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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

Authors' Contribution:

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Some myopia patients with unsatisfactory corneas consider corneal refractive surgery for different reasons. Accelerated corneal collagen crosslinking (ACXL) is an effective method to enhance the resistance of the cornea. The present investigation was designed to evaluate the changes of biomechanical properties in patients with myopia and thin corneas after femtosecond-laser *in situ* keratomileusis (FS-LASIK) concurrent with ACXL.





Material/Methods: A prospective study was designed. A total of 22 eyes of 11 myopia astigmatism patients with unsatisfactory corneas were enrolled. The patients were assigned to femtosecond-laser *in situ* keratomileusis concurrent with accelerated corneal collagen crosslinking (FS-LASIK-ACXL). The follow-up duration was 24 months. Manifest refraction, uncorrected (UDVA), and corrected distance visual acuity (CDVA), ultra-high-speed camera (Corvis-ST), corneal topography, anterior segment OCT (AS-OCT), Pentacam, and endothelial cell density (ECD) were examined before and after the operation. The corneal biomechanical and refractive data was analyzed using SAS9.3. Data were analyzed through normal distribution test and variance of analysis. The difference was considered as statistically significant when $p < 0.05$.

Results: The steep K (Ks) values, flat K (Kf) values, average keratometry values (Avek) values, and central corneal thickness (CCT) declined significantly after FS-LASIK-ACXL operation. The values of first applanation length (A1L), the second applanation length (A2L), the first applanation velocity (A1V), the second applanation velocity (A2V), deformation amplitude (DA), highest concavity peak distance (PD), and radius of curvature at the time of highest concavity (HCR) did not show significant difference after the operation.

Conclusions: FS-LASIK-ACXL is an effective and safe surgery for improving visual acuity for myopic patients with thin corneas, and it does not increase the risk of iatrogenic keratectasia.

MeSH Keywords: **Biomechanical Phenomena • Cornea • Cross-Linking Reagents • Myopia**

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Background

Laser *in situ* keratomileusis (LASIK) is the most commonly performed refractive surgical procedure for the surgical correction of refractive errors. It causes little discomfort and results in faster visual recovery than surface ablations. Advantages of femtosecond assisted LASIK (FS-LASIK) over conventional micro keratome assisted LASIK (MK-LASIK) include the reduced risk of flap complications (button hole or free cap formation), the better flap thickness predictability, the less iatrogenic astigmatism and the less biomechanical insults to the cornea [1]. FS-LASIK can improve the reproducibility, stability, precision, and versatility of refractive surgery. It enables patients with high myopia and/or thin corneas to get better uncorrected visual acuity by corneal refractive surgery [2]. Some patients who have received LASIK might suffer from post-LASIK keratectasia (PLK) due to the decreased corneal thickness and changes of biomechanical characteristic post-operation. PLK and keratoconus have similar symptom and phenomenon. The general incidence of PLK is around 0.04–0.60%. However, the acute epidemiology results about PLK have not been reported. The most commonly viewpoint is that the flap and decrease of corneal stoma are the main reasons for PLK. For patients with high myopia and a thin cornea, the post-operative residual corneal bed will be much thinner. Thus, it is believed that high myopia and thin cornea are risk factors of PLK [3,4]. Corneal collagen crosslinking (CXL) with riboflavin and ultraviolet A radiation is a new therapeutic strategy for PLK. The mechanism of this method is to achieve crosslinking of corneal stromal collagen and strengthen the cornea by riboflavin and ultraviolet A radiation induced photochemical process [5]. Riboflavin–ultraviolet-A (UVA) corneal collagen crosslinking (CXL) has been demonstrated to be safe and effective for keratoconus and other corneal ectatic disorders [6,7]. However, the standard treatment protocol is more than one hour. Recently, in an attempt to reduce treatment time, ACXL protocols using higher fluencies and shorter exposure times have been postulated [8]. Some refractive surgery centers have established clinical research about the effects of FS-LASIK-ACXL. However, changes of corneal biomechanical characteristics after FS-LASIK-ACXL need to be further explored. The present research detected the biomechanical parameters pre and post FS-LASIK-ACXL in myopic patients with thin corneas. Furthermore, we analyzed these data and evaluated the safety of FS-LASIK-ACXL.

Material and Methods

Patients

A total of 22 eyes of 11 patients were enrolled in this prospective study. These patients were scheduled for corneal refractive surgery from January 2014 to January 2015 in the

Department of Ophthalmology Refractive Center, Chinese PLA General Hospital (Beijing, China). The primary inclusion criteria were bilateral myopia or myopia with astigmatism (0.5 diopter (D) or less changes in spherical equivalence for at least one year), age older than 18 years; a CDVA was 20/32 or better in each eye; the central corneal thickness was more than 450 μm ; the predicted post-operative corneal stromal was more than 280 μm but less than 290 μm ; asymmetry of corneal curvature (difference value of AveK was more than 1 but less than 1.7); and Belin showed yellow or red part.

Moreover, patients had to stop wearing soft corneal contact lens for more than two weeks. The primary exclusion criteria included a history of intraocular or corneal surgery, a history of systemic disease, active ocular disease, and a history of herpes keratitis. Patients were excluded from the study if they did not have follow-up with all parameters recorded for at least one-year. All these patients underwent FS-LASIK concurrent with ACXL procedures. They were comprehensively informed of the benefits and risks involving these procedures. Informed consents were obtained from the candidates and the study was approved by Ethics Committee of General Hospital of Chinese PLA. All the procedures adhered to the tenets of the Declaration of Helsinki. All surgeries were performed by the same surgeon, in the Refractive Surgery Center of General Hospital of Chinese PLA.

Surgical technique

Femtosecond laser (FS200, Alcon Laboratories, Inc., USA) was used to create a corneal flap of 110 μm thickness with an 8.00 mm diameter [1]. Excimer laser (WaveLight EX500, Alcon Laboratories, Inc., USA) was used for the myopic ablation, and the ablation zone diameter was 6.00 to 6.50. After the excimer laser ablation (with the flap folded on itself), Vibex Xtra riboflavin solution containing 0.25% riboflavin (Avedro Inc., USA) was placed on the exposed stromal bed for 90 seconds. Following stromal soaking, the stroma was washed with BBS and the flap was repositioned in place. The cornea was then irradiated with ultraviolet-A (UVA) light (KXL System, Avedro Inc.) with a wavelength of 365 nm and an irradiance of 30 mW/cm^2 for 90 seconds (total energy 2.7 J/cm^2). After irradiation, a bandage contact lens was placed on the corneal surface for pain relief. After surgery, 0.5% lavo-ofloxacin eye drops were applied four times per day for two weeks; 0.1% fluorometholone eye drops were used four times per day for the first week, and then reduced gradually; 0.1% sodium hyaluronate eye drops were used four times per day for four weeks. The bandage contact lens was removed when the corneal epithelium healed.

Data collection

All eyes were measured for UDVA, CDVA, manifest refraction spherical equivalent (MRSE), corneal topography for Ks, Kf, and

Table 1. Demographics of the patients and eyes before operation.

Parameters	Before operation	After operation					P value (before and 24 months)
		1 month	3 months	6 months	12 months	24 months	
UCVA	0.18±0.14	0.69±0.27	0.88±0.31	0.99±0.35	1.02±0.15	1.03±0.19	<0.001
CDVA	0.89±0.16	0.67±0.23	0.91±0.53	0.99±0.54	1.01±0.19	1.07±0.34	0.12
MRSE (D)	-5.53±2.27	0.38±1.04	0.18±0.88	0.08±0.91	0.03±0.94	0.03±0.82	0.001
Mean K(D)	44.15±0.96	38.03±4.20	38.99±3.91	39.53±5.22	39.24±3.31	39.75±3.50	0.008
CCT (µm)	484.38±15.29	415.27±26.39	407.76±25.89	405.33±27.98	404.12±28.31	404.88±28.25	<0.001

Data of sex were showed in percentage, in the present study, male patients was 18.18%, while female patients was 81.82%.

Table 2. The parameters and data before operation and at 1, 3, 6, 12 and 24 months after operation are shown.

Parameters	Before operation	After operation					P value (before and 24 months)
		1 month	3 months	6 months	12 months	24 months	
UCVA	0.18±0.14	0.69±0.27	0.88±0.31	0.99±0.35	1.02±0.15	1.30±0.19	<0.001
CDVA	0.89±0.16	0.67±0.23	0.91±.53	0.98±0.54	1.01±0.19	1.07±0.34	0.128
MRSE (D)	-5.53±2.27	0.38±1.04	0.18±0.88	0.08±0.091	0.03±0.94	0.03±0.82	0.001
Mean K(D)	44.15±0.96	38.03±4.20	38.99±3.91	39.53±5.22	39.24±3.31	39.75±3.50	0.008
CCT (µm)	484.38±15.29	415.27±26.39	407.76±25.89	405.33±27.98	404.12±28.31	404.88±28.25	.001

Avek within the 3.0 mm radius (Placido topography using the Topolyzer Vario, and Scheimpflug imaging using the Oculyzer II, both Wavelight Laser Technologie AG, USA). CCT, intraocular pressure (IOP), A1L, A2L, A1V, A2V, DA, PD, and HCR was detected with corneal visualization Scheimpflug technology (Corvis-ST; Oculus Optikgerate GmbH, Wetzlar, Germany). After the operation, all these parameters were detected at one-week, three-month, six-month, one-year and two-year visits. In addition, the post-operative evaluation included slit lamp examination, and corneal haze.

Statistics

The corneal biomechanical and refractive data was analyzed using SAS9.3. Repeated data (different time points) were first analyzed through normal distribution test, and variance of analysis was used to compare the difference among the repeated data (different time points). The difference was considered as statistically significant when $p < 0.05$

Results

A total of 11 patients (22 eyes) were recruited in the present study between January 2013 and January 2015 at the Chinese

PLA General Hospital (PLA, Beijing, China). Among them, two patients were male (18.18%) and nine patients were female (81.82%), with the mean age of 23.19±7.88 years (range: 18–34 years). The mean CCT was 484.38±15.29 µm. The mean spherical equivalent (SE) was -5.53±2.27 D. The mean astigmatism was -1.31±1.31 D, and the mean IOP was 14.88±3.72 mm Hg. Post-operatively, nine eyes (40.91%) experienced different irritations such as photophobia, lacrimation, and foreign-body sensation. All of these symptoms were relieved within seven days after operation. The characteristics of the patients and eyes are listed in Table 1. The ablation depth was 41–125 µm. All of the eyes had visual improvement after the operation. Parameters and data before operation and at one, three, six, 12, and 24 months after operation are shown in Table 2. We compared the corneal biomechanical parameters before the operation and 24 months after the operation. The CCT decreased significantly after the operation. However, the IOP, A1L, A2L, A1V, A2V, HCR, PD, and DA did not show any significant difference after the operation (Table 3). In terms of every biomechanical parameter, we compared data of different time points. For A1, there was no difference among time points; similar results were found in A2L, A1V, DA, and HCR. For A2V, differences were found between one month and 12 months; and one month and 24 months post-operation. For

Table 3. Corneal biomechanical parameters in both groups preoperatively and postoperatively.

	Preoperatively	Postoperatively	P value
IOP			
Range	10.30–18.60	16.4–21.0	
Mean ±SD	14.88±3.72	17.78±1.87	0.138
CCT			
Range	472.00–509.00	363.00–460.00	
Mean ±SD	484.38±15.29	404.88±28.25	0.000
A1 length			
Range	1.60–1.83	1.25–1.97	
Mean ±SD	1.77±0.09	1.66±0.23	0.348
A2 length			
Range	0.85–2.04	0.93–2.21	
Mean ±SD	1.20±0.44	1.60±0.50	0.259
HCR			
Range	4.99–7.56	4.94–6.45	
Mean ±SD	5.95±1.02	5.53±0.58	0.111
HC peak distance			
Range	2.60–5.52	2.63–5.57	
Mean ±SD	3.21±1.14	4.06±1.50	0.227
Deformation amplitude			
Range	1.09–1.50	1.08–1.37	
Mean ±SD	1.28±0.16	1.26±0.12	0.571

PD, differences were found between one month and 24 months post-operation. Figures 1–3 show the differences among time points. For pre- and post- operation, significant decreases were found in Ks, Kf, and Avek ($p=0.002$, $p=0.023$, and $p=0.008$, respectively). For CCT, critical differences were found between pre-operation and one-month post-operation; pre-operation and 24 months post-operation; and one month and 24 months post-operation. For IOP, a significant difference was found between pre-operation and 24 months post-operation. We considered the visual acuity was satisfactory if the patient’s UCVA was better than 0.8. Then we compared the ratio of satisfaction between one-year and two-years after surgery. The result showed no difference ($p=1.0$) (Table 4). There were 17 eyes (77.27%) that experienced glare in the first week after surgery (mild or severe). However, this symptom disappeared gradually in most eyes. We compared the incidence of glare between six-months and two-years after surgery. The results showed no difference ($p=0.219$) (Table 5). One eye (4.54%) responded poorly to surgery. This patient (21 year old male) had visual acuity decline 23 months after surgery. He came to our clinic and complained about blurred vision. His visual acuity

was OD0.6 OS1.0, and his optometry result showed -1.5DS, -2.0DC×135° (OD, with no improvement after correction). His UCVA was OD1.0 OS1.0 at one-, six- and 12-months post-operative assessment. We examined and compared the examination results of one-month post-operation. We found his CCT declined 9 μm, IOP declined 0.2 mm Hg, A1L declined 0.09 mm, A2L increased 0.1 mm, A1V declined 0.07 msec, A2V declined 0.05 msec, DA declined 0.05 mm; PD increased 0.7 mm; HCR declined 0.08 mm; and Ks increased 2.25. The Pentacam results showed maximum elevation corneal (back) increased 6, but the thinnest location did not overlap with the steepest or maximum elevation corneal locations. We reviewed his pre-operative parameters, but did not find anything unusual. We made a prescription of RGP for him, and asked him to come back for assessment at intervals of three months.

Discussion

Despite the low morbidity rate of LASIK ectasia, its clinical outcomes are disastrous [9]. In our clinical experience, patients

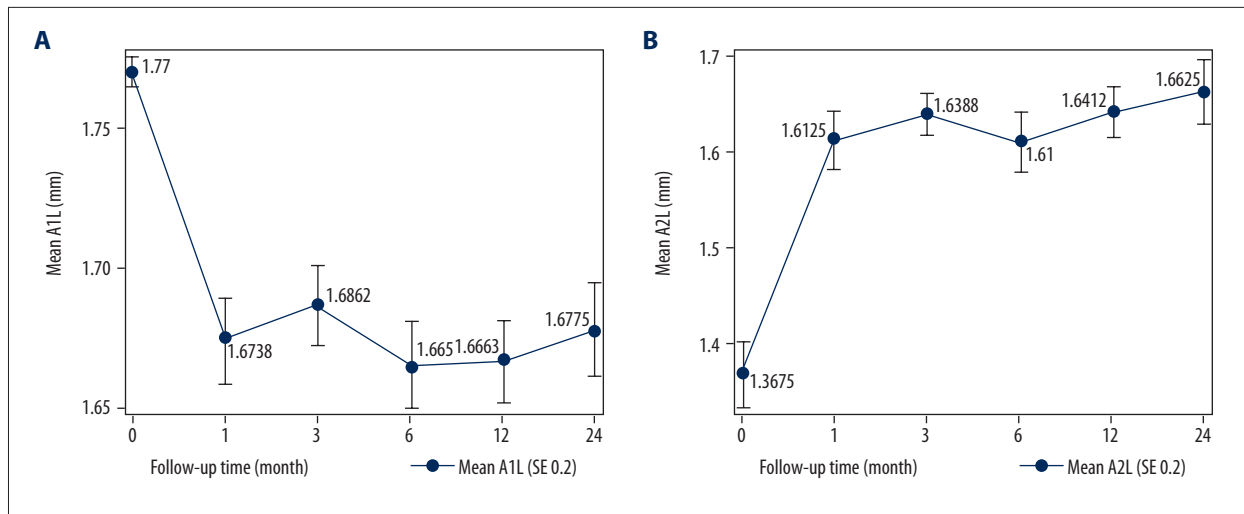


Figure 1. A1L and A2L changes before the operation and at 1, 3, 6, 12, and 24 months after the operation. 0: before surgery; 1: 1 month after surgery; 3: 3 months after surgery; 6: 6 months after surgery; 12: 12 months after surgery; 24: 24 months after surgery. **(A)** After FS-LASIK-ACXL, the mean A1L declined; however, the difference did not show statistical significance between pre- and post-operation. **(B)** After the operation, mean A2L increased, which did not show statistical significance between pre- and post-operation.

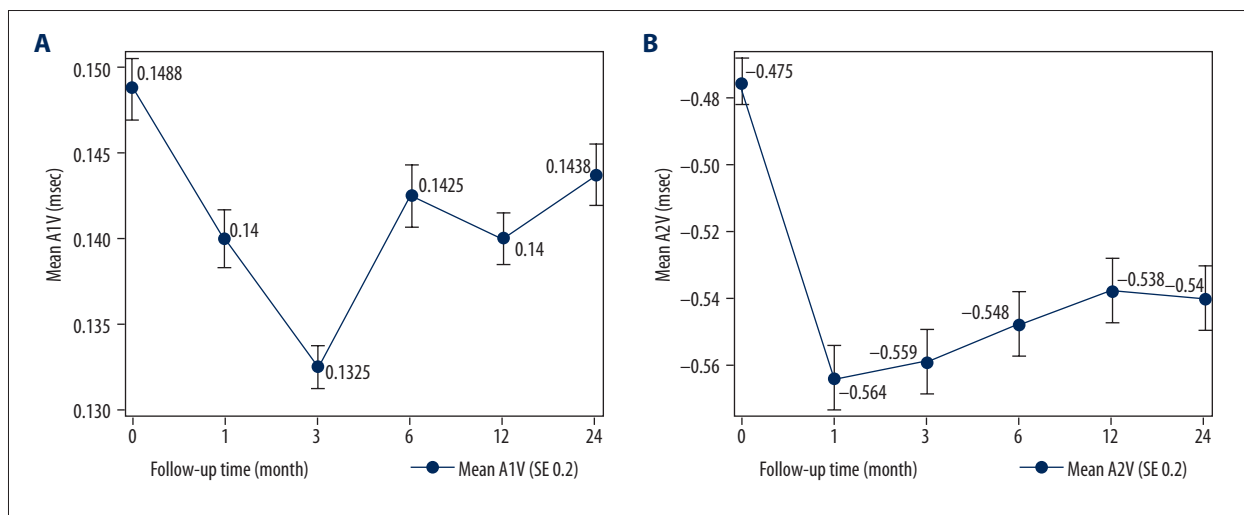


Figure 2. A1V and A2V changes before the operation and at 1, 3, 6, 12, and 24 months after the operation. 0: before surgery; 1: 1 month after surgery; 3: 3 months after surgery; 6: 6 months after surgery; 12: 12 months after surgery; 24: 24 months after surgery. **(A)** After FS-LASIK-ACXL, the mean A1L declined; however, the difference did not show statistical significances between pre- and post-operation. At different follow-up time points, the trend showed a little fluctuation, but no statistical significance. **(B)** After the operation, the mean A2L declined, which did not show statistical significance between pre- and post-operation.

often have thin corneas, which are not very suitable for traditional FS-LASIK. However, they often insisted they do not want to wear glasses (for reasons such as intolerance of anisometropia, for beauty or aesthetics reasons, or other reasons). We communicate with them sufficiently about the possible risks and intraocular lens (IOL) operation. However, they insist on FS-LASIK-ACXL. It is well-known that the incidence of keratoconus is much higher in males than in females. However, in our

patients, the incidence of keratoconus was 18.18% in males and 81.82% in females. More female myopia patients want to stop wearing glasses for appearance reasons, which may be responsible for the aforementioned results.

Previous studies chose consecutive patients then evaluating the effect and safety of LASIK combined with CXL or ACXL [9–11]. However, we do not think it is compulsory to use FS-LASIK-ACXL

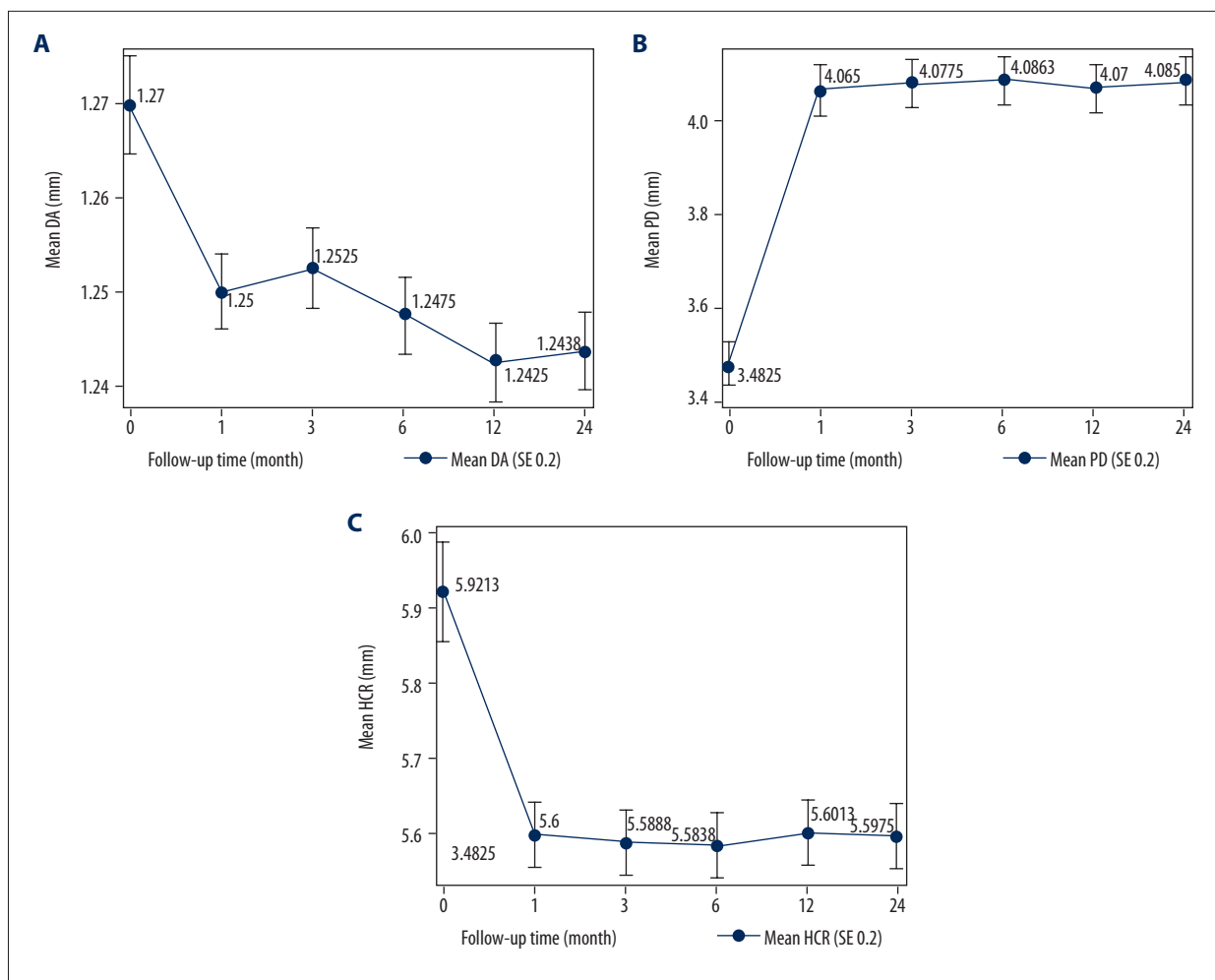


Figure 3. DA, PD, and HCR changes before the operation and at 1, 3, 6, 12, and 24 months after the operation. 0: before surgery; 1: 1 month after surgery; 3: 3 months after surgery; 6: 6 months after surgery; 12: 12 months after surgery; 24: 24 months after surgery. **(A)** After the operation, the mean DA declined; however, the difference did not show statistical significance between pre- and post-operation. **(B)** After the operation, the mean PD increased; however, the difference did not show statistical significances between pre- and post-operation. **(C)** After the operation, the mean HCR declined; however, the difference did not show statistical significance between pre- and post-operation.

in patients with normal corneas. In our study, we chose the “unsatisfactory cornea” cases for FS-LASIK-ACXL. Thus we included patients whose predict residual corneal bed was between 280–298 μm, or their Pantacam/corneal topography records imply some risk for common FS-LASIK (asymmetry, steep, alarm of Berlin). In the present study, we chose these high-risk patients, then compared visual acuity and corneal biomechanical parameters before operation and after operation (at one month, three months, six months, 12 months, and 24 months). One month post-operation, UCVA was worse than that at three months post-operation. This may be ascribed to the corneal edema and inflammatory reaction caused by ACXL and FS-LASIK. With the subsiding of corneal edema, UCVA improves gradually. UCVA of three months and 24 months post-operatively did not show any differences. All patients UCVA

improved significantly and this improvement remained steady for the two-year follow-up. These findings suggested that FS-LASIK-ACXL was an effective method for myopia and astigmatism in high-risk patients.

In fact, we paid particularly more attention to the influences on corneal biomechanical character. It has been shown that biomechanical parameters may be associated with diseases such as keratoconus and stromal keratopathy. They could also be measured according to the risk of iatrogenic keratectasia [12–15]. Generally, the corneal biomechanical character can be estimated through *in vivo* and *in vitro* methods. It is believed that *in vivo* examination could provide more clues for clinical work. Ocular response analyzer (ORA) is a widely used *in vivo* method. However, some experts proposed that ORA

Table 4. Percentage of satisfactory visual acuity 6 months and 2 years after surgery.

6 moths	2 years		Total
	Satisfactory	Dissatisfactory	
Satisfactory	19	1	20
Dissatisfactory	0	2	2
Total	19	3	22

We considered it as satisfactory visual acuity if UCVA was better than 0.8. Percentage of visual satisfaction between 6 months (90.91%) and 2 years (86.38%) after surgery did not show statistical difference, $P=1.0$

Table 5. Incidence of glare 6 months and 2 years after surgery.

6 moths	2 years		Total
	Glare	No glare	
Glare	2	5	7
No glare	1	14	15
Total	3	19	22

Incidence of glare between 6 months and 2 years after surgery did not show statistical difference, $P=0.219$. Three eyes had glare in the second year after surgery. Two of them had mild glare only at night, which did not bother their lives. One patient complained visual decline and glare at day and night. It was the patient who responded poorly to the surgery.

cannot show corneal biomechanical character directly since the exact relation between ORA record parameter and classical biomechanical parameter has not yet been established. Moreover, ORA cannot record the deformation dynamic process of the cornea when external force acts upon it. Recently the Corvis-ST was designed to record the deformation dynamic process of the cornea and capture the reaction of the cornea to a defined air pulse by the ultra-high speed Scheimpflug camera. With the action of the air pulse, the cornea is forced to move inward and flatten to the first applanation (A1); then the cornea rebounds to its nature shape. During the process of corneal deformation, Corvis-ST records such parameters as deformation amplitude (DA), first/second applanation time (A1/A2-time), highest concavity-radius (HCR), and peak distance (PD). These data could reflect tension, stiffness, elasticity, and glutinousness. Post-operatively, in our study, the CCT was much thinner than pre-operatively. However, IOP, A1 time, A2 time, A1 length, A2 length, HCR, HC PD, and DA were steady except for one month post-operation. One month post-operation, the wound by FS-LASIK-ACXL had not healed completely. Corneal biomechanical data of this period was transient. With time, the cornea completed remodeling. Corneal biomechanical data became steady after three months post-operation (Figures 1–3 shows this trend), which suggested that at corneal remodeling could be completed at three months after FS-LASIK-ACXL. Tian et al. [16] reported that the A1T of keratoconus was much shorter than that of the normal cornea. The more severe keratoconus is, the shorter the A1T. With the

progression of keratoconus, the CCT and central corneal tissue volume decreases. So resistance of cornea to the air pulse pressure becomes weaker, which results in changes in corneal biomechanics with keratoconus [17,18]. In the present research, at the end of follow-up, we found that the CCT decreased significantly, but A1V and A2V were similar to that of pre-operation. Symptom and disease course of post-LASIK keratectasia (PLK) are similar to that of keratoconus, and the exact nosogenesis of PLK is still unknown. DA decrease of corneal thickness and resistibility could result in PLK. Currently, it is widely recognized that corneal thickness less than 500 μm (pre-operation) or residuary corneal bed less than 250 μm could add the risk of PLK [18,20]. Results from the present study suggest that although FS-LASIK-ACXL ablated corneal thickness, it did not add the risk of iatrogenic keratectasia post-operatively. This could be because ACXL strengthens the connections of corneal collagen fibers, which enhances stiffness of the cornea.

In the present study, 17 eyes (77.27%) experienced glare in the first week after FS-LASIK-ACXL. With healing of the cornea, patients' visual quality improved gradually. Stimulation of the operation and corneal edema could explain this. Our results showed that seven eyes had glare six months after surgery, but only two eyes had glare two years after surgery. This implies that the cornea heals slowly in some eyes. Patients and doctors should be patient and confident of visual quality improvement. The two patients reported mild glare at night; however, they said it did not bother their lives. They did not

complain about dizzy or headache. One patient had glare and visual decline in the second year after surgery. That was the patient who responded poorly to FS-LASIK-ACXL.

Conclusions

FS-LASIK-ACXL can result in changes to corneal morphology without adverse effects on biomechanical character; shape of these high-risk corneas could remain steady for a period of two years. Iatrogenic keratectasia did not occur in any of the

patients receiving FS-LASIK-ACXL. The follow-up data suggested that the surgical outcomes remained stable. FS-LASIK-ACXL could correct visual acuity effectively and strengthen corneal structure satisfactorily. It could act as a safe and effective strategy for myopia with high-risk corneas. In the present study, we found one eye respond poorly to FS-LASIK-ACXL. Post-operative morphology parameter of the eye suggested corneal ectasia tendency. We could not find a difference between this single eye and other eyes, since the sample was only one. A large-sample and long follow-up study should be done.

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