Original Article

Efficacy and Safety of the Modified Cretan Protocol in Patients with Post-LASIK Ectasia

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Abstract

Objectives: To investigate the clinical efficacy and safety of the modified Cretan protocol in patients with post-laser in situ keratomileusis (LASIK) ectasia (PLE).

Materials and Methods: In this retrospective study, 26 eyes of 16 patients with PLE were treated with the modified Cretan protocol (combined transepithelial phototherapeutic keratectomy and accelerated corneal collagen cross-linking). Visual, refractive, tomographic, and aberrometric outcomes and point spread function (PSF) were recorded preoperatively and at 6, 12, and 24 months after treatment.

Results: Both uncorrected and best corrected visual acuity were stable at 24 months postoperatively compared to baseline (from 0.89±0.36 to 0.79±0.33 LogMAR and 0.31±0.25 to 0.24±0.19 logarithm of the minimum angle of resolution [LogMAR], respectively, $p>0.05$ for all values). The mean K1, K2, Kmean, thinnest corneal thickness, and spherical aberration at baseline were 45.76±5.75 D, 48.62±6.17 D, 47.13±5.89 D, 433.16±56.86 µm, and -0.21±0.63 µm respectively. These values were reduced to 42.86±6.34 D, 45.92±6.74 D, 44.21±6.4 D, 391.07±54.76 µm, and -0.51±0.58 µm at 24 months postoperatively ($p<0.001$, $p=0.002$, $p<0.001$, $p=0.001$, and $p=0.02$, respectively). The mean spherical equivalent, manifest cylinder, Kmax, central corneal thickness, other corneal aberrations (root mean square, trefoil, coma, quatrefoil, astigmatism), and PSF remained stable ($p>0.05$ for all variables), while anterior and posterior elevation were significantly improved at 24 months postoperatively ($p<0.001$ and $p=0.02$, respectively). No surgical complications occurred during the 24-month follow-up.

Conclusion: The modified Cretan protocol is a safe and effective treatment option for PLE patients that provides visual stabilization and significant improvement in topographic parameters during the 24-month follow-up. Further studies are needed to support our results.

Keywords: Post-LASIK ectasi

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Introduction

Post-laser in situ keratomileusis (LASIK) ectasia (PLE) is characterized as progressive thinning and steepening of the cornea resulting in refractive aberrations and severe visual loss.[1] Iatrogenic keratectasia, a potentially vision-threatening complication following LASIK, manifests in 0.1% of instances.[2] Due to the removal of corneal tissue, corneal biomechanics can potentially be compromised by all excimer laser procedures.

Corneal collagen crosslinking (CXL) is a minimally invasive surgical procedure that utilizes riboflavin and ultraviolet A (UVA) to strengthen the biomechanical properties of an ectatic cornea by creating covalent bonds within and between the collagen and proteoglycan molecules. It is effective in stabilizing the progression of corneal ectasias including progressive keratoconus (KC), pellucid marginal degeneration (PMD), and post-refractive corneal ectasia. In the conventional CXL procedure, a dosage of 5.4 J/cm^2 energy is applied at an intensity of 3 mW/cm^2 over a duration of 30 minutes.[3] Accelerated CXL (aCXL) is an alternative approach that utilizes a higher UVA irradiance intensity and shorter overall exposure time, following the principles of the Bunsen-Roscoe law.[4] The aCXL protocol is as effective and safe as the conventional CXL protocol in both adult and pediatric KC patients.[5,6] Mechanical debridement or excimer laser ablation (transepithelial phototherapeutic keratectomy, tPTK) may be used to remove the epithelium during CXL. The Cretan protocol, introduced by Kymionis et al.[7], employs tPTK for the removal of corneal epithelium in the conventional CXL procedure. The utilization of this protocol leads to superior visual and refractive outcomes in KC patients when compared to mechanical epithelial debridement.[8,9] Our group demonstrated that the combined tPTK+aCXL (modified Cretan protocol) is an effective treatment option for PMD and pediatric KC patients.[10,11] However, no study in the literature has reported the efficacy of this protocol in patients with PLE.

In this retrospective study, we evaluated the visual, refractive, topographic, and optical quality outcomes of combined tPTK+aCXL treatment in PLE patients over 24 months.

Materials and Methods

Study Population

The single-center study adhered to the principles of the Declaration of Helsinki and received approval from the Ankara City Hospital-No.1 Clinical Research Ethics Committee (date: 23.06.2021, no: E1/1910/2021). Written informed consent was obtained from all patients. The records of PLE patients who received the combined tPTK+aCXL and had 24 months of follow-up were retrospectively reviewed. Clinical and topographic evaluations of all patients were performed preoperatively and at 6, 12, and 24 months after treatment. Exclusion criteria included corneal thickness <400 µm, presence of a central or paracentral corneal scar, previous ocular surgeries other than LASIK, a history of herpetic keratitis, active ophthalmic inflammation or infection, contact lens usage, and pregnancy or lactation.

Patients were diagnosed with corneal ectasia when they exhibited progressive corneal steepening, along with a worsening myopic and/or astigmatic refractive error, occurring at least two months after LASIK surgery. All patients demonstrated progression of the myopic refractive error with or without an increase in manifest astigmatism, a decrease in uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA), progressive inferior corneal steepening on topography, and/or decreasing inferior corneal thickness.[12]

Ophthalmologic and Topographic Examination

Patients underwent a comprehensive ophthalmologic examination that included measurements of spherical refractive error, spherical equivalent (SE), manifest cylinder (CYL) value, UCVA, and BCVA. Visual acuity was assessed using the Snellen chart, and the results were subsequently transformed into the logarithm of the minimum angle of resolution scale for statistical analysis. The examination also involved a slit-lamp examination, intraocular pressure measurement, fundoscopic examination, and topographic analysis of the cornea using the Sirius 3D rotating Scheimpflug camera and topography system (CSO, Italy).

The topographic corneal analysis included measurements of simulated keratometry values (flat: K1, steep: K2, mean: Kmean, maximum: Kmax), central corneal thickness (CCT), corneal thickness at the thinnest point (TCT), anterior and posterior elevation, and point spread function (PSF). Corneal higher-order aberrations (HOAs) in the central 6.0 mm, including total root mean square (RMS), coma, trefoil, astigmatism, and spherical aberration, were quantified using Zernike coefficients, considering aberrations ranging from 3rd to 8th order. PSF evaluation is used to assess image quality, which is related to the theoretical performance of the optical system.[13] We computed the Strehl ratio of the PSF in addition to HOAs to assess the impact of treatment on corneal optical performance using the Sirius imaging system. For all eyes in the study, two-dimensional corneal PSFs were computed, and the Strehl ratio was employed to represent them.[14]

Surgical Technique

All procedures were performed in an operating room by the same surgeon (Ö.S.) under sterile conditions and topical anesthesia with 0.5% proxymetacaine hydrochloride eyedrops (Alcaine, Alcon Laboratories Inc.). The tPTK method was used to remove the corneal epithelium with a scanning spot excimer laser (Esiris, Schwind eye-tech-solutions GmbH&Co., Kleinostheim, Germany). The laser ablation was performed in a single-step in an 8.5-mm zone at a fixed depth of 50 µm. The laser profiles were independent of refractive parameters, topography, or wavefront guidance.[10]

We used an ultrasonic pachymeter (Palmscan AP-2000-Ultima, Micromedical Devices, Inc.) to measure corneal thickness before and after epithelial removal. Following epithelial removal (by tPTK), we applied hypotonic 0.1% riboflavin in 0.9% sodium chloride drops to the cornea every 2 minutes for 30 minutes until the cornea swelled to more than 400 µm and the aqueous became stained yellow. UVA radiation was then applied for 10 minutes at 9 mW/cm^2 power using a commercially available UVA system (Meran Tip, BNM, Inc. Istanbul, Türkiye), with the riboflavin solution being applied every 2 minutes to maintain saturation during the procedure.[10] After surgery, we placed a therapeutic silicone hydrogel contact lens and left it in place until reepithelialization was complete. Postoperatively, the patient received topical ofloxacin drops 4 times a day for 1 week, topical fluorometholone drops 4 times a day for 1 month (with a tapering schedule), and artificial tears 4 times a day for 6 months.

Statistical Analysis

The statistical analysis was performed using SPSS Statistics 21.0 (IBM Corp, Armonk, NY). Before conducting the analysis, we verified the normal distribution of the data using the Shapiro-Wilk W test. All variables are expressed as mean and standard deviation. Changes from the preoperative value at each follow-up were assessed using the paired-sample t-test. Statistical significance was attributed to differences with a p value <0.05.

Results

This study included 26 eyes of 16 PLE patients (11 men, 5 women) who were treated with combined tPTK+aCXL. The mean age was 37.06±6.28 years (range 29 to 49 years). Therapeutic contact lenses were taken out within 5 days postoperatively, and the epithelium was found to be intact in all eyes. None of the patients experienced any complications during the procedure or the 24-month follow-up period.

Table 1 displays the preoperative and postoperative visual, refractometric, and topographic outcomes of the patients. During the 24 months of follow-up, the mean UCVA and BCVA values remained stable compared to baseline (p>0.05). There was a stabilization in both UCVA and BCVA at 24 months postoperatively (p>0.05 for both values). While 10 eyes (38.4%) had at least one Snellen line of improvement in UCVA (mean 1.9 Snellen lines, range 1-7), 14 eyes (53.8%) had stable UCVA at postoperative 24 months. While 8 eyes (30.7%) had at least one Snellen line of improvement in CDVA (mean 2.1 Snellen lines, range 1-4), 16 eyes (61.5%) had stable CDVA at postoperative 24 months. Among the eyes that underwent the treatment, 2 eyes (7.69%) had one Snellen line of decrease in their UCVA, and 2 eyes (7.69%) had two Snellen lines of decrease in their CDVA. The mean SE and CYL started to decrease in 6 months. However, this decrease could not reach a statistically significant level and remained stable throughout the follow-up period (p>0.05 for all visits).

As seen in Table 1, regarding the topographic values, a significant reduction in the mean K1, K2, and Kmean values was noted at 6, 12, and 24 months when compared to preoperative values (p=0.009, p=0.001, and p=0.02 for K1; p=0.002, p<0.001, and p<0.001 for K2; and p=0.002, p<0.001, and p<0.001 for Kmean, respectively). The reduction in K1, K2, and Kmean values was also observed at 6 and 12 months compared to the previous visit, with stabilization noted after 12 months (Table 2). Although the mean Kmax increased at 6 months, it decreased at 12 and 24 months of follow-up, but this difference was not statistically significant (p>0.05 for all visits). The mean CCT value was significantly decreased at postoperative 6 months, although it started to recover at postoperative 12 months (p<0.001 and p=0.002, respectively). It was stable compared to baseline throughout the 24 months of follow-up (p=0.08). A significant decrease in mean TCT was observed at postoperative 6 months, and this decrease was stable during the 24-month follow-up period (p<0.001, p<0.001, and p=0.005, respectively) (Table 1). Both CCT and TCT values remained stable after postoperative month 6 when compared to the previous visit (Table 2). There was also a significant decrease in the mean anterior elevation value that started at postoperative 6 months and continued throughout the follow-up period (p=0.03, p<0.001, and p<0.001, respectively). The mean posterior elevation value significantly decreased from 73.40±47.76 µm to 69.70±41.1 µm at postoperative 24 months (p=0.02) (Table 1). Anterior elevation values were significantly

Table 1. Visual acuity, refractometric, and topographic values before and after transepithelial phototherapeutic keratectomy and accelerated corneal collagen cross-linking treatment

	Preoperative	**6 months**	**12 months**	**24 months**
LogMAR UCVA p value*	0.89±0.36	0.76±0.31 p=0.093	0.77±0.44 p=0.734	0.79±0.33 p=0.327
LogMAR BCVA p value*	0.31±0.25	0.31±0.18 p=0.974	0.26±0.22 p=0.520	0.24±0.19 p=0.439
Spherical equivalent (D) p value*	-5.19±4.56	-4.8±3.6 p=0.315	-3.25±2.6 p=0.237	-2.77±2.27 p=0.234
Manifest cylinder (D) p value*	-2.44±1.63	-2.59±1.68 p=0.820	-2.17±1.15 p=0.105	-2.26±1.26 p=0.166
CCT (µm) p value*	441.08±56.35	404.83±53.0 **p<0.001**	408.25±52.07 **p=0.002**	429.5±55.91 p=0.08
TCT (µm) p value*	433.16±56.86	387.7±51.62 **p<0.001**	388.93±48.98 **p<0.001**	391.07±54.76 **p=0.005**
K1 (D) p value*	45.76±5.75	45.57±5.92 **p=0.009**	44.61±6.41 **p=0.001**	42.86±6.34 **p=0.02**
K2 (D) p value*	48.62±6.17	48.28±6.3 **p=0.002**	47.26±6.67 **p<0.001**	45.92±6.74 **p<0.001**
Kmean (D) p value*	47.13±5.89	46.87±6.06 p=0.002	45.89±6.51 **p<0.001**	44.21±6.4 p<0.001
Kmax (D) p value*	59.56±8.87	61.67±9.39 p=0.117	57.82±8.89 p=0.109	58.8±7.9 p=0.836
Posterior elevation (µm) p value*	73.40±47.76	68.83±39.0 p=0.131	57.0±41.24 p=0.716	69.7±41.1 **p=0.02**
Anterior elevation (µm) p value*	20.32±18.76	15.62±20.35 **p=0.03**	13.68±19.94 **p<0.001**	9.07±20.73 **p<0.001**

Data expressed as mean ± standard deviation. *Compared to preoperative value with paired-samples t-test, significant values shown in bold (p<0.05). LogMAR: Logarithm of the minimum angle of resolution, UCVA: Uncorrected visual acuity, BCVA: Best corrected visual acuity, D: Diopters, CCT: Central corneal thickness, TCT: Thinnest corneal thickness, K1: Flat keratometry, K2: Steep keratometry, Kmean: Mean keratometry, Kmax: Maximum keratometry decreased at 6 and 12 months, while posterior elevation values were significantly decreased at 12 months compared to the previous visit. Both values exhibited stabilization from the 12th month onwards (Table 2).

At 24 months of follow-up, all measured aberrometric values except for spherical aberration (RMS, trefoil, coma, quadrafoil, and astigmatism) and PSF value remained stable compared to the preoperative values ($p>0.05$ for each variable). There was a statistically significant change in spherical aberration value from -0.21±0.63 µm to -0.51±0.58 µm at postoperative 24 months ($p=0.02$). During both preoperative and postoperative evaluations, the measured HOAs of all included eyes with PLE deviated from the normal corneal HOA values (Table 3).

Discussion

LASIK is the most commonly performed refractive surgical procedure and is known for its effectiveness and safety.[15] Although postoperative complications are rare, they can be devastating.[16] PLE with progressive corneal steepening, either centrally or inferiorly, leads to severe progressive irregular astigmatism and decreased UCVA and BCVA.[1,16,17] Ectatic changes can occur shortly after LASIK or may be delayed for several years.[18,19] The underlying cause of postoperative ectasia is related to a biomechanical instability of the cornea.[1,17]

The treatment of corneal ectasia involves addressing two key aspects: enhancing corneal biomechanical stability and improving the optical characteristics of the irregular cornea. CXL is a minimally invasive treatment that induces corneal crosslinking to increase corneal stiffness and stability and has shown clinical success in effectively preventing the progression of ectasia.[3] Kohlhaas et al.[20] were the first to describe the successful use of CXL to treat PLE in 2005. Yildirim et al.[21] showed in a retrospective study including 20 eyes with PLE that UCVA and BCVA improved significantly and CYL and Kmax decreased significantly over a 42-month follow-up period after conventional CXL. In recent years, several additional procedures have been suggested in combination with CXL to enhance the visual outcome, such as tPTK, topography-guided photorefractive keratectomy (PRK), intrastromal corneal ring segment implantation, and phakic intraocular lens implantation.[22] These procedures have varying degrees of impact on the cornea or anterior chamber structure.[23] To prevent changes in the anterior chamber, our focus in treating eyes with PLE was on corneal surgery. During the CXL procedure, it is necessary to remove the corneal epithelium to ensure uniform and sufficient absorption of riboflavin into the corneal stroma.[24] Traditionally, mechanical removal of the epithelium has been used,[3] but more recently, excimer lasers have been employed for this purpose.[8] The tPTK procedure removes the irregular epithelial layer of an ectatic cornea with localized thinning over the cone apex and ring-shaped thickening around the cone. The procedure utilizes excimer lasers to smooth out the Bowman layer and irregular stroma, which can effectively reduce optical irregularities and astigmatism. It typically involves an ablation depth of around 50 µm.[7,25] Additionally, it has been found that removal of the Bowman layer during tPTK may enhance the effectiveness of CXL treatment.[25] The Cretan protocol incorporates tPTK for corneal epithelium removal during conventional CXL[7] and has demonstrated better visual and refractive outcomes in comparison to mechanical debridement at 1-year follow-up in

Table 2. Topographic values before and after transepithelial phototherapeutic keratectomy and accelerated corneal collagen cross-linking treatment

	Preoperative	6 months	12 months	24 months
CCT (µm) p value*	441.08±56.35	404.83±53.0 **p<0.001**	408.25±52.07 p=0.104	429.5±55.91 p=0.079
TCT (µm) p value*	433.16±56.86	387.7±51.62 **p<0.001**	388.93±48.98 p=0.568	391.07±54.76 p=0.054
K1 (D) p value*	45.76±5.75	45.57±5.92 **p=0.009**	44.61±6.41 **p=0.014**	42.86±6.34 p=0.105
K2 (D) p value*	48.62±6.17	48.28±6.3 **p=0.002**	47.26±6.67 **p=0.003**	45.92±6.74 p=0.132
Kmean (D) p value*	47.13±5.89	46.87±6.06 **p=0.002**	45.89±6.51 **p=0.004**	44.21±6.4 p=0.102
Kmax (D) p value*	59.56±8.87	61.67±9.39 p=0.117	57.82±8.89 p=0.071	58.8±7.9 p=0.214
Posterior elevation (µm) p value*	73.40±47.76	68.83±39.01 p=0.131	57.0±41.24 **p=0.026**	69.7±41.1 p=0.091
Anterior elevation (µm) p value*	20.32±18.76	15.62±20.35 **p=0.03**	13.68±19.94 **p=0.009**	9.07±20.73 p=0.068

Data expressed as mean ± standard deviation. *Compared to the previous time point with paired-samples t-test, significant values shown in bold ($p<0.05$). CCT: Central corneal thickness, TCT: Thinnest corneal thickness, K1: Flat keratometry, D: Diopters, K2: Steep keratometry, Kmean: Mean keratometry

Table 3. Corneal aberration and point spread function values before and after transepithelial phototherapeutic keratectomy and accelerated corneal collagen cross-linking treatment

	Preoperative	6 months	12 months	24 months
RMS (µm) p value*	2.32±1.02	3.06±1.53 **p=0.001**	2.65±1.07 p=0.212	2.51±1.42 p=0.077
Trefoil (µm) p value*	0.75±0.48	0.87±0.52 p=0.144	0.69±0.40 **p=0.004**	0.80±0.43 p=0.959
Coma (µm) p value*	1.77±0.96	1.51±1.11 p=0.065	1.31±0.88 **p=0.001**	1.59±0.94 p=0.142
Quadrifoil (µm) p value*	0.24±0.13	0.34±0.23 p=0.08	0.24±0.07 p=0.725	0.20±0.19 p=0.868
Astigmatism (µm) p value*	0.50±0.34	0.51±0.35 p=0.778	0.49±0.28 p=0.759	0.52±0.26 p=0.751
Spherical aberration (µm) p value*	-0.21±0.63	-0.27±0.66 p=0.085	-0.26±0.67 p=0.398	-0.51±0.58 **p=0.02**
Strehl ratio of PSF p value*	0.05±0.02	0.04±0.02 p=0.88	0.04±0.01 p=0.511	0.04±0.02 p=0.897

Data expressed as mean ± standard deviation, *Compared to preoperative value with paired-samples t-test, significant values shown in bold ($p<0.05$). RMS: Root mean square, PSF: Point spread function

studies of progressive KC.[26,27] In our previous study, we compared the outcomes of using tPTK (modified Cretan protocol) versus mechanical epithelial removal during aCXL for pediatric KC and observed enhanced visual outcomes in the first year after the procedure compared to mechanical epithelial removal.[11] However, at 36-month follow-up, both techniques showed similar results. We also used tPTK+aCXL for progressive PMD patients and observed stabilization in visual acuity and Kmax, as well as a decrease in cylindrical refraction and SE after 36 months of follow-up.[10] In our current study, we performed a new technique, tPTK+aCXL, for the treatment of PLE.

In this retrospective study, we treated 26 eyes of 16 PLE patients with combined tPTK+aCXL and reported both short and long-term outcomes. The aCXL technique shortens the duration of UV irradiation, potentially enhancing patient comfort during treatment compared to conventional CXL. Performing mechanical epithelial debridement before conventional CXL poses a risk of damaging the LASIK flap. The lack of this risk can be seen as advantageous for tPTK. Research has demonstrated that the excimer laser for corneal epithelial removal may increase the risk of corneal complications, including epithelial hypertrophy, delayed epithelial healing, hyperopic shift, and corneal haze, compared to mechanical debridement methods.[28,29] In our current study, no complication was observed during 24-month follow-up. According to our visual outcomes, although the improvement in UCVA and BCVA during the 24-month follow-up period was not statistically significant, 38.4% of eyes showed at least one Snellen line UCVA improvement, and 30.7% had at least one Snellen line CDVA improvement. In a study by Richoz et al.[1] involving 23 PLE eyes and 3 PRK-induced ectasia eyes that underwent mechanical epithelial debridement followed by conventional CXL treatment, significant improvements in mean BCVA and Kmax were observed at 25 months of follow-up. However, it is worth noting that their patients had thinner corneas than the patients in our study. Toprak et al.[30] demonstrated that preoperative TCT serves as one of the predictive factors for the outcome of CXL treatment in KC patients, influencing changes in visual acuity and maximum keratometry. The flattening effect of CXL treatment may be greater in thinner corneas, potentially resulting in increased visual acuity and reduced Kmax in patients with advanced PLE.

Furthermore, our study revealed promising topographic outcomes. Keratometry values showed a flattening during the 24 months of follow-up compared to preoperative values. Specifically, K1, K2, and Kmean decreased significantly by approximately 0.3 diopters (D) at 6 months and 3.0 D by 24 months postoperatively. These values also demonstrated stabilization after the 12th month. However, Kmax, SE, and CYL remained stable throughout the entire 24 months of follow-up. Changes in the profile of corneal epithelial thickness can be observed in various corneal pathologies, including corneal ectasias.[31] It was advocated that a corneal epithelial thickness of 51-60 µm was the therapeutic window for highly aberrated corneas when performing tPTK.[31,32] It can be considered that although applying the tPTK (50 µm depth) without preoperative corneal epithelial mapping may reduce the flattening effect of CXL in the cone region, the progressive steepening in the cone region of a PLE cornea can be halted with tPTK+aCXL treatment. It could be a reason for the stabilization in visual acuity, refraction values, and Kmax after the modified Cretan protocol in PLE. Kymionis et al.[9] reported beneficial outcomes with the Cretan protocol in the treatment of 23 eyes with KC, with UCVA and BCVA improving and the K1 and K2 decreasing at a mean follow-up of 33.83 months. They concluded that the combined approach was effective and safe for the long-term treatment of KC patients. In a comparative study showing 36-month results in progressive KC, the modified Cretan protocol was more effective in improving UCVA, BCVA, K1, K2, Kmax, and PSF than mechanical debridement-assisted aCXL.[33] On the other hand, another study by our group comparing mechanical debridement-assisted aCXL with tPTK+aCXL in pediatric KC patients demonstrated no superiority of tPTK over mechanical debridement in the long term.[11] Gaster et al.[27] proposed that despite tPTK being as effective as manual debridement before CXL, it does not yield significant and enduring visual, topographic, or refractive benefits for progressive KC. Due to the variable results reported with tPTK+CXL treatment in corneal ectasias, we believe that prospective comparative studies with larger patient series are needed in patients with corneal ectasia, including PLE.

A reduction in corneal thickness is expected after CXL treatments, especially when combined with excimer laser procedures. This reduction in thickness is usually significant and can last for months.[8] Similarly, we observed a significant decrease in both CCT and TCT values at postoperative 6 months in the current study. The decrease in CCT and TCT at 6 months after CXL might also be affected by the Scheimpflug imaging artifact that arises from the stromal scatter that is commonly observed during the early postoperative period.[10] Although TCT remained decreased throughout the 24-month follow-up, CCT started to increase after 6 months, and there was no statistically significant difference compared to baseline at the 24-month follow-up. The mean anterior elevation value improved during the 24-month follow-up, with a total reduction of 11 µm compared to baseline. The mean posterior elevation value also showed a significant reduction at 24-month follow-up compared to the preoperative value.

Evaluation of PSF and corneal aberrations is crucial for assessing the optical quality of the eye. However, Zernike polynomials exhibit a varying effect on visual function. In this study, we observed stability in PSF and all aberration values except for spherical aberrations, which is consistent with our visual acuity results. The spherical aberration value decreased at postoperative 24 months, which might be linked to the flattening of the central cornea following CXL treatment.

Excimer laser ablation alone is not considered the established treatment option to enhance refractive results for patients with PLE. Combined therapies, such as tPTK+CXL or topography-guided PRK+CXL, have demonstrated advantages in terms of both halting progression and enhancing visual function.[34] Zhou et al.[23] used a combined therapy (tPTK+PRK+CXL) for the treatment of 16 eyes with PLE. PTK ablation was performed in an 8.5-mm zone at a depth of 50 µm (like our ablation depth), while PRK ablation was limited to a maximum depth of 80 µm for all cases before conventional CXL. They demonstrated that UCVA improved significantly, while K1, K2, and CYL decreased significantly. The mean CCT and endothelial cell count did not change significantly at 24 months of follow-up. The tPTK+PRK+CXL therapy seems to be effective and safe in the treatment of PLE. Nonetheless, it was suggested that tPTK+CXL should be considered as an alternative in cases of low corneal thickness or when PRK+CXL cannot be performed for better outcomes.[7] Therefore, the combined tPTK+aCXL therapy may be a better treatment option for ectatic corneal diseases such as PLE with low corneal thickness.

Study Limitations

Our study has several limitations. It is retrospective, has a small sample size, and lacks preoperative corneal epithelium data, a group of PLE patients treated with mechanical debridement-assisted aCXL, and a group of untreated PLE patients as controls. Nevertheless, our study included a substantial number of eyes with PLE compared to other studies in the literature, likely due to the rarity of PLE as a complication of LASIK. Another potential study limitation is not measuring the stromal demarcation line. This boundary marks the transition between cross-linked stroma and untreated tissue after CXL, which some researchers consider crucial for the procedure's success. However, there has been debate recently about whether the depth of the stromal demarcation line accurately reflects CXL effectiveness.[35] Furthermore, safety concerns, particularly the risk of endothelial damage, are significant considerations for both combined and conventional CXL procedures.[34] Unfortunately, we could not assess the count and morphology of endothelial cells in the central cornea using specular microscopy. Despite these limitations, our study provides valuable insights into the effectiveness of tPTK+aCXL combined therapy for PLE.

Conclusion

Our long-term results demonstrate that tPTK+aCXL treatment (modified Cretan protocol) effectively and safely halts progressive PLE over 24 months. Additional prospective studies with larger cohorts and extended follow-up are essential to validate these results in this challenging ectatic condition.

Ethics

Ethics Committee Approval: Ankara City Hospital-No. 1 Clinical Research Ethics Committee (date: 23.06.2021, no: E1/1910/2021).

Informed Consent: Obtained.

Authorship Contributions

Surgical and Medical Practices: Ö.S., Concept: B.T., Ö.S., N.Ç., Design: B.T., Ö.S., N.Ç., Data Collection or Processing: B.Te., E.D.Ş., Analysis or Interpretation: Ö.S., B.Te., E.D.Ş., B.T., Literature Search: B.T., Ö.S., B.Te., Writing: B.T., Ö.S., B.Te., N.Ç.

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References

1. Richoz O, Mavrakanas N, Pajic B, Hafezi F. Corneal collagen cross-linking for ectasia after LASIK and photorefractive keratectomy: long-term results. Ophthalmology. 2013;120:1354-1359.
2. Binder PS. Ectasia after laser in situ keratomileusis. J Cataract Refract Surg. 2003;29:2419-2429.
3. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol. 2003;135:620-627.

4. Gatzioufas Z, Richoz O, Brugnoli E, Hafezi F. Safety profile of high-fluence corneal collagen cross-linking for progressive keratoconus: preliminary results from a prospective cohort study. J Refract Surg. 2013;29:846-848.
5. Tomita M, Mita M, Huseynova T. Accelerated versus conventional corneal collagen crosslinking. J Cataract Refract Surg. 2014;40:1013-1020.
6. Sarac O, Caglayan M, Uysal BS, Uzel AGT, Tanriverdi B, Cagil N. Accelerated versus standard corneal collagen cross-linking in pediatric keratoconus patients: 24 months follow-up results. Cont Lens Anterior Eye. 2018;41:442-447.
7. Kymionis GD, Grentzelos MA, Kankariya VP, Pallikaris IG. Combined transepithelial phototherapeutic keratectomy and corneal collagen crosslinking for ectatic disorders: cretan protocol. J Cataract Refract Surg. 2013;39:1939.
8. Kymionis GD, Grentzelos MA, Kounis GA, Diakonis VF, Limnopoulou AN, Panagopoulou SI. Combined transepithelial phototherapeutic keratectomy and corneal collagen cross-linking for progressive keratoconus. Ophthalmology. 2012;119:1777-1784.
9. Kymionis GD, Grentzelos MA, Kankariya VP, Liakopoulos DA, Karavitaki AE, Portaliou DM, Tsoulnaras KI, Pallikaris IG. Long-term results of combined transepithelial phototherapeutic keratectomy and corneal collagen crosslinking for keratoconus: Cretan protocol. J Cataract Refract Surg. 2014;40:1439-1445.
10. Cagil N, Sarac O, Yesilirmak N, Caglayan M, Uysal BS, Tanriverdi B. Transepithelial Phototherapeutic Keratectomy Followed by Corneal Collagen Crosslinking for the Treatment of Pellucid Marginal Degeneration: Long-term Results. Cornea. 2019;38:980-985.
11. Sarac O, Kosekahya P, Caglayan M, Tanriverdi B, Taslipinar Uzel AG, Cagil N. Mechanical versus transepithelial phototherapeutic keratectomy epithelial removal followed by accelerated corneal crosslinking for pediatric keratoconus: Long-term results. J Cataract Refract Surg. 2018;44:827-835.
12. Kanellopoulos AJ, Binder PS. Management of corneal ectasia after LASIK with combined, same-day, topography-guided partial transepithelial PRK and collagen cross-linking: the athens protocol. J Refract Surg. 2011;27:323-331.
13. Mafusire C, Krüger TP. Strehl ratio and amplitude-weighted generalized orthonormal Zernike-based polynomials. Appl Opt. 2017;56:2336-2345.
14. Uysal BS, Sarac O, Yaman D, Akcay E, Cagil N. Optical Performance of the Cornea One Year Following Keratoconus Treatment with Corneal Collagen Cross-Linking. Curr Eye Res. 2018;43:1415-1421.
15. Sandoval HP, Donnenfeld ED, Kohnen T, Lindstrom RL, Potvin R, Tremblay DM, Solomon KD. Modern laser in situ keratomileusis outcomes. J Cataract Refract Surg. 2016;42:1224-1234.
16. Seiler T, Koufala K, Richter G. Iatrogenic keratectasia after laser in situ keratomileusis. J Refract Surg. 1998;14:312-317.
17. Giri P, Azar DT. Risk profiles of ectasia after keratorefractive surgery. Curr Opin Ophthalmol. 2017;28:337-342.
18. Lifshitz T, Levy J, Klemperer I, Levinger S. Late bilateral keratectasia after LASIK in a low myopic patient. J Refract Surg. 2005;21:494-496.
19. Rao SN, Epstein RJ. Early onset ectasia following laser in situ keratomileusus: case report and literature review. J Refract Surg. 2002;18:177-184.
20. Kohlhaas M, Spoerl E, Speck A, Schilde T, Sandner D, Pillunat LE. Eine neue Behandlung der Keratektasie nach LASIK durch Kollagenvernetzung mit Riboflavin/UVA-Licht [A new treatment of keratectasia after LASIK by using collagen with riboflavin/UVA light cross-linking]. Klin Monbl Augenheilkd. 2005;222:430-436.
21. Yildirim A, Cakir H, Kara N, Uslu H, Gurler B, Ozgurhan EB, Colak HN. Corneal collagen crosslinking for ectasia after laser in situ keratomileusis: long-term results. J Cataract Refract Surg. 2014;40:1591-1596.
22. Kymionis GD, Grentzelos MA, Portaliou DM, Kankariya VP, Randleman JB. Corneal collagen cross-linking (CXL) combined with refractive procedures for the treatment of corneal ectatic disorders: CXL plus. J Refract Surg. 2014;30:566-576.
23. Zhou W, Wang H, Zhang X, Tian M, Cui C, Li X, Mu G. Management of Corneal Ectasia after LASIK with Phototherapeutic Keratectomy Combined with Photorefractive Keratectomy and Collagen Cross-Linking. J Ophthalmol. 2019;2019:2707826.
24. Shalchi Z, Wang X, Nanavaty MA. Safety and efficacy of epithelium removal and transepithelial corneal collagen crosslinking for keratoconus. Eye (Lond). 2015;29:15-29.
25. Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. J Refract Surg. 2009;25:812-818.
26. Kapasi M, Dhaliwal A, Mintsioulis G, Jackson WB, Baig K. Long-Term Results of Phototherapeutic Keratectomy Versus Mechanical Epithelial Removal Followed by Corneal Collagen Cross-Linking for Keratoconus. Cornea. 2016;35:157-161.
27. Gaster RN, Ben Margines J, Gaster DN, Li X, Rabinowitz YS. Comparison of the Effect of Epithelial Removal by Transepithelial Phototherapeutic Keratectomy or Manual Debridement on Cross-linking Procedures for Progressive Keratoconus. J Refract Surg. 2016;32:699-704.
28. Cagil N, Sarac O, Cakmak HB, Can G, Can E. Mechanical epithelial removal followed by corneal collagen crosslinking in progressive keratoconus: short-term complications. J Cataract Refract Surg. 2015;41:1730-1737.
29. Deshmukh R, Reddy JC, Rapuano CJ, Vaddavalli PK. Phototherapeutic keratectomy: Indications, methods and decision making. Indian J Ophthalmol. 2020;68:2856-2866.
30. Toprak I, Yaylalı V, Yildirim C. Factors affecting outcomes of corneal collagen crosslinking treatment. Eye (Lond). 2014;28:41-46.
31. Abtahi MA, Beheshtnejad AH, Latifi G, Akbari-Kamrani M, Ghafarian S, Masoomi A, Sonbolastan SA, Jahanbani-Ardakani H, Atighechian M, Banan L, Nouri H, Abtahi SH. Corneal Epithelial Thickness Mapping: A Major Review. J Ophthalmol. 2024;2024:6674747.
32. Reinstein DZ, Archer TJ, Gobbe M, Rothman RC. Epithelial thickness changes following realignment of a malpositioned free cap. J Cataract Refract Surg. 2014;40:1237-1239.
33. Ozdas D, Yesilirmak N, Sarac O, Cagil N. 36-Month Outcomes of Mechanical and Transepithelial PTK Epithelium Removal Techniques Prior to Accelerated CXL for Progressive Keratoconus. J Refract Surg. 2022;38:191-200.
34. Zhu W, Han Y, Cui C, Xu W, Wang X, Dou X, Xu L, Xu Y, Mu G. Corneal Collagen Crosslinking Combined with Phototherapeutic Keratectomy and Photorefractive Keratectomy for Corneal Ectasia after Laser in situ Keratomileusis. Ophthalmic Res. 2018;59:135-141.
35. Gatzioufas Z, Balidis M, Kozeis N. Is the corneal stromal demarcation line depth a true indicator of corneal collagen crosslinking efficacy? J Cataract Refract Surg. 2016;42:804.