Long-term Results of an Accelerated Corneal Cross-linking Protocol (18 mW/cm^2) for the Treatment of Progressive Keratoconus

HASSAN HASHEMI, MOHAMMAD MIRAFTAB, MOHAMMAD AMIN SEYEDIAN, FARHAD HAFEZI, HOOMAN BAHRMANDY, SHAHAB HEIDARIAN, KAZEM AMANZADEH, HAMIDREZA NIKBIN, AKBAR FOTOUHI, AND SOHEILA ASGARI

• PURPOSE: To compare the long-term outcomes of accelerated and standard corneal cross-linking protocols in the treatment of progressive keratoconus.

• DESIGN: Prospective randomized clinical trial.

• METHODS: Thirty-one eyes with keratoconus were treated with an accelerated protocol (18 mW/cm^2, 5 min) and all contralateral eyes were treated with the standard method (3 mW/cm^2, 30 min) using the same overall fluence of 5.4 J/cm^2.

• RESULTS: At 18 months after the procedure, the standard group showed significant improvement in spherical equivalent ($P < .05$), K-readings ($P < .05$), Q value ($P < .05$), index of surface variance ($P < .05$), and keratoconus index ($P = .008$) and decline in central corneal thickness ($P < .05$), but no significant change in visual acuity, corneal hysteresis, corneal resistance factor, P2 area, or endothelial cell density. In the accelerated group, central corneal thickness was the only parameter with statistically significant change. However, neither of these parameters showed significant differences between the standard and the 18 mW/cm^2 accelerated protocol, except K-reading ($P = .059$) and index surface variance ($P = .034$).

• CONCLUSION: An accelerated cross-linking protocol, using 18 mW/cm^2 for 5 minutes, shows a comparable outcome and safety profile when compared to the standard protocol, but better corneal flattening is achieved with the standard method than the accelerated method. Overall, both methods stop the disease progression similarly. This study will continue to examine more long-term results. (Am J Ophthalmol 2015;160(6):1164–1170.

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From the Noor Ophthalmology Research Center, Noor Eye Hospital, Tehran, Iran (H.H., M.M., M.A.S., H.B., S.H., K.A., H.N., S.A.); Center for Applied Biotechnology and Molecular Medicine (CABMM), University of Zurich, Zurich, Switzerland (F.H.); Medical Faculty, University of Geneva, Geneva, Switzerland (F.H.); Eye Care & Laboratory Research - Zurich Associates, Zurich, Switzerland (F.H.); Department of Ophthalmology, Keck School of Medicine, University of Southern California, Los Angeles, California (F.H.); and Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran (A.F.).

Inquiries to Soheila Asgari, Noor Ophthalmology Research Center, Noor Eye Hospital, No. 96 Esfandiar Blvd, Vali'asr Ave, Tehran, Iran; e-mail: soheilaasgari@gmail.com

THE STANDARD METHOD OF CORNEAL CROSS-linking (CXL) with riboflavin and ultraviolet (UV) A (3 mW/cm^2, 30 minutes), now widely known as the "Dresden protocol," was originally developed by Wollensak and associates[1] for the treatment of progressive keratoconus. The long-term safety and efficacy of this method has been demonstrated through many investigations.[2–6] In 2010, several accelerated CXL protocols were introduced with the purpose of reducing illumination time by increasing intensity while maintaining the fluence at 5.4 J/cm^2. Both clinical and experimental studies in this area have reported ambiguous results.[7–9] In the first report of this randomized clinical trial,[10] we demonstrated a similar trend for these 2 methods in terms of 6-month changes in vision, refraction, keratometry, corneal shape, endothelial cell density (ECD), and corneal biomechanics, which are in agreement with previously published data.[11] The only intermethod difference was the decrease in the central corneal thickness (CCT), which was greater in the standard group than in the accelerated group. Clinically, it is important to compare long-term results of the 2 methods; thus, here we present 18-month results with these methods and their comparison.

METHODS

THIS STUDY WAS PERFORMED AT NOOR EYE HOSPITAL, Tehran, Iran between March 6, 2013 and February 14, 2015. The methodology of this study has been described previously.[10] In brief, this prospective single-masked randomized clinical trial enrolled patients with bilateral progressive keratoconus. To ensure concealment, randomization was done by a person other than the ophthalmic surgeon. In each patient, the contralateral eye served as the control (standard CXL) for the other eye. Inclusion criteria were a diagnosis of progressive keratoconus (at least 1 diopter [D] increase in maximum keratometry [K_{max}], manifest cylinder, or manifest refraction spherical equivalent [MRSE] or the loss of at least 2 lines of corrected distance visual acuity [CDVA] within the past 12 months), age between 15 and 35 years, keratometry reading less than 55.0 D, and a minimum CCT of 400 μm. Patients with any

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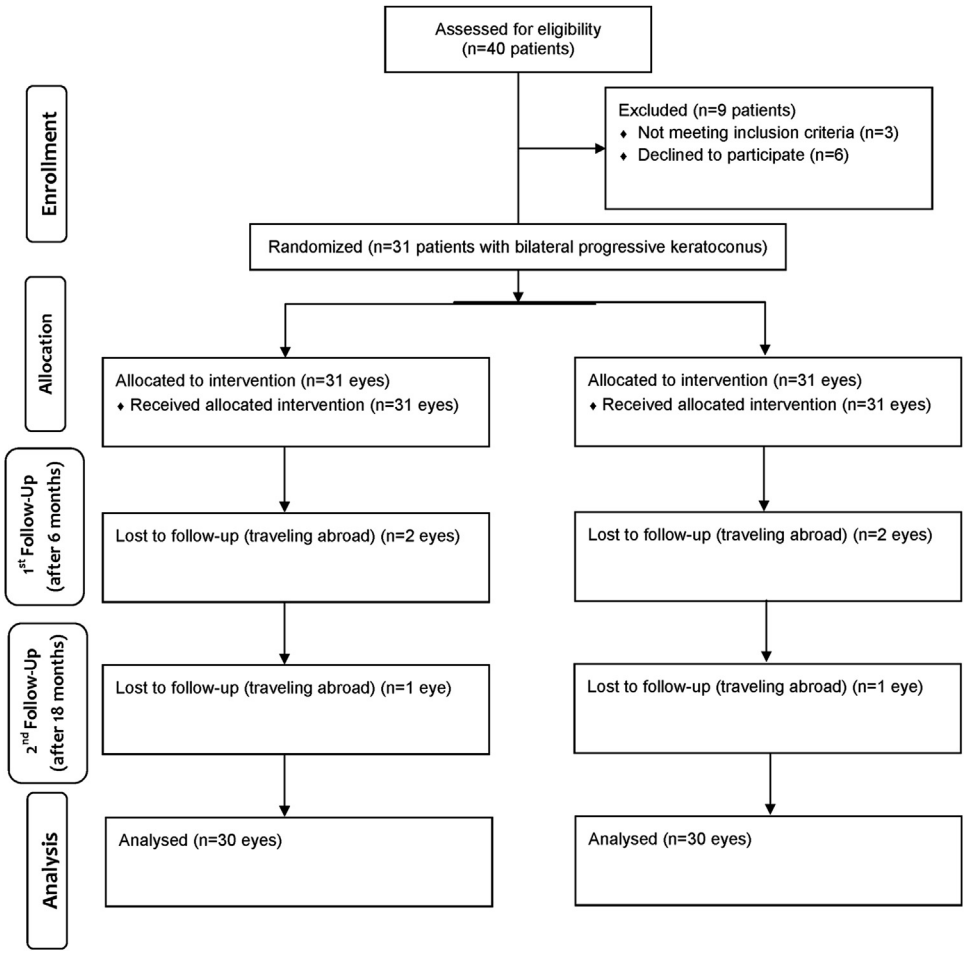

FIGURE 1. Flow diagram depicting the passage of participants in this randomized controlled trial comparing accelerated 18 mW/cm^2 and standard corneal cross-linking protocols in progressive keratoconus.

history of eye surgery or eye disease were excluded from the study. Hard and soft contact lens users were instructed not to wear their lenses for 3 weeks and 3 days, respectively, before the procedure (Figure 1).

The study was reviewed and approved by the Institutional Review Board of Noor Ophthalmology Research Center and the Iranian Registry of Clinical Trials, a member of the WHO Registry Network (registration number: IRCT201207244333N1; registry date: August 30, 2012). Written signed informed consents were obtained from participants.

• **SURGICAL TECHNIQUE:** In the control group, proparacaine hydrochloride 0.5% was used for local anesthesia, and the central 9.0 mm of the corneal epithelium was removed manually using a hokey knife. After removal of the lid speculum, riboflavin drops 0.1% in 20% dextran (Streuli Pharmeceuticals, Uznach, Switzerland) were instilled onto the corneal surface every 3 minutes for 30 minutes. Intraoperative pachymetry was done in all cases before irradiation. At this stage, none of the eyes had corneal thickness under 400 μm to require a swelling solution. After anterior chamber saturation with riboflavin, irradiation was commenced at a wavelength of 370 nm and power of 3 mW/cm^2 from a distance of 5 cm. Irradiation was done using the UVX system (IROC, Zürich, Switzerland). Riboflavin instillation continued every 3 minutes during the 30 minutes of irradiation. At the end of this stage, the corneal surface was rinsed with sterile balanced saline solution, a soft bandage contact lens (Night & Day; Ciba Vision, Duluth, Gorgia, USA) was applied, and a drop of levofloxacin was instilled. Postoperative medications included levofloxacin eye drops 4 times daily, betamethasone 0.1%, and preservative-free artificial tears (Hypromelose, Chauvin, Aubenas, France) as required. Patients were examined on days 1 and 3 after the procedure, and the lens was removed after epithelial healing. After removal of the lens, levofloxacin was discontinued and betamethasone was continued 4 times daily for another week. When the epithelium was not healed, daily visits were continued until complete healing. No case of intraoperative or postoperative complication was observed.

TABLE 1. Eighteen-Month-Postprocedure Visual and Refractive Outcomes (Mean ± Standard Deviation) in the Treatment of Progressive Keratoconus Using the Accelerated 18 mW/cm^2 Cross-linking Compared to the Standard Protocol

Treatment Group	Baseline n = 31	6 Months n = 29	18 Months n = 30	*P* Value[a]	*P* Value[b]
UDVA (logMAR)					
Accelerated	0.72 ± 0.53	0.61 ± 0.49	0.63 ± 0.49	.176	.745
Standard	0.74 ± 0.50	0.72 ± 0.51	0.68 ± 0.49	.107	
CDVA (logMAR)					
Accelerated	0.20 ± 0.18	0.19 ± 0.17	0.20 ± 0.19	.451	.551
Standard	0.22 ± 0.18	0.20 ± 0.21	0.23 ± 0.22	.943	
Spherical error (D)					
Accelerated	−1.44 ± 2.32	−1.43 ± 2.50	−1.37 ± 2.48	.312	.415
Standard	−1.62 ± 1.80	−1.67 ± 2.29	−1.32 ± 2.13	.124	
Cylinder error (D)					
Accelerated	−2.45 ± 1.69	−2.51 ± 1.73	−2.47 ± 1.70	.569	.370
Standard	−2.72 ± 1.92	−2.78 ± 1.90	−2.51 ± 1.85	.487	
SE (D)					
Accelerated	−2.67 ± 2.70	−2.56 ± 2.85	−2.61 ± 2.83	.479	.178
Standard	−3.02 ± 2.26	−3.06 ± 2.65	−2.58 ± 2.35	.041	

CDVA = best corrected distance visual acuity; SE = spherical equivalent refraction; UDVA = uncorrected distance visual acuity.
[a]Eighteen months compared to baseline.
[b]Intergroup differences in 18-month changes.

In the treatment group, all steps were similar to the control group, except that irradiation was at 18 mW/cm^2 for 5 minutes using the UV system (PESCHKE Meditrade GmbH, Waldshut-Tiengen, Germany).

• **EXAMINATIONS:** Examinations included testing for uncorrected distance visual acuity (UDVA) and best corrected distance visual acuity (CDVA) using the Snellen chart, and spherical equivalent (SE) using a retinoscope (ParaStop HEINE BETA 200; HEINE Optotechnik, Herrsching, Germany). We also measured topographic indices with the Pentacam (Oculus Optikgeräte GmbH, Wetzlar, Germany), corneal biomechanical properties using the Ocular Response Analyzer (ORA; Reichert Ophthalmic Instruments, Buffalo, New York, USA; software version: 3.01), and the ECD with noncontact specular microscopy (Konan Medical, Hyogo, Japan). Treatment results such as demarcation line and potential complications were assessed through slit-lamp (Haag-Streit, Cleveland, Ohio, USA) examinations.

• **STATISTICAL ANALYSIS:** Analysis was done using the intention-to-treat approach. In this report, the main analysis was focused on 18-month changes compared with preoperative values using repeated-measures analysis of variance. Additionally, 18-month changes were compared to 6-month-postoperative results in each group using the same method. Since study power impacts the significance of associations,[12] the powers of the tests used in the analyses were calculated by the Biologically Significant Effect Size approach[13] using the G Power 3.1.9.2 software (Universitate Kiel, Kiel, Germany). The level of significance considered for results was 0.05.

RESULTS

CONSIDERING THE INCLUSION CRITERIA, 31 PATIENTS (31 eyes in each group) were enrolled in the study. The mean age of the participants was 25.13 ± 4.21 years, and 59.4% of them were male.

• **VISUAL AND REFRACTIVE RESULTS:** Table 1 summarizes the vision and refraction data in the 2 study groups. At 18 months, the improvement in UDVA was statistically similar in the 2 groups ($P = .745$, power = 67%). CDVA was similarly unchanged in both groups ($P = .551$, power = 94%). Eighteen-month changes in spherical error ($P = .415$, power = 83%), refractive astigmatism ($P = .370$, power = 79%), and spherical equivalent ($P = .178$, power = 78%) were not significantly different between the 2 groups.

• **TOPOGRAPHIC RESULTS:** K_{max} showed no significant change in the accelerated group ($P = .407$) but significantly decreased in the standard group ($P = .005$). The intergroup difference was borderline statistically significant with low power in this regard ($P = .093$, power = 68%). The trend of changes in mean keratometry (K_{mean}) was similar to

TABLE 2. Eighteen-Month-Postprocedure Topographic Indices (Mean ± Standard Deviation) in the Treatment of Progressive Keratoconus Using the Accelerated 18 mW/cm^2 Cross-linking Compared to the Standard Protocol

Treatment Group	Preoperative (31 Patients)	Postoperative 6 Months (29 Patients)	Postoperative 18 Months (30 Patients)	*P* Value[a]	*P* Value[b]
Maximum keratometry (D)					
Accelerated	47.89 ± 3.22	48.24 ± 3.48	47.83 ± 3.77	.407	.093
Standard	48.77 ± 3.65	48.65 ± 3.75	48.13 ± 3.18	.005	
Mean keratometry (D)					
Accelerated	46.39 ± 3.28	46.44 ± 3.38	46.18 ± 3.43	.309	.059
Standard	47.10 ± 2.84	46.87 ± 3.14	46.39 ± 2.94	.004	
Central corneal thickness (μm)					
Accelerated	489.60 ± 32.32	482.89 ± 33.22	480.32 ± 36.35	<.001	.324
Standard	489.63 ± 34.94	471.70 ± 36.91	469.50 ± 38.75	<.001	
Q-value					
Accelerated	−0.62 ± 0.25	−0.66 ± 0.30	−0.56 ± 0.29	.366	.426
Standard	−0.72 ± 0.32	−0.74 ± 0.44	−0.64 ± 0.38	.019	
Index of surface variance					
Accelerated	66.23 ± 29.68	70.09 ± 30.29	65.41 ± 28.73	.601	.034
Standard	77.27 ± 38.92	78.27 ± 40.20	72.32 ± 35.38	.001	
Index of vertical asymmetry					
Accelerated	0.72 ± 0.35	0.77 ± 0.38	0.70 ± 0.35	.095	.720
Standard	0.86 ± 0.49	0.80 ± 0.42	0.81 ± 0.44	.018	
Keratoconus index					
Accelerated	1.17 ± 0.10	1.17 ± 0.09	1.15 ± 0.09	.244	.622
Standard	1.21 ± 0.13	1.19 ± 0.13	1.19 ± 0.13	.008	
Center keratoconus index					
Accelerated	1.04 ± 0.03	1.04 ± 0.03	1.04 ± 0.04	.900	.341
Standard	1.05 ± 0.04	1.05 ± 0.05	1.04 ± 0.04	.162	
Index of height asymmetry					
Accelerated	24.30 ± 20.12	21.64 ± 19.17	29.60 ± 25.32	.097	.397
Standard	24.84 ± 20.63	29.60 ± 25.32	28.19 ± 22.08	.500	
Index of height decentration					
Accelerated	0.08 ± 0.07	0.06 ± 0.04	0.09 ± 0.05	.547	.409
Standard	0.07 ± 0.05	0.08 ± 0.05	0.10 ± 0.05	.061	

D = diopters.
[a]Eighteen months compared to preoperative.
[b]Intergroup differences in 18-month changes.

K_{max} in both groups, and the intergroup difference in K_{mean} changes was borderline statistically significant ($P = .059$, power = 72%). CCT decreased similarly in both groups ($P = .324$, power = 79%). The Q-value was unchanged in the accelerated group ($P = .366$), but shifted to oblate in the standard group ($P = .019$); the intergroup difference in this regard was not significant ($P = .426$, power = 67%). In terms of changes in keratoconus indices, the intergroup difference was statistically significant for the index of surface variance (ISV) ($P = .034$, power = 62%) but not for the index of vertical asymmetry (IVA) ($P = .720$, power = 54%), the keratoconus index (KI) ($P = .622$, power = 56%), the center keratoconus index (CKI) ($P = .341$, power = 77%), the index of height asymmetry (IHA) ($P = .397$, power = 70%), or the index of height decentration (IHD) ($P = .409$, power = 70%) (Table 2).

• **ENDOTHELIAL CELL DENSITY:** The 2 groups were not significantly different in terms of 18-month decrease in ECD ($P = .434$, power = 95%) (Figure 2).

• **CORNEAL BIOMECHANICAL PROPERTIES:** At 18 months after the procedure, changes in corneal hysteresis (CH) ($P = .983$, power = 96%), corneal resistance factor (CRF) ($P = .596$, power = 97%), CH−CRF ($P = .815$, power = 96%), and P2 area ($P = .643$, power = 60%) were not statistically significant between the 2 groups (Table 3).

Trends of changes from 6 to 18 months were compared between the 2 groups. Among studied parameters, CCT showed a decrease at 18 months compared to 6 months in both the accelerated ($P = .029$) and the standard ($P = .053$) groups. The descending trend in K_{max} was also

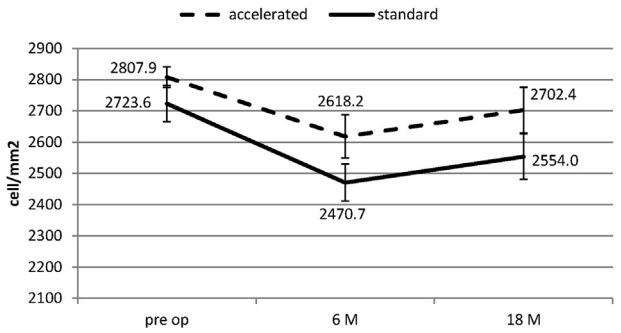

FIGURE 2. Comparison of accelerated 18 mW/cm^2 and standard corneal cross-linking protocols in the treatment of progressive keratoconus in terms of their effect on endothelial cell count over an 18-month period.

significant in both the accelerated ($P = .011$) and the standard ($P = .008$) groups. Similarly, K_{mean} had a significant decrease in both groups ($P < .001$) compared to 6-month results.

DISCUSSION

CXL IS AN ESTABLISHED PROCEDURE TO STOP PROGRESSIVE keratoconus, and long-term studies based on the standard Dresden protocol have demonstrated its efficacy in stabilizing corneal indices, as well as flattening the keratoconus cornea.[2,3] Corneal stiffening occurs owing to intrafibril bonds that form under the effect of UV.[14] With the first standard method, presented by Wollensak and associates, an irradiation time of 30 minutes after riboflavin saturation is necessary for reactions to occur. Since high-powered UV devices became available, a new idea has been to decrease UV exposure time by increasing its intensity. An experimental study in 2011[15] showed similar stress-strain results with rapid (10 mW/cm^2, 9 min) and standard methods of irradiation. Since then, clinical studies have been designed and conducted to assess the results of various accelerated protocols.

In our study, at 18 months after the procedure, visual acuity and refraction were not significantly different between the 2 groups. Similarly, Cinar and associates[16] found no significant intergroup (3 mW/cm^2, 30 min vs 10 mW/cm^2, 9 min) difference in postoperative visual acuity. Studies on accelerated and standard methods of CXL are inconclusive as to whether visual acuity and refraction improve or remain unchanged. Cinar and associates[16] reported improved vision and no change in refraction in their accelerated group (30 mW/cm^2 for 3 min), while the standard group had no change in vision and improved refraction. In the single-group study by Vega-Estrada amd associates[17] with the same method (30 mW/cm^2 for 3minutes), UDVA improved, CDVA and SE were unchanged, and cylinder error decreased. These discrepancies could imply that, in a single population, different CXL protocols have similar results, and if standard CXL can improve or stabilize vision and refraction, the accelerated approach might have the same effect. It must also be noted that repeatability of refraction in keratoconus patients is low owing to the degradation of optical quality.[18,19] We believe the power of the present study supports the similarity of visual and refractive results with the 2 protocols.

Previous reports have shown corneal flattening with both CXL protocols.[16,20,21] We did not observe any significant change in keratometry parameters in the accelerated group, but the decreases observed in the standard group were significant. The powers of our study for showing these intergroup K_{max} and K_{mean} differences were 68% and 72%, respectively. Since intergroup changes in ISV were significant, and K-readings had borderline significant difference with moderate statistical power (less than 0.8), we could argue that if we had a higher power for examining intergroup K-reading differences, we would find a statistically significant difference. Especially since type 1 error could increase owing to multiple statistical tests, a higher power is needed to reveal significant differences. Therefore, we could say better corneal flattening is achieved with the standard protocol than with the accelerated one.

While the cornea showed greater thickness reduction in the standard group at 6 months, the decreases in CCT were similar in the 2 groups at 18 months after the procedure. Mita and associates[21] also reported a decrease in CCT after accelerated CXL (30 mW/cm^2, 3 min). The descending trend in corneal thickness has been reported up to 36 months postoperatively.[21,22] Corneal thickness reduction was about 12 μm in the study by Mita and associates[21] and about 9 μm in our accelerated group.

We observed reduced ECD in both groups after 18 months, and the rate of endothelial cell loss was identical in the 2 groups. This is while it was stable in the studies by Mita[21] and Cinar.[16] Though the decrease in ECD has been small, it shows that the possibility for endothelial cell damage is real, and it is of paramount importance to adhere to strict guidelines regarding the minimum corneal thickness and intraoperative CCT measurement.

In our study, biomechanical properties were measured with ORA, and in addition to CH and CRF, we made an intergroup comparison of the P2 area. As stated in the results and in agreement with the study by Tomita and associates,[23] we observed no change in corneal biomechanical parameters in either group. Lack of change in these parameters has been reported by other studies on the standard method[24,25] and the accelerated method.[20,23]

As mentioned, one of the limitations of this study was the small sample size in groups and the low power for some comparisons. The Bonferroni correction, however plausible, was not applied despite making multiple

TABLE 3. Eighteen-Month-Postprocedure Corneal Biomechanical Properties (Mean ± Standard Deviation) in the Treatment of Progressive Keratoconus Using the Accelerated 18 mW/cm^2 Cross-linking Compared to the Standard Protocol

Treatment Group	Preoperative (31 Patients)	Postoperative 6 Months (29 Patients)	Postoperative 18 Months (30 Patients)	*P* Value[a]	*P* Value[b]
CH (mm Hg)					
Accelerated	7.10 ± 1.73	7.30 ± 1.63	7.00 ± 2.03	.762	.983
Standard	7.36 ± 1.94	7.23 ± 1.53	7.26 ± 1.66	.723	
CRF (mm Hg)					
Accelerated	6.32 ± 1.53	6.46 ± 1.51	6.35 ± 1.69	.908	.596
Standard	6.75 ± 1.90	6.78 ± 1.80	6.59 ± 1.77	.538	
CH−CRF (mmHg)					
Accelerated	0.73 ± 0.89	0.87 ± 0.75	0.95 ± 0.73	.366	.815
Standard	0.58 ± 0.67	0.43 ± 0.77	0.80 ± 0.81	.569	
P2 area					
Accelerated	1132.63 ± 615.27	1155.23 ± 618.81	988.30 ± 382.16	.346	.643
Standard	1161.74 ± 677.10	1010.03 ± 508.36	1123.32 ± 554.24	.824	

CH = corneal hysteresis; CRF = corneal resistance factor.
[a]Eighteen months compared to preoperative.
[b]Intergroup differences in 18-month changes.

comparisons, because it would reduce the power even further. If *P* values were to be adjusted, the reduced power would confirm the present results. Studies with larger sample sizes and longer follow-ups are needed to compare accelerated protocols in terms of efficacy, stability of results, and overall effect on disease progression. Also, improving methods to quantify corneal haze using optical coherence tomography could improve our ability to assess and compare results.

In conclusion, an accelerated CXL protocol using 18 mW/cm^2 for 5 minutes seems to be safe with regard to endothelial cell damage. The clinical results are in line with previously published experimental data,[9] indicating that the induction of cross-links is still present using 18 mW/cm^2 intensity, but might be less pronounced when compared to 9 mW/cm^2 or even 3 mW/cm^2. Further long-term follow-up will show whether this reduced effect will still be sufficient to arrest keratoconus progression.

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Biosketch

Dr Hassan Hashemi, professor of ophthalmology at Tehran University of Medical Sciences, is the head and founder of Noor Eye Hospital and Ophthalmic Research Center. He completed his cornea and anterior segment fellowship in 1991. His research interests include refractive surgery, corneal cross-linking, and ophthalmic epidemiology. In addition to various clinical studies, he has several national projects and population-based studies including Tehran Eye Study and the ongoing Shahroud Eye Cohort Study.