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ORIGINAL ARTICLE

High Order Aberration Outcomes of Corneal Collagen Crosslinking in Eyes with Keratoconus and Post-LASIK Ectasia

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ABSTRACT

Purpose: To evaluate the effect of riboflavin and ultraviolet-A-induced corneal collagen crosslinking (CXL) on high order aberrations (HOA) up to third-order at 6 months using the iTrace wavefront aberrometer in patients with progressive keratoconus and post-LASIK ectasia.

Materials and methods: Ongoing retrospective chart review of patients having undergone CXL. The iTrace (Tracey Technologies, Houston, TX) was used to evaluate HOA. Patient data was collected from a single clinical site pre- and 6 months postoperatively. Data collected included logMAR uncorrected distance visual acuity (UDVA), logMAR corrected distance visual acuity (CDVA), manifest refraction, and HOA measurements. Data was analyzed with paired two-tailed student's t-test.

Results: 18 eyes (9M:4F, mean age 29.2 years, range 16-45) had 6 months of follow-up. Total HOAs, total coma and total trefoil were significantly reduced at 6 months by 16, 33 and 26% respectively ($p < 0.05$). Nonsignificant trends toward improvement were seen in spherical aberration, secondary astigmatism and UDVA. There were no statistically significant changes in manifest refraction or CDVA.

Conclusion: Improvement in high order aberration profile is one mechanism by which corneal collagen crosslinking enhances visual function in ectatic corneas. Total HOA and total coma measures are the most commonly reported improvements in HOA measures in previous studies, while total trefoil has only been observed in one other study. The improvements seen in HOAs remain fairly modest which likely accounts for the lack of measureable improvement in high-contrast visual acuity measures, such as Snellen UDVA and CDVA. This study is the first to report HOA outcomes with the iTrace wavefront aberrometer.

Keywords: Crosslinking, Keratoconus, Ectasia.

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INTRODUCTION

Keratoconus is a progressive, non-inflammatory, ectatic disorder of the cornea with an incidence of approximately 1 in 2000.[1] Progressive deformation of the cornea with associated thinning leads to an increase in irregular astigmatism, progressive myopia and increasing high order aberrations.[2-8] Recently, it has been suggested that aberrometry may be useful in both the detection and grading of keratoconus.[9-12]

Aberrometry is the science of the detection and analysis of wavefront aberrations. Low order aberrations, also known as first and second degree aberrations, are simple refractive errors, such as defocus and astigmatism which can be readily corrected by conventional refraction. High order aberrations (HOAs) are defined as third-order aberrations and higher. Aberrations are mathematically described by Zernike polynomials, and are reported as a standard deviation across the pupil or root mean square in microns (RMS).[13] HOAs have long been known to increase with conventional laser refractive surgery. As a result, wavefront-guided procedures aimed at reducing the induction of these aberrations have rapidly gained popularity due to the potential benefits in uncorrected visual acuity and contrast sensitivity. Large measured values of high order aberrations, such as coma and trefoil, as seen in keratoconus, have been shown to contribute to decreased visual performance both in visual acuity and contrast sensitivity measures.[14,15]

Over the last decade corneal collagen crosslinking has revolutionized the treatment of mild to moderate keratoconus. Studies with medium- and long-term follow-up have demonstrated the ability of crosslinking to slow or halt disease progression in both pediatric and adult populations with relatively few complications.[16-20] As an added benefit, many studies have reported improvements in both visual acuity and corneal topographical measures following crosslinking.[3,16,17,21-27]

The purpose of this study is to further elucidate the changes seen in high order aberrations using the iTrace Wavefront Aberrometer (Tracey Technologies, Houston, TX), a combined ray-tracing aberrometer and Placido disk videokeratoscope.

MATERIALS AND METHODS

This was a retrospective case series in Brandon, Manitoba. Ethics approval was obtained through the University of Manitoba in accordance with the Declaration of Helsinki. Procedures were performed between February of 2009 and April 2011. Data was analyzed with the paired two-tailed student's t-test. Patients who had undergone corneal collagen crosslinking were identified from procedure lists routinely maintained by office staff and were included if they met the following criteria: a preoperative diagnosis of keratoconus with pre- and postprocedural measurements available, including uncorrected and best-corrected visual acuity (UDVA, CDVA), refraction and wavefront analysis with the iTrace Wavefront Aberrometer. Patients who had undergone previous or concurrent procedures affecting topographical measures, such as Intacs or phototherapeutic keratectomy were excluded.

The procedure was performed as originally described by Wollensak, Spoerl and Seiler in 2003.[20] In brief, a 7 mm central corneal debridement was performed with an Amoils epithelial brush (Innovative Excimer Solutions Inc., Toronto, ON) and a riboflavin 0.1% solution was applied every 2 minutes for 30 minutes. The debrided area was then exposed to 370 nm wavelength UVA irradiation for 30 minutes while q2 min riboflavin instillation continued. Following the procedure, a bandage contact lens was placed and patients were followed-up as per standard PRK protocol. Where necessary, hypotonic riboflavin solution was used to ensure a corneal thickness of 400 μm prior to the crosslinking procedure.

Total ocular aberrations, the combination of both corneal and internal aberrations, were measured using the iTrace Wavefront Aberrometer at a pupillary size of 5 mm both preoperatively and at the 6 month postoperative follow-up.

Table 1: Pre- and post-procedural total higher order aberrations

(n = 21)	*Pre-CXL mean*	*6 month post CXL mean*	*Mean difference*
HO total	1.50 ± 0.73	1.26 ± 0.64	–0.25 ± 0.41 (p = 0.02)
Coma	1.31 ± 0.63	0.85 ± 0.53	–0.41 ± 0.74 (p = 0.03)
Spherical	–0.12 ± 0.37	–0.17 ± 0.42	–0.04 ± 0.28 (p = 0.44)
Trefoil	0.76 ± 0.50	0.57 ± 0.37	–0.17 ± 0.30 (p = 0.01)
2º astigmatism	0.29 ± 0.29	0.22 ± 0.14	–0.07 ± 0.23 (p = 0.25)

RESULTS

Demographics

Eighteen eyes of 13 patients were included in the analysis. 9 males and 4 females were included with a mean age of 29.2 ± 10.1 years (r = 16-45).

High Order Aberrations

The total high order aberrations, coma and trefoil were statistically significantly lower ($p < 0.05$, Table 1). Nonsignificant trends toward improvement were seen in spherical aberration and secondary astigmatism.

Visual Acuity

A trend towards improved uncorrected distance visual acuity (UDVA) was seen at 6 months, however, no statistically significant difference was seen between the pre- and postprocedural uncorrected or corrected distance LogMAR visual acuities (p = 0.06 and p = 0.78 respectively) (Table 2). Approximately, 89% of eyes remained stable (n = 16) or gained ≥2 lines of best corrected Snellen visual acuity (n = 3). Two eyes of one patient (11%) lost ≥2 lines of CDVA, 3 lines in the right eye and 2 lines in the left at 6 months.

REFRACTIVE CHANGES

No statistically significant changes in mean sphere or astigmatism were seen at 6 months. A nonsignificant trend was seen towards decreased myopia (p = 0.12) (Table 3).

DISCUSSION

In our study, the total high order aberrations, total coma and total trefoil were statistically significantly lower ($p < 0.05$, Table 1). Nonsignificant trends toward

Table 2: Pre- and postprocedural LogMAR uncorrected and corrected distance visual acuities

(n = 25)	*Pre-CXL mean*	*Post-CXL mean*	*Mean difference*
UDVA	0.60 ± 0.45	0.47 ± 0.41	0.12 ± 0.26 (p = 0.06)
CDVA	0.16 ± 0.22	0.17 ± 0.21	–0.01 ± 0.15 (p = 0.78)

Table 3: Changes in mean sphere and astigmatism

(n = 21)	*Pre (D)*	*6 months post (D)*	*Mean difference*
Mean sphere	–3.22 ± 4.4	–2.76 ± 4.1	0.46 ± 1.1 (p = 0.18)
Astigmatism	1.72 ± 1.3	1.46 ± 1.1	–0.18 ± 1.1 (p = 0.24)

improvement were seen in spherical aberration and secondary astigmatism, in addition to a nonsignificant trend toward decreasing myopia. In spite of these improvements, no statistically significant improvements were seen in uncorrected ($p = 0.06$) or corrected ($p = 0.78$) distance visual acuity at 6 months. Two eyes of one patient lost ≥2 lines of corrected distance visual acuity, 3 lines in the right eye and 2 lines in the left respectively. This patient had post-LASIK ectasia with a preoperative pachymetry under 400 µm requiring hypotonic riboflavin drop instillation prior to the application of UV-A light.

Several studies have reported aberrometric measurements following corneal collagen crosslinking.[3,16,18,19,22,28-33] These are summarized in Table 4. Although the studies are heterogenous with respect to the study populations (adult *vs* pediatric) and procedure (standard crosslinking *vs* transepithelial), all report improvement in at least one HOA measure. To further complicate the issue, several different aberrometers were used in these studies, including the CSO EyeTop Topographer (4/10) (CSO Eyetop, Florence, Italy), Optical Path Difference Platform Scan versions I (2/10) and II (1/10) (OPD; Nidek, Gamagori, Japan), Keratron Scout (3/10) (Optikon, Rome, Italy), the Pentacam (Oculus, Wetzlar, Germany) and LADARWave (1/10) (Alcon, Hünenberg, Switzerland). Forty percent (4/10) of studies report Total HOAs, ninety percent (9/10) studies report corneal HOAs and thirty percent (3/10) report both.

Total Coma is the most consistently significantly improved measure, with significant improvements in every study with the exception only of the corneal HOA measurements in Vinciguerra et al (2012), followed by total HOAs and total corneal HOAs in 4/4 and 6/10 studies respectively. Spherical aberrations were improved in 3/4 total HOA studies but only in 1/9 corneal HOA measurements. Trefoil (1/4), 3rd Order Coma (1/4, 1/9) and vertical coma (1/9) were also reported to significantly improve. Our findings with the iTrace aberrometer add yet another observation of improved total HOAs and total coma, but also the uncommonly observed improvement in Total Trefoil.

Coma is known to be markedly increased in keratoconus, which supports other findings that crosslinking may induce some regression of the features of keratoconus in some patients. This is similar to previously reported findings of decreasing refractive and keratometric measurements in long-term follow-up,[3,16,17,21-27] and, as suggested by Greenstein et al, this is likely due to both direct crosslinking effects and wound healing processes improving the cornea's optical structure.[34]

In their paper reporting HOA outcomes of crosslinking, Greenstein et al[34] noted that the improvements seen in HOAs were not associated with the improvements seen in UDVA and CDVA, similar to their previous studies which found that changes in topography, pachymetry, corneal haze and corneal biomechanics were not associated with post CXL changes in vision.[30,34-36] This may be due in part to the fact that improvements in HOAs, while statistically significant, remain fairly modest. Total coma, e.g. saw mean improvements of 10% or less in all of the studies to date, with the exception of Vinciguerra et al who reported a 23% decrease in the total coma from 0.57 ± 0.15 µm to 0.44 ± 0.09 µm, Caporossi et al with patients showing up to a 36% (–0.93 µm) mean improvement in total corneal coma at 48 months and our study reporting a 33% decrease from 1.26 ± 0.63 to 0.85 ± 0.53 in total coma.[3,33] Further, Sabesan et al. in their comparative study of normal and keratoconic eyes have also suggested that correction of HOAs in keratoconus may lead to less-than-expected immediate improvements owing to what may be adaptation to long-term poor retinal image quality.[37] There have been recent reports of excellent results following simultaneous topography-guided PRK and CXL for the treatment of keratoconus and post-LASIK ectasia, which may be at least partially owing to the correction of HOAs which has been shown to be beneficial when seen at high measured levels.[15,38,39]

The variation in the reported improvements in HOAs between studies is likely accounted for by the use of different aberrometers as well as differing lengths of follow-up. The Keratron and OPD-scan, for example, have been shown to have greater repeatability in measuring Total HOAs, while the iTrace has been shown to have the greatest repeatability in measuring corneal HOAs in one study.[40]

Although it may have been of greater academic interest to have been able to report the changes in both total and corneal HOAs, we only routinely measure total HOAs as this accounts for both anterior and posterior corneal surfaces which have both been implicated in the increasing HOAs seen in keratoconus.[7-11,30] The findings of this study reinforce what was previously known regarding improvements in total HOA and total coma measures, while adding the uncommonly observed finding of improvement in total trefoil in the first study to our knowledge reporting outcomes on the iTrace wavefront aberrometer.

Improvement in high order aberration profile is one mechanism by which corneal collagen crosslinking enhances visual function in keratoconic corneas; however, many other factors likely contribute to these outcomes. It is likely the result of both the procedure directly in addition to the wound healing process. The limitations of this study include the retrospective nature with only

Table 4: Summary of previously published studies

Authors	*Years*	*Number of eyes (patients)*	*Follow-up*	*Aberro-meter*	*Pupil size*	*Total HOA ∆s*	*Corneal HOA ∆s*
Caporossi et al	2006	10 (10)	6 mths	CSO EyeTop	5 mm		Corneal HOAs: Improved Total coma: Improved (values not provided, P-values not provided)
Vinciguerra et al	2009	28 (28)	12 mths	OPD-scan	3 mm both	Total HOAs: 0.46 ± 0.12 to 0.38 ± 0.07 µm Total coma: 0.68 ± 0.13 to 0.65 ± 0.08 µm Spherical aberration: 0.16 ± 0.02 to 0.14 ± 0.01 µm ($p < 0.05$ for all)	Corneal HOAs: 0.87 ± 0.13 µm to 0.73 ± 0.15 µm (<0.05) No significant change in total coma or spherical aberration
Agrawal et al	2009	37 (25)	12-16 mths	Keratron Scout (Optikon, Italy)	Not listed		Total coma: 'very significant'; (values not provided, $p < 0.0003$) Spherical aberration and total HOAs not significant
Caporossi et al	2010	44 (44)	48-62 mths	CSO EyeTop	Not listed		Corneal HOAs: Improved Total coma: Improved (values not provided, $p < 0.001$ for all) Spherical aberration not significant
Caporossi et al	2011	91 (<18 yo) 108 (19-26 yo) 35 (27 + yo)	12-48 mths	CSO EyeTop	Not listed		Total coma: Improved in all age groups at all visits up to 48 mo ($p < 0.01$) Greatest improvements seen in 19-26 years age group 2.61 µm at baseline, –0.93 µm mean improvement at 48 mths
O'Brart	2011	22 (22)	18 mths	Keratron Scout	6 mm		Total coma: ($p = 0.008$) Pentafoil: ($p = 0.03$)
Caporossi et al	2012	152 (152) pediatric	12-36 mths	CSO EyeTop	Not listed		Total coma: Improved (values not provided, $p < 0.01$)
Filipello et al	2012	20 (20) Trans-epithelial CXL	18 mths	Keratron Scout	Not listed		Total coma: ($p < 0.05$) Spherical: ($p < 0.05$)
Greenstein et al	2012	96 (73)	12 mths	Pentacam and Ladarwave	6.5 mm both	Total HOAs: 2.80 ± 1.0 µm to 2.59 ± 1.06 µm Total coma: 2.60 ± 1.03 µm 2.42 ± 1.07 µm 3rd Order Coma: 2.57 ± 1.03 µm 2.39 ± 1.07 µm Trefoil: 0.98 ± 0.46 µm 0.88 ± 0.49 µm Spherical aberration: 0.90 ± 0.42 µm 0.83 ± 0.38 µm ($p = 0.01$ for all)	Corneal HOAs: 4.68 mm ± 2.33 to 4.27 ± 2.25 µm Total coma: 4.40 ± 2.32 µm to 4.01 ± 2.29 µm 3rd order coma: 4.36 ± 2.30 µm to 3.96 ± 2.27 µm Vertical coma:4.04 ± 2.27 µm to 3.66 ± 2.22 µm ($p < 0.001$ for all)
Stojanovic et al	2012	61 (53) Transepithelial CXL	12 mths	OPD-scan II	Not listed	Total HOAs: 4.80 ± 2.93 µm to 4.54 ± 2.72 µm ($p = 0.05$) S3,5,7: 1.40 ± 0.80 µm to 1.32 ± 0.80 µm ($p = 0.04$) S4,6,8: not significant	
Vinciguerra et al	2012	40 (40) pediatric	24 mths	OPD-scan	3 mm both	Total HOAs: 0.38 ± 0.09 µm to 0.26 ± 0.07 µm Total coma: 0.57 ± 0.15 µm to 0.44 ± 0.09 µm Spherical aberrations: 0.14 ± 0.05 µm to 0.10 ± 0.02 µm ($p < 0.05$ for all)	Corneal HOAs: 0.56 ± 0.11 µm to 0.43 ± 0.12 µm ($p < 0.05$) No significant changes in coma or spherical aberration observed

6 months of follow-up in addition to wavefront imaging being performed only for total higher order aberrations.

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