.53 (-2.75/-9.0)	-4.93±2.72 (-2.75/-9.0)

UDVA; Uncorrected distance visual acuity, CDVA; Corrected distance visual acuity, logMAR; Logarithm of the minimal angle of resolution, D=Diopter; \*P<0.05

## TOPOGRAPHICAL RESULTS

Table 2 shows the preoperative and postoperative topography values of the groups. In Group 1, an insignificant increase was observed in  $K_{max}$  at months 1 and 3 ( $p=0.216$ ,  $p=0.315$  respectively). At month 6, a decrease of 1.3 D according to the preoperative values was determined; however it was not significant ( $p=0.141$ ). An increase in  $K_{max}$  was observed in 5 patients. Similarly, insignificant increases were observed in  $K_{min}$  and  $K_{mean}$  at months 1 and 3 ( $K_{min}$ :  $p=0.328$ ,  $p=0.419$ ,  $K_{mean}$ :  $p=0.452$ ,  $p=0.484$  respectively). At month 6, there were decreases of 0.5 D for  $K_{min}$  and 0.8 D for  $K_{mean}$  determined according to the preoperative values; however the differences were not significant ( $p=0.253$ ,  $p=0.333$  respectively). The corneal thickness at the thinnest point was significantly lower at all postoperative follow-ups compared to preoperative values ( $p<0.001$ ). No significant difference was observed in either the anterior or posterior astigmatism of the cornea at any of the follow-ups (anterior astigmatism;  $p=0.354$ ,  $p=0.388$ ,  $p=0.139$ , posterior astigmatism;  $p=0.962$ ,  $p=0.588$ ,  $p=0.570$  respectively). Anterior elevation values slightly increased at month 1 versus the preoperative values ( $p=0.004$ ), whereas no significant difference was observed at months 3 and 6 ( $p=0.095$ ,  $p=0.061$  respectively). No significant changes were detected in posterior elevation at any of the follow-ups ( $p=0.558$ ,  $p=0.187$ ,  $p=0.163$  respectively). In Group 2, there was an insignificant increase in  $K_{max}$  at months 1 and 3

( $p=0.070$ ,  $p=0.495$  respectively). A decrease was detected at month 6 at a rate of 1.5 D versus preoperative values and this was significant ( $p=0.002$ ). Two patients showed increases in  $K_{max}$ . Similarly, insignificant increases were observed in  $K_{min}$  and  $K_{mean}$  at months 1 and 3 ( $K_{min}$ :  $p=0.253$ ,  $p=0.402$ ,  $K_{mean}$ :  $p=0.298$ ,  $p=0.354$  respectively), whereas at month 6, there were decreases of 0.6 D for  $K_{min}$  and 0.8 D for  $K_{mean}$  determined according to the preoperative values; these were significant ( $p=0.033$ ,  $p=0.026$  respectively). The corneal thickness at the thinnest point was significantly lower than the preoperative values at all postoperative follow-ups ( $p<0.001$ ). For both anterior and posterior astigmatism of the cornea, no significant difference was determined in any of the follow-ups (anterior astigmatism;  $p=0.656$ ,  $p=0.074$ ,  $p=0.186$ , posterior astigmatism;  $p=0.543$ ,  $p=0.660$ ,  $p=0.892$  respectively). Similarly, no significant difference was detected at any of the follow-ups for the anterior and posterior elevations, (anterior elevation;  $p=0.155$ ,  $p=0.079$ ,  $p=0.314$  posterior elevation;  $p=0.946$ ,  $p=0.756$ ,  $p=0.084$  respectively).

## HIGHER-ORDER ABERRATION RESULTS

Table 3 shows the preoperative and postoperative HOAs values of the groups. In Group 1, no significant change was determined in coma at month 1 ( $p=0.265$ ), whereas at months 3 and 6 there were significant decreases versus the preoperative values ( $p=0.005$ ,  $p<0.001$ , respectively). There were no sig-

**TABLE 2:** Preoperative and postoperative topography values of the groups.

Parameter (Range)	Group 1 (Age < 18 years)				Group 2 (Age ≥ 18 years)			
	Preoperative (n=41)	1 <sup>st</sup> Month (n=41)	3 <sup>rd</sup> Month (n=41)	6 <sup>th</sup> Month (n=41)	Preoperative (n=47)	1 <sup>st</sup> Month (n=47)	3 <sup>rd</sup> Month (n=47)	6 <sup>th</sup> Month (n=47)
K <sub>max</sub> , D	57.4±6.8 (47.2-77.6)	57.8±6.7 (46.4-80.6)	57.9±6.8 (47.0-80.9)	56.1±4.2 (47.0-78.0)	56.9±5.08 (45.0-71.1)	57.7±6.4 (42.4-72.9)	57.0±6.7 (42.0-74.3)	55.4±3.8* (42.3-74.0)
K <sub>mean</sub> , D	53.8±4.4 (44.3-61.1)	54.7±5.1 (42.4-62.4)	54.1±5.0 (42.0-62.3)	53.0±3.7 (42.3-62.8)	53.4±3.9 (43.8-64.6)	53.8±4.7 (43.2-65.2)	53.5±5.0 (43.0-65.2)	52.6±3.3* (42.4-65.8)
K <sub>min</sub> , D	50.7±4.2 (43.1-58.2)	57.7±4.4 (42.7-58.7)	51.1±4.0 (42.8-58.9)	50.2±4.2 (42.6-59.1)	50.4±3.5 (44.2-59.2)	50.7±4.0 (44.7-60.1)	51.0±4.3 (44.1-60.5)	49.8±4.1* (43.6-60.7)
Thinnest CT, µm	459±47 (367-558)	435±55* (296-496)	432±46* (335-517)	428±32* (349-496)	451±41 (366-549)	426±55* (294-534)	416±42* (293-536)	416±41* (289-554)
Front Ast., D	4.7±1.9 (1.6-9.2)	4.8±2.0 (1.5-9.2)	4.5±1.8 (1.5-8.4)	4.3±1.3 (1.6-8.2)	3.55±2.09 (0.2-9.6)	3.57±2.1 (0.2-10.1)	3.81±2.0 (0.6-11.2)	3.39±1.1 (0.9-10.9)
Back Ast., D	0.9±0.4 (0.0-1.8)	0.9±0.3 (0.2-1.7)	0.9±0.3 (0.2-1.5)	0.9±0.3 (0.0-1.6)	0.7±0.4 (0.1-2.4)	0.7±0.4 (0.1-2.0)	0.8±0.4 (0.0-2.5)	0.7±0.3 (0.0-1.6)
AE, µm	25.9±12.5 (1-56)	28.3±13.4* (0-71)	23.4±14.1 (4-65)	23.4±8.4 (3-42)	27.1±10.9 (0-51)	24.9±12.6 (-12-45)	24.3±10.3 (-17-48)	26.3±9.4 (0-49)
PE, µm	57.7±24.6 (22-144)	57.5±21.6 (14-129)	55.4±17.7 (22-103)	59.1±14.7 (31-108)	63.8±22.8 (18-120)	63.5±30.5 (11-139)	64.0±25.8 (18-144)	66.7±19.7 (32-141)

K<sub>max</sub>: Maximum keratometry, K<sub>mean</sub>: Mean Keratometry, K<sub>min</sub>: Minimum Keratometry, CT: Corneal Thickness, D: Diopter, Ast: Astigmatism, AE: Anterior Elevation, PE: Posterior Elevation, \*P<0.05.

**TABLE 3:** Preoperative and postoperative higher order aberrations of the groups.

Parameter (Range)	Group 1 (Age < 18 years)				Group 2 (Age ≥ 18 years)			
	Preoperative (n=41)	1 <sup>st</sup> Month (n=41)	3 <sup>rd</sup> Month (n=41)	6 <sup>th</sup> Month (n=41)	Preoperative (n=47)	1 <sup>st</sup> Month (n=47)	3 <sup>rd</sup> Month (n=47)	6 <sup>th</sup> Month (n=47)
Coma, µm	-0.47±1.27 (-3.96-2.12)	-0.57±0.66 (-3.52-2.46)	-0.15±0.74* (-3.28-2.24)	0.06±0.43* (-2.23-2.24)	0.57±1.15 (-3.07-2.38)	0.17±1.09* (-2.94-2.20)	0.20±0.79* (-2.63-2.05)	0.15±0.66* (-2.02-2.17)
Trefoil, µm	0.0±0.64 (-1.60-2.60)	-0.05±0.66 (-2.32-2.56)	-0.13±0.63 (-2.55-2.41)	-0.09±0.28 (-1.17-1.78)	-0.57±1.15 (-3.07-2.38)	-0.17±1.09* (-2.94-2.20)	-0.20±0.79* (-2.63-2.05)	0.15±0.66* (-2.02-2.17)
SA, µm	-0.85±0.81 (-3.30-0.98)	-0.95±1.07 (-3.88-1.36)	-0.91±0.67 (-3.81-1.37)	-0.63±0.45 (-2.85-0.86)	-0.25±0.39 (-0.83-1.26)	0.35±0.45 (-1.32-0.93)	-0.14±0.72 (-1.06-2.51)	-0.13±0.26 (-1.01-0.58)
HORMS, µm	2.57±1.27 (0.70-5.90)	2.72±1.21 (0.68-6.10)	2.42±1.23 (0.78-7.66)	2.16±0.66* (0.90-6.20)	-0.69±0.67 (-2.21-0.75)	-0.77±0.83 (-2.35-1.55)	-0.86±0.72 (-3.04-0.94)	-0.43±0.54* (-1.57-1.28)
Total RMS, µ	10.38±4.17 (2.68-23.03)	11.09±4.30 (3.10-25.03)	10.79±5.43 (3.04-26.54)	8.51±2.51* (1.54-25.05)	2.59±0.83 (0.85-4.59)	2.93±0.81 (0.78-4.18)	2.74±1.14 (0.90-7.41)	2.26±0.77* (0.60-5.20)

SA: Spherical Aberration, HORMS: Higher-Order Root Mean Square \*P<0.05

nificant changes at any of the follow-ups in spherical aberration (SA) and trefoil (SA; p=0.160, p=0.112, p=0.071 trefoil; p=0.191, p=0.600, p=0.486). Higher-Order Root Mean Square (HO-RMS) and total RMS showed no significant change at months 1 and 3, whereas significant decreases occurred at month 6 (HO-RMS; p=0.103, p=0.058, p=0.043,

total RMS; p=0.154, p=0.334, p=0.002 respectively). In Group 2, at all follow-ups significant decrease in coma compared to the preoperative values was observed (p=0.017, p=0.025, p=0.015), whereas in trefoil there were no significant changes at any of the follow-ups (p=0.067, p=0.224, p=0.069). SA, HO-RMS and total RMS showed no significant changes

at months 1 and 3, whereas a significant decrease occurred at month 6 (SA;  $p=0.056$ ,  $p=0.083$ ,  $p=0.003$ , HORMS;  $p=0.600$ ,  $p=0.882$ ,  $p=0.007$ , total RMS;  $p=0.841$ ,  $p=0.371$ ,  $p=0.005$  respectively).

## COMPARATIVE RESULTS

The preoperative UDVA values of the groups were similar ( $p=0.293$ ) while CDVA was higher in Group 1 ( $p=0.004$ ). The spherical and cylindrical refraction values were similar ( $p=0.468$ ,  $p=0.543$  respectively). All topographical data (except anterior astigmatism,  $p=0.003$ ) and HOAs values were similar ( $p>0.05$ ). The changes that occurred at the 6<sup>th</sup> month after treatment and the p values that formed in relation to their comparisons are shown in Table 4. VA improved at higher rates in Group 1. However, the changes in the spherical and cylindrical refraction values, topographical data and aberration data (except coma) were similar in both groups. Coma decreased at higher rates in Group 2. In the follow-ups, only one patient (age 14) developed a scar that affected vision. Other than that, there were no complications.

## DISCUSSION

The most important finding of our study is that the improvement in visual acuity was greater in the pediatric patient group, although there were similar topographic changes in the pediatric and adult age groups after accelerated corneal CXL.

Currently, there is no standard corneal CXL protocol and various individual protocols have been published. The aim of this study was to evaluate outcomes of accelerated corneal CXL (9 mW/cm<sup>2</sup>) according to age groups in patients with progressive keratoconus, because in children, keratoconus not only progresses more aggressively but also the biomechanical characteristics of the cornea are different from those of adults.<sup>2,16,17</sup> In addition, wound healing is more rapid and effective in children.<sup>5</sup> Therefore, the effectiveness of corneal CXL might be different in children.

To perform corneal CXL reliably, the corneal thickness without epithelium must be at least 400  $\mu\text{m}$ .<sup>11</sup> Hafezi suggested that the stroma be swollen

**TABLE 4:** Changes in datas of the groups at month 6 and the p value generated upon their comparison.

Parameter	Group 1 (Age<18 n=41)	Group 2 (Age $\geq$ 18 n=47)	p Value
$\Delta$ UDVA (logMAR)	0.25 $\pm$ 0.24	0.08 $\pm$ 0.12	.002*
$\Delta$ CDVA (logMAR)	0.19 $\pm$ 0.16	0.12 $\pm$ 0.12	<.001*
$\Delta$ Spher (D)	0.31 $\pm$ 0.23	0.49 $\pm$ 0.31	.725
$\Delta$ Cyl (D)	0.28 $\pm$ 0.20	0.32 $\pm$ 0.27	.802
$\Delta$ Kmax (D)	1.33 $\pm$ 2.79	1.48 $\pm$ 1.87	.728
$\Delta$ Kmean (D)	0.78 $\pm$ 1.23	0.83 $\pm$ 1.22	.745
$\Delta$ Kmin (D)	0.53 $\pm$ 0.89	0.62 $\pm$ 1.13	.523
$\Delta$ Thinnest Point ( $\mu$ )	31.3 $\pm$ 37.4	34.6 $\pm$ 30.9	.861
$\Delta$ Frontal Astig (D)	0.47 $\pm$ 1.66	0.26 $\pm$ 1.10	.462
$\Delta$ Back Astig (D)	0.03 $\pm$ 0.17	0.03 $\pm$ 0.14	.543
$\Delta$ Ant Elevation ( $\mu$ )	2.52 $\pm$ 4.0	0.82 $\pm$ 4.18	.519
$\Delta$ Post Elevation ( $\mu$ )	1.47 $\pm$ 5.7	2.9 $\pm$ 6.47	.834
$\Delta$ Trefoil ( $\mu$ )	0.09 $\pm$ 0.13	0.12 $\pm$ 0.17	.601
$\Delta$ Coma ( $\mu$ )	0.53 $\pm$ 1.04	0.72 $\pm$ 0.66	.025*
$\Delta$ SA ( $\mu$ )	0.22 $\pm$ 0.34	0.26 $\pm$ 0.36	.318
$\Delta$ HORMS ( $\mu$ )	0.41 $\pm$ 1.08	0.33 $\pm$ 0.25	.587
$\Delta$ Total RMS ( $\mu$ )	1.87 $\pm$ 3.62	1.04 $\pm$ 2.35	.373

UDVA; Uncorrected distance visual acuity, CDVA; Corrected distance visual acuity, logMAR; Logarithm of the minimal angle of resolution, Spher; Spherical, Cyl; Cylindrical, D; Diopter, K<sub>max</sub>= Maximum keratometry, K<sub>mean</sub>; Mean Keratometry, K<sub>min</sub>; Minimum Keratometry, SA; Spherical aberration, HORMS; Higher-Order Root Mean Square, \*P<0.05.

by using hypo-osmolar riboflavin solution for thin corneas before UVA. According to this procedure, if the thickness is below 400  $\mu\text{m}$  after the stroma is saturated with iso-osmolar riboflavin solution, then the stroma is swollen by using hypo-osmolar riboflavin solution and the use of the iso-osmolar riboflavin solution is continued during UVA.<sup>18</sup> However, subsequent studies showed that in this procedure the final corneal thickness was not different from corneal thickness that was not swollen using hypo-osmolar riboflavin solution, because the use of iso-osmolar riboflavin solution leads to rapid thinning during UVA.<sup>19</sup> For this reason, Raiskup suggested using hypo-osmolar riboflavin solution during the whole procedure for thin cornea.<sup>20</sup> However, severe thinning was seen not only in thin corneas but also in thick corneas during conventional corneal CXL.<sup>12,13</sup> Therefore, we use hypo-osmolar riboflavin solution for all patients.

In this study, we determined the improvement in UDVA and CDVA was significantly higher in Group 1 (<18 age) than in Group 2 ( $\geq$ 18 age). In our study, the more obvious improvement in visual acuity in pediatric patients may be related to the better preoperative vision. In some previous studies, it was determined that the improvement in visual acuity was greater in patients with good preoperative visual acuity.<sup>21</sup> Insignificant and similar decreases were determined in the refraction values of both groups. Even though the Siena CXL Pediatrics Trial also determined that the visual results were better in the pediatric age group, the difference compared to the adult age group was not significant.<sup>22</sup> In another study, the refractive results were found to be better in the adult age group.<sup>6</sup> Ulusoy et al. reported that the increase in mean CDVA after accelerated corneal CXL in the pediatric group (<18 years) was 0.15 logMAR in patients with corneal thickness greater than 450  $\mu$ m and 0.22 logMAR in patients with corneal thickness less than 450  $\mu$ m.<sup>23</sup>

In both groups, decrease in  $K_{\max}$ , i.e., flattening of the cornea, was detected (1.3/1.5D respectively) at month 6. The rates of decrease were similar in both groups but only the flattening in Group 2 was statistically significant. There are varying data in the literature with regard to the rate of flattening in pediatric age groups. In one study, in accelerated corneal CXL (9 mW/cm<sup>2</sup>), a decrease of 2.04 D was detected in  $K_{\max}$ . On the other hand, in the Siena CXL Pediatrics Trial, the rate of reduction following conventional corneal CXL under protocol was found to be 0.7 D.<sup>22,24</sup> Ulusoy et al. found a decrease of 1 D in mean keratometry in pediatric patients.<sup>23</sup> Similarly, variable results (0.06-0.8 D) were obtained in adult groups following accelerated corneal CXL.<sup>15,25</sup>

Another finding of our study was that the number of patients whose progression did not halt was higher in the pediatric group (5/41) compared to the adult group (2/47). This is probably due to the fact that keratoconus is more aggressive at pediatric ages. In addition, 4 out of 5 patients with ongoing progression in the pediatric group had histories of allergic conjunctivitis.

It is known that after conventional corneal CXL the cornea gets thinner and this may last 3 years.<sup>26,27</sup> The physiology of this initial thinning and subsequent rethickening is currently unclear. Anatomic and structural changes in collagen fibrils, changes in corneal hydration and edema, keratocyte apoptosis and changes in glycosaminoglycans might be implicated.<sup>28</sup> Thickness increases in time with keratocyte repopulation and the increase in the diameter of collagen fibrils. It might take 3 years for the thickness to return to normal in adults.<sup>26</sup> On the other hand, at pediatric ages, even if a similar rate of corneal thinning occurs, it is found that the corneal thickness returns to normal earlier (1 year) due to rapid and effective wound healing.<sup>5,6</sup> In our study, the corneal thinning was also found to be similar in both groups (31 / 35  $\mu$ m), however since our follow-up time was short, we were unable to compare the time taken for the corneal thickness to return to normal.

In this study the change in topographical astigmatism at both the anterior and the posterior surfaces of the cornea was insignificant and similar in the two groups. The fact that corneal CXL flattened the cornea but did not change astigmatism was related to similar rates of flattening of the cornea in the flat and steep meridians.<sup>29</sup> Similarly, no significant change was found between the groups in terms of either the anterior or the posterior elevation. There are studies that support this data in the literature, whereas there are also studies that detected decreases in the anterior elevation.<sup>5,27</sup>

It is known that in keratoconus, HOAs increase and this situation contributes to the decrease in visual acuity.<sup>30</sup> In our study, we determined decreases in coma, HO-RMS and total RMS in both groups, as well as a decrease in SA in Group 2 in the 6<sup>th</sup> month following the accelerated corneal CXL. This data substantiates other similar studies.<sup>6,31,32</sup> The rate of reduction between the two groups in terms of HO-RMS and total RMS were similar; however the decrease in coma was more apparent in Group 2. This data is compatible with data from the Siena CXL Pediatrics Trial.<sup>22</sup> The reduction in higher-order aberration might be related to the reshaping of the corneal architecture,

directly to the effect of corneal CXL or to the wound healing process.<sup>33</sup>

We did not conduct an endothelial count before the treatment and therefore could not evaluate the effects on the endothelium. Previous studies did not identify any endothelial toxicity in accelerated corneal CXL.<sup>8,15</sup> Another limitation of the study is that we measured the aberration using Pentacam. According to the literature, there are conflicting data on the repeatability of Pentacam in the measurement of aberrations.<sup>34</sup> One of the most important disadvantages of our study and aforementioned studies in which comparing the efficacy of corneal CXL according to age group is that did not compare the depth of the demarcation line with anterior segment optic coherence tomography (AS-OCT). It is known, one of the most important parameters used to compare efficacy of corneal CXL in recent years is the depth of the demarcation line created in the stroma after corneal CXL. The stromal penetration of riboflavin solution may vary depending on age group, because it is known that there are significant structural changes in the cornea with age.<sup>35,36</sup> As a result though there was no difference identified in the topographic parameters between the groups, the demarcation line depth may be different. Nevertheless, the most important limitations of our study are its retrospective design and short follow-up time. The decreasing effect of corneal CXL on aberrations may continue through the years, so the long term results may turn out differently.<sup>6</sup>

In conclusion, similar refractive, topographic and higher-order aberration (except coma) improvements were obtained after accelerated corneal CXL (9mW/cm<sup>2</sup>) in pediatric and adult patients. However, the improvement in VA is higher in the pediatric patient group. Nevertheless, prospective and controlled long term studies with a high number of cases are required in order to verify these results.

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#### 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:** Mustafa Koç; **Design:** Mustafa Koç, Mehmet Murat Uzel; **Control/Supervision:** Yaran Koban; **Data Collection and/or Processing:** Mehmet Murat Uzel, Pelin Yilmazbaş; **Analysis and/or Interpretation:** Mustafa Koç; **Literature Review:** Mustafa Koç; **Writing the Article:** Mustafa Koç; **Critical Review:** Mehmet Murat Uzel; **References and Findings:** Yaran Koban; **Materials:** Pelin Yilmazbaş.

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