Accelerated (9-mW/cm^2) Corneal Collagen Crosslinking for Keratoconus—A 1-Year Follow-up

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Purpose: The aim of this study was to assess the efficacy of accelerated crosslinking (irradiance of 9 mW/cm^2; 10 minutes) in keratoconus-affected eyes through topographical, visual, and refractive end points.

Methods: Mild-moderate keratoconus-affected eyes that underwent accelerated corneal collagen crosslinking (CXL) treatment and had 6 and 12 months of follow-up were reviewed retrospectively. Data regarding uncorrected distance visual acuity (UDVA), manifest refraction, corrected distance visual acuity (CDVA), and computerized corneal topography data before surgery and post-CXL treatment were extracted and analyzed.

Results: Sixteen eyes of 14 patients were included in the study. The mean patient age was 24.9 ± 5.8 years (range: 17.1–38.3 years). No statistically significant changes were found in the mean CDVA, mean refractive cylinder, or mean manifest refraction spherical equivalent at either time point. There was a gain of 0.13 logarithm of the minimum angle of resolution lines in the mean UDVA ($P = 0.012$) at 12 months. All corneal parameters including K_{steep}, K_{flat}, average K (K_m), corneal astigmatism (K_{cyl}), and maximal curvature reading at the corneal apex (K_{max}) were stable at 6 and 12 months in all patients. No complications were observed during the follow-up period.

Conclusions: Accelerated corneal CXL is effective in stabilizing topographic parameters after 12 months of follow-up in mild-moderate keratoconus-affected corneas. Improvement in the UDVA and stabilization of all tested corneal parameters were noted after the treatment. However, a longer follow-up with larger cohorts is necessary to validate these findings.

Key Words: accelerated collagen crosslinking, accelerated CXL, high-fluence CXL, keratoconus

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Since its introduction in 1998, corneal collagen crosslinking (CXL) has emerged as the principal treatment for the stabilization of the cornea in patients with progressive keratoconus.[1] Numerous studies have highlighted the efficacy[2–4] and safety[5–7] of the standard corneal CXL procedure as a corneal stabilizing measure for treating keratoconus. Often, some degree of accompanying improvement in the corneal parameters and in the refractive outcome has been found after treatment.[8,9]

As our understanding of corneal CXL has deepened, variations made to the standard protocol have evolved to expand the scope and quality of the practice. These modifications include the use of preoperative drops, such as pilocarpine, to minimize ultraviolet A (UVA) damage to internal ocular structures; the introduction of hypoosmolar riboflavin to treat thin corneas; use of transepithelial corneal CXL; inclusion of combined CXL and refractive surgery; incorporation of iontophoresis; and use of accelerated CXL.[1] Accelerated corneal CXL is gaining popularity as caregivers, researchers, and patients strive for better outcomes with a shorter treatment duration. Accelerated corneal CXL uses higher energy settings (up to an irradiance of 30 mW/cm^2) compared with that used in the standard corneal CXL treatment (irradiance of 3 mW/cm^2). This enables a shortening of the treatment duration from 30 minutes to as little as 3 to 10 minutes while maintaining the total radiant exposure (5.4 J/cm^2). However, there is a paucity of clinical data concerning the efficacy of accelerated corneal CXL treatment.[10–13] Preclinical testing has shown that accelerated CXL (irradiance of 10 mW/cm^2; 9 minutes) imparts equivalent biomechanical changes in porcine corneas ex vivo compared with those in standard treatment.[14,15] Recently, encouraging confocal microscopy findings in vivo have shown that accelerated CXL has an equivocal effect when compared with that of the conventional CXL.[16]

The safety profile of high-fluence corneal CXL for progressive keratoconus was evaluated by Gatzioufas et al[10] in a small cohort of 7 eyes with a 6-month follow-up. They found no change in endothelial cell density or epithelial healing time using accelerated CXL at 18 mW/cm^2, for 5 minutes. No morphological alterations in the corneal limbus were observed.

Our study aims to evaluate the clinical outcomes of accelerated corneal CXL in mild-moderate keratoconus after 1 year.

PATIENTS AND METHODS

This study was approved by the institutional research ethics committee at the University Health Network, Toronto, ON, Canada. A retrospective review of patients with keratoconus eyes undergoing accelerated CXL treatment between February 2012 and October 2012 revealed 56 eyes of 39 patients. We have included in the study only mild-moderate (grade I–II by the Amsler–Krumeich classification[17,18]) keratoconus-affected eyes that had both 6 and 12 months of follow-up visits. Therefore, 16 eyes (14 patients) were included in the study, and 40 eyes (25 patients) that did not complete the follow-up to 12 months were omitted. Early complications in the omitted eyes were examined for completeness. Accelerated CXL was performed following objective and/or subjective evidence of visual deterioration. Progression of the ectasia was defined as a decrease in visual acuity of at least 1 line, a steepening of at least 1.0 diopter (D) in the steepest keratometry over the past 6 months, or >1 change in the prescription of glasses or contact lenses over the past 2 years. Patients were instructed to discontinue the use of hard contact lens at least 2 weeks before any assessment and CXL treatment. Informed consent for the CXL treatment was obtained from all the patients before performing the procedure. Uncorrected distance visual acuity (UDVA), manifest refraction, corrected distance visual acuity (CDVA), and computerized corneal topography data including steep K (K_{steep}), flat K (K_{flat}), average keratometry reading (K_m), corneal astigmatism (K_{cyl}), maximal corneal curvature reading at the corneal apex (K_{max}) before the CXL and at 6- and 12-month visits were extracted from charts and analyzed. Pre-CXL and Post-CXL topography data were recorded using the OPD-III scan (Nidek, Japan). Endothelial cell counts were not performed.

Accelerated corneal CXL was conducted under sterile conditions as follows: the patient's eye was anesthetized with proparacaine hydrochloride 0.5% (Alcaine; Alcon Laboratories, Inc, Mississauga, Canada). Ultrasound corneal thickness (central and peripheral) was measured in all cases before and after epithelial removal, and thinnest pachymetry was recorded. An 8-mm diameter area of the corneal epithelium was removed by using 50% alcohol for 5 seconds to allow better diffusion of riboflavin into the stroma. After epithelial removal, single-use isotonic eye drops of riboflavin 0.1% and 20% dextran solution (Habers pharmacy, Toronto, Canada) were instilled every 2 minutes for 30 minutes. In patients in whom the thinnest pachymetry was <400 μm, hypoosmolar riboflavin (riboflavin 0.1% diluted with physiologic salt solution with no dextran added to the solution; Habers pharmacy, Toronto, Canada) was used in the same manner. UVA irradiation was performed using an optical system (UV-X 2000; IROC AG, Zurich, Switzerland) with a light source consisting of an array of UV diodes (365 nm). Irradiance was performed for 10 minutes at 9 mW/cm^2. During the period of UVA exposure, riboflavin solution was applied every 2 minutes to saturate the stroma with riboflavin. 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 on day 4. Postoperatively, the patients were given a combination of moxifloxacin 0.5% (Vigamox; Alcon Laboratories, Inc, Mississauga, Canada), and dexamethasone 0.1% (Maxidex, Alcon Laboratories, Inc) eye drops. Vigamox was applied 4 times a day until contact lens removal, and the Maxidex was applied hourly for 2 days as a precaution against developing early haze after CXL[4] and then 4 times a day for 2 weeks. The patients were encouraged to use preservative-free artificial tears at least 4 times daily.

Statistical Analysis

Geometric visual acuity was converted to the logarithm of the minimum angle of resolution (logMAR) units, and manifest refraction was converted to manifest refraction spherical equivalent (MRSE). Friedman test was used to compare the logMAR visual acuity (UDVA and CDVA), refractive cylinder, MRSE, and corneal curvature before and after CXL, with Wilcoxon signed-rank test with Bonferroni correction as appropriate. Statistical analysis was performed using SPSS 20 (IBM, Armonk, NY), and a P value of <0.05 was considered significant.

RESULTS

Sixteen eyes of 14 patients (3 females, 11 males) were included in this study. The mean patient age was 24.9 ± 5.8 (range: 17.1–38.3) years. Demographic, visual, and refractive data before and post-CXL are summarized in Table 1.

Keratometric data showed a nonstatistically significant difference in all evaluated parameters (K_{steep}, K_{flat}, K_m, K_{cyl}, and K_{max}; Table 2) preoperatively and postoperatively after 6 and 12 months from the CXL. The mean preoperative K_{max} was 51.30 ± 3.99 (range: 44.84–56.36) D. Keratoconus was classified as stable if the change in K_{max} was <1.0 D, progressive if the K_{max} increased by ≥1.0 D, and regressive if the K_{max} decreased by ≥1.0 D (Fig. 1). At 12 months, 50% of the eyes (8/16) had flatter K_{max} values by a mean of 0.48 ± 0.38 D, and 50% (8/16) had steeper K_{max} values by a mean of 0.36 ± 0.24 D; however, none of these changes were statistically significant.

No statistically significant difference was noted in the mean CDVA, mean refractive cylinder, and mean MRSE after treatment. At 6 months, 63% of the eyes (10/16) had either gained logMAR lines or remained stable, and at 12 months, 81% of the eyes (13/16) had either gained logMAR lines or remained stable in CDVA (Fig. 2). No eye lost >0.12 logMAR lines of CDVA. A gain of 0.13 logMAR lines in the mean UDVA (P = 0.012) was evident at 12 months. At 6 months, 88% of the eyes (14/16) had either gained logMAR lines or remained stable, and at 12 months, 94% of the eyes (15/16) had either gained logMAR lines or had remained stable with 1/16 eyes losing 0.10 logMAR lines of UDVA.

No complications, such as chronic epithelial defects, haze, or infectious keratitis were reported throughout the postoperative follow-up period in the study population. A review of the patient charts omitted from the primary study revealed 7 eyes (12.5% of all treated eyes) with trace subepithelial haze in the early postoperative period that resolved before the patients were lost to follow-up. None of

TABLE 1. Summary of Demographic Patient Data and Visual and Refractive Outcomes Presurgery and Postsurgery

No. eyes					11 Right, 5 left	
No. patients					3 Females, 11 males	
Age					24.95 ± 5.76	
	Preoperative	**6 mos**	**12 mos**	***P****	***P*†**	***P*‡**
MRSE	−2.22 ± 3.87	−2.31 ± 3.57	−2.47 ± 3.25	0.801		
Refractive Cyl	−2.35 ± 1.51	−2.52 ± 1.47	−2.52 ± 1.47	0.766		
UDVA (logMAR)	0.78 ± 0.51	0.70 ± 0.49	0.65 ± 0.48§	0.008	0.114	0.012
CDVA (logMAR)	0.02 ± 0.10	0.05 ± 0.12	0.01 ± 0.09	0.266		

Measures denoted as mean ± SD.
*Friedman test.
†Wilcoxon signed-rank test with Bonferroni correction (preop vs. 6 months).
‡Wilcoxon signed-rank test with Bonferroni correction (preop vs. 12 months).
§Significant difference ($P < 0.05$) preoperative and postoperative.

these patients exhibited delayed epithelial healing or infectious keratitis. The bandage contact lens was typically removed at day 4 in all patients when no epithelial defect was observed.

DISCUSSION

In their original protocol, Wollensak et al[2] described the CXL procedure with UVA light application of an intensity of 3 mW/cm^2 for 30 minutes (total radiant exposure of 5.4 J/cm^2) for a given treatment. This was defined at that time to be the safest threshold that can be applied to a cornea thicker than 400 μm, without any damage to the endothelium, the crystalline lens, and/or the retina.[5,7] These results have been confirmed in a later study that evaluated the safety of CXL.[6] As technology evolves, better treatments and medical instrumentation afford us the means to improve our quality of treatment. Newer devices that provide the option of higher energy power settings are capable of reducing the duration of the CXL procedure. Shortening of treatment time has major implications for cost effectiveness, throughput, and patient comfort. However, applying the same amount of energy over a shorter period of time during CXL treatment does not necessarily mean that the CXL process has the same clinical efficacy, or that the treatment depth confines only to the anterior 300 μm of the stroma, as was demonstrated for standard treatment.[19,20]

Preclinical studies[14,15] that investigated the biomechanical properties of porcine corneas after accelerated (10 mw/cm^2, 9 minutes) versus standard treatment showed that the accelerated CXL treatment can be regarded as equivalent to the standard procedure in terms of an increase in corneal stiffness causing a 1.3-fold increase as measured by the Young modulus. Another study by Wernli et al[15] investigating graded irradiation intensities resulting in a total radiant exposure of 5.4 J/cm^2 found an increase by a factor of approximately 2.2 in porcine corneal stiffness using 9 minutes of a 10-mW/cm^2 treatment.

Currently, there is a paucity of clinical data regarding the safety and efficacy profiles of higher energy CXL settings; nonetheless, different machines with different settings providing this treatment modality are already in clinical use. Our study focuses on the outcomes of the accelerated 10-minute CXL procedure. We show that in accordance with published studies on standard CXL, and with recently published studies on accelerated CXL, the 10-minute accelerated CXL (irradiance of 9 mW/cm^2) is effective for corneal stabilization and for halting the progression of keratoconus throughout the 12-month follow-up period.

TABLE 2. Patient Topographical Data Presurgery and Postsurgery

	Preoperative	**6 mos Postoperative**	**12 mos Postoperative**	***P***
K_{steep} (D)	46.50 ± 2.21	46.75 ± 2.53	46.52 ± 2.26	0.199
K_{flat} (D)	44.19 ± 1.54	44.17 ± 1.60	44.20 ± 1.59	0.888
K_m (D)	45.35 ± 1.78	45.46 ± 1.94	45.36 ± 1.84	0.314
K_{cyl} (D)	2.31 ± 1.39	2.58 ± 1.70	2.32 ± 1.33	0.156
K_{max} (D)	51.30 ± 3.99	51.48 ± 3.93	51.24 ± 3.79	0.779

Measures denoted as mean ±SD.
K_{cyl}, corneal astigmatism; K_m, average keratometry; K_{max}, maximal corneal curvature readings.

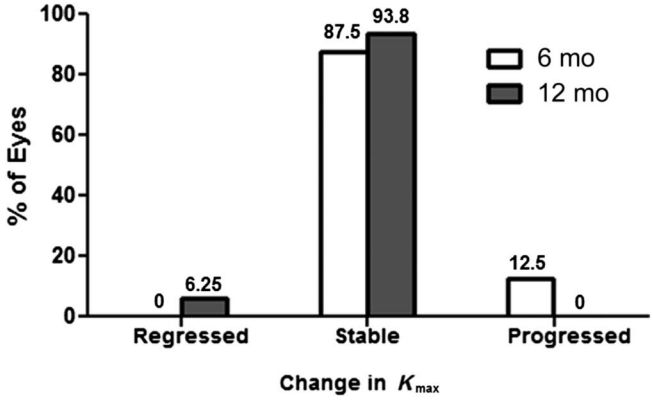

FIGURE 1. Change in K_{max} at 6 and 12 months postoperation.

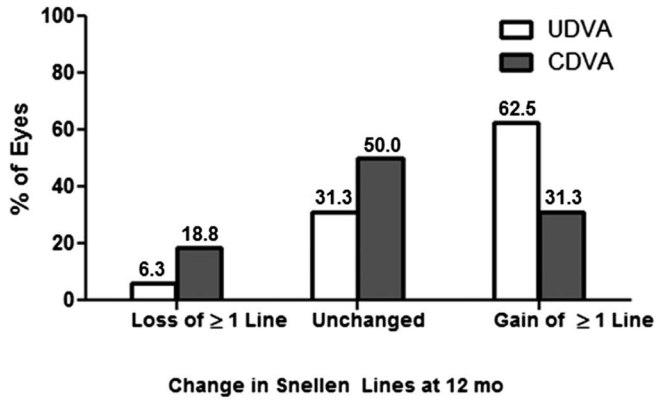

FIGURE 2. Change in the UDVA and CDVA at 12 months postoperation.

Multiple studies have shown encouraging long-term results of standard CXL for halting the progression of keratoconus. Some of the studies have even shown regression of the disease with a significant reduction in corneal curvature and improvement in visual outcomes.[3,8,9] The Siena eye cross-study[8] found a constant slow corneal flattening (K_{mean} decrease) starting at 3 months after the treatment and stabilizing after 24–48 months. The K_{mean}, K_{max}, and minimal K values were shown to be reduced by a mean of 2 D after 48 months of follow-up. Similarly, in a different study[9] reporting on the long-term results (up to 6 years) of standard CXL for keratoconus, a significant reduction in corneal steepening was observed over time, peaking at 4 years after the procedure was carried out.

However, certain studies have highlighted a stabilization phenotype after standard CXL rather than a regression.[3,4,21,22] One of the most thorough studies conducted among this group was that of Hashemi et al[3] who could not find a significant decrease in any of the computerized topography data. However, they could still show stabilization in the K_{mean}, K_{max}, UDVA, and refractive astigmatism over the 5 years of follow-up. In their study, the gain in the UDVA and CDVA was noted to be of 0.11 logMAR lines for both parameters after a year and of 0.02 and 0.12 (P = 0.016) logMAR lines after 5 years, respectively.

If accelerated CXL behaves comparably with standard CXL, then regression or at least stabilization in corneal parameters is expected. In a previous study, Kanellopoulos[13] compared high-fluence CXL of 7 mW/cm^2 for 15 minutes in 1 eye with standard 3 mW/cm^2 for 30 minutes in the other eye in 21 patients with bilateral progressive keratoconus with a mean follow-up of 46 months. He found a significant decrease in the K_{steep} from 49.5 to 46.1 D with a significant reduction in MRSE and improvement in UDVA and CDVA in both groups. However, the significant regression in his study may be at least partially explained by the use of transepithelial phototherapeutic keratectomy to debride the corneal epithelium before UV exposure as opposed to the alcohol debridement used in our patients. Transepithelial PTK may have some refractive effect especially in advanced keratoconus where the epithelium thickness over the cone is significantly $<$50 μm, allowing it to ablate part of the corneal stroma and therefore to flatten it.[23] Recently, 2 other studies conducted by the same author[11,12] have examined the clinical outcomes of accelerated CXL after 6 months of follow-up. Indeed, in these studies, where the epithelium was mechanically debrided, a less prominent reduction in corneal steepening was noted, from a mean K_{max} of 57.91 to 56.56 D (P = 0.03) after 6 months of follow-up. Contrary to these published findings, our study shows stabilization in CDVA, MRSE, refractive cylinder, and all corneal parameters after 12 months of follow-up (Fig. 1). It may be that the significantly less progressed keratoconus in our study accounts for the "nonregression" noted in our cohort. In addition, the slight statistically nonsignificant increase in the MRSE noted in our patients is misleading as 4 of the 16 eyes had high mixed myopic astigmatism as opposed to the compound myopic astigmatism of the rest of the cohort. This yielded a lower hyperopic refractive error (a myopic shift) after the treatment and therefore resulted in pseudoworsening of the mean MRSE. The statistically insignificant and clinically negligible change in the mean refractive cylinder may also be attributed to the difficulty in adjusting spherocylindrical spectacle correction in irregularly astigmatic corneas. The mean CDVA did not show a significant improvement after the treatment, likely because of the excellent preoperative CDVA values in our cohort. In the 3 cases where there was a loss of CDVA at 12 months, the preoperative CDVA was 20/20 or better and regressed to no more beyond 20/25, likely reflecting daily fluctuations in acuity and variance in measurements rather than a true deterioration in vision. All 3 of these patients reported excellent vision.

Of note, the results reported here relate to a cohort of mild to moderate keratoconus eyes. In more advanced cases (Amsler–Krumeich Grade III–IV) where vision is more impaired, we opt for a combinatory approach of same-day PTK, variable size intracorneal ring segment, and accelerated CXL to not only stabilize the cornea but also to enhance visual rehabilitation. If corneal scarring or thinning is too extensive to enable intracorneal ring segment insertion or safe CXL, a recommendation for corneal transplant is pursued. Standard CXL has been shown to prevent further progression in 27 of 28 eyes with advanced (K_{max} $>$ 55 D) progressive keratoconus[24]; however, the effect of accelerated CXL in this group remains to be elucidated.

Demonstrating the safety of higher energy settings is beyond the scope of our study as we did not control for endothelial cell loss. However, despite the higher energy profile, none of our patients developed corneal decompensation or cataracts through the follow-up period. Moreover, although no patients in our study population demonstrated any postoperative complications within the follow-up period, 7 eyes of those patients initially excluded because of the lack of a full 12-month follow-up had signs of trace subepithelial haze that resolved before being lost to the follow-up. This represents 12.5% of all treated eyes during the period examined. This is comparable with the 9.8% of the patients who experienced temporary haze within the first 3 months as reported by Caporossi et al[8] in their epithelium-off protocol.

In addition to the higher energy settings, the new UV-X 2000 has a unique beam-optimized profile that applies more energy in the corneal periphery to accommodate the

increased distance from the light source to the peripheral cornea. Therefore, a larger corneal volume is crosslinked compared with that in the standard treatment. Nevertheless, to show the clinical implications of this technical change, and the biomechanical differences between standard and accelerated CXL, comparative and longer follow-up studies are warranted.

A limitation of our study is the selection bias resulting from the retrospective nature of the study and our inclusion criteria. We have included only patients who had 6 and 12 months of follow-up to show long-term stability of the outcomes. This may have underestimated our complication rate, as only a subcohort of the total treated patients was assessed for the full 12 months. However, the charts of the patients excluded from the primary study were assessed for complications during the period in which they were followed, to offer as much completeness as possible. The patients in our refractive center routinely choose to be monitored by their local ophthalmologist and are therefore lost to follow-up. However, this type of selection bias may actually have underestimated our topographic and visual results as uncomplicated cases elect to be followed in the community and patients with progression in keratoconus and/or worsening in vision would have typically been referred to our center for continuing treatment and follow-up.

In conclusion, our study shows that accelerated CXL treatment (irradiance of 9 mW/cm^2; 10 minutes) is a viable option in the treatment of mild-moderate keratoconus. This represents a step toward optimizing CXL treatment and may have implications in the treatment of pellucid marginal degeneration, bullous keratopathy, and infectious keratitis[1] where CXL is used as well. A longer follow-up duration is needed to uncover further change (progression or regression) in our cohort. Also, different energy profiles should be clinically evaluated in larger cohorts to continuously improve CXL treatment for keratoconus-affected patients.

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