Refractive Changes After Two Years Accelerated Corneal Cross-Linking in Patients with Keratoconus

Matilde Mora, MD
Shirley Rosenstiehl, MD
Hernan Andres Rios, MD
Marcela Lonngi, MD
From Fundación Oftalmológica Nacional, Colombia
Universidad del Rosario, Colombia

Funding: None
Proprietary/financial interest: None

Corresponding author: Matilde Mora, MD
Fundación Oftalmológica Nacional
Calle 50 #13-30 Bogota,110231 Colombia
Email: lmmora@fon.org.co

Date of submission: 16/07/2017 **Date of Approval:** 21/08/2017

ABSTRACT

Purpose: To describe the visual and topographical changes after accelerated corneal collagen cross-linking (ACXL) in keratoconus-affected eyes.

Methods: Clinical records of patients with keratoconus-affected eyes that underwent ACXL treatment and had 24 months of follow-up were reviewed. Data regarding demographics, visual acuity (VA), refraction and Sheimpflug values before and post ACXL were analyzed. We included patients with keratoconus older than 12 years old, with corneal thickness greater than 400 microns and steepest keratometry <60 diopters by Sheimpflug (Pentacam), with reported uncorrected distant visual acuity (UDVA), manifest refraction and best-corrected visual acuity (BCVA) evaluation pre ACXL and 24 months after surgery. The exclusion criteria were: history of ocular trauma, anterior segment surgery, retinal detachment or any type of maculopathy.

Results: 21 eyes were included. Mean age was 27 years. Mean uncorrected distant VA (UDVA) before the procedure was 1.01 logMAR (20/200 Snellen) and after 24 months improved significantly to 0.62 logMAR (20/83 Snellen) with a p value of 0.005. No statistical significant difference was found between preoperative and postoperative refractive, keratometric and pachymetric data. Induced astigmatism value was -1.11 D (range 0.13 D – 2.28 D).

Conclusions: ACXL is a technique to prevent the progression of keratoconus, however refractive and VA changes could be expected after procedure. The observed changes must be considered when performing the procedure together with refractive surgery.

Keywords: collagen cross-linking, refractive changes, induced astigmatism, keratoconus.

INTRODUCTION

A few decades ago, the treatment of choice for individuals diagnosed with keratoconus had no effect on the natural history of the disease, and in many cases patients with advanced disease required corneal transplantation for visual rehabilitation. In 2012, accelerated corneal collagen crosslinking (ACXL) emerged as a variation of conventional Dresden Crosslinking protocol for the stabilization of the cornea in patients with progressive keratoconus[1,2] and its main characteristic is its duration time of only 14 minutes. It is based on a theory that the decreased biomechanical strength of the cornea in eyes with keratoconus may be related to a decrease in intra and inter-fibrillar crosslinks within collagen fibers.[3] The current technique involves the use of riboflavin (vitamin B2), which is exposed to a measured dose of longer wavelength ultraviolet A light (UVA) radiation. Riboflavin plays two roles in corneal collagen crosslinking, acting both as a photosensitizer and absorbing ultraviolet radiation to limit the depth of the treatment effect. In the photosensitizing process, free radicals are produced, which catalyse a reaction resulting in the formation of covalent bonds between the collagen molecules and microfibrils[4,5], leading to increased rigidity and biomechanical stabilization of the cornea.[5,6]

The standard corneal CXL procedure was conceived in Dresden in 2002.[5] In this procedure, UVA illumination of 3 mW/cm^2 irradiance with 370nm light source was used to irradiate riboflavin instilled cornea for 30 min. After 30 min, a cumulative dose of 5.4 J/cm^2 was used to treat the corneal ectasia.[5] Numerous studies have highlighted the efficacy and safety of the standard corneal CXL treatment as a corneal stabilizing procedure;[5,7-11] however, ACXL is gaining popularity for better or same outcomes with a shorter treatment duration. It uses higher energy settings (up to an irradiance of 30 mW/cm^2) compared with that used in the standard corneal CXL treatment (irradiance of 3 mW/cm^2). This enables a shortening of the treatment duration from 30 minutes to as little as 7 minutes while maintaining the total radiant exposure (5.4 J/cm^2).[2,12-14]

Nowadays, there is a trend to perform crosslinking associated with surface ablation procedures in order to obtain refractive results in the same surgical time.[15] Nevertheless, not taking into account the changes on the sphere and cylinder that could be generated by corneal CXL procedure means that it could result in unpredictable refractive outcomes. There are few reports regarding the efficacy and stability of ACXL treatment[16], and even more important is the lack of evidence about corneal refractive changes after this procedure.

METHODS

This is a retrospective observational clinical record review of 21 eyes of twelve keratoconus patients that adhered to the Declaration of Helsinki and was approved by an Institutional Review Board. The clinical records of the patients with keratoconus undergoing ACXL treatment by one surgeon (MM), between June 2012 and December 2013 were reviewed. We included patients with keratoconus older than 12 years old, with corneal thickness greater than 400 microns and steepest keratometry <60 diopters by Sheimpflug (Pentacam), with reported uncorrected distant visual acuity (UDVA), manifest refraction and best-corrected visual acuity (BCVA) evaluation pre ACXL and 24 months after surgery. The exclusion criteria were: history of ocular trauma, anterior segment surgery, retinal detachment, or any type of maculopathy. All eyes were treated under ACXL, conducted under sterile conditions as follows: the patient's eye was anesthetized with proparacaine hydrochloride 0.5% (Alcaine®). An 8-mm diameter area of the corneal epithelium was removed by using 50% alcohol for 20 seconds to allow better diffusion of riboflavin into the corneal stroma. After epithelial removal, isotonic eye drops of riboflavin 0.1% hydroxypropyl methyl cellulose (VibeX Rapid®) was applied every 2 minutes during 10 minutes. The UVA irradiation was performed using an optical system (Avedro®) with a continuous wave light source consisting of an array of UV diodes (7.2 mJ). Irradiance was performed for 4 minutes at 30 mW/cm^2 during the period of UVA exposure. At the end of the procedure, a silicone-hydrogel bandage contact lens was applied and left in place until full corneal reepithelialization was complete, typically between 2-3 days. Postoperative management included tobramycin 0.3% and dexamethasone 0.1% ophthalmic suspension every eight hours for 2 to 3 weeks and sodium hyaluronate 0.4% eye drops every 2 hours for al least one month. Pain was managed with oral combination of acetaminophen 500 mg and codeine 8mg. Ultraviolet (UV) light protection was required with sunglasses for at least 6 months in the postoperative period.

UDVA, manifest refraction, BCVA, gained lines of visual acuity and Sheimpflug (Pentacam) data including steep keratometry (Ksteep), flat keratometry (Kflat), average keratometry reading (Km), corneal induced astigmatism (Kcyl-i), pachymetry and crystalline density (CD), before the ACXL and at 24 months visit were extracted from charts and analyzed. For the induced astigmatism the Fourier analysis was used.[1] Pre-ACXL and post-ACXL data were recorded using the Scheimpflug (Pentacam). Snellen visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) units. T student test was used for the paired samples and Wilcoxon for non-parametric samples, a p value of <0.05 was considered significant. Statistical analysis was performed using SPSS ver 21 (ser. 572110343).

RESULTS

21 eyes of twelve patients (10 females, 2 males) were included in the study. Mean patient age was 27 years (range: 12–46 years) **(table 1)**. All patients had a history of allergic conjunctivitis. Mean UDVA before the procedure was 1.01(SD± 0.55) logMAR (20/200 Snellen) and after 24 months improved significantly to 0.62 (SD± 0.30) logMAR (20/83 Snellen) with a p value of 0.005. The UDVA improved in 11 eyes (52.3%) with a range of gain lines between 1 and 5 lines. There was loss of vision lines in two eyes (9.5%); it was

DEMOGRAPHIC PATIENT DATA	
Number of eyes	21
Number of patients	12
Mean age (SD)	27 (±11)
Sex F:M	10:2
Follow-up, months	24

Tabla 1

found that corneal haze developed in these two cases. 9 eyes (80%) with preoperative visual acuity of 20/200 or worse had an average gain of 4 vision lines at 24 months. Mean BCVA before ACXL treatment was 0.18 (SD±0.15) logMAR (20/30 Snellen) and after 24 months was 0.22 (SD±0.12) logMAR (20/33 Snellen). BCVA remained unchanged in 5 eyes (23.8%), there was an improvement of 4 lines of vision in 8 eyes (38%) and a loss of 2 lines of vision in 2 eyes (9.5%) was found.

The crystalline density was measured with Pentacam, the mean preoperatory CD was 7,93% (n = 17 eyes) SD ± 0,86 and postoperatory mean was 7,94 % (n = 17 eyes) SD ± 0,74.

No statistical significant difference was found between the preoperative and postoperative refractive, keratometric and pachymetric data in the analyzed eyes, (tables 2 and 3). The study found that mean induced astigmatism was -1.11 D (SD± 0.63 D) with a range of 0.13 D – 2.28 D.

VISUAL AND REFRACTIVE OUTCOMES PRESURGERY AND POSTSURGERY DEMOGRAPHIC PATIENT DATA			
UDVA, logMAR (SD)	1.01(±0.55)	0.62(±0.30)	0.005
CDVA, logMAR (SD)	0.18(±0.15)	0.22(±0.12)	0.37
Sphere (SD)	-2.49 (±4.02)	-3.55 (±4.47)	0.546
Cylinder (SD)	-3.01 (±2.02)	-1.45 (±3.59)	0.291
MGLVA* UDVA	Baseline	2.29	-
MGLVA* CDVA	Baseline	0.11	-

Tabla 2 *Mean Gain Lines Visual Acuity

PATIENT TOPOGRAPHICAL DATA PRESURGERY AND POSTSURGERY			
	Preoperative	24 months	P
Ksteep (SD), diopters	50,13 (±5,14)	50,06 (±4,60)	0.439
Kflat (SD) diopters	46,36 (±4,62)	46,36 (±4,21)	0.976
Km (SD) diopters	48,24 (±4,73)	48,21 (±4,27)	0.898
Pachymetry, micras (SD)	464,94 (±47,43)	450,25 (±38,65)	0.989

Tabla 3

DISCUSSION

The ACXL is a safe and effective technique to prevent the progression of corneal ectasia.[16,18-19] A strength of the study is that not only the topographical and visual results were taken into account, in addition, the refractive data were assessed too. All of these changes are relevant in the current trend to associate crosslinking to other techniques looking for a refractive outcome.

Other studies have shown a variable visual acuity as a result in different follow-up, with no improvement on UCVA or BCVA, and without changes on keratometry. In our study clinically and statistically improvement in UDVA was observed, and a tendency to stability in BCVA was observed, which is clinically significant. Cinar et al[13] found no statistically significant difference on UCVA and keratometry values. On this report, the number of eyes was similar, but the follow-up was 6 months. Buzzonetti et al[27] reported a statistically significant improvement on UDVA with worsening of topometric data, however, this study was performed in pediatric population. Aurora et al[28] divided into 2 groups based on their mean central

keratometry at 12 months follow-up. The group with keratometries less than 57.00 D, showed a statistically significant improvement in UCVA, in contrast to the group with higher keratometries.

The variability on results in the different types of study may be due to different periods of follow-up, different sample size (usually small samples), and different stages of the disease.

Two patients had 2 lines of vision loss secondary to corneal haze, ages 12 and 14 years old; those lost lines could influence the statistical analysis outcomes. As reviewed in the literature, no studies reporting the incidence of haze in children was found. This is a relevant finding to be taken into account in children with keratoconus that require CXL. More studies are needed to elucidate this knowledge. Vinciguerra et al. reported better functional and morphological results of CXL for keratoconus management in adults between 18 and 39 years of age than in children.[20-26]

The study found no statistically significant difference comparing the averages of the keratometric changes and corneal thickness difference. Refractive results, like induced astigmatism of 1.1 D and changes on sphere (ranges between -5.00 D to +3.00 diopters) are clinically significant if the purpose is associating the ACXL to a refractive procedure. However low predictability in the refractive results of this procedure requires being very careful when making the decision to incorporate CXL treatment with a refractive surgery in the same surgical time.

Retrospective studies are based on secondary data source (non-randomized and non-controlled studies), are not made with rigorous designed and therefore require carefully interpretation, even more with associations.

We can conclude that functional, topographic and refractive results of crosslinking can be unpredictable.

Randomized and controlled studies are required to clarify the relevance of the association of both procedures and extend our knowledge of these techniques in order to improve clinical outcomes. ■

REFERENCES

1. Chan E, Snibson GR. Current status of corneal collagen cross-linking for keratoconus: A review. Clin Exp Optom 2013; 96(2):155–64.
2. Kanellopoulos AJ. Long term results of a prospective randomized bilateral eye comparison trial of higher fluence, shorter duration ultraviolet A radiation, and riboflavin collagen cross linking for progressive keratoconus. Clin Ophthalmol 2012; 6(1):97–101.
3. Andreassen TT, Simonsen AH, Oxlund H. Biomechanical properties of keratoconus and normal corneas. Exp Eye Res 1980; 31(4):435–41.
4. Sung H-W, Chang W-H, Ma C-Y, Lee M-H. Crosslinking of biological tissues using genipin and/or carbodiimide. J Biomed Mater Res A 2003; 64(3):427–38.
5. 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.
6. Mazzotta C, Balestrazzi A, Traversi C, Baiocchi S, Caporossi T, Tommasi C, et al. Treatment of progressive keratoconus by riboflavin-UVA-induced cross-linking of corneal collagen: ultrastructural analysis by Heidelberg Retinal Tomograph II in vivo confocal microscopy in humans. Cornea 2007; 26(4):390–397.
7. Wollensak G, Spörl E, Reber F, Pillunat L, Funk R. Corneal endothelial cytotoxicity of riboflavin/UVA treatment in vitro. Ophthalmic Res 2003; 35(6):324–328.
8. Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA-riboflavin cross-linking of the cornea. Cornea 2007; 26(4):385–389.
9. Wollensak G, Spoerl E, Wilsch M, Seiler T. Endothelial cell damage after riboflavin-ultraviolet-A treatment in the rabbit. J Cataract Refract Surg 2003; 29(9):1786–1790.
10. Legare ME, Iovieno A, Yeung SN, Kim P, Lichtinger A, Hollands S, et al. Corneal collagen cross-linking using riboflavin and ultraviolet A for the treatment of mild to moderate keratoconus: 2-year follow-up. Can J Ophthalmol 2013; 48(1):63–68.
11. 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.
12. Gatzioufas Z, Richoz O, Brugnoli E, Hafezi F. Safety profile of high-fluence corneal collagen cross-linking for progressive keratoconus: preliminary results from a prospective cohort study. J Refract Surg 2013; 29(12):846–848.
13. Cınar Y, Cingü AK, Türkcü FM, Cınar T, Yüksel H, Ozkurt ZG, et al. Comparison of accelerated and conventional corneal collagen cross-linking for progressive keratoconus. Cutan Ocul Toxicol 2013; 9527:1–5.
14. Cınar Y, Cingü AK, Turkcu FM, Yüksel H, Sahin A, Yıldırım A, et al. Accelerated corneal collagen cross-linking for progressive keratoconus. Cutan Ocul Toxicol 2014; 33(2):168–171.
15. Kymionis GD, Portaliou DM, Kounis GA, Limnopoulou AN, Kontadakis GA, Grentzelos MA. Simultaneous Topography-Guided Photorefractive Keratectomy Followed by Corneal Collagen Cross-linking for Keratoconus. Am J Ophthalmol 2011; 152(5):748–755.
16. Elbaz U, Shen C, Lichtinger A, Zauberman N a, Goldich Y, Chan CC, et al. Accelerated (9-mW / cm 2) Corneal Collagen Crosslinking for Keratoconus- A 1-Year Follow-up. Cornea 2014; 33(8):769-773.
17. Thibos LN, Wheeler W, Horner D. Power vectors: an application of Fourier analysis to the description and statistical analysis of refractive error. Optom Vis Sci 1997; 74(6):367–375.
18. Marino GK, Torricelli AA, Giacomin N, Santhiago MR, Espindola R, Netto M V. Accelerated Corneal Collagen Cross-linking for Postoperative LASIK Ectasia: Two-Year Outcomes. J Refract Surg 2015; 31(6):380–384.
19. Kymionis GD, Grentzelos MA, Kankariya VP, Liakopoulos DA, Portaliou DM, Tsoulnaras KI, et al. Safety of high-intensity corneal collagen crosslinking. J Cataract Refract Surg 2014; 40(8):1337–1340.
20. Vinciguerra R, Romano MR, Camesasca FI, Azzolini C, Trazza S, Morenghi E, 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.
21. Cagil N, Sarac O, Cakmak HB, Can G, Can E. Mechanical epithelial removal followed by corneal collagen cross-linking in progressive keratoconus: Short-term complications. J Cataract Refract Surg 2015; 41(8):1730–1737.
22. Greenstein SA, Fry KL, Bhatt J, Hersh PS. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refract Surg 2010; 36(12):2105–2114.
23. Greenstein SA, Hersh PS. Characteristics influencing outcomes of corneal collagen crosslinking for keratoconus and ectasia: implications for patient selection. J Cataract Refract Surg 2013; 39(8):1133–1140.
24. Koppen C, Wouters K, Mathysen D, Rozema J, Tassignon M-J. Refractive and topographic results of benzalkonium chloride-assisted transepithelial crosslinking. J Cataract Refract Surg 2012; 38(6):1000–1005.
25. McAnena L, O'Keefe M. Corneal collagen crosslinking in children with keratoconus. J AAPOS 2015; 19(3):228–232.
26. Viswanathan D, Kumar NL, Males JJ. Outcome of corneal collagen crosslinking for progressive keratoconus in paediatric patients. Biomed Res Int 2014;2014:140461.
27. Buzzonetti L, Petrocelli G. Transepithelial corneal cross-linking in pediatric patients: early results. J Refract Surg 2012;28:763–767
28. Ritu Arora, Parul Jain, J. L. Goyal, Deepa Gupta. Comparative Analysis of Refractive and Topographic Changes in Early and Advanced Keratoconic Eyes Undergoing Corneal Collagen Crosslinking. Cornea. 2013 Oct; 32(10): 13591364.