



REVIEW

Lasik Xtra[®] Provides Corneal Stability and Improved Outcomes

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ABSTRACT

A new procedure which combines LASIK and corneal cross-linking (Lasik Xtra[®]) has been proposed as an alternative to traditional LASIK. It is aimed at restoring strength to the cornea, increasing stability in visual outcomes, increasing the accuracy of the refractive correction, and potentially lowering enhancement rates. This article reviews the current clinical evidence which has been published on the topic and reviews both the safety and efficacy argument for the procedure.

Keywords: Laser in situ keratomileusis; LASIK; Riboflavin; UVA mediated corneal cross-linking

INTRODUCTION

Laser in situ keratomileusis (LASIK) is the most commonly performed refractive procedure in the United States, due in part to rapid visual recovery, minimal postoperative discomfort, and perceived improvement in patient quality of life [1]. However, despite advancements in femtosecond and excimer laser technology, and the adoption of more thorough diagnostic screening approaches, the procedure is not without impact on the biomechanical properties of the cornea. LASIK requires the creation of a flap and the removal of tissue, which may result in weakening of the anterior corneal stroma and decreasing overall corneal rigidity [2, 3]. This may be one mechanism that contributes to regression of refractive effect leading to “enhancement” (retreatment) procedures [4]. In rare cases, weakening can result in corneal ectasia and associated progressive degradation of vision [5]. As the effects of corneal weakening become better understood, effort is being applied to reduce impact on treatment outcomes. A very promising approach for restoration of corneal stability in these instances is riboflavin/ultraviolet A (UVA)-mediated corneal cross-linking (CXL).

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CXL was first introduced in the late 1990s in Dresden, Germany as a means of stabilizing the cornea, and the procedure has been rapidly adopted outside of the United States as a standard therapy for treatment of keratoconus (KC) and iatrogenic corneal ectasia [6]. The conventional CXL treatment approach for KC and ectasia has been shown to not only stabilize the cornea, but to result in corneal flattening, on the order of more than 1 D [7]. Many of the mechanisms and controls underlying CXL have been studied and predictive chemical [8] and biomechanical methods [9, 10] have been developed to better understand CXL. Details of the mechanisms underlying CXL are an area of fertile research, beyond the scope of this paper.

While the initial cross-linking technique utilized a low irradiance (3 mW/cm^2) UVA source requiring 30 min of irradiation time, accelerated cross-linking techniques, first proposed 7 years ago [11], have more recently been introduced clinically to dramatically shorten procedure time [12]. Accelerated cross-linking using higher irradiance (30 mW/cm^2) has been demonstrated to be effective at stabilizing and reducing corneal curvature in patients with keratoconus or iatrogenic corneal ectasia. Studies have shown that its effects are equivalent to conventional CXL in terms of efficacy at stabilizing the cornea, with an equivalent or better safety profile [13–15].

LASIK in combination with CXL (Lasik Xtra[®] Avedro, Massachusetts, USA) is an alternative to traditional LASIK aimed at restoring strength to the cornea, increasing stability in visual outcomes, increasing the accuracy of the refractive correction, and potentially lowering enhancement rates. Corneal cross-linking has been shown to enhance the structural integrity of the cornea, in both animal studies [16] and in clinical practice, stiffening the cornea [17] and halting the progression of ectasia such as keratoconus [18]. It

is logical to anticipate that stiffening a cornea, which has been structurally weakened by LASIK, through the addition of CXL, may minimize the negative effects associated with this biomechanical compromise. In other words, the aim of Lasik Xtra is to further reduce the rare incidence of iatrogenic ectasia, as well as to reduce the rate of treatment regression and enhancements.

Although not yet approved in the United States, Lasik Xtra is in clinical use in more than 50 countries worldwide. The procedure is frequently performed on patients who are considered good candidates for the LASIK procedure, but may fall into categories associated with greater risk of post-LASIK regression: those with hyperopia [19] high amounts of myopia [20], younger patients and those with borderline-predicted residual stromal bed thickness [21].

This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

THE LASIK XTRA PROCEDURE

The Lasik Xtra procedure is performed as follows: the creation of the LASIK flap and the excimer ablation are performed in the usual manner; however, many surgeons adjust their treatment algorithm to account for reduction or elimination of regression, typically seen in LASIK and photorefractive keratectomy procedures. Lasik Xtra is performed immediately following the excimer ablation. Because the LASIK flap no longer contributes to the biomechanical strength of the cornea, the region of stroma targeted for CXL is the area directly beneath the ablation zone. At the completion of the excimer ablation, eyes receive 1–5 drops of Dextran-free riboflavin formulation (VibeX[™] Xtra Avedro, Massachusetts, USA), carefully applied to the

stromal bed (avoiding application to the LASIK flap). The riboflavin solution is allowed to soak for a period of up to 90 s after which the riboflavin is rinsed from the stroma using balanced salt solution. Once well rinsed, the LASIK flap is repositioned into place and the flap interface copiously irrigated and stroked into place. A 375 nm UV source with a homogenous 30mW/cm² top hat beam profile (KXL[®], Avedro, MA, USA) is then used to apply a 2.7 J/cm² dose of irradiation through the closed flap [22].

When used in conjunction with LASIK (Lasik Xtra), the goal of CXL is to restore corneal strength without creating an additional change in refraction beyond that provided by the LASIK correction. Traditional CXL, when applied to the ectatic cornea, is known to cause a flattening of the cornea of several diopters; therefore, it is important to consider the differences between Lasik Xtra and conventional CXL.

The soak and irradiance times described above differ significantly from the conventional CXL treatment protocol for KC and ectasia [23], with shorter total riboflavin soaking times and lesser total UVA dose. The direct application of riboflavin to the stroma afforded by the lifted LASIK flap reduces the required time for sufficient riboflavin to diffuse into the targeted area of the corneal stroma. Similarly, while cross-linking for treatment of ectasia is intended to stiffen a pathologically weak cornea, it is plausible that less cross-linking may be required to return an otherwise healthy cornea to its native strength subsequent to LASIK.

Theoretical modeling using finite element analysis by Dupps et al. at The Cleveland Clinic has demonstrated that focal weaknesses of the cornea result in the progressive topographic abnormalities observed in keratoconus, and that CXL results in dramatic flattening of

corneal curvature [24]. This finite element analysis model was applied by the same group to evaluate the impact of Lasik Xtra on response to deformation in the residual stromal bed when intra-ocular pressure is doubled, and the effect on refractive outcome. A myopic LASIK procedure with a −4.25 D spherical correction was simulated using a wavefront optimized ablation profile with an optical zone diameter of 6.5 mm and overall treatment diameter of 9 mm. The response to deformation and refractive correction was evaluated with and without the addition of simulated CXL, modeled as an increase in stiffness of the central 9 mm of the stromal bed with an effective depth of 200 μ and a stiffening factor of 1.5×. The addition of CXL resulted in less displacement when IOP was increased (ie, cornea is stiffer), however, simulations demonstrated refractive equivalence between the cross-linked and uncross-linked eyes [25]. This modeling demonstrated a theoretical basis for increasing the corneal stiffness without changing refractive outcome.

CLINICAL OUTCOMES

A number of clinical studies have been performed to evaluate the performance of Lasik Xtra using a variety of treatment methods, examining changes in tissue morphology, refractive stability and treatment safety. These studies are summarized in Table 1.

Tissue Morphology

In a case report using laser scanning in vivo confocal microscopy to evaluate a patient treated with Lasik Xtra, Mazzotta et al. [26] observed morphological changes including hyper-reflectivity and keratocyte apoptosis,

Table 1 Summary of Lasik Xtra[®] published research, including treatment protocols used and reported findings

| Author (year) | Eyes (n): Lasik Xtra, LASIK | Mean follow-up (months) | Mean age (years) | Mean pre-OP sphere | Riboflavin (%); soak time (s) | Irradiance (mW/cm ²); UVA time (s); Dose (J/cm ²) | Post-op sphere (longest follow-up) | Complications: Lasik Xtra group | Chief findings |
|--------------------------|-----------------------------|-------------------------|------------------|------------------------------|-------------------------------|---|------------------------------------|---|--|
| Celik (2012) | 4 | 12 | 29–39 | -5.56 ± 1.5 | 0.1; 1 drop | 30; 180; 5.4 | -0.18 ± 0.31 | Early stromal haze resolving within 1 month | UDVA equal to or better in the Lasik Xtra eye vs. LASIK alone eye in all cases. No decrease in CDVA or ECC in either group. No statistical differences in <i>K</i> from 1 to 12 months in either group |
| Tamayo (2012) | 66 42 | 1 | 27.28 26.55 | -2.97* -2.25* | 0.1; 60 | 30; 60; 1.8 | 0.49 0.17 | None | Postoperative visual recovery comparable between LASIK and Lasik Xtra groups |
| Kanellopoulos (2012) | 34 34 | 24 | - | +3.15 ± 1.46 +3.40 ± 1.78 | 0.1; 60 | 10; 180; 1.8 | -0.20 ± 0.56 +0.20 ± 0.40 | None | Lesser regression of <i>K</i> and refraction in the Lasik Xtra group (0.22 ± 0.31 Lasik Xtra vs. +0.72 ± 0.19, <i>p</i> = 0.0001) |
| Kanellopoulos (2012) [2] | 43 | 42 | 26 ± 7 | -7.5 ± 2.5* | 0.1; 60 | 10; 180; 1.8 | -0.2 ± 0.50* | None | No loss in ECC, no loss of CDVA, <i>K</i> stability through 24 month follow-up |

Table 1 continued

| Author (year) | Eyes (n): Lasik Xtra, LASIK | Mean follow-up (months) | Mean age (years) | Mean pre-OP sphere | Riboflavin (%); soak time (s) | Irradiance (mW/cm ²); UVA time (s); Dose (J/cm ²) | Post-op sphere (longest follow-up) | Complications: Lasik Xtra group | Chief findings |
|----------------------|-----------------------------|-------------------------|--------------------------|------------------------------|-------------------------------|---|------------------------------------|---|---|
| Aslanides (2013) | 5 5 | 48 36 | 39 42 | +3.6 ± 2.10 +4.15 ± 2.00 | 0.1; 120 | 3; 1800; 5.4 | - - | Early stromal haze resolving within 1 month | Predictable refractive outcome with 4 (80%) of eyes in the Lasik Xtra group achieving plano MRSE and 1 eye having myopia of 0.25 D at 1 month follow-up. Non-significant trend toward greater refractive stability in the Lasik Xtra group |
| Kanellopoulos (2014) | 67 72 | 6 | 27.5 ± 6.1 24.2 ± 5.8 | -6.58 ± 2.31 -5.13 ± 1.59 | 0.1; 60 | 30; 80; 2.4 | -0.20 ± 0.28 -0.20 ± 0.30 | None | Evaluation of epithelial thickness changes: no significant differences between groups, except in the -8.00 to -9.00 subgroup, where significantly less changes in epithelial thickness were observed in the standalone Lasik Xtra group |

Table 1 continued

| Author (year) | Eyes (n); Lasik Xtra, LASIK | Mean follow-up (months) | Mean age (years) | Mean pre-OP sphere | Riboflavin (%); soak time (s) | Irradiance (mW/cm ²); UVA time (s); Dose (J/cm ²) | Post-op sphere (longest follow-up) | Complications: Lasik Xtra group | Chief findings |
|--------------------------|-----------------------------|-------------------------|------------------|--------------------|-------------------------------|---|------------------------------------|---------------------------------|---|
| Kanellopoulos (2014) [2] | 73 | 12 | 27.1 ± 6.0 | -6.62 ± 2.12 | 0.1; 60 | 30; 80; 2.4 | -0.19 ± 0.17* | None | Reduced refractive drift in the Lasik Xtra vs. LASIK alone group (<i>p</i> = 0.063). Increased <i>K</i> stability in the Lasik Xtra group (+0.03 and +0.05 D vs. +0.67 and +0.55 change in steep and flat <i>K</i> , Lasik Xtra vs. Lasik, respectively; <i>p</i> = 0.039) |
| | 82 | | 24.9 ± 5.9 | -5.05 ± 1.74 | - | - | -0.27 ± 0.23* | None | |
| Mazzotta (2014) | 1 | 6 | 33 | -5.00 | 0.25; 90 | 30; 90; 2.7 | - | None | In vivo confocal microscopy reveals changes consistent with corneal cross-linking beyond the flap-stroma interface to a depth of 160µm. No adverse effects at the interface or endothelium |

Table 1 continued

| Author (year) | Eyes (n): Lasik Xtra, LASIK | Mean follow-up (months) | Mean age (years) | Mean pre-OP sphere | Riboflavin (%); soak time (s) | Irradiance (mW/cm ²); UVA time (s); Dose (J/cm ²) | Post-op sphere (longest follow-up) | Complications: Lasik Xtra group | Chief findings |
|---------------|-----------------------------|-------------------------|---------------------------|------------------------------|-------------------------------|---|------------------------------------|---|---|
| Tan (2015) | 70 64 | 3 | 34.56 ± 9 31.29 ± 8.44 | -8.73 ± 1.82 -8.52 ± 1.13 | 0.25; 45 | 30; 45; 1.35 - | -0.10 ± 25* -0.38 ± 0.50* | None | Greater percentage of eyes within ±0.50 D of intended MRSE correction in the Lasik Xtra group (88%) vs. the Lasik alone group (65%) <i>p</i> = 0.005. No significant differences were observed in cylinder correction or stability of <i>K</i> between groups |
| Tomita (2014) | 24 24 | 12 | 30.4 ± 4.7 | -4.03 ± 1.97 -4.05 ± 2.04 | 0.1; 60 | 30; 60; 1.8 | 0.15 ± 0.38 0.20 ± 0.35 | Mild edema observed at 1 day, resolved by 1 week. Superficial punctate keratitis in 1 eye of each group | Demarcation line with mean depth of 200.04 ± 27.01 μm (178–278 μm) in 95.8% of eyes. No significant differences in visual or <i>K</i> outcomes between groups. No significant differences in ECC between groups |

Table 1 continued

| Author (year) | Eyes (n): Lasik Xtra, LASIK | Mean follow-up (months) | Mean age (years) | Mean pre-OP sphere | Riboflavin (%); soak time (s) | Irradiance (mW/cm ²); UVA time (s); Dose (J/cm ²) | Post-op sphere (longest follow-up) | Complications: Lasik Xtra group | Chief findings |
|----------------------|-----------------------------|-------------------------|------------------|--------------------|-------------------------------|---|------------------------------------|---------------------------------|---|
| Kanellopoulos (2015) | 65 | 24 | 27.5 ± 6.1 | -6.60 ± 2.02 | 0.1; 60 | 30; 80; 2.4 | -0.18 ± 0.17* | None | Greater % of cases achieved UDVA of 20/20 or better ($p = 0.045$) or 20/25 or better ($p = 0.039$) in the Lasik Xtra group vs. the LASIK alone group. Less refractive ($p = 0.065$) and K ($p = 0.032$) regression in the Lasik Xtra group vs. the LASIK alone group over 24 months ($p = 0.065$). No significant decrease of ECC in either group |
| | 75 | | 24.2 ± 5.8 | -5.14 ± 1.74 | - | - | -0.32 ± 0.24* | | |

CDVA spectacle-corrected distance visual acuity, *ECC* Endothelial cell count, *K* keratometry, *MRSE* Manifest Refractive Spherical Equivalent, *UDVA* unaided distance visual acuity

* MRSE rather than sphere reported

- Data not available or not applicable

which are consistent with conventional corneal cross-linking. The stromal depth of these features was 150–160 μm , shallower than conventional CXL. This was for a treatment using VibeX Xtra, soaking on the stromal bed for 90 s, and illuminated at 30 mW/cm^2 for a total dose of 2.7 J/cm^2 . Keratocyte repopulation occurred by 6 months postoperatively, and no endothelial damage was observed. These preliminary findings suggest, as expected, microstructural changes which occur in Lasik Xtra and are similar to those found with conventional cross-linking.

Increased Stability in Visual Outcomes

International studies have shown the benefits of Lasik Xtra for patients with high myopic and high hyperopic corrections.

Kanellopoulos [27] reported 2-year follow-up on a cohort of 34 consecutive patients treated using Lasik Xtra in conjunction with bilateral, topography-guided Hyperopic LASIK treatment. Hyperopic LASIK is well understood to be subject to significant regression of LASIK treatment effect. In this study, patients received LASIK + CXL in one eye (CXL group) and LASIK without CXL in the contralateral eye (no CXL group). In the CXL group, a single drop of riboflavin solution was placed under the flap after excimer ablation. The flap was repositioned, and the CXL eye was irradiated through the closed flap with 10 mW/cm^2 UVA light for 3 min (KXL). Follow-up evaluations included refraction, keratometry, topography and tomography. At baseline, mean spherical equivalent refractive error (MRSE), cylinder, and uncorrected distance visual acuity (UDVA) (decimal) were equivalent in the CXL and no CXL groups, with MRSE $+3.15 \pm 1.46$ D, cylinder 1.20 ± 1.18 D, and UDVA of 0.1 ± 0.26 in the CXL group and MRSE

$+3.40 \pm 1.78$ D, cylinder 1.40 ± 1.80 D and UDVA of 0.1 ± 0.25 in the no CXL group. Mean MRSE at 2 years postoperatively was -0.20 ± 0.56 D and $+0.20 \pm 0.40$ D in the CXL and no CXL groups, respectively. Mean UDVA was 0.95 ± 0.15 (CXL group) and 0.85 ± 0.23 (no CXL group). Greater refractive regression was observed in the no CXL group ($+0.72 \pm 0.19$ D) vs. the CXL group ($+0.22 \pm 0.31$ D) ($p = 0.0001$).

The same group evaluated the effect of Lasik Xtra on epithelial thickness profiles in myopic patients [28]. One hundred thirty-nine consecutive eyes undergoing LASIK for myopic correction were enrolled in this prospective study. Mean baseline refractive error was -6.58 ± 2.31 D sphere, with cylinder -1.39 ± 1.4 . Eyes were treated with LASIK + CXL (Lasik Xtra group, $n = 67$) or standalone LASIK (LASIK-only group, $n = 72$). Riboflavin solution was applied to the stromal bed in the Lasik Xtra group immediately after completion of the excimer ablation. Riboflavin was soaked for 60 s and then rinsed from the eye prior to repositioning of the flap. The Lasik Xtra eyes were then irradiated with 30 mW/cm^2 UVA for 80 s (KXL). LASIK-only eyes did not receive CXL. Eyes in each treatment group were divided into subgroups for evaluation by intended refractive correction. In the high myopia subgroups, statistically significant differences in the mid-peripheral epithelial thickness profile were observed between the Lasik Xtra and LASIK-only group. In the “ -7.00 to -8.00 D” subgroup, mid-peripheral epithelial thickness increased by 3.95 μm in the Lasik Xtra treatment group vs. 7.14 μm in the LASIK-only group ($p = 0.041$). In the “ -8.00 to -9.00 D” subgroup, mid-peripheral epithelial thickness increased by 3.79 μm in the Lasik Xtra group vs. 9.32 μm in the LASIK-only group ($p = 0.032$). No statistically significant

differences were observed in the subgroups with lower myopia. The authors proposed that the greater epithelial hyperplasia observed in the highly myopic LASIK-only groups may be correlated with greater refractive regression, and that less hyperplasia may be observed in the matched Lasik Xtra groups due to greater stromal biomechanical stability resulting in less oscillation of the cornea.

Kanellopoulos also reported a 2-year follow-up of a prospective observational longitudinal study of 140 consecutive eyes enrolled for myopic LASIK correction. Sixty-five eyes in this cohort underwent Lasik Xtra according to treatment protocol described in the previous study. After 24 months follow-up, UDVA was better than 20/20 in a greater percentage of eyes in the Lasik Xtra group (93.8%) than in the LASIK-only group (84.8%) ($p = 0.045$). Good refractive accuracy was obtained in both groups, with linear regression of the scatterplot of attempted vs. achieved correction revealing a coefficient of determination (r^2) of 0.975 in the LASIK Xtra group vs. 0.968 in the LASIK-only group. However, 2-year postoperative mean MRSE showed greater refractive shift in the LASIK-only group vs. the Lasik Xtra group ($p = 0.065$), supported by a similar difference in keratometric stability ($p = 0.032$). [20].

A study by a group in Singapore provides further support for refractive stability improvement associated with Lasik Xtra for high myopia [29]. In this study, 70 consecutive eyes undergoing LASIK for correction of high myopia (-8.00 to -19.00 D manifest refractive spherical equivalent) were prospectively recruited and treated with Lasik Xtra and compared with a retrospective consecutive control group of 64 eyes who had undergone LASIK alone for correction of high myopia. Immediately following the laser

ablation, while the flap remained in the taco position, the stromal bed of the Lasik Xtra eyes was coated with 6–8 drops of dextran-free isotonic riboflavin-5-phosphate 0.25% solution in normal saline (VibeX Xtra). After 45 s, the riboflavin was rinsed from the stromal bed using balanced salt solution (BSS), and the flap was carefully repositioned over the stromal bed. Additional rinsing with BSS was performed after the flap was replaced. After confirming that the flap was properly positioned, the KXL device was used to apply 365 nm UVA light exposure for 45 s at a power of 30 mW/cm² for a total energy dose of 1.35 J/cm² to the Lasik Xtra eyes, through the closed flap. At 3 months follow-up, 61% of LASIK-only eyes achieved UDVA of 20/25 or better, compared to 98% of Lasik Xtra eyes ($p < 0.001$). A greater percentage of eyes were within ± 0.50 of the intended correction in the Lasik Xtra group (88%) than in the LASIK-only group (65%) at 3 months ($p = 0.005$). Linear regression of the scatterplot of attempted vs. achieved correction reveals a coefficient of determination of 0.83 in the LASIK-only group vs. 0.99 in the Lasik Xtra group. A trend ($p = 0.051$) towards greater refractive drift in the LASIK group (-0.13 D) vs. the Lasik Xtra group (-0.04 D) was observed.

Treatment Safety

CXL treatment for KC and corneal ectasia has been found to have a low rate of side effects. It is not surprising that, as Lasik Xtra produces similar tissue effects to these treatments, and uses lower doses for treatment effect, the safety profile is favorable.

In addition to the studies described above, in which there were no side effects beyond those typically associated with LASIK treatment, several papers have looked at the safety of this prophylactic treatment.

The earliest study was a pilot fellow-eye case series in 4 subjects with 12-month follow-up conducted in Turkey [30]. At the 12-month follow-up, the Lasik Xtra group had a UDVA and manifest refraction equal to or better than those in the LASIK-only group. No eye lost 1 or more lines of spectacle-corrected distance visual acuity at the final visit. The endothelial cell loss in the Lasik Xtra eye was not greater than in the fellow eye. No side effects were associated with either procedure.

A Japanese study [31] found Lasik Xtra to be safe. In this study, 24 bilateral myopic LASIK patients underwent unilateral accelerated cross-linking with the KXL system in the non-dominant eye. After LASIK, riboflavin 0.1% was instilled in the residual stromal bed for 60 s. After the riboflavin was washed out and the flap was placed in its original position, UVA light (30 mW/cm^2) was administered for 60 s, and the Lasik Xtra eyes were compared with the LASIK-only eyes. As anticipated, increased hyper-reflectivity and a demarcation line similar to that seen after cross-linking were observed in the Lasik Xtra eyes. A demarcation line (mean depth $200.04 \mu\text{m} \pm 27.01$, range 178–278 μm) was observed in 23 eyes (95.8%). The line was well-defined in two eyes (8.3%) and faint in 21 eyes (87.5%). The study found no significant differences in corrected and uncorrected distance visual acuity, manifest refraction spherical equivalent, endothelial cell density, or 37 parameters dynamic bidirectional applanation readings.

Additionally, in another large study of routinely treated subjects [21], 601 Lasik Xtra patients showed stable uncorrected distance visual acuity over 1 year of follow-up. These patients showed no significant changes in manifest refraction spherical equivalent and average K readings during the 1-year follow-up.

Most recently, TLC Laser Eye Centers[®], in Toronto, Canada performed a safety and efficacy analysis on a series of 30 patients (data on file). In this series, data were gathered on 30 consecutive Lasik Xtra cases, with patients selected to be at higher risk of regression, i.e., those with high myopia (from -8 to -10) or hyperopia, high astigmatism, or mixed astigmatism. Data are being gathered on the long-term efficacy, but the safety profile of the procedure has been extremely positive, with no adverse events.

DISCUSSION

CXL has been utilized in clinical practice for more than 15 years. The procedure has an exemplary history of safety and efficacy, as reported in over 100 clinical studies. While treatment of KC and corneal ectasia are the mainstays of these publications, applications include treatment of corneal infections and ulcerations (keratitis), and, of course treatment in conjunction with refractive surgery.

As described above, Lasik Xtra extends the application of CXL. The reduction in treatment dose, compared to treatment of KC and ectasia suggests a reduction in risk of treatment-related side effects. In six studies, evaluating over 600 eyes, no significant side effects have been associated with treatment.

Lasik Xtra treatment has been shown to significantly improve post-LASIK refractive stability, when compared to LASIK alone. This has been shown for both myopic and hyperopic refractive treatments, particularly in those with high diopter corrections who are at greater risk of refractive drift. And while the number of treatments and follow-up is not sufficient to draw definitive conclusions regarding the ability of Lasik Xtra to reduce the risk of

corneal ectasia, the treatment profile may support prophylactic use.

The combination of low-risk profile and significant improvement in refractive stability supports Lasik Xtra as a promising adjunct to LASIK in reducing the likelihood of enhancement procedures, particularly in those patients with high diopter corrections, and those with hyperopic corrections. Four studies that included a total of 41,468 eyes have found that LASIK has an average retreatment rate of 12%. Most of these occur during the first 2 years after the LASIK procedure [4, 32–34]. If the refractive results with Lasik Xtra are truly more stable, this should logically result in lower retreatment rates over time.

CONCLUSION

Lasik Xtra is a new, innovative procedure, aimed at reducing some of the challenges associated with LASIK (weaker corneas, and regression of the refraction over time). As the clinical evidence concerning the procedure continues to grow, many practices are finding that Lasik Xtra is a worthwhile addition to their armamentarium. The clinical benefits of this new application of cross-linking technology are welcome by both patients and practitioners alike and continued careful evaluation of outcomes is warranted.

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manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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Compliance with ethics guidelines. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

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REFERENCES

1. Solomon KD, Fernández de Castro LE, Sandoval HP, et al. LASIK world literature review: quality of life and patient satisfaction. *Ophthalmology*. 2009;116(4):691–701.
2. Jaycock PD, Lobo L, Ibrahim J, Tyrer J, Marshall J. Interferometric technique to measure biomechanical changes in the cornea induced by refractive surgery. *J Cataract Refract Surg*. 2005;31:175–84.
3. Binder PS. Analysis of ectasia after laser in situ keratomileusis: risk factors. *J Cataract Refract Surg*. 2007;3:1530–8.

4. Yuen LH, Chan WK, Koh J, Mehta JS, Tan DT. A 10-year prospective audit of LASIK outcomes for myopia in 37,932 eyes at a single institution in Asia. *Ophthalmology*. 2010;117:1236–44.
5. Randleman JB, Russell B, Ward MA, Thompson KP, Stulting RD. Risk factors and prognosis for corneal ectasia after LASIK. *Ophthalmology*. 2003;110:267–75.
6. Raiskup F. et al. Corneal collagen crosslinking with riboflavin and ultraviolet-A light in progressive keratoconus: ten-year results. *J Cataract Refract Surg*. 2015;41(1):41–46.
7. Sorkin N, Varssano D. Corneal collagen crosslinking: a systematic review. *Ophthalmologica*. 2014;232(1):10–27.
8. Kamaev P, Friedman MD, Sherr E, Muller D. Photochemical kinetics of corneal cross-linking with riboflavin. *Invest Ophthalmol Vis Sci*. 2012;53(4):2360–7.
9. Roy AS, Dupps WJ. Patient-specific computational modeling of keratoconus progression and differential responses to collagen cross-linking. *Investig Ophthalmol Vis Sci*. 2011;52(12):9174–87.
10. Kling S, Remon L, Pérez-Escudero A, Merayo-Llodes J, Marcos S. Corneal biomechanical changes after collagen cross-linking from porcine eye inflation experiments. *Investig Ophthalmol Vis Sci*. 2010;51(8):3961–8.
11. Krueger RR, Herekar S, Spoerl E. First proposed efficacy study of high vs. standard irradiance and fractionated riboflavin/UVA cross-linking with equivalent energy exposure. *Eye Contact Lens*. 2014;40(6):353–7.
12. Lytle G. Advances in the technology of corneal cross-linking for keratoconus. *Eye Contact Lens*. 2014;40(6):358–64.
13. Kanellopoulos AJ. Long term results of a prospective randomized bilateral eye comparison trial of higher fluence, shorter duration ultraviolet A radiation, and riboflavin collagen cross linking for progressive keratoconus. *Clin Ophthalmol*. 2012;6:97–101.
14. Mita M, Waring GO, Tomita M. High-irradiance accelerated collagen crosslinking for the treatment of keratoconus: six-month results. *J Cataract Refract Surg*. 2014;40(6):1032–40.
15. Tomita M, Mita M, Huseynova T. Accelerated versus conventional corneal collagen crosslinking. *J Cataract Refract Surg*. 2014;40(6):1013–20.
16. Wollensak G, Spoerl E, Seiler T. Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. *J Cataract Refract Surg*. 2003;29(9):1780–5.
17. Scarcelli G, et al. Brillouin microscopy of collagen crosslinking: noncontact depth-dependent analysis of corneal elastic modulus. *Invest Ophthalmol Vis Sci*. 2013;54(2):1418–25.
18. Chang CY, Hersh PS. Corneal collagen cross-linking: a review of 1-year outcomes. *Eye Contact Lens*. 2014;40(6):345–52.
19. Aslanides IM, Mukherjee AN. Adjuvant corneal crosslinking to prevent hyperopic LASIK regression. *Clin Ophthalmol (Auckl N Z)*. 2013;7:637–41.
20. Kanellopoulos AJ, Asimellis G. Combined laser in-situ keratomileusis and prophylactic high fluence corneal collagen cross-linking for high myopia: two years safety and efficacy. *J Cataract Refract Surg*. 2015;41(7):1426–33.
21. Tomita M. LASIK Xtra in Clinical Practice. In: Presentation at: American Academy of Ophthalmology; 2013 Nov 16–19. New Orleans, USA.
22. Avedro product literature: KXL cross-linking protocols for Lasik Xtra™, keratoconus and corneal ectasia. April 2015. MA-00255C.
23. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135(5):620–7.
24. Roy AS, Dupps WJ. Patient-specific computational modeling of keratoconus progression and differential responses to collagen cross-linking. *Invest Ophthalmol Vis Sci*. 2011;52(12):9174–87.
25. Seven I, Roy AS, Dupps WJ. Adjunctive collagen crosslinking of the residual stromal bed in LASIK: finite element analysis of impact on refractive outcome and surgically induced deformation. *Invest Ophthalmol Vis Sci*. 2014;55:E-Abstract 2990.
26. Mazzotta C, Balestrazza A, Traversia C, Caragiulia S, Caporossib A. In vivo confocal microscopy report after lasik with sequential accelerated corneal collagen cross-linking treatment. *Case Rep Ophthalmol*. 2014;5:125–131.
27. Kanellopoulos AJ, Kahn J. Topography-guided hyperopic LASIK with and without high irradiance collagen cross-linking: initial comparative clinical findings in a contralateral eye study of 34 consecutive patients. *J Refract Surg*. 2012;28(11):S837–40.
28. Kanellopoulos AJ, Asimellis G. Epithelial remodeling after femtosecond laser-assisted high

- myopic LASIK: comparison of stand-alone with LASIK combined with prophylactic high-fluence cross-linking. *Cornea*. 2014;33(5):463–9.
29. Tan J, Lytle GE, Marshall J. Consecutive laser in situ keratomileusis and accelerated corneal crosslinking in highly myopic patients: preliminary results. *Eur J Ophthalmol*. 2015;25(2):101–7.
30. Celik HU, Alagöz N, Yildirim Y, et al. Accelerated corneal crosslinking concurrent with laser in situ keratomileusis. *J Cataract Refract Surg*. 2012;38(8):1424–31.
31. Tomita M, Yoshida Y, Yamamoto Y, Mita M, Waring G. In vivo confocal laser microscopy of morphologic changes after simultaneous LASIK and accelerated collagen crosslinking for myopia: One-year results. *J Cataract Refract Surg*. 2014;40:981–990 (Q 2014 ASCRS and ESCRS).
32. Alió JL, Muftuoglu O, Ortiz D, Pérez-Santonja JJ, Artola A, Ayala MJ, Garcia MJ, De Luna GC. Ten-year follow-up of laser in situ keratomileusis for high myopia. *Am J Ophthalmol*. 2008;145(1):46–54.
33. Hersh PS, Fry KL, Bishop DS. Incidence and associations of retreatment after LASIK. *Ophthalmology*. 2003;110:748–54.
34. Randleman JB, White AJ, Lynn MJ, Hu MH, Stulting RD. Incidence, outcomes, and risk factors for retreatment after wave front-optimized ablations with prk and LASIK. *J Refract Surg*. 2009;25(3):273–6.