

## Prophylactic corneal crosslinking in myopic small-incision lenticule extraction - Long-term visual and refractive outcomes

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**Purpose:** To analyze the efficacy, safety, predictability, and stability in myopic and astigmatic small-incision lenticule extraction (SMILE) with simultaneous prophylactic corneal crosslinking (CXL) in thin corneas. **Methods:** A total of 48 eyes from 24 patients who underwent myopic and astigmatism SMILE with simultaneous prophylactic CXL were included in this retrospective study. All patients had a 24-month follow-up. A femtosecond laser was performed with VisuMax (Carl Zeiss Meditec). CXL treatment was applied when the predicted stromal thickness was less than 330  $\mu\text{m}$ . **Results:** The patients' mean age was  $31.58 \pm 6.23$  years. The previous mean spherical equivalent was  $-6.85 \pm 1.80$  ( $-9.75$  to  $-2.00$ ) D. The postoperative mean spherical equivalent was  $-0.50 \pm 0.26$  ( $-1.00$  to  $+0.25$ ) D; 60% of the eyes had 20/20 or better; 19% lost one line; 58% were within  $\pm 0.50$  D; and 8.3% of the eyes changed 0.50 D or more between 3 and 24 months. **Conclusion:** Prophylactic CXL with simultaneous SMILE for myopia and astigmatism femtosecond laser surgery technique appears to be partially effective, safe, predictable, and stable after 24 months of follow-up.

**Key words:** Corneal crosslinking, refractive surgery, small incision lenticule extraction, SMILE, XTRA

Small incision lenticule extraction (SMILE) is a minimally invasive procedure in which no corneal flap is performed. In the last decade,<sup>[1]</sup> femtosecond laser has obtained more accuracy with better outcomes and several uses.<sup>[2,3]</sup> The ability to make high-precision cuts in the cornea led to the birth of intrastromal surgery, which is less invasive<sup>[4]</sup> than the femtosecond laser-assisted *in situ* keratomileusis (LASIK). During SMILE, the femtosecond laser is used to create an intrastromal lenticule with a small 2-mm incision in an arched and peripheral shape. After the creation of the lenticule, the anterior and posterior tissue bridges of the lenticule are separated.<sup>[5]</sup> The lenticule is then removed with a tweezer via the small incision. This process is performed 100% with the femtosecond laser.<sup>[6]</sup> SMILE is currently a surgical technique that is performed in subjects with myopia, although it is getting results in hyperopia.<sup>[7]</sup> A study has analyzed the possibility of preserving the lenticule obtained from the surgery in a myopic patient and implanting it in a hyperopic patient.<sup>[8]</sup> Although, more recently, a study has pointed to carving the extracted lenticule with a curvature favorable to hyperopia.<sup>[9]</sup>

Prophylactic corneal crosslinking (CXL) has emerged in order to prevent post-laser ectasia (PLE)<sup>[10]</sup> in the eyes with a low residual stromal bed or generally in thin corneas (less than 500  $\mu\text{m}$ )<sup>[11]</sup>. Corneal biomechanical could be modified by low riboflavin concentration and ultraviolet (UV) radiation.<sup>[12]</sup> CXL results in stromal fiber photopolymerization by the combined action of riboflavin (photosensitizing substance) and ultraviolet-A (UVA) light.<sup>[13]</sup> Thus, corneal stroma gains tensile strength and stability.<sup>[14]</sup> Wollensak *et al.*<sup>[15]</sup> demonstrated that the biomechanical effect of CXL using the femtosecond laser pocket technique is about 50% less pronounced than that after standard CXL. Kampik *et al.*<sup>[16]</sup> reported that CXL reduces the amount of refractive change after LASIK for myopia, although the laser ablation rate is unaffected. The previous authors had already studied prophylactic CXL with SMILE with different follow-up.<sup>[17-19]</sup> They found that SMILE with CXL is a promising tool to prevent ectasia in high-risk patients. It is a safe and simple procedure that can be offered to patients undergoing SMILE with the risk of ectasia. To the best of our knowledge, this is the highest sample study in prophylactic CXL with simultaneous SMILE.

The aim of our retrospective study is to analyze the efficacy, safety, predictability, and stability in myopic and astigmatism SMILE with simultaneous prophylactic CXL.

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## Methods

### Design

A total of 48 eyes from 24 patients who underwent myopic and astigmatism SMILE with simultaneous prophylactic CXL were included in this retrospective, observational, and longitudinal study. The patients underwent surgery between January 2015 and December 2016. All surgeries were performed at the facilities of the Ophthalmology Center Tecnolaser Clinic Vision<sup>®</sup>, Seville, Spain. All patients had a 24-month follow-up.

### Ethical aspects

All the patients included in this work were adequately informed verbally and in writing of the benefits, characteristics, and risks of the surgeries. All the patients signed informed consent prior to the surgery and after the interview with the ophthalmologist. This study was conducted in accordance with the tenets of the Helsinki Declaration and received approval from the institution's ethics committee.

### Subjects

Twenty-four patients (16 women and 8 men) voluntarily went to the clinic to perform the tests. After the ophthalmologist determined their suitability for surgery, they underwent myopic and astigmatism SMILE surgery after informed consent. The inclusion criteria were (1) bilateral myopia or myopia with astigmatism, (2) age older than 18 years and less than 45 years, (3) stable refraction for at least 1 year, that is, a change  $\leq$  of 0.50 diopters (D) in the spherical and cylindrical refraction (4) presence of myopia in spherical equivalent (MSRE) between  $-1.00$  D and  $-10.00$  D, (5) presence of astigmatism between 0.00 D and  $-4.50$  D, (6) best preoperative corrected distance visual acuity of 20/25 or better in each eye, (7) calculated residual stromal bed of 300  $\mu$ m or less (8) the maximum and minimum values of the corneal curvature could not differ by more than 5 D, and (9) a disparity of  $\leq$  0.50 D in the keratometry between two measurements with a minimum interval of 1 week in the contact lens wearers. The contact lens wearers were advised not to use them at least 15 days before the surgery. The exclusion criteria were (1) eye diseases, such as glaucoma and cataracts, (2) progressive corneal ectatic disorders (keratoconus, suspicious keratoconus, and pellucid marginal degeneration), (3) ocular surface diseases, (4) signs of retinal vascular pathology, (5) immunodeficient patients or those diagnosed with connective tissue diseases, (6) pregnant or lactating patients, (7) patients with known sensitivity to the drugs used in standard laser refractive surgery, (8) patients with eye muscle disorders such as strabismus or nystagmus, or any other disorder that affects ocular fixation, and (9) patients with no visibility or with amblyopia in the other eye. A control group was not performed in this study since the prophylactic SMILE candidate subjects had thin corneas, and therefore, the second option was implantable Collamer lens (ICL). From an ethical point of view, SMILE was not performed without XTRA on a thin cornea. Following the Cao *et al.*<sup>[20]</sup> procedure, due to the small sample eyes both eyes enrolled in the study; separate analysis with one eye in each subject showed similar results (data not shown).

### Preoperative examinations

Before undergoing SMILE with prophylactic CXL surgery, a thorough preoperative examination was carried out in all the patients. The examination was performed by an expert

optometrist and it included uncorrected and corrected visual acuity in the distance (UDVA and corrected distance visual acuity (CDVA), decimal and Snellen scale), manifest refraction with and without cycloplegia by the fogging method of refraction. Astigmatism was assessed by the Jackson cross-cylinder technique. Data were verified with the Wavefront Supported Custom Ablation (WASCA) autorefractor-aberrometer (Carl Zeiss Meditec AG, Jena, Germany). Horizontal and vertical heterophoria, near the point of convergence study, was carried out in all the patients. Corneal pachymetry, keratometry, and tomography patterns were measured with the Pentacam<sup>®</sup> single rotation Scheimpflug camera (Oculus Optikgeräte GmbH, Wetzlar, Germany). The intraocular pressure was measured with Perkins Mk3 applanation tonometer (Haag-Streit, UK). The epithelial thickness and retinal optical coherence tomography were measured with spectral-domain optical coherence tomography (SD-OCT) (Optovue Inc., Fremont, CA). Finally, prior to the surgery planning, refraction was verified once again by a different optometrist from the one who had performed the first examination.

### Surgical technique

All surgeries were performed by two experienced surgeons in SMILE correction. Ten minutes prior to surgery, the eye contour was disinfected with 5% povidone-iodine (Betadine; Meda Manufacturing, Bordeaux, France). Immediately before the surgery, a drop of double anesthetic (tetracaine 0.1% and oxybuprocaine 0.4%) (Alcon Cusi, El Masnou, Barcelona, Spain) was instilled in both eyes. The procedures were performed with the VisuMax Femtosecond Laser System (Carl Zeiss Meditec AG, Jena, Germany) using topical anesthesia in the drops. The patient was placed on the table under the cone. The laser was focused on the patient's pupil. The patient was asked to observe a green light inside the cone. The pulses of the laser were applied with a pulse energy of approximately 130 nJ. Focusing on a precise depth in the corneal tissue, the laser created a micro photo disruption in the form of a gas bubble of carbon dioxide and water to create tissue separation. The spot distance of each laser spot was 4.5  $\mu$ m. The frequency of the laser was 500 kHz. The femtosecond incisions were performed in the following order: the back surface of the lenticule, the height of lenticule's edge, the anterior lenticule surface, and the lateral cut incision to access the lenticule. The diameter of the lenticule was fixed at 6.5 mm, and the stromal lid was terminated at the depth of 120  $\mu$ m, 7.3 mm in diameter centered on the pupil. The side cut was set to the width of 3.5 mm and was located at the 12 O'clock position.

### Corneal crosslinking

After lenticule extraction, one drop of Vibex Rapid<sup>™</sup> (Avedro, Inc., Waltham, MA, USA) containing 0.25% saline-diluted riboflavin mixed with balance salt solution was placed in the intrastromal pocket. The corneal stromal bed was soaked with the solution for 90 s. The excess of riboflavin was completely irrigated. The surface was irradiated with 30 mW/cm<sup>2</sup> ultraviolet light of 375 nm using the KXL System<sup>®</sup> (Avedro, MA, USA) for 90 s with a total energy of 2.7 J/cm<sup>2</sup> and a diameter area treatment of 9.00 mm. CXL data are reported in Table 1 according to the corneal CXL: standardizing terminology and protocol nomenclature.<sup>[21]</sup>

### Postoperative evaluation

The patients were trained to use soft eye patches before sleeping for 2 nights. Tobramycin 0.3%, dexamethasone 0.1%,

**Table 1: Prophylactic Crosslinking parameters**

Parameter	Variable
Treatment target	Prophylaxis
Fluence (total) (J/cm <sup>2</sup> )	2.7
Soak time (seconds)	90
Intensity (mW)	30
Treatment time (seconds)	90
Epithelium status	On (Intrastromal Pocket)
Chromophore	Riboflavin (Vibex Rapid Avedro)
Chromophore carrier	Balanced Salt Solution
Chromophore osmolarity	Iso-Osmolar
Chromophore concentration	0.25 %
Light source	UVA (KXL System, Avedro)
Irradiation mode (interval)	Continuous
Protocol modifications	None
Protocol abbreviation in manuscript	Prophylactic CXL

and fluorometholone 0.3% were applied five times daily for the first week. Then three times daily for the second week. The treatment was then tapered till complete withdrawal. The patients were revised at day 1, 15 days, and 1, 3, 6, 12, and 24 months after surgery.

### Statistical analysis

Statistical analysis was carried out with SPSS statistics 26.0 (IBM Corporation, Armonk, NY, USA). All visual acuity data were converted into Snellen formats. The Student's *t*-test was performed for parametric dependent variables. All statistical tests were performed with a 95% confidence level ( $P < 0.05$ ).

## Results

The patients' mean age was  $31.58 \pm 6.23$  (22–45) years. Prior to surgery, the mean sphere was  $-6.18 \pm 1.62$  ( $-8.50$  to  $-1.75$ ) D, the mean cylinder was  $-1.33 \pm 1.13$  ( $-4.25$  to  $0.00$ ) D, and the mean spherical equivalent was  $-6.85 \pm 1.80$  ( $-9.75$  to  $-2.00$ ) D. The preoperative UDVA was  $20/148.75 \pm 52.13$  (20/200 to 20/70). The preoperative corrected distance visual acuity (CDVA) was  $20/21.87 \pm 2.44$  (20/25 to 20/20). The postoperative UDVA was  $20/22.91 \pm 3.97$  (20/32 to 20/20). The postoperative mean sphere at 24 months of follow-up was  $-0.31 \pm 0.29$  ( $-1.00$  to  $+0.50$ ) D, the mean cylinder was  $-0.38 \pm 0.31$  ( $-1.25$  to  $+0.00$ ) D, and the mean spherical equivalent was  $-0.50 \pm 0.26$  ( $-1.00$  to  $+0.25$ ) D. The visual acuity data were expressed in the Snellen scale.

The efficacy in terms of distance cumulative Snellen visual acuity (20/x or better) is presented in Fig. 1a; 81% of the eyes obtained 20/25 or better, 60% of the eyes obtained 20/20 or better. The efficacy index as a result of postoperative UDVA divided by CDVA was 0.95. Regarding safety, 19% of the eyes lost one line and the results are presented in Fig. 1b (three eyes due to incomplete bubble separation and six eyes due to lenticule adherence to the cap). The safety index, defined by postoperative CDVA divided by preoperative CDVA, was 0.95. The achieved spherical equivalent refraction versus attempted spherical equivalent refraction is presented in Fig. 1c. The postoperative spherical equivalent refraction accuracy data are presented in Fig. 1d. The postoperative refractive astigmatism data are presented in Fig. 1e. Finally, regarding

stability, the preoperative spherical equivalent was  $-6.85 \pm 1.80$  D and, 24 months later it changed to  $-0.50 \pm 0.26$  D, out of which 8.3% of eyes changed 0.50 D or more between 3 and 24 months [Fig. 1f].

At the 3<sup>rd</sup> and 6<sup>th</sup> months of follow-up, two patients did not attend their appointment. Regarding reported complications, two eyes needed an enhancement, and they were removed from the results. Retreatment was performed with topographic and wavefront-guided photorefractive keratectomy (PRK). No eye had PLE after surgery.

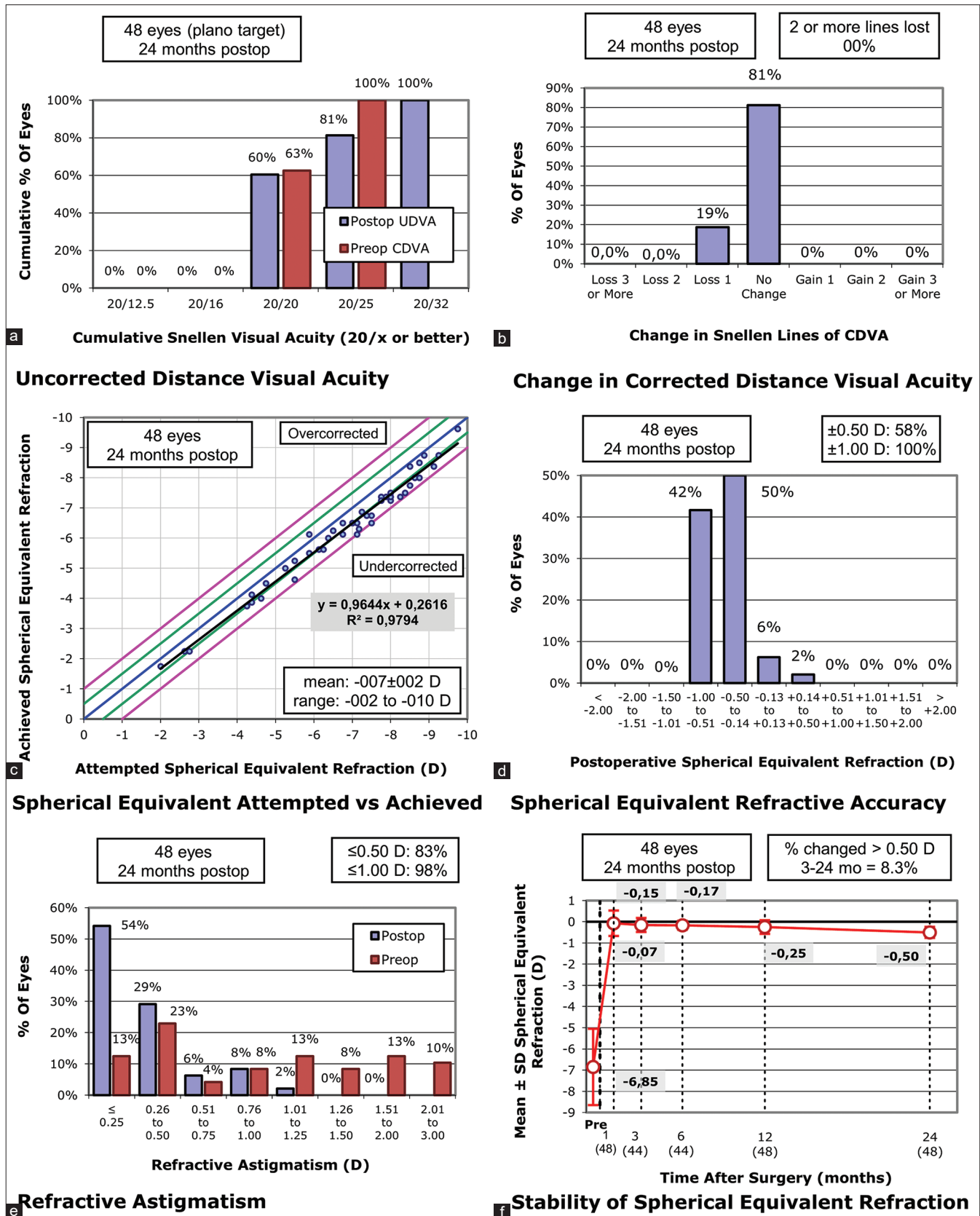
## Discussion

Our retrospective study reported visual and refractive outcomes after performing prophylactic CXL with simultaneous SMILE in 48 myopic and astigmatism eyes after 24 months of follow-up. We the reported efficacy, safety, predictability, and stability. To the best of our knowledge, this publication has the biggest sample size. In terms of efficacy, we found that 60% of the eyes achieved 20/20 or better UDVA [Fig. 1a]. Other studies similar to our study have been reported in Table 2. Some authors found similar results to ours,<sup>[18]</sup> while others reported better efficacy results in UDVA.<sup>[17,19]</sup> The studies with the worst results share a small sample size or short follow-up periods. The best visual outcome, in terms of efficacy with UDVA of 20/16 or better, were Ganesh and Brar<sup>[17]</sup> with 12.5% of the eyes within this efficacy. In terms of safety, our results showed no eyes with one or more lines of loss in CDVA [Fig. 1b]. Ganesh and Brar<sup>[17]</sup>, Ng *et al.*,<sup>[18]</sup> and Osman *et al.*<sup>[19]</sup> safety results are presented in Table 2. Our results matched with those of Ng *et al.*<sup>[18]</sup> but disagreed with Ganesh and Brar,<sup>[17]</sup> and Osman *et al.*<sup>[19]</sup> However, SMILE is not exempt of PLE. The previous research<sup>[22,23]</sup> studies have described two eyes case reports of unilateral ectasia after SMILE without prophylactic crosslinking. Furthermore, Ge *et al.*<sup>[24]</sup> demonstrated that phototherapeutic keratectomy combined with CXL for ectasia after SMILE could be an effective and safe option to treat PLE after SMILE in the long term.

In terms of predictability, our results obtained  $0.9644x + 0.2616$  ( $R^2 = 0.9794$ ). Most of the authors who studied the results of prophylactic CXL in SMILE did not present the predictability in terms of a regression line between the attempted refraction versus achieved refraction. Among the authors who did report the predictability data had a difference of opinion. All the details are presented in Table 2. Our results showed the lowest percentage of eyes within  $\pm 0.50$  D against the previous studies.<sup>[17–19]</sup> Finally, regarding stability, our results showed a change of  $-0.35$  D from the 3 months of follow-up ( $-0.15$  D) to the 24 months ( $-0.50$  D). If we analyze the stability in the rest of the articles studied with a follow-up equal to or greater than 1 year, and with a significant sample equal to or greater than 40 eyes, we can only identify with Osman *et al.*'s<sup>[19]</sup> study and they found a lower refractive regression rate with a final refractive achievement after 24 months of  $-0.18$  D. Although the number of studies that can be compared is scarce. All authors proved the presence of a slight regression. ICL has been described as the other option to correct high myopia.<sup>[25]</sup> Even though Wei *et al.*<sup>[26]</sup> reported a similar efficacy, safety, and predictability outcomes in correcting high myopia, ICL produced a lower high-order aberration induction than SMILE.

Recently Konstantopoulos *et al.*<sup>[27]</sup> investigated if SMILE with CXL was associated with less PLE risk against LASIK combined





**Figure 1:** Small-incision lenticule extraction (SMILE) with simultaneous prophylactic corneal crosslinking (CXL) standard graphs for reporting refractive surgery. (a) Uncorrected visual distance acuity (UDVA)—efficacy histogram. (b) Change in corrected distance visual acuity (CDVA)—safety histogram. (c) Spherical equivalent attempted versus achieved. (d) Spherical equivalent refractive accuracy. (e) Refractive astigmatism. C, D, and E graphs represent predictability. (f) Stability of spherical equivalent refraction

**Table 2: Prophylactic CXL with SMILE results among previous studies. Efficacy. Percentage postoperative uncorrected binocular distance and visual acuity (UDVA) (with 20/25 and 20/20 or better) (Efficacy index is also shown if available). Safety. Percentage of eyes with corrected distance visual acuity CDVA with one and two lines of loss or more. Predictability. Percentage of eyes with spherical equivalent refraction accuracy within  $\pm 0.50$  and  $\pm 1.00$  D. Stability. Last spherical equivalent (SE) available in diopters (D)**

Author (year)	Ganesh and Brar <sup>[17]</sup> 2015	Ng <i>et al.</i> <sup>[18]</sup> 2016	Osman <i>et al.</i> <sup>[19]</sup> 2019	Present study
SMILE SE (D)	-5.03	-7.08	-8.60	-6.85
Femtosecond Technique	VisuMax	VisuMax	VisuMax	VisuMax
Riboflavin Solution Type	Vibex XTRA	Vibex XTRA	Medio Cross	Vibex XTRA
Corneal Crosslinking	Avedro	Schwind	Schwind	Avedro
Treatment Group Eyes (Patients)	40 (20)	21 (12)	30 (15)	48 (24)
Follow-up (months)	12	6	24	24
Efficacy (20/25 or better)	100%	96%	97%	81%
Efficacy (20/20 or better)	95%	67%	90%	60%
Efficacy (20/16 or better)	12.5%	0%	0%	0%
Safety (lost one line)	0%	33%	3%	19%
Safety (two or more lines)	0%	0%	0%	0%
Complications (eyes)	Mild haze (1)	None	None	Enhancement (2)
Predictability ( $\pm 0.50$ D)	87.50%	89%	87%	58%
Predictability ( $\pm 1.00$ D)	100%	100%	100%	100%
Stability (Final SE)	-0.25	-0.17	-0.18	-0,50

with prophylactic CXL in rabbits. They concluded that SMILE may have less ectasia risk potential than LASIK when both used prophylactic CXL simultaneously in the refractive treatment. In a similar research line, Zhou *et al.*<sup>[28]</sup> reported microstructural modifications measured with *in vivo* confocal microscopy in 43 eyes with SMILE and CXL. They found a demarcation line depth at 296.12  $\mu\text{m}$ , an increase in hyperreflectivity, and no variations in the endothelium. However, in a current research by Torres-Netto *et al.*,<sup>[29]</sup> they evaluated the biomechanical effect of CXL in 26 *ex vivo* human corneas after PRK and SMILE. Their findings reported that CXL in PRK and SMILE human corneal ectasia obtained similar biomechanical properties. These data suggest that prophylactic CXL could be an option to limit corneas.

Among the limitations of our study, it is a retrospective study, and it is essential to achieve a longer follow-up of these patients. In addition, a control group for ethical reasons has not been included and both eyes have been included due to the low sample size.<sup>[20]</sup> Among the strengths, to the best of our knowledge, is the highest sample research of prophylactic CXL with simultaneous SMILE reported. Future research lines could be the possibility to use SMILE with simultaneous CXL to treat medium keratoconus.<sup>[30,31]</sup>

## Conclusion

Prophylactic CXL with simultaneous SMILE has demonstrated that myopic and astigmatism femtosecond laser surgery technique is partially effective, safe, predictable, and stable after 24 months of follow-up. Phakic intraocular lenses could be a better option to consider. A greater volume of patients and a longer follow-up is essential to confirm the reported results.

## Human research (Ethics)

This study was conducted in accordance with the tenets of the Helsinki Declaration and obtained Institutional Review Board approval.

## Consent to participate (Ethics)

All patients included in this work were adequately informed verbally and in writing of the benefits, characteristics, and risks of the surgeries. All patients signed an informed consent prior to the surgery and after the interview performed with the ophthalmologist.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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