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Corneal Collagen Crosslinking Combined with Phototherapeutic Keratectomy and Photorefractive Keratectomy for Corneal Ectasia after Laser in situ Keratomileusis

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Keywords
Crosslinking · Ectasia · Laser in situ keratomileusis · Phototherapeutic keratectomy · Photorefractive keratectomy

Abstract
Purpose: The aim of this study was to analyze the effects of corneal crosslinking (CXL) combined with phototherapeutic keratectomy (PTK) and photorefractive keratectomy (PRK) in halting the progression and improving the visual function of corneal ectasia after laser in situ keratomileusis (LASIK). ***Methods:*** PTK-PRK-CXL was performed on 14 eyes of 14 patients who developed corneal ectasia after LASIK. The visual acuity, spherical refraction and cylinder, corneal topography indices, thinnest corneal thickness (TCT), and endothelial cell count were evaluated at baseline and at 1, 3, 6, and 12 months postoperatively. ***Results:*** The mean uncorrected visual acuity improved significantly from 0.64 ± 0.36 logMAR preoperatively to 0.19 ± 0.12 logMAR at 12 months of follow-up ($p < 0.001$), while the mean best corrected visual acuity improved from 0.21 ± 0.14 logMAR at baseline to 0.04 ± 0.10 logMAR at 12 months postoperatively ($p < 0.001$). A significant decrease was observed in Kmax and Kmean values from 52.51 ± 6.74 and 43.55 ± 3.37 D at baseline to 45.72 ± 5.18 ($p < 0.001$) and 40.60 ± 3.05 D ($p < 0.001$) at the 1-year follow-up. The mean TCT decreased significantly from 419.07 ± 36.56 μm before treatment to 320.93 ± 39.78 μm at 12 months of follow-up ($p < 0.001$), and there was no significant endothelial cell loss ($p > 0.05$) beyond 6 months after treatment. ***Conclusion:*** PTK-PRK-CXL is a promising procedure to halt the progression of post-LASIK keratectasia with significant visual quality improvement.

Introduction

Keratectasia following laser in situ keratomileusis (LASIK), first described by Seiler et al. [1] in 1998, is a sight-threatening complication after LASIK with a reported prevalence of 1/2,500 [2]. It is characterized by progressive corneal steepening and thinning, increasing astigmatism, and declining visual acuity. Corneal crosslinking (CXL) is an effective and promising novel approach for the management of corneal ectasia by induc-

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Table 1. The values (mean ± SD) of manifest refraction of the patients before and after treatment

Manifest refraction	Preoperative	Postoperative			
		1 month	3 months	6 months	12 months
Spherical refraction	–4.07±3.78	–2.94±3.61	–2.85±3.55	–2.28±2.98	–2.09±2.89
Cylinder	–3.07±1.88	–1.19±0.66	–0.98±0.67	–0.73±0.51	–0.69±0.34

ing additional crosslinks between collagen fibers [3, 4]. However, visual recovery usually remains modest after CXL [5–7], despite the proven effectiveness in halting the progression of iatrogenic ectasia. Recently, the combination of CXL with photorefractive keratectomy (PRK) and phototherapeutic keratectomy (PTK) has offered exciting results in halting the progression of ectasia and providing visual improvement [8–10]. So far, there has been little research in simultaneous PTK-PRK-CXL applied for post-LASIK keratectasia. In our study, we enrolled 14 eyes of 14 patients to observe the efficacy and safety of the procedure in the management of ectasia after LASIK.

Patients and Methods

Patients

A total of 14 eyes of 14 patients (9 male, 5 female) with a mean age of 28.71 ± 3.22 years (range 25–35) diagnosed as progressive post-LASIK corneal ectasia in Shandong Provincial Hospital from October 2014 to March 2015 were enrolled in this retrospective study. The mean time of confirmed progressive keratectasia in these patients was 5.9 years (range 3–11) after LASIK.

The progressive ectasia was defined as 1 or more of the following changes over a period of 24 months after LASIK: (1) an increase of 1.00 D (diopter) or more in the steepest keratometry (K) measurement, (2) an increase of 1.00 D or more in the manifest cylinder, (3) an increase of 0.50 D or more in the manifest refraction spherical equivalent [5]. None of the patients had any of the following features: a history of corneal surgery other than LASIK, corneal pachymetry less than 350 μm at the thinnest point, a Kmax value higher than 65.0 D, history of delayed epithelial healing, keratitis, corneal opacities or scars, autoimmune diseases, or pregnancy or lactation during the treatment.

The study was approved by the Ethics Committee of Shandong Provincial Hospital affiliated to Shandong University under the principles of the Declaration of Helsinki (No. 2016-312). All patients provided informed consent prior to PTK-PRK-CXL treatment.

Treatments

After administration of topical anesthesia using proparacaine hydrochloride 0.5% eye drops, the central 9.0-mm-diameter epithelium with a 50 μm depth was removed by PTK using an excimer laser system (EX500; Wavelight Technologies, Germany). Then, PRK was applied to correct the refractive errors partly or completely on the corneal flap according to the ablation depth and flap thickness. The maximum ablation depth on the flap was limited to 75 μm (mean 57) with the residual flap depth ensured of no less than 10 μm. Subsequently, CXL was performed according to the standard procedure. Riboflavin solution (0.1%) was applied every 3 min for 30 min. After ascertaining the presence of riboflavin in the anterior chamber by slit-lamp examination, the corneal thickness was measured with optical coherence tomography (OCT, Cirrus HD-OCT 4000; Carl Zeiss Meditec Inc., Dublin, CA, USA) to confirm the stroma thickness over 400 μm. If the stroma thickness was less than 400 μm, 0.1% hypotonic riboflavin solution was instilled [11].

Next, the cornea was irradiated with UVA light (370 nm, 3.0 mW/cm^2, UV-X illumination system version 1000, UVXTm; IROCAG, Zurich, Switzerland) for 30 min at a distance of 5 cm, with riboflavin solution applied every 3 min. At the end of the procedure, a bandage soft contact lens was placed until corneal reepithelization. Antibiotic eye drops were administrated 4 times daily for 1 week, and 0.1% fluorometholone eye drops were administrated 4 times daily for 4 weeks.

Evaluations

All the patients were examined before treatment and followed up at 1, 3, 6, and 12 months postoperatively. The main evaluations included slit-lamp evaluation, uncorrected visual acuity (UCVA; logMAR), best corrected visual acuity (BCVA; logMAR), manifest refractions, Kmax, Kmean, thinnest corneal thickness (TCT) with corneal topography (WaveLight Oculyzer II; WaveLight GmbH, Erlangen, Germany), corneal flap thickness with the RTVue-100 Fourier-domain anterior segment OCT system (Optovue Inc., Fremont, CA, USA), and endothelial cell count (ECC; SP-3000P; Topcon Corp., Tokyo, Japan).

Statistical Analysis

All values are expressed as mean values ± standard deviation. Statistical analyses were performed using SPSS 20.0 (version 20.0; SPSS Inc.). The paired sample *t* test was used to analyze the postoperative outcome changes compared with baseline values at different time points, with a level of $p < 0.05$ being accepted as statistically significant.

Results

Fourteen eyes of 14 patients treated with the PTK-PRK-CXL procedure were analyzed. The average central flap thickness was 146.6 ± 6.4 μm before treatment. After

Table 2. The results of the post-LASIK keratectasia patients before and after treatment

Indices (mean ± SD)	Preoperative	Postoperative			
		1 month	3 months	6 months	12 months
UCVA, logMAR	0.64±0.36	0.52±0.28	0.36±0.17*	0.25±0.11*	0.19±0.12*
p value	–	0.052	0.002	<0.001	<0.001
BCVA, logMAR	0.21±0.14	0.22±0.11	0.14±0.10*	0.07±0.11*	0.04±0.10*
p value	–	0.775	0.01	<0.001	<0.001
Kmean, D	43.55±3.37	42.44±3.37*	41.63±3.20*	40.73±3.05*	40.60±3.05*
p value	–	<0.001	<0.001	<0.001	<0.001
Kmax, D	52.51±6.74	49.35±6.30*	47.53±5.91*	46.23±5.35*	45.72±5.18*
p value	–	<0.001	<0.001	<0.001	<0.001
TCT, μm	419.07±36.56	363.57±37.74*	341.21±40.42*	320.71±38.99*	320.93±39.78*
p value	–	<0.001	<0.001	<0.001	<0.001
ECC, cells/mm^2	3,104.07±257.59	2,249.31±368.37*	2,620.31±334.54*	3,063.86±225.48	3,073.51±188.74
p value	–	<0.001	<0.001	0.147	0.291

UCVA, uncorrected visual acuity; BCVA, best corrected visual acuity; Kmean, average keratometry; Kmax, maximum keratometry; TCT, thinnest corneal thickness; ECC, endothelial cell count. * $p < 0.05$, statistically significant differences compared with preoperation.

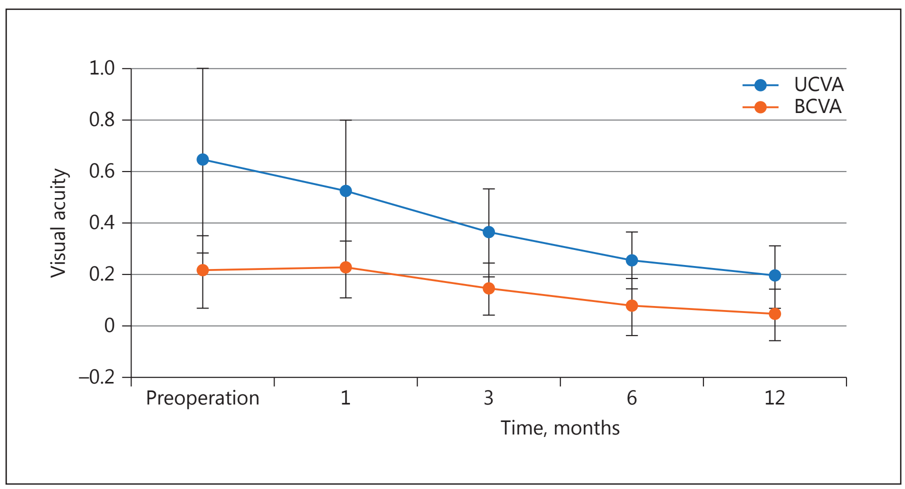

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Fig. 1. UCVA and BCVA changes before and after surgery.

removing the epithelium by PTK, the mean spherical refraction and cylinder values, which we planned to correct on the corneal flap by PRK, were –1.55 ± 1.02 and –2.38 ± 1.27 D. At 12 months, the reduction of spherical refraction and cylinder were recorded as 1.98 and 2.38 D. In addition to temporary corneal matrix edema and haze postoperatively, no other intraoperative or postoperative complications were observed in any of the patients. Table 1 shows the changes of manifest refraction after treatment.

Visual acuity and topographic index improvements were observed in all eyes. The changes in UCVA and BCVA compared with baseline reached statistical significance at 3, 6, and 12 months of follow-up ($p < 0.05$; Table 2; Fig. 1). At the last follow-up, the mean UCVA and BCVA had improved by 0.45 logMAR and 0.17 logMAR. UCVA was 0.1 logMAR or better in 5 of the 14 eyes, and BCVA was 0.1 logMAR or better in 12 of the 14 eyes at 12 months of follow-up. The topographic measurements before and after treatment are presented in Table 2 and Figures 2 and 3. The Kmean and Kmax changes were statistically significant at different time points after surgery ($p < 0.001$). The mean preoperative to postoperative Kmean change was 2.95 D and that of Kmax was 6.79 D. As for

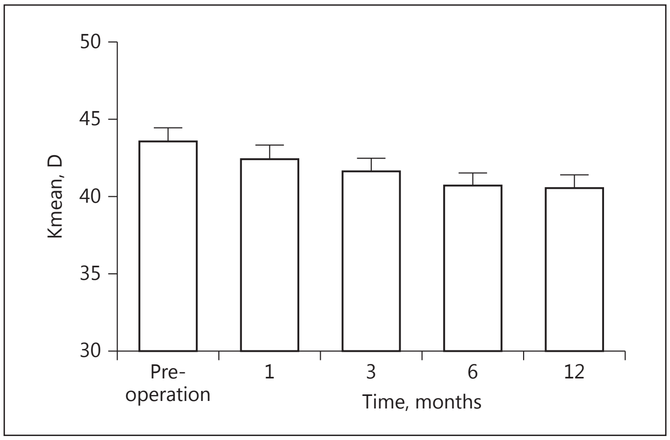

Fig. 2. Kmean changes before and after surgery.

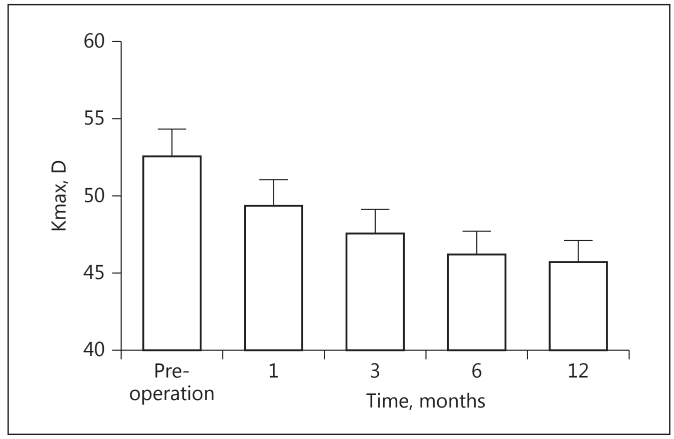

Fig. 3. Kmax changes before and after surgery.

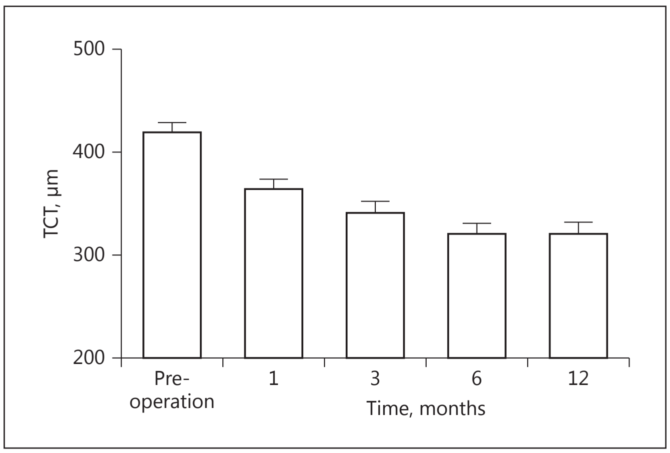

Fig. 4. TCT changes before and after surgery.

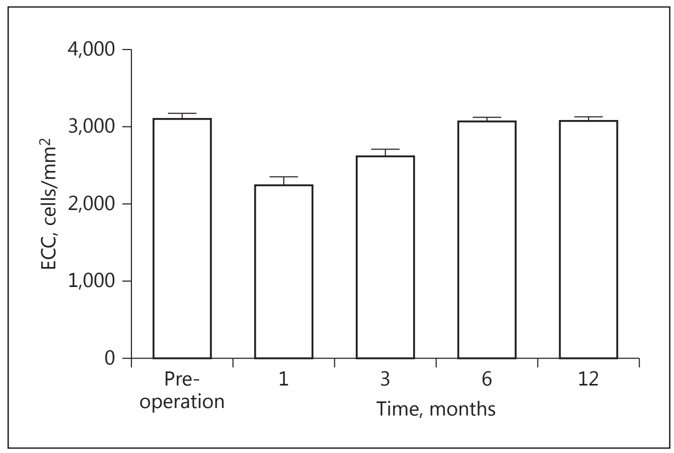

Fig. 5. ECC changes before and after surgery.

safety indices, TCT gradually stabilized beyond 6 months after surgery and reduced from 419.07 ± 36.56 μm before treatment to 320.93 ± 39.78 μm at 12 months (Table 2; Fig. 4). ECC recovered to the baseline level (3,104.07 ± 257.59 cells/mm^2) at 6 months postoperatively (3,063.86 ± 225.48 cells/mm^2, $p = 0.291$), which is shown in Table 2 and Figure 5. Figure 6 presents the corneal topography comparison of 1 patient before operation and at the 12-month follow-up.

Discussion

Corneal ectasia is an uncommon but serious complication after corneal refractive surgery with a decline of biomechanical stability and visual impairment. Attention should be paid to arresting the progression of ectasia and reestablishing visual function [12].

CXL, a minimally invasive treatment, has been proven to be clinically successful in halting the progression of ectasia by inducing corneal cross-linking to increase corneal stiffness and stability [13]. Most surgeons suggest that the procedure should be undergone once the progression process has been demonstrated. Many studies have reported the positive results of CXL in treating keratoconus and post-LASIK ectasia. As for the treatment of ectasia after LASIK, Hafezi et al. [3] reported a series of 10 eyes with 25 months of follow-up in which there was a reduction in Kmax at 12 months in all cases and an improvement of CDVA in 40% of the cases. Good results were also observed by Vinciguerra et al. [14]. However, the role of CXL alone in improving the visual function

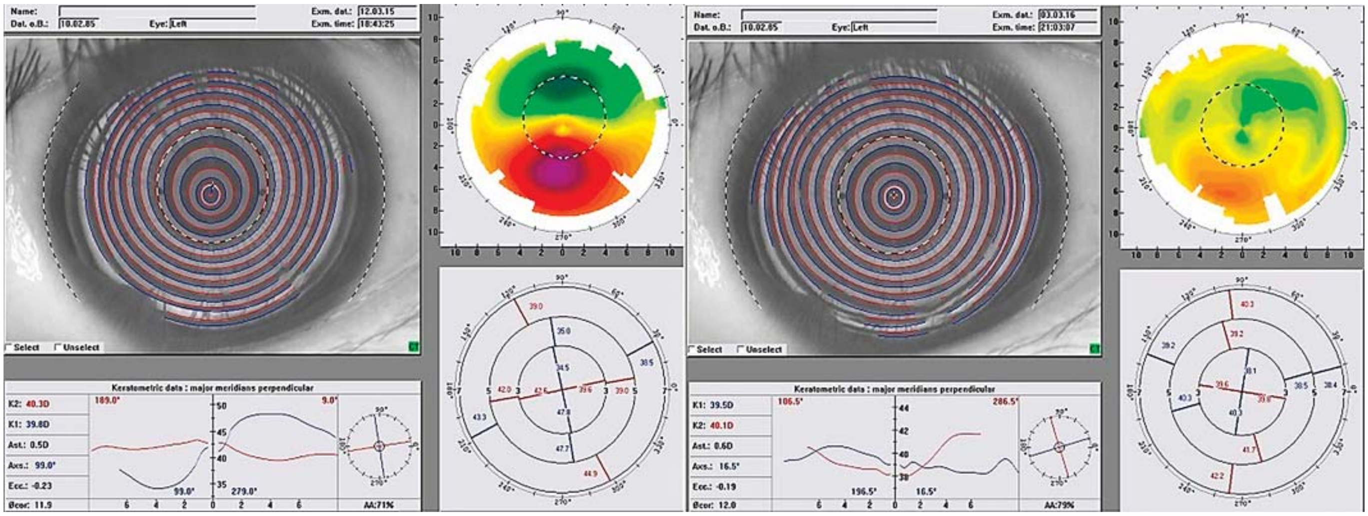

Fig. 6. Topography comparison before the operation and at 12 months after surgery.

was limited while the effectiveness of halting the progression process has been demonstrated.

In this case, excimer laser surface ablation has been adopted in the treatment of forme fruste keratoconus for visual promotion. In the 2-year follow-up study by Cennamo et al. [15], treating 25 eyes with topography-guided PRK showed favorable results in terms of topography and visual acuity. However, laser ablation alone has not been accepted as the standard treatment while combined therapy, such as transepithelial PTK-CXL or topography-guided PRK-CXL, has been gradually adopted and has shown some benefits in halting progression while improving visual function. Kapasi et al. [16] reported favorable results with Kmean decreased by 2.01 D at 12 months of follow-up using PTK-CXL in the management of keratoconus. Beneficial conclusions were reached by Kymionis et al. [17] with the Kmean decreased by 1.92 D, and uncorrected and corrected distance visual acuity (UDVA and CDVA) improved by 0.33 logMAR and 0.13 logMAR, respectively, at 1 year of follow-up. Furthermore, PRK-CXL has also been demonstrated effectively in eyes with keratoconus and corneal ectasia after LASIK, such as the promising results in studies by Kymionis et al. [18] and Kanellopoulos and Binder [19]. Another study by Kontadakis et al. [20], which investigated tPRK-CXL for progressive keratoconus, demonstrated an improvement in UDVA of 0.56 logMAR and in CDVA of 0.17 logMAR, with the Kmean decreased by 2.63 D over 3 years.

Considering the benefits of combined therapy, we applied the combined PTK-PRK-CXL procedure for post-LASIK ectasia. PTK as a way of removing the corneal epithelium can reduce the refractive error and smooth the anterior corneal surface. PRK acted as an additional treatment to CXL for the visual rehabilitation of our patients. After treatment, the residual refractive errors were corrected by spectacles or rigid gas permeable lenses. The results of this combined procedure were promising in our study. The mean UCVA and BCVA improved by 0.45 logMAR and 0.17 logMAR, while all the patients had good BCVA over 1 year. Interestingly, there was no apparent improvement of visual acuity at 1 month postoperatively, which might be related to corneal edema and haze at an early stage after surgery. In addition, the patients in our study showed a marked improvement in topography parameters. Kmean, Kmax, and TCT decreased significantly from 43.55 ± 3.37 D, 52.51 ± 6.74 D, and 419.07 ± 36.56 μm preoperatively to 40.60 ± 3.05 D, 45.72 ± 5.1 8 D, and 320.93 ± 39.78 μm at 12 months of follow-up. Compared with other studies [5, 21] in which CXL alone was applied, the decreased range of the K value and TCT in our study was greater. This is because we ablated anterior stroma from the corneal flap according to refraction and flap thickness, leading to a marked reduction in the K value and TCT. Also, deeper CXL can be achieved owing to the thinner flap thickness compared to CXL alone, as CXL is known to act in the anterior 250–350 μm part of the corneal stroma [11]. A similar phenomenon was also found in a study by Kontadakis et al. [20].

As both PTK and PRK are performed on the corneal flap, flap thickness plays an important role in the procedure. In our study, the central flap thickness was adopted since it could provide a useful reference to determine the maximum ablation depth and the corrected refractive error. According to our measurements, we designed the maximum ablation depth to be 75 μm (mean 57), while the residual stromal depth of the flap was set to be no less than 10 μm to ensure the ablation did not reach the residual stromal bed, which was in contrast to the 50-μm maximum ablation depth in other studies. However, because of the restriction of flap thickness, the small diopter was corrected completely and the large diopter was partly corrected. The reason we performed PRK on the corneal flap was because it does not contribute to postoperative corneal tensile strength [22]. The cornea is a complex biomechanical composite. The stroma and Bowman layer are the chief collagenous layers and thus provide the majority of the cornea's tensile strength. The interlamellar cohesive strength of the anterior stroma and corneal periphery is greater than that of the posterior stroma and corneal center. During LASIK, an immediate circumferential severing of the corneal lamellae occurs and the normal collagen fibrils structure cannot regenerate during the healing process. Therefore, the residual stromal bed thickness plays an important role in the biomechanical stability of the post-LASIK cornea, which is closely related to the development of corneal ectasia. In our study, PTK was used to remove the corneal epithelium for fast and efficient riboflavin diffusion and PRK was used to ablate flap stroma for refraction correction and to induce a deeper CXL due to thinner flap compared with intact flap CXL.

Safety problems are the major concerns of this PTK-PRK-CXL procedure, especially the potential damage to the endothelium, as the corneal thickness of our patients was less than 400 μm after PTK and PRK treatment. However, we ensured the corneal thickness was no less than 400 μm by swelling the corneas before UVA irradiation. There was no apparent endothelium cell loss after 6 months of follow-up, which is similar to a study by Hafezi et al. [11]. However, a different phenomenon was observed in that CXL in thin corneas seemed to result in a significant endothelial cell count loss postoperatively [23]. Recently, Mooren et al. [24] found that ex vivo human corneal endothelium was far more resistant to riboflavin-enhanced UVA irradiation than previously estimated. There was no difference in ECC between control and experimental groups, in which clinical dosage of UVA was directly irradiated on human donor corneal endothelium. Also, no endothelial cytotoxicity was found even in corneas with a stroma thickness after CXL of less than 400 μm. In our study, a significant reduction of ECC was observed in the first 3 months after treatment, and we speculate the decrease of ECC may be associated with corneal edema or haze that reduced the veracity of ECC examination. Although the safety of the endothelium in CXL is confirmed in most studies, we still need to cautiously follow the endothelial cytotoxicity of UVA.

The possible complications of the combined therapy in the thin corneas mainly include permanent corneal haze, corneal edema, corneal stromal scar, aseptic infiltration, lamellar keratitis, and infectious keratitis, etc. Besides temporary corneal edema and haze at an early stage after surgery, no other complications were observed during 12 months of follow-up in our study.

Our study showed that the combination of PTK-PRK-CXL was effective in the halting of post-LASIK keratectasia with a significant reduction in Kmax and enhanced visual acuity improvement. No serious complication was observed during 12 months of follow-up. However, studies with more patients and longer follow-up times are still required to further establish the safety and effectiveness of this procedure.

Disclosure Statement

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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