Accelerated Corneal Collagen Cross-linking for Postoperative LASIK Ectasia: Two-Year Outcomes

Gustavo K. Marino, MD; Andre A. M. Torricelli, MD; Natalia Giacomin, MD; Marcony R. Santhiago, MD, PhD; Rodrigo Espindola, MD; Marcelo V. Netto, MD

ABSTRACT

PURPOSE: To evaluate the effectiveness and safety of accelerated corneal collagen cross-linking for postoperative LASIK ectasia after 2 years.

METHODS: A prospective, single-center case series was performed with patients treated for postoperative LASIK ectasia. All eyes underwent accelerated corneal collagen cross-linking (CCL-Vario Crosslinking; Peschke Meditrade GmbH, Zurich, Switzerland) at 9 mW/cm^2 for 10 minutes. The main outcome measures were changes in uncorrected distance visual acuity, corrected distance visual acuity, central corneal thickness, corneal topography, and endothelial cell density. These parameters were assessed at baseline and at the 6-month and 1- and 2-year follow-up visit.

RESULTS: The study enrolled 40 eyes of 24 patients (15 male and 9 female) with a mean age of 33.8 ± 7.5 years (range: 24 to 52 years) that attained at least 2 years of follow-up. The surgical procedure was uneventful in all cases. All eyes stabilized after treatment without any further signs of progression and no statistically significant changes in the mean uncorrected distance visual acuity (P = .649), corrected distance visual acuity (P = .616), mean keratometry (P =.837), steep keratometry (P = .956), ultrasonic pachymetry (P = .135), slit-scanning pachymetry (P = .276), and endothelial cell density (P = .523). In addition, 72.5% of the patients presented stable or gains of Snellen lines over time.

CONCLUSIONS: Accelerated corneal collagen cross-linking seems to be safe and effective in halting postoperative LASIK ectasia progression after 2 years of follow-up. However, a longer follow-up period with a larger cohort is needed to validate these findings.

[*J Refract Surg.* 2015;31(6):380-384.]

Postoperative LASIK ectasia is a dramatic and undesirable complication for both the patient and surgeon. It is characterized by progressive stromal thinning and irregular steepening that can lead to corneal refractive changes and loss of visual acuity.[1] Postoperative LASIK ectasia pathophysiology is not completely understood yet; however, reduction of biomechanical strength induced by the surgery seems to be an essential element in the chain of events.[2]

The therapeutic options for postoperative LASIK ectasia are similar to those for keratoconus, which include rigid gas permeable contact lenses, intrastromal corneal ring segments, penetrating or lamellar keratoplasty, and, more recently, corneal collagen cross-linking (CXL).[2-6]

CXL has proven to be a safe and effective procedure to increase corneal biomechanical stability and stiffness at the expense of new intrafibrillar and interfibrillar covalent bonds among stromal collagen fibers, thus halting corneal ectasia progression.[7,8] The standard CXL protocol involves epithelial removal and saturation of the cornea with riboflavin 0.1% followed by 30 minutes of ultraviolet A (UVA) radiation application at 3 mW/cm^2.

Accelerated CXL has emerged as a beneficial alternative to standard CXL because it shortens the procedure time and provides more comfort and tolerance for patients.[9] The accelerated CXL principle is based on the Bunsen–Roscoe photochemical law of reciprocity, which assumes that the effects (induced cross-links) of the photochemical reaction are similar if the intensity and time are changed while the total energy dose remains the same.[10,11] As a consequence, the amount of cross-links induced by irradiation at 9 mW/cm^2 for 10 minutes (accelerated CXL) and 3 mW/cm^2 for 30

From the Department of Ophthalmology, University of São Paulo, São Paulo, Brazil (GKM, AAMT, NG, MRS, RE, MVN); and Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio (GKM).

Submitted: December 5, 2014; Accepted: April 15, 2015

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

Correspondence: Marcelo V. Netto, MD, Av. Dr. Enéas de Carvalho Aguiar, 155, Cerqueira César, São Paulo/SP, Brazil 05403-000. E-mail: mvnetto@gmail.com

doi:10.3928/1081597X-20150521-04

minutes (standard CXL) should be equivalent, but with a reduced procedure time by a factor of three.[9]

Although previous studies have shown that accelerated CXL provides encouraging outcomes, there is still a lack of long-term data regarding accelerated CXL for postoperative LASIK ectasia. Therefore, the current study aims to evaluate the effectiveness and safety of this promising procedure after 2 years of follow-up.

PATIENTS AND METHODS

Study Population

The study was approved by the institutional review board of the University of São Paulo Medical School and adhered to the tenets of the Declaration of Helsinki. Informed consent was also obtained from all patients after detailed discussion, including alternatives and potential complications.

A prospective case series was performed for patients treated with accelerated CXL for progressive postoperative LASIK ectasia at the University of São Paulo, São Paulo, Brazil, between September 2011 and July 2012.

All patients had a history of LASIK surgery and were referred to our clinic after the onset of ectasia signs and/or symptoms. Determining the reasons for biomechanical instability was not part of the goal of this study. The follow-up period was 2 years after accelerated CXL treatment. The study included eyes that developed ectasia after LASIK submitted to accelerated CXL. Postoperative LASIK ectasia was defined as progressive inferior steepening, increasing myopia and astigmatism, and loss of uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA).[1,12] All patients with ectasia included in the analysis had uneventful surgery with initially good outcomes prior to developing the aforementioned findings. Exclusion criteria included central corneal thickness less than 350 µm measured by ultrasonic pachymetry, a history of corneal surgery besides LASIK, herpetic keratitis, chemical injury or delayed epithelial healing, severe dry eye, concomitant autoimmune diseases, and pregnant or lactating women during the treatment.

A complete ophthalmologic examination was performed on all patients at baseline and postoperatively at 6 months and 1 and 2 years, including UDVA and CDVA, slit-lamp evaluation, Goldmann applanation tonometry, central corneal thickness measured by slit-scanning device (Orbscan; Bausch and Lomb, Orbitech Inc., Rochester, NY), ultrasonic pachymetry (Corneogage Plus; Sonogage, Inc., Cleveland, OH), Placido-based corneal topography of the central 3 mm (Atlas 9000; Carl Zeiss Meditec, Inc., Dublin, CA), and endothelial cell density (ECD) using noncontact specular microscopy (Konan Medical, Inc., Hyogo, Japan).

Accelerated CXL

Accelerated CXL procedures were conducted under sterile conditions in an operating room by the same surgeon (MVN). After topical anesthesia with tetracaine hydrochloride 1% and phenylephrine hydrochloride 0.1% eye drops and setting the sterile field with a blepharostat, the central 9.0 mm of corneal epithelium were debrided with a blade. Riboflavin 0.1% solution (Ophthalmos, São Paulo, Brazil) was instilled every 3 minutes for 30 minutes before the procedure for complete stromal saturation, confirmed by aqueous fluorescence with blue light slit-lamp biomicroscopy. In 7 eyes of 5 patients whose ultrasonic pachymetry was thinner than 400 µm prior to the treatment, hypo-osmolar riboflavin solution was used to promote corneal swelling up to a safe cut-off and, finally, UVA irradiation was applied (CCL-Vario Crosslinking; Peschke Meditrade GmbH, Zurich, Switzerland). Prior to treatment, the intended 9 mW/cm^2 surface irradiance was calibrated using a UVA meter at a working distance of 5 cm. During irradiation, riboflavin solution was applied every 3 minutes to keep corneal saturation.

After UVA exposure, the treated eye was rinsed with balanced salt solution and a bandage contact lens was placed and maintained for 5 days until total reepithelialization. Gatifloxacin ophthalmic solution and prednisolone acetate 1% ophthalmic suspension were prescribed four times a day for 1 week. Non-preserved artificial tears were also prescribed four to eight times a day as needed.

Statistical Analysis

Statistical analyses were performed with the SPSS 20.0 (SPSS, Inc., Chicago, IL), and all data were reported as mean ± standard deviation. Comparison was performed using generalized estimation equations, first order autoregressive correlation matrix between moments, normal distribution, and identity link function. A *P* value less than .05 was considered statistically significant.

RESULTS

The study comprised 40 eyes of 24 patients (15 male and 9 female) with a mean age of 33.8 ± 7.5 years (range: 24 to 52 years) that attained at least 2 years of follow-up. The surgical procedure and the postoperative period were uneventful in all cases regarding ocular or systemic adverse events.

Figures 1-2 present preoperative Placido-based corneal topographies and postoperative accelerated CXL and anterior segment optical coherence tomography showing depth correlation of corneal demarcation line induced by accelerated CXL and the previous LASIK corneal flap from one of the cases.

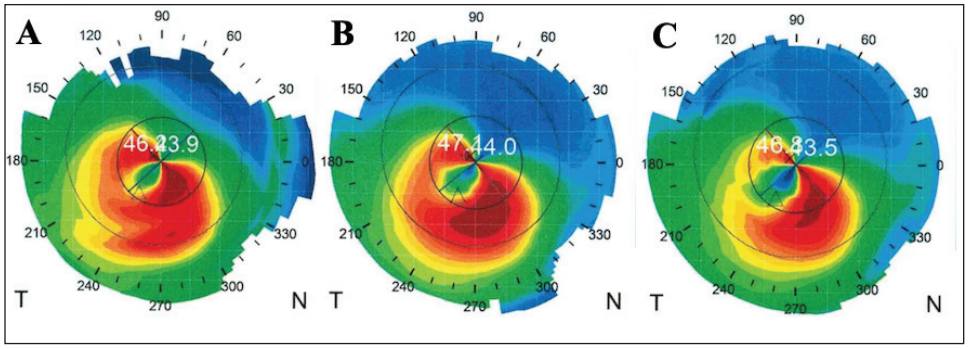

Figure 1. Placido-based corneal topographies. (A) Diagnostic of postoperative corneal ectasia, (B) confirmation of postoperative LASIK ectasia progression, and (C) keratometric stability after 2 years of accelerated corneal collagen cross-linking.

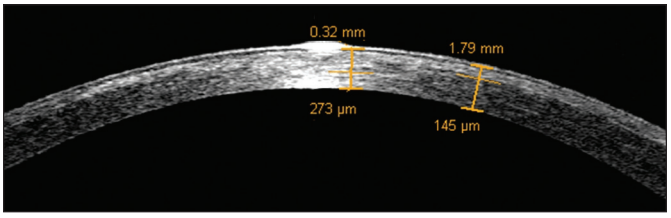

Figure 2. Anterior segment optical coherence tomography showing depth correlation of corneal demarcation line induced by accelerated corneal collagen cross-linking and the previous LASIK corneal flap.

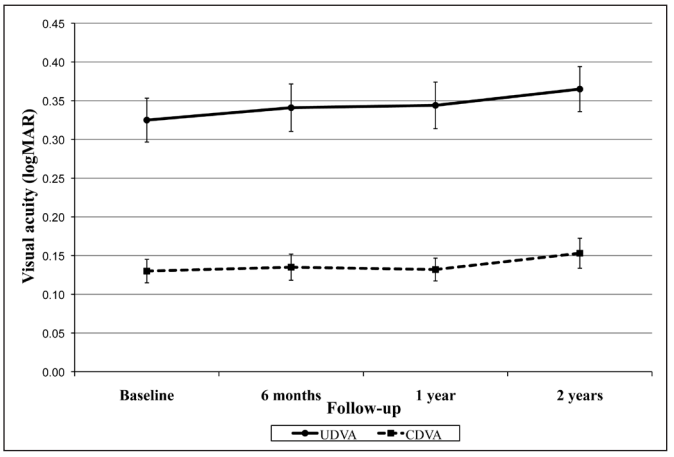

Figure 3. Uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA) at baseline and at 6 months and 1 and 2 years of follow-up.

Visual Acuity

The UDVA and CDVA outcomes during the follow-up period are provided in **Figure 3**. UDVA changed from 0.33 ± 0.18 to 0.37 ± 0.18 logMAR (20/42 to 20/46 Snellen) after 2 years of follow-up, whereas CDVA changed from 0.13 ± 0.10 to 0.15 ± 0.12 logMAR (20/26 to 20/28 Snellen). Although a slight trend toward reduction of both UDVA and CDVA could be observed, no statistically significant difference was noted during the follow-up period (P = .649 and .616 for UDVA and CDVA, respectively). Also, CDVA was stable or improved in 72.5% of all patients after 2 years, whereas 10% of patients lost three Snellen lines (**Figure 4**).

Corneal Topography

Mean and steep keratometry values were 45.81 ± 1.87 and 48.89 ± 2.85 at baseline, respectively; 45.81 ± 1.97 and 49.04 ± 2.86 at 6 months postoperatively; 45.88 ± 2.12 and 48.91 ± 2.91 at 1 year postoperatively; and 45.93 ± 2.18 and 49.21 ± 3.15 at 2 years postoperatively. No keratometric parameter reached statistical significance (P = .837 and .956 for mean and steep keratometry, respectively).

Central Corneal Thickness

Ultrasonic pachymetry values at baseline and 6 months and 1 and 2 years postoperatively were 466 ± 63, 456 ± 56, 456 ± 56, and 453 ± 53 µm, respectively. Again, no statistical difference was noted among measurements (P = .135).

ECD

Mean preoperative ECD was 2,997 ± 119 cells/mm^2. Over time, the endothelial cell densities were 2,965 ± 103 cells/mm^2 at 6 months postoperatively, 2,997 ± 122 cells/mm^2 at 1 year postoperatively, and 2,988 ± 70 cells/mm^2 at 2 years postoperatively. No statistically significant decrease in the central ECD was observed during the follow-up period (P = .523).

DISCUSSION

CXL represents a landmark in the treatment of corneal ectasia because for the first time it directly targets the underlying pathology (stromal instability stemming from collagen abnormalities) rather than only addressing the refractive consequences of the disorder.[10] By inducing additional bonds between and within collagen fibers using UVA light and riboflavin as photomediators, it increases corneal biomechanical stability and stiffness, thus delaying or avoiding the disease progression. Based on the encouraging outcomes of the accelerated CXL protocols for the keratoconus treatment,[11,13] we present a prospective case series of eyes treated for postoperative LASIK ectasia with accelerated CXL (9 mW/cm^2 for 10 minutes).

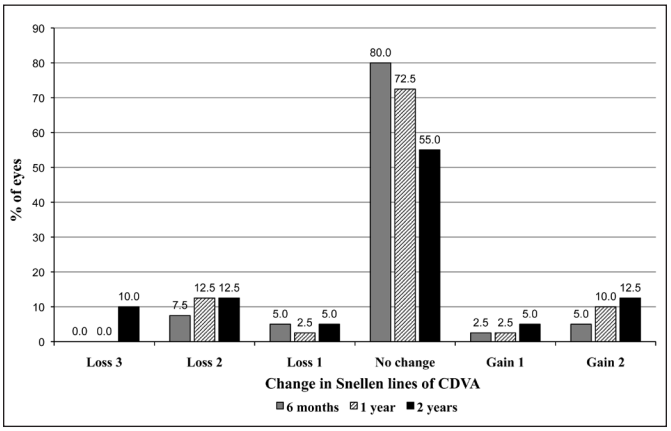

Figure 4. Change in Snellen lines of corrected distance visual acuity (CDVA) at 6 months and 1 and 2 years of follow-up.

The current study shows stabilization of both UDVA and CDVA in the majority of the patients during the follow-up period. Moreover, the keratometric readings and the pachymetry measures also remained stable, and no reduction in the ECD was noted. To the best of our knowledge, this is the first 2-year follow-up study to evaluate the effectiveness and safety of accelerated CXL in postoperative LASIK ectasia.

The aforementioned findings are in agreement with previous studies that reported the course of progressive postoperative LASIK ectasia is halted by CXL treatment.[2,5] In addition, it extends to the postoperative surgery ectatic eyes findings of Elbaz et al.,[14] which demonstrated the efficacy of accelerated CXL in stabilizing moderate keratoconus-affected corneas after 12 months of follow-up. Accelerated CXL has been shown to be as safe as the standard CXL and provides similar results in the treatment of keratoconic eyes.[11,13] However, a paucity of studies addresses this new approach in postoperative LASIK ectatic eyes.

Although stabilization in both UDVA and CDVA was acheived in the current study, the keratometric readings did not improve as reported in studies involving keratoconic eyes.[13,15] Possible reasons for distinct responses between keratoconic eyes and postoperative LASIK ectatic eyes after CXL treatment include: the anterior two-thirds of the cornea (responsible for more biomechanical strength than the posterior stroma and the main site affected by cross-linking) is weakened by flap generation and tissue ablation[2]; a possible difference in the riboflavin stromal diffusion rate due to the flap interface; and an intrinsic pathophysiologic difference among the disorders.[16] These hypotheses may explain in part why the keratometric readings remained unchanged after 2 years of follow-up instead of corneal flattening as previously described.

Regarding ECD, our study corroborates the recent data in the literature. Mita et al.[11] demonstrated a stable ECD 6 months after accelerated CXL (30 mW/cm^2 for 3 minutes) in 39 keratoconic eyes. Vinciguerra et al.[5] found that standard CXL did not induce endothelial damage after 1 year of treatment. Kymionis et al.[9] reported neither a statistically significant change in ECD nor lost lines of CDVA in 10 keratoconic eyes treated with accelerated CXL (9 mW/cm^2 for 10 minutes) after 3 months.

No ocular complication was noted, such as clinically significant persistent corneal haze, infectious keratitis, cataract formation, or retinal damage. Accelerated CXL seems to be a safe and effective approach in halting the progression of postoperative LASIK ectasia after 2 years of follow-up. A longer follow-up period with a larger cohort and a comparative study are needed to validate these findings; however, accelerated CXL appears to be a good alternative to standard CXL in postoperative LASIK ectasia cases.

AUTHOR CONTRIBUTIONS

Study concept and design (MVN); data collection (NG, RE, MVN); analysis and interpretation of data (GKM, AAMT, MRS, MVN); writing the manuscript (GKM, AAMT, NG); critical revision of the manuscript (MRS, RE, MVN); statistical expertise (GKM, AAMT); supervision (MRS, MVN)

REFERENCES

1. Randleman JB, Russell B, Ward MA, Thompson KP, Stulting RD. Risk factors and prognosis for corneal ectasia after LASIK. *Ophthalmology*. 2003;110:267-275.
2. Hafezi F, Kanellopoulos J, Wiltfang R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2007;33:2035-2040.
3. Cheema AS, Mozayan A, Channa P. Corneal collagen crosslinking in refractive surgery. *Curr Opin Ophthalmol*. 2012;23:251-256.
4. Nguyen MK, Chuck RS. Corneal collagen cross-linking in the stabilization of PRK, LASIK, thermal keratoplasty, and orthokeratology. *Curr Opin Ophthalmol*. 2013;24:291-295.
5. Vinciguerra P, Camesasca FI, Albè E, Trazza S. Corneal collagen cross-linking for ectasia after excimer laser refractive surgery: 1-year results. *J Refract Surg*. 2010;26:486-497.
6. Woodward M, Randleman JB, Russell B, Lynn MJ, Ward MA, Stulting RD. Visual rehabilitation and outcomes for ectasia after corneal refractive surgery. *J Cataract Refract Surg*. 2008;34:383-388.
7. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135:620-627.
8. Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA-riboflavin cross-linking of the cornea. *Cornea*. 2007;26:385-389.
9. Kymionis GD, Grentzelos MA, Kankariya VP, et al. Safety of high-intensity corneal collagen crosslinking. *J Cataract Refract Surg*. 2014;40:1337-1340.
10. Raiskup F, Spoerl E. Corneal crosslinking with riboflavin and ultraviolet A: I. Principles. *Ocul Surf*. 2013;11:65-74.

11. Mita M, Waring GO 4th, Tomita M. High-irradiance accelerated collagen crosslinking for the treatment of keratoconus: six-month results. *J Cataract Refract Surg*. 2014;40:1032-1040.
12. Santhiago MR, Smadja D, Gomes BF, et al. Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal preoperative topography. *Am J Ophthalmol*. 2014;158:87-95.
13. Tomita M, Mita M, Huseynova T. Accelerated versus conventional corneal collagen crosslinking. *J Cataract Refract Surg*. 2014;40:1013-1020.
14. Elbaz U, Shen C, Lichtinger A, et al. Accelerated (9-mW/cm^2) corneal collagen crosslinking for keratoconus-A 1-year follow-up. *Cornea*. 2014;33:769-773.
15. Richoz O, Mavrakanas N, Pajic B, Hafezi F. Corneal collagen cross-linking for ectasia after LASIK and photorefractive keratectomy: long-term results. *Ophthalmology*. 2013;120:1354-1359.
16. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *J Cataract Refract Surg*. 2011;37:149-160.