

CXL Updates

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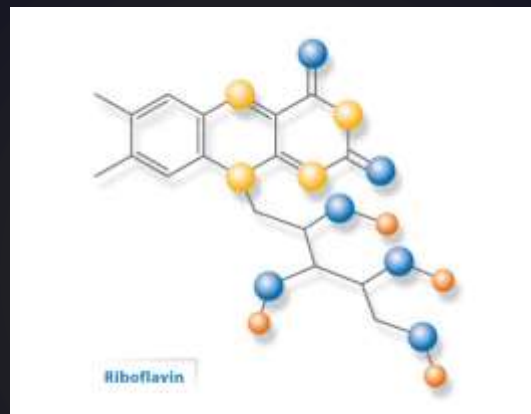
The Speaker Has No Financial Interest



Options for treatment

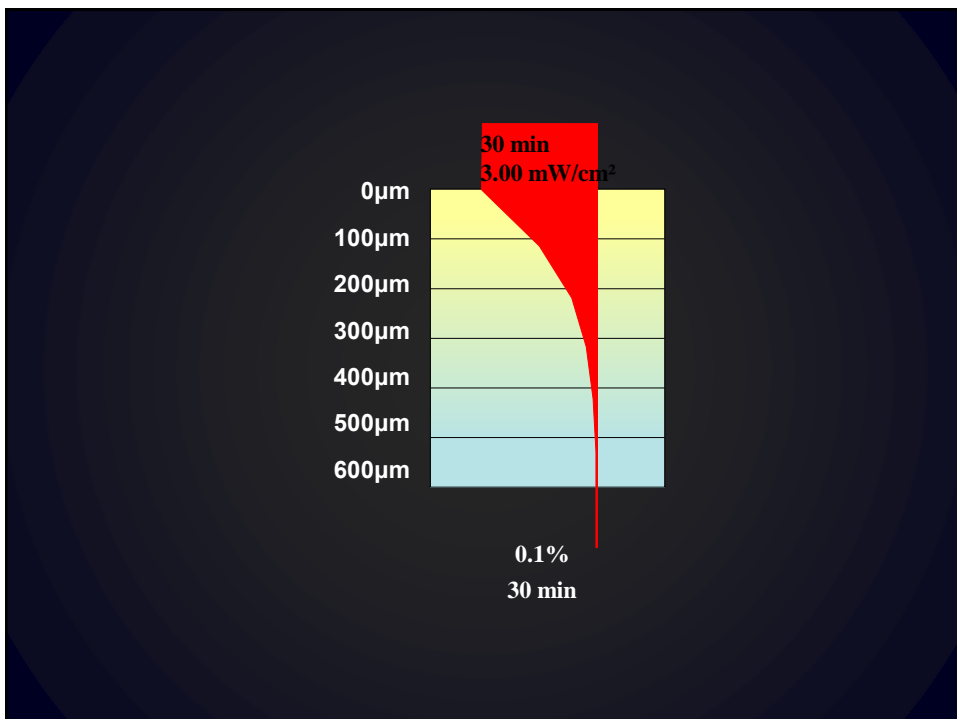
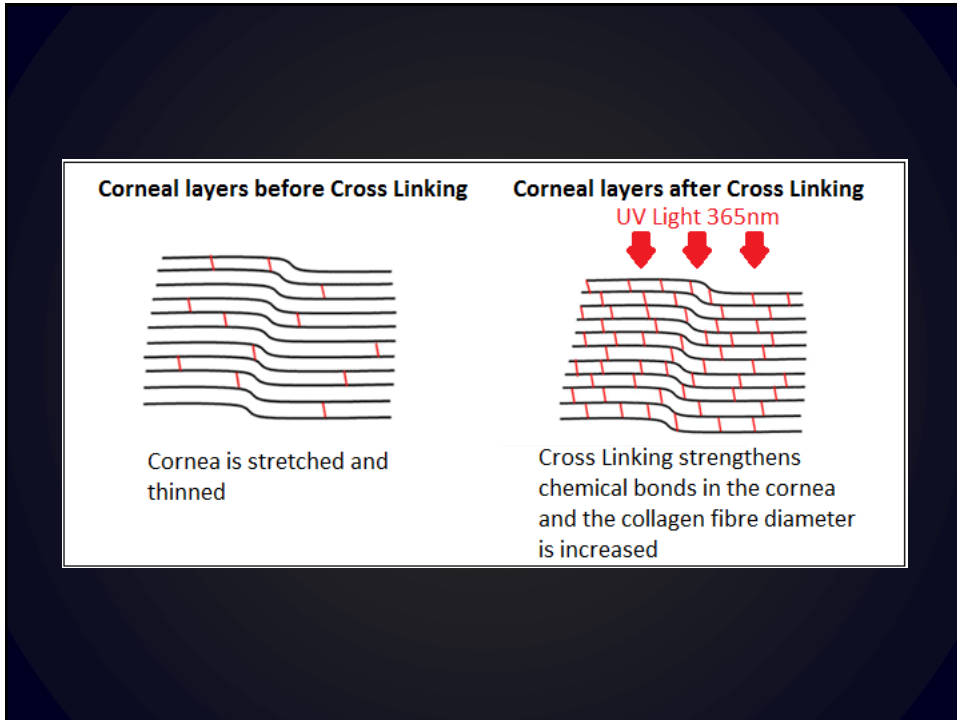
- Lower intraocular pressure
- RGP lens
- **Collagen cross-linking**
- Intracorneal ring segments
- Phakic IOLs/CLE
- Deep lamellar keratoplasty
- PKP
- Combinations

CXL: BASICS



Hydrophilic VS lipophilic epithelium.

Electrostatic repulsion between the anionic riboflavin-5-phosphate and the negatively charged surface of the cornea

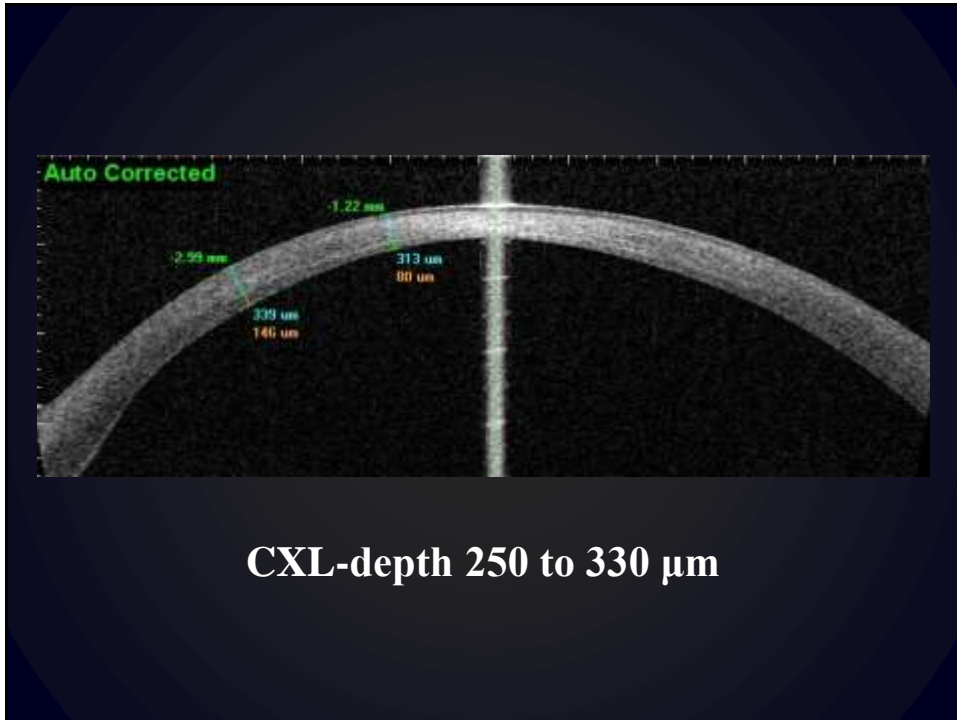


The Protocol CXL: Power x Time

- The standard Dresden protocol:
 - $3 \text{ mW/cm}^2 \times 30 \text{ min} = 5.4 \text{ J/cm}^2$
- Accelerated Cxl:
 - $9 \text{ mW/cm}^2 \times 10 \text{ min} = 5.4 \text{ J/cm}^2$
 - $10 \text{ mW/cm}^2 \times 9 \text{ min} = 5.4 \text{ J/cm}^2$
 - $18 \text{ mW/cm}^2 \times 5 \text{ min} = 5.4 \text{ J/cm}^2$
 - $30 \text{ mW/cm}^2 \times 3 \text{ min} = 5.4 \text{ J/cm}^2$
 - $45 \text{ mW/cm}^2 \times 2 \text{ min} = 5.4 \text{ J/cm}^2$

Continuous Vs Pulsed

- Rapid oxygen depletion with accelerated protocols leads to a reduced efficacy
- 1S On 1S Off



ARTICLE

Efficacy of different accelerated corneal crosslinking protocols for progressive keratoconus

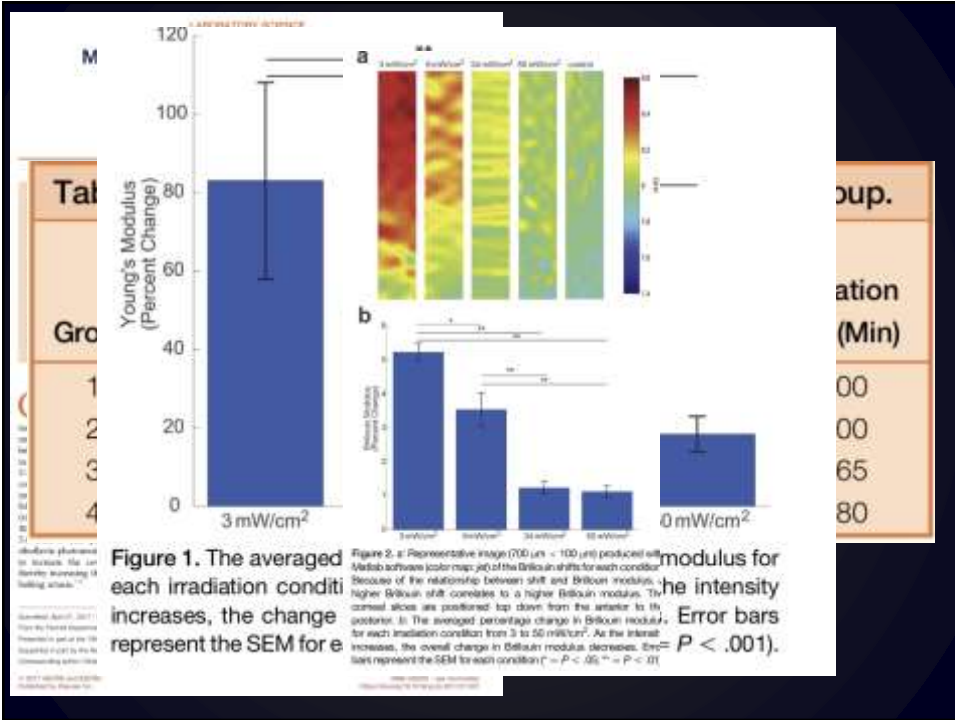
Ibra Taher, MD, Eren Civanlar, MD, JEB Phd, Deniz Ozdemir Ozcan, MD, Ozge Ergonen Aksoydogru, MD

Table 5. Mean depth of the demarcation line by group.

Group	Demarcation Line Depth (μm)	
	Mean ± SD	Min, Max
Conventional CXL	266 ± 40	210, 310
9 mW ACXL	273 ± 31	200, 343
30 mW cACXL	173 ± 20	135, 210
30 mW pACXL	166 ± 22	130, 207

cACXL = continuous accelerated corneal crosslinking; CXL = corneal crosslinking; pACXL = pulsed-light accelerated corneal crosslinking

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The Solution

Riboflavin Type	Commercially available brands
Isotonic Riboflavin 0.1% (with 20% Dextran)	Mediocross-D, Vibex , Ricrolin
Riboflavin 0.1% in HPMC (without Dextran)	Mediocross-M, Vibex Rapid
Hypotonic Riboflavin (0.1% Riboflavin with buffered salt solution)	Mediocross-H, InnoCross-R Hypotonic
TransEpithelial Riboflavin 0.25% with HPMC+BAK/EDTA/Tromethamine	Mediocross TE, Ricrolin TE, ParaCel
Riboflavin 0.25% in NaCl (saline)	FreshK, Vibex Xtra

The LAMP

TABLE. SPECIFICATIONS OF CXL LAMPS

								
Manufacturer	ROC Business AG	Softr Nika Sp.A.	Opto Global Pty Ltd.	Avedra, Inc.	Reichle Mediatec GmbH	ROC Business AG	Appassony	Avedra, Inc.
Name of device	UVX 000	Waga	Cera-Block	ROC 1 System	CCL 800 HE	UVX 000	C-UVS	CXL 8 System
Country of origin	Switzerland	Italy	Israel	United States	Switzerland	Switzerland	India	United States
Wavelength, nm	365	375	365	365	365	365	365	365
Intensity of illumination, mW/cm ²	30	30	35-45	30-45	Up to 300	Up to 12	30	Up to 100 (max 90)
Variable intensity?	No	No	Yes	Yes	No	No	No	Yes
Duration of CXL treatment, min	30	30	30	5	5	30	30	>30
Working distance, cm	30	30	30	25	40-50	40	35	35
Light delivery	Continuous	NS	NS	Continuous	Continuous	Continuous	NS	NS
Beam profile	Rectangular	Rectangular	Rectangular	Rectangular	Rectangular	Circular	NS	Irregular/beam distribution
Beam diameter, mm	4.5 and 9	4.5	4-20	Fixed 20	7-71	7-71	NS	Up to 10
Weight, kg	27	NS	NS	NS	25	17	NS	NS
CE Mark	Yes	Yes	Yes	Yes	Yes	Yes	NS	Expected in late 2017
No. of treated eyes reported in the literature	1000	300	20	NS	NS	NS	NS	0

Abbreviations: CXL, cross-linking; NS, not specified

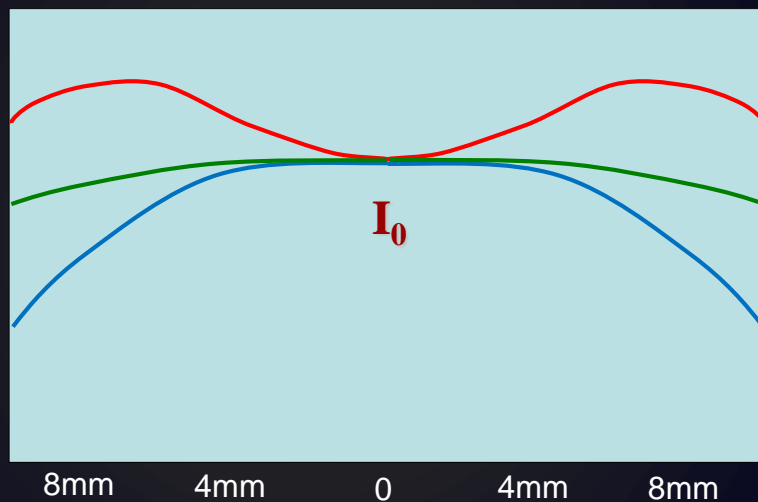
UV Beam

In order to create a homogeneous CXL-effect also in the periphery of the cornea

irradiation with a top hat-profile is not good enough.

3 mm away from the center the light intensity needs to be increased by at least 25%

profile



Transepithelial Cross-linking

- To avoid Postoperative pain, haze, and infection.
- Techniques:
 - Pharmacological cleavage of epithelial tight junctions
 - Application via intrastromal pocket/channels.
 - Iontophoresis-assisted CXL (I-CXL)
- Efficacy was lower as compared to conventional treatment particularly in stabilizing or improving keratometry.

As in nano

Giuseppe Lamberti, M. Scudiero

Transepithelial corneal collagen crosslinking for progressive keratoconus: 24-month clinical results

Abdelrahman G. Salama

Alko Caporossi, MD, FRCS, Cornea, Montreal, MD, PhD, Anna Lucia Pinna, MD, Stefano Basciotti, MD, PhD, Davide Margolis, MD, Tommaso Caporossi, MD

PURPOSE: To evaluate the effectiveness and safety (CXL) in children with keratoconus and the effects.

SETTING: Ophthalmology Department, An-Sharei.

DESIGN: Prospective comparative case series.

METHODS: Patients younger than 18 years with KC. The improvement in the mean (SD) was statistically significant (P < .05). The uncorrected distance visual acuity (UDVA) and topography at 12 months were the main results.

RESULTS: The mean age of the 32 patients (22 eyes) CXL, the improvement in the mean (SD) was statistically significant (P < .05). The uncorrected distance visual acuity (UDVA) and topography at 12 months were the main results.

CONCLUSIONS: Preliminary results of transepithelial CXL, with no evidence of progression of keratoconus.

Financial Disclosure: The author has no financial or interest.

J Cataract Refract Surg 2013; 39:1157-1163. © 2013

PURPOSE: To assess the clinical results of transepithelial collagen crosslinking (CXL) in patients 20 years and younger with progressive keratoconus suitable for myopia refractive surgery.

SETTING: Department of Ophthalmology, Sams University Hospital, Sams, Italy.

DESIGN: Prospective case series.

METHODS: The study included 26 eyes (26 patients) treated by transepithelial collagen crosslinking (CXL). The mean age was 22 years (range 11 to 30 years) (13 younger than 18 years, 10 between 18 years and 24 years). Preoperative and postoperative examinations included unaided distance visual acuity (UDVA) and corrected UDVA, distance visual acuity, corrected minimum keratometry (K), coma and spherical aberration, and tomographic videokeratometry topography optical pachometry. The solutions for transepithelial CXL (Riboflavin 0.1%, 30 min 15%), riboflavin 0.1%, and riboflavin 0.1% and riboflavin 0.1% were used.

RESULTS: Mean values improvement in the first 2 to 6 months, the UDVA and CDVA gradually returned to baseline preoperative values. After 12 months of stability, the unaided UDVA and CDVA were 24 months. Corneal astigmatism showed no statistically significant change. Statistical significance increased at 24 months. Postoperatively showed a progression, statistically significant decrease at 24 months. The amount of positive patients was reduced only after 24 months. There is significant improvement of all parameters after 12 months of follow-up.

CONCLUSIONS: Functional results after transepithelial CXL showed astigmatism stability, in particular in pediatric patients 18 years old and younger. There was also functional regression in patients between 18 years and 24 years old after 24 months of follow-up.

Financial Disclosure: An author has a financial or proprietary interest in any material or method mentioned.

J Cataract Refract Surg 2013; 39:1157-1163. © 2013 ASCRS and FRCO

Abstract: Keratoconus is a noninflammatory progressive disease of the cornea. Its incidence in the general population is reported to be approximately 1 in 200.¹ In most cases, keratoconus starts at puberty and progresses at a variable rate eventually, approximately 30% of keratoconus eyes require penetrating keratoplasty.²

Based on more than 12 years of basic research^{3,4} and clinical studies,⁵⁻¹⁰ at the structural level, riboflavin and ultraviolet-A (UVA) induced cross-linking crosslinking (CXL) has become a therapy for progressive keratoconus and secondary astigmatism.¹¹⁻¹² Its aim is to slow and possibly arrest the progression to avoid the need for corneal transplantation.¹³ The technique involves photo-oxidation of collagen fibrils in the corneal stroma.¹⁴⁻¹⁶ It acts as the combined action of riboflavin and UVA light to improve the biomechanical properties of the cornea, specifically resistance¹⁷ to stretching¹⁸ and to breakdown by collagenase.¹⁹ It prevents the disorganization of the corneal profile and corneal thinning,²⁰⁻²² steepening (refractive decompensation of visual acuity) and its myopia (near-sightedness).

in some degree²³ of functional improvement.²⁴ The efficacy in terms of long-term stabilization of keratoconus of the epithelium and epithelial progression is also assessed by many clinical studies.²⁵⁻³⁰ and in pediatric patients.^{31,32} Reports of the morphofunctional effects of repeat CXL, which partially explain its functional impact, can also be found in the literature.³³

A transepithelial method of CXL (trans-epithelial CXL) is an recently proposed.³⁴ Among its objectives is to reduce postoperative pain and the risk for infection and to obviate the necessity of creating some white-sclera stability of the disease.³⁵ In the first international in vivo studies in humans by laser confocal microscopy,^{36,37} we showed the safety of standard CXL. In a similar morphological study,³⁸ we

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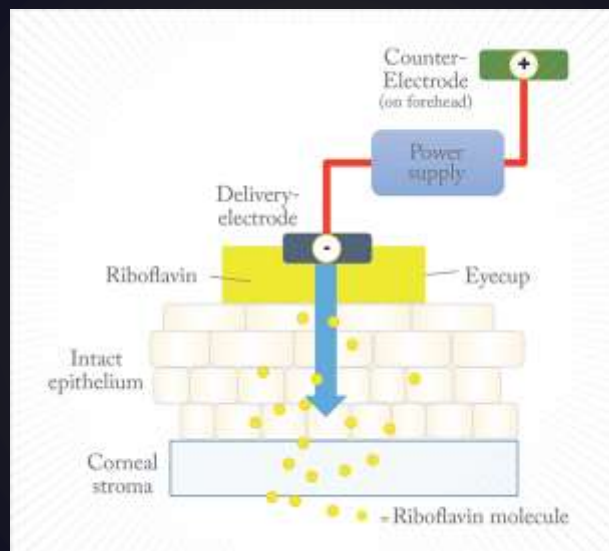
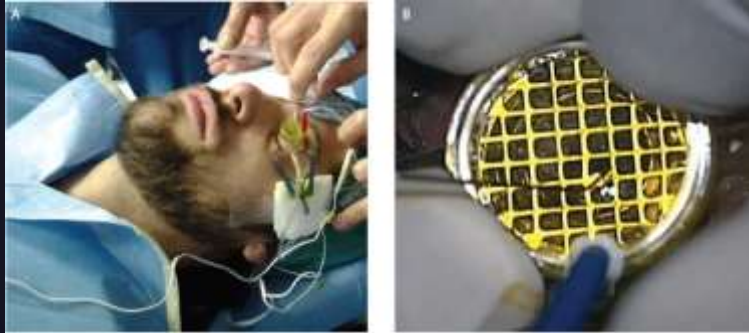
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Supported by the Sams University.

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Iontophoresis-assisted CXL (I-CXL)



THE PROBLEM WITH EPI-ON TECHNIQUES

Successful CXL requires three components:

- 1. Adequate, homogeneous stromal loading of riboflavin.**
- 2. Adequate, unblocked transmission of UV-A light energy through the epithelium.**
- 3. Adequate oxygen, the rate-limiting reagent for the photochemical reaction that causes cross-linking when both Nos. 1 and 2 are present**

Cross-linking in Thin Corneas

- Hypoosmolar cross-linking with instillation of hypotonic riboflavin
- Transepithelial crosslinking
- Customized pachymetry-guided epithelial debridement
- Contact lens-assisted collagen crosslinking (CACXL)
- Stromal thickness augmentation using refractive lenticule
- New protocols according to CT
- Riboflavin with HPMC

LABORATORY SCIENCE

Biomechanical stiffening: Slow low-irradiance corneal crosslinking versus the standard Dresden protocol

Sahay Singh, PhD, Gerhard Hoffer, PhD, PhD

Purpose: To assess whether ultra-low-irradiance crosslinking can be achieved with corneal crosslinking (CXL) when applying a reduced standard UVB fluence using the standard treatment time.

Setting: Laboratory of Vision and Ocular Health, Center for Applied Biomechanics and Molecular Medicine, University of South, South Australia.

Design: Experimental study.

Methods: Five bovine corneal stromal sections were dehydrated and treated with hyperosmolar solution (1% sodium borate, 30 minutes; 20% sucrose, 30 minutes; 1.0 M sodium ascorbate, 20 minutes) and crosslinked with standard CXL (30 minutes at 3 mW/cm², fluence 3.4 J/cm²). The control was treated with standard CXL for 30 minutes at 30 mW/cm². Elastic stress, axial and tangential biomechanical deformation were measured with a

Results: Corneas crosslinked with low and standard UV fluence rates at significantly higher corneal stress, modulus (300.0 kPa ± 10.7 MPa and 37.1 ± 3.0 MPa, respectively from control 30.0 ± 11.0 MPa and 1.27 MPa, respectively from low UV fluence of crosslinker and hyperosmolar solution CXL, with low and standard UV fluence rates (2.18 kPa and 100 ± 10 MPa, respectively compared with control (33.0 ± 32.2 MPa, P < 0.05). No difference was observed in corneal modulus independent of UV fluence (P > 0.05).

Conclusions: The low fluence UV CXL might be achieved while maintaining the biomechanical stiffness by using a lower UV fluence and the same treatment duration. The right dose remains to be determined in vivo by the clinician.

Keywords: corneal crosslinking, crosslinker, fluence, low irradiance, ultra-low irradiance

Introduction: The first application for keratoconus in 2003,^{1,2} the procedure for corneal crosslinking (CXL) has been modified several times. Although the first efforts were aimed at adapting the CXL procedure to corneas thinner than 500 µm,³⁻⁵ the latest efforts relate to smaller treatment durations.⁶⁻⁸

According to the Biomechanical Index of Susceptibility, the photochemical effect should only depend on the total ultraviolet A (UVA) energy (fluence), independent of the duration of administration and irradiance. However, studies⁹⁻¹¹ reported that this has caused results to be applied to CXL when matching the CXL effect of several doses of protocols during the same fluence but different energy/irradiance combinations. The observed significant decrease in the CXL effect at high irradiances is potentially due to the oxygen. Ex vivo studies of porcine eyes¹² have shown that oxygen is essential to the biomechanical stiffening effect of CXL. Krause et al.¹³ found that oxygen is rapidly consumed during CXL. The more oxygen available, the stronger the CXL-induced stiffening effect.¹⁴ Oxygen availability has an inverse relationship with corneal thickness, and thinner corneas should therefore experience stronger stiffening after CXL than thicker corneas, even if the UV dose is adapted to find the relative UV absorption along the corneal stroma to be equal. This hypothesis was recently verified experimentally.¹⁵

Thus, CXL protocols of previous age mainly limited by oxygen diffusion and depletion by irradiation duration, which means that the UV irradiance could be decreased without reducing the stiffening effect. In the field of optobiology, Anandhan et al. experimentally measured the rate of oxygen consumption in a reaction cell to study the photochemical reaction of CXL. The rate of oxygen consumption was found to be proportional to the UV fluence rate and the oxygen concentration. The rate of oxygen consumption was found to be proportional to the UV fluence rate and the oxygen concentration. The rate of oxygen consumption was found to be proportional to the UV fluence rate and the oxygen concentration.

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PiXL: Photorefractive Intrastramal Cross-linking

The diagram illustrates the PiXL workflow. On the left, an Oculus Pentacam Tomography device is shown, which provides corneal topography data. This data is processed by Avedro Mosaic Treatment Design software, which creates a Customized UVA Pattern. This pattern is then used by the Avedro Mosaic treatment device to perform the cross-linking procedure on the patient's eye. The final step shows a close-up of the eye being treated with the customized UVA pattern.

LASIK Xtra

- A higher concentration 0.25% riboflavin is applied on the stromal bed subsequent to excimer laser ablation with a soak time of 90 s. The interface is washed thoroughly and the flap is repositioned.
- UV-A: 30 mW/cm² for 90 s = 2.7 J/cm².

REPORT

Corneal Ectasia After LASIK Combined With Prophylactic Corneal Cross-linking

Suzhi Taneri, MD; Sanku Kizilek; Dip-Ing; Anika Patel, MSc; H. Sulfhand Doh, MD

ABSTRACT

PURPOSE: To report a case of anterior corneal ectasia following LASIK surgery combined with prophylactic corneal cross-linking (CXL) in a young patient.

METHODS: Case report.

RESULTS: Preoperative topography was unremarkable in both eyes with a minimum corneal thickness of 554 μm in the right eye and 545 μm in the left eye. Postoperative corrected distance visual acuity (CDVA) was 1.0 (20/20 Snellen) in both eyes with a refraction of +1.25 -0.75 × 10 in the right eye and +0.50 -0.25 × 103 in the left eye. LASIK combined with CXL was unremarkable. After 12 months, postoperative topography was unremarkable with an unexpected ectatic visual acuity (CVA) of 1.0 in both eyes. Two years after surgery, the patient presented with a case of visual (CVA) 2.0, and an inferior steepening of topography in the left eye. The CXL was performed to arrest further progression.

CONCLUSIONS: This report illustrates that the currently used prophylactic CXL protocol in combination with LASIK may not be effective in preventing corneal ectasia in every case.

J Refract Surg. 2017;33(10):66-62.

Keratoectasia after LASIK is a rare complication but may potentially lead to a permanent loss of visual quality.¹ Prophylactic corneal cross-linking (CXL) may be added after laser ablation to increase corneal rigidity, thus reducing the risk of ectasia after LASIK.² We report the first case of unilateral corneal ectasia following LASIK combined with prophylactic CXL (LASIK-CXL) in a patient with unremarkable preoperative findings.

CASE REPORT

A healthy 18-year-old man was seeking laser vision correction. His preoperative refraction was -1.25 -0.75 × 10 in the right eye and -0.50 -0.25 × 103 in the left eye. The corrected distance visual acuity (CDVA) was 1.0 (20/20 Snellen) in both eyes. Objective results (Schwabe Eye, Bausch & Lomb, Rochester, NY) demonstrated an asymmetric bow tie pattern in the left eye only but were within normal limits with a maximum keratometry value of 43.20 diopters (D) and corneal astigmatism of 2.00 D in the right eye, and 43.20 D with corneal astigmatism of 1.90 D in the left eye, respectively. Minimum corneal thickness was 554 and 545 μm in the right and left eye, respectively (Figure 1, available in the online version of this article). The following preoperative measurements were performed with long examination, wavefront analysis, endothelial specular microscopy, keratometry, (Holladay examination, and dilated fundus examination. No risk factors for ectatic disease was found. The patient denied rubbing his eyes and did not use any long-term medications. He did not have floppy eyelids or sleep apnea. The patient's family history was negative; no relatives had high astigmatism or was wearing rigid contact lenses.

Microkeratome-assisted LASIK combined with CXL was unremarkable (Zyoptix 3D microkeratome with Zeiss Compression head; Bausch & Lomb; suction ring with 5.5-mm inner diameter). A new microkeratome blade was used for each flap cut. Intended flap thickness was 120 μm in both eyes. Achieved flap thickness was 88 μm in the right eye and 113 μm in the left eye as intraoperatively assessed using ultrasonic, ultrasonic pachymetry. Central corneal thickness was recorded three times using the same ultrasonic probe (DGH-1000 Pachmeter; DGH Technology, Inc., Exton, PA) immediately before applying the suction ring. After lifting the flap, the pachymeter was again used three times to determine central corneal bed thickness before ablation. The difference between the mean values was considered to be the flap thickness. Flap diameter was 4.9 mm in the right eye and 4.8 mm in the left eye as measured with a measuring tool in the anterior segment optical coherence tomography (OCT) image 2 months postoperatively. Maximum laser ablation was 50 μm in the right eye and 31 μm in the left eye, leaving a residual stromal thickness of 287 μm in the right eye and 290 μm in the left eye (Technolas 25 RP laser; Bausch & Lomb). Optical zone was 7 mm in both eyes with a blend zone of 12 × 10.1 mm in the right eye and 11.9 × 9.8 mm in the left eye.

Intraoperative CXL was performed as follows. Immediately after laser ablation, riboflavin phosphate 0.25% (Vibex Xtra; Avendo Inc., Wallham, MA) was

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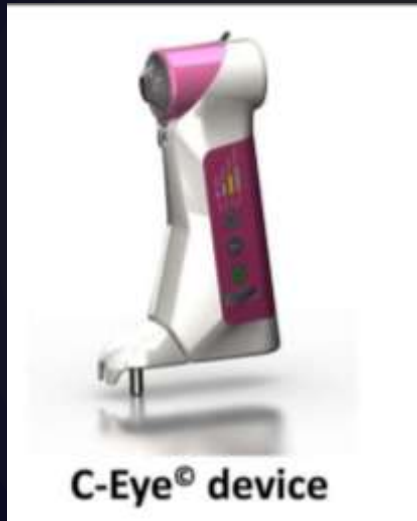
The authors have no financial or proprietary interest in the materials presented herein.

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CXL: Corneal infection



Take home message

- Revise your Riboflavin
- Revise your protocol
- Be cautious with Epi On
- Other options are still for research purposes

