Effect of accelerated corneal collagen cross-linking combined with transepithelial photorefractive keratectomy on dynamic corneal response parameters and biomechanically-corrected intraocular pressure measured with the Corvis ST

Running head: DCR parameters and biomechanically-corrected IOP after PRK with accelerated CXL

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ABSTRACT

PURPOSE: To investigate the effect of accelerated collagen cross-linking combined with transepithelial photorefractive keratectomy (tPRK-CXL) on changes in new dynamic corneal response (DCR) parameters and biomechanically-corrected intraocular pressure (bIOP) measured by corneal visualization Scheimpflug technology (Corvis ST)

SETTING: Yonsei University College of Medicine, Eyereum Eye Clinic.

DESIGN: Retrospective, comparative, observational case series

METHODS: Medical records of 69 eyes of 69 patients undergoing tPRK(n=35) or tPRK-CXL(n=34) were examined retrospectively. Patients underwent a complete ophthalmic examination, including Corvis ST and manifest refraction, before and 6 months after surgery. Main outcome variables were bIOP and new DCR parameters including deformation amplitude (DA) ratio 1 mm, DA ratio 2 mm, stiffness parameter at first applanation (SP-A1), as well as integrated inverse radius. Paired *t*-test, simple linear regression analysis, and ANCOVA with spherical equivalent change or corneal thickness change as a covariate, were performed.

RESULTS: DA ratio 1 mm, DA ratio 2 mm, and integrated inverse radius significantly increased, while SP-A1 significantly decreased after surgery in both groups, all consistent with decreased stiffness. Changes in DA ratio 2 mm and integrated inverse radius in tPRK group are significantly larger than those in tPRK-CXL group without and with ANCOVA, indicating less decreased stiffness in tPRK-CXL group. No significant differences in bIOP were noted before and after surgery in either group.

CONCLUSIONS: We speculate that prophylactic CXL combined with tPRK has a role in reducing the change in biomechanical properties of the corneal tissue. The Corvis ST

showed stable bIOP measurement before and after both tPRK and tPRK-CXL.

Keywords: accelerated corneal collagen cross-linking combined with transepithelial photorefractive keratectomy; Corvis ST; dynamic corneal response parameters; biomechanically-corrected intraocular pressure

INTRODUCTION

Collagen cross-linking (CXL) is a recently introduced surgical procedure whereby riboflavin sensitization with ultraviolet-A (UVA) radiation produces stromal cross-linking.[1] This procedure is known to alter the biomechanics of the cornea by strengthening the corneal microstructure with the addition of crosslinks, resulting in significantly increased stiffness of the anterior corneal stroma.[2] An accelerated CXL protocol consisting of higher-intensity UV irradiation applied for a shorter period of time than the standard protocol, has recently been developed and can be applied in many clinical settings. This protocol has shown outcomes comparable with those of conventional CXL, with no evidence of changes in endothelial cell density (ECD).[3]

Corneal visualization Scheimpflug technology (Corvis ST; OCULUS Optikgeräte GmbH, Wetzlar, Germany) allowing *in vivo* characterization of corneal biomechanical deformation response to an applied air puff has become a useful instrument for evaluating biomechanical response parameters of the cornea.[4] The Corvis ST captures the dynamic corneal deformation caused by an air puff using an ultra-high-speed camera that operates at greater than 4300 frames/sec to capture a series of 140 sequential horizontal Scheimpflug images of the temporal-nasal cross-section of the cornea. The Corvis ST enables the calculation of a variety of parameters by analyzing timing and patterns of deformation at the highest concavity (HC), as well as applanation during inward deformation (loading) and outward recovery (unloading). The original parameters have been reported to be influenced most strongly by intraocular pressure (IOP), as well as age and central corneal thickness (CCT).[5-7] Recently, new corneal biomechanical parameters have been introduced, including deformation amplitude (DA) ratio 1 mm, DA ratio 2 mm, stiffness parameter at first applanation (SP-A1), stiffness parameter during highest concavity (SP-HC), integrated inverse radius, maximum inverse radius, and biomechanically-corrected IOP (bIOP).[8]

While the Corvis ST has been previously used to measure changes in corneal biomechanical response parameters after laser vision correction procedures such as photorefractive keratectomy (PRK), laser in situ keratomileusis (LASIK), and small incision lenticule extraction (SMILE), as well as CXL, the new dynamic corneal response (DCR) parameters have not yet been studied.[9-13] Until now, a well-organized analysis investigating the effect of accelerated corneal CXL combined with transepithelial PRK (tPRK) using new corneal biomechanical parameters has not been reported. Moreover, knowledge remains limited with respect to understanding how corneal biomechanical properties are modified by prophylactic CXL concurrently with myopic tPRK.

Therefore, in the present study, we investigated the biomechanical response of the cornea in terms of new DCR parameters and assessed the stability of the bIOP estimates using Corvis ST before and after both tPRK and tPRK-CXL.

MATERIALS AND METHODS

We performed a retrospective, comparative, observational case series with the approval of the Institutional Review Board of Yonsei University College of Medicine (Seoul, South Korea). The study adhered to the tenets of the Declaration of Helsinki and followed good clinical practices.

Patients included in the study were older than 19 years and underwent tPRK alone (tPRK group) or tPRK with accelerated corneal CXL (tPRK-CXL group) by the same surgeon (DSYK) between May 2014 and April 2015. Prophylactic crosslinking was decided by informed consent with the patient after the risks of crosslinking had been explained.

We excluded patients with previous ocular or intraocular surgery, ocular abnormalities other than myopia or myopic astigmatism with a corrected distance visual acuity (CDVA) of 1.00 (20/20 Snellen) or better in both eyes, ECD of less than 2000 cells/mm^2, cataract, ocular inflammation, infection, or moderate and severe dry eye. Patients with signs of keratoconus on Scheimpflug tomography (displacement of the corneal apex, decrease in thinnest-point pachymetry, and asymmetric topographic pattern) were also excluded.

We retrospectively reviewed the medical records of 69 eyes of 69 patients that met the inclusion and exclusion criteria. Only one randomly selected eye from each patient was included in the analysis to avoid bias of the relationship between bilateral eyes that could influence the results.

Examinations and Measurements

Before and 6 months after surgery, all patients underwent complete ophthalmic examinations including uncorrected distance visual acuity (UDVA) and CDVA with Snellen chart, manifest refraction spherical equivalent (MRSE), slit-lamp examination (Haag-Streit, Gartenstadtstrasse, Köniz, Switzerland), IOP (noncontact tonometer; NT-530, NCT Nidek Co., Ltd., Aichi, Japan), autokeratometry (ARK-530A; Nidek Co., Ltd.), ultrasound pachymetry (UP-1000; Nidek Co., Ltd.), and fundus examination.

As described in detail previously[8], corneal biomechanical parameters were measured preoperatively and at 6 months postoperatively using the Corvis ST. New dynamic corneal response (DCR) parameters include the DA ratio 1 mm, DA ratio 2 mm, SP-A1, SP-HC, and integrated inverse radius. DA ratio 1 mm and DA ratio 2 mm are defined as the ratios between the deformation amplitude (DA) of the apex and the average of two points located 1 mm and 2 mm, respectively, on either side of the apex. The higher the value of either of these parameters, the more compliant is the cornea and the lower is its resistance to deformation. The stiffness parameter, SP-A1, is defined as applied load divided by displacement, in an analogous manner to one dimensional stiffness. The applied load is the air pressure, calculated at first applanation, minus bIOP. The displacement is the distance the corneal apex moves from the pre-deformation state to first applanation (A1). Therefore, the higher SP-A1, the greater the stiffness. The SP-HC parameter is also defined as load divided by displacement. However, is this case, the displacement is the distance from the position of A1 to the position of HC. The integrated inverse radius came from the integration of the inverse radius values which are the reciprocal of radius of curvature during the concave state of the cornea. A greater concave radius is associated with greater resistance to deformation or a stiffer cornea. Conversely, a higher integrated inverse radius is associated with greater compliance or a softer cornea.

Together with DCR parameters, the Corvis ST provides a new and validated bIOP measurement.[8,14] The algorithm for bIOP is based on numerical simulation of the Corvis ST procedure, as applied on human eye models with different tomographies (including thickness profiles), material properties and true IOPs.[14-19] The bIOP is an estimate of true IOP or the corrected value of measured IOP, which considers the biomechanical response of the cornea to air pressure including the effects of variation in CCT and material behavior.[8,14]

Surgical Technique

Transepithelial photorefractive keratectomy

Photoablation was performed using an excimer laser (Amaris 1050 Excimer Laser platform; Schwind eye-tech-solutions GmbH and Co KG, Kleinostheim, Germany), which uses a flying-spot laser with a repetition rate of 1050 Hz. Ablation profile planning was carried out using the integrated Optimized Refractive Keratectomy-Custom Ablation Manager software (version 5.1; Schwind eye-tech-solutions GmbH and Co KG). Mitomycin 0.02% was applied to all corneas for 20 seconds followed by thorough rinsing with chilled balanced salt solution (BSS). Postoperatively, 1 drop of topical levofloxacin 0.5% (Cravit; Santen Pharmaceutical, Osaka, Japan) was instilled at the surgical site, and a bandage contact lens (Acuvue Oasys; Johnson & Johnson Vision Care, Inc, Jacksonville, FL, USA) was placed on the cornea for both groups. Following surgery, topical levofloxacin 0.5% and fluorometholone 0.1% (Flumetholon; Santen Pharmaceutical) were applied 4 times per day for 1 month. The dosage was tapered over 3 months.

Transepithelial photorefractive keratectomy with accelerated collagen cross-linking

After completion of excimer laser ablation, patients were treated with 0.1% riboflavin with hydroxypropyl methylcellulose (Vibex Rapid; Avedro Inc, Waltham, MA, USA) placed on the corneal surface and carefully spread with an irrigating cannula for 90 seconds. Then, the corneal surface was rinsed thoroughly with 30 cc of chilled BSS. A UVA beam (wavelength, 365 nm) 9.0 mm in diameter was applied to the cornea in a continuous fashion in a uniform circular pattern by the KXL system (Avedro Inc). The UVA exposure was performed for 90 seconds for continuous and 180 seconds for pulsed irradiation protocols at a power of 30 mW/cm^2 (total dose; 2.7 J/cm^2). Mitomycin 0.02% was applied to all corneas for 20 seconds after cessation of UVA irradiation, followed by thorough rinsing with chilled BSS. Postoperatively, 1 drop of topical levofloxacin 0.5% was instilled at the surgical site and a bandage contact lens was placed on the cornea for both groups. Following surgery, topical levofloxacin 0.5% and fluorometholone 0.1% were applied 4 times per day for 1 month. The dosage was tapered over 3 months.

Statistical analysis

Statistical analysis was performed using SPSS software version 22.0 (IBM, Armonk, NY, USA). Differences were considered statistically significant when the *P* values were less than 0.05. The results are expressed as the mean ± standard deviation. The Kolmogorov-Smirnov test was used to confirm data normality. To statistically compare preoperative and postoperative data between tPRK and tPRK-CXL groups, we used independent t-test for continuous variables and χ^2 test for categorical variables. We performed the paired *t*-test to evaluate the differences between preoperative and 6-month postoperative parameters including DCR parameters, IOP-NCT, bIOP, and Corvis-CCT in each group. Simple linear regression analysis was used to determine the relationship between changes in DCR parameters and bIOP, and ΔMRSE or ΔCCT in each group. Finally, we performed ANCOVA to compare changes in DCR parameters and bIOP between the two groups, with the ΔMRSE or ΔCCT as a covariate.

RESULTS

Data were collected from 69 eyes of 69 patients undergoing tPRK (n=35) or tPRK-CXL (n=34). Mean patient age was 24.9 ± 5.2 years (range, 19 to 41 years). Table 1 shows the preoperative characteristics of both groups with no significant statistical difference between them as regards age, gender, preoperative sphere, cylinder, MRSE, mean keratometric values, CCT, optic zone, total ablation zone, and white-to-white. There were no significant differences in preoperative uncorrected distance visual acuity (UDVA) and postoperative UDVA, sphere, cylinder, MRSE between the two groups.

Table 2 summarizes the changes in new DCR parameters before and after both tPRK and tPRK-CXL. There were no significant differences in preoperative DCR parameters between the two groups. In both groups, all parameters were significantly different before and after surgery (all $P < 0.001$). The DA ratio 1 mm, DA ratio 2 mm, and integrated inverse radius significantly increased, whereas SP-A1 and SP-HC significantly decreased after surgery, all consistent with decreased stiffness or less resistance to deformation. There were significant differences in changes of DA ratio 2 mm and integrated inverse radius between the two groups (*P* = 0.009 for DA ratio 2 mm and *P* = 0.029 for integrated inverse radius), whereas no significant differences in changes of DA ratio 1 mm, SP-A1, and SP-HC.

When comparing the changes in DCR parameters and bIOP between the two groups using ANCOVA with the ∆MRSE as a covariate, there were significant differences in ∆DA ratio 2 mm and ∆ integrated inverse radius (*P* = 0.002 and *P* = 0.010, respectively; Table 2). The ∆DA ratio 2 mm and ∆ integrated inverse radius in tPRK group are significantly larger than those in tPRK-CXL group, consistent with less decrease in stiffness with tPRK-CXL. No significant differences were noted in ∆DA ratio 1 mm, ∆SP-A1, ∆SP-HC, and ∆bIOP between the two groups (*P* = 0.155 for ∆DA ratio 1 mm, *P* = 0.653 for ∆SP-A1, *P* = 0.367 for ∆SP-HC, and *P* = 0.329 for ∆bIOP, respectively).

When comparing the changes in DCR parameters and bIOP between the two groups using ANCOVA with the ∆CCT as a covariate, there were significant differences in ∆DA ratio 2 mm and ∆ integrated inverse radius (*P* = 0.003 and *P* = 0.018, respectively; Table 2). The ∆DA ratio 2 mm and ∆ integrated inverse radius in tPRK group were significantly larger than those in tPRK-CXL group, also indicating less increase in compliance or less decrease in stiffness. No significant differences were noted in ∆DA ratio 1 mm, ∆SP-A1, ∆SP-HC, and ∆bIOP between the two groups (*P* = 0.243 for ∆DA ratio 1 mm, *P* = 0.888 for ∆SP-A1, *P* = 0.448 for ∆SP-HC, and *P* = 0.357 for ∆bIOP, respectively).

Figure 1 and Table 3 demonstrate the scatter plots and results for simple linear regression analysis between changes (∆) in DCR parameters and bIOP, compared to ∆MRSE or ∆CCT for the two groups.

Table 4 summarizes the changes in IOP-NCT, bIOP, and Corvis-CCT before and after tPRK and tPRK-CXL. The bIOP was stable before and after tPRK and tPRK-CXL (*P* = 0.739 for tPRK group and *P* = 0.326 for tPRK-CXL group). There were no significant differences in changes of bIOP between the two groups (*P* = 0.351).

DISCUSSION

In the present study, we investigated the changes in newly developed DCR parameters and bIOP before and after both tPRK and tPRK-CXL, and demonstrated that changes in DA ratio 2 mm and integrated inverse radius between before and after surgery are significantly smaller in tPRK-CXL than tPRK group, indicating less decrease in stiffness with tPRK-CXL. The original parameter DA is defined as the maximum amplitude when the cornea is deformed to its greatest concave curvature by an air puff and is influenced by corneal stiffness.[20] Thinner corneas are expected to demonstrate higher DA than thicker corneas under the same value of IOP, since they would be less resistant to deformation.[20] Changes in DA ratio 2 mm after adjustment for corneal thickness change or refractive error change are significantly smaller in tPRK-CXL than tPRK group. Regarding the DA ratio 1 mm, there were no significant differences in changes of the DA ratio 1 mm between the two groups. It might be attributed to the smaller region of DA ratio 1 mm, describing the ratio between deformation amplitude at apex and at 1 mm from the apex. This smaller region may be less sensitive, and might not be enough to reflect the overall corneal biomechanics after tPRK surgery, when compared with the DA ratio 2 mm covering the deformation amplitude changes at apex and at 2 mm from the apex. Regarding the integrated inverse radius, changes in integrated inverse radius without or with adjustment for corneal thickness change or refractive error change are significantly smaller in tPRK-CXL than tPRK group. Considering that greater concave radius is associated with greater resistance to deformation, corneas with accelerated CXL were more resistant to deformation than those after tPRK alone.

Based upon the current results, we could postulate that application of prophylactic CXL concurrently with myopic tPRK is expected to relatively increase mechanical stiffness by changing the microstructure of the corneal tissue with the addition of crosslinks, when compared to the same procedure without CXL. All refractive procedures cause a reduction in corneal stiffness, which appears to be less with the addition of CXL. Corneal biomechanics demonstrated by the response of corneal tissue to applied force involves interactions between the externally applied force, the intrinsic properties of the cornea as well as IOP.[21,22] Several studies demonstrated the safety and efficacy of application of prophylactic CXL concurrently with myopic LASIK surgery.[23-25] Considering the achievement of greater improvements in refractive and keratometric stability after concurrent CXL and LASIK, it could be speculated that combined application of CXL and tPRK would have a positive effect on conservation of the biomechanical properties of the cornea.[23,25] To date, no studies have evaluated the effects of combined tPRK and accelerated CXL on corneal biomechanical properties. Based on our results, it can be concluded that application of prophylactic CXL concurrently with tPRK would cause less change in biomechanical properties in the corneal tissue which is demonstrated by significantly smaller postoperative changes in DA ratio 2 mm and integrated inverse radius.

The bIOP obtained from the Corvis ST was stable before and after tPRK and tPRK-CXL. Considering that not only corneal thickness changes but also corneal biomechanical properties have been reported to have a crucial impact on IOP measurements with applanation tonometry, unaltered bIOP measurements by the Corvis before and after both tPRK and tPRK-CXL are clinically important.[26] Our results are in line with recent published study by Vinciguerra *et al.* demonstrating that corrected and clinically validated bIOP estimates were significantly less affected by corneal parameters, CCT, and age than measurements using a non-contact tonometer.[8] Moreover, our group demonstrated that bIOP estimates are not only less influenced by changes in CCT and MRSE, but also less sensitive to changes in biomechanical properties induced by refractive surgery than the uncorrected IOP measurements.

We performed the ANCOVA with change in either corneal thickness or refractive error as a co-factor – these factors were selected for the thickness effect on corneal biomechanics and the refractive error's influence on the surgical procedure parameters.[27] Interestingly, ∆SP-HC showed a significant relationship with ∆CCT only in the tPRK-CXL group, with greater reduction in CCT associated with greater reduction in SP-HC. This is in contrast to the SP-A1 parameter which showed a significant relationship in both groups. It is possible that the difference between groups is only evident with the larger displacement in SP-HC while the cornea is concave. It may be that in a softer cornea, CCT has less biomechanical effect than in a stiffer cornea. We did not include changes in bIOP as a co-factor during the ANCOVA analysis because the bIOP obtained from the Corvis ST was stable before and after both tPRK and tPRK-CXL.

The present study had a number of limitations, including its retrospective design, the relatively small number of patients and the short follow-up duration of 6 months.

Subsequently, using the bIOP and DCR parameters obtained from the Corvis ST, we plan to conduct a prospective controlled comparative paired-eye study comparing tPRK and tPRK with accelerated CXL.

In summary, we investigated the biomechanical response of the cornea, using the recently introduced DCR parameters and bIOP obtained from the Corvis ST in both tPRK and tPRK-CXL groups. Based on our results regarding significantly smaller magnitude of changes in DA ratio 2 mm and integrated inverse radius in tPRK-CXL group, we suggest that tPRK combined with a prophylactic CXL appears to cause a smaller reduction in corneal stiffness relative to uncrosslinked tPRK. Furthermore, the bIOP obtained from the Corvis ST can be helpful in assessing intraocular pressure before and after both tPRK and tPRK with CXL.

WHAT WAS KNOWN

• There was no well-organized study investigating the effect of accelerated corneal CXL combined with tPRK on changes in new DCR parameters and bIOP.

WHAT THIS PAPER ADDS

• Prophylactic CXL combined with tPRK is shown to reduce the change in corneal biomechanical properties, compared with tPRK alone, along with no significant effect on bIOP measured with the Corvis ST.

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FIGURE LEGENDS

Figure 1. Scatter plots and results for simple linear regression analysis between changes in dynamic corneal response parameters and biomechanically-corrected intraocular

pressure, and changes in manifest refraction spherical equivalent or central corneal thickness between transepithelial photorefractive keratectomy alone or transepithelial photorefractive keratectomy with accelerated corneal collagen cross-linking. DA, deformation amplitude; MRSE, manifest refraction spherical equivalent; SP-A1, stiffness parameter at first applanation; SP-HC, stiffness parameter during highest concavity; bIOP, biomechanically-corrected intraocular pressure; tPRK, transepithelial photorefractive keratectomy; CXL, collagen cross-linking.