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RESEARCH

Scotopic contrast sensitivity and glare after accelerated corneal cross-linking

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Background: The aim was to assess one-year changes in uncorrected and corrected contrast sensitivity (CS) and glare under scotopic conditions after accelerated cross-linking (CXL) using the 18 mW/cm^2 protocol for the treatment of progressive keratoconus and compare results with unoperated controls.

Methods: In this non-randomised clinical trial, 30 eyes were enrolled in the CXL group and 30 were assigned to the control group. Scotopic CS at spatial frequencies (SFs) of 0.5, 1.1, 2.2, 3.4, 7.1 and 15 cycles per degree (cpd) were assessed using the MonCv3System (Metrovision, Pérenchies, France) under scotopic conditions (0.5 lux) at baseline and at six and 12 months.

Results: The mean ages of the participants in the CXL and control groups were 24.32 ± 5.17 and 30.93 ± 7.43 years, respectively ($p < 0.001$). After adjusting for age, changes in uncorrected and corrected CS and glare were similar in the two groups (all $p > 0.05$) except for corrected CS at SF 7.1 cpd (1.45 ± 4.31 versus 3.21 ± 4.69 dB, $p = 0.010$) and 15 cpd (1.12 ± 4.63 versus 3.03 ± 5.48 dB, $p = 0.007$), which were reduced as an effect of CXL. Based on covariate analyses, among corrected CS indices, corrected CS7.1 and CS15 were related to CXL and their baseline values (all $p < 0.050$). Uncorrected CS in all SFs and uncorrected and corrected glare were related to their preoperative values (all $p < 0.001$).

Conclusion: Accelerated CXL can reduce scotopic corrected CS at SFs higher than 7.0 cpd in cases with better baseline values of these parameters. Changes in uncorrected CS and glare are only a factor of baseline values and the indices reduce in cases with better baseline values after one year.

Key words: accelerated cross-linking, contrast sensitivity, glare, scotopic condition

Loss of contrast sensitivity (CS), as an index independent of changes in visual acuity (VA), has been reported in keratoconic patients in different studies.[1–3] In keratoconus, increasing higher order aberrations (HOAs) have a more deteriorating effect on CS compared to VA.[4] After corneal cross-linking (CXL), photopic CS improves as a result of reduced HOAs, especially vertical coma.[5,6] Also, it has been shown that night time halo and driving problems may reduce after CXL.[7]

Under low light conditions, the pupil dilates and HOAs increase and this increases patients' troubles, especially when driving. Therefore, it is important to assess CS under low light conditions after the CXL procedure. The recommended road luminance is 0.3 to 2.0 cd/m^2 in Europe and 0.3 to 1.2 cd/m^2 in the United States.[8] In Iran, according to the regulations by the Ministry of Roads and Urban Development, night time luminous intensity based on traffic volume is two to 12 lux in the streets and 16 lux in roads with high traffic loads. Therefore, it seems pertinent to examine CS under scotopic conditions (0.5 lux) in keratoconus patients undergoing CXL.

To the best of our knowledge, no previous study has been done in this regard and scotopic CS and glare have not been studied after CXL. The objective of the present study is to assess CS and glare under scotopic lighting conditions in a group of patients undergoing accelerated CXL (18 mW/cm^2, five minutes) and compare results with a group of unoperated keratoconus patients as controls to examine the effect of the procedure on night vision.

METHODS

This prospective non-randomised clinical trial began in June 2013 at Noor Eye Hospital, Tehran, Iran. The present report examines CS and glare in patients with progressive keratoconus (at least one dioptre increase in maximum keratometry [Kmax], manifest cylinder or manifest refraction spherical equivalent in the last 12 months) in a group undergoing accelerated CXL (18 mW/cm^2, five minutes) (30 eyes) and a control group receiving no intervention (30 eyes). The control group included patients who were simply monitored for one year without any intervention; those who received treatment at any time were excluded from the study. Inclusion criteria for the CXL group were age between 15 and 35 years, Kmax less than

55 D and a minimum central corneal thickness of 400 μm. Exclusion criteria were any history of ocular surgery or disease other than keratoconus. Soft and hard contact lens wearers discontinued using lenses three days and three weeks, respectively, before the examinations.

Ethics consideration

The proposal of the study was reviewed and approved by the Ethics Committee of Tehran University of Medical Sciences. The study adhered to the tenets of the Declaration of Helsinki at all stages. Written informed consent was obtained from all participants.

Surgical technique

The surgical technique has been described elsewhere.[9] In brief, after local anaesthesia and removing the central 9.0 mm of the corneal epithelium, the lid speculum was removed and 0.1 per cent riboflavin in 20 per cent dextran (Streuli Pharmaceuticals, Uznach, Switzerland) was instilled onto the cornea every three minutes for half an hour. The cornea was then irradiated at 18 mW/cm^2 using the CCL 365 (PESCHKE Meditrade GmbH, Kiefersfelden, Germany). After rinsing the corneal surface, a soft bandage contact lens (Night & Day, Ciba Vision, Duluth, Minnesota, USA) was placed and a drop of levofloxacin was instilled. The post-operative regimen included levofloxacin eye drops four times daily, betamethasone 0.1 per cent and preservative free artificial tears as needed. Follow-up examinations were conducted and the bandage contact lens was removed after complete re-epithelialisation was observed. Upon removal of the lens, levofloxacin was discontinued and betamethasone, four times daily was continued for another week.

Pre- and post-operative examinations

Tests for CS and glare were conducted with and without correction under scotopic conditions (0.5 lux) using the Metrovision MonCv3 (Metrovision, Pérenchies, France) at baseline and at six and 12 months after the procedure and results were compared between the CXL and control groups. All baseline and follow-up examinations were conducted in a clinic room designated for this purpose by the same optometrist, who was masked to group allocation.

To adjust lighting of 0.5 lux, entry of sunlight into the room was completely blocked and after turning on the MonCv3, room light intensity was measured using the Sekonic L-308 DC light meter (Sekonic Corporation, Tokyo, Japan). Patients were seated in the room for 10 to 15 minutes prior to testing to adapt to the lighting conditions.

Psychophysical CS testing was done using Metrovision vertical gratings of sine waves of various spatial frequencies (SFs). With this method, contrast is gradually increased until the patient's subjective response is received and the result is recorded. After testing CS at SF of 0.5 (CS0.5), 1.1 (CS1.1),

	Study group	Baseline	Follow-up		12-month change	p-value*
			6 months	12 months		
CS0.5 (dB)	Cross-linking	14.91 ± 3.30	16.35 ± 2.35	17.00 ± 1.86	2.04 ± 3.96	0.555
	Control	15.75 ± 1.60	16.29 ± 2.37	17.39 ± 2.54	1.69 ± 3.26	
CS1.1 (dB)	Cross-linking	17.61 ± 3.56	18.83 ± 2.19	19.70 ± 2.64	2.04 ± 4.36	0.139
	Control	18.89 ± 2.01	19.39 ± 2.47	20.32 ± 2.52	1.45 ± 2.56	
CS2.2 (dB)	Cross-linking	19.30 ± 1.69	19.83 ± 2.77	20.39 ± 3.01	1.21 ± 2.59	0.313
	Control	20.21 ± 2.51	21.18 ± 2.39	21.79 ± 2.54	1.55 ± 2.77	
CS3.4 (dB)	Cross-linking	18.48 ± 2.48	18.70 ± 2.36	19.83 ± 2.87	1.29 ± 2.29	0.684
	Control	20.07 ± 2.71	20.86 ± 2.81	21.07 ± 2.75	1.00 ± 2.10	
CS7.1 (dB)	Cross-linking	14.87 ± 3.39	16.48 ± 2.91	16.22 ± 4.19	1.45 ± 4.31	0.010
	Control	16.39 ± 4.44	17.39 ± 4.37	19.71 ± 3.39	3.21 ± 4.69	
CS15 (dB)	Cross-linking	7.39 ± 3.54	8.30 ± 2.91	8.65 ± 4.30	1.12 ± 4.63	0.007
	Control	9.04 ± 4.91	9.25 ± 5.03	12.18 ± 3.71	3.03 ± 5.48	

*Inter-group comparison of one-year changes using repeated measures analyses of covariance.

Table 1. One-year changes in scotopic corrected contrast sensitivity in cases treated with accelerated cross-linking compared to untreated cases of progressive keratoconus

	Study group	Baseline	Follow-up		12-month change	p-value*
			6 months	12 months		
CS0.5 (dB)	Cross-linking	15.64 ± 1.55	16.07 ± 1.21	16.50 ± 2.77	0.87 ± 1.60	0.273
	Control	16.75 ± 0.50	17.25 ± 0.50	16.75 ± 0.96	0.10 ± 1.37	
CS1.1 (dB)	Cross-linking	16.93 ± 3.43	17.29 ± 2.76	18.07 ± 3.15	0.87 ± 2.53	0.757
	Control	18.75 ± 1.26	19.75 ± 2.22	19.50 ± 1.73	0.50 ± 1.43	
CS2.2 (dB)	Cross-linking	16.50 ± 3.13	16.64 ± 2.98	18.36 ± 3.85	1.43 ± 3.07	0.967
	Control	19.00 ± 2.71	20.50 ± 3.42	20.00 ± 2.58	1.00 ± 1.05	
CS3.4 (dB)	Cross-linking	15.43 ± 4.60	15.21 ± 3.47	16.93 ± 4.71	0.48 ± 3.96	0.475
	Control	18.25 ± 4.19	19.75 ± 3.40	20.25 ± 3.30	0.40 ± 2.91	
CS7.1 (dB)	Cross-linking	13.00 ± 5.70	13.86 ± 4.26	14.21 ± 6.45	0.04 ± 3.73	0.374
	Control	14.75 ± 2.75	18.00 ± 4.08	17.75 ± 4.92	0.80 ± 4.18	
CS15 (dB)	Cross-linking	5.14 ± 3.39	5.43 ± 3.84	7.14 ± 5.71	0.61 ± 4.27	0.701
	Control	10.25 ± 2.50	11.00 ± 6.63	10.00 ± 6.78	–0.20 ± 4.41	

*Inter-group comparison of one-year changes using repeated measures analyses of covariance.

Table 2. One-year changes in scotopic uncorrected contrast sensitivity in cases treated with accelerated cross-linking compared to untreated cases of progressive keratoconus

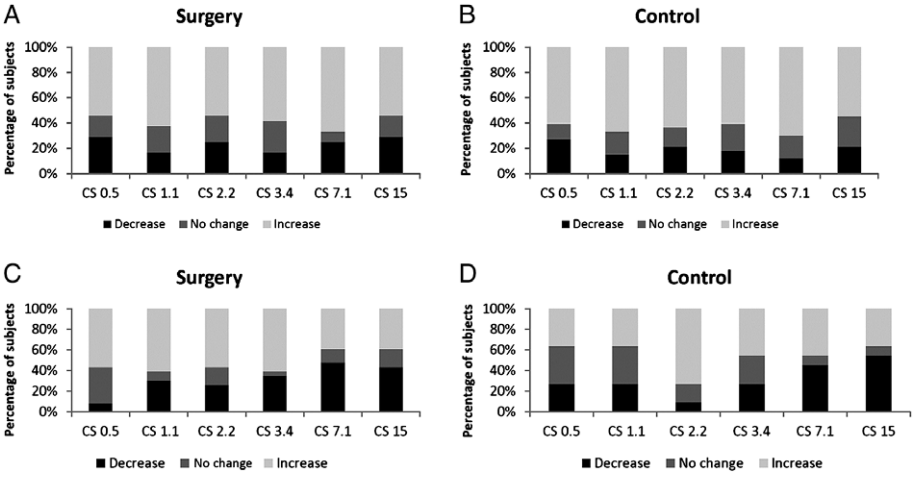

Figure 1. One-year changes in scotopic corrected (A and B) and uncorrected (C and D) contrast sensitivity in cases treated with accelerated cross-linking compared to untreated cases of progressive keratoconus

2.2 (CS2.2), 3.4 (CS3.4), 7.1 (CS7.1) and 15 (CS15) cpd, the device displays the graph of the CS function and registers CS at each SF in the dB unit. Testing was done monocularly at two metres (manufacturer's recommended distance).

For testing glare, we used optotypes with a luminance of 100 cd/m^2 on a dark background while a strong source of white light (luminance = 200,000 cd/m^2) was projected toward the patient to create glare. Displayed optotypes were 15 arcmin, which is equivalent to 0.33 VA. Testing was done monocularly at 2.5 metres. Different optotype arrangements were used for each eye. The final score was recorded as the percentage of correct responses, which was calculated based on the algorithm for each optotype and the distance from the source of glare.

Initially, to test the repeatability, 30 eyes of 30 emmetropic volunteers were examined twice, 30 to 60 minutes apart. All these tests were done by the same optometrist in the same designated room.

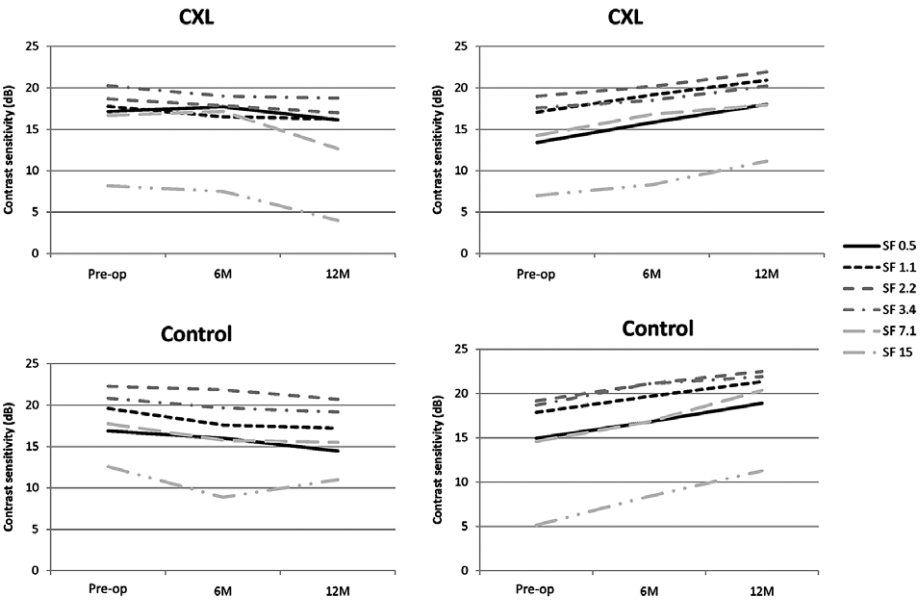

Figure 2. One-year changes of scotopic corrected contrast sensitivity (CS) in subgroups with reduced (left) and improved (right) CS after accelerated cross-linking compared to untreated cases. Changes were statistically significant between the two groups in spatial frequencies of 7.1 and 15 cycles per degree.

Statistical analyses

One-year changes in the CXL group were compared to the control group using repeated measures analysis of covariance (RM ANCOVA). In the analyses, adjustments were made for age and the correlation between fellow eyes for binocular cases. The level of significance was set at 0.05.

RESULTS

At the end of one year, 26 eyes in the CXL group (86.7 per cent) and 30 eyes in the control group (100.0 per cent) completed CS and glare tests; 54.4 per cent of patients in the CXL group and 50.0 per cent of those in the control group were male. As the study was non-randomised, baseline parameters were compared between the two groups. The mean age of the participants was 24.32 ± 5.17 years in the CXL group and 30.93 ± 7.43 in the control group ($p < 0.001$); since the difference was statistically significant, the effect of age was controlled as a covariate in all analyses. In the CXL and control groups, baseline Kmax was 46.53 ± 3.31 and 47.24 ± 3.46 D, baseline Kmin was 43.68 ± 2.67 and 44.56 ± 2.19 D, baseline distance VA was 0.15 ± 0.16 and 0.13 ± 0.18 logMAR and uncorrected distance vision (UDV) was 0.45 ± 0.41 and 0.51 ± 0.40 logMAR, respectively (all $p > 0.050$). One year after CXL, mean reduction of Kmax and Kmin was 0.48 ± 0.10 D and 0.02 ± 0.89 D, respectively. Also, VA and UDV improved to 0.12 ± 0.14 logMAR and 0.39 ± 0.36 logMAR in these two groups, respectively. CXL-induced haze was observed in four cases after one year.

In the repeatability analyses, the within-subject standard deviation (Sw) was 0.86, 0.75, 0.68, 0.64, 0.80 and 1.48 dB for SF of 0.5 to 15 cpd, respectively, and precision of measurement (mean difference of two measurements ± 1.96 × Sw) was 3.37, 2.96, 2.68, 2.49, 3.15 and 1.00 dB, respectively.

Table 1 compares corrected scotopic CS and Table 2 compares uncorrected

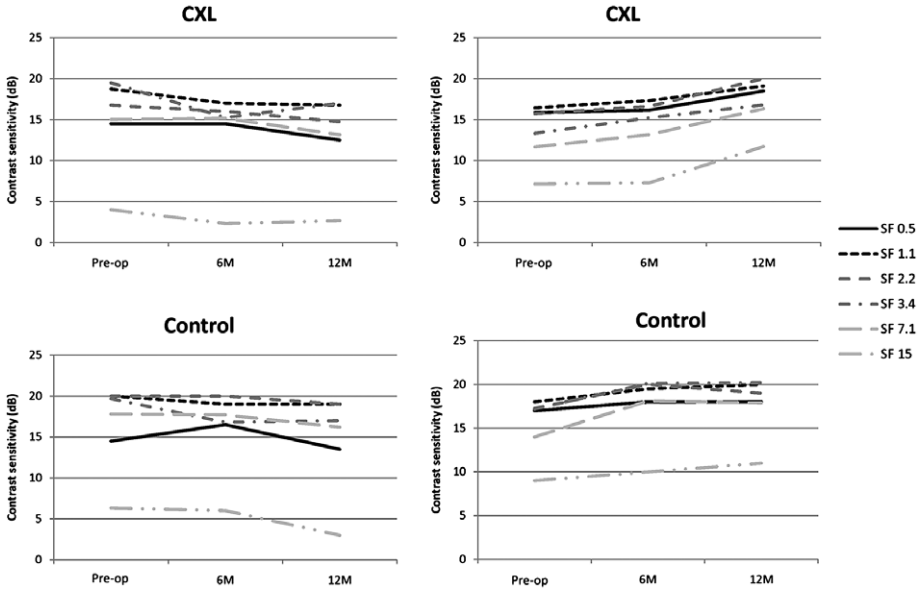

Figure 3. One-year changes of scotopic uncorrected contrast sensitivity (CS) in subgroups with reduced (left) and improved (right) CS after accelerated cross-linking compared to untreated cases.

scotopic CS in different SFs between the two groups. Comparison of changes in different parameters showed no significant differences between the two groups (all $p > 0.050$) except for corrected CS7.1 ($p = 0.010$) and corrected CS15 ($p = 0.007$). The percentage of subjects with increase, decrease and stability of corrected CS and uncorrected CS are illustrated in Figure 1.

RM ANCOVA showed that among corrected CS indices, only corrected CS7.1 and CS15 were correlated to surgery and baseline values and at both SFs, surgery lead to reduced CS in cases with better baseline CS and improved CS in cases with lower CS (all $p < 0.050$) (Figure 2). At one year, uncorrected CS in all SFs were correlated only to baseline CS (all $p < 0.001$) and not surgery (Figure 3).

Also, as demonstrated in Figure 4, uncorrected glare and corrected glare had similar trends over the one year period and surgery had no significant impact on either parameter (all $p > 0.050$). Both parameters were only influenced by baseline values (both $p < 0.001$); cases with higher baseline glare showed reduced glare at one year and vice versa.

DISCUSSION

In this report, we aimed to explore the effect of accelerated CXL on CS and glare in scotopic conditions and related factors. As age can influence scotopic CS, especially in SFs less than 1.2 cpd, and CS tends to reduce at older age[10] and since the CXL group in this study was younger than the control group, age was controlled for in the analyses, as a confounding factor. After controlling for age, our one-year follow-up study showed that CXL only affected corrected CS in SFs higher than 7.0 cpd and reductions were observed only in cases with a mean baseline scotopic CS more than 16 dB but in those with a lower mean baseline, CXL led to improved CS. CXL had no effect on uncorrected CS or on uncorrected or corrected glare and similar to the control group, those with better baseline values showed a reduction, while those with worse baseline values showed improvement.

Previous studies indicate that HOAs are reduced at one year after standard CXL[11,12] and tend to remain stable afterwards in the long-term.[6] Also, photopic CS is improved after surgery.[5] Although CS in normal cases (1.80 ± 0.13 cpd) is better than in keratoconic patients,[1] no information is available about CS improvement after CXL compared to normal eyes.

An important point is how CS and glare change under low light conditions, when pupil dilation leads to increased aberrations. In the study by Vinciguerra and colleagues,[13] at one year after CXL, there was a greater reduction in coma and spherical aberrations in the 7.0 mm pupil (0.95 and 0.82 μm) compared to the 3.0 mm pupil (0.32 and 0.09 μm). The change in coma was not statistically significant though, and CS changes were not examined. Reduced contrast in low light conditions is more pronounced compared to photopic conditions because rod photoreceptors require more contrast difference for target detection compared to cones (20 versus one per cent).[14] Disability glare occurs under certain conditions, such as driving in the night. Intraocular light scattering (straylight), which is an optic phenomenon independent of neurophysiology, results in reduced retinal image contrast.[15] Therefore, any type of inhomogeneity in the ocular media can exacerbate the scattering. As a result, a more regular cornea after CXL is expected to be associated with improved CS and reduced disability glare.

As the parameters in our study changed in different directions, supplementary analyses were done separately in each group. In these analyses, we observed that accelerated CXL can cause a reduction in scotopic

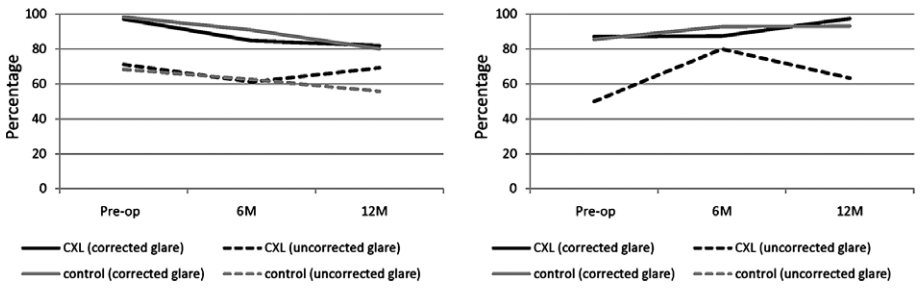

Figure 4. One-year changes of corrected and uncorrected glare in subgroups with reduced (left) and improved (right) glare after accelerated cross-linking compared to untreated cases. None of the cases in the control group showed increased uncorrected glare.

corrected CS in SFs higher than 7.0 cpd in cases with better baseline values of this index. This can be due to the stronger influence of scattering on higher SFs such as its effect on VA. Mathematically, higher SFs are closer to VA[16] and studies indicate that cases with VA better than 6/12 can experience reduced vision after CXL[17] and the reduction in corrected CS at higher SFs can be in line with the same effect.

A limitation of this study is being non-randomised and the possibility of unknown factors influencing results. Overall, we can say that changes in uncorrected CS and glare in keratoconic patients and also after accelerated CXL only depend on baseline values and there can be improvement in cases with worse baseline values and vice versa. Changes in corrected glare have the same pattern but changes in corrected CS at higher SFs were affected by surgery, such that surgery resulted in reduced CS in cases with better baseline values (CS15 >8 dB and CS7.1 >16 dB) and vice versa.

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