

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

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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/cm² 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/cm² 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/cm²) compared with that used in the standard corneal CXL treatment (irradiance of 3 mW/cm²). 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/cm²).^{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 treatment¹⁶, 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 Scheimpflug (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/cm² 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 at 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 Scheimpflug (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 preoperative CD was 79,3% (n = 17 eyes) SD ± 0,86 and postoperative mean was 79,4 % (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.

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 al¹³ 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 al²⁷ reported a statistically significant improvement on UDVA with worsening of topometric data, however, this study was performed in pediatric population. Aurora et al²⁸ divided into 2 groups based on their mean central

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

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

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. ■

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