• Clinical Research •

Visual outcomes and corneal biomechanical evaluation between LASIK and LASIK combined with accelerated corneal crosslinking

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Abstract

● **AIM:** To assess the visual outcomes and corneal biomechanical properties of myopia patients between laser *in situ* keratomileusis (LASIK) and LASIK combined with accelerated corneal crosslinking (LASIK Xtra).

● **METHODS:** This prospective study analyzed 52 consecutive myopia patients treated with LASIK Xtra and 45 consecutive myopia patients treated with LASIK. Only the right eyes in the two groups were analyzed. The uncorrected distance visual acuity (UDVA), keratometry values, postoperative central corneal thickness (CCT), corneal demarcation line depth, the corneal compensated intraocular pressure (IOPcc), Goldmann-correlated IOP (IOPg), corneal resistance factor (CRF) and corneal hysteresis (CH) from Ocular Response Analyzer (ORA) were analyzed. Further, the correlation between the demarcation line depth and ORA-related biomechanical parameters were analyzed.

● **RESULTS:** No significant differences in UDVA, postoperative CCT, or mean K values were found between the 2 groups at 1 to 12mo postoperative follow-up (all $P>0.05$). The changes of CRF was significantly lower in the LASIK Xtra group compared to the LASIK group (all $P<0.05$) at all the postoperative visits. The changes of CH were significantly higher in the LASIK Xtra group (all $P<0.05$). No significant differences were discovered regarding the changes of IOPcc and IOPg posperatively (all $P>0.05$). Out of 52 cases in the LASIK Xtra group, the demarcation line was present in 40 eyes (77%). The average depth of the demarcation was 220.73±42.70 μm (136 to 288 μm). No significant correlation was observed between the depth of the demarcation line and any of the ORA-related biomechanical parameters such as IOPcc, IOPg, CRF and CH at 12mo (all $P>0.05$).

● **CONCLUSION:** Both procedures demonstrate comparable outcomes in terms of visual acuity, refraction and ablation predictability. This study confirms that corneal biomechanical properties of the included patients weakened after both procedures, but the cornea after LASIK Xtra are stiffer than conventional LASIK.

● **KEYWORDS:** myopia; femto-laser *in situ* keratomileusis; laser *in situ* keratomileusis combined with accelerated corneal crosslinking; corneal biomechanics

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INTRODUCTION

Laser-assisted *in situ* keratomileusis (LASIK) is a well-accepted corneal refractive surgery, with satisfactory visual outcomes and patient comfort[1-2]. The use of femtosecond laser and advanced preoperative screening strategies investigating both anterior and posterior corneal surfaces and corneal biomechanical behavior have led to a reduction in risk of iatrogenic keratectasia from 0.66% to 0.033%[3-4]. The mean percentage change in the curvature radius after flap creation was more than 50% smaller by using the femtosecond laser than by mechanical microkeratome[5].

Although the incidence of iatrogenic ectasia is very low, it is still the most severe complication for young refractive surgery candidates. It is reported to be associated with a thin cornea (≤500 μm), anterior topographic map irregularities, younger age, ectasia risk score >3, percent tissue thickness alteration (PTA) (≥40%), and low residual stromal bed (RSB; ≤280 μm)[3,6-9]. Clinically, RSB≤280 μm and PTA≥40% were most commonly used for excluding LASIK candidates. However, Bohac *et al*[3] examined over 30 000 LASIK cases and reported the incidence of ectasia, they found only three ectasia cases (30%) had an RSB lower than 300 μm (no lower than 250 μm), and only two cases (20%) had PTA higher than 40%. Contrariwise, over 15% of the stable-LASIK cases had RSB less than 300 μm and more than 20% of such cases had PTA higher than 40%[10]. Ectasia occurs due to biomechanical decompensation of the stroma, which may be also related to altered biomechanical properties before operation, or to a severe impact on corneal structure (*i.e.*, laser ablation for high myopia)[10].

Corneal crosslinking (CXL) has been introduced some fifteen years ago to increase corneal biomechanical strength by creating cross-links, *i.e.,* extra bonds between the collagen fibers, induced by a photochemical reaction, between riboflavin (a chromophore) and ultraviolet-A light (UVA) (activator)[11]. By that way the progression of keratoconus, pellucid marginal degeneration, as well as iatrogenic keratectasia, may be halted[11-12]. LASIK Xtra is a combined procedure of LASIK and accelerated CXL, performing vision correction surgery and corneal stroma strengthening in one step. Theoretically, it may potentially decrease the risk of iatrogenic ectasia at the initial stage[13].

Some researchers have investigated the long-term refractive safety outcomes after LASIK Xtra and the results were inconsistent. While some studies showed that the LASIK Xtra procedure was more likely to reach favorable visual outcomes than the conventional LASIK alone for both high myopia and low-moderate population[14-15], and that the additional CXL may help stabilize the corneal posterior elevation after LASIK, as noticed by swept-source optical coherence tomography[16], and may improve postoperative refractive stability with respect to myopic regression by alleviating the over-remodeling of the corneal epithelium cells[13,17]. Others found that the refractive safety and efficiency of LASIK Xtra were comparable with the LASIK alone in patients with high myopia and borderline myopia, but appears to offer no additional benefit regarding the refractive safe index in the long-term follow-up time[18-19].

It is logical to hypothesize that the LASIK Xtra procedure may be preferable in the treatment of high myopia and/or in cases with low RSB (<280 μm) since the CXL may enhance postoperative corneal biomechanical strength. Tomita *et al*[20] evaluated the corneal biomechanical behavior after LASIK Xtra in moderate myopia cases by a contralateral controlled study, and found no difference was found between the two groups. However, to our knowledge, for high myopia cases or low-moderate myopia associated with low RSB populations, there is no study clarifying the corneal bio-mechanical changes after LASIK Xtra compared to the conventional LASIK procedure alone in the treatment of high myopia or low to moderate myopia associated with low RSB populations. Hence, the current study aimed to evaluate the differences in the corneal biomechanical changes between femtosecond (FS) LASIK Xtra and conventional FS-LASIK. We also compared the anterior morphological stability and refractive outcomes between the two procedures.

PARTICIPANTS AND METHODS

Ethical Approval The study was approved by the Ethics Committee of Beijing Tongren Hospital (No.TREC2019-XJS08) and conducted following the principles of the Declaration of Helsinki. The informed consent was signed by the patients.

Participants Patients presenting for refractive surgery (no previous corneal laser surgery history) at the Refractive Center of Beijing Tongren Hospital between May and December 2020 were invited to participate in the current prospective study. A total of 97 consecutive patients were enrolled in this study. The LASIK Xtra group consisted of 52 patients (24 males and 28 females) on whom concurrent prophylactic CXL was applied, while the conventional LASIK group consisted of 45 patients (20 males and 25 females) on whom no CXL was implemented. All patients received bilateral surgery, but only data from the right eye of each patient was included in the data analysis in the current study. Inclusion criteria for the study were as follows: aged >18y, predicted vision acuity postoperatively ≥20/25, refractive change less than 0.5 D during the past 2y, borderline corneal topography abnormality (defined as 1 D or greater inferior steepening in some areas but an inferior-superior difference value of less than 1.25 D, or unevenly distributed corneal thickness), or more than -6 D spherical equivalent, or low-moderate myopia but associated with a low RSB thickness of <300 μm. All patients underwent cessation of soft contact lens wear for 1wk and rigid contact lens wear for 1mo before the surgery.

Exclusion criteria included: active ocular inflammation or infection, abnormal corneal topography, and any systemic disease.

Preoperative Assessment Preoperatively, all participants underwent comprehensive ophthalmic assessments, which included the slit lamp microscopy, non-contact intraocular pressure (IOP) tonometer (Canon TX-20P, Japan), fundoscopy, auto-refraction (KR-8100, Topcon, Japan), subjective manifest refraction and cycloplegic refraction, corneal topography by TMS-4 (Tomey Corp, Nagoya, Japan), Lenstar LS900 (Haag-Streit Corp, Switzerland), RTVue OCT (Optovue Inc., Fremont, California, USA) and Ocular Response Analyzer II (ORA; Reichert, Inc., Depew, NY, USA). The image quality was controlled by an experienced physician before analysis.

In order to reduce the impact of the corneal demarcation line and decreased corneal transparency caused by CXL on corneal thickness measurements, the central corneal thickness (CCT) was measured in this study using the Lenstar LS900, with optical low coherence reflectometry technique, and was centered on the visual axis. This method achieved remarkable reproducibility with an error margin of only ±2 μm. The demarcation line was obtained through RTVue OCT and measured 2wk visiting after surgery. The picture was taken during the corneal reflex visibility and the demarcation line was detected as a highly reflective line in the stroma. The depth of the demarcation line was measured using the manufacturer's caliper tool. To measure the demarcation line depth, the caliper tool was positioned at the posterior end of the hyperreflective line in the central cornea.

The flap depth creation also plays a role in the corneal stiffness/biomechanical behavior change. A study found that the 32% increase in displacement of flap movement observed after 160-μm depth flap creation was more than 3.5 times greater than the 9% increase measured when 90-μm flaps were created[21]. Possible explanations included that the anterior one-third stroma offers twice the mechanical strength of its posterior two-thirds; while the epithelium has an insignificant mechanical function. Therefore, in the current study, we performed a 100 μm flap to maximumly preserve the corneal integrity and biomechanical properties postoperatively.

Surgical Procedures All procedures were performed by a single experienced refractive surgeon (Zhai CB). For all the treated eyes, corneal flaps were created using a VisuMax femtosecond laser system (Carl Zeiss, Jena, Germany). Flap creation settings were as follows: flap thickness was set to 100 μm and the diameter was 8.1 mm; the side-cut angles of flaps were 90°; The hinges were set at superior with a hinge length of 4.0 mm; the subsequent stromal ablation was performed using a WaveLight® EX500 excimer laser system (Alcon Labs, Ft. Worth, TX, USA), and the optical zone was 6.0-6.5 mm.

FS-LASIK Xtra procedure was same as the control group. After flap creation and laser ablation, 0.22% riboflavin in isotonic saline solution (Vibex XtraTM, Avedro, Waltham, MA, USA) was used to soak the RSB for 90s. The 0.9% balanced salt solution (BSS) was used to wash out the riboflavin solution, and then the corneal flap was repositioned. UVA by the KXL system (Avedro, VibeX Xtra, Avedro Inc, USA) was used to radiate the cornea for 90s at an intensity of 30 mW/cm^2 (total energy of 2.7 J/cm^2), using a continuous radiation mode. Soft bandage contact lenses (BAUSCH+LOMB, Inc., NY, USA) were placed for 1d after surgery.

For the first postoperative week, all patients were prescribed levofloxacin 0.5% ophthalmic solution (Cravit® Santen Pharmaceutical Co., Ltd., Osaka, Japan) four times daily, corticosteroid eye drops fluorometholone 0.1%, (FLAREX® Alcon Laboratories, Inc. USA) 4 times daily tapering for 2wk, bromfenac sodium 0.1% (Santec Pharmaceutical Co., Ltd., Osaka, Japan) twice daily. Additionally, the patients were instructed to use the ocular lubricant SYSTANE® (Alcon Laboratories, Inc. USA) four times daily during the first three months after surgery.

Observation Index All patients were asked to attend the regular ocular examinations the next day after the surgery and at 1wk, 1, 3, 6, and 12mo post-operatively. At 1d and 1wk visit time, the slit lamp microscopy, uncorrected distance vision acuity (UDVA), autorefraction, and IOP were measured. At 1mo and at the following postoperative visits, the slit lamp microscopy, corneal topography, UDVA, autorefraction, IOP, and Lenstar LS900 and ORA were performed.

Statistical Analysis All data were analyzed using IBM SPSS Version 23.0 (IBM Corp., Chicago, IL, USA). Descriptive data were expressed as mean±standard deviation (SD). The Shapiro-Wilk test was applied to determine the normality of the data. The differences in preoperative and postoperative data between the LASIK Xtra group and the conventional LASIK group were determined by Student's independent *t*-test if they were normal distribution. For samples that did not satisfy normal distribution, we used the Mann-Whitney *U* test. For the correlation between the demarcation line depth and ORA-related corneal biomechanical properties, the Pearson correlation was used. The *P* value less than 0.05 was considered statistically significant for two-tailed tests.

RESULTS

Mean patient ages was 26.19±3.97y (range: 18 to 36y) in the LASIK Xtra group and was 27.89±4.96 (range:18 to 38y). All patients completed 12-month follow up. Demographic details and surgical plans were listed in Table 1. Preoperative CCT measured by Lenstar was 491.75±15.67 μm in the LASIK Xtra group and 496.71±15.58 μm in the LASIK group (*P*=0.122). In the respective groups, preoperative spherical equivalent refraction (SER) was -8.06 and -7.5 D (*P*=0.257), spherical refraction was -7.5 (2.00) and -7.5 (3.13) D (*P*=0.337), and PTA were 40.36 (2.05) and 40.41 (1.74) (*P*=0.803). No significant differences were found among all baseline preoperative data between the two groups.

Visual Acuity, Refractive and Cornea Keratometry The UDVA, refractive, and mean K values did not differ between the two groups at 1 to 12mo postoperative follow-up according

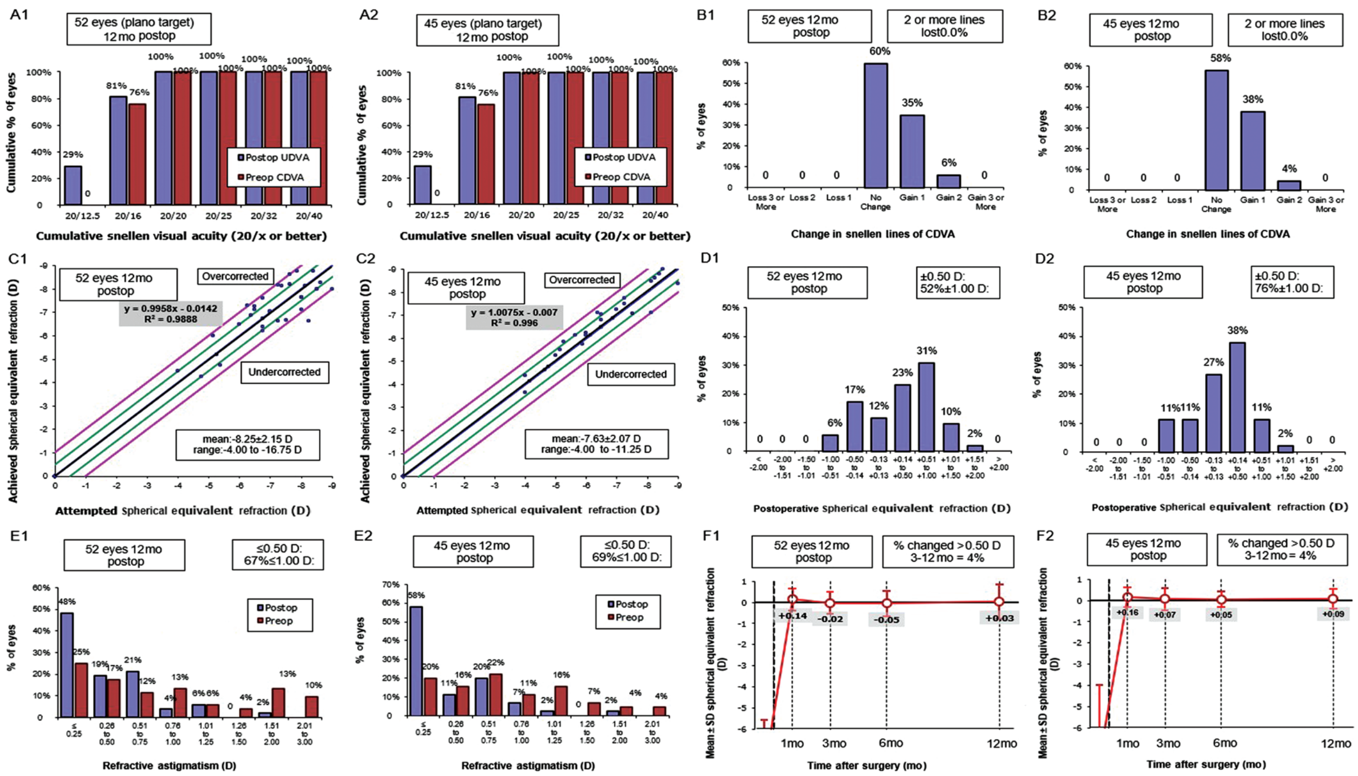

Figure 1 Visual and refractive outcomes of the LASIK Xtra group (A1-F1) and LASIK group (A2-F2) A: Cumulative Snellen visual acuity preoperatively and at 12mo follow-up in the LASIK Xtra (A1) and LASIK (A2) groups; B: Difference between the postoperative UDVA and the preoperative CDVA at 12mo follow-up in the LASIK Xtra (B1) and LASIK (B2) groups; C: Spherical equivalent attempted *vs* achieved in the LASIK Xtra (C1) and LASIK (C2) groups; D: Spherical equivalent refraction at 12mo follow-up in the LASIK Xtra (D1) and LASIK (D2) groups; E: Refractive astigmatism preoperatively and at 12mo follow-up in the LASIK Xtra (E1) and LASIK (E2) group; F: Stability of spherical equivalent refraction from preop. to 12mo postop. in the LASIK Xtra (F1) and LASIK (F2) groups. LASIK: Laser-assisted *in situ* keratomileusis; LASIK Xtra: Procedure which combines LASIK and corneal cross-linking; UDVA: Uncorrect distant visual acuity; CDVA: Correct distant visual acuity.

to Table 2. The spherical refraction exhibited similar values between the two groups throughout the follow-up visits. The postoperative CCT did not show significant inter-group differences at all follow-up visits (all $P>0.05$). Figure 1 showed the safety, effectively, predictability and stability of the two groups.

Corneal Biomechanical Properties Table 3 showed the ORA-related corneal biomechanical changes at each visit. No significant difference was discovered regarding the corneal compensated IOP (IOPcc), Goldmann-correlated IOP (IOPg). △CRF was significantly lower in the LASIK Xtra group compared to the LASIK group (all $P<0.05$) at all the postoperative visits. Changes of cornea hysteresis (△CH) were significantly higher in the LASIK Xtra group (all $P<0.05$).

Presence of Demarcation Line Depth and Percentage of the Demarcation Line in the LASIK Xtra Group Out of 52 cases in the LASIK Xtra group, the demarcation line was present in 40 eyes (77%). The average depth of the demarcation was 220.73±42.70 μm, ranging from 136 to 288 μm. No demarcation line was found to locate at the flap part of the stroma in the LASIK Xtra group. Upon conducting a correlation analysis, no significant correlation was observed

Table 1 Baseline data between the LASIK Xtra group and LASIK group

Parameters	LASIK Xtra group (52 eyes)	LASIK group (45 eyes)	*P*
Age (y)	26.19±3.97	27.89±4.96	0.07[a]
IOP (mm Hg)	15.59±2.14	14.89±2.55	1.467[a]
SER (D)	-8.06 (2.50)	-7.5 (3.50)	0.257[b]
Spherical refaction (D)	-7.50 (2.00)	-7.50 (3.13)	0.337[b]
Astigmatism (D)	-0.75 (1.19)	-0.75 (0.75)	0.812[b]
Preoperative CCT (μm)	491.75±15.67	496.71±15.58	0.122[a]
RSB (μm)	293.00 (13.25)	292.00 (12.00)	0.786[b]
PTA (%)	40.36 (2.05)	40.41 (1.74)	0.803[b]
Km (D)	43.64±1.55	43.71±1.06	0.821[a]
IOPcc (mm Hg)	16.36±2.97	16.40±2.75	0.944[a]
IOPg (mm Hg)	15.8±2.38	15.2±2.27	0.101[a]
CH	8.89±1.09	8.85±1.47	0.792[a]
CRF	8.95±1.21	8.75±1.25	0.164[a]

LASIK: Laser-assisted *in situ* keratomileusis; LASIK Xtra: Procedure which combines LASIK and corneal cross-linking; IOP: Intraocular pressure; SER: Spherical equivalent refraction; CCT: Central corneal thickness; RSB: Residual stromal bed thickness; PTA: Percentage of tissue alteration; Km: Anterior mean keratometry; IOPcc: The corneal compensated IOP; IOPg: Goldmann-correlated IOP; CH: Corneal hysteresis; CRF: Corneal resistance factor. [a]Student's independent *t*-test; [b]Mann-Whitney *U* test.

Table 2 Postoperative visual and refractive outcomes, corneal topographic results

Groups	1mo	3mo	6mo	12mo
UDVA (logMAR)				
LASIK Xtra	-0.08 (0.18)	-0.08 (0.13)	-0.08 (0.18)	-0.08 (0.18)
LASIK	-0.08 (0.10)	-0.09 (0.05)	-0.08 (0.10)	-0.08 (0.14)
P	0.148[b]	0.580[b]	0.107[b]	0.841[b]
Sphere (D)				
LASIK Xtra	0.29±0.45	0.16±0.46	0.08±0.54	0 (0.76)
LASIK	0.30±0.50	0.18±0.54	0.11±0.31	0 (0.43)
P	0.902[a]	0.813[a]	0.698[a]	0.774[b]
Cylinder (D)				
LASIK Xtra	0 (0.72)	-0.19 (0.62)	-0.31 (0.72)	-0.37 (0.62)
LASIK	0 (0.50)	0 (0.44)	0 (0.50)	0 (0.56)
P	0.845[b]	0.173[b]	0.089[b]	0.245[b]
Postoperative CCT (μm)				
LASIK Xtra	377.26±13.08	383.61±12.01	383.48±12.58	388.32±13.07
LASIK	379.49±11.34	384.82±11.45	387.33±11.31	389.77±12.90
P	0.456[a]	0.671[a]	0.189[a]	0.887[a]
Km (D)				
LASIK Xtra	37.25±1.84	37.76±1.98	37.34±1.91	37.20±2.13
LASIK	37.13±1.59	37.19±1.54	37.32±1.58	37.22±1.51
P	0.078[a]	0.204[a]	0.974[a]	0.975[a]

UDVA: Uncorrected distance visual acuity; CCT: Central corneal thickness; Km: Anterior mean keratometry. [a]Student's independent *t*-test; [b]Mann-Whitney *U* test.

Table 3 Changes of ORA related parameters after surgery between the two groups

Parameters	3mo	6mo	12mo
△IOPcc			
LASIK Xtra	1.76±3.20	1.41±3.22	1.32±3.30
LASIK	2.42±2.57	2.16±2.81	2.39±2.92
P	0.266[a]	0.221[a]	0.091[a]
△IOPg			
LASIK Xtra	5.87±2.50	5.32±2.37	5.37±2.44
LASIK	5.59±2.22	5.60±2.36	5.74±2.31
P	0.569[a]	0.567[a]	0.436[a]
△CH			
LASIK Xtra	2.80 (1.63)	3.05 (1.97)	3.00 (1.68)
LASIK	2.20 (1.90)	2.50 (1.55)	2.60 (1.50)
P	0.011[b]	0.045[b]	0.025[b]
△CRF			
LASIK Xtra	2.84±1.23	2.59±1.53	2.70 (2.08)
LASIK	3.52±1.38	3.71±1.34	3.80 (1.55)
P	0.012[a]	<0.001[a]	0.001[b]

ORA: Ocular Response Analyzer; LASIK: Laser-assisted *in situ* keratomileusis; LASIK Xtra: Procedure which combines LASIK and corneal cross-linking; △IOPcc: Changes of IOPcc postoperatively; △IOPg: Changes of IOPg postoperatively; △CH: Changes of cornea hysteresis; △CRF: Changes of cornea resistance factor. [a]Student's independent *t*-test; [b]Mann-Whitney *U* test.

between the depth of the demarcation line and any of the ORA-related biomechanical parameters such as IOPcc, IOPg, CRF and CH at 12mo (all $P>0.05$).

DISCUSSION

Overall, in the current study, the visual outcomes, postoperative CCT, and anterior corneal curvature were all comparable between the two groups, indicating that the laser ablation predictability were excellent in both procedures, and the additional CXL procedure did not affect the changes in the long-term healing process. We found that the ORA-related corneal biomechanical parameters show significant advanced benefit in the LASIK Xtra group compared with the conventional LASIK group during the first-year follow-up.

LASIK Xtra procedure involves soaking the stroma beneath the flap for 90s, then repositioning the flap on the RSB, and applying UVA light to the total residual cornea, including the anterior flap and posterior stroma bed. The question that may arise from this procedure is whether the cross-linking effect has any influence on stromal morphological data including topographic values and further on the visual outcomes, despite of the theoretical assumption that the laser ablation accuracy should not be affected by CXL since it is performed after the laser ablation and usage of low-dose UVA energy.

Because the traditional CXL did have an effect on the corneal curvature, which flattened the corneal maximum K value around up to 3 D[22-23]. Herein, we analyzed the anterior mean

K value and visual outcomes including the spherical refraction, astigmatism, postoperative UDVA after both procedures. Our findings indicate that there were no significant differences regarding the K value and the visual outcomes between the two procedures during the first-year follow-up period. These results align with previous studies and suggest comparable outcomes between the two procedures[20,24]. However, others found that the LASIK Xtra has superior refractive outcomes compared with LASIK only group[15]. Especially, the keratometric stability plots were stable in the LASIK Xtra group and slightly regressing in the standard LASIK group. One of the possible explanations could be that the corneal epithelial remodeling effect (thickening after myopic ablation) in the LASIK Xtra group is less profound than in the LASIK group[25].

Furthermore, the postoperative CCT are very consistent between the two groups, even though we only measured the central corneal thickness by Lenstar rather than other common corneal topographies such as Scheimpflug and optical coherence tomography (OCT) based technologies. Because their CCT results all showed good agreement and repeatability among those technologies[26-27]. Laser ablation predictability involved in the two groups was excellent because the laser was performed before riboflavin soakage in the LASIK Xtra. Further, the cross-linked effect was mild in the LASIK Xtra eyes, according to the CCT values measured at each observation point, which showed that the CCT was stable with only very slight fluctuation. It would be more convincing if, in the future, the sectional corneal thicknesses could be evaluated after the LASIK Xtra procedure.

In the current study, we found that all the ORA-related corneal biomechanical parameters were significantly decreased after surgery. In terms of postoperative changes of related parameters, △CRF in the LASIK Xtra group at each visiting point were significantly lower than the ones in the conventional LASIK group. However, △CH in the LASIK Xtra group were significantly higher. In the ORA system, the difference between P1 (pressure at applanation in the inward direction) and P2 (pressure at applanation in the outward direction) is called CH[28] and represents the viscoelastic response of the cornea to an applied force defined by a specific air-pressure curve. CRF is determined by its correlation with CH and is influenced by the weight assigned to CCT. Despite all the ORA-related corneal bio-mechanical parameters decreased after surgery, our results suggest that corneal stiffness increased whereas corneal tissue elasticity(hysteresis) decreased after LASIK Xtra compared with conventional LASIK. When compared with the results from Japan, they found that similar weakening trend as ours, which exhibited a higher decreasing effect on both the CH and CRF in the LASIK Xtra group, yet showing no significant differences observed in the two groups[20]. There are no significant difference regarding △IOPcc and △IOPg at each visiting point between the two groups. Besides, the other different variable in the two groups such as preoperative IOP, the postoperative CCT, Km, and age were all similar in the two groups. Previous study had shown that corneal stiffness are also positively correlated with aging due to the natural corneal cross-linking that happened in the advanced glycation end product (AGE)-mediated cross-linking that occurs as a result of the reaction of glycated proteins, including collagen, to non-enzymatically react with surrounding proteins[20]. Conversely, in the current case, the preoperative IOP, postoperative sphere refraction, cylinder refraction, CCT, and age are comparable in both groups, the corneal stiffness (wall tension) will be similar if the treatment interventions in the two groups are the same. So, we may conclude that the corneal stiffness in the LASIK Xtra group is significantly harder than in the LASIK-only group.

The IOPcc theoretically was proven to be less dependent on corneal stiffness. The IOPcc in the ORA system has been designed to be less sensitive to a reduction in the corneal properties, based on empirical data from the pre-and post-LASIK eyes, where true IOP was assumed to remain unchanged. IOPcc was not derived from measurements in pathologic corneas or in post-CXL corneas with an increase in corneal stiffness, where the conditions of the original calibration are not fully met[29]. Therefore, the use of IOPcc as a normalizing "true IOP" value has not been proven in the setting of CXL, and it is hypothesized that true IOP has not changed significantly in these patients within 3mo after CXL. Nevertheless, IOPcc changes after CXL varied from study to study. Vinciguerra *et al*[30] found that neither IOPcc nor IOP changed at 6mo after CXL in keratoconus (KC) cases. Contrarily, Sedaghat *et al*[31] found IOPcc to decrease less than 1 mm Hg at 6mo after CXL. Whilstin a randomized controlled trial[3], they found that the IOPcc decreased in both KC and post-refractive surgery ectasia cases, and the maximum change for any patient was 1.5 mm Hg.

We further found that there is no significant correlation between the ORA-derived parameters and the demarcation line depth. The explanation for these negative results might be that the ORA measures the whole layer of overall corneal deformation, but the cross-linked effect in the LASIK Xtra is more likely only happened in the RSB under the flap within the central 8 mm area, which may not be able to be detected by the whole layer of information.

An additional question that may arise is whether crosslinking occurs on the stroma underneath the flap alone, on the flap-stroma, or on both the flap and the posterior stroma bed if a certain portion of the cornea either on the flap or stroma bed is exposed to riboflavin inevitably even though the flap and hinge were carefully protected when soaking riboflavin[15]. Our study found that the average demarcation line depth was 220.73.4±42.70 μm, ranging from 136 to 288 μm. These results are accompanied by the one published previously, which showed a mean demarcation line depth of 200.04±27.01 μm (range 178 to 278 μm)[19]. In the LASIK Xtra case, if there is rare riboflavin exposed to the flap-stroma, then there would be no chance for the flap to be cross-linked. The reason is that after riboflavin soaking, before re-positioning the flap and UVA radiation, surgeons will use BSS to remove the remaining riboflavin until the RSB is clear and no riboflavin remains. On the other hand, on collateral benefits, a "CXL" flap-stromal interface might positively affect flap adherence if a small amount of riboflavin was soaked inadvertently in the flap[24].

In summary, both procedures demonstrated comparable outcomes in terms of visual acuity, refraction and ablation predictability. The LASIK Xtra group exhibited a demarcation line visible on OCT. This study confirmed that corneal biomechanical properties weakened after both procedures and ORA detect significant differences between the two procedures and confirmed that the cornea after LASIK Xtra were stiffer than conventional LASIK. Lastly, in terms of the corneal biomechanical evaluation, it might be interesting if try newer generations of technology such as Corvis ST, air-puff OCT, and air-puff biometry in the LASIK Xtra cases[29].

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