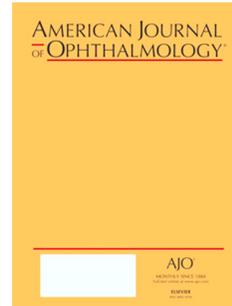


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Comparison of Femto-LASIK with combined Accelerated Crosslinking to Femto-LASIK in high myopic eyes: a prospective randomized trial

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Abstract:

Purpose: To evaluate the safety and efficacy of femtosecond (FS) laser-assisted in situ keratomileusis (LASIK) combined with accelerated corneal crosslinking (LASIK Xtra) compared to conventional FS-LASIK (convLASIK) in high myopic patients.

Design: Prospective, randomized, fellow-eye controlled, clinical trial.

Methods:

Setting: Department of Ophthalmology, Goethe University, Frankfurt/Germany.

Study Population: 26 patients with high myopia and/or myopic astigmatism received randomized treatment with LASIK Xtra (30 mW/cm², 90 seconds with continuous UVA) in one eye and convLASIK in the other eye.

Main outcome measures: Uncorrected distance visual acuity (UDVA), best spectacle corrected VA (BSCVA), manifest spherical equivalent (MRSE), endothelial cell count (ECC) and corneal thickness.

Results: The UDVA improved from 1.26±0.13logMAR preoperative to -0.02±0.15logMAR in LASIK Xtra eyes and from 1.27±0.12logMAR to 0.01±0.15LogMAR in the convLASIK eyes ($p>0.05$). The MRSE changed from -7.35±1.15D and -7.5±1.12D to -0.17±0.43D and -0.25±0.46D, respectively. There was no significant difference in outcomes between both groups during the 12 months follow-up except the conLASIK eyes showing slightly better BSCVA after 1 week ($p<0.05$). ConvLASIK eyes revealed a non-significant trend towards myopic regression from 3 to 12 months postoperative with a change in MRSE of -0.15D compared to -0.1D in LASIK Xtra eyes. Topography showed stability of corneal curvature with no signs of keratectasia in both groups at 12 months.

Conclusion: While apparently safe, LASIK Xtra showed no advantages over conventional LASIK. At 12 months, both groups showed no difference regarding UDVA and refractive stability, and no signs of keratectasia.

**Comparison of Femto-LASIK with combined Accelerated Crosslinking to
Femto-LASIK in high myopic eyes: a prospective randomized trial**

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Short title: LASIK combined with accelerated crosslinking in myopic eyes

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Five keywords: Myopia, LASIK, crosslinking, post-LASIK ectasia, myopic regression

Introduction

Because of increasing numbers of myopia in the world population ¹ and demands of patients regarding esthetics, an active lifestyle, and occupational requirements for first responders, military, athletes, media, and other professions, along with long-term financial benefits and decreased risk compared to contact lens wear ², there is an increasing request for surgical correction of refractive errors as myopia, hyperopia, and astigmatism . Due to the low risk of severe complications, the fast visual rehabilitation and the effectiveness of refractive surgery, especially the less invasive procedures like femtosecond-assisted laser in situ keratomileusis (fs-LASIK) register a rising demand . One very rare but severe complication is the so called post LASIK ectasia where, due to the cut of the corneal flap and intraoperative ablation of corneal stroma, the cornea is biomechanically weakened and starts to develop an ectasia . Risk factors would include the amount of tissue altered and therefore the residual stromal thickness of the cornea, hyperopic treatments, and young age ^{3,4} Another complicating development, which may be less severe but resulting in patient aggravation and dissatisfaction is the development of myopic regression after the treatment.

Crosslinking was first described in 1997 by Spöerl et al and evolved into a widely used option for keratectasia treatment in keratoconus patients ⁵. Since corneal Riboflavin UV-Crosslinking is a safe and efficacious way to stabilize the cornea of keratoconus and post LASIK ectasia eyes ⁶⁻⁸ LASIK protocols with intraoperative accelerated crosslinking were developed. There exists some current evidence showing that patients do have a prolonged visual recovery after LASIK treatment combined with accelerated crosslinking (LASIK Xtra), but that it seems to be equally safe and efficacious as compared to the conventional LASIK ⁹⁻¹¹. A recent review states LASIK Xtra is reducing some of the challenges associated with conventional LASIK as biomechanically weakening of corneas and regression of refraction ¹⁰ but there is still rarely adequate evidence to prove that these are reduced in patients with combined crosslinking compared to LASIK alone.

Therefore, crosslinking could be considered in daily clinical practice, especially for patients with medium to high ectasia risk scores (ERS) as patients suffering from high myopia. Thus, it needs to be demonstrated that these treatment protocols show superior long term outcomes regarding refractive stability and less risk for the development of ectasia⁴. This randomized, contralateral-eye controlled study was conducted to test whether eyes with increased ERS scores can be safely treated, and evaluate how LASIK Xtra affects outcomes in this population.

Methods

Study design

In this prospective, randomized, fellow-eye controlled, comparative clinical trial, 26 patients with myopia and / or myopic astigmatism from -6.00D to -12.00D underwent LASIK Xtra in one eye and convLASIK in the other eye at the Department of Ophthalmology at Goethe University, Frankfurt am Main, Germany. The study protocol was approved by the local ethics committee and the tenets of the Declaration of Helsinki were followed. All patients signed an informed consent form. The hypotheses of the study were that convLASIK and LASIK Xtra show similar refractive and optical outcomes, that both can be considered safe procedures, that LASIK Xtra shows potential to improve postoperative refractive stability regarding myopic regression, and that it therefore could lower the risk of post LASIK ectasia. The randomization was performed by the same study nurse for all patients. For each patient the eye that received the intraoperative crosslinking was determined after the study nurse pulled a small piece of paper with either “left” or “right” out of a raffle box. There was the same amount of left and right eyes (26) in the box at the beginning of the trial.

The trial is registered at clinicaltrials.gov, registration number: NCT 03913338.

Surgical procedures

The patients were treated by two different procedures. One eye was randomly selected to receive a convLASIK while the other eye received the LASIK Xtra procedure, which combines fs-LASIK with intraoperative accelerated UV-riboflavin crosslinking. After cutting the fs-LASIK flap and ablation the corneal bed was saturated with 5 drops of dextran-free riboflavin ophthalmic solution (VibeX Xtra, Avedro Inc., USA) and after 90 seconds rinsed with NaCl 0.9%. The flap was repositioned and the cornea was irradiated through the closed flap with UV-A light $30\text{mW}/\text{cm}^2$ for 90 seconds (Figure 1) with the KXL System (Avedro Inc., USA). Both types of fs-LASIK procedures were performed as a routine procedure according to the clinic's standard by a single surgeon (T.K.) at the Department of Ophthalmology, Goethe-University, Frankfurt, Germany. The LASIK flaps were created by using the Intralase FS60 femtosecond laser system (AMO/Abbott, USA)¹², the ablation of the cornea was done with the Armaris 750 excimer laser platform (Schwind, Kleinostheim, Germany). The amount and duration of the UVA radiation was set by the consideration that the strengthening of the cornea depends on the overall amount of radiant exposure ($30\text{mW}/\text{cm}^2$ for 90 seconds; $2.7\text{J}/\text{cm}^2$)¹³. Similar protocols of accelerated crosslinking have already seemed to strengthen the corneal tissue in previous trials¹⁴. There was no nomogram adjustment used in both groups.

Outcome parameter

Primary objectives were uncorrected and corrected distance visual acuity, and manifest refractive spherical equivalent 1 week, 1, 3, 6, and 12 months postoperative (LogMAR). Secondary objectives were manifest refraction, manifest astigmatism, endothelial cell count (ECC, cells/ mm^2), and corneal thickness (μm). ECC was measured by the Nidek CEM-530 (Nidek Co, Japan) three times in the central cornea per eye and the mean of those measurements was used. Corneal thickness was measured by Pentacam (Oculus, Germany). The optician who performed the visual testing and the measurements was blinded regarding which eye received the intraoperative crosslinking.

Ectasia Risk Score:

The ectasia risk score (ERS) does describe the risk of a possible ectasia after corneal refractive surgery in patients ⁴. It consists out of multiple parameters, each given a score depending on the patients attributes, and adding up to a score from 0 - to 4 points in 5 categories. The following parameters are evaluated: Residual stromal bed thickness (RSB; $>300\mu\text{m}$ = 0 points), age (>30 = 0 points), corneal thickness (CT; $>510\mu\text{m}$ = 0 points), spherical equivalent manifest refraction (MRSE -8 diopter less = 0 points), and corneal topography (e.g. symmetric bowtie = 0 points).

A score of 4 ore more implicates a high risk for postoperative ectasia.

Patients

Inclusion criteria were that patients were eligible for bilateral myopic fs-LASIK with -6.00 to -12.00 D (diopters) with a maximum of 5.00 D astigmatism, age > 18 years and provided written informed consent. The difference between the MRSE and cycloplegic SE was limited to 0.75 D and the MRSE needed to be stable for the last 12 months (<0.5 D). Exclusion criteria were prior corneal surgery, forme fruste or manifest keratoconus, history of corneal scarring, melting, ulceration or repeating inflammations of the eye and taking vitamin C 1 week prior to the treatment. We enrolled 26 patients (52 eyes).

Statistics

A sample size calculation was performed by the department of biostatistics at the Department of Ophthalmology, Goethe University, Frankfurt, Germany. To detect a mean difference of 0.1 logMAR with a standard deviation of 0.15 logMAR, 20 eyes per group were determined as minimal sample size for a significance level (α) of 0.05 and a test power of 0.8. Parameters were tested for normal distribution by the Kalmogorov-Smirnov test. In the absence of normal distribution, a Wilcoxon-Mann-Whitney-test was performed. If normal distribution was given we performed a paired t-test. A result was considered statistically significant if the p-value was

under 0.05. For statistical analysis, Excel 2010 (Microsoft Corporation) and SPSS Statistics 24 (IBM Corporation) were used.

Results

Preoperative

We included 26 patients, 16 (61%) women and 10 men (39%). The mean age was 35 ± 13 years in both groups. The mean preoperative UDVA and BSCVA was 1.26 ± 0.13 logMAR and -0.03 ± 0.09 logMAR for LASIK Xtra and 1.27 ± 0.12 logMAR and -0.03 ± 0.13 logMAR for the convLASIK group respectively. The preoperative MRSE was -7.5 ± 1.2 D for the convLASIK and -7.35 ± 1.15 D for the LASIK Xtra eyes and astigmatism was -0.66 ± 0.63 D and -0.68 ± 0.6 D respectively. The ECC (cells/mm²) were 2647 ± 226 cells/mm² and 2616 ± 196 cells/mm², the mean corneal thickness was 554 ± 27 μ m for both groups. There was no significant difference in preoperative parameter between both groups (table 1). The preoperative ERS was not statistically different between the groups, 11 eyes had a ERS of 4 or higher.

Complete 12-month data from 23 out of 26 patients was available for statistical analysis. One patient died during the follow-up period due to factors unrelated to the treatment and 2 patients did not show up for the last visit (loss of follow-up). The data of those 3 patients was included in the 1 week, 1,3 and 6 months data but excluded for the 12 months analysis.

Visual acuity

The UDVA changed in the convLASIK group from preoperatively 1.27 ± 0.12 logMAR to 0.01 ± 0.15 logMAR postoperatively and in the LASIK Xtra group from 1.26 ± 0.13 logMAR to -0.02 ± 0.15 logMAR 12-months after treatment. The change of visual acuity from pre- to postoperative was statistically significant in both groups ($p<0.001$), but not in between the groups, after 12 months. The BSCVA changed from -0.03 ± 0.13 logMAR to -0.08 ± 0.1 logMAR and -0.03 ± 0.09 logMAR to -0.09 ± 0.09 logMAR in the convLASIK group and the LASIK Xtra group respectively (table 2). There was no statistically significant difference between pre- and

postoperative or between both groups. The BSCVA 1, 3, 6, and 12 months after treatment can be found for both groups in figure 2 and table 2. The only statistically significant difference regarding the visual acuity was a better BSCVA in the convLASIK group after 1 month with -0.04 ± 0.1 logMAR compared to 0.01 ± 0.1 logMAR in the LASIK Xtra group ($p=0.008$). 87% of the convLASIK group and 96% of the LASIK Xtra eyes had a BSCVA of 0.0 logMAR or better. There was no eye in both groups that lost 2 or more lines of BSCVA (figure 3). 83% of the convLASIK and 91% of the Lasik Xtra eyes had a UDVA of 0.1 logMAR or better (figure 4).

MRSE

The manifest refraction was measured after 1 week, 1, 3, 6, and 12 months postoperative and is listed in table 2. The MRSE was $-0.05 \pm 0.34D$ after one month and $-0.17 \pm 0.43D$ after one year in the LASIK Xtra and $-0.1 \pm 0.3D$ and $-0.25 \pm 0.46D$ in the convLASIK eyes. The astigmatism changed from $-0.12 \pm 0.19D$ to $-0.22 \pm 0.28D$ and from $-0.2 \pm 0.21D$ to $-0.22 \pm 0.34D$ in the LASIK Xtra and the convLASIK eyes from one month to one year (figure 5). The preoperative astigmatism compared to the 12 months postoperative astigmatism is shown in figure 6. 78% of the convLASIK and 82% of the LASIK Xtra eyes were within $\pm 0.5D$ and 91% and 95% respectively within $\pm 1.0D$ of target refraction (figure 7). Both groups showed a strong correlation (convLASIK $r^2 = 0.85142$; Lasik Xtra $r^2 = 0.86395$) between attempted and achieved spherical equivalent (figure 8). As expected, there was a significant difference to preoperative regarding MRSE and astigmatism, but no significant difference during the postoperative between both groups (table 2). The MRSE 3 and 12 months compared in both groups does not vary significantly but seems to indicate a trend toward myopic regression in the convLASIK group with $p=0.09$ rather than in the LASIK Xtra eyes with $p=0.86$. The number of patients with a change of 0.5D or more was not statistically different between both groups (figure 6). To further investigate the myopic regression we evaluated the posterior keratometria (mean K; Pentacam) and the Total Corneal Refractive Power (mean TCRP; Pentacam) that takes the anterior and posterior surface of the cornea into account. There was no significant difference between the

posterior mean K from 3 to 12 months postoperative ($p=0.527$) and in-between both groups ($p=0.421$). The TCRP was significantly higher after 12 months compared to 3 months postoperative in convLASIK ($37.15D \pm 0.38$ vs. $37.3D \pm 0.38$; $p=0.011$) and LASIK Xtra eyes ($37.07D \pm 0.4$ vs. $37.21D \pm 0.39$; $p=0.008$) but did not vary statistically comparing both groups at 12 months ($p=0.19$; figure 9).

Corneal thickness and endothelial cell count

The corneal thickness postoperative differed significantly from preoperative in both groups with $554 \pm 27 \mu\text{m}$ to $446 \pm 30.7 \mu\text{m}$ in the LASIK Xtra eyes 12 months postoperative and $554 \pm 27 \mu\text{m}$ to $445.9 \pm 27.6 \mu\text{m}$ in the convLASIK eyes (table 2). In the postoperative follow-up, the corneal thickness was stable with no significant difference between both groups during the follow-up. But in both groups, the corneal thickness was significantly higher after 12 months compared to 1 month postoperative ($p < 0.001$). The underlying reason to the corneal thickening would need further observations since we did not include epithelial mapping in the study design. The ECC in the LASIK Xtra group was 2593 ± 174 cells/ mm^2 after 12 months and 2649 ± 195 cells/ mm^2 in the convLASIK eyes (table 2). This means the ECC was significantly higher in both groups 1 month after surgery compared to preoperatively and higher in the LASIK Xtra eyes compared to the control group. Since both groups had similar ECC preoperatively, we interpret these incidental findings as measurement errors since the ECC in our study did have a high measurement variance. The reason of the variance in ECC measurements remains unclear for the authors. Further inquiries would be needed to test if there is an underlying reason for the lack repeatability.

Retreatments

One patient wanted to have a LASIK retreatment after 12 months for the convLASIK eye with a MRSE, UDVA and BSCVA of $-1.5D$, 0.4 logMAR and 0.1 log MAR compared to $0.0D$ and -0.1 logMAR in the LASIK Xtra eye of the patient. Since the MRSE of this patient is still changing

and did not reach a stable status, no retreatment was been performed yet .The preoperative MRSE was -7.125D in the convLASIK and -8.0D in the LASIK Xtra eye. The mentioned MRSE could be due to a myopic regression. The initial MRSE 1 week after surgery was -1.0D probably due to dry eyes. After 1, 3, and 6 months the MRSE was -0.25D, -0.375D and -1.125D. The MRSE of the LASIK Xtra eye stayed 0.0D during the complete follow-up. The preoperative examinations of this patient did not indicate a higher risk of regression. There was no forme fruste keratoconus or a remarkable thin cornea. The retreatment has not yet been conducted due to variability of the refraction.

Complications

There was no case of post-LASIK ectasia or other postoperative severe complications as e.g. prolonged diffuse lamellar keratitis, infection, flap complications, or any occurrence with influence on the postoperative BSCVA in both groups during the 1-year follow-up except for one patient that suffered from myopic regression in the convLASIK eye as described above.

Discussion

Riboflavin crosslinking was first introduced in the early 2000's as a method to stabilize the stromal structure of the cornea. Wollensak et al reported in 2003 results of 23 eyes treated with corneal crosslinking for keratoconus ¹⁵. In all eyes, the progression stopped and 70% showed a regression of the Kmax and refractive error. Hafezi et al published a trial in 2007 with 10 patients diagnosed with post LASIK ectasia and reported that the treatment arrested and partly reversed the ectasia during their 25-month follow-up ¹⁶In the initial Dresden protocol, a low irradiance UVA source was used with $3\text{mW}/\text{cm}^2$ for 30 minutes to treat keratoconus patients ¹⁵. Later, accelerated crosslinking was introduced in which different protocols were invented with a higher irradiation delivered over a shorter treatment time to achieve the same amount of corneal strengthening as the original protocol ¹⁷. Since crosslinking can stop progression of ectasia, prophylactic crosslinking could possibly have the effect of stabilizing the cornea during and after

LASIK treatment. Celik et al published a prospective pilot interventional case series in 2012¹⁸. Four patients were treated with LASIK in one eye and LASIK with intraoperative crosslinking (LASIK-CXL) in the other eye with a 12-month follow-up. The LASIK-CXL eyes had an equal or better visual acuity compared to the LASIK eyes and no eye lost one or more lines of BSCVA. Therefore, they concluded that more and bigger clinical trials should be conducted to prove safety and efficiency of LASIK-CXL.

In this study we compared conventional fs-LASIK and fs-LASIK combined with intraoperative accelerated Riboflavin UV-A crosslinking. 23 patients completed the 12-month postoperative follow-up. There were no significant differences regarding the UCVA and BSCVA between both groups except for a better BSCVA one week postoperative in the conventional LASIK group. Similar results under a similar treatment protocol were published by Kanellopoulos et al in 2012 with 43 consecutive LASIK cases combined with intraoperative crosslinking with a mean follow-up of 3.5 years and the conclusion that crosslinking is a safe and efficacious adjunction to LASIK regarding myopic regression and ectasia¹⁹. The procedure showed good results regarding safety and efficacy of the treatment with no significant differences regarding visual acuity. In a second trial Kanellopoulos et al showed that the postoperative visual acuity was comparable after two years comparing LASIK-CXL to LASIK. The UDVA was 0.95 ± 0.15 logMAR and 0.85 ± 0.23 logMAR in the LASIK-CXL and the LASIK group⁹. In 2015, a consecutive randomized prospective comparative study was published by Kanallopoulos et al in which 140 eyes received myopic LASIK and 65 were treated with additional crosslinking²⁰. In contrast to the results of our study, they found a significant difference between UCVA of both groups at 20/20 and 20/25 levels ($p=0.045$ and 0.038). Seiler et al published a trial in 2015 including 76 eyes with a ectasia risk score (ERS) of 3-6 and performed LASIK-CXL in comparison to a control group of 76 eyes with ERS below 2 after conventional LASIK²¹. The riboflavin formulation characteristics, UV irradiation protocol ($9\text{mW}/\text{cm}^2$) and UV delivery device in this study differed from the parameters used in our study. Mean preoperative measurements were comparable. Postoperative measurements showed the LASIK-CXL eyes with significantly

more short-term complications like diffuse lamellar keratitis or corneal erosions. Therefore, the UCVA after one month was better in the conventional LASIK group. However, after one year, all eyes regained the UCVA and no difference was found between the two groups. This finding is in line with the finding in our study showing a lower BSCVA in the LASIK Xtra group one week after treatment probably due to prolonged corneal wound healing after Crosslinking. Nevertheless, the outcome after one year was comparable in both groups. Since our findings and the mentioned trials show a similar outcome of UDVA and BSCVA LASIK Xtra seems to be comparable to convLASIK regarding safety, efficiency and both procedures show comparable outcomes of MRSE and refractive stability. There is no significant difference of MRSE or cylinder between the groups at any time. The only finding was a borderline non-statistically significant trend towards myopic regression in the convLASIK eyes from 3 to 12 months. This could indicate an advantage regarding refractive stability without compromising on predictability. Since changes in refraction can occur postoperatively due to lack of a sufficient tear fluid the MRSE from 1 month was not used for the evaluation of the amount of myopic regression^{22,23}. Kanellopoulos found a difference regarding regression in the conventional LASIK group, which goes along with our findings⁹. Similar results regarding safety and predictability were published by Wu et al including 96 myopic eyes of 48 patients comparing the 6-months results after LASIK with combined accelerated crosslinking and conventional LASIK²⁴. They found no significant difference between the groups and concluded that crosslinking is a safe adjunction to LASIK. Chan et al 2016²⁵ arrived at the same conclusion. They compared LASIK Xtra to conventional LASIK including 60 eyes of 30 patients in each group. In line with our finding the initial visual outcomes were worse in the crosslinking eyes, and Chan reports a wider variance of MRSE 6-month postoperatively. These are results we cannot verify with our data. Tamayo et al concluded in 2012 that the LASIK Xtra protocol has non-inferior refractive outcome and safety compared to conventional LASIK in 66 LASIK and 42 LASIK Xtra eyes one month after treatment²⁶. Since the follow-up of one month is rather short, no conclusions could be made about a possible effect on myopic regression or ectasia. The MRSE was not significantly

different in both groups but as mentioned above a trend of higher myopic regression in the conventional LASIK eyes was seen in our study after the one year follow-up. Tan et al published in 2014 a consecutive comparative case series with 70 eyes undergoing LASIK for correction of myopia from -6.00 to -19.00D with combined crosslinking compared to a retrospective group of 64 after LASIK only²⁷. More eyes in the LASIK Xtra group reached a UDVA of 20/20 or better and had a MRSE ± 0.5 D compared to the conventional LASIK eyes. These results could not be reproduced in our trial. However, these results could be due to the higher MRSE preoperative in the trial published by Tan since we included patients up to -12.0D and Tan included patients up to -19.0D. Similarly, Low et al (2018) published a retrospective study comparing 50 consecutive eyes undergoing LASIK Xtra for high myopia (-6.63 to -15.50) to a matched control group of 50 eyes undergoing conventional LASIK²⁸. After 3 months more LASIK Xtra eyes had a VA of 20/20 or better without a significant difference regarding the amount of MRSE ± 0.5 D. Stability of spherical equivalent refractive outcome at post-operative 6 to 12 months was achieved in the LASIK Xtra group with no regression ($p=0.243$). A similar outcome regarding the visual acuity reported Low et al in a recently published paper²⁸. 12 months postoperatively there was no statistical difference between both groups regarding refractive stability and visual acuity. The authors conclude, similar to our conclusion that Lasik Xtra seems to be a safe and efficient procedure but a possible benefit on post LASIK ectasia still remains to be proven by longterm outcomes.

.As seen in previous studies and in our results as well, Tan reports a trend towards higher myopic regression in the conventional LASIK eyes compared to LASIK with combined crosslinking²⁷. A longer follow-up of two or more years could prove a difference between LASIK only and LASIK Xtra treatments. Regarding the stability of the posterior corneal surface no difference can be shown between the groups in our trial comparing TCRP and posterior mean K. But since the epithelial mapping was not performed it is not possible to reach a final conclusion regarding the mechanism of the regression shown in the convLASIK eyes.

There are a few limitations of this study. We present the results of a prospective and randomized trial with a follow-up of one year postoperative including 26 patients with high myopia up to -12.0D. As mentioned above epithelial mapping would be desirable to determine the source of the myopic regression. To evaluate the occurrence of post LASIK ectasia as an extremely rare and long term complication of LASIK procedures^{29,30}, the number of patients treated in order to prove superior safety regarding postoperative keratectasia would need to be about 10 000²¹ and a longer follow-up time would be necessary. Therefore, our trial and the trials mentioned above focused on safety and efficiency indicators like loss of BSCVA or myopic regression compared to conventional LASIK eyes to prove non-inferiority of the LASIK Xtra protocol even in patients with high myopia up to -12.0D, as in our study.

Conclusion

LASIK Xtra provides a similar long-term safety and efficiency compared to conventional LASIK. Our study and a review of literature shows that fs-LASIK combined with accelerated intraoperative crosslinking provides similar visual and refractive outcomes and shows a trend towards less myopic regression in our patient collective. Further research with a longer follow-up time and a higher sample size would be needed in order to prove this and test if LASIK Xtra treatment can prevent the development of ectasia. The LASIK Xtra protocol could be interesting for patients with a increased ERS that suffer under their myopic conditions, are limited in their career choice by spectacles or contact lenses, and are unsuitable for alternative treatments, or patients with retreatments after myopic regression to improve long term stability without compromising visual and refractive outcomes and safety.

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C: none

Reference List:

1. Foster PJ, Jiang Y. Epidemiology of myopia. *Eye (Lond)*. 2014;28(2):202-208.
2. Masters J, Kocak M, Waite A. Risk for microbial keratitis: Comparative metaanalysis of contact lens wearers and post-laser in situ keratomileusis patients. *J Cataract Refract Surg*. 2017;43(1):67-73
3. Saad A, Binder PS, Gatinel D. Evaluation of the percentage tissue altered as a risk factor for developing post-laser in situ keratomileusis ectasia. *J Cataract Refract Surg*. 2017;43(7):946-951. 0
4. Randleman JB, Trattler WB, Stulting RD. Validation of the Ectasia Risk Score System for preoperative laser in situ keratomileusis screening. *Am J Ophthalmol*. 2008;145(5):813-818.
5. Spörl E, Huhle M, Kasper M, Seiler T. [Increased rigidity of the cornea caused by intrastromal cross-linking]. *Ophthalmologe*. 1997;94(12):902-906.
6. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK, United States Crosslinking Study Group. United States Multicenter Clinical Trial of Corneal Collagen Crosslinking for Keratoconus Treatment. *Ophthalmology*. 2017;124(9):1259-1270.
7. Hersh PS, Stulting RD, Muller D, Durrie DS, Rajpal RK, U.S. Crosslinking Study Group. U.S. Multicenter Clinical Trial of Corneal Collagen Crosslinking for Treatment of Corneal Ectasia after Refractive Surgery. *Ophthalmology*. 2017;124(10):1475-1484.
8. Tong JY, Viswanathan D, Hodge C, Sutton G, Chan C, Males JJ. Corneal Collagen Crosslinking for Post-LASIK Ectasia: An Australian Study. *Asia Pac J Ophthalmol (Phila)*. 2017;6(3):228-232.
9. 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 Suppl):S837-840.
10. Rajpal RK, Wisecarver CB, Williams D, et al. Lasik Xtra® Provides Corneal Stability and Improved Outcomes. *Ophthalmol Ther*. October 2015.
11. Tomita M. Combined laser in-situ keratomileusis and accelerated corneal cross-linking: an update. *Curr Opin Ophthalmol*. 2016;27(4):304-310.
12. Kohnen T, Schwarz L, Remy M, Shajari M. Short-term complications of femtosecond laser-assisted laser in situ keratomileusis cuts: Review of 1210 consecutive cases. *J Cataract Refract Surg*. 2016;42(12):1797-1803.
13. Krueger RR, Spoerl E, Herkar S. Rapid vs standard collagen CXL with equivalent dosing. Presented at the: 4th International Congress of Corneal Cross Linking; December 5, 2008; Dresden, Germany. <http://www.slideshare.net/legen/krueger-herekar-rapid-cross-linking>.
14. Kanellopoulos AJ, Asimellis G, Karabatsas C. Comparison of prophylactic higher fluence corneal cross-linking to control, in myopic LASIK, one year results. *Clin Ophthalmol*. 2014;8:2373-2381.
15. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-a-induced collagen crosslinking for the treatment of keratoconus. *Am J Ophthalmol*. 2003;135(5):620-627.
16. Hafezi F, Kanellopoulos J, Wiltschko R, Seiler T. Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis. *J Cataract Refract Surg*. 2007;33(12):2035-2040.
17. Tomita M, Mita M, Huseynova T. Accelerated versus conventional corneal collagen crosslinking. *J Cataract Refract Surg*. 2014;40(6):1013-1020. doi:10.1016/j.jcrs.2013.12.012
18. Celik HU, Alagöz N, Yildirim Y, et al. Accelerated corneal crosslinking concurrent with laser in situ keratomileusis. *J Cataract Refract Surg*. 2012;38(8):1424-1431.
19. Kanellopoulos AJ. Long-term safety and efficacy follow-up of prophylactic higher fluence collagen cross-linking in high myopic laser-assisted in situ keratomileusis. *Clin Ophthalmol*. 2012;6:1125-1130.

20. Kanellopoulos AJ, Asimellis G. Combined laser in situ keratomileusis and prophylactic high-fluence corneal collagen crosslinking for high myopia: two-year safety and efficacy. *J Cataract Refract Surg.* 2015;41(7):1426-1433.
21. Seiler TG, Fischinger I, Koller T, Derhartunian V, Seiler T. Superficial corneal crosslinking during laser in situ keratomileusis. *J Cataract Refract Surg.* 2015;41(10):2165-2170.
22. Hassan Z, Szalai E, Berta A, Modis L, Nemeth G. Assessment of tear osmolarity and other dry eye parameters in post-LASIK eyes. *Cornea.* 2013;32(7):e142-145. d
23. Wang B, Naidu RK, Chu R, Dai J, Qu X, Zhou H. Dry Eye Disease following Refractive Surgery: A 12-Month Follow-Up of SMILE versus FS-LASIK in High Myopia. *J Ophthalmol.* 2015;2015:132417.
24. Wu Y, Tian L, Wang L-Q, Huang Y-F. Efficacy and Safety of LASIK Combined with Accelerated Corneal Collagen Cross-Linking for Myopia: Six-Month Study. *Biomed Res Int.* 2016;2016:5083069.
25. Chan TCY, Yu MCY, Ng ALK, et al. Short-term Variance of Refractive Outcomes After Simultaneous LASIK and High-Fluence Cross-linking in High Myopic Correction. *J Refract Surg.* 2016;32(10):664-670.
26. Tamayo GE. Predictable visual outcomes with accelerated corneal cross-linking concurrent with laser in situ keratomileusis. *J Cataract Refract Surg.* 2012;38(12):2206; author reply 2207-2208.
27. Tan J, Lytle GE, Marshall J. Consecutive laser in situ keratomileusis and accelerated corneal crosslinking in highly myopic patients: preliminary results. *Eur J Ophthalmol.* December 2014:0.
28. Low JR, Lim L, Koh JCW, Chua DKP, Rosman M. Simultaneous Accelerated Corneal Crosslinking and Laser In situ Keratomileusis for the Treatment of High Myopia in Asian Eyes. *Open Ophthalmol J.* 2018;12:241.
29. Pallikaris IG, Kymionis GD, Astyrakakis NI. Corneal ectasia induced by laser in situ keratomileusis. *J Cataract Refract Surg.* 2001;27(11):1796-1802.
30. Randleman JB. Post-laser in-situ keratomileusis ectasia: current understanding and future directions. *Curr Opin Ophthalmol.* 2006;17(4):406-412.

Figure Captions

Figure 1: Intraoperative LASIK Xtra protocol combining a conventional femtosecond-LASIK with Riboflavin UV-A crosslinking under the flap (Lasik Xtra = LASIK with combined intraoperative crosslinking, NaCl = sodium chlorid, UV-A = ultraviolet A light).

Figure 2: Best spectacle corrected distant visual acuity of convLASIK and LASIK Xtra eyes postoperative during the follow-up in logMAR (logarithm of the minimum angle resolution) (Lasik Xtra = LASIK with combined intraoperative crosslinking)

Figure 3: Change in corrected distant visual acuity (CDVA) 12 months postoperatively compared to preoperatively (Lasik Xtra = LASIK with combined intraoperative crosslinking)

Figure 4: Cumulative percentage of patients with uncorrected distance visual acuity (UDVA) in logMAR (logarithm of the minimum angle resolution) 12 months postoperatively compared to preoperatively (Lasik Xtra = LASIK with combined intraoperative crosslinking)

Figure 5: Stability of the manifest refractive spherical equivalent (MRSE) postoperative during the follow-up in diopters (Lasik Xtra = LASIK with combined intraoperative crosslinking)

Figure 6: Amount of patients with a refractive astigmatism of $\pm 0.25D$, $0.26D - 0.5D$, $-0.51D - 0.75D$, $-0.76D - 1.0D$, $-1.01D - 1.25D$, and $-1.26D - 1.5D$ 12 months postoperative compared to preoperative (Lasik Xtra = LASIK with combined intraoperative crosslinking)

Figure 7: Postoperative spherical equivalent after 12 months in diopters (D), (Lasik Xtra = LASIK with combined intraoperative crosslinking).

Figure 8: Attempted versus achieved spherical equivalent refraction after 12 months (Lasik Xtra = LASIK with combined intraoperative crosslinking)

Figure 9: Mean Total Corneal Refractive Power (TCRP; Pentacam, Oculus, Germany) of LASIK Xtra and convLASIK eyes 3 and 12 months postoperatively in diopter (D). The increase between 3 and 12 months is statistically significant in both groups ($p < 0.05$). There is no statistically significant difference between both groups ($p > 0.05$).

Tables

Table 1: Preoperative data of LASIK Xtra and LASIK-only eyes, visual acuity is displayed in logMAR (logarithm of the minimum angle resolution); UDVA = uncorrected distance visual acuity, BSCVA = best spectacle corrected distance visual acuity; MRSE = mean refractive spherical equivalent in diopters (D); ECC = endothelial cell count (xx/mm^2); corneal thickness is displayed in micrometers, Lasik Xtra = LASIK with combined intraoperative crosslinking

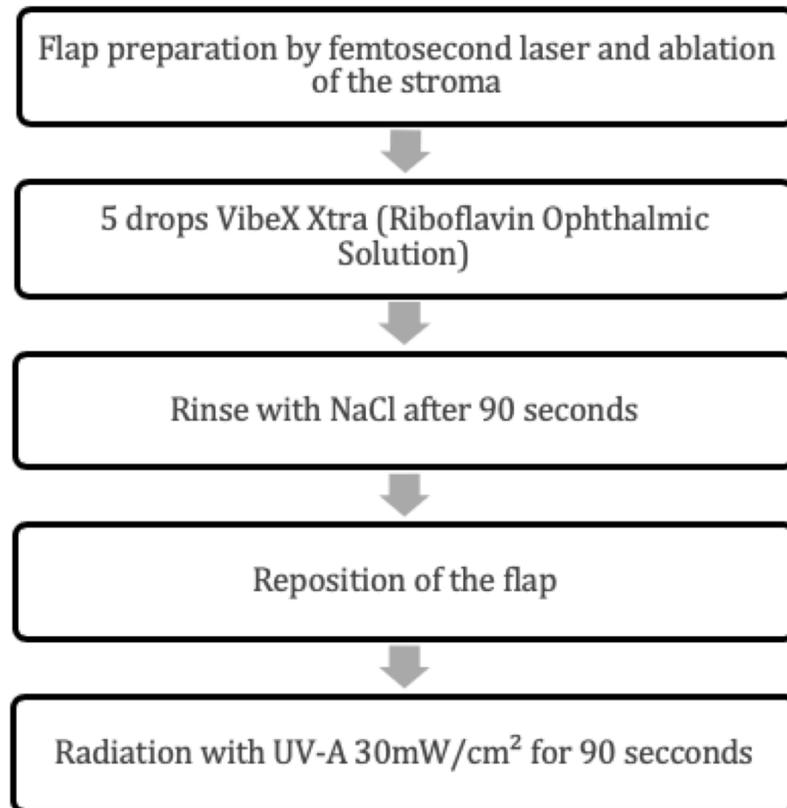
Table 2: Postoperative data of LASIK Xtra and LASIK-only eyes, visual acuity is displayed in logMAR (logarithm of the minimum angle resolution); UDVA = uncorrected distance visual acuity, BSCVA = best spectacle corrected distance visual acuity; MRSE = mean refractive spherical equivalent in diopters (D); ECC = endothelial cell count (xx/mm^2); corneal thickness is displayed in micrometers, Lasik Xtra = LASIK with combined intraoperative crosslinking

Table 1: Preoperative data of LASIK Xtra and LASIK-only eyes

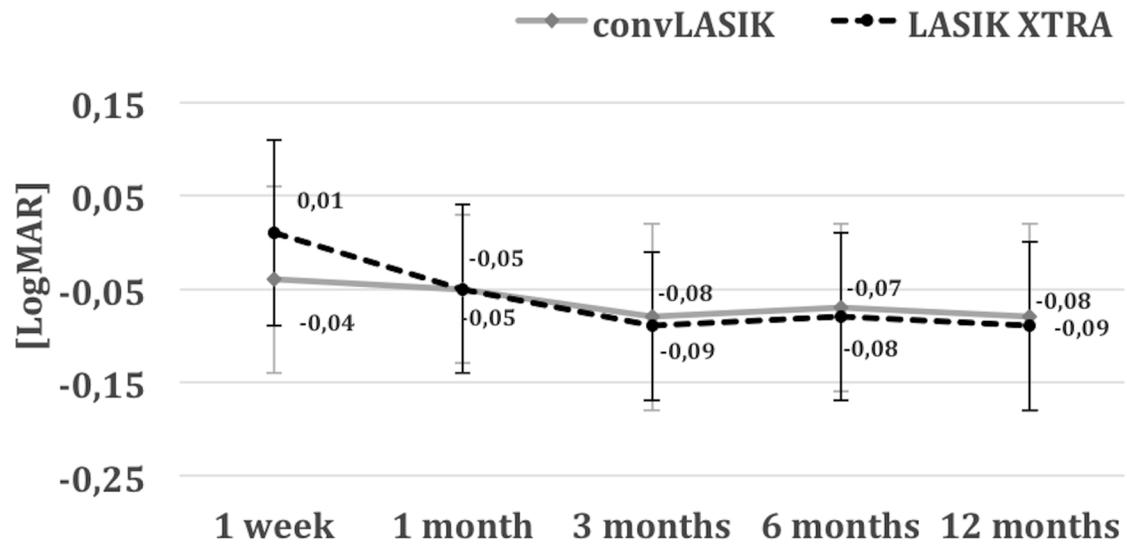
	convLASIK	LASIK Xtra	p
Age (years)	35±13	35±13	1.0
Women	16 (61%)	16 (61%)	1.0
Men	10 (39%)	10 (39%)	1.0
MRSE (diopters)	-7.35±1.15	-7.5±1.12	0.67
Cylinder (diopters)	-0.68±0.6	-0.66±0.63	0.69
UDVA (logMAR)	1.26±0.13	1.27±0.12	0.41
BSCVA (logMAR)	-0.03±0.09	-0.03±0.13	0.85
ECC (xx/mm²)	2647±226	2616±196	0.33
Corneal thickness (µm)	554±27	554±27	0.78
Ectasia Risk Score	2.04 ± 2.03 (0 – 7)	2.17 ± 1.95 (0 – 8)	0.69

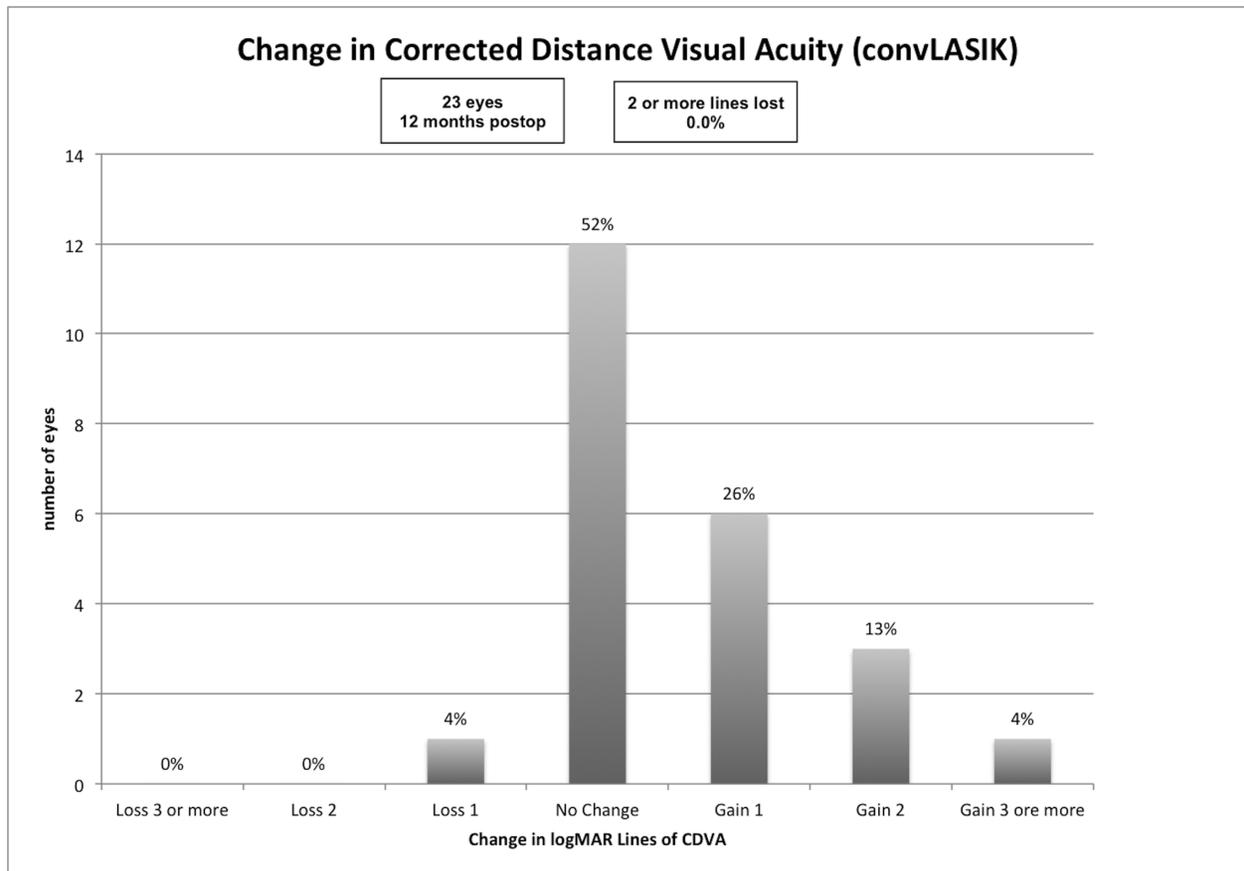
Table 2: Postoperative data of LASIK Xtra and LASIK only eyes

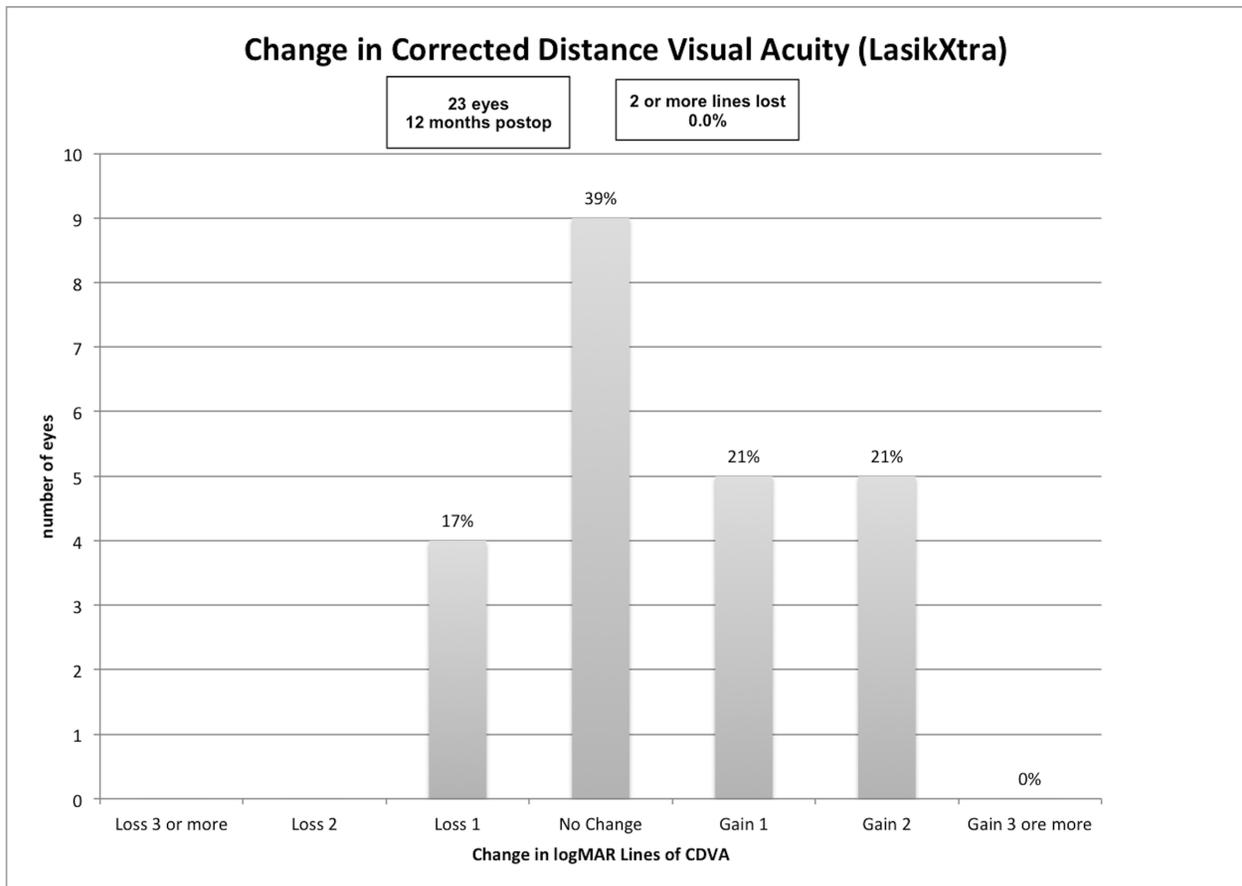
		1 week	1 month	3 months	6 months	12 months
UDVA (logMAR)	LASIK Xtra	0.08±0.14	0.02±0.14	-0.01±0.14	0.0±0.11	-0.02±0.15
	convLASIK	0.04±0.13	0.0±0.11	-0.01±0.16	-0.01±0.12	0.01±0.15
	p	0.146	0.434	0.852	0.561	0.645
BSCVA (logMAR)	LASIK Xtra	0.01±0.1	-0.05±0.09	-0.09±0.08	-0.08±0.09	-0.09±0.09
	convLASIK	-0.04±0.1	-0.05±0.08	-0.08±0.1	-0.07±0.09	-0.08±0.1
	p	0.008	1.0	0.776	0.564	0.417
MRSE (diopters)	LASIK Xtra	-0.02±0.42	-0.05±0.34	-0.07±0.41	-0.09±0.31	-0.17±0.43
	convLASIK	-0.08±0.26	-0.1±0.3	-0.1±0.3	-0.17±0.29	-0.25±0.46
	p	0.707	0.498	0.795	0.464	1.0
Cylinder (diopters)	LASIK Xtra	-0.13±0.22	-0.12±0.19	-0.14±0.2	-0.14±0.19	-0.22±0.28
	convLASIK	-0.16±0.2	-0.2±0.21	-0.18±0.23	-0.2±0.36	-0.22±0.34
	p	0.329	0.068	0.506	0.709	0.62
ECC (xx/mm²)	LASIK Xtra		2762±252			2649±195
	convLASIK		2680±201			2593±174
	p		0.036			0.014
Corneal thickness (μm)	LASIK Xtra		432.8±33.3	437.7±31.5	440.7±30.9	446±30.7
	convLASIK		437.9±26	439.6±26	441.1±25.7	445.9±27.6
	p		0.217	0.649	0.928	0.99

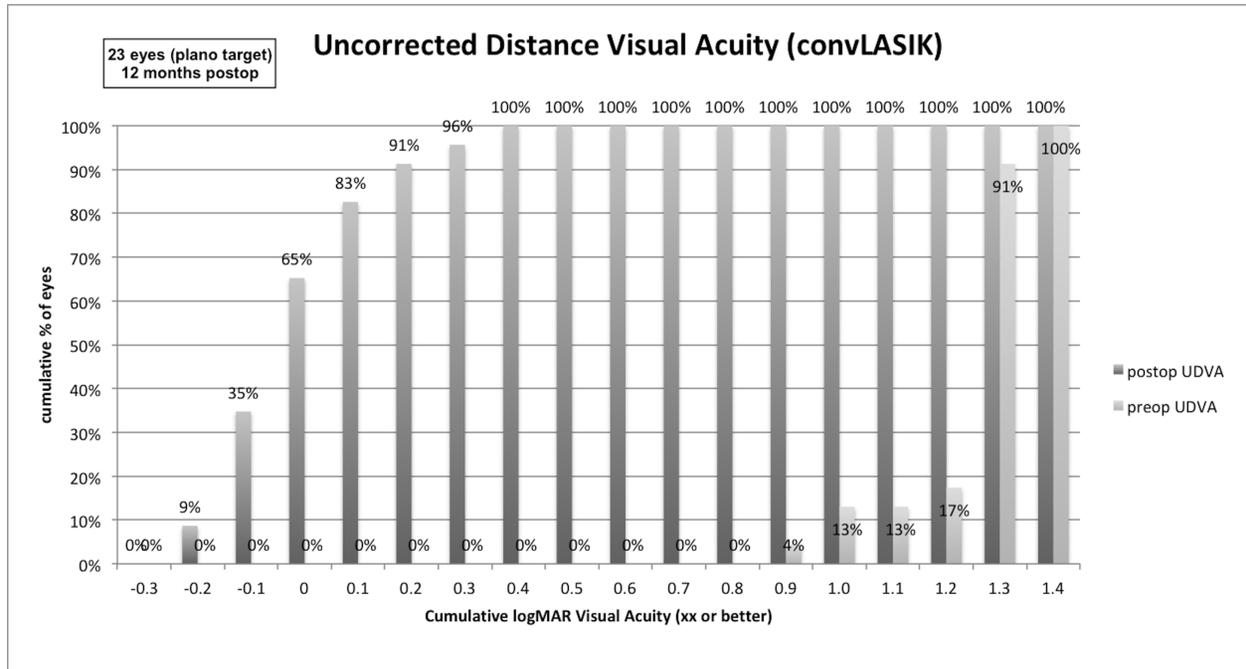


Best spectacle corrected visual acuity

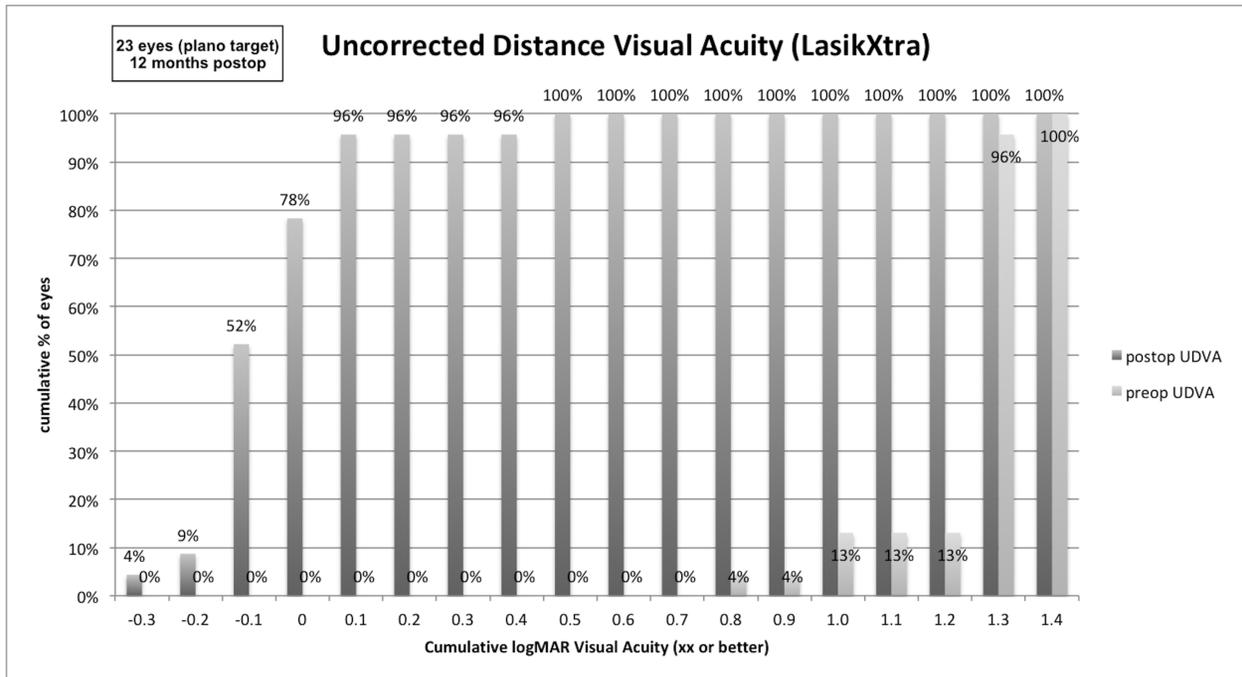




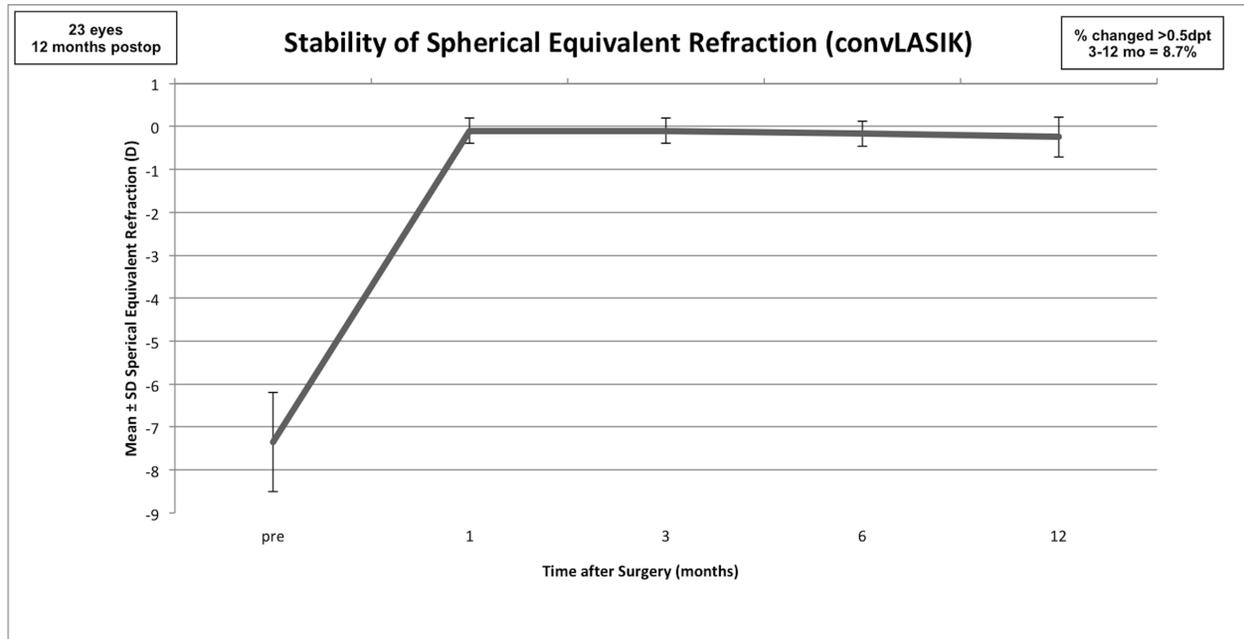


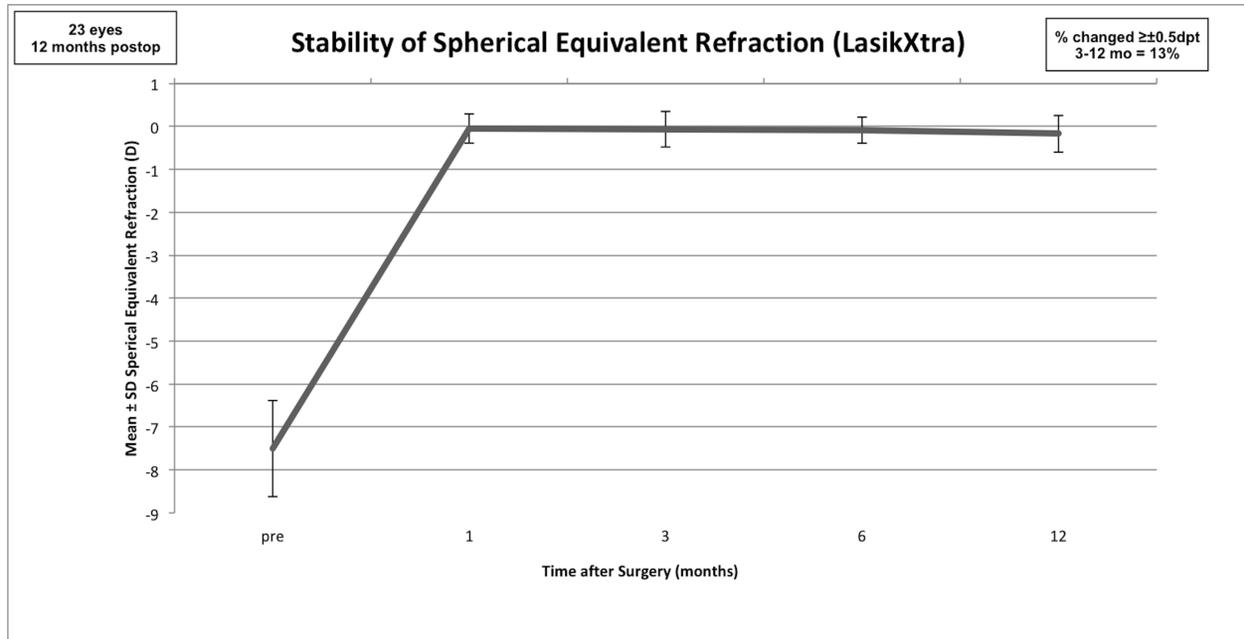


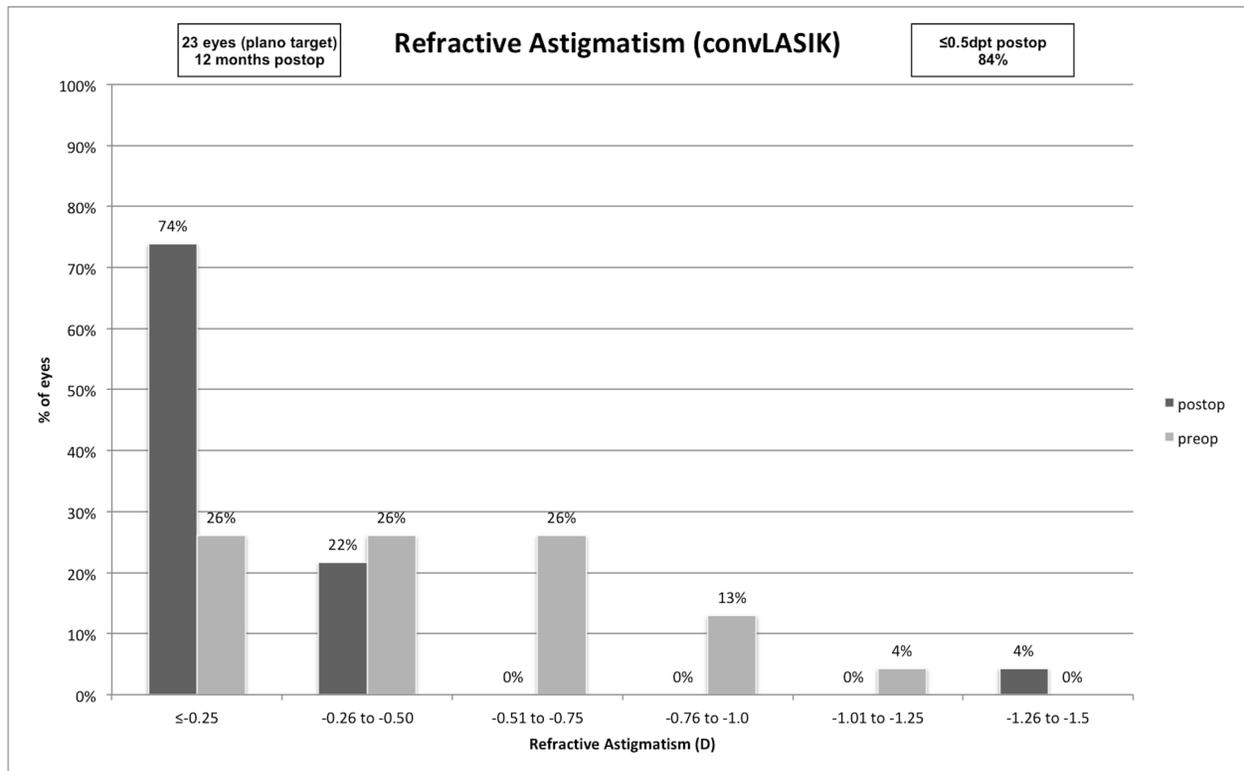
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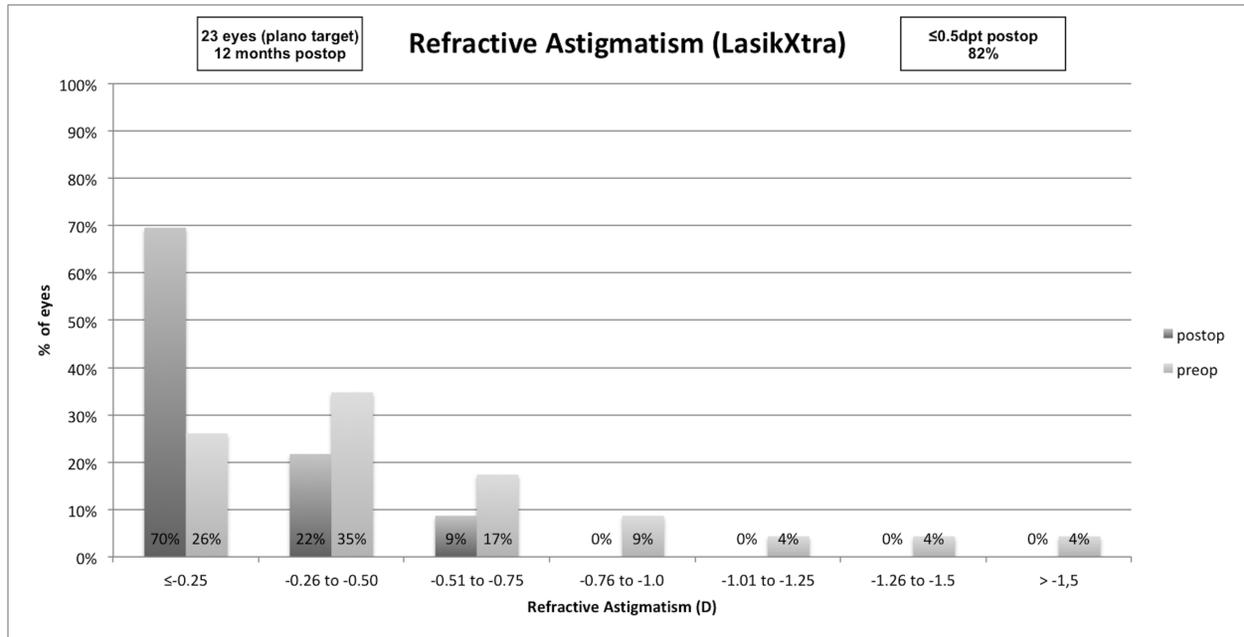


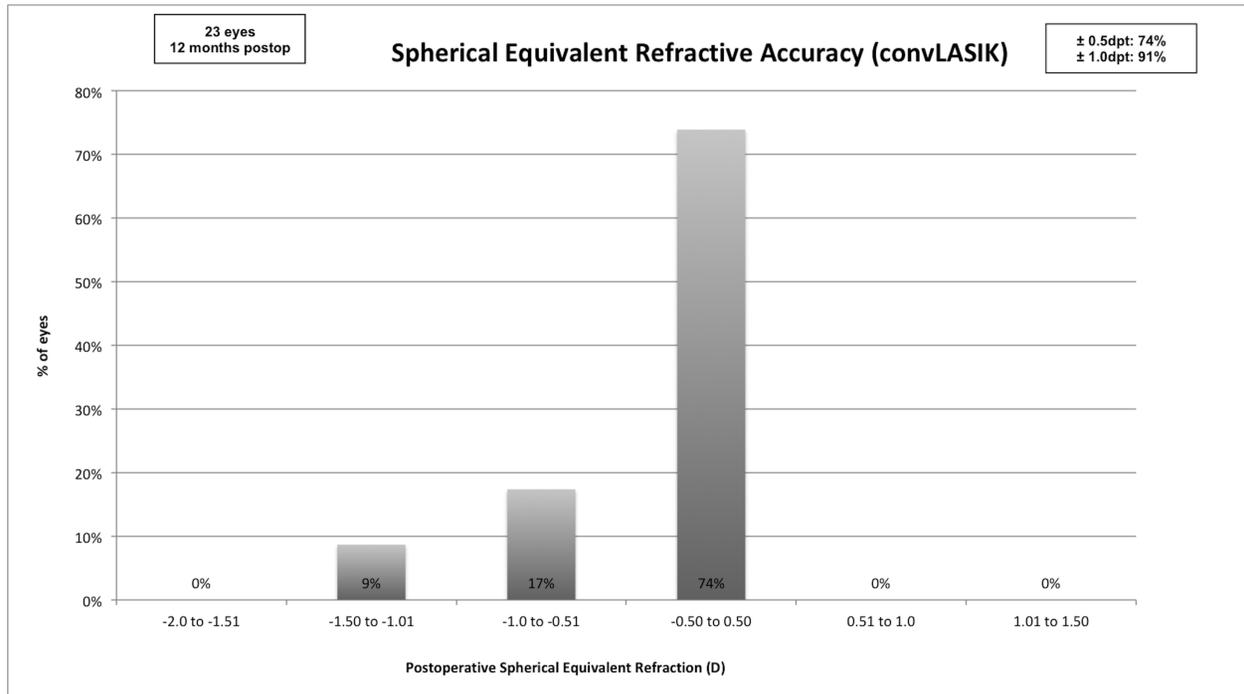
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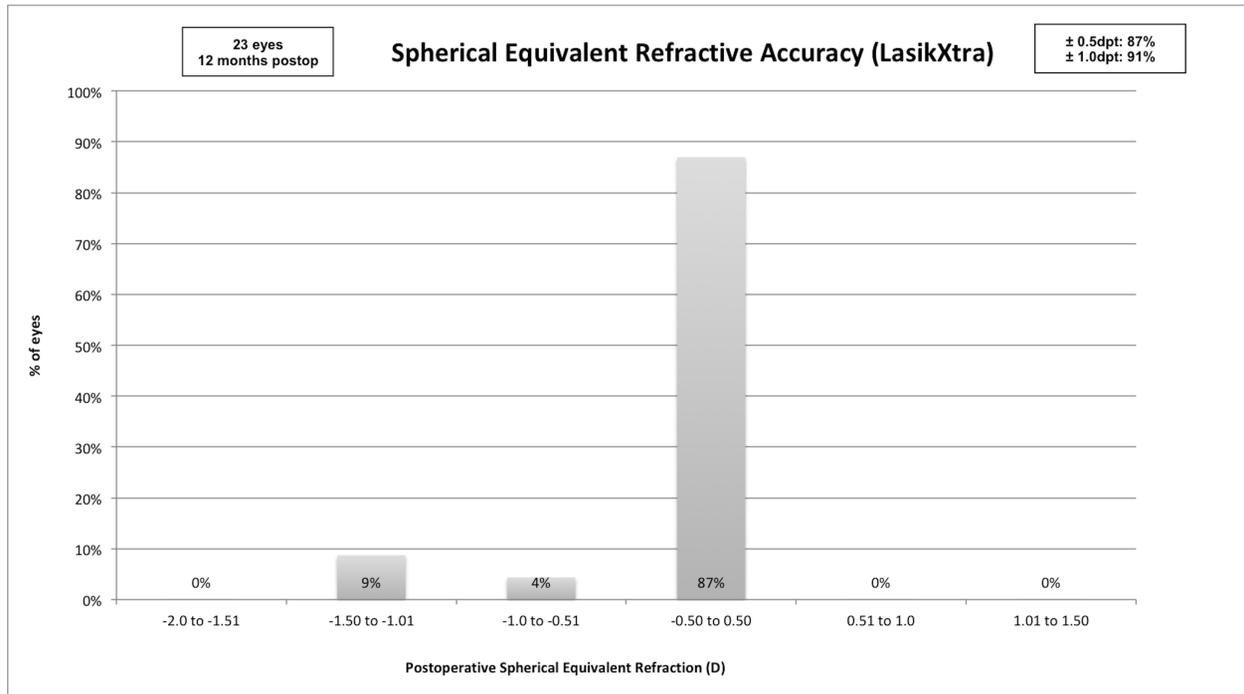


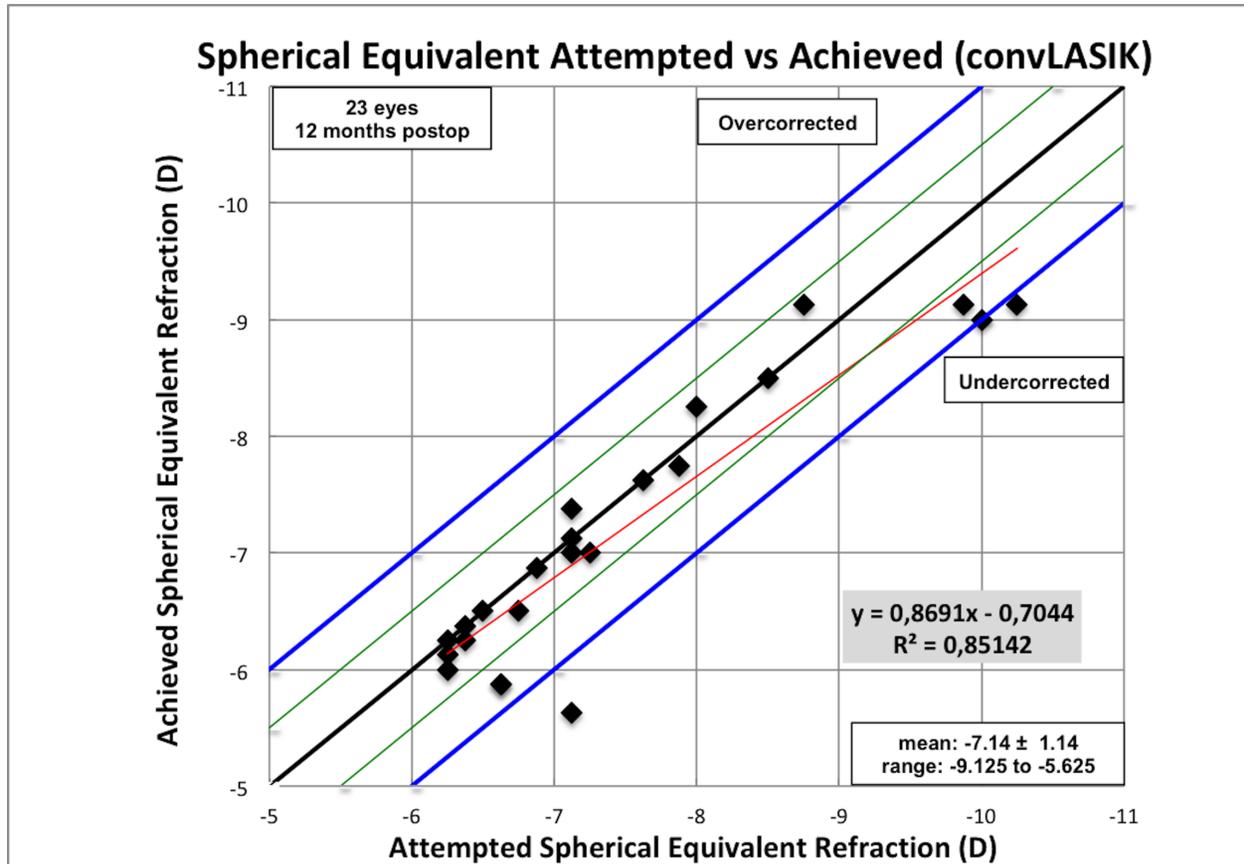


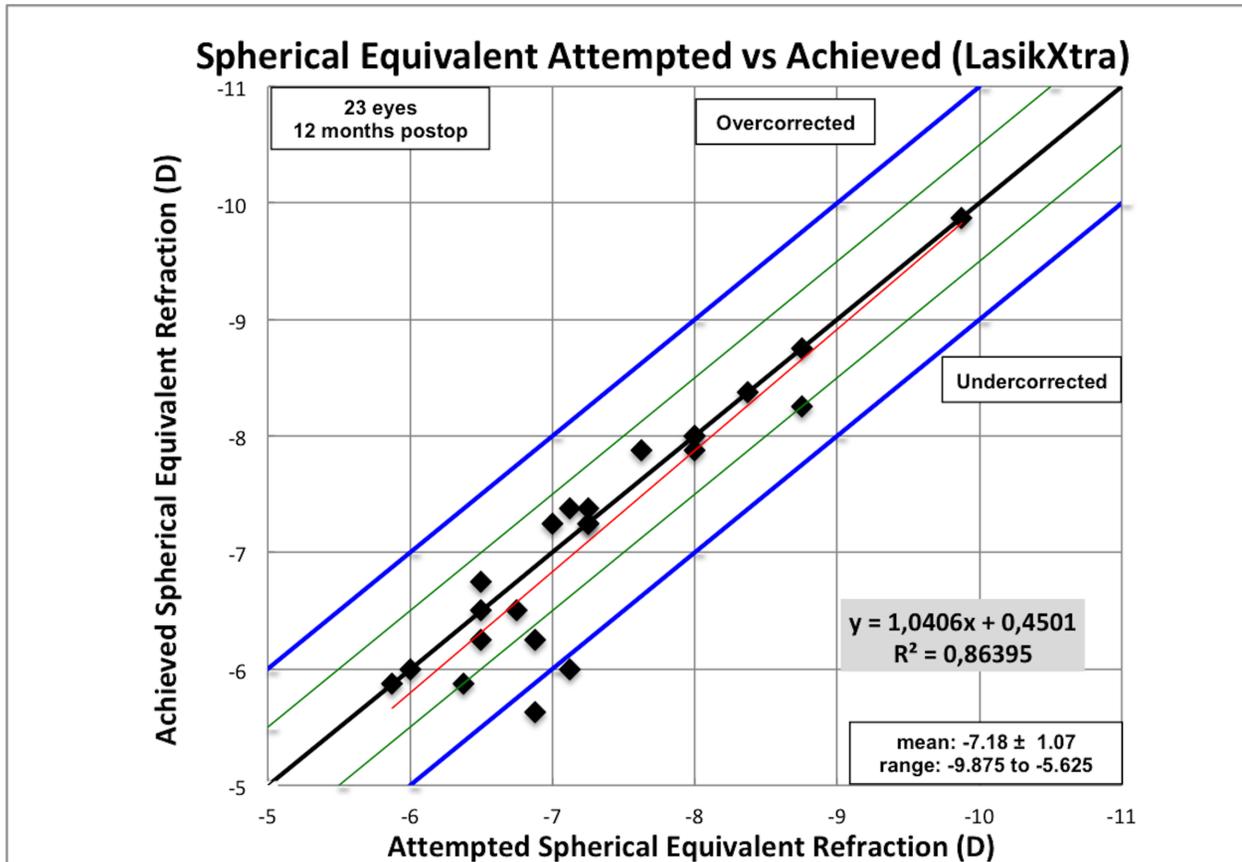


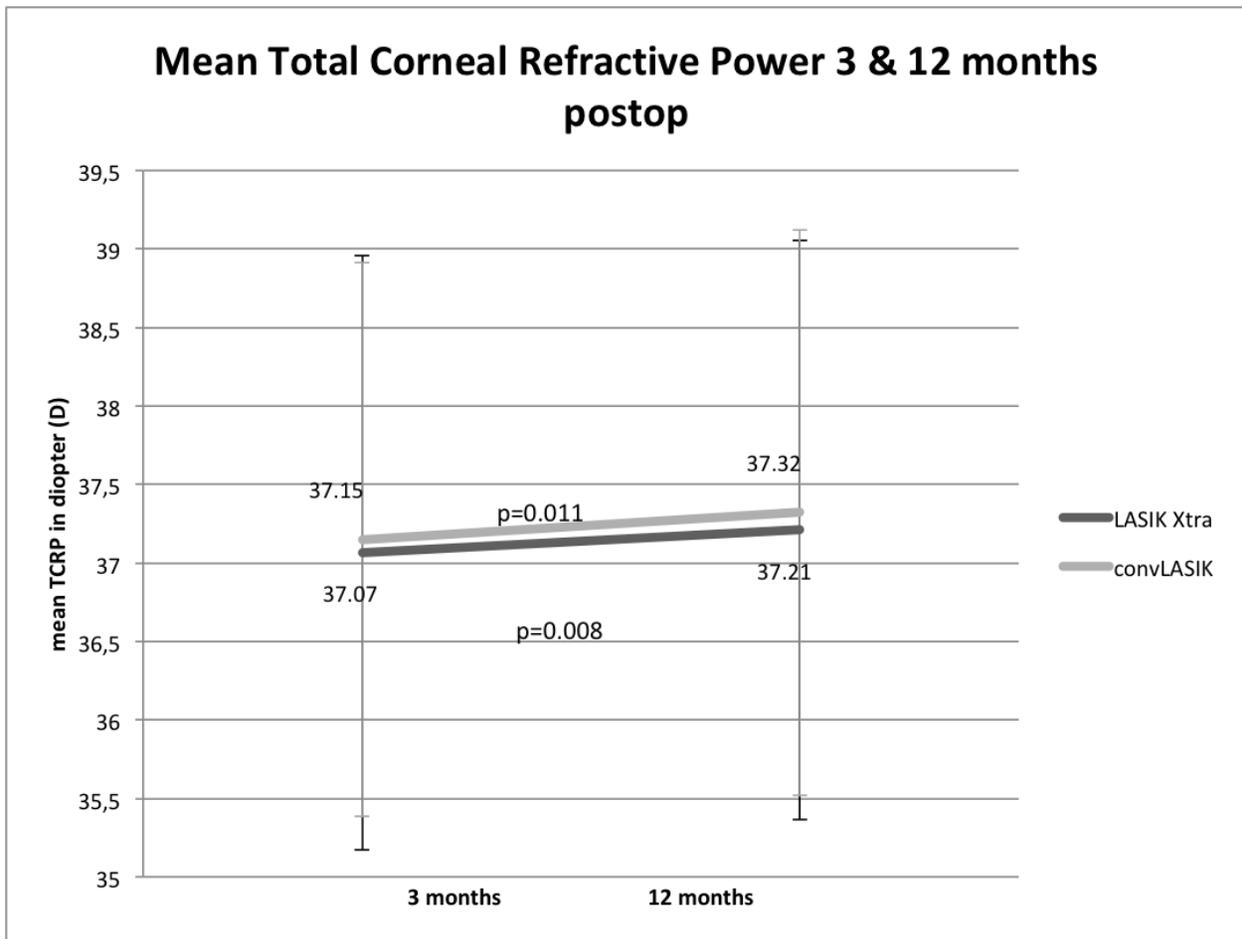












LASIK Xtra offers a potential benefit regarding myopic regression without compromising on safety and efficiency compared to conventional LASIK in high myopic patients after 12 months. It could be a promising treatment option in high myopic patients seeking to gain spectacle independence.

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Table of Contents Statement

This prospective, randomized, intra-patient controlled, clinical trial evaluates the safety and efficacy of femtosecond laser-assisted in situ keratomileusis combined with accelerated corneal crosslinking compared to conventional FS-LASIK in high myopic patients. LASIK with combined crosslinking seems to be an equally efficacious procedure compared to LASIK alone in high myopic patients. At 12 months both groups showed no difference regarding UDVA, refractive stability, and no signs of keratectasia.

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