Original research

Mesopic visual quality after accelerated corneal cross linking: A 12-month follow-up study

Hassan Hashemi, Soheila Asgari

Noor Ophthalmology Research Center, Noor Eye Hospital, Tehran, Iran
Noor Research Center for Ophthalmic Epidemiology, Noor Eye Hospital, Tehran, Iran
Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

Available online 21 October 2016

Abstract

Purpose: To determine the 1-year changes of mesopic higher order aberrations (HOAs) and contrast sensitivity (CS) after accelerated corneal cross linking (CXL) in progressive keratoconus.

Methods: In this prospective case series, 70 eyes of 62 keratoconic patients underwent accelerated CXL (18 mW/cm², 5 min). HOAs and CS were measured using the OPD Scan III and CSV-1000 CS test charts under mesopic conditions before and 6 and 12 months after CXL.

Results: At 1 year, logarithmic mesopic CS in spatial frequencies of 3, 6, 12, and 18 cycles per degree (CPD) had increased by 0.05 ± 0.29 (P = 0.029), 0.04 ± 0.88 (P = 0.012), 0.27 ± 0.46 (P = 0.172), and 0.06 ± 0.22 (P = 0.020), respectively. The decrease in ocular HOAs (0.10 ± 0.69 μm, P = 0.992) [coma (0.08 ± 1.01 μm, P = 0.613), trefoil (0.03 ± 0.37 μm, P = 0.659), and spherical aberration (SA) (0.10 ± 0.59 μm, P = 0.743)] and corneal HOAs (0.40 ± 1.69 μm, P = 0.874) [coma (0.39 ± 1.59 μm, P = 0.401), trefoil (0.33 ± 2.16 μm, P = 0.368), and SA (1.27 ± 1.14 μm, P = 0.354)] were not statistically significant. The correlations between mesopic CS and HOAs were weak before and after CXL.

Conclusion: One year after accelerated CXL, CS significantly improved, but changes in HOAs were statistically insignificant. CS changes were independent of HOAs.

Introduction

Collagen corneal cross linking (CXL) is a novel treatment that arrests the progression of keratoconus and strengthens the cornea through the creation of new covalent bonds. Studies have reported halting disease progression and even improvement of visual acuity and refraction after standard CXL (3 mW/cm², 30 min). With the accelerated protocol (18 mW/cm², 5 min), patient treatment and irradiation time is reduced, total energy dose delivered to the cornea remains the same, and comparable efficacy can be achieved.

Since the quality of vision and visual function are important parts of postoperative visual rehabilitation, evaluation of the changes of contrast sensitivity (CS) and aberrations is of great importance. In terms of visual quality, Lamy et al. reported that photopic CS measured with the Pelli–Robson test improved after standard CXL. For changes in higher order aberrations (HOAs) after CXL, some long-term studies have reported a decrease, and some suggested no significant change after a 1 year follow-up. Nonetheless, studies regarding visual quality in low light conditions after CXL are limited.

Conflict of interest: The authors have no financial or proprietary interest in a product, method, or material described herein.
Funding source: None.
Corresponding author.
E-mail address: soheilaasgari@gmail.com (S. Asgari).
Peer review under responsibility of the Iranian Society of Ophthalmology.
In this study, we aimed to evaluate the effect of accelerated CXL (18 mW/cm², 5 min) on mesopic CS as a function of visual quality. Moreover, we report the changes in corneal and total aberrations measured with the OPD Scan III (Nidek, Japan).

**Methods**

This prospective case series study was performed on 70 eyes of 62 patients who were selected through consecutive sampling. Inclusion criteria were a diagnosis of progressive keratoconus (at least 1.0 diopter (D) increase in maximum keratometry (Kmax), manifest cylinder, or spherical equivalent (SE) refraction, or loss of at least 2 lines of best corrected visual acuity in the 12 months before the operation), age between 15 and 35 years, keratometry less than 55.0 D, and a central corneal thickness ≥450 μm. The use of hard and soft contact lenses was stopped 3 weeks and 3 days before CXL, respectively. Patients with any history of eye surgery or eye disease were excluded from the study.

The Institutional Review Board of Noor Ophthalmology Research Center reviewed the protocol and approved the study. Written informed consent was obtained from all participants, and the tenets of the Declaration of Helsinki were followed in all stages of the study.

**Surgical technique**

After local anesthesia with 0.5% proparacaine hydrochloride, the epithelium of the central 9 mm of the cornea was manually removed. Then riboflavin drops (0.1% in 20% dextran, Streuli Pharma, Uznach, Switzerland) were instilled on the corneal surface every 3 min for 30 min. After that, the cornea was irradiated (370 nm, 18 mW/cm²) for 5 min using the UVX system (PESCHKE Meditrade GmbH, Germany) at a distance of 5 cm. At the end of this stage, the corneal surface was irrigated with sterile balanced saline solution, a soft bandage contact lens (Night & Day, Ciba Vision, Duluth, GA) was placed on the eye, and levofloxacin eye drops were instilled.

The postoperative regimen included levofloxacin eye drops four times daily, betamethasone 0.1%, and preservative free artificial tears (Hypromellose) as needed. The patients were examined on days 1 and 3 after CXL. The contact lens was removed after the epithelium was healed. Levofloxacin was discontinued after removing the lens, and betamethasone was continued four times daily for 1 week. If the epithelium was not healed, daily visits continued until complete healing was observed.

We used CSV-1000 grating charts (VectorVision, Inc., Greenville, OH) to measure CS under mesopic conditions. For this purpose, daylight was blocked from the test room, and the room illumination was measured by a light meter (Sekonic L-308DC, Japan) and set at 15 lux. The patient stayed in the room for 15 min before the test to adapt to the illumination condition of the room. Monocular CS was measured with best correction in physiologically dilated eyes. The test was performed without glare at a distance of 4 m.

Also, non-dilated aberrometry was performed using the OPD Scan III, which also provided measurements of Kmax and corneal asphericity (Q value). Ocular and corneal HOAs including coma, trefoil, spherical aberration (SA), and total HOAs were evaluated under mesopic conditions. All tests were done at baseline and at 6 and 12 months after CXL.

**Statistical analysis**

The trend of the changes of the indices was evaluated with repeated measures analysis of covariance to adjust for the correlation between fellow eyes. Linear regression analysis was used to assess the contribution of each type of aberration to the total aberrations. Pearson correlation coefficients were determined to examine the correlations between CS and aberrations. In the analyses, CS values in log units were used. The level of significance was considered 0.05.

**Results**

Seventy eyes of 62 keratoconus patients were enrolled in the study, 68 (97.1%) and 67 eyes (95.7%) completed 6 months and 1 year follow-up visits, respectively. Finally 65 eyes (92.9%) had 2 follow-up data. Eight patients had bilateral keratoconus. The mean age of the participants was 24.80 ± 3.81 years, and 69.5% of them were male. At 12 months, mean uncorrected distance visual acuity changed from 0.33 ± 0.41 to 0.38 ± 29 logMAR (P = 0.548), and mean corrected distance visual acuity changed from 0.05 ± 0.06 to 0.15 ± 0.19 logMAR (P = 0.300). In manual refraction, 48.2% of cases had scissor reflex before CXL, and this was reduced to 39.4% (P = 0.045) at 12 months after the procedure. Mean Kmax reduced from 46.94 ± 3.79 D to 45.48 ± 2.80 D (P = 0.032). Mean asphericity (Q value) changed from −0.07 ± 1.75 to −0.20 ± 1.21 (P = 0.049). At the end of the 6th month, 7 eyes (10%) had corneal haze, but at 1 year, no case of haze was observed upon slit-lamp exams.

The 12-month increases in the log-C3 and log-C6 were statistically significant (P = 0.029 and P = 0.012, respectively). The change in log C12 was not statistically significant despite the increasing trend (P = 0.172). Log- C18 showed a significant improvement (P = 0.020) (Fig. 1).

Table 1 summarizes results of total ocular and corneal HOAs. The decrease in ocular HOAs (0.10 ± 0.69 μm, P = 0.992) including coma (0.08 ± 1.01 μm, P = 0.613), trefoil (0.03 ± 0.37 μm, P = 0.659), and SA (0.10 ± 0.59 μm, P = 0.743) were not statistically significant. Also, the decreases in corneal HOAs (0.40 ± 1.69 μm, P = 0.874) including coma (0.39 ± 1.59 μm, P = 0.401), trefoil (0.33 ± 2.16 μm, P = 0.368), and SA (1.27 ± 1.14 μm, P = 0.354) were not statistically significant.

Pearson coefficients (r) for the correlation between CS and ocular and corneal HOAs are presented in Table 2. Coefficients were less than 0.4 in all cases and statistically insignificant.
CXL is the treatment that stops the progression of corneal protrusion and steepening in keratoconus. In this procedure, Ultraviolet (UV) irradiated riboflavin stimulates the formation of intra and inter-fibrillar covalent bonds in the corneal stroma which strengthen the cornea and lead to flattening and regularization of the cornea and vision improvement. According to the findings of our study, during 12 months after CXL, mesopic CS improved while HOAs remained unchanged. The safety and efficacy of accelerated CXL, as compared to the standard approach, has been demonstrated. In terms of vision and refraction outcomes and its effect on corneal biomechanics, the two protocols have shown comparable results, and accelerated CXL has been capable of halting the progression of the disease in keratoconus patients.

The studies on CS changes after CXL are limited. Lamy et al reported an improvement in CS after the standard method. Although we used a different approach and applied accelerated CXL, a similar improvement in CS was observed. Since the cornea is regular as an effect of surgery, CS in low light conditions is expected to be better.

Before CXL, corneal coma was the dominant corneal HOA (β = 1.08) in our patients, which is in agreement with the study by Pantanelli et al. The HOA that showed the most change as a result of CXL was SA followed by coma, and neither one was statistically significant. In the study by Caporossi et al at 3 months after CXL, the mean decrease in total HOAs and coma was 0.5 mm and 0.3 mm, respectively, compared to 0.68 mm and 0.4 mm, respectively, in our study. While the mean changes in these two studies may seem comparable, they were statistically significant in their study and insignificant in ours. The variance is not reported by Caporossi et al, but it was high in our study. In addition to different follow-up times, the wide range of the variance in our sample can be responsible for the lack of a significant change.

### Table 1

| Ocular and corneal higher order aberrations (HOAs; μm) at baseline and at 6 and 12 months after accelerated corneal cross linking (CXL). |
|---|---|---|---|---|
| | Before CXL | After CXL | 6 months | 12 months |
| Ocular Total HOAs | 1.55 ± 0.84 | 1.56 ± 0.85 | 1.46 ± 0.81 | 0.992 |
| Coma | 1.24 ± 1.07 | 1.18 ± 0.73 | 1.15 ± 1.11 | 0.643 |
| Trefoil | 0.83 ± 0.53 | 0.82 ± 0.53 | 0.79 ± 0.48 | 0.659 |
| SA | 0.29 ± 0.23 | 0.21 ± 0.19 | 0.37 ± 0.71 | 0.524 |
| Corneal Total HOAs | 3.85 ± 6.78 | 3.86 ± 6.65 | 3.17 ± 4.22 | 0.874 |
| Coma | 2.68 ± 3.00 | 2.51 ± 1.48 | 2.30 ± 2.38 | 0.401 |
| Trefoil | 1.73 ± 4.75 | 1.79 ± 3.24 | 1.40 ± 2.55 | 0.368 |
| SA | 1.86 ± 7.16 | 1.90 ± 3.63 | 0.63 ± 0.86 | 0.354 |

*Comparing preoperative to 12-month changes in measurements. HOAs: higher order aberrations; SA: spherical aberration.

### Discussion

CXL is the treatment that stops the progression of corneal protrusion and steepening in keratoconus. In this procedure, Ultraviolet (UV) irradiated riboflavin stimulates the formation of intra and inter-fibrillar covalent bonds in the corneal stroma which strengthen the cornea and lead to flattening and regularization of the cornea and vision improvement. According to the findings of our study, during 12 months after CXL, mesopic CS improved while HOAs remained unchanged. The safety and efficacy of accelerated CXL, as compared to the standard approach, has been demonstrated. In terms of vision and refraction outcomes and its effect on corneal biomechanics, the two protocols have shown comparable results, and accelerated CXL has been capable of halting the progression of the disease in keratoconus patients.

The studies on CS changes after CXL are limited. Lamy et al reported an improvement in CS after the standard method. Although we used a different approach and applied accelerated CXL, a similar improvement in CS was observed. Since the cornea is regular as an effect of surgery, CS in low light conditions is expected to be better.

Before CXL, corneal coma was the dominant corneal HOA (β = 1.08) in our patients, which is in agreement with the study by Pantanelli et al. The HOA that showed the most change as a result of CXL was SA followed by coma, and neither one was statistically significant. In the study by Caporossi et al at 3 months after CXL, the mean decrease in total HOAs and coma was 0.5 mm and 0.3 mm, respectively, compared to 0.68 mm and 0.4 mm, respectively, in our study. While the mean changes in these two studies may seem comparable, they were statistically significant in their study and insignificant in ours. The variance is not reported by Caporossi et al, but it was high in our study. In addition to different follow-up times, the wide range of the variance in our sample can be responsible for the lack of a significant change.

### Table 2

Pearson correlation coefficient between the logarithmic mesopic contrast sensitivity (CS) and corneal higher order aberrations (HOAs) before and after accelerated corneal cross linking (CXL).

| | Before CXL | 12 months after CXL |
|---|---|---|
| Total HOAs | C3 | C6 | C12 | C18 | C3 | C6 | C12 | C18 |
| Coma | −0.40 | −0.34 | −0.38 | −0.40 | −0.35 | −0.04 | −0.09 | −0.10 |
| Trefoil | −0.35 | −0.17 | −0.20 | −0.19 | −0.27 | −0.04 | −0.08 | −0.11 |
| Spherical aberration | −0.11 | −0.04 | −0.10 | −0.11 | −0.19 | −0.02 | −0.04 | −0.04 |

None of the correlations were statically significant (all P > 0.050).

CXL: Corneal cross linking
HOAs: Higher order aberrations
In our study, the mean decrease of corneal HOAs was much more than ocular HOAs, indicating that the cornea and not the underlying layers was affected by CXL, which is in contrast to a study by Vinciguerra et al who reported a substantial decrease in ocular HOAs and believed that the decrease of the total aberrations indicated the effect of CXL on the corneal posterior surface. On the other hand, comparison of the 6-month and 1-year decrease of ocular and corneal aberrations in 3 and 5 mm pupils in the study showed that despite the significant decrease in ocular versus corneal aberrations, the decrease in the absolute value of corneal aberrations was more than ocular aberrations, which is clinically important. Also, the difference in the preoperative severity of the disease can be an important reason for the different results in these two studies (Kmaxour study = 46.94 and Kmaxviniguerra = 48.08). However, in a report by Greenstein et al, the changes of aberrations measured by the Pentacam were similar to our findings with no significant change.

Okamoto et al showed that CS decreases in keratoconus patients due to increases in HOAs. Their conclusion is based on the significant correlation between the letter-CS test and coma and SA, but all Pearson’s correlation coefficients in Okamoto study were weak between CS at different spatial frequencies and corneal HOAs (< 0.40). Since the value of r is a better indicator of the strength of correlations than the level of significance, it is not very easy to comment on the effect of HOAs on CS. In our study, CS seemed independent of HOAs. The reason for the significant improvement of mesopic CS and insignificant improvement of HOAs might be that CS is affected by neural factors in addition to optical factors while HOAs exclusively show optical aberrations. Another reason could be the high variance in aberration indices and the need for a larger sample size to show the significance of changes. On the other hand, CS appeared independent of HOAs in short-term studies such as ours and the study by Wisse et al, but the two parameters were related in a long-term study, therefore, the effect of HOAs on CS could develop in the long run.

The study has several limitations. Due to large standard deviation, the sample size is small. Also, we did not have a control group of eyes receiving the standard protocol. Such data would enable us to perform a more comprehensive assessment of the effect of accelerated CXL on visual quality. Another limitation was the inclusion of eyes with cornal haze (7 eyes) in the analysis that may affect the measurements, although the number of eyes in this subgroup was low. In conclusion, according to our findings, accelerated CXL improved mesopic CS without any significant change in HOAs. In light of the observed trend in the studied parameters, longer follow-ups are necessary for further evaluations.

References

1. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003;135(5):620–627.
2. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. J Cataract Refract Surg. 2003;29(9):1780–1785.
3. Hashemi H, Seyedian MA, Miraftab M, Fotouhi A, Asgari S. Corneal collagen cross-linking with riboflavin and ultraviolet A irradiation for keratoconus: long-term results. Ophthalmology. 2013;120(8):1515–1520.
4. Glikà M, Labirìs G, Giarmoukakis A, Koutsogianni A, Koutsogianni A, Kozobolis V. Evaluation of corneal hysteresis and corneal resistance factor after corneal cross-linking for keratoconus. Graefes Arch Clin Exp Ophthal mol. 2012;250(4):565–573.
5. Golich Y, Markovich AL, Barkana Y, et al. Clinical and corneal biomechanical changes after collagen cross-linking with riboflavin and UV irradiation in patients with progressive keratoconus: results after 2 years of follow-up. Cornea. 2012;31(6):609–614.
6. Hashemi H, Fotouhi A, Miraftab M, et al. Short-term comparison of accelerated and standard methods of corneal collagen crosslinking. J Cataract Refract Surg. 2015;41(3):533–540.
7. Hashemi H, Miraftab M, Seyedian MA, et al. Long-term results of an accelerated corneal cross-linking protocol (18 mW/cm²) for the treatment of progressive keratoconus. Am J Ophthalmol. 2015;160(6):1164–1170.
8. Lamy R, Netto CF, Reis RG, et al. Effects of corneal cross-linking on contrast sensitivity, visual acuity, and corneal topography in patients with keratoconus. Cornea. 2013;32(5):591–596.
9. Vinciguerra R, Romano MR, Camesasca FI, et al. Corneal cross-linking as a treatment for keratoconus: four-year morphologic and clinical outcomes with respect to patient age. Ophthalmology. 2013;120(5):908–916.
10. Ghanem RC, Santinigrò MR, Berti T, Netto MV, Ghanem V. Topographic, corneal wavefront, and refractive outcomes 2 years after collagen cross-linking for progressive keratoconus. Cornea. 2014;33(1):43–48.
11. Wisse RP, Gadiot S, Soetens N, Godefrooij DA, Imhof SM, van der Leij A. Higher-order aberrations 1 year after corneal collagen cross-linking for keratoconus and their independent effect on visual acuity. J Cataract Refract Surg. 2016;42(7):1046–1052.
12. Wollensak G. Crosslinking treatment of progressive keratoconus: new hope. Curr Opin Ophthalmol. 2006;17(4):356–360.
13. Jankov II MR, Jovanovic V, Nikolic L, Lake JC, Kymionis G, Coskunseven E. Corneal collagen cross-linking. Middle East Afr J Ophthal mol. 2010;17(1):21–27.
14. Wollensak G, Wilsh M, Spoerl E, Seiler T. Collagen fiber diameter in the rabbit cornea after collagen crosslinking by riboflavin/UNA. Cornea. 2004;23(1):503–507.
15. Saffarian L, Khakshoor H, Zarei-Ghanavati M, Esmaily H. Corneal crosslinking for keratoconus in Iranian patients: outcomes at 1 year following treatment. Middle East Afr J Ophthalmol. 2010;17(4):365–368.
16. Pantanelli S, Macrae FA, Jeon YC. Characterizing the wave aberration in eyes with keratoconus or penetrating keratoplasty using a highdynamic range wavefront sensor. Ophthalmology. 2007;114(11):2013–2021.
17. Caporossi A, Biaocchi S, Mazzotta C, Traversi C, Caporossi T. Parasurgical therapy for keratoconus by riboflavin-ultraviolet type A rays induced cross-linking of corneal collagen: preliminary refractive results in an Italian study. J Cataract Refract Surg. 2006;32(5):837–845.
18. Vinciguerra P, Albe E, Tracza S, et al. Refractive, topographic, tomographic, and aberrometer analysis of keratoconic eyes undergoing corneal crosslinking. Ophthalmology. 2009;116(3):369–378.
19. Greenstein SA, Fry KL, Hersh MJ, Hersh PS. Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. J Cataract Refract Surg. 2012;38(2):292–302.
20. Okamoto C, Okamoto F, Samejima T, Miyata K, Oshika T. Higher-order wavefront aberration and letter-contrast sensitivity in keratoconus. Eye (Lond). 2008;22(12):1488–1492.
21. Elliott DB. Contrast sensitivity decline with ageing: a neural or optical phenomenon? Ophthalmic Physiol Opt. 1987;7(4):415–419.