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Original Article

Accelerated versus Conventional Corneal Collagen Cross-Linking for Progressive Keratoconus

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ABSTRACT

We aimed to compare the effect of accelerated and conventional corneal collagen cross-linking (CXL) on visual, refractive, and topographic parameters in patients with progressive keratoconus. Between December 2014 and February 2016, at Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Iran, we compared 37 eyes of 21 patients treated by conventional CXL (CCXL; 3 mW/cm2 in 30 minutes) with 34 eyes of 18 patients treated by accelerated CXL (ACXL; 18 mW/cm2 in 5 minutes) based on generalizing estimation equation analysis in terms of corrected distance visual acuity (CDVA), uncorrected distance visual acuity (UDVA), corneal endothelial cell indices, and topographic parameters before and at 3, 6 and 12 months after the operation. The mean UDVA and spherical equivalent changes were similar in the two groups, but an improvement in CDVA was only observed in the CCXL group ($P = 0.003$). Keratometry (minimum and maximum) was significantly decreased in the CCXL group ($P = 0.043$ and $P = 0.008$, respectively). Indices of keratoconus progression—surface asymmetry index (SAI), keratoconus prediction index (KPI), and keratoconus index (KCI)—were significantly lower in the CCXL group than in the ACXL group ($P = 0.002$, $P < 0.001$, and $P < 0.001$, respectively). The thinnest corneal thickness (TCT) was not significantly different between the two groups ($P = 0.15$). The reduction of corneal endothelial cell density was also similar between the two groups; however, polymorphism and polymegethism were significantly lower in the ACXL group than in the CCXL group. In conclusion, we showed that although ACXL at 18 mW/cm2 slowed keratoconus progression safely during a 1-year follow-up, CCXL at 3 mW/cm2 may be superior in the prevention of keratoconus progression.

KEY WORDS

Progressive keratoconus; Conventional collagen cross-linking; Accelerated collagen cross-linking; ultraviolet-A; Keratometry; Keratoconus Index; Polymegethism; Polymegethism; Ahwaz

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INTRODUCTION

Keratoconus is a noninflammatory progressive degeneration of the cornea manifested by a reduction of corneal collagen and alterations in its organization [1-3]. It has been suggested that a greater reduction in collagen cross-links and pepsin digestion may result in structural weakness and stiffness in patients with keratoconus [4]. That structural instability causes visual acuity impairment, irregular astigmatism, progressive myopia, corneal thinning, and scar formation in the central cornea [5]. Keratoconus occurs mostly in young people and its prevalence is about 1 in 2000 of the general population [5, 6]. In 2003, Wollensak et al. presented a new method for the treatment of keratoconus, named collagen cross-linking (CXL). This technique uses a combination of ultraviolet-A (UVA) light and riboflavin [7] to form covalent bonds between collagen fibers in the anterior corneal stroma [8]. The traditional (conventional) technique of collagen cross-linking is widely used in the treatment of keratoconus [9]. However, it has some disadvantages such as diffuse lamellar keratitis, herpetic keratitis, and permanent corneal haze due to the damage caused by the UVA irradiation to the keratocytes, corneal endothelial cells, crystalline lens, and retina [10-12]. To decrease these harmful results, some researchers have postulated that the increment of intensity and decrement of irradiation duration could yield the same therapeutic effect, with higher satisfaction levels among patients and physicians [13]. Thus, a second-generation CXL technique was developed in recent years to decrease the illumination time and increase the intensity at 5.4-J/cm^2 fluence [14-16]. The results of treatment for keratoconus are not consistent. Therefore, we aimed to compare the effect of accelerated and conventional corneal CXL in patients with progressive keratoconus referring to Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences in Iran.

MATERIALS AND METHODS

This retrospective study included 71 eyes from 39 patients with progressive keratoconus referring to Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences in Iran from December 2014 to February 2016. The criteria for enrollment were: age 10–35 years; an increment of more than one diopter in keratometry in the steep meridian and an increment of one diopter or more in refractive errors in the last 6 months; corneal thickness more than 400 µm at the thinnest point; clear cornea on slit-lamp examination; and lack of subepithelial and stromal scar, ocular surgery history, previous corneal herpetic infection, and pregnancy or breastfeeding. All patients were fully examined and allocated to conventional or accelerated CXL surgery. The conventional CXL (CCXL) group received 3 mW/cm^2 in 30 minutes (37 eyes from 21 patients) and the accelerated CXL (ACXL) group received 18 mW/cm^2 in 5 minutes (34 eyes of 18 patients). All patients were tested for corrected distance visual acuity (CDVA) and uncorrected distance visual acuity (UDVA) using an E chart at 3, 6, and 12 months after surgery, and the measurements were converted to the logMAR notation. Slit-lamp examination, fundoscopy, autorefractometry, tonometry, specular microscopy (SP-3000P Specular Microscope, TOPCON, Tokyo, Japan), Orb scan (Orbscan IIz, Technolas, Munich, Germany), and topography (TMS-4 Topographic Modeling System, Tomey, Nagoya, Japan) were performed for all patients before and after the operation.

Prior to procedure, topical anesthesia and a miotic pilocarpine drop were administered. A speculum was placed on the eyelids. Then, using a spatula and alcohol at 60°, 9 mm of the central epithelial zone was removed. For the CCXL technique, a sponge ring was placed in the cornea and riboflavin 0.1% in 20% dextran (MedioCROSSD, Medio-Haus-Medizinprodukte GmbH, Kiel, Germany) was instilled to the de-epithelialized cornea every 3 minutes for 30 minutes, followed by irradiation at 3 mW/cm^2. The corneal surface was irradiated at a 5-cm working distance with a 9-mm treatment zone for 30 minutes using a UVA system device (UV-X, IROC AG, Zurich, Switzerland). The riboflavin solution was administered to the cornea every 5 minutes throughout the irradiation procedure. For the ACXL technique, isotonic riboflavin 0.1% was administered to the de-epithelialized cornea every 3 minutes for 30 minutes, followed by irradiation at 18 mW/cm^2 using a UVA system device (CCL-365-18, MLase AG, Munich, Germany). The corneal surface was irradiated at a 5-cm working distance with a 9-mm treatment zone for 5 minutes. At the end of the CCXL and ACXL procedures, a therapeutic soft contact lens (AIR OPTIX, Alcon, and Fort Worth, USA) was placed on each cornea until complete epithelial healing. Chloramphenicol 0.5% (RAHA Pharmaceutical Co., Isfahan, Iran) four times a day for 1 week and betamethasone 0.1% (RAHA Pharmaceutical Co. Isfahan,

Iran) six times a day for 5 days and then 4 times a day for 1 week were administered. The study was approved by the Institutional Review Board of Jundishapur University of Medical Sciences and adhered to the tenets of Declaration of Helsinki. The study protocol was explained to all patients and informed consent was obtained. The data were analyzed using Statistical Package for Social Studies version 20 (SPSS Inc., Chicago, IL). Categorical data are presented as numbers (%), and continuous data as means ± standard deviation (SD). We used the Student's t-test to compare continuous variables. To compare the groups and to compare the times after intervention, the generalized estimating equation (GEE) was used. $P < 0.05$ was considered significant.

Abbreviations

UDVA = Uncorrected Distance Visual Acuity
CDVA = Corrected Distance Visual Acuity
CXL = Collagen Cross-Linking
CCXL = Conventional Collagen Cross-Linking
ACXL = Accelerated Collagen Cross-Linking
SAI = Surface Asymmetry Index
SRI = Surface Regulatory Index
KPI = Keratoconus Prediction Index

RESULTS

A total of 71 eyes from 39 patients were evaluated. Two patients in the ACXL group were lost to follow-up and were excluded from the study. The mean age of the two groups was not significantly different ($P = 0.93$). At 12 months of follow-up, there was a greater improvement of UCVA in the ACXL group than in the CCXL group, but the difference was not statistically significant ($P = 0.08$). The improvement of BCVA was significantly greater in the CCXL group than in the ACXL group ($P = 0.006$) (Table 1 and Fig 1).

The mean changes of manifest refraction spherical equivalent (MRSE) during the 12 months of follow-up were not significantly different in either of the two groups ($P = 0.90$). The increment of astigmatism was significantly lower in the ACXL group than in the CCXL group ($P = 0.02$). The changes of keratometry (maximum and minimum) were significant in the CCXL group ($P = 0.04$) but not in the ACXL group, and there were significant differences between two groups ($P = 0.008$). Indices of keratoconus progression—surface asymmetry index (SAI), keratoconus prediction index (KPI), and keratoconus index (KCI)—were significantly lower in the CCXL group than in the ACXL group ($P = 0.002$, $P < 0.001$, and $P < 0.001$, respectively). The surface regularity index (SRI) was the same in the two groups. The thinnest corneal thickness (TCT) was significantly decreased in the two groups ($P < 0.001$), but there were no significant differences between the two groups ($P = 0.15$) (Table 2, Fig 2).

The reduction of corneal endothelial cell density was similar in the two groups, and there were no significant differences between the two groups ($P = 0.64$) (Fig 3).

The increment of polymorphism ($P = 0.015$) and polymegethism ($P = 0.05$) was significant in both groups, but the difference between the two groups was not significant ($P = 0.052$) (Table 2).

DISCUSSION

We showed that although ACXL at 18 mW/cm2 slowed keratoconus progression safely during a 1-year follow-up, CCXL at 3 mW/cm2 may be superior in the prevention of keratoconus progression.

It is well known that CCXL can inhibit keratoconus progression [17, 18]. The procedure takes approximately 1 hour per eye and several studies indicated that it is safe and effective [8, 9, 13, 17-25]. The ACXL procedure is faster, with an increase in energy without any change in the total energy [18, 23, 26-29].

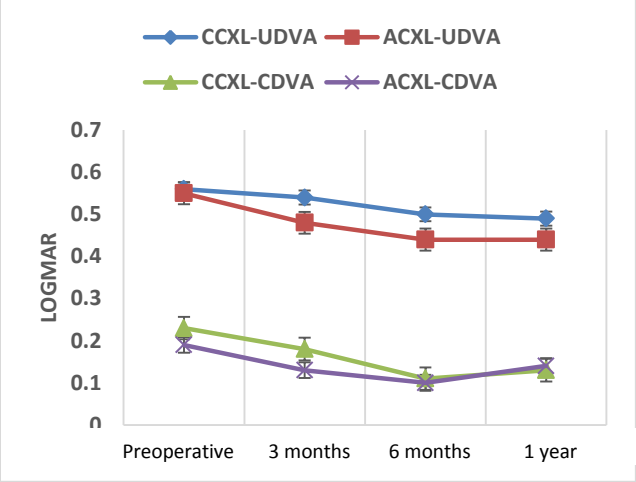

Figure 1. Uncorrected Distance Visual Acuity (UDVA) and Best-Corrected Distance Visual Acuity (BCVA) changes in Conventional Collagen Cross-Linking (CCXL) and Accelerated Collagen Cross-Linking. Blue Line: Uncorrected Distance Visual Acuity (UDVA) in the CCXL group was decreased after 3 and 6 months and slightly increased after 12 months, yet it did not reach the preoperative level. Red Line: UDVA in the ACXL group was decreased after 3, 6, and 12 months compared to the preoperative level. Green Line: Corrected Distance Visual Acuity (CDVA) in the CCXL group was decreased after 3 and 6 months and increased after 12 months, yet it did not reach the preoperative level. Purple Line: CDVA in the ACXL group did not change after the operation

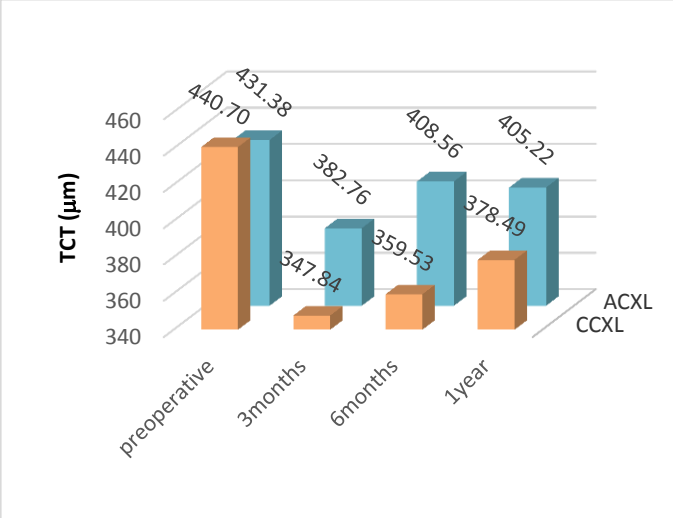

Figure 2. Thinnest Corneal Thickness (TCT) in Conventional Collagen Cross-Linking (CCXL) and Accelerated Collagen Cross-Linking. Orange Bars: mean TCT in the CCXL group was decreased significantly at 3 months and increased at 6 and 12 months. Blue Bars: mean TCT in the ACXL Group was decreased significantly at 3 months and increased at 6 and 12 Months.

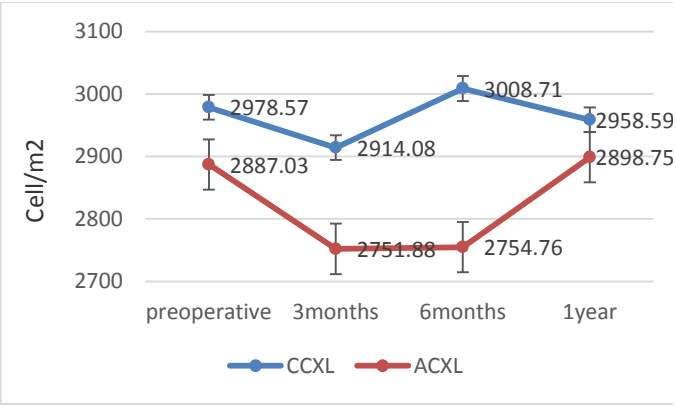

Figure 3. Endothelial Cell Density Changes in Conventional Collagen cross-Linking (CCXL) and Accelerated Collagen Cross-Linking.

Blue Line: in the CCXL Group, the Mean Corneal Endothelial Cell Density was decreased after 3 months and increased after 6 months, reaching the preoperative after 12 months. Red line: In the ACXL Group, the Mean Corneal Endothelial Cell Density was decreased after 3 months and 6 months, reaching the preoperative level after 12 months.

That increase, to a certain extent, has been shown to be effective [22, 30]. In the current study, 37 eyes of 21 patients were treated by CCXL (3 mW/cm^2 in 30 minutes) and were compared with 34 eyes of 18 patients treated by ACXL (18 mW/cm^2 in 5 minutes).

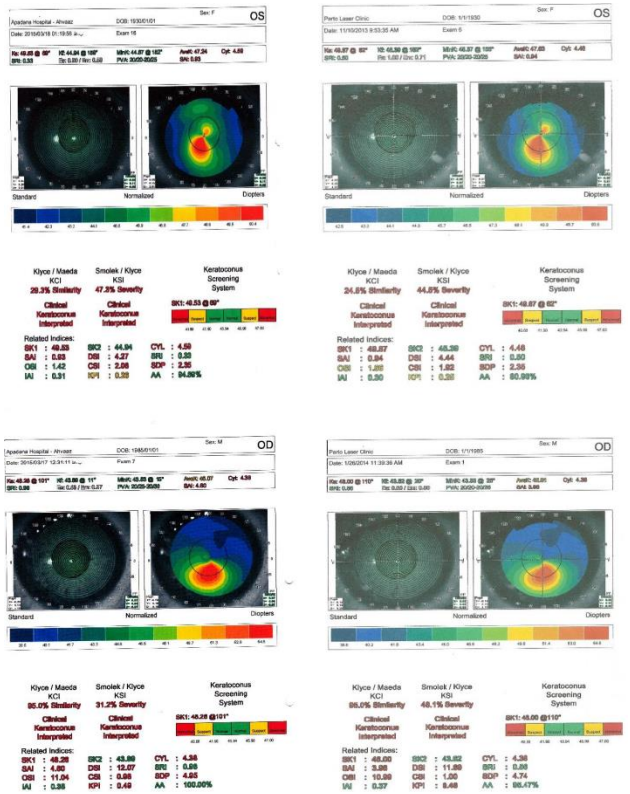

Figure 4. Left Eye Topography in a Patient from the Conventional Collagen Cross-Linking (CCXL) Group (Upper Maps) and Right Eye Topography in another Patient form the Accelerated Collagen Cross-Linking (ACXL) Group (Lower Maps). Topographic Indices at Preoperation (Right-Side Maps) and 1 Year after the Operation (Left-Side Maps) show the Stability of Keratoconus in these Patients.

Table 1: Mean ± SD of the Refraction Changes during 12 Months

Treatment group	Preoperatively	3 months	6 months	12 months	P-value 1	P-value 2
UDVA (logMAR)						0.081
Conventional	0.56 ± 0.47	0.54 ± 0.47	0.50 ± 0.48	0.49 ± 0.27	0.032	
Accelerated	0.55 ± 0.47	0.48 ± 0.40	0.44 ± 0.37	0.44 ± 0.38	0.003	
BCDVA (logMAR)						0.006
Conventional	0.23 ± 0.32	0.18 ± 0.21	0.11 ± 0.13	0.13 ± 0.20	0.003	
Accelerated	0.19 ± 0.22	0.13 ± 0.15	0.10 ± 0.11	0.14 ± 0.17	0.011	
MRSE (D)						0.907
Conventional	-5.93 ± 5.26	-5.86 ± 4.98	-4.86 ± 4.05	-4.83 ± 3.72	0.042	
Accelerated	-4.25 ± 3.64	-5.02 ± 3.65	4.79 ± 3.69-	-4.80 ± 4.18	0.058	
Cylinder (D)						0.021
Conventional	3.91 ± 2.29	4.61 ± 2.66	4.20 ± 2.42	4.03 ± 2.66	0.592	
Accelerated	3.94 ± 2.21	3.72 ± 2.08	3.83 ± 2.22	3.87 ± 2.31	0.377	

SD = Standard Deviation; logMAR = Log of the Minimum Angle of Resolution; MRSE = Manifest Refraction Spherical Equivalent; BCDVA = Best-Corrected Distance Visual Acuity; UDVA = Uncorrected Distance Visual Acuity; D = Diopter; Accelerated = Accelerated Collagen Cross-Linking; Conventional = Conventional Collagen Cross-Linking. P-value 1 = 12 Months Compared to Baseline; P-value 2: Intergroup Differences at 12 Months.

Table 2: Mean ± SD of the Topographic and Specular Microscopy Index Changes during 12 Months.

Treatment groups	Preoperatively	3 months	6 months	12 months	P-value 1	P-value 2
Minimum keratometry						
Conventional	46.01±3.10	45.78±2.81	45.41±4.37	44.99±2.78	< 0.001	0.008
Accelerated	45.00±2.36	44.68±1.61	44.14±1.34	44.92±2.34	0.992	
Maximum keratometry						
Conventional	49.42±4.78	49.46±4.77	49.65±6.13	48.85±4.67	0.006	0.043
Accelerated	48.55±3.70	48.13±2.98	47.11±2.66	48.47±3.54	0.665	
Thinnest corneal thickness						
Conventional	440.70±58.89	347.84±58.80	359.53±72.43	378.49±73.04	<0.001	0.510
Accelerated	431.38±51.93	382.76±64.69	408.56±62.44	405.22±61.72	0.001	
Surface asymmetry index						
Conventional	1.87±1.06	2.38±1.60	2.60±1.88	1.77±1.04	0.434	0.002
Accelerated	2.04±1.37	1.93±1.19	1.97±1.26	1.99±1.37	0.897	
Surface regularity index						
Conventional	0.72±0.59	0.99±0.56	0.89±0.68	0.76±0.52	0.641	0.91
Accelerated	0.66±0.46	0.61±0.35	0.60±0.34	0.68±0.49	0.515	
Keratoconus predictability index						
Conventional	0. 34±0.10	0.36±0.10	0.36±0.12	0.33±0.09	0.914	<0.001
Accelerated	0.35±0.12	0.34±0.09	0.34±0.10	0.34±0.11	0.796	
Keratoconus index						
Conventional	62.66±34.09	65.89±33.55	58.09±37.94	57.33±36.09	0.061	<0.001
Accelerated	57.95±36.32	58.60±33.72	58.38±35.41	56.24±38.04	0.861	
Endothelial cell density						
Conventional	2978.57±260.24	2914.08±251.53	3008.71±319.53	2958.59±271.59	0.495	0.641
Accelerated	2887.03±244.75	2751.88±211.34	2754.76±168.83	2898.75±265.17	0.718	
Hexagonality of endothelial cells						
Conventional	54.85±14.45	48.89±13.80	49.55±14.40	53.27±12	0.588	0.015↓
Accelerated	61.50±11.59	57.80±12.05	57.68±9.78	57.94±9.42	0.048	
CV of endothelial cells						
Conventional	32.88±5.16	36.43±8.17	34.85±6.27	34.46±6.69	0.19	0.052
Accelerated	31.14±4.49	29.28±5.11	32.25±7.18	32.00±5.33	0.15	

SD = Standard Deviation; Accelerated = Accelerated Collagen Cross-Linking; Conventional = Conventional Collagen Cross-Linking. CV = Coefficient of variation. P-value 1 = 12 Months compared to Baseline; P-value 2: Intergroup Differences at 12 Months.

Then, the patients were followed for 12 months after the operation. The CDVA and UDVA improved significantly in each of the two groups during the 12 months of follow-up. However, the difference between the two groups was not significant. In accordance with our findings, Cinar et al. reported that the two techniques were comparable regarding the improvement of CDVA and UDVA [23]. Similarly, Tomita et al. also showed that the efficacy of the two techniques was similar [27]. In our study, the improvement of CDVA and UDVA in the ACXL was similar to that of the study by Cinar et al. and greater than that in the study by Tomita et al; however, the CDVA remained unchanged in the latter [23]. In a trial by Shetty et al., the improvement of CDVA at doses of 30 mW/cm^2 was not significant, but was significant at 18 mW/cm^2 or less. Moreover, the improvement of CDVA in ACXL was greater than in CCXL. In contrast to our experience, the UDVA in ACXL was higher than that in the CCXL [29]. Moreover, in another study, the difference between the two techniques was not significant during 18 months [28]. This inconsistency may be a result of the corneal irregularity in these patients. This issue may require more attention during the ocular examination. Therefore, it is possible that different specialists obtain different measurements of CDVA and UDVA at different times.

The recovery of BCVA in the studies by Hashemi et al. and Tomita began at 6 months after the operation, which was similar to our study (Fig 1). In the study by Hashemi et al., the spherical equivalent changes were significantly lower in the CCXL group compared to the ACXL group [28]. In contrast, in our study, these changes were not statistically significant between two groups. However, the cylinder was significantly different between the two groups, which were in contradiction with the results obtained by their study [28]. This discrepancy may be explained by different data analysis methods and low repeatability of refractive errors due to optic disorders [28]. Several studies have indicated that the cornea becomes flat in both techniques [18, 22, 31]. Cinar et al. have noted that maximum keratometry is a guide for keratoconus progression, and that the maximum keratometry value is significantly decreased (by 1.4 in 6 months) [23]. Hashemi et al. revealed a significant reduction in keratometric parameters in CCXL but not in ACXL, and concluded that CCXL makes cornea flatter than ACXL [28], which is in line with our findings. The changes in keratoconus parameters, SAI, KPI and KCI, were significantly lower in the CCXL group than in the ACXL group ($P = 0.002$, $P < 0.001$, and $P < 0.001$, respectively) (Fig 4). The SRI was similar in the two groups. These findings showed that CCXL was more effective than ACXL in slowing keratoconus progression. Our results were in agreement to those of Hafezi et al., who detected the linear reduction of corneal stability at a dose of 18 mW/cm^2; however, the difference was not significant when the dose was increased to 30 mW/cm^2 [32]. We reported that the TCT was significantly decreased at 3 months but increased at 6 and 12 months after the operation in both techniques, yet it did not reach the pre-operation level. In line with these findings, Shetty et al. revealed that both techniques decreased the TCT; however, the reduction of the thickness was significantly greater in the CCXL method than in the ACXL group [29]. In our study, the difference between the two techniques was not significant ($P = 0.51$). The exact reason for the initial reduction and increase of thickness at months 6 and 12 is not completely understood. However, a possible explanation for the reduction of initial thickness is the compression of collagens or apoptosis of keratocytes [31]. Another explanation has been provided by Caporossi et al. They showed that the demarcation line is detectable up to 6 months after the surgery by the Orbscan due to hyperreflectivity, and this finding may be considered as thickness [33]. In this study, the ECD (endothelial cell density) was reduced during the 3 months after the operation and returned to pre-operation level after 12 months; the values were the same in both groups ($P = 0.641$), which was similar to the results of Hashemi [28], Cinar [23], and Shetty [29]. These findings may be related to the mild edema and haze of the central corneal stroma, due to the improvement process and migration of peripheral endothelial cells to the center of the cornea. Although the dose of energy was different between the two groups, in both techniques the process is the same [24] (Fig 2). The increase of variation among individual endothelial cell areas and shapes was greater in the CCXL group than in the ACXL group, indicating that ACXL may be safer than CCXL. The specular microscopy procedure takes the samples from one site of the cornea, which may lead to inter-sampling variation; moreover, in most of the patients, specular microscopy does not measure the central corneal endothelial cells, and sometimes peripheral cells are measured. These limitations may lead to different measurements of endothelial cells in one patient across different examinations and among different patients. To overcome these limitations, multiple sampling by the specular microscopy should be performed. Moreover, the duration of corneal

examination should take longer. The strength of this study was the statistical GEE analysis, which evaluated the correlation between eyes at different time points. To the best of our knowledge, all former studies have used repeated measures analysis. The main limitations of our study were the relatively small sample size and the short duration of follow-up (12 months). Further investigations with longer follow-up and larger series are required to validate the findings reported here. In conclusion, we showed that although ACXL at 18 mW/cm^2 was a safe technique regarding its effect on the endothelial cells, CCXL at 3 mW/cm^2 was more efficient than ACXL regarding the topographic characteristics.

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DISCLOSURE

No funding or sponsorship was received for this study. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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