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Comparison of safety and efficiency of corneal topography-guided photorefractive keratectomy and combined with crosslinking in myopic correction

An 18-month follow-up

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Abstract

To compare the safety and efficiency of simple corneal topography-guided (T-CAT) photorefractive keratectomy (PRK) and T-CAT PRK combined with crosslinking (CXL) to correct myopia with borderline suspicious tomography.

Eyes with suspicious tomography (not classified as forme fruste keratoconus) underwent PRK combined with CXL. The suspicious tomography showed irregular posterior corneal morphology or maximum elevation value of the central 6 mm zone of the posterior surface (MEL) >15 μm, or Belin/Ambrósio Enhanced Ectasia Index (BAD-D) was >1.6. The PRK group was generated and matched within 2 μm for MEL, 0.3 for BAD-D value, and 0.5 D for manifest refractive spherical equivalent (MRSE) compared with the PRK-CXL group.

PRK-CXL exhibited a larger MRSE (0.09 ± 0.22 D vs −0.03 ± 0.24 D, *P* = .02) and a larger sphere (0.14 ± 0.22 D vs 0.01 ± 0.21 D, *P* = .002) compared with PRK alone at 18 months postoperatively. The magnitude change and relative change rate of stiffness parameter A1 in the PRK-CXL were smaller than in the PRK group (−15.72 ± 14.56 vs −19.95 ± 14.37, *P* = .04, for magnitude change and −0.16 ± 0.15 vs −0.20 ± 0.14, *P* = .02, for relative change rate). In the PRK-CXL and PRK groups, 4.8% and 6.9% of eyes suffered grade 0.5 haze at postoperative 18-month. No cases of ectasia were reported in either group.

PRK in combination with prophylactic crosslinking showed comparable safety and efficacy, but higher biomechanical stability compared to PRK alone, thus, the additional CXL plays a measurable role in reducing the change in corneal biomechanical properties after PRK in suspicious eyes.

Abbreviations: 1/R = the inverse of the radius of curvature during the highest concavity, BAD-D = Belin/Ambrósio Enhanced Ectasia Index, CDVA = corrected distance visual acuity, CST = Corvis ST, CXL = corneal crosslinking, DA ratio = deformation amplitude ratio, IOP = intraocular pressure, MEL = maximum elevation value of the central 6 mm zone of the posterior surface, MRSE = manifest refractive spherical equivalent, PRK = photorefractive keratectomy, SP-A1 = stiffness parameter A1, UDVA = uncorrected distance visual acuity.

Keywords: biomechanics, corneal topography-guided, cross-linking, PRK

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1. Introduction

Iatrogenic corneal ectasia is a clinically rare but catastrophic complication after corneal refractive surgery.[1] Although the exact reason for its development is still unknown, a recent large long-term study investigating ectasia risk after surgery and included 30,000 eyes, suggests that questionable tomography results may be a risk factor toward the development of iatrogenic ectasia.[2] However, patient with suspicious tomography was not totally forbidden to undergo simple photorefractive keratectomy (PRK) in clinical work. As shown in a recent study, patients with "suspected keratoconus" who showed preoperative suspicious tomography that underwent PRK may have a good outcome and stability even after 5 years of follow-up.[3] Cases of postoperative ectasia in patients with suspicious tomography after PRK have been reported,[4] and may be due to weakened corneal biomechanics after kerato-refractive surgery.[5]

Prophylactic corneal crosslinking (CXL) is currently combined with refractive surgery to correct ametropia and simultaneously prevent postoperative corneal ectasia or myopic regression by enhancing corneal stiffness.[6] The CXL procedure can stiffen the cornea by significantly increasing the stiffness of corneal stroma after refractive surgery with stress up to +130% and Young's modulus up to +79%.[7] Moreover, a recent publication about the comparison of the outcome of the PRK alone and PRK combined with simultaneous and half-influence CXL for treatment of patients with a thinner corneal thickness or suspicious tomography indicated that the PRK-CXL surgery showed excellent safety and efficacy results.[8] The tomography of the control group was normal in their group, it was different from the study group, and the tomographic difference may affect the comparison. As we knew, there was still no study compared outcomes of PRK in combination with CXL and simple PRK on patients with suspicious tomography.

The commercially available device Corvis ST (CST) operates in vivo clinically, and uses a high-speed Schieimpflug camera with an acquisition rate of 4300 frames/s under air puff to analyze images and estimate numerous dynamic corneal response (DCR) parameters as well as intraocular pressure (IOP).[9] A recent publication emphasized the important role of the CST in measuring corneal biomechanics and diagnosing keratoconus.[10] Moreover, researchers have shown that many CST biomechanical parameters were significantly different among patients with preoperative regular tomography who underwent PRK-CXL and patients who underwent PRK alone.[11] To the best of our knowledge, no study has investigated the CST biomechanics of PRK in combination with CXL on patients with tomographic irregularities, and we hope to observe corneal stiffness changes after PRK-CXL by adding CST biomechanical indicators.

In this study, we compared the safety and efficacy of PRK in combination with prophylactic CXL and PRK alone on vision, refraction, and corneal biomechanics using novel stiffness parameters in patients with mild to moderate myopia and suspicious tomography.

2. Patient and methods

2.1. Patients

This retrospective study was performed from September 2016 to December 2018 with the approval of the Guangzhou Aier Ethics Committee. Inclusion criteria were selected as follows:

1. age $>$ 20 years,
2. MRSE < -6.0 D, cylinder < -2.0 D, change in MRSE $<$ 0.5 D within 2 years,
3. the thinnest central corneal thickness $>$ 500 μm,
4. suspicious tomographic criteria that met more than two of the following criteria:
   (a) The maximum elevation value of the central 6 mm zone of the posterior surface of more than 15 μm,
   (b) The posterior surface of corneal tomography (Pentacam HR; Oculus, Wetzlar, Germany) displayed an irregular morphology as "slanted hourglass," "tongue extension," or "island" (Fig. 1),

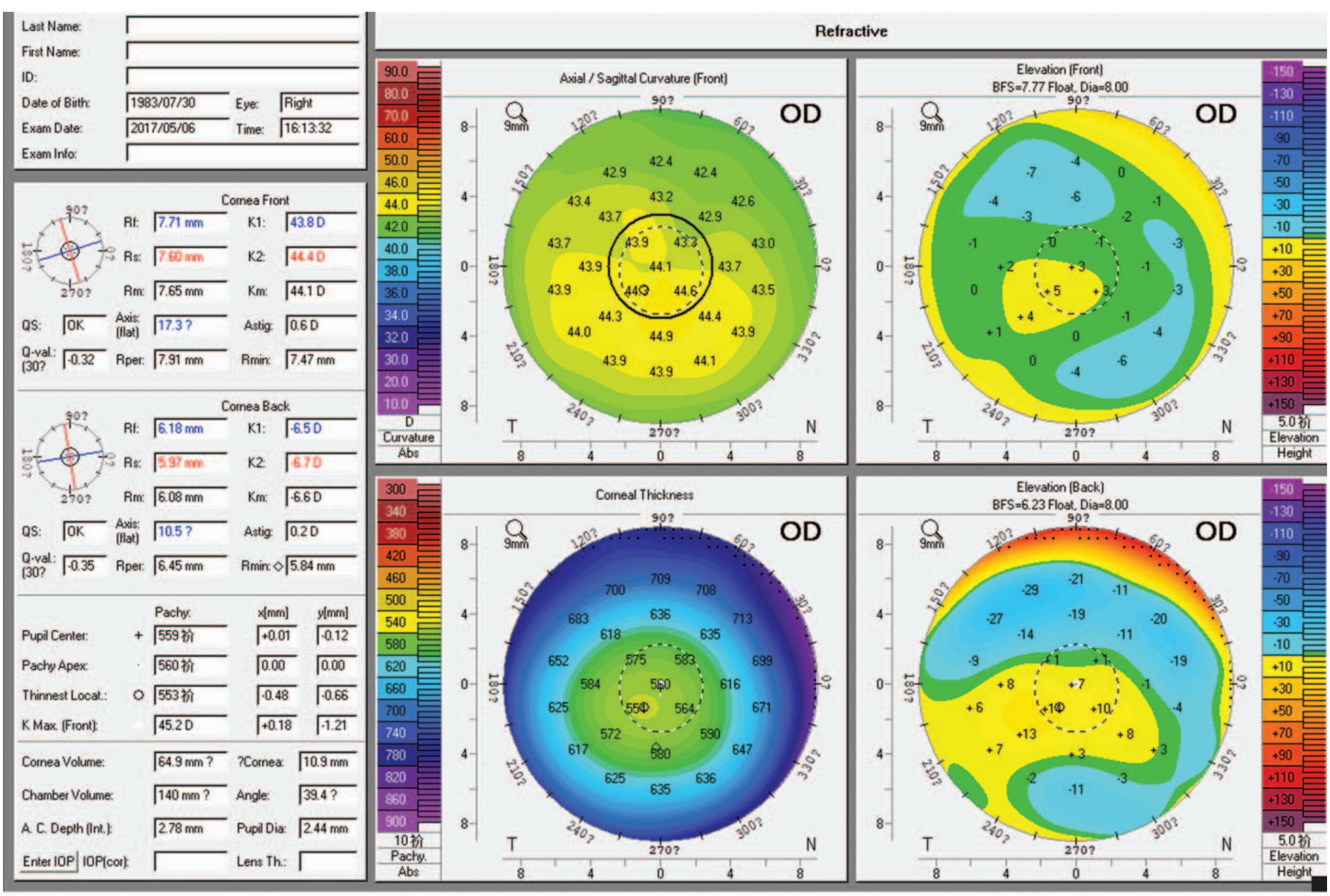

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Figure 1. Preoperative corneal tomography of a patient underwent PRK combined with cross-linking correction. Manifest refraction: −2.25 to 0.75 × 60 (20/20). Corneal tomography demonstrates a tongue extension in posterior surface (A) with an overall BAD-D of yellow, and the value is 2.14, which is more than 1.6 standard deviations (B). Abbreviation: OD (right eye).

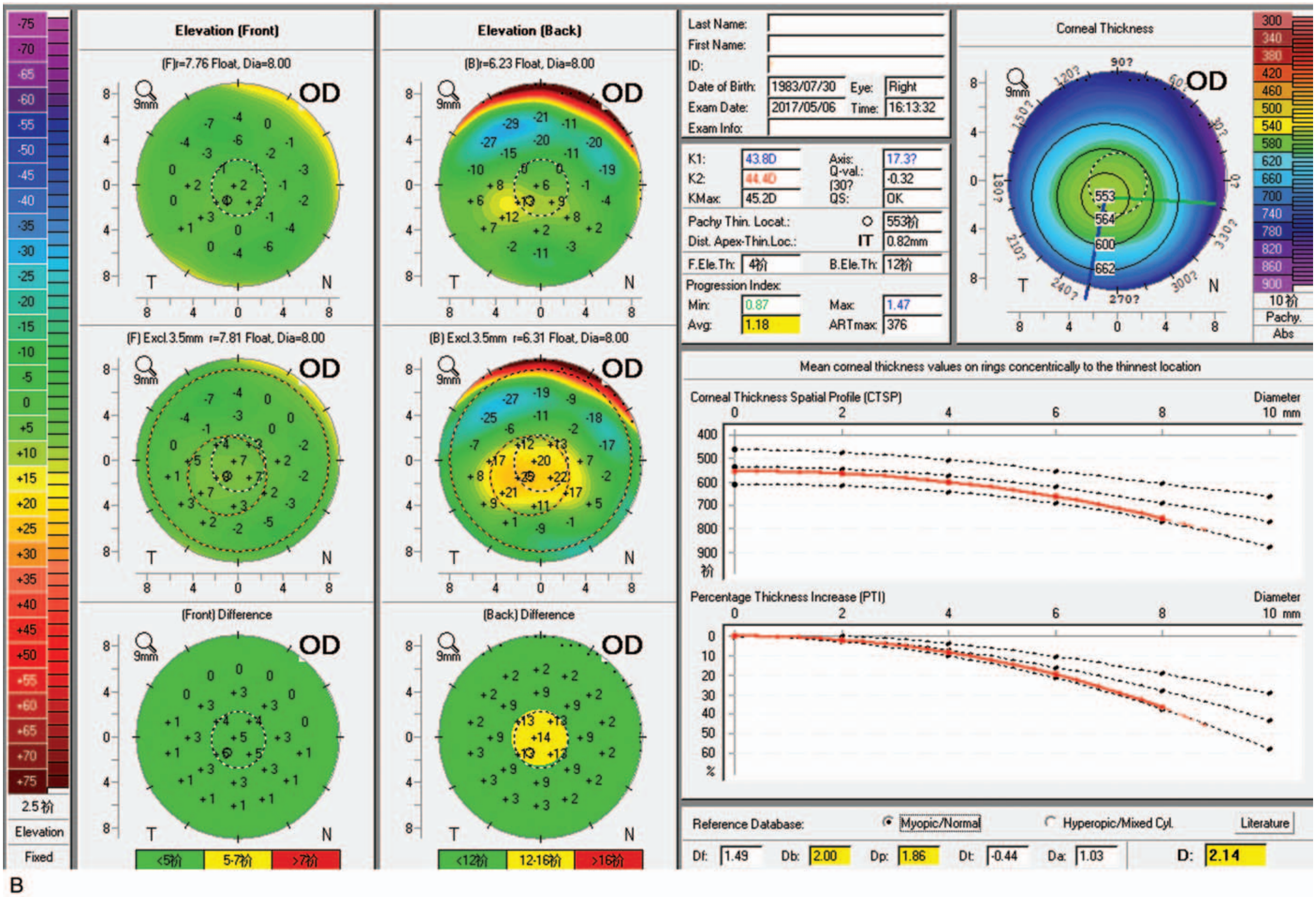

Figure 1. (Continued).

(c) The BAD-D was > 1.6 standard deviations.

The control group who underwent simple PRK surgery and generated matched within 2 μm for MEL, 0.3 for BAD-D value, and 0.5 D for MRSE compared with the PRK-CXL group. Individuals with a high-risk index of postoperative corneal ectasia were excluded from both groups: inferior–superior index > 1.9 D in the 6 mm central corneal topography, keratometry reading (K1/K2) > 48.0 D, Kmax > 49.0 D, central corneal thickness (CCT) < 470 μm, or a total BDA-D > 2.6.[12] Furthermore, no case exhibited a family history of keratoconus, keratoconus, or suspected keratoconus with the Sirius topography test (Sirius; CSO, Firenze, Italy). A complete preoperative ophthalmologic examination was performed to ensure that there were no present or past ocular diseases other than refractive error. Patients were not allowed to use contact lenses for 2 weeks before their preoperative exam. All patients received an explanation of the risks of the procedure and provided informed consent.

2.2. Examinations and measurements

The same examiner carried out the following examinations preoperatively and postoperatively for up to 18 months: uncorrected distance visual acuity (UDVA), manifest refraction, corrected distance visual acuity (CDVA), CST biomechanical parameters, and corneal tomography.

2.2.1. Stiffness parameters. The deformation amplitude (DA) ratio is calculated between the vertical displacement at the apex and at 2 mm, and the $1/R$ mean the inverse of the radius of curvature during the highest concavity (HC) phase of the deformation. The DA ratio and $1/R$ are associated with corneal biomechanics and are not affected by IOP.[13] The stiffness parameter A1 (SP-A1) and stiffness parameter Highest Concavity (SP-HC) was recently predicted by Prof. Roberts and defined as the resultant pressure divided by displacement and were adjusted by biomechanical IOP.[14] Both SP-A1 and SP-HC could effectively detect corneal stiffness after CXL surgery, and the SP-HC parameter might be a stronger biomarker in relation to sclera.[15] We selected the DCR parameters DA ratio, 1/R, and SP-A1 to analyze corneal biomechanical stiffness. Each eye was examined three times by the same examiner using the 1.5r1902 version of CST.

2.2.2. Surgical technique. All operations were completed by the same surgeon (Dr Wang). The PRK surgical procedure was performed by first anesthetizing with lidocaine hydrochloride and then mechanically removing epithelium from the central 9 mm area of the cornea with a corneal epithelium knife. The cornea was ablated with Wavelight EX500 (Alcon Laboratories, Inc, Fort Worth, TX) covering a 6.0 to 6.5 mm treatment zone; T-CAT was used throughout the entire PRK procedure. The combined PRK-CXL procedure was performed as follows[8]:

after ablation of the PRK surgery was completed, patients were treated with 0.22% riboflavin (Vibex Xtra; Avedro, Waltham, MA) that was placed on the corneal surface and carefully spread with an irrigating cannula for 90 s. The corneal surface was then rinsed thoroughly with 30 mL of balanced salt solution. A 9.0 mm diameter UVA beam (wavelength: 365 nm) was applied to the cornea by the KXL system (Avedro). UVA exposure was performed for 90 s at a power of 30 mW/cm^2 and total energy of 2.7 J/cm^2.

Postoperatively, a bandage contact lens (PureVision [balafilcon A] Visibility Tinted Contact Lenses; Bausch & Lomb Incorporated, USA) was placed on the cornea and removed after 1 week in both the PRK and PRK-CXL groups. Topical levofloxacin hydrochloride (Levofloxacin Eye Drops; Santen Pharmaceutical, Japan), 0.3% sodium hyaluronate eye drops (Santen Pharmaceutical, Japan), and 0.1% fluorometholone (Flumetholon, Santen) were applied four times per day for 1 month in both groups. The dosage of sodium hyaluronate eye drops and fluorometholone were adjusted over 4 months.

2.2.3. Statistical analysis. Statistical analysis was performed using SPSS software (version 22.0, International Business Machines Corp). P values $<.05$ were considered statistically significant, and results were expressed as mean ± SD. The Kolmogorov–Smirnov test was used to confirm data normality. To compare preoperative and postoperative data between the PRK and PRK-CXL groups, the independent t test was used for continuous variables and the chi-square test for categorical variables. The paired t test was used to evaluate the differences between preoperative and postoperative parameters including visual acuity, refraction, and CST parameters.

3. Results

Table 1 summarizes the patient demographic characteristics prior to the operation, and there were no significant differences in all parameters between the two groups except gender. The PRK-CXL group consisted of 104 eyes from 39 women and 13 men, and the PRK group consisted of 78 eyes from 20 women and 19 men ($\chi^2=11.0$, $P<.001$). Other than gender, there was no significant difference among other demographic parameters (all P-value $>.05$). The mean preoperative MRSE was −4.15 ± 1.07 D (range: –2.50 D to –6.13 D) in the PRK-CXL group, and −3.99 ± 1.10 D (range: –2.25 D to –6.00 D) in the PRK group. At 18 months postoperatively, 4.8% of eyes suffered grade 0.5 haze in the PRK-CXL group, and the rate of the PRK group was 6.4% ($\chi^2=0.22$, $P=.54$). There were no side effects like corneal ectasia or delayed epithelial healing associated with either group.

Table 1

Demographics and preoperative data in the PRK and PRK-CXL groups.

Parameter	PRK-CXL Group	PRK Group	P
No. of eyes	104	78	–
Gender (male:female)	26:78	38:40	<.001
Age (years)	26.3 ± 4.7	26.1 ± 4.6	.93
Preoperative sphere (D)	−3.70 ± 1.01	−3.70 ± 0.72	.86
Cylinder (D)	−0.83 ± 0.51	−0.62 ± 0.42	.32
Spherical equivalent (D)	−4.15 ± 1.07	−3.99 ± 1.10	.67
CCT (μm)	525.2 ± 31.1	529.2 ± 32.3	.78
UDVA	0.92 ± 0.22	0.85 ± 0.23	.17
CDVA	0.005 ± 0.017	0.003 ± 0.011	.47
BAD-D	2.12 ± 0.34	1.9 ± 0.64	.35
MEL (μm)	12.8 ± 4.8	12.8 ± 3.7	.42
Kmax (D)	44.4 ± 1.5	44.1 ± 1.6	.06

BAD-D = Belin-Ambrósio deviation index (a Pentacam parameter that can detect keratoconus and its susceptibility), CCT = central corneal thickness, CDVA = corrected distance visual acuity, Kmax = maximum K value, MEL = the maximum elevation value at the central 6 mm of the posterior cornea, PRK = only PRK surgery, PRK-CXL = PRK combined with accelerated corneal CXL, UDVA = uncorrected distance visual acuity.

3.1. Postoperative visual and refractive outcomes

The postoperative UDVA (Log MAR) of the PRK-CXL and PRK groups was −0.046 ± 0.056 and −0.041 ± 0.058 ($P=.59$). As shown in Figure 2, 97% of UDVA were 20/20 or better in the PRK-CXL group after 18 months, and the rate of the PRK group was 95%. Moreover, in the PRK-CXL group, 50% of UDVA scores were 20/16 or better, while the rate of the PRK group was 60% ($P=.28$). In the PRK-CXL group, 98% of CDVA scores reached or exceeded the preoperative CDVA level, and the rate of the PRK group was 97% ($P=.61$).

At the 18-month follow-up, the mean MRSE was 0.09 ± 0.22 D in the PRK-CXL group, which was larger than−0.03 ± 0.24 D in the PRK group ($P=.02$), and the mean spherical diopter in PRK-CXL was also larger than in the PRK group (0.14 ± 0.22 D vs 0.01 ± 0.21 D, $P=.002$).

The PRK-CXL group exhibited a safety index $\left(\frac{\text{postoperative CDVA}}{\text{preoperativeCDVA}}\right)$ of 1.14 ± 0.14 which was 1.14 ± 0.13 in the PRK group ($P=.25$). The efficacy index $\left(\frac{\text{postoperativeUDVA}}{\text{presoperative CDVA}}\right)$ was 1.12 ± 0.15 and 1.14 ± 0.15 in the PRK-CXL and PRK group, respectively ($P=.74$).

3.2. Corneal tomography and morphology

A backward displacement was induced in both PRK-CXL and PRK groups when similar diameters were used to compare preoperative and postoperative stations for direct comparison. The changing amplitude (preoperative MEL) was smaller in the PRK-CXL group compared to the PRK group (4.6 ± 4.0 μm vs 5.5 ± 3.2 μm, $P=.02$). Moreover, there was no significant difference in postoperative changes of corneal pachymetry and Km between the two groups (Table 2).

3.3. Corneal biomechanical parameters

As shown in Table 3, after 18 months of surgery, the corneal stiffness decreased significantly in both groups, as $1/R$ and DA ratio increased, and SP-A1 decreased, that compared to the preoperative values. The postoperative SP-A1 of the PRK-CXL group was 75.2 ± 16.1 which was significantly higher than 71.0 ± 19.3 of the PRK group ($P=.04$). The magnitude change (Δ) and relative change rate (Δ/Pre) of SP-A1 of the PRK-CXL group were smaller than those of the PRK group and statistically significant for SP-A1 (Δ: −15.7 ± 14.6 vs −19.9 ± 14.4, $P=.04$; Δ/Pre: −0.16 ± 0.15 vs −0.20 ± 0.14, $P=.02$).

4. Discussion

Based on the permission to the significant stiffing impaction of the cornea after CXL, additional CXL has been combined with corneal refractive surgery in patients with high refraction or preoperatively borderline corneas, to reduce postoperative ectasia or regression.[8,16,17] As shown in our results, patients from both groups with suspicious tomography after PRK-CXL and PRK alone could obtain improved visual acuity (i.e., the

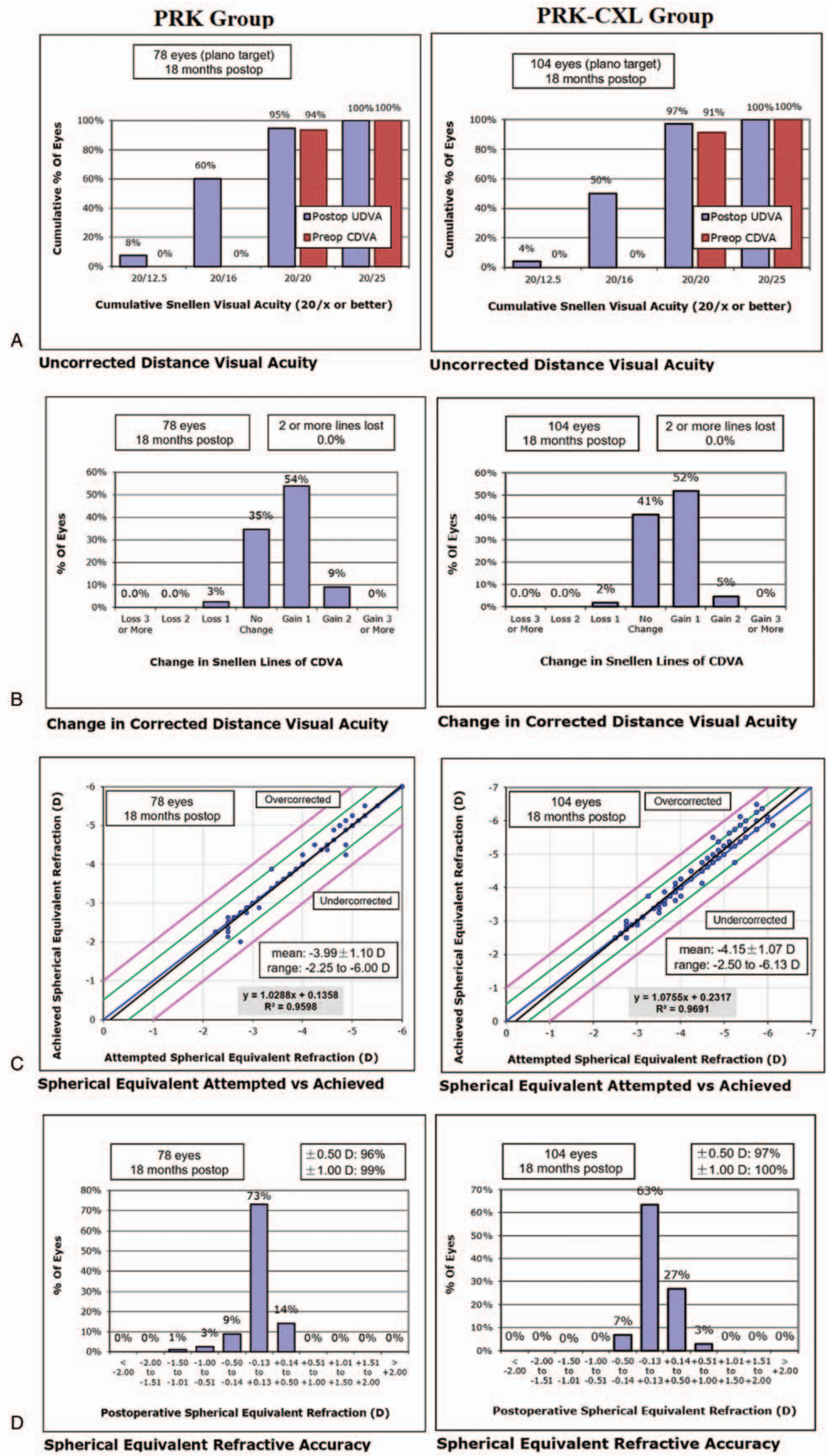

Figure 2. Standard graphs for the outcomes of PRK and PRK combined with corneal cross-linking surgery (PRK-CXL). (A) Postoperative UDVA at 18 months postoperatively. (B) Visual changes in CDVA compared preoperative CDVA. (C) Distribution of achieved SE outcomes at 18 months postoperatively. (D) The spherical equivalent refractive accuracy at 18 months postoperatively (CDVA=corrected distance visual acuity; UDVA=uncorrected distance visual acuity).

Table 2

Comparison of tomographic properties between eyes that undergo PRK-CXL and PRK.

Parameter	PRK-CXL group (n=104 eyes)				PRK Group (n=78 eyes)				
	Preop	Postop	Δ	P^*	Preop	Postop	Δ	P^*	$P^†$
Mean *K* (Km), D	43.7±1.4	39.8±2.8	−0.28±0.42	<.001	43.9±1.5	40.1±1.8	−0.23±0.40	.04	.57
MEL, μm	12.8±4.8	8.1±3.8	4.6±4.0	.01	12.8±3.7	7.8±3.7	5.5±3.2	.02	.02
CCT, um	525.2±31.1	446.2±40.5	78.8±24.3	<.001	529.2±32.3	462.0±42.4	72.2±23.4	<.001	.16

Results are expressed as mean±SD; Δ, change (Post–Pre); PRK-CXL, PRK combined with accelerated corneal CXL; PRK, only PRK surgery; Mean *K* (Km): the average of the step and flat *K* readings. CCT=central corneal thickness, MEL=the maximum elevation value at the central 6 mm of the posterior cornea.
P^* value between preoperative and 18-month postoperative corneal tomographic properties in each group; $P^†$ value between changes in preoperative and postoperative corneal tomographic properties of the PRK-CXL and PRK groups.

postoperative mean efficacy and safety indexes of both groups were >1). We postulated that this may relate to T-CAT technology which can effectively ablate irregular elements from the anterior corneal surface, thus improve optical outcome and visual quality postoperatively.[18]

In a previous publication, Malta et al assessed the outcome of no-simultaneous CXL combined with PRK surgery in patients with suspicious tomography (patient first underwent CXL procedure and then underwent an extra PRK procedure 6 months subsequently).[19] They demonstrated similarly excellent safety and refractive results of the PRK-CXL group compared to the simple PRK group, while the rate of the haze of the study group was higher (56.8% vs 15.1%, for 18 months, and 18.2% vs 4.6%, for 30 months). They deduced that the high frequency of haze after the PRK-CXL surgery might be related to the additional and non-simultaneous PRK procedure, which allows extra keratocytes and causes activated fibroblasts after the original CXL procedure.

Kanellopoulos et al[20] first added the prophylactic and half-influence CXL (LASIK-Xtra) within the flap to LASIK in 2010. In their subsequent studies, the LASIK-Xtra had even more stable refractive outcomes compared to LASIK alone in myopic correction.[16,21] It seems that there is no need to correct or adjust the nomogram for the PRK-Xtra surgery.

Sachdev et al compared the outcome of PRK and PRK in combination with CXL for treatment of patients with thinner corneal thickness and tomographic abnormalities, and they indicated that the PRK-CXL surgery showed comparable safety, efficacy, and stability compared to PRK alone.[8] In their study, at 12 months postoperatively, there were 9 eyes (8.3%) that developed grade 1 haze after PRK-CXL. The rate of appearance of haze in the study by Sachdev[8] with half-influence CXL protocol was significantly less than that of the study by Malta[19] with full-influence CXL protocol. Moreover, many recent PRK-Xtra studies used a half-influence and accelerate protocol.[11,22] Therefore, in our study, we treated myopic patients with a half-influence and simultaneous protocol.

In our results, the PRK-CXL group showed identical and great postoperative inverse concave radius (1/*R*) and stiffness parameter A1 (SP-A1) compared to the refraction- and age-matched PRK group. Moreover, compared to the PRK group, the PRK-CXL group exhibited significantly smaller values of magnitude change (Δ) and relative change rate (Δ/Pre) of the CST biomechanical response parameters (SP-A1, 1/R, and DA ratio), and indicates that prophylactic CXL plays a role in enhancing corneal stiffness. The biomechanical response parameters can be relative to stiffness in terms of resistance to deformation. The stiffer an elastic material is, the larger of biomechanical parameters (e.g.,

Table 3

Comparison of corneal biomechanical parameters (tests by Corvis ST) between eyes that underwent PRK-CXL and PRK alone.

Parameter	PRK-CXL Group (n=104 eyes)	*P*	PRK Group (n=78 eyes)	*P*	P^*
DA ratio (2 mm), unitless		<.001		<.001	
Preop	4.51±0.36		4.54±0.30		.73
Postop	5.19±0.48		4.99±0.58		.07
Δ	0.76±0.40		0.77±0.38		.43
Change (Δ/Preop)	0.16±0.10		0.18±0.10		.28
Inverse concave radius (1/*R*), mm		<.001		<.001	
Preop	8.61±1.01		8.83±0.87		.22
Postop	10.43±0.97		9.91±1.23		.03
Δ	1.83±0.89		1.61±0.87		.23
Change (Δ/Preop)	0.15±0.15		0.18±0.11		.15
SP-A1,unitless		<.001		<.001	
Preop	91.9±15.0		92.2±21.7		.24
Postop	75.2±16.1		71.0±19.3		.04
Δ	−15.7±14.6		−19.9±14.4		.04
Change (Δ/Preop)	−0.16±0.15		−0.20±0.14		.02

Results are expressed as mean ± SD.
Δ=change (Postop–Preop), Change (Δ/Preop)=the ratio between Δ and the preoperative value, DA=deformation amplitude, PRK=PRK surgery alone, PRK-CXL=PRK combined with accelerated corneal CXL.
P: independent *t* test between preoperative and 18-month postoperative corneal biomechanical properties in each group; P^*: independent *t* test between the two groups regarding changes in the dynamic corneal response parameter.

SP-A1 and 1/R) are, and the less biomechanical parameters of deformation and parametric changes there are. Stiffer materials have greater resistance to deformation than softer materials under outside air puff with the CST device.

Up-to-date, no study has compared novel stiffness parameters of patients with irregular tomography and underwent PRK in combination with prophylactic CXL. A recent study by Lee et al[23] compared novel stiffness parameters between PRK and PRK-CXL surgery treating myopic patients with normal tomography, and they demonstrated that PRK-CXL surgery exhibited a significantly smaller change amplitude of the DA ratio and SP-A1 compared to the PRK group. They postulated that prophylactic CXL could effectively enhance corneal stiffness after PRK surgery. Similarly, our study also demonstrated a biomechanical enhancing tendency after combined surgery.

Progressive corneal flattening that caused overcorrection was one of the concerns after PRK-Xtra. At 18 months after surgery, the PRK-CXL group in our study exhibited slight hyperopic station and higher spherical lens, and the PRK group exhibited myopia and smaller spherical lens (MRSE: 0.09 D vs −0.03 D, spherical lens: 0.14 D vs 0.01 D). Compared to previous studies, the MRSE of the PRK-CXL had a range from −0.04 D to 0.17 D, and the MRSE of the PRK had a range from −0.01 D to 0.31 D.[8,11,19] Lee et al[11] found a lower MRSE and spherical lens in the transepithelial photorefractive keratectomy (t-PRK)-Xtra group compared t-PRK alone, although both Sachdev et al[8] and Malta et al[19] found a similar postoperative MRSE between the PRK-Xtra and PRK groups. We suggested that because of the difference of corneal epithelial removal methods and laser platforms, thus, the comparison of the refractive outcome of PRK and PRK-Xtra was different among the above researches.

Previous research[24] has suggested that the case corrected by CXL combined with refractive surgery which had normal corneal collagen and was less heterogeneous and would not produce a similar photochemical effect and elastic modulus changing as cornea with keratoconus. Moreover, they also demonstrated that the flattening effect is correlated to the CXL effect. Based on the Bunsen–Roscoe law, the CXL effect was decided by the total energy of the UVA. In a previous study by Malta,[19] none of the patients with suspicious topography who underwent full-influence PRK-CXL (5.4 J/cm^2) suffered progressive corneal flattening leading to overcorrection. In our study, the total energy of CXL was lower as 2.7 J/cm^2, then the flattening effect of our study may be slighter.

Additionally, there was a backward shifting of the corneal posterior surface in both groups in our results, and the PRK-CXL group showed a small magnitude compared to PRK alone. This finding was consistent with a previous and similar study done by Lee et al, who also found a smaller backward shifting after PRK-Xtra surgery compared to PRK alone.[25] After refractive surgery, the central corneal tissue is removed and the connection between the peripheral corneal collagen fibers and the center is disrupted, and the peripheral cornea may produce a force under the IOP that may push the central cornea backward shifting.[9] Moreover, because of the positively stiff effect of CXL, the backward shifting of the PRK-CXL group could be smaller than the PRK alone.

At 18 months after surgery, the PRK-CXL group had fewer patients with haze (4.8%, five eyes) than the PRK group (6.4%, five eyes). Our finding demonstrated a difference in the probability of postoperative haze (0 − 8.3%) when PRK was combined with simultaneous CXL compared with previous and similar studies.[8,11] A study by Lee et al[11] observed no haze, whereas a study by Sachdev et al[8] observed that 8.3% of patients suffered from grade 1 haze after PRK-CXL surgery. In the studies by Lee et al[11] and Sachdev et al,[8] they used mitomycin C (MMC) which may reduce the probability of haze because it can inhibit DNA and RNA replication and prevent cell mitosis.[26] Moreover, Lee et al[11] used the SCHWIND Amaris laser machine to ablate corneal epithelium, which provides compensation based on the corneal epithelium distribution mode of the population; this means that the amount of cutting of the peripheral epithelium will be higher than that of the central part. Other studies reported that postoperative epithelial recovery occurred more rapidly with a reduced probability of haze when a laser method was used rather than mechanical or alcohol methods.[27] The usage of MMC and different corneal epithelial removal methods may explain why the probability of haze was lowest in the study by Lee et al.[11] For some unknown reason, we had no MMC in our study period, however, as time progressed, the haze reaction was greatest at 1 month, plateaued at 3 months, and diminished over time.[28]

Based on one retrospective study, the incidence of corneal dilatation after refractive surgery with abnormal topography was about 5.8%; based on the incidence, we calculated a sample size of 50, which is smaller than in our study.[2] In a previous study by Randleman,[29] the average time of the appearance of ectasia after LASIK was 16.3 months (range from 1 to 45 months), and our follow-up time was 18 months, which was longer. While there are still some cases of ectasia that may occur after 18 months, we will continuously monitor and report the results with longer follow-up.

5. Conclusions

In eyes with borderline corneal tomography, combined PRK and prophylactic CXL demonstrated comparable predictability, efficacy, and safety compared with PRK alone as well as minimal corneal biomechanical changes. Prophylactic crosslinking combined with PRK could be proposed as an alternative to traditional PRK, particularly for patients considered good candidates for PRK but have a non-satisfied cornea, such as one with a borderline suspicious tomography.

Author contributions

Conceptualization: Li Li, Zheng Wang.
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Formal analysis: Li Li, Zheng Wang.
Funding acquisition: Zheng Wang.
Investigation: Li Li, Zheng Wang.
Methodology: Li Li, Zheng Wang.
Project administration: Zheng Wang.
Resources: Li Li.
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References

[1] Randleman JB, Woodward M, Lynn MJ, et al. Risk assessment for ectasia after corneal refractive surgery. Ophthalmology 2008;115:37–50.

[2] Moshirfar M, Smedley JG, Muthappan V, et al. Rate of ectasia and incidence of irregular topography in patients with unidentified preoperative risk factors undergoing femtosecond laser-assisted LASIK. Clin Ophthalmol 2014;8:35–42.
[3] Guedj M, Saad A, Audureau E, et al. Photorefractive keratectomy in patients with suspected keratoconus: five-year follow-up. J Cataract Refract Surg 2013;39:66–73.
[4] Randleman JB, Caster AI, Banning CS, et al. Corneal ectasia after photorefractive keratectomy. J Cataract Refract Surg 2006;32:1395–8.
[5] Francis M, Khamar P, Shetty R, et al. In vivo prediction of air-puff induced corneal deformation using LASIK, SMILE, and PRK finite element simulations. Investig Ophthalmol Vis Sci 2018;59:5320–8.
[6] Tomita M. Combined laser in-situ keratomileusis and accelerated corneal cross-linking: an update. Curr Opin Ophthalmol 2016;27:304–10.
[7] Kanellopoulos AJ, Kontos MA, Chen S, et al. Corneal collagen cross-linking combined with simulation of femtosecond laser-assisted refractive lens extraction: an ex vivo biomechanical effect evaluation. Cornea 2015;34:550–6.
[8] Sachdev GS, Ramamurthy S, Dandapani R. Comparative analysis of safety and efficacy of photorefractive keratectomy versus photorefractive keratectomy combined with crosslinking. Clin Ophthalmol 2018;12: 783–90.
[9] Roberts CJ. Concepts and misconceptions in corneal biomechanics. J Cataract Refract Surg 2014;40:862–9.
[10] Ambrosio RJr, Lopes BT, Faria-Correia F, et al. Integration of Scheimpflug-based corneal tomography and biomechanical assessments for enhancing Ectasia detection. J Refract Surg 2017;33:434–43.
[11] Lee H, Yong Kang DS, Ha BJ, et al. Comparison of outcomes between combined transepithelial photorefractive keratectomy with and without accelerated corneal collagen cross-linking: a 1-year study. Cornea 2017;36:1213–20.
[12] Mas Tur V, MacGregor C, Jayaswal R, et al. A review of keratoconus: diagnosis, pathophysiology, and genetics. Surv Ophthalmol 2017;62: 770–83.
[13] Vinciguerra R, Elsheikh A, Roberts CJ, et al. Influence of pachymetry and intraocular pressure on dynamic corneal response parameters in healthy patients. J Refract Surg 2016;32:550–61.
[14] Roberts CJ, Mahmoud AM, Bons JP, et al. Introduction of two novel stiffness parameters and interpretation of air puff–induced biomechanical deformation parameters with a dynamic Scheimpflug analyzer. J Refract Surg 2017;33:266–73.
[15] Vinciguerra R, Romano V, Arbabi EM, et al. In vivo early corneal biomechanical changes after corneal cross-linking in patients with progressive keratoconus. J Refract Surg 2017;33:840–6.
[16] Kanellopoulos AJ, Asimellis G. Combined laser in situ keratomileusis and prophylactic high-fluence corneal collagen crosslinking for high myopia: two-year safety and efficacy. J Cataract Refract Surg 2015;41: 1426–33.
[17] Xu W, Tao Y, Wang L, et al. Evaluation of biomechanical changes in myopia patients with unsatisfactory corneas after femto second-laser in situ Keratomileusis (FS-LASIK) concurrent with accelerated corneal collagen cross-linking using corvis-ST: two-year follow-up results. Med Sci Monit 2017;23:3649–56.
[18] Durrie D, Stulting RD, Potvin R, et al. More eyes with 20/10 distance visual acuity at 12 months versus 3 months in a topography-guided excimer laser trial: Possible contributing factors. J Cataract Refract Surg 2019;45:595–600.
[19] Malta JBNS, Kaz Soong H, Moscovici BK, et al. Two-year follow-up of corneal cross-linking and refractive surface ablation in patients with asymmetric corneal topography. Br J Ophthalmol 2019;103:137–42.
[20] Kanellopoulos AJ, Pamel GJ. Review of current indications for combined very high fluence collagen cross-linking and laser in situ keratomileusis surgery. Indian J Ophthalmol 2013;61:430–2.
[21] Kanellopoulos AJ, Asimellis G, Karabatsas C. Comparison of prophylactic higher fluence corneal cross-linking to control, in myopic LASIK, one year results. Clin Ophthalmol 2014;8:2373–81.
[22] Hyun S, Lee S, Kim JH. Visual outcomes after SMILE, LASEK, and LASEK combined with corneal collagen cross-linking for high myopic correction. Cornea 2017;36:399–405.
[23] Lee H, Roberts CJ, Ambrosio RJr, et al. Effect of accelerated corneal crosslinking combined with transepithelial photorefractive keratectomy on dynamic corneal response parameters and biomechanically corrected intraocular pressure measured with a dynamic Scheimpflug analyzer in healthy myopic patients. J Cataract Refract Surg 2017;43:937–45.
[24] Santhiago MR, Giacomin NT, Medeiros CS, et al. Intense early flattening after corneal collagen cross-linking. J Refract Surg 2015;31:419–22.
[25] Lee H, Kang DS, Ha BJ, et al. Changes in posterior corneal elevations after combined transepithelial photorefractive keratectomy and accelerated corneal collagen cross-linking: retrospective, comparative observational case series. BMC Ophthalmol 2016;16:139.
[26] Barbosa FL, Chaurasia SS, Kaur H, et al. Stromal interleukin-1 expression in the cornea after haze-associated injury. Exp Eye Res 2010;91:456–61.
[27] Aslanides IM, Georgoudis PN, Selimis VD, et al. Single-step transepithelial ASLA (SCHWIND) with mitomycin-C for the correction of high myopia: long term follow-up. Clin Ophthalmol 2015;9:33–41.
[28] Greenstein SA, Fry KL, Bhatt J, et al. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: Scheimpflug and biomicroscopic analysis. J Cataract Refract Surg 2010;36:2105–14.
[29] Randleman JB. Post-laser in-situ keratomileusis ectasia: current understanding and future directions. Curr Opin Ophthalmol 2006;17: 406–12.