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.

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, hyposmolar 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/cm² 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.
**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).

**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 (\(P = .135\)).

**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).

**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.\(^\text{10}\) By inducing additional bonds between and within collagen fibers using UVA light and riboflavin as photo-mediators, 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,\(^\text{11,13}\) we present a prospective case series of eyes treated for postoperative LASIK ectasia with accelerated CXL (9 mW/cm\(^2\) for 10 minutes).
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. In addition, it extends to the postoperative surgery ectatic eyes findings of Elbaz et al., 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.

However, a paucity of studies addresses this new approach in postoperative LASIK ectatic eyes. Although stabilization in both UDVA and CDVA was achieved in the current study, the keratometric readings did not improve as reported in studies involving keratoconic eyes. 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; a possible difference in the riboflavin stromal diffusion rate due to the flap interface; and an intrinsic pathophysiologic difference among the disorders. 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. demonstrated a stable ECD 6 months after accelerated CXL (30 mW/cm² for 3 minutes) in 39 keratoconic eyes. Vinciguerra et al. found that standard CXL did not induce endothelial damage after 1 year of treatment. Kymionis et al. reported neither a statistically significant change in ECD nor lost lines of CDVA in 10 keratoconic eyes treated with accelerated CXL (9 mW/cm² 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**


