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EFFECTS OF CORNEAL CROSSLINKING ON OCULAR RESPONSE ANALYZER WAVEFORM-DERIVED VARIABLES IN KERATOCONUS AND POST-REFRACTIVE SURGERY ECTASIA

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Abstract

Purpose—To assess changes in Ocular Response Analyzer (ORA) waveforms after UVA/riboflavin corneal collagen crosslinking (CXL) using investigator-derived and manufacturer-supplied morphometric variables in keratoconus (KC) and post-refractive surgery ectasia patients.

Design—Prospective, randomized trial of a standard, epithelium-off CXL protocol

Participants—Patients with progressive KC (24 eyes of 21 patients) or post-refractive surgery ectasia (27 eyes of 23 patients) were enrolled.

Methods—Replicate ORA measurements were obtained prior to and 3 months after CXL. Pre-treatment and post-treatment waveform variables were analyzed for differences by paired student's t-tests using measurements with the highest waveform scores.

Main Outcome Measures—Corneal Hysteresis, Corneal Resistance Factor, 37 second-generation manufacturer-supplied ORA variables, 15 investigator-derived ORA variables

Results—No variables were significantly different 3 months after CXL in the KC group, and no manufacturer–supplied variables changed significantly in the post-refractive surgery ectasia group. Four custom variables (ApplanationOnsetTime, P1P2avg, Impulse, and Pmax) increased by small but statistically significant margins after CXL in the post-refractive surgery ectasia group.

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Conflict of Interest: WJD is listed as an inventor on intellectual property held by Cleveland Clinic Innovations related to corneal biomechanical measurement. WJD and ASR have conducted sponsored research related to collagen crosslinking for Avedro and Topcon. RDS was the medical monitor for the FDA trial (Clinical trial.gov identifier NCT00567671).

Conclusions—Changes in a small subset of investigator-derived variables suggested an increase in corneal bending resistance after CXL. However, the magnitudes of these changes were low and not commensurate with the degree of clinical improvement or prior computational estimates of corneal stiffening in the same cohort over the same period. Available air-puff derived measures of the corneal deformation response underestimate the biomechanical changes produced by CXL.

Introduction

Keratoconus (KC) and post-refractive surgery ectasia are characterized by progressive corneal distortion and vision loss related to a decrease in corneal biomechanical integrity. Corneal collagen crosslinking (CXL) has been introduced as a treatment that specifically targets this biomechanical weakness[1–3] and confers a stiffening effect through incompletely understood mechanisms that include formation of covalent bonds within and between collagen chains.[3] Clinically, CXL has been shown to be effective in stabilizing ectatic disease[2,4] and in many patients, reducing corneal topographic steepness[2,5,6] and improving visual acuity.[5,6]

The Ocular Response Analyzer (ORA, Reichert Ophthalmic Instruments, Buffalo, NY) is a modified non-contact pneuomotonometer that measures aspects of the corneal biomechanical response during an air puff perturbation. Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF) are two standard ORA variables that reflect the viscoelastic damping capabilities and elastic resistance of the cornea,[7] and both have been shown to be significantly lower in eyes with ectatic disease.[8–10] CXL has been associated with an increase in corneal elastic modulus in ex vivo studies[1,2,11–14] and in an inverse computational modeling study that derived stiffening effect from clinical CXL results.[15] While several reports have demonstrated the lack of significant changes in CH and CRF after CXL[16–20], Spoerl et al reported an increase in the second-generation ORA variable p2area—the area under the second of the two infrared signal applanation curves—after CXL.[18]

Our group has described a set of custom ORA variables that characterize the temporal, applanation signal intensity, and pressure features of the corneal deformation response produced by the ORA.[21] A subset of these investigator-derived variables was more sensitive and specific than CH and CRF for discriminating eyes with KC from normal eyes and described dynamic features of the deformation response that are consistent with a biomechanically compromised cornea.[21] This study aims to investigate biomechanical changes after standard CXL with riboflavin/ultraviolet-A (UVA) in KC and post-refractive surgery ectasia patients using standard and second-generation manufacturer-supplied ORA variables and our panel of custom variables.

Subjects and Methods

Patient selection

Patients with progressive KC or post-refractive corneal ectasia were enrolled in a prospective, randomized, single-site clinical trial to determine the safety and efficacy of the UV-X system (IROC, Zurich, Switzerland) for performing CXL. The study was a physician-

sponsored Investigational New Drug performed under the guidelines of the Food and Drug Administration and approved by the Emory investigational review board (Clinical Trials.gov identifier: NCT00567671). All participants signed a written informed consent for research.

Candidates underwent a complete history and ophthalmologic examination. Criteria for inclusion were 1) age 14 years or older; 2) diagnosis of corneal ectasia after corneal refractive surgery including LASIK, PRK or epi-LASIK; 3) evidence of progressive KC defined as an increase of ≥ 1.00 D in the steepest keratometry value (simK), an increase of ≥ 1.00 D in regular astigmatism evaluated by subjective manifest refraction, a myopic shift (decrease in the spherical equivalent) of ≥ 0.50 D on subjective manifest refraction, and/or a decrease ≥ 0.1 mm in the BOZR (Back Optical Zone Radius) in rigid contact lens wearers where other information is not available; 4) axial topography or Pentacam consistent with KC or corneal ectasia; 5) presence of one or more of the following slit lamp findings: Fleischer ring, Vogt striae, corneal thinning and or corneal scarring; 6) maximum keratometric curvature value (Kmax) ≥ 47.00 D; 7) I-S ratio > 1.5 on the Pentacam map or Orbscan map; 8) BSCVA worse than 20/20 (<55 letters on ETDRS chart); 9) willingness to comply with schedule for follow-up visits. Patients were excluded for 1) presence of normal topographic maps or classification as keratoconus suspect, 2) history of previous corneal surgery or the insertion of intrastromal ring segments, 3) corneal pachymetry ≤ 400 microns at the thinnest point measured by Pentacam in the eye to be treated when isotonic riboflavin solution was to be used or ≤ 300 microns when hypotonic riboflavin was to be used, provided that the corneal thickness after treatment with the riboflavin solution is > 400 microns, 4) history of corneal disease (e.g., herpes simplex, herpes zoster keratitis, recurrent erosion syndrome, corneal melt, or corneal dystrophy, etc.), scar or chemical injury, 5) nystagmus, 6) active pregnancy, plan to become pregnant, or lactation during the course of the study, or 7) known allergy to study medications.

After initial evaluation, eyes that met the criteria were randomized to either the treatment or control group. Only eyes in the treatment group were evaluated in this study. A total of 24 eyes of 21 KC patients and 27 of 23 post-refractive surgery ectasia patients qualified for analysis.

Surgical Procedure

The surgical procedures were performed by two surgeons (JBR and RDS). After instillation of topical proparacaine 0.5% (Alcaine, Alcon, Fort Worth, TX, USA), the central 9 mm of the corneal epithelium was removed using a blunt knife to facilitate riboflavin diffusion into the cornea. Corneal thickness measurements were obtained with ultrasound pachymetry (DGH 550 Pachette 2, DGH Technology Inc, Exton, PA, USA) before and after the epithelium removal to assure a residual corneal thickness of at least 350 microns. After epithelial debridement was performed, one drop of riboflavin 0.1% ophthalmic solution was instilled topically every two minutes for 30 minutes. At the end of the 30 minute riboflavin pre-treatment period, the eye was examined with blue light for the presence of a yellow flare in the anterior chamber as an indicator of adequate riboflavin saturation of the corneal tissue. If the corneal thickness was < 400 microns, two drops of hypotonic riboflavin 0.1% were instilled every ten to 15 seconds until the corneal thickness increased to at least 400 microns.

A lid speculum was placed between the lids of the eye to be treated and the eye was aligned under the UV-X system. The UVA irradiation was applied at a 50 mm working distance for 30 minutes using a 3 mW/cm2 irradiance. The correct aperture setting was selected according to the size of the eye (7.5, 9.5, or 11 mm), and the eyes were irradiated for 30 minutes during which instillation of riboflavin continued at one drop every two minutes.

A bandage contact lens was placed immediately after the treatment and removed four to seven days later. Postoperative medications consisted of moxifloxacin 0.5% (Vigamox, Alcon, Fort Worth, TX, USA) four times a day for one week, prednisolone 1% ophthalmic suspension (PredForte, Allergan, Irvine, CA, USA) one drop four times a day for two weeks, and ketorolac tromethamine 0.4% (Acular LS, Allergan, Irvine, CA, USA) one drop four times a day for up to four days as needed for pain.

Examination and Measurements

Pentacam (Oculus Inc, Lynnwood, WA, USA), Orbscan corneal topography (Bausch & Lomb, Rochester, NY, USA), OPDScan (Nidek Inc, Fremont, CA, USA), and ORA measurements (Reichert Inc, Depew, NY, USA) were performed at the screening visit and three months after the crosslinking treatment.

The ORA method of operation has been previously described in detail.[7] Briefly, an air jet generates a force directed at the central cornea that causes deformation of the cornea into a slight concavity followed by a return to its pre-perturbation convex shape. During the cycle, applied pressure and the intensity of an infrared signal that reflects upon the cornea are measured. The measurements with highest waveform scores, an indicator of measurement quality, were used for analysis.

Manufacturer-provided ORA variables

The ORA software provides 37 second-generation variables in addition to the standard CH and CRF values (Table 1).[20] CH is calculated as the difference between the pressure values at the ingoing and outgoing corneal applanation events. CRF is a linear combination of these values, P1 - (k * P2), where k is an empirically derived constant with a value of 0.7 designed to maximize the dependence of CRF on central corneal thickness. This formulation also biases CRF towards the pressure associated with the ingoing applanation event and thus the initial elastic resistance of the cornea to an air puff.

Custom ORA variables

Fifteen custom variables were derived from aspects of the ORA signal and have been previously described in detail.[21] Briefly, variables are classified based on their relationship to the ORA applanation signal intensity, applied pressure, temporal aspects of the infrared signal, or a combination of these features (Table 2). Custom code was developed to compute variable values using exported time-resolved infrared signal and pressure data from the Ocular Response Analyzer.

Statistical analysis

Paired, two-tailed Student *t* tests were performed to compare ORA variables before and 3 months after CXL. A correction of the significance criterion was performed according to the Bonferroni method. For a total of 54 comparisons of ORA variables, an adjusted *P* value of 0.05/54 = 0.0009 was considered significant. Demographic variables between groups were compared with non-paired t tests with a signficance criterion of $p<0.05$, and clinical disease severity measures before and after CXL were compared using paired t tests ($p<0.05$).

Results

Subject demographics are described in Table 3. Age was not different between groups. Pre-procedural and post-procedural clinical features are described in Table 4. Three months post-CXL, both KC and post-refractive surgery ectasia patients demonstrated increased visual acuity and decreases in the tomographic thickness measured at the cornea's thinnest point.

Cornea-compensated intraocular pressure (IOPcc) significantly increased in KC (pre-CXL 13.7±2.7 mmHg; post-CXL 14.7± 2.5 mmHg, $p = 0.03$) and post-refractive surgery ectasia eyes (pre-CXL 13.6±2.7 mmHg; post-CXL 15.0±3.2 mmHg, $p = 0.005$). IOP-Goldmann (IOPg) as measured by the ORA did not change after CXL at three months in the KC group (pre-CXL 9.8± 3.2 mmHg; post-CXL 10.6± 3.1 mmHg, $p = 0.07$). In post-refractive surgery ectasia eyes, IOPg significantly increased (pre-CXL 9.4±3.1 mmHg; post-CXL 10.9±3.2 mmHg, $p=0.0003$).

A summary of all variable measures before and after CXL in the KC and post-refractive surgery ectasia groups is provided in Table 5. Mean CH and CRF were not statistically different in either group (Table 5). No variables were statistically different at 3 months after crosslinking in KC patients. No manufacturer-supplied variables were statistically different in the post-refractive ectasia group. However, 4 of the 15 investigator-derived variables (ApplanationOnsetTime, P1P2avg, Impulse, Pmax) did demonstrate a significant increase after CXL (Table 6).

Discussion

Corneal crosslinking is the only treatment for ectatic disease that directly targets alteration of intrinsic biomechanical properties. It has been shown to improve vision,[5] halt topographic progression, and in many patients, effect a degree of topographic regression of disease[4,2,19]. However, measurements such as visual acuity, topography, and tomography are secondary measures of the intended effect of CXL. Direct clinical assessment of CXL-induced changes in corneal biomechanical properties has been more challenging.

The ORA is a commercially available device that allows for *in vivo* characterization of the corneal deformation response to an air-puff stressor. In this study, we investigated the changes that CXL confers upon the dynamic behavior of KC and post-refractive ectasia corneas through the analysis of novel waveform-derived ORA variables related to pressure, applanation signal intensity, or stress response time.

Previous studies have not found significant changes in CH and CRF in response to CXL beyond one month from the procedure. Vinciguerra et al found that CH and CRF significantly increased intraoperatively and through the post-procedural one month point; but, similarly to our study, these standard variables were not significantly different at the three month mark or beyond.[20] Likewise, no change was found six months post-CXL in a study of 56 KC eyes[19], and Spoerl et al also found no significant change in CH or CRF one year after CXL.[18] These and other published results suggest that CH and CRF may not be sensitive enough measures of biomechanical stiffening after CXL.

In our analysis, no variables related to the applanation signal intensity, which relies on specular reflection from the precorneal tear film, were significantly different after CXL in either therapeutic group. This may be related to measurement variabily related to early epithelial remodeling or intrinsic inter-individual variability in the epithelial remodeling process that also could reduce statistical power to detect a difference. Vinciguerra et al similarly showed no significant difference in the peak 1 and 2 amplitudes in the immediate post-operative period. However, by month 6 and 12 after crosslinking, the peaks had significantly increased.[20] Similarly, p2area had significantly increased by 35% one year after CXL in an investigation of 50 KC eyes.[18] The current clinical study design did not include acquisition of ORA measurements beyond 3 months, so comparison to 1 year results should be done with caution.

The current study does, for the first time, demonstrate statistically signficant increases in certain pressure-related variables and a single temporal response variable after CXL in the post-refractive surgery ectasia group. P1P2avg—the average value of the pressures at the first and second applanation points—increased by 7%. Impulse—the area under the pressure curve—increased by 4%, and the applied pressure peak (Pmax) increased by 5%. ApplanationOnsetTime, or the time it takes to achieve the first applanation event, increased by 3%. The directionality of these changes is consistent with increased bending resistance and shows that at 3 months post-CXL, these variables have greater sensitivity than other ORA variables for detecting evidence of a stiffening effect conferred by CXL in post-refractive surgery ectasia eyes. However, the magnitudes of these changes were not commensurate with the degree of clinical improvement seen over the same follow-up period. The degree of change in these ORA variables was also less than the post-CXL changes observed in ex vivo studies. After standard CXL in porcine eyes, Young's modulus has been found to increase by 100%[22] and by a factor of 1.8[2] when tested with a biomaterial load frame. One study examining rabbit eyes showed a 101.45% increase in Young's modulus after standard CXL[13] and another showed an increase of 79.3% immediately after the procedure, 78.4% at 3 months, and 87.4% at 8 months.[23] With an optical coherence elastography technique, human donor corneas had a 33% mean increase in relative lateral stiffness after CXL.[24] Via inflational experiments, the theoretical computations of Young's modulus increased by 1.58× 24 hours after CXL in porcine corneas.[12] Of particular relevance to the current results, prior computational estimates from this research group used inverse finite element modeling to deduce a mean stiffening of 1.8× in 16 KC and post refractive surgery ectasia eyes from the same study cohort presented here.[15] These estimates were obtained over the same followup period, and indicate a high level of effective corneal

stiffening in KC eyes despite the absence of any significant changes in ORA-derived variables the same group.

Interestingly, ORA variables were not significantly different in the KC group. The pathophysiological differences in post-refractive surgery ectasia and KC could be a contributing factor, but low measurement sensitivity and high interindividual variability could be important factors. At least one contributing factor to the development of post-refractive ectasia is a low residual bed thickness.[25–27] Compared to the focal areas of weakness in KC, the biomechanically affected are in post refractive surgery ectasia may represent a larger geometric area; since the ORA samples a 3mm region of the cornea and captures bulk biomechanical properties, it may be more apt to detect CXL changes in the post-refractive ectasia group compared to the KC group.

IOP has been shown to influence the cornea's biomechanical response, with higher IOP correlating with stiffer behavior.[28] While we did not stratify groups by pre-CXL IOP in this study, we have previously shown that IOP has a small influence on our custom ORA variables.[21] Furthermore, normalization of a custom variable by IOPcc in that study led to no change in the performance of the variable as a predictor of disease.[21] Thus, differences in IOP did not seem to significantly confound the discriminative value of these custom ORA variables. Data on IOP changes after CXL, as measured by the ORA, have varied from study to study. Vinciguerra et al found that neither IOPcc nor IOPg changed after CXL[20], whereas both had increased in the one month post-procedural period in a separate evaluation before returning to baseline at six months.[16] Contrarily, Sedaghat et al found IOPcc to decrease at six months, though the absolute change was less than one mmHg.[19] Our study found that IOPg did not change after CXL in KC but increased in the post-refractive ectasia group. Measurements of IOPcc increased in both groups, and the maximum change for any patient was 1.5 mmHg. The variability in IOPcc trends following CXL may be attributable to the limited range under which IOPcc is accurate. The ORA's corneal-compensated IOP was designed to be less sensitive to reductions in corneal properties based on empirical data (Luce DA. IOVS 2006; 47:ARVO E-Abstract 2266) comparing pre- and post-LASIK eyes, where true IOP was assumed to not change. IOPcc was not derived from measurements in pathologic corneas or in post-CXL corneas with increased corneal stiffness where the conditions of the original calibration are not fully met. Consequently, using IOPcc as a normalizing "true IOP" value has not been validated in the setting of CXL, and the assumption is made that true IOP in these patients has not changed significantly 3 months after CXL.

In summary, this study demonstrated changes in novel custom ORA variables after CXL that are consistent with an increase in bending resistance 3 months after CXL in post-refractive ectasia corneas but not KC. The low sensitivity of these air-puff derived response variables illustrates the importance of more sensitive measures of conreal biomechanical change for assessing the material effects of collagen stiffening treatments.

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Table1

Manufacturer-supplied ORA variables

Waveform derivative	
Areas	p1area, p2area, p1area1, p2area2
Heights	h1, h2, h11, h21
Widths	w1, w2, w11, w21
Aspect ratios	aspect1, aspect2, aspect11, aspect21
Slopes	uslope1, dslope1, uslope2, dslope2, uslope11, dslope11, uslope21, dslope21
Slew rates	slew1, slew2, mslew1, mslew2
Paths	path1, path2, path11, path21
Irregularity	aindex, bindex
Dive	dive1, dive2
High frequency	aphf

Table 2

CH, CRF, and custom ORA variable descriptions

Group	Variable	Operational Definition	Related to:
1: Applanation Signal Intensity	A1	Peak intensity of 1st applanation event	Maximum surface area achieving planarity during inward deformation
	A2	Peak intensity of 2nd applanation event	Maximum surface area achieving planarity during recovery
	ApplanationPeakDiff	A2 – A1	Difference in maximum planarity between inward and recovery phases
	ConcavityMin	Minimum applanation intensity between A1 and A2	Depth and irregularity (non-planarity) of deformation
	ConcavityMean	Mean applanation intensity between A1 and A2	Depth and irregularity of deformation, averaged
2: Pressure	Corneal Resistance Factor (CRF), mmHg	P1 - 0.7P2	Difference in applanation pressures, weighted toward pressure required to produce the first applanation, maximizes correlation to central corneal thickness
	Corneal Hysteresis (CH), mmHg	P2 - P1	Difference in pressures between the two applanation events (a single cross-section of the pressure-deformation relationship)
	P1P2Avg	(P1+P2)/2	Average of the pressures at the two applanation events
	Pmax	Peak value of pressure signal	Force and time required to reach first applanation event
3: Response Time (msec)	ConcavityDuration	Time lapse between A1 and A2	Temporal delay of deformation recovery between applanation events
	ConcavityTime	Time from onset of applied pressure to ConcavityMin	Time required to achieve maximum deformation from onset of impulse
	LagTime	Time between Pmax and ConcavityMin	Delay between peak applied pressure and maximal deformation
	ApplanationOnsetTime (AOT)	Time from onset of applied pressure to A1	Time required to achieve first applanation from onset of impulse
4: Applanation Intensity and Response Time ($msec^{-1}$)	SlopeUp	Positive slope of the first applanation peak, from inflection point to peak	Rate of achieving peak planarity
	SlopeDown	Negative slope of the first applanation peak, from peak to inflection point	Rate of loss of peak planarity
5: Pressure and Applanation Intensity 6: Pressure and Time	Hysteresis Loop Area (HLA)	Area enclosed by pressure vs. applanation function	Hysteresis aggregated over entire deformation cycle except concavity
	Impulse	Area under pressure vs. time curve	Air pressure intensity

Adapted from Hallahan et al, Ophthalmol 2014.

Table 3

Demographics and pre-operative intraocular pressure

	Keratoconus	Post-refractive surgery Ectasia	P value
Number of eyes	24	27	
Age, mean ± SD	40.1±11.0	43.5±10.4	*p=0.3*
Gender, n (%)			
Male Female	14 (58%) 10 (42%)	17 (63%) 10 (37%)	
IOPg (mmHg)	9.8±3.2	9.4±3.1	*p=0.7*
IOPcc (mmHg)	13.7±2.7	13.6±2.7	*p=0.7*

Table 4

Preoperative clinical features and cross-linking outcomes at 3 months of patients with keratoconus and postoperative corneal ectasia (mean ± sd)

Keratoconus (n=27)	**CDVA (ETDRS letters)**	**SE (D)**	**Sim-Ks (D)**	**K-Max (D)**	**Thinnest CT (μm)**
Pre OP	32.6±11.6	−5.24±4.34	50.28±4.33	59.90±7.91	440±55
3 months post CXL	40.2±10.4	−3.91±4.04	49.05±4.34	58.63±8.86	411±54
	p=0.01	*p=0.2*	*p=0.9*	*p=1*	*p=0.04*
Postoperative Corneal Ectasia (n=30)					
Pre Op	37.79±10.64	−3.37±4.23	46.39±4.04	55.54±6.17	433±67
3 months post CXL	43.54±10.15	−3.02±4.35	44.56±9.62	54.19±7.02	407±64
	p=0.04	*p=0.7*	*p=0.3*	*p=0.8*	*p=0.04*

CXL – Corneal collagen cross-linking
SD – Standard deviation
D – Diopters
μm – micrometers
SE – spherical equivalent manifest refraction
CDVA – Total number of letters seen with best spectacle correction and distance target
Sim-K – Mean Sim-Ks measured by Scheimpflug tomography
K Max – Steepest corneal curvature measured by Scheimpflug tomography
Thinnest CT – Corneal thinnest point measured by Scheimpflug tomography

Table 5

Corneal Hysteresis (CH) and Corneal Resistance Factor (CRF) before and after crosslinking (CXL)

	Keratoconus			Post Refractive Surgery Ectasia		
Variable	**pre-CXL**	**post-CXL**	**P value**	**pre-CXL**	**post-CXL**	**P Value**
IOPg	9.79±3.21	10.6±3.1	0.07	9.45±3.08	10.9±3.2	0.0003*
IOPcc	13.7±2.7	14.7±2.5	0.03*	13.6±2.7	15.0±3.2	0.005*
CRF	6.61±1.67	6.6±1.8	0.9	6.39±2.73	6.67±1.24	0.1
CH	7.95±1.30	7.62±1.50	0.1	7.80±0.96	7.64±1.13	0.5
aindex	7.19±2.27	8.02±2.11	0.2	8.59±1.84	7.77±1.23	0.1
bindex	7.48±2.59	8.39±2.42	0.1	9.20±1.26	9.44±0.76	0.4
p1area	2380±1570	2470±1420	0.8	2870±1410	3080±1270	0.5
p2area	1840±1210	1790±1180	0.8	2040±850	2000±851	0.8
aspect1	17.9±10.1	20.4±14.7	0.4	21.3±7.5	19.3±11.9	0.5
aspect2	19.8±13.7	20.5±13.5	0.8	24.2±10.4	24.5±14.6	0.9
uslope1	58.6±29.7	65.3±49.6	0.5	76.3±35.4	67.3±40.6	0.3
uslope2	81.8±66.9	91.9±51.9	0.5	107±54	116±58	0.5
dslope1	28.9±18.3	32.0±24.8	0.5	32.8±13.6	29.5±21.1	0.5
dslope2	27.4±17.8	28.2±23.8	0.9	32.6±15.4	32.7±23.8	1
w1	19.7±4.6	19.3±6.1	0.8	19.2±4.2	21.7±5.2	0.09
w2	18.3±8.9	15.6±4.74	0.2	15.3±4.3	15.4±3.8	0.9
h1	334±162	329±159	0.9	390±117	372±133	0.5
h2	295±169	290±141	0.9	341±107	337±115	0.9
dive1	287±157	279±155	0.9	356±126	287±163	0.06
dive2	218±126	219±122	1	259±122	234±107	0.4
path1	33.6±9.3	29.6±10.7	0.1	30.1±8.5	26.0±9.3	0.1
path2	33.5±8.8	34.0±13.2	0.9	31.7±7.5	30.8±8.9	0.7
mslew1	113±55	110±57	0.8	127±51	110±48	0.2
mslew2	132±80	136±67	0.8	159±63	166±70	0.6
slew1	66.7±29.4	67.7±47.9	0.9	79.5±36.9	69.1±40.4	0.3

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	Keratoconus			Post Refractive Surgery Ectasia		
Variable	**pre-CXL**	**post-CXL**	**P value**	**pre-CXL**	**post-CXL**	**P Value**
slew2	88.3±62.5	95.7±47.4	0.6	110±53	116.1±57.4	0.6
aplhf	1.86±0.39	1.88±0.40	0.8	1.53±0.33	1.69±0.37	0.06
p1area1	978±701	1040±650	0.7	1210±730	1280±620	0.7
p2area1	777±564	761±493	0.9	867±413	859±449	0.9
aspect11	31.1±16.9	29.6±19.1	0.8	34.5±15.3	27.9±18.9	0.2
aspect21	31.3±18.6	30.0±19.7	0.8	35.3±14.9	34.9±18.7	0.9
uslope11	65.3±35.7	70.5±46.3	0.7	78.8±35.9	65.2±43.8	0.2
uslope21	75.8±65.4	72.5±40.9	0.8	89.5±53.6	93.5±52.9	0.8
dslope11	59.7±42.0	48.7±42.6	0.3	65.6±35.4	53.7±40.3	0.3
dslope21	46.6±27.9	45.1±30.6	0.8	53.5±23.3	54.5±34.5	0.9
w11	7.71±3.00	8.79±3.16	0.2	8.48±3.06	10.4±2.9	0.02
w21	7.46±4.34	7.29±2.88	0.9	7.00±2.15	7.37±2.53	0.5
h11	223±108	219±106	0.9	260±78	248±89	0.5
h21	197±113	193±94	0.9	228±71	225±77	0.9
path11	43.7±12.8	38.5±11.7	0.1	41.6±12.7	38.7±12.7	0.4
path21	41.5±11.3	42.0±10.7	0.9	42.6±11.8	43.1±12.7	0.9
Concavity Duration	11.5±0.5	11.5±0.5	0.5	11.7±0.6	11.4±0.6	0.001
ApplanationOnsetTime	7.18±0.51	7.23±0.53	0.5	7.12±0.48	7.35±0.49	<0.0001 *
HLA	77300±39700	77500±37000	1	85600±26600	90600±24200	0.1
SlopeUp	25.8±9.31	26.6±14.1	0.7	34.3±13.3	32.8±22.0	0.8
SlopeDown	−22.7±15.4	−25.9±11.2	0.3	−33.9±23.2	−39.4±54.9	0.6
P1P2Avg	146±23	150±22	0.2	144±22	155±24	<0.0001 *
A1	538±237	520±243	0.6	628±167	600±200	0.5
A2	480±256	482±212	1	559±162	557±171	0.9
Concavity Mean	114±53	117±52	0.6	128±35	131±34	0.6
Impulse	4080±460	4170±363	0.2	4100±337	4260±367	<0.0001 *
ApplanationPeakDiff	−57.4±160.0	−38.2±170.0	0.7	−68.8±128.0	−43.8±163.1	0.5

	Keratoconus			Post Refractive Surgery Ectasia		
Variable	**pre-CXL**	**post-CXL**	**P value**	**pre-CXL**	**post-CXL**	**P Value**
LagTime	1.21±0.56	0.959±0.646	0.2	1.03±0.57	1.11±0.60	0.4
Concavity Min	53.9±20.4	55.5±21.3	0.7	58.3±13.4	60.2±14.3	0.4
Concavity Time	13.1±0.7	13.0±0.6	0.4	13.0±0.5	13.2±0.7	0.02
Pmax	363±49	373±39	0.1	365±36	383±39	<0.0001 *

* denotes significant P value <0.05

** denotes significant P value <0.0009 for variables after Bonferonni correction

Table 6

Variables that changed significantly after CXL in post-refractive surgery ectasia.

Variable	Pre-CXL	Post-CXL	% change	P-value
ApplanationOnsetTime	7.12±0.48	7.35±0.49	+3%	*p<0.0001*
P1P2avg	144±22	154±24	+7%	*p<0.0001*
Impulse	4098±337	4261±367	+4%	*p<0.0001*
Pmax	365±36	383±39	+5%	*p<0.0001*