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Improving keratoconus management with central corneal regularization and corneal collagen cross-linking protocol treatment

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Abstract

Purpose. To evaluate safety and efficacy of customized central corneal regularization (CCR), together with simultaneous accelerated corneal collagen cross-linking (A-CXL) – CCR-CXL protocol, to treat keratoconus-related corneal ectasia.

Design. Retrospective, comparative observational case series.

Methods. Patients that had undergone combined CCR-CXL protocol. Main inclusion criteria were keratoconus visual acuity deterioration and contact lens intolerance. All patients underwent complete ophthalmological evaluation, corrected distance visual acuity (CDVA) and Scheimpflug-corneal tomography. Central corneal regularization was performed by ablation using flying spot laser. Subsequently, the stroma was saturated with 0.17% riboflavin-5-phosphate added every 2 minutes, followed by A-CXL 9 mW/cm^2 for 10 minutes. CDVA, medium keratometry value (Kmed), and total corneal morphological irregularity index (CMI) of patients were analyzed before surgery and after 1, 3 and 12 months. A P value of .05 or less was considered statistically significant.

Results. 46 eyes of 39 keratoconus patients were treated. At 1 month, the mean CDVA (LogMar) increased from 0.19 ± 0.02 to 0.12 ± 0.02 (P < .05), and the difference remained stable at month 12. Kmax decrease was statistically significant from 57.02 ± 5.65 to 50.21 ± 4.48 (P < .05). CMI decreased significantly from 47.8 ± 2.84 to 30.1 ± 2.4 (P < .01).

Conclusions. CCR-CXL protocol is safe and effective in arresting keratectasia progression and increasing corneal optic regularity in keratoconus. These findings showed a significant improvement in CDVA, keratometry values and corneal optical aberrations after being treated with the CCR-CXL protocol. ***Clin Ter 2022; 173 (3):274-279- doi: 10.7417/CT.2022.2431***

Key words: *corneal crosslinking, excimer laser ablation, keratoconus, riboflavin, central corneal regularization*

Introduction

Corneal collagen cross-linking (CXL) is a minimally invasive procedure used for stabilizing corneal ectatic disorders such as keratoconus, pellucid marginal corneal degeneration, and postoperative corneal ectasia.(1) This strategy is based on treating the underlying pathology of the disease, in which a local failure of the corneal biomechanical strength results in abnormal corneal protrusion and thinning, with poor visual quality and acuity (2, 3).

CXL strengthens corneal tissue by using topical riboflavin - vitamin B2 - as a photosensitizer and ultraviolet radiation A (UVA) to promote the formation of intra- and inter- fibrillar covalent bonds by photosensitized oxidation, leading to an increase on corneal resistance and inhibiting progression of ectatic disorders (4). Although the primary aim of corneal cross-linking is stopping the progression of keratectasia, it may also cause a reduction in the corneal curvature and a flattening of the apex as a beneficial side effect (5).

Different corneal parameters - i.e. topographic items - can improve after CXL due to the steepening effect and corneal curvature regularization (6,7). Nevertheless, in many cases, patients cannot achieve a satisfactory visual acuity without the use of contact lenses, generally rigid gas permeable, because of significant residual corneal irregularity and refractive error. Despite topographic stabilization and improvement of topographic maps, patients often complain about low uncorrected distance visual acuity (UDVA), low corrected distance visual acuity (CDVA), poor visual quality, dependency on contact lens and intolerance to spectacles after a CXL procedure.

Evidences suggest that these visual and topographic outcomes can be further improved by combining CXL with simultaneous refractive techniques to reshape the corneal surface. In these protocols, generally known as CXL-Plus, the fundamental method is CXL, and the other refractive procedures can be topography-guided photorefractive keratectomy (PRK), transepithelial topography-guided PRK, intracorneal ring segments (ICRS), phakic intraocular lens

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implantation (PIOL) or multiple techniques that are combined, either sequentially or simultaneously.(8,9) Among the various CXL-Plus procedures, CXL associated with excimer laser used in PRK, also termed Central Corneal Regularization and Corneal Collagen Crosslinking - CCR–CXL protocol - can be found.(10,11) It is based on two sequential treatments in order to improve visual quality and acuity maintaining the biomechanical effect of CXL: starting with a sequential excimer laser debridement of the epithelium and partial topography-guided excimer laser stromal ablation is performed, followed by a high-fluence accelerated corneal collagen cross-linking procedure (A-CXL) with 9 mW/cm2 for 10 min.(12) Central Corneal Regularization is a relatively novel procedure introduced by the iVis Suite customized excimer laser ablation treatment platform (iVis Technologies S. r. l., Taranto, Italy) to partially reverse corneal ectasia by reducing elevation of the cone and smoothening the overall contour.(13) The cornea is regularized by a topo/tomography-guided ablation with minimum stromal tissue removal and surgical invasiveness, thanks to the involvement of a very narrow central optical zone. This is surrounded by a customized "connecting refraction zone" that gradually decreases towards the periphery in a continuous refractive surface, aiming at an optimal optical smoothness within a large total ablation diameter. This allows to reduce glare, haloes, aberrations, and improving the quality of vision as well as the risk of regression of treatment.

The aim of this study is to evaluate the safety and efficacy of the CCR-CXL protocol performed on keratoconus patients with visual acuity deterioration and contact lens intolerance.

Methods

This retrospective, single-center, 2-year study adhered to the tenets of the Declaration of Helsinki and was approved by the medical center institutional review board. It was comprised of patients with a diagnosis of keratoconus who had undergone the CCR-CXL protocol. Inclusion criteria were: minimal corneal thickness of 400 μm, topographic changes consistent with moderate severity - Amsler-Krumeich stage I-II - of the disease. visual acuity affected to the point where spectacles and contact lens could not offer satisfactory results (6,14,15).

Exclusion criteria were patients with any other eye conditions that may influence their visual acuity or the course of the disease. Moreover, patients with indications for CXL other than keratoconus, other inflammatory or non-inflammatory disorders that could affect the outcomes, significant scars on the cornea; previous eye surgery, any systemic disease, pregnancy or current medications with potential ocular side effects were excluded.

The Precisio HD (iVisTechnologies S.r.l., Taranto, Italy) Scheimpflug tomographer elevation data, pachymetry maps and Amsler-Krumeich grading were used for the keratoconus diagnosis.

Standardized examinations included slit-lamp biomicroscopy, the quantification of UDVA and CDVA (logMAR), and Precisio HD imaging to evaluate tomographic, aberrometric and densitometric indices. Examinations were performed at baseline, and at 1, 3, and 12 months after the procedures. Pachymetric and keratometric values were calculated for the total corneal surface within the central 2 mm zone and the adjacent annulus extending from 2 mm to 6 mm. For calculating the aberrations with the Precisio HD software, we considered a pupil diameter of 3.5 mm. For their measurement, the the Precisio HD manufacter introduced a parameter describing optical regularity of the corneal surface, named Corneal Morphological Irregularity index (CMI). The CMI index is the sum of all corneal irregularities that exceed the second order regular surface, thus measuring the regularity of the corneal surface. The CMI of the anterior corneal surface (ACMI) is calculated as the difference between the positive index of irregularity of the anterior corneal surface (Ia+) and the negative index of irregularity of the anterior corneal surface (Ia-), which are, respectively, the maximum and the minimum difference between the anterior corneal surface and the best fit toric surface calculated within the predefined domain (D). As a result, the higher the measured CMI, the worse the quality of vision (Fig. 1).

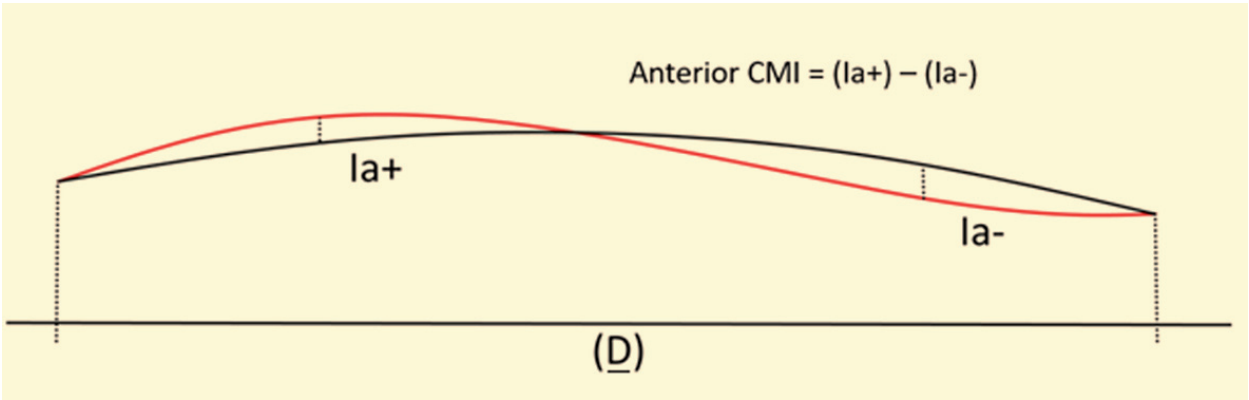

Fig. 1. The Corneal Morphological Irregularity index (CMI) represents all the refractive aberrations cumulatively exceeding the second order regular surface, as indication of the surface regularity, which is related to the quality of vision of the patient: the higher the measured CMI, the worse the quality of vision.

Anything that causes irregular astigmatism on either stable or ectatic corneas induces an increase of the CMI (14). Statistical analysis was performed using the statistical package for social sciences software (SPSS, Inc. Version 16.0. Chicago, IL, USA). Data were shown as means ± SD, and range. Preoperative and postoperative differences were evaluated using the paired t-test. A P value of less than 0.05 was considered statistically significant.

Surgical Procedures

The CCR-CXL protocol was performed using the iVIS Suite platform. We used a Precisio HD Scheimpflug tomographer to acquire corneal elevation maps, each consisting of 39.000 measurement points with an auto-validated repeatability of ≤ 3µm.(16) Customized surface ablations were planned in the CCR mode of the CIPTA (Corneal Interactive Programmed Topographic Ablation) software. The ectatic corneal shape was regularized by CCR in a narrow optical zone (1.3–1.9 mm in diameter) to achieve minimal tissue removal, as this is very significant in the biomechanically compromised corneas. The small optical zone is centered on the apex, with a very large transition zone until a total ablation diameter of up to 9.8 mm is reached, which ensures the quality of the postoperative corneal optics. The large "connecting refractive zone" between the central optical zone and the untreated periphery features a smooth customized transition with a constant radial slope. The connecting zone is the surface between the refractive zone and the untouched corneal surface which is designed with a constant slope in each radial direction, resulting in a linear increase or decrease of curvature (17). Prior to ablation, we applied a balanced salt solution (BSS) on the corneal surface using a Merocel sponge (Medtronic Inc.) to avoid uneven wetting.

A single-step laser treatment, comprising a predefined ablation profile to achieve epithelial removal and a customized component to achieve corneal regularization, was executed with an uninterrupted ablation (17). The predefined ablation profile to remove the epithelium was preprogrammed with a proprietary algorithm. CCR was performed by a 1000-Hz iRES (iVis Technologies S. r. l., Taranto, Italy) excimer laser, which has a small spot size of 0.65 mm. The cornea was then cooled by irrigation with cold BSS.

A-CXL followed CCR. Corneal imbibition was obtained with riboflavin 0.1% solution for a total time of 15 minutes, and was continued every 2 minutes during the UVA exposure. Corneal cross-linking was performed using a CCL-365 Vario (MLase AG) calibrated to 9 mW/cm2 for 10 minutes, resulting in irradiance of 5.4 J/cm2. Postoperatively, eyes were rinsed with a balanced salt solution and a therapeutic bandage soft contact lens was applied. An antibiotic regimen of 0.3% ofloxacin and 0.03% flurbiprofen drops was administered four and two times a day, respectively, until contact lens removal. Then, 0.1% dexamethasone as topical corticosteroid drops, were administered and gradually tapered for 1 month. Artificial tears drops were recommended four times a day.

Results

A total of 46 eyes of 39 keratoconus patients (16 females, 41%) with a mean age was 26.53 years (±7.02, range 19.51 to 33.55) were elegible for the CCR-CXL protocol.

Patients were examined before and after the surgical procedures at 1, 3 and 12 months. The visual, refractive, tomographic and aberrometric outcomes are summarized at baseline and after 1, 3 and 12 months in Table 1.

Table 1. Preoperative and postoperative patient characteristics

Parameter	(Mean ± SD)				P value [b]
	Baseline	1 month	3 months	12 months	
Sex (F/M) 16/23					
Age	26.53 (± 7.02)				
Minimum Mean Corneal Thickness (µm)	482.14 (± 48.67)	428.17 (± 23.57)	430.56 (± 26.52)	435.13 (± 28.67)	< .01
CDVA (LogMAR)	0.19 (± 0.02)	0.12 (± 0.02)	0.13 (± 0.020)	0.12 (± 0.01)	< .05
MRSE (D)	-1.79 (± 2.56)	-1.06 (± 0.79)	-0.99 (± 1.01)	-0.89 (± 1.53)	< .01
Kmed (D)	49.14 (± 2.20)	47.69 (± 2.10)	47.56 (±2.02)	47.49 (± 1.93)	< .05
Kmax (D)	57.02 (± 5.65)	51.25 (± 4.99)	50.55 (± 5.01)	50.21 (± 4.48)	< .05
Cylinder (D) [a]	2.81 (± 1.49)	2.14 (± 1.29)	2.11(± 1.39)	2.13 (± 1.42)	< .05
CMI	47.80 (± 2.84)	30.4 (± 2.41)	30.2 (± 2.43)	30.1 (± 2.40)	< .01

CDVA: corrected distance visual acuity; MRSE: mean refractive spherical equivalent; Kmed: average keratometry; Kmax: steepest radius of anterior curvature; CMI: Corneal Morphological Irregularity index (Mean values at 3.5 mm); D: diopters.
a Topographic corneal cylinder error.
b Baseline vs 12 months; Statistically significant.

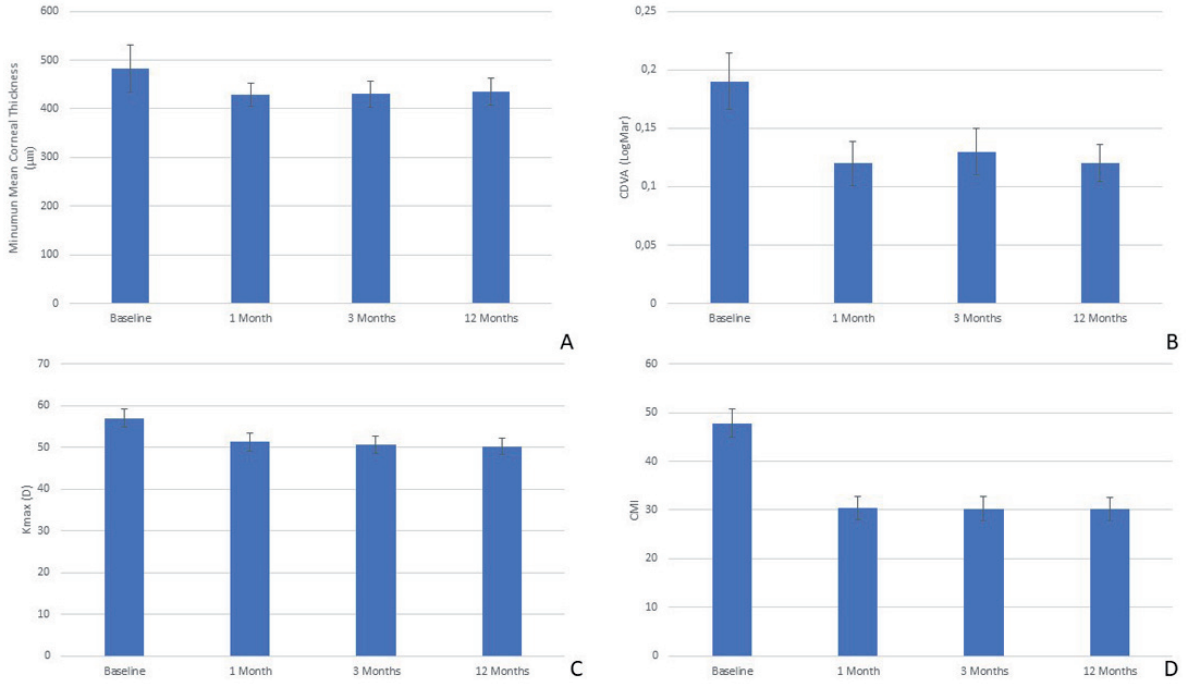

Fig. 2. Pre and postoperative data. (A) Minimum Mean Corneal Thickness; (B) Corrected distance visual acuity (CDVA); (C) Kmax; (D) Corneal Morphological Irregularity index (CMI) (Mean values at 3.5 mm)

Regarding corneal thickness at the thinnest location, the excimer laser ablation performed a reduction in the values, from 482.14 µm ± 48.67 preoperatively to 428.17 µm ± 23.57 at the end of the first postoperative month ($P < .01$) (Fig. 2A).

At the first follow-up, 1 month after treatment, the mean CDVA increased significantly and the difference remained unchanged in the subsequent follow-up at 12 months ($P < .05$) (Fig. 2B).

Similarly, differences in spherical equivalent were statistically significant at 12 months ($P < .01$) postoperatively, and the total corneal morphological irregularity index decreased significantly from 47.8 ± 28.4 to 30.4 ± 24.1 postoperatively ($P < .01$).

In addition, keratometric values Kmed (medium keratometry value) and Kmax (Fig. 2.C) showed a decrease at 1 month after treatment, which remained stable and statistically significant after 1 year ($P < .05$), as well as the topographic corneal cylinder error and CMI (Figure 2.D), the values of which were reduced from baseline to postoperative analysis ($P < .05$).

Comparing preoperative and postoperative data, a statistically significant improvement was detected for all other considered parameters. Regarding the postoperative data, no statistical differences were observed in the 1, 3 and 12 months evaluations of the data. In terms of safety, no serious complications were registered: three eyes (6.52%) reported delayed epithelial healing despite all eyes showed complete epithelial healing within 8–11 postoperative days; anterior corneal haze - clinically graded according to the Fantes scale - was recorded in five eyes (10.87%), which improved with a steroid-base therapy and recovered within 2 – 4 weeks postoperatively. Finally, there were no recorded cases of treatment failure with postoperative keratoconus progression after one year.

Discussion

Corneal collagen crosslinking provides tensile strength and stability to the cornea by inducing corneal stroma crosslinks, thus arresting keratoconus (18). CXL is able to achieve topographic stabilization and a slight improvement of topography, but in most of cases, this technique alone is inadequate to improve visual function, (8) especially in the case of contact lens and spectacle intolerance.

This limitation of CXL can be resolved by the CXL Plus protocols.

Topography-guided PRK (tPRK) combined with CXL was the first CXL-Plus method and uses excimer laser ablation. Several studies have shown not only is an effective treatment of choice for keratoconus and keratectasia, (19,20) but also has proven to be stable in the long-term (21). Kanellopoulos and colleagues first have described a single case report of a patient with keratoconus who was treated with CXL followed by a tPRK procedure after 1 year, showing a significant clinical improvement (22). The same authors described the use of simultaneous CXL combined with PRK aimed at reducing the spherical equivalent by up to 3 diopters. This procedure was known as the Athens Protocol and included ablation of 50 µm of the anterior cornea to provide a therapeutic tool in keratoconus followed by CXL,

to irradiate the cornea with 370 nm UVA and an irradiance of 3 mW/cm2.(23) The effectiveness of a combined protocol has also been demonstrated, in patients with keratoconus and ectasia following LASIK surgery, by Kymionis et al., who described a significant improvement in spherical equivalent, defocus, UCVA, CDVA and keratometric values.(20) Alessio et al. compared visual, topographic, and aberrometric outcomes after customized photorefractive keratectomy followed by cross-linking, and described better outcomes versus CXL alone.(24) Compared to the first excimer laser assisted approaches, CCR-CXL protocol provides a narrower optical zone, as the most relevant portion of the cornea of interest for the distinct vision is the central 1.0 mm, and a minimized ablation, avoiding adjuvant substances such as mitomycin C.

From the literature, it remains controversial whether simultaneous excimer laser procedures or sequential CXL followed by excimer laser is optimal. Regarding the timing of the procedures, one of the main factors is in treatment planning. CXL alone has been shown to gradually induce flattening in the anterior corneal curvature, which does not stabilize until several months postoperatively, so the ablation rate of crosslinked corneas in the sequential approach may vary from that of the untreated corneas, making the procedure less predictable. Moreover removing cross-linked corneal tissue during subsequent excimer laser ablation may reduce the CXL benefits.(25) On the other hand, a recent meta-analysis (while comparing heterogeneous protocols) reports greater improvements in the sequential group, with CXL followed by excimer laser surface ablation later.(9) Multiple studies have revealed the safety and efficacy of simultaneous topography-guided excimer laser ablation and CXL for treating patients with corneal ectasia;(26) according to these, our findings show a significant improvement in CDVA, keratometry values and corneal irregularity index after the simultaneous CCR-CXL combined treatment. As for the Athens protocol, CCR-CXL consists of a same day surgery.

In keratoconic eyes, the corneal epithelium plays a crucial refractive role, and acts like a masking agent, being thinner at the apex of the cone. CCR treatment provides refractive improvements, comprising a predefined ablation profile to achieve epithelial removal without any corneal manipulation, acting as a customized component to perform the subsequent corneal regularization. The one-step procedure of correcting epithelial and stromal irregularities is an advantage of CCR, which allows epithelial removal together with stromal ablation in a single, uninterrupted ablation, without the need for a preliminary excimer laser assisted step or mechanical epithelial removal. This is made possible thanks to the transition zone that in CCR represents a pure topography-guided custom ablation with gradually decreasing power, which creates an optically active blend zone, making it possible to use a very small optical zone that restricts the ablation to a few tens of a micron, unlike purely refractive ablations, which have large optical zones and relatively small transition zones. CCR combined with CXL approach versus other CXL-Plus protocols consist of a less invasive approach to reach a similar refractive goal, when compared with intracorneal tunnels or implants requiring techniques.

In our study, an immediate reduction in the pachymetry values due to the action of the excimer laser-induced stromal ablation was demonstrated, which remained stable during the 12 months of follow-up period, with only minor changes. However, safety parameters remain crucial in choosing eligible patients, such as the minimal corneal thickness after the excimer ablation must still be above the safety threshold of 400 μm for epi-off CXL, and this may constitute a major limitation of this technique.

Main limitation of this study is that the findings should be seen in light of a retrospective study without a control group. Moreover, as we consider the increase in visual quality particularly relevant for the patients, due to the reduction of corneal irregularities, a limitation in our analysis may consist in the absence of a standardized visual function questionnaire, not included in the routine clinical evaluation, which may constitute an interesting direction of future efforts in the preoperative and postoperative clinical examination.

The results of our study show that the CCR-CXL protocol seems to be safe and effective in arresting corneal ectasia progression and in increasing corneal morphological parameters in keratoconus, being a promising management for those patients with progressive keratoconus, poor visual quality and contact lens intolerance.

The author has no financial or proprietary interest in any product or company quoted in this manuscript. The authors declare that there is no conflict of interest regarding the publication of this paper.

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