Combined laser in situ keratomileusis and prophylactic high-fluence corneal collagen crosslinking for high myopia: Two-year safety and efficacy

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PURPOSE: To evaluate the safety, efficacy, and refractive and keratometric stability of myopic femtosecond laser in situ keratomileusis (LASIK) with concurrent prophylactic high-fluence corneal collagen crosslinking (CXL) compared with the outcomes of standard femtosecond LASIK.

SETTING: Private clinical practice, Athens, Greece.

DESIGN: Consecutive randomized prospective comparative study.

METHODS: Eyes that had myopic LASIK or myopic LASIK with concurrent high-fluence CXL were evaluated preoperatively and up to 2 years postoperatively for manifest refraction spherical equivalent (MRSE), refractive astigmatism, visual acuity, corneal keratometry (K), and endothelial cell count.

RESULTS: One hundred forty consecutive eyes had myopic LASIK; 65 of the eyes were treated additionally with CXL. In the LASIK–CXL eyes, the mean postoperative MRSE was −0.18 diopter (D) ± 17.0 (SD) from −6.67 ± 2.14 D preoperatively. The postoperative flat K was 37.67 D from 43.92 D, and the steep K was 38.38 D from 45.15 D. The correlation coefficient of SE correction predictability was 0.975. In the LASIK-only eyes, the mean postoperative MRSE was −0.32 ± 0.24 D from −5.49 ± 1.99 D preoperatively. The flat K was 38.04 D from 43.15 D, and the steep K was 38.69 D from 44.03 D. The correlation coefficient of SE correction predictability was 0.968. The differences between the 2 groups at the 20/20 and 20/25 levels were statistically significant ($P = .045$ and $P = .039$, respectively).

CONCLUSION: Two-year results indicate that the application of prophylactic CXL concurrently with high-myopic LASIK appears to improve refractive and keratometric stability, presumably by affecting corneal biomechanical properties.

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Laser in situ keratomileusis (LASIK) is a widely accepted method to correct refractive errors[1,2] and offers predictable and stable refractive and visual outcomes,[3] specifically in the correction of moderate to high myopia (equal to or greater than −6.00 diopters [D] in the least minus meridian of both eyes).[4,5] However, some studies have reported significant long-term regression.[6–8] In a study by Alió et al.,[9] 1 in 5 (ie, 20.8%) cases with high myopia required retreatment because of overcorrection, undercorrection, or regression.

Our experience with LASIK correction of high myopia suggests a slight (0.5 D) trend toward long-term postoperative corneal steepening.[10] We have therefore attempted prophylactic in situ corneal collagen crosslinking (CXL) on the stromal bed concurrent with LASIK, particularly in highly myopic eyes with thin residual stroma and young patients who

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may not yet have exhibited ectasia risk factors.[11,12] The application aims to enhance corneal rigidity and thus reduce the likelihood of a long-term myopic shift.[13–15]

This study comparatively investigated the potential long-term differences in safety, efficacy, and refractive and keratometric results in myopic LASIK using the FS200 femtosecond laser (Alcon Surgical, Inc./Wavelight Laser Technologie AG) and the EX500 excimer laser refractive surgery platform (Alcon Surgical, Inc./Wavelight Laser Technologie AG). The study included 2 groups, a LASIK–CXL group and a LASIK-only group in which no concurrent CXL was applied.

PATIENTS AND METHODS

This prospective observational longitudinal study received approval by the institution's ethics committee and adhered to the tenets of the Declaration of Helsinki. Informed written consent was provided and documented from each patient at the time of the first study visit by the surgeon. The patients selected for the LASIK–CXL treatment were comprehensively informed of the benefits and risks involving this procedure, which is Conformité Européenne-marked in Europe.

Inclusion and Exclusion Criteria

The study comprised consecutive patients enrolled for primary myopic LASIK correction. Inclusion criteria were no previous ocular surgery and documented refractive stability for at least 3 years. Contact lens use was discontinued for at least 2 weeks before the intervention. A complete preoperative ophthalmologic evaluation ensured no present or past ocular pathology other than refractive error. Exclusion criteria were systemic or ocular disease, a history of corneal dystrophy or herpetic eye disease, topographic evidence of ectatic corneal disorder, epithelial warpage from contact lens use, corneal scaring, glaucoma, severe dry eye, and collagen vascular diseases.

One eye of each patient was randomly selected (randomization tables) to be included in the study; bilateral surgery was performed in all patients. All surgery was performed by the same surgeon (A.J.K.). According to our clinical protocol for the past 6 years, the myopic LASIK treatments were allocated to receive the additional prophylactic CXL treatment if the keratometric astigmatism in the eye was greater than 1.5 D measured by Scheimpflug imaging–derived simulated keratometry (K) and/or the predicted residual stromal thickness was less than 330 μm. As a result, the LASIK-only group included no eyes with myopia greater than −10.0 D.

Surgical Technique

In both groups, the femtosecond laser was used to create a corneal flap of 110 μm thickness with an 8.00 mm diameter.[16] The myopic ablation (6.00 to 6.50 mm ablation zone diameter) was accomplished with the excimer laser.[17]

In the LASIK–CXL group, after the excimer laser ablation and with the flap folded on itself and protected with a dry cellulose sponge (Weck-Cel), 1 drop of saline-diluted riboflavin 0.1% (Vibex Rapid) was placed on the exposed stromal bed for 60 seconds.

Following stromal soaking, the flap was properly repositioned in place and the residual riboflavin was irrigated. Ultraviolet-A (UVA) fluence of 30 mW/cm^2 (KXL system, Avedro, Inc.) was applied for 80 seconds (total energy 2.4 J/cm^2).

In both study groups, to avoid the risk for same-day accidental flap contact or rubbing, a planar bandage soft contact lens was placed on the ocular surface and removed the following day. The patients were treated postoperatively with moxifloxacin (Vigamox) and dexamethasone–chloramphenicol 0.1% solution (Dispersadron-C) 4 times a day for 1 week.

Data Collection

All eyes were measured for uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), manifest refraction spherical equivalent (MRSE) via manifest refraction and autorefraction measurements (Speedy-i, K Model, Nidek Co., Ltd.), visual acuity (Functional Vision Analyzer, Stereo Optical Co., Inc.), corneal topography for steep K and flat K within the 3.0 mm radius (Placido topography using the Topolyzer Vario and Scheimpflug imaging using the Oculyzer II, both Wavelight Laser Technologie AG), and corneal thickness using the Oculyzer II and optical coherence tomography (OCT) (Rtvue-100 system, Optovue, Inc.).[18]

Optical coherence tomography was also used to provide meridional scans. The hyperreflectivity lines are considered an indirect indication of CXL efficacy,[19] as demonstrated by an earlier investigation[20] in which the CXL demarcation lines were evident even after 3 years. An OCT meridional image scan of a treated cornea is presented in Figure 1, which shows increased reflectivity of the upper stromal bed.

The postoperative evaluation included slitlamp examination, clinical evaluation of dry eye, indications of epithelial ingrowth,[21] and corneal haze. In addition, endothelial cell counts were measured preoperatively and postoperatively at the 1-month visit using noncontact specular microscopy (FA-3709, Konan Medical).

Postoperative examinations were conducted at 1 day, 1 week, 3 and 6 months, 1 year, and up to 2 years. This study presents the refractive and keratometric data analysis from the 2-year follow-up visits. Data were processed by the web-based ophthalmic outcome analysis software application IBRA (Zubisoft GmbH).[22] Descriptive statistics and analysis were performed using Minitab software (version 16.2.3, Minitab Ltd.). A P value less than 0.05 indicated a statistically significant result.

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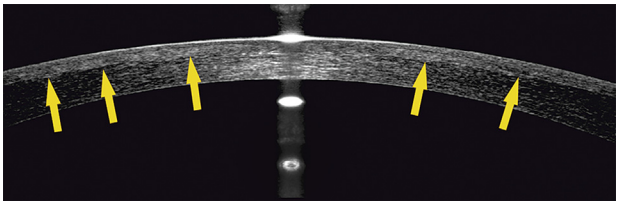

Figure 1. Anterior-segment OCT high-resolution cross-sectional (6.0 mm) image obtained 1 year postoperatively of an eye treated with LASIK–CXL for −4.50 D of sphere and −0.25 D of astigmatism. The intrastromal hyperreflective sections might correlate with the depth of the prophylactic CXL effect.

RESULTS

One hundred forty consecutive patients were enrolled in the study. The LASIK–CXL group, in which concurrent prophylactic CXL was performed, comprised 65 eyes (33 right eyes, 32 left eyes) of 38 women and 27 men. The LASIK-only group, in which no additional intervention was performed, comprised 75 eyes (37 right eyes, 38 left eyes) of 39 women and 36 men. Preoperative and postoperative parameters are reported in Table 1.

In the LASIK–CXL group, the mean preoperative refractive error was sphere −6.60 D ± 2.02 (SD) (range −2.50 to −11.50 D), cylinder −0.98 ± 0.15 D (range 0.00 to −5.00 D), and MRSE −6.67 ± 2.14 D (range −2.50 to −11.50 D). In the LASIK-only group, the preoperative mean refractive error was sphere −5.14 ± 1.74 D (range −2.50 to −9.50 D), cylinder −0.85 ± 0.13 D (range 0.00 to −4.50 D), and MRSE −5.49 ± 1.99 D (range −2.50 to −9.50 D).

No adverse events, such as epithelial ingrowth, diffuse lamellar keratitis, postoperative haze, or other complications were detected in either group. Endothelial cell counts did not differ significantly between the preoperative and 3-month postoperative examinations in either group.

Visual Acuity and Stability

In the LASIK–CXL group, the postoperative UDVA (Figure 2) was 20/20 (1.0 decimal) or better in 61 eyes (93.8%) and 20/25 (0.5 decimal) or better in 62 eyes (95.5%) (Figure 2). In the LASIK-only group, the postoperative UDVA was better than 20/20 in 55 eyes (84.8%) and better than 20/25 in 58 eyes (89.3%). The between-group differences in the percentage of cases achieving a UDVA of 20/20 and 20/25 were statistically significant ($P = .045$ and $P = .039$, respectively), with the LASIK–CXL group performing better.

Efficacy of Corrected Visual Acuity

The gain–loss data (preoperative CDVA versus postoperative UDVA) (Figure 3) show that in the LASIK–CXL group, 23 eyes (35.4%) were unchanged, 37 eyes (56.9%) gained 1 Snellen line, and 5 eyes (7.9%) gained 2 or more Snellen lines. No eye lost a line. In the LASIK-only group, 26 eyes (34.7%) were unchanged, 45 eyes (60.0%) gained 1 Snellen line, and 3 eyes (4.0%) gained 2 or more lines. One eye (1.3%) lost 1 line.

Table 1. Demographics and preoperative data in the 2 groups.

Parameter	LASIK–CXL (65 Eyes)	LASIK Only (75 Eyes)
Age (y)		
Mean ± SD	27.5 ± 6.1	24.2 ± 5.8
Range	19, 39	18, 42
MRSE (D)		
Preop		
Mean ± SD	−6.67 ± 2.14	−5.44 ± 1.99
Range	−2.5, −11.5	−2.5, −9.5
Postop		
Mean ± SD	−0.18 ± 0.17	−0.32 ± 0.24
Range	−0.55, +0.52	−0.67, +0.45
Preop CCT (µm)		
Mean ± SD	545.96 ± 33.93	553.51 ± 19.11
Range	474, 595	503, 592
Planned residual (µm)		
Mean ± SD	329.22 ± 32.15	344.34 ± 20.55
Range	299, 398	313, 408
Postop CCT (µm)		
Mean ± SD	438.11 ± 28.35	452.25 ± 21.18
Range	414, 506	423, 510

CCT = central corneal thickness; CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis; MRSE = manifest refraction spherical equivalent

Refractive Predictability and Accuracy

The refractive predictability is demonstrated in Figure 4, in which the achieved spherical equivalent (SE) versus attempted SE (in diopters) 2 years postoperatively is plotted in the form of a linear regression scatterplot. The coefficient of determination was $r^2 = 0.975$ in the LASIK–CXL group and $r^2 = 0.968$ in the LASIK-only group. Figure 5 shows the postoperative SE refraction at intervals of 0.50 D. An SE refraction between −0.50 D and 0.00 D was achieved in 55 eyes (84.6%) in the LASIK–CXL group and in 61 eyes (81.3%) in the LASIK-only group; the difference was not statistically significant ($P = .0754$). Figure 6 shows the postoperative refractive astigmatism at intervals of 0.50 D, representing the accuracy of the cylinder correction. The mean preoperative cylinder was −0.98 ± 0.05 D in the LASIK–CXL group and −0.85 ± 0.03 D in the LASIK-only group. The postoperative refractive astigmatism was less than 0.25 D in 60 eyes (92.3%) in the

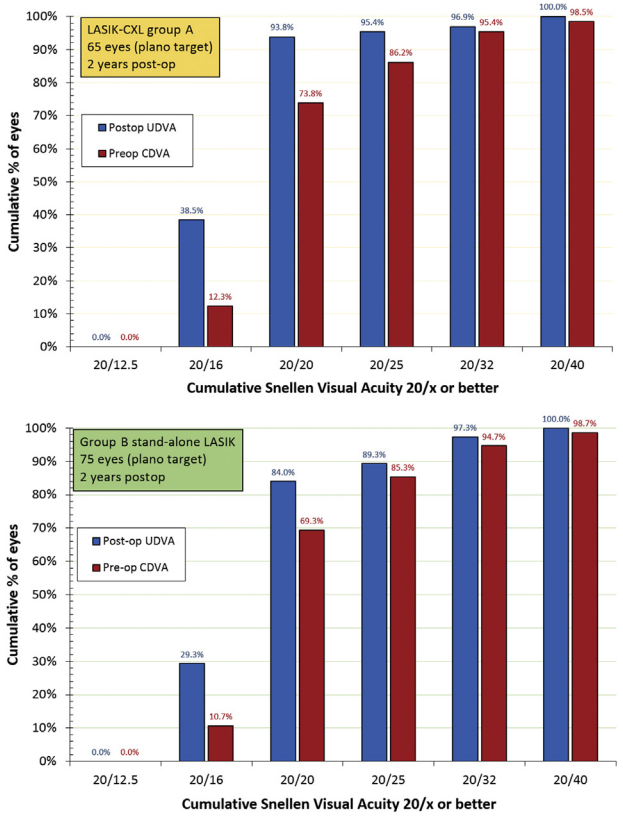

Figure 2. Postoperative UDVA versus preoperative CDVA 2 years postoperatively (CDVA = corrected distance visual acuity; CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis; UDVA = uncorrected distance visual acuity).

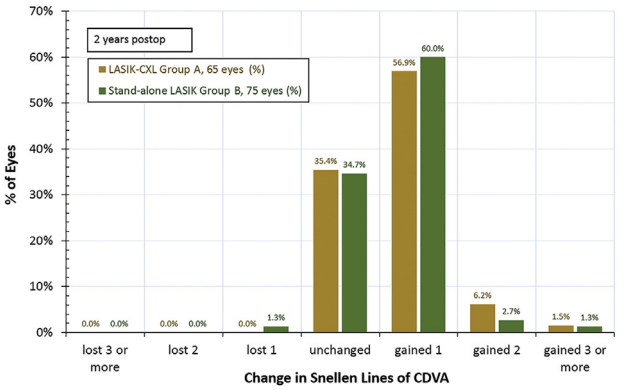

Figure 3. Change in CDVA as a percentage of eyes with gain/loss in Snellen lines of CDVA 2 years postoperatively (CDVA = corrected distance visual acuity; CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis).

LASIK–CXL group and 70 eyes (93.3%) in the LASIK-only group, and the mean cylinder was −0.15 ± 0.04 D and −0.15 ± 0.04 D, respectively.

Refractive and Keratometric Stability

The refractive stability is demonstrated by the MRSE correction at the 1, 3, 6, 12, and 24-month postoperative visits (Figure 7). The 2-year postoperative mean MRSE was −0.18 ± 0.17 D in the LASIK–CXL group and −0.32 ± 0.23 D in the LASIK-only group. These findings indicate the refractive shift was less in the LASIK–CXL group than in the LASIK-only group ($P = .065$). The keratometric stability is demonstrated by the flat K and steep K mean values up to the 24-month postoperative visit (Figure 8). The results suggest that keratometric stability was better in the LASIK–CXL group (+0.03 D in the flat K and +0.06 D in the steep K at 2 years versus 1-month baseline) than in the LASIK-only group (+0.63 D and +0.57 D, respectively); the difference was statistically significant ($P = .032$).

DISCUSSION

Improved diagnostics, ablation profiles, and laser beam–tracking refinements of the LASIK procedure,[23] with improvements attributed to femtosecond laser–assisted flap creation,[24–26] have contributed to an excellent track record in myopic correction.

However, there are some indications for the possibility of refractive regression in corrections of high myopia. For example, a correlation between increased epithelial thickness and myopic correction up to 1 year postoperatively was noted in a study by Spadea et al.[27] of highly myopic patients (myopia between −8.50 D and −12.25 D). This epithelial thickening in high myopia was recently corroborated in femtosecond LASIK high myopic correction.[28] In addition, a comparison of LASIK combined with prophylactic high-fluence CXL and LASIK only in high myopia reported a statistically significant reduction in epithelial increase in the LASIK–CXL cases compared with the LASIK-only cases. This difference may correlate with higher regression rates and/or may depict increased biomechanical instability in LASIK-only procedures.[29] We believe that this finding is a manifestation of the same aspect because the application of preventive CXL was the primary difference between the 2 groups in the study. As we have shown in previous work,[30] CXL affects epithelial thickness remodeling, leading to reduced overall thickness.

In our current study, we investigated up to 2 years of postoperative refractive and stability results in 2 groups that had femtosecond laser myopic LASIK: a LASIK–CXL group, in which prophylactic high-fluence CXL was performed concurrently with LASIK, and a LASIK-only group. The 2 groups were matched in all other parameters such as ablation zone, flap thickness, surgeon, lasers used, and postoperative

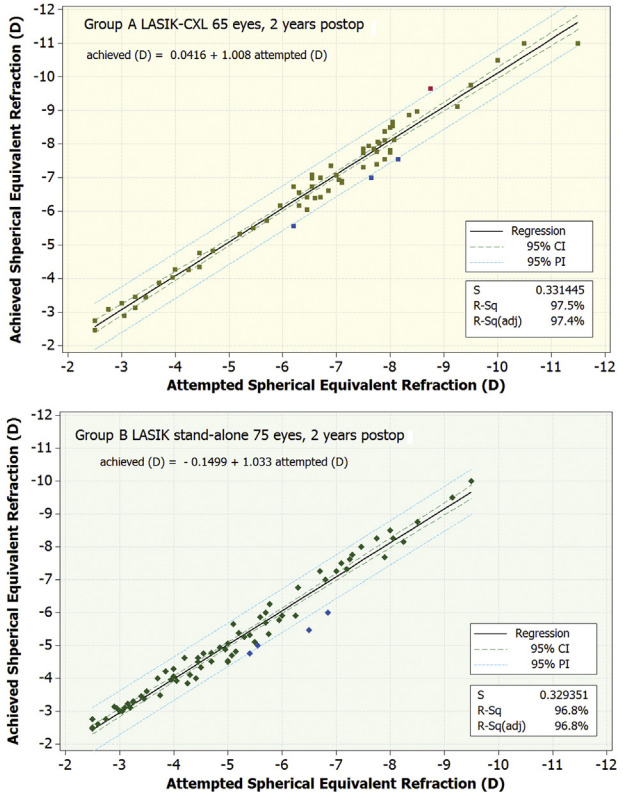

Figure 4. Predictability of SE correction measured 2 years postoperatively showing achieved SE versus attempted SE (adj = adjusted; CI = confidence interval; CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis; PI = prediction interval; S = sum of residuals).

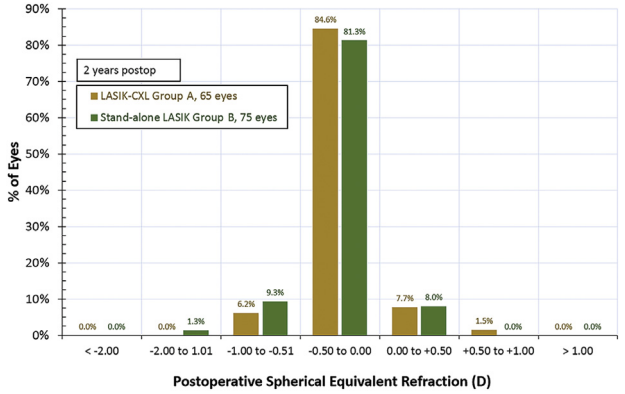

Figure 5. Postoperative SE refraction in both groups 2 years postoperatively (CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis).

medication and treatment. However, the mean spherical and cylindrical errors treated in the LASIK–CXL group (mean spherical −6.67 D, maximum spherical −11.50 D; mean cylindrical −0.98 D, maximum cylindrical −5.25 D) were statistically significantly different from those in the LASIK-only group (mean spherical −5.49 D, maximum spherical −9.50 D; mean cylindrical −0.85 D, maximum cylindrical −3.50 D). This was attributed to the higher-risk cases, such as those with astigmatism greater than 1.50 D and/or thin residual stroma (less than 330 μm), being allocated to the LASIK–CXL group. Thus, the LASIK–CXL group had a higher percentage of cases with high myopia that might pose a greater challenge to safely providing refractive correction.

Comparison of the stability results in the 2 groups indicates that in the LASIK-only group, there was a slight positive slope in the K readings at both the flat and steep meridians (Figure 8), which suggests mild progressive corneal steepening. The recorded changes correspond to +0.57 D in the flat meridian and +0.54 D in the steep meridian. The data show a trend toward mild corneal steepening in the long-term postoperative period. A similar refractive shift was reported by our team in large myopic LASIK corrections with no prophylactic CXL application.[10]

The trend of a keratometric shift was not seen in the LASIK–CXL group (+0.03 D and +0.05 D, respectively). Other differences between the 2 groups were slightly increased stability of the SE refraction (Figure 7) as well as improved predictability (Figure 4) despite the larger range of attempted correction and increased preoperative astigmatism (Figure 6).

Our team recently investigated the potential effectiveness of in situ (intralamellar) high-fluence, accelerated CXL in the stroma (under a LASIK flap). Our preliminary results suggest a 35% increase in corneal rigidity shown by transverse biaxial resistance measurements of the central section. This finding may indicate a biomechanical strengthening of the corneal stroma under the flap, partially explaining the increased keratometric stability in the LASIK–CXL group suggested by the data in the current study.

In our surgical technique, it is important to avoid riboflavin immersion of the flap and the hinge. For this purpose, the flap is protected while it is in a folded shape (Figure 1[13]) to inhibit flap CXL. However, minimal riboflavin absorption and thus CXL will inevitably occur as a result of osmosis during the UVA exposure (however short) as the flap is in contact with the riboflavin-soaked stroma. One has to consider the following aspects: A riboflavin presoaked flap will strongly absorb UVA (as it precedes the residual stroma along the illumination propagation path); however, it will not contribute further to the corneal biomechanical stability and may negatively affect the post-refractive outcome, given that a 110 μm thick flap has perhaps only a 60 μm stromal (collagen) content. Crosslinking such a thin stromal

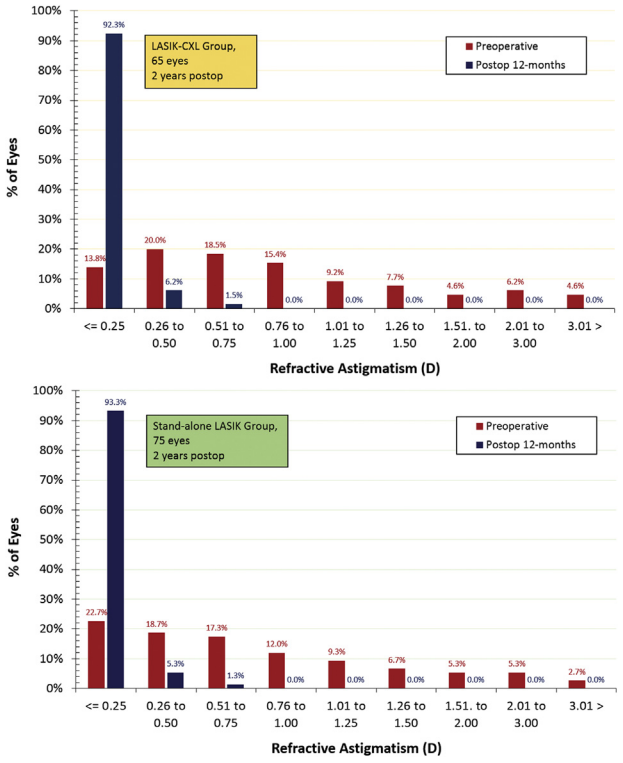

Figure 6. Refractive astigmatism preoperatively and 2 years postoperatively and the percentage of eyes versus refractive astigmatism (CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis).

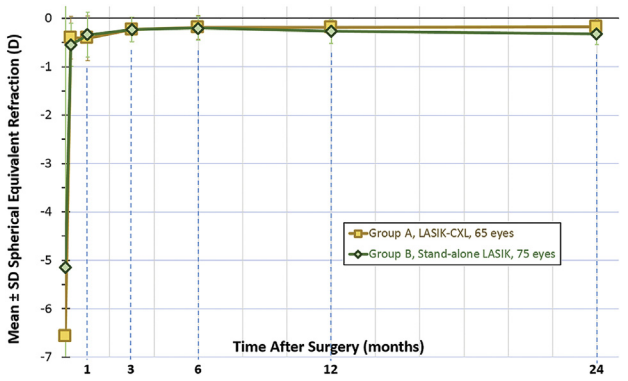

Figure 7. Stability of manifest SE refraction in both groups up to 2 years postoperatively (CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis).

layer may lead to undesirable stromal shrinking. However, one collateral benefit is that a crosslinked flap–stromal interface might positively affect flap adherence.[31]

The design of UVA irradiation parameters (fluence and exposure time) was influenced by the following considerations: (1) providing about half the full treatment energy compared with the traditional CXL protocol, (2) minimizing UVA exposure to constrain CXL within the overlaying flap, and (3) minimizing flap dehydration and possible shrinkage.

The superficial application of UVA following the in situ application of riboflavin instillation was designed taking into account the following aspects:

- Crosslinking the underlying stroma increases flap dehydration and the potential predisposition for striae.
- Crosslinking through the repositioned flap results in some riboflavin reflux in the dehydrated flap and CXL of the inner flap collagen and the underlying surface stroma. This may increase flap–underlying stroma adherence and potentially reduce or eliminate the inadvertent space created between them that has been shown to be filled with amorphous deposits in postmortem standard LASIK histopathology.
- Crosslinking has well-known disinfectant, if not antimicrobial, activity. Conducting the CXL through a repositioned flap reduces the chance for flap contamination by airborne microorganisms or fomites in the operating room environment and/or acts as an adjunct disinfectant of the LASIK procedure.

One aspect that should be considered is the possibility of refractive flattening as a result of the CXL applied. Our clinical experience, as well as the reports in the peer-reviewed literature, is suggestive of the continued progression of the CXL effect over time.[32] We have reported that the long-term keratometry flattening progression in the fully crosslinked cornea is on the order of −0.30 D.[29] One has to acknowledge the following 2 parameters that differentiate this finding when considering LASIK–CXL: The keratoconus management cases were fundamentally unstable ectatic corneas, whereas in the current study, the corneas were healthy and the keratoconus management cases received the full-energy treatment (up to 6 J/cm^2); also in the current study (LASIK–CXL) the cases received a partial-energy treatment (2.4 J/cm^2) only, corresponding to less than half the standard protocol energy.

When one considers the above aspects, it may be estimated that the possibility of long-term keratometric flattening be restricted. Additional long-term studies are required to investigate this aspect.

Our group has reported a large number of successful LASIK–CXL procedures over the past 8 years, and we view this prophylactic treatment as a pivotal biomechanical enhancement of a LASIK procedure in adults younger than 30 years with high myopia and/or astigmatism and in any

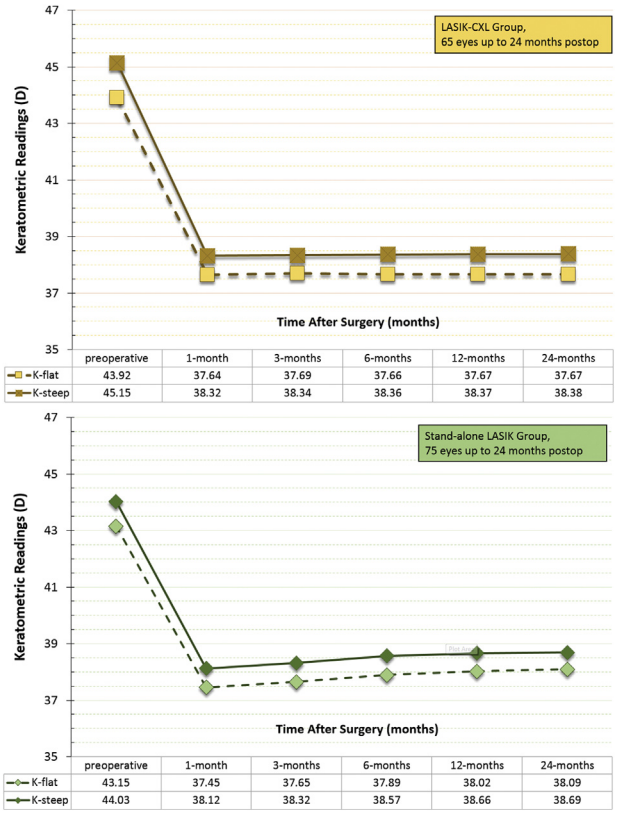

Figure 8. Stability of corneal keratometry in both groups expressed in diopters up to 2 years postoperatively (CXL = corneal collagen crosslinking; LASIK = laser in situ keratomileusis).

patient with a between-eye difference in the amount of astigmatism greater than 0.5 D. In our opinion, it does not merit "leniency" with preoperative forme fruste keratoconus criteria. All cases in this study, as well as in our previous reports, were screened thoroughly for signs of tomographic cornea irregularity.

In this study, we propose and document that keratometric stability may be a more objective measure of 2-year efficacy and the data indicate that this measure was statistically significantly better in the LASIK–CXL group ($P = .032$). In our opinion, this correlation is compelling. Also, regarding visual acuity results, the difference in the percentage of cases achieving a UDVA of 20/20 and 20/25 in the 2 groups was statistically significant ($P = .045$ and $P = .039$, respectively), with the LASIK–CXL group performing better.

In conclusion, LASIK combined with prophylactic CXL intervention in eyes with high myopia appears to provide predictability as well as refractive and keratometric stability. The data reported in this study provide evidence of the safety and efficacy of this approach. The adjuvant CXL procedure may provide enhanced corneal biomechanical stability, especially in highly myopic and younger eyes.

WHAT WAS KNOWN

- There can be regression after LASIK in high myopia treatments. This may reflect altered cornea biomechanical properties.
- Comparative clinical data are lacking about the combined procedure of LASIK with prophylactic CXL application.

WHAT THIS PAPER ADDS

- Laser in situ keratomileusis combined with CXL in patients with higher myopia appears to be a safe and effective treatment.
- Laser in situ keratomileusis combined with CXL appears to reduce the likelihood of postoperative regression.

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