Accepted Manuscript

Long-term results of an accelerated corneal cross-linking protocol 18mW/cm^2 for the treatment of progressive keratoconus

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PII: S0002-9394(15)00533-4

DOI: 10.1016/j.ajo.2015.08.027

Reference: AJOPHT 9455

To appear in: *American Journal of Ophthalmology*

Received Date: 20 April 2015

Revised Date: 18 August 2015

Accepted Date: 18 August 2015

Please cite this article as: Hashemi H, Miraftab M, Seyedian MA, Hafezi F, Bahrmandy H, Heidarian S, Amanzadeh K, Nikbin H, Fotouhi A, Asgari S, Long-term results of an accelerated corneal cross-linking protocol 18mW/cm^2 for the treatment of progressive keratoconus, *American Journal of Ophthalmology* (2015), doi: 10.1016/j.ajo.2015.08.027.

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 (18mW/cm^2, 5min) and all contralateral eyes were treated with the standard method (3mW/cm^2, 30min) 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 SE ($P<0.05$), K-readings ($P<0.05$), Q value ($P<0.05$), index of surface variance ($P<0.05$), and keratoconus index ($P=0.008$) and decline in central corneal thickness ($P<0.05$), 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 ($P=0.059$) and index surface variance ($P=0.034$).
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.

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Short title: Accelerated vs. Standard Corneal Cross-linking

Introduction

The standard method of corneal cross-linking (CXL) with riboflavin and UVA (3mW/cm^2, 30 minutes), now widely known as the "Dresden protocol", was originally developed by Wollensak et al.[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 two 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 inter-method difference was the decrease in the central corneal thickness (CCT) which was greater in the standard group than the accelerated group. Clinically, it is important to compare long-term results of the two methods, and thus, here we present 18 month results with these methods and their comparison.

Methods and Materials

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 1D 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 diopters (D), and a minimum CCT of 400 μm. Patients with any history of eye surgery or eye disease were excluded from the study. Hard and soft contact lens users were instructed not to wear them 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 9.0mm of the corneal epithelium was removed manually using a hokey knife. After removing the lid speculum, riboflavin drops 0.1% in 20% dextran (Streuli pharmeceuticals, Uznach, Switzerland) were instilled onto the corneal surface every 3 minutes for half an hour. Intraoperative pachymetry was done in all cases before irradiation. At this stage, none of the cases had corneal thickness under 400μm to require a swelling solution. After anterior chamber saturation with riboflavin, irradiation was commenced at a wavelength of 370nm and power of 3mW/cm^2 from a distance of 5cm. Irradiation was done using the UVX system (IROC, Zürich, Switzerland). Riboflavin instillation continued every three 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, GA) was applied, and a drop of levofloxacin was instilled. Postoperative medications included levofloxacin eye drops four times daily, betamethasone 0.1%, and preservative free artificial tears (Hypromelose) as required. Patients were examined on day 1 and 3 after the procedure, and the lens was removed after epithelial healing. After removing 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.

In the treatment group, all steps were similar to the control group, except that irradiation was at 18mW/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, USA; software version: 3.01), and the ECD with non-contact specular microscopy (Konan Medical, Hyogo, Japan). Treatment results such as demarcation line and potential complications were assessed through slit lamp (Haag-Streit, 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. 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 two study groups. At 18 months, the improvement in UDVA was statistically similar in the two groups (P=0.745, power=67%). CDVA was similarly unchanged in both groups (P=0.551, power=94%). Eighteen month changes in spherical error (P=0.415, power=83%), refractive astigmatism (P=0.370, power=79%), and spherical equivalent (P=0.178, power=78%) were not significantly different between the two groups.

Topographic results. K_{max} showed no significant change in the accelerated group (P=0.407), but significantly decreased in the standard group (P=0.005). The inter-group difference was borderline statistically significant with low power in this regard (P=0.093, power=68%). The trend of changes in K_{mean} was similar to K_{max} in both groups, and the inter-group difference in K_{mean} changes were borderline statistically significant (P=0.059, power=72%). CCT decreased similarly in both groups (P=0.324, power=79%). The Q-value was unchanged in the accelerated group (P=0.366), but shifted to oblate in the standard group (P=0.019); the inter-group difference in this regard was not significant (P=0.426, power=67%). In terms of changes in keratoconus indices, the inter-group difference was statistically significant for the index of surface variance (ISV) (P=0.034, power=62%) but not for the index of vertical asymmetry (IVA) (P=0.720, power=54%), the keratoconus index (KI) (P=0.622, power=56%), the center keratoconus index (CKI) (P=0.341, power=77%), the index of height asymmetry (IHA) (P=0.397, power=70%), or the index of height decentration (IHD) (P=0.409, power=70%) (Table 2).

Endothelial cell density. The two groups were not significantly different in terms of 18 month decrease in ECD (P=0.434, power=95%). (Figure 2)

Corneal biomechanical properties. At 18 months after the procedure, changes in CH (P=0.983, power=96%), CRF (P=0.596, power=97%), CH-CRF (P=0.815, power=96%), and P2 area (P=0.643, power=60%) were not statistically significant between the two groups (Table 3).

Trends of changes from 6 to 18 months were compared between the two groups. Among studied parameters, CCT showed a decrease at 18 months compared to 6 months in both the accelerated (P=0.029) and the standard (P=0.053) groups. The descending trend in K_{max} was also significant in both the accelerated (P=0.011) and the standard (P=0.008) groups. Similarly, K_{mean} had a significant decrease in both groups (P<0.001) 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 due to intra fibril bonds that form under the effect of UV.[14] With the first standard method presented by Wollensak, 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 two groups. Similarly, Cinar et al.[16] found no significant inter-group (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 et al.[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 et al. [17] with the same method (30mW/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 due 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 two 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 inter-group K_{max} and K_{mean} differences were 68% and 72%, respectively. Since inter-group 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 inter-group k-reading differences, we would find a statistically significant difference. Especially since type one error could increase due 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 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 two groups at 18 months after the procedure. Mita et al.[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 12μm in the study by Mita et al.[21] and about 9μm in our accelerated group.

We observed reduced ECD in both groups after 18 months, and the rate of endothelial cell loss was identical in two 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 inter-group comparison of the P2 area. As stated in the results and in agreement with the study by Tomita et al.,[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 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.

Acknowledgment

All authors have completed and submitted the ICMJE form for disclosure of potential conflicts of interest, and none were reported. Farhad Hafezi is named co-inventor of PCT 2012/000090 application. The authors indicate no funding support. Contributions to Authors: Design of study (HH); Data collection (HH, MM, MAS, HB, SH, KA, HN); Analysis and interpretation of data (MM, MAS, FH, AF, SA); Writing of article (SA); Critical revision and final approval of article (HH, MM, FH, MAS, HB, SH, KA, HN, AF, SA).

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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

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

Table 1. Eighteen-month post-procedure 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*	P-value**
UDVA (logMAR)	accelerated	0.72±0.53	0.61±0.49	0.63±0.49	0.176	0.745
	standard	0.74±0.50	0.72±0.51	0.68±0.49	0.107	
CDVA (logMAR)	accelerated	0.20±0.18	0.19±0.17	0.20±0.19	0.451	0.551
	standard	0.22±0.18	0.20±0.21	0.23±0.22	0.943	
Spherical error (D)	accelerated	-1.44±2.32	-1.43±2.50	-1.37±2.48	0.312	0.415
	standard	-1.62±1.80	-1.67±2.29	-1.32±2.13	0.124	
Cylinder error (D)	accelerated	-2.45±1.69	-2.51±1.73	-2.47±1.70	0.569	0.370
	standard	-2.72±1.92	-2.78±1.90	-2.51±1.85	0.487	
SE (D)	accelerated	-2.67±2.70	-2.56±2.85	-2.61±2.83	0.479	0.178
	standard	-3.02±2.26	-3.06±2.65	-2.58±2.35	0.041	

UDVA: uncorrected distance visual acuity; CDVA: best corrected distance visual acuity; SE: spherical equivalent refraction

* 18 months compared to baseline

** Inter-group differences in 18 month changes

Table 2. Eighteen-month post-procedure 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

		Pre operative	Post operative -6 months	Post operative -18 months	P-value*	P-value**
No of patients	Treatment group	31	29	30		
Maximum Keratometry (D)	accelerated	47.89±3.22	48.24±3.48	47.83±3.77	0.407	0.093
	standard	48.77±3.65	48.65±3.75	48.13±3.18	0.005	
Mean Keratometry (D)	accelerated	46.39±3.28	46.44±3.38	46.18±3.43	0.309	0.059
	standard	47.10±2.84	46.87±3.14	46.39±2.94	0.004	
central corneal thickness (μm)	accelerated	489.60±32.32	482.89±33.22	480.32±36.35	<0.001	0.324
	standard	489.63±34.94	471.70±36.91	469.50±38.75	<0.001	
Q-value	accelerated	-0.62±0.25	-0.66±0.30	-0.56±0.29	0.366	0.426
	standard	-0.72±0.32	-0.74±0.44	-0.64±0.38	0.019	
Index of surface variance	accelerated	66.23±29.68	70.09±30.29	65.41±28.73	0.601	0.034
	standard	77.27±38.92	78.27±40.20	72.32±35.38	0.001	
Index of vertical asymmetry	accelerated	0.72±0.35	0.77±0.38	0.70±0.35	0.095	0.720
	standard	0.86±0.49	0.80±0.42	0.81±0.44	0.018	
Keratoconus index	accelerated	1.17±0.10	1.17±0.09	1.15±0.09	0.244	0.622
	standard	1.21±0.13	1.19±0.13	1.19±0.13	0.008	
Center keratoconus index	accelerated	1.04±0.03	1.04±0.03	1.04±0.04	0.900	0.341
	standard	1.05±0.04	1.05±0.05	1.04±0.04	0.162	
Index of height asymmetry	accelerated	24.30±20.12	21.64±19.17	29.60±25.32	0.097	0.397
	standard	24.84±20.63	29.60±25.32	28.19±22.08	0.500	
Index of height decentration	accelerated	0.08±0.07	0.06±0.04	0.09±0.05	0.547	0.409
	standard	0.07±0.05	0.08±0.05	0.10±0.05	0.061	

* 18 months compared to preoperative

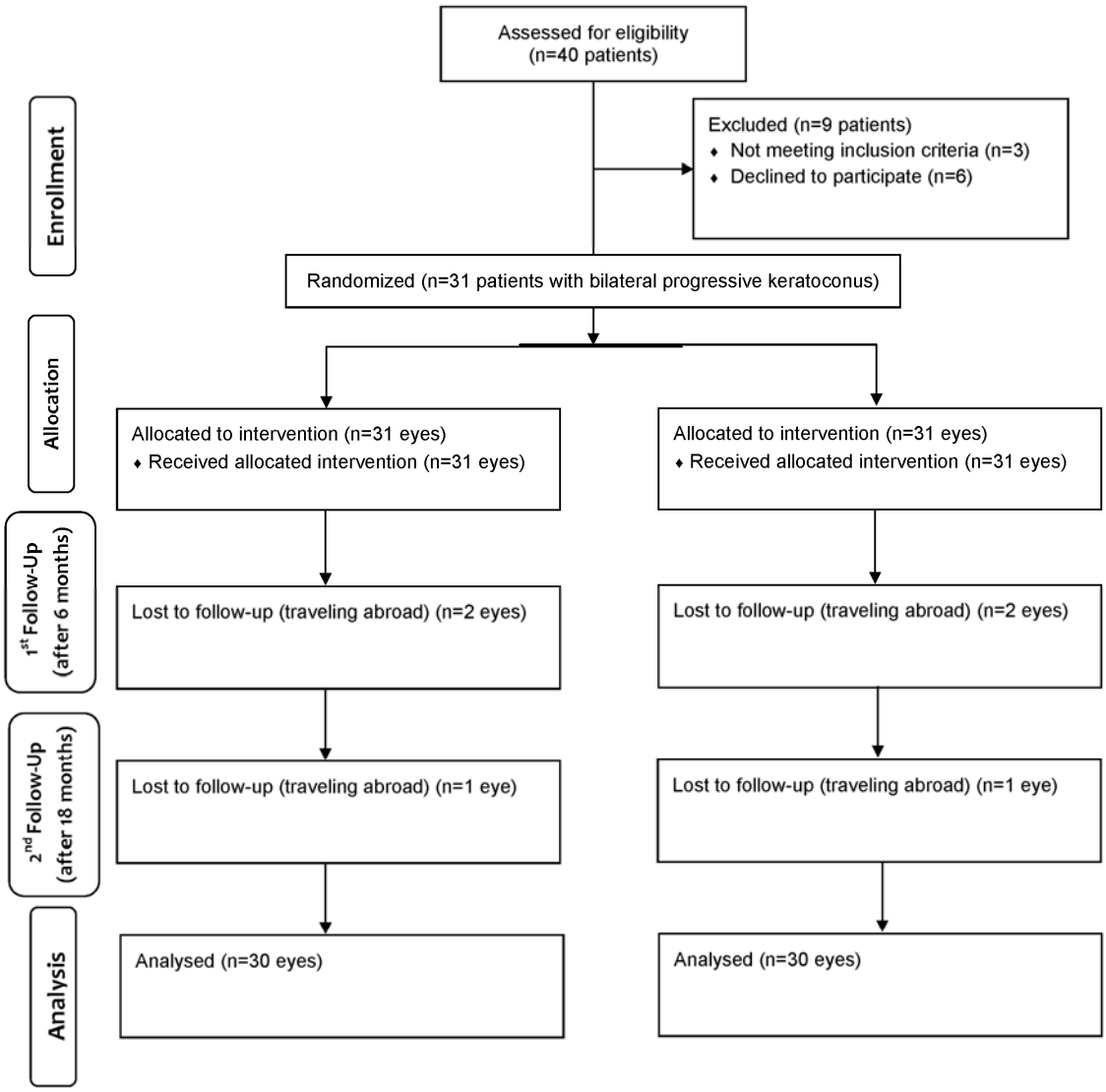
** Inter-group differences in 18 month changes

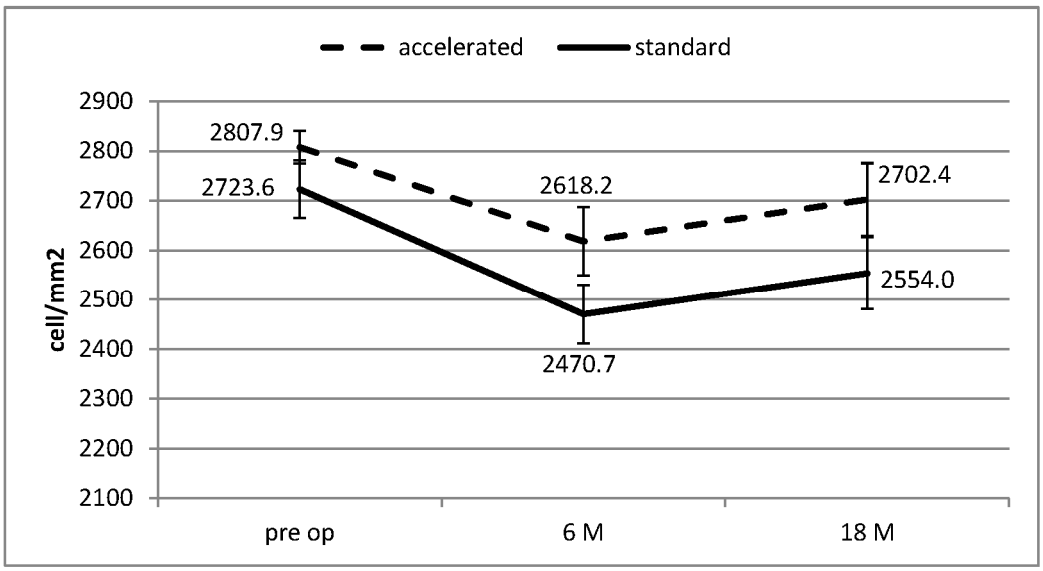
Table 3. Eighteen-month post-procedure corneal biomechanical properties (mean ±standard deviation) in the treatment of progressive keratoconus using the accelerated 18 mW/cm^2 cross-linking compared to the standard protocol

		Pre operative	Post operative - 6 months	Post operative - 18 months	P-value*	P-value**
No of patients	Treatment group	31	29	30		
CH (mmHg)	accelerated	7.10±1.73	7.30±1.63	7.00±2.03	0.762	0.983
	standard	7.36±1.94	7.23±1.53	7.26±1.66	0.723	
CRF (mmHg)	accelerated	6.32±1.53	6.46±1.51	6.35±1.69	0.908	0.596
	standard	6.75±1.90	6.78±1.80	6.59±1.77	0.538	
CH-CRF	accelerated	0.73±0.89	0.87±0.75	0.95±0.73	0.366	0.815
	standard	0.58±0.67	0.43±0.77	0.80±0.81	0.569	
P2area	accelerated	1132.63±615.27	1155.23±618.81	988.30±382.16	0.346	0.643
	standard	1161.74±677.10	1010.03±508.36	1123.32±554.24	0.824	

* 18 months compared to preoperative

** Inter-group differences in 18 month changes


Assessed for eligibility
(n=40 patients)
Excluded (n=9 patients)
♦ Not meeting inclusion criteria (n=3)
♦ Declined to participate (n=6)
Randomized (n=31 patients with bilateral progressive keratoconus)
Enrollment
Allocation
Allocated to intervention (n=31 eyes)
♦ Received allocated intervention (n=31 eyes)
Allocated to intervention (n=31 eyes)
♦ Received allocated intervention (n=31 eyes)
1st Follow-Up (after 6 months)
Lost to follow-up (traveling abroad) (n=2 eyes)
Lost to follow-up (traveling abroad) (n=2 eyes)
2nd Follow-Up (after 18 months)
Lost to follow-up (traveling abroad) (n=1 eye)
Lost to follow-up (traveling abroad) (n=1 eye)
Analysis
Analysed (n=30 eyes)
Analysed (n=30 eyes)



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.