Combined small-incision lenticule extraction and intrastromal corneal collagen crosslinking to treat mild keratoconus: Long-term follow-up

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PURPOSE: To report visual, refractive, and topographic outcomes of sequential, same-day small-incision lenticule extraction and intrastromal corneal collagen crosslinking (CXL) in eyes with mild keratoconus.

SETTING: Institute of Ophthalmology Conde de Valenciana, Mexico City, Mexico.

DESIGN: Prospective interventional case series.

METHODS: Fifteen eyes with forme fruste keratoconus and/or irregular corneas, corrected distance visual acuity 20/40 or better, stable refraction of at least 1 year, age 18 years or older, and residual corneal thickness of greater tan 400 μm before performing collagen crosslinking were studied. Patients were treated with small-incision lenticule extraction followed by intrastromal injection of riboflavin inside the pocket. Ultraviolet A light with a wavelength of 370 nm to 3 mW/cm^2 was applied for 30 minutes. Follow-up was done at 1 day, at 1 week, and at 1, 3, 6, 12, 18, and 24 months.

RESULTS: Eight patients were included in the study. The mean age was 29.5 years ± 5.5 (SD) (range 20 to 36 years). Twenty-four months of follow-up were completed in 13 eyes, and 12 months were completed in 2 eyes. Preoperative uncorrected distance visual acuity improved from 1.6 ± 0.3 LogMAR (Snellen 20/796) to postoperative 0.12 ± 0.20 LogMAR (Snellen 20/26) and was statistically significant ($P < .001$). Best-corrected distance visual acuity did not change significantly ($P = .186$), from 0.006 ± 0.02 LogMAR (Snellen 20/20) preoperatively to 0.04 ± 0.05 LogMAR (Snellen 20/21) postoperatively, and spherical equivalent improved from −4.3 ± 1.02 preoperatively to 0.2 ± 0.66 ($P < .001$).

CONCLUSION: Although further follow-up and larger samples are needed to fully confirm these findings, the results suggest that combined small-incision lenticule extraction and intrastromal corneal collagen crosslinking are a promising treatment option for patients for whom conventional laser refractive surgery is contraindicated.

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Keratoconus is a bilateral, asymmetrical, noninflammatory, and progressive ecstatic disorder of the cornea, which generally presents in teenagers and young adults as a progressive steepening of the cornea attributed to weakness of the corneal collagen, ultimately altering corneal biomechanics.[1] The optic consequence of this steepening is impairment of visual quality due to myopia and irregular astigmatism.[1,2]

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Mild, moderate, and severe keratoconus are generally treated with spectacles, contact lenses, and corneal transplantation, respectively. When refractive surgery was first established, it appeared to be a useful option, until reports of postoperative progression arose; thus keratoconus was considered a contraindication to laser refractive surgery. Currently, however, there are several viable options to delay or avoid keratoplasty in contact lens–intolerant patients.[3]

The aim of treatment is to prevent progression, improve refractive status and aberrations, and restore the normal prolate shape of the cornea.[4] Surgical alternatives for optical correction of keratoconus vary according to the severity of the case. These procedures include intrastromal corneal rings, corneal collagen crosslinking (CXL), phakic intraocular lenses, refractive lens exchange, lamellar or penetrating keratoplasty, or a combination of the these.[4–6]

CXL has been shown to stop the progression of keratoconus or other forms of ectasia, and can be applied alone or combined with keratorefractive procedures.[7] In selected cases, surface laser ablation has been performed, such as photorefractive keratectomy combined with sequential or simultaneous CXL, with encouraging results.[5,7]

Recently introduced into the refractive therapeutic armamentarium, small-incision lenticule extraction (SMILE, Carl Zeiss Meditec AG) uses a femtosecond laser to create a lenticule with refractive power, within the corneal stroma, which is extracted through a small peripheral incision without major disruption of the Bowman layer.[8] We propose a novel technique consisting of small-incision lenticule extraction in combination with intrastromal CXL to address both the biomechanical and refractive status in early keratoconus.

PATIENTS AND METHODS

This study was designed as a consecutive, nonrandomized, interventional clinical study, comprising patients diagnosed with keratoconus, graded I to II according to Amsler Krumeich classification, who were recruited from the Department of Cornea and Refractive Surgery at the Instituto de Oftalmologia "Conde de Valenciana." The study adhered to the principles of the Declaration of Helsinki and was approved by the institutional review board and bioethics committee of the Instituto de Oftalmologia Conde de Valenciana, Mexico City, Mexico. All patients provided signed informed consent, which included an explanation of all possible options of treatment and their inherent side effects and possible complications, including keratoconus progression and the probable need to perform keratoplasty in the future.

Inclusion criteria were age 18 years or older, myopia or myopic astigmatism within the range of correction with small-incision lenticule extraction (myopia $\leq$10 D, astigmatism $\leq$5 D), corneal ectasia, best spectacle-corrected visual acuity equal to 20/40 or better, contact lens intolerance or discomfort, and corneal thickness at the thinnest point equal to 400 µm or greater, calculated after lenticule extraction.[9] Exclusion criteria were active ocular diseases and spherical equivalent of plano or hyperopia. A particular scotopic pupil size was not considered as a criterion for either inclusion or exclusion.

Definition of Keratoconus

Keratoconus diagnosis was based on corneal topography and slit-lamp observation. Diagnostic criteria included virtually all keratoconus signs, such as asymmetry of astigmatism in corneal topography of 1.5 diopters or more, hemimeridians oblique 20 degrees or more, inferior steepening, Fleischer's ring line, and central subepithelial opacities.[1] All patients showed asymmetric bowtie pattern with or without skewed axes and presence of stromal thinning and conical protrusion of the cornea at the apex.

Preoperative Assessment

Patients underwent preoperative examinations including autokeratometry, autorefractometry, intraocular pressure tonometry, corneal tomography (Visante OMNI, Carl Zeiss; Sirius, CSO; or Pentacam HR, Oculus), corneal measurement of uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA), slit lamp evaluation of the anterior segment, and fundoscopy. All eyes were evaluated using the Ectasia Risk Score System.[10]

Small-Incision Lenticule Extraction

Small-incision lenticule extraction was performed using a Visumax 500 kHz femtosecond laser (Carl Zeiss Meditec AG). Patients underwent the standard algorithm for the small-incision lenticule extraction procedure, which is performed in non-keratoconus patients. Refractive target was intended to achieve emmetropia. The surgery was carried out under topical anesthesia (3 drops of tetracaine 5 mg/mL, Sophia Laboratories) administered 2 to 3 minutes before surgery. The patient was positioned under the curved contact glass of a femtosecond laser with the eye fixated on a blinking target. After appropriate centration, suction was applied to the contact glass. We used 500 kHz, cut energy index 180 nJ femtosecond laser pulsed, and 4.5 µm spot spacing. First, the back of the intrastromal lenticule was created by photodisruption from the periphery to the center, followed by creation of the lenticule front from the center to the periphery and an incision tunnel located at the 11 o'clock meridian. The lenticule diameter was 6.5 mm and the cap diameter was 7.5 mm. The incision length was 3.0 to 3.5 mm; the intended cap thickness was set to 120 µm. After laser treatment, the remaining tissue bridges

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were broken with a thin blunt spatula inserted through the incision site and the stromal lenticule was loosened, pulled out, and removed using McPherson forceps (Geuder, GmbH). Once the lenticule was removed, the stromal pocket was flushed with saline solution.

Intrastromal Corneal Collagen Crosslinking

Riboflavin 0.1% eye drops containing 20% dextran (Mediocross) were applied to the cornea stroma through the pocket every 1 to 3 minutes over a 15-minute period. Riboflavin application was continued every 1 to 3 minutes during the 30 minutes of ultraviolet-A (UVA) light exposure, together with topical anesthetic as required. The UV-X device (UV-X 1000, IROC) was used to deliver UVA radiation of 370-nm wavelength with an aperture of 9 mm at a distance of 50 mm from the apex of the cornea. The UV-X device output parameters were verified, and source output was confirmed to be 3.0 mW/cm^2 (range 2.74 to 3.1 mW/cm^2) before and after every treatment using the UV Light Meter (model YK-34UV, Lutron Electronic Enterprise Co. Ltd.). After 30 minutes of irradiation, the stromal pocket was rinsed with a balanced saline solution (Alcon Laboratories).

Follow-up and Postoperative Regimen

Moxifloxacion (Vigamox) and fluorometholone acetate 0.1% (Flarex) were given 4 times daily for 1 week. The steroid was tapered over the first month of follow-up. UDVA, binocular CDVA manifest refraction, corneal tomography, intraocular pressure, anterior segment biomicroscopy, and fundoscopy were performed at every visit. Eyes were examined at 1 day, 1 week, and at 1, 3, 6, 12, 18 and 24 months.

Statistical Analysis

The difference from baseline for each parameter was calculated at each time point (3, 6, 12, and 24 months) for each eye. For statistical purposes, Snellen visual acuity was converted to LogMAR. The differences were compared using 1-sample *t* tests, and results were reported through standardized graphs for refractive surgery.

RESULTS

Eight patients (15 eyes) were included in the study. Six patients (11 eyes) were female. The mean age was 29.5 years ± 5.5 (SD) (range 20 to 36 years). Thirteen eyes were followed up for at least 24 months and 2 eyes for 12 months. Table 1 summarizes the preoperative characteristics of the patients.

At the end of follow-up, uncorrected distance visual acuity improved from preoperative 1.6 ± 0.3 LogMAR (Snellen 20/796) to postoperative 0.12 ± 0.20 LogMAR (Snellen 20/26), which was statistically significant ($P < .001$). Best-corrected distance visual acuity did not change significantly ($P = .186$), from 0.006 ± 0.02 LogMAR preoperatively (Snellen 20/20) to 0.04 ± 0.05 LogMAR postoperatively (Snellen 20/21), and finally spherical equivalent improved from −4.3 ± 1.02 preoperatively to 0.2 ± 0.66 ($P < .001$). Standardized graphs (Figure 1) revealed an excellent correlation between attempted versus achieved correction, with an *R* value of 0.99 (Figure 1, *C* and 1, *D*). In all, 73% of eyes were within 0.5 D of the attempted correction, and 100% were within ±1.0 D of emmetropia. An example of preoperative and postoperative topographies is shown in Figure 2.

Complications

All eyes developed intrastromal haze; of these, 60% (9 eyes of 5 patients) had clinically significant opacity. The haze appeared to be maximal at around the first month of follow-up, but improved gradually. At the third-month visit, almost no haze was detectable (Figure 3, *C*). One eye (6.6%) had a torn lenticule (because complete removal of the lenticule was not achieved), which accounted for a mild mixed astigmatism (−0.75 +3.00 × 70 degrees) with a loss of 2 lines of CDVA (20/30) at a final follow-up of 24 months postoperatively. This eye was also assesed refractive and topographically without any signs of keratoconus progression (Figure 4). 1 eye (6.6%) had an epithelial defect that resolved within 24 hours. CDVA decreased 1 line (20/25) in 2 eyes (13.3%) best explained by residual stromal haze (Figure 1, *B*).

DISCUSSION

In this study, we found that a combination of small incision lenticule extraction and simultaneous intrastromal CXL may be a viable therapeutic approach to correct refractive error and improve stability in patients with early or mild keratoconus.

Until recently, the presence of keratoconus or forme fruste keratoconus (the milder, nonprogressive form of the disease) was an absolute contraindication to excimer laser refractive surgery, because a high rate of postoperative ectasia progression was observed.[11] Corneal ectasia after surgery can appear as early as 1 week after surgery and up to several years later.[10] The incidence is greater after laser in situ keratomileusis (LASIK), but keratoconus can also occur after photorefractive keratectomy (PRK).[12] Risk factors associated with ectasia

Table 1. Preoperative characteristics of the patients.

Eyes Treated (n = 15)	Mean ± SD	Range
UDVA LogMAR (Snellen VA)	1.6 (20/796) ± 0.3	1.3, −2
CDVA LogMAR (Snellen VA)	.006 (20/20) ± 0.02	0, −0.09
Sphere (D)	−3.1 ± 1.4	−0.75, −5.5
Cylinder (D)	−2.3 ± 1.4	−0.5, −5.0
Spherical Equivalent (D)	−4.3 ± 1.2	−2.8, −5.8
Mean K (D)	44.8 ± 1.4	43.1, 47.7
Kmax (D)	46.1 ± 1.4	44.3, 49 .3
Corneal Thickness (μm)	539 ± 46.9	470, 601
Ectasia risk score system*	5.8 ± 1.2	4, 8

CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity

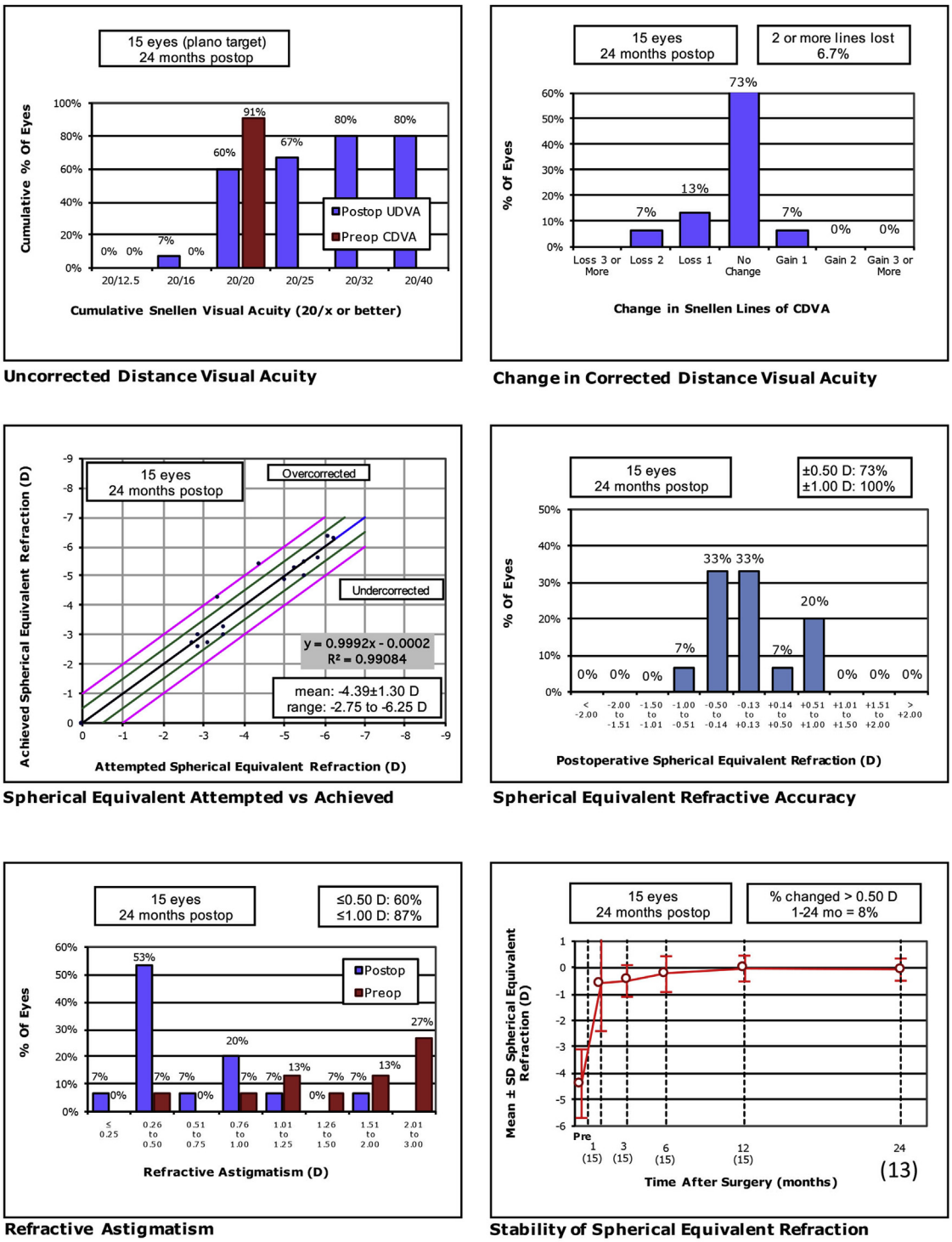

Figure 1. Standardized refractive surgery graphs depicting UDVA, change in CDVA, spherical equivalent attempted versus achieved, spherical equivalent refractive accuracy, refractive astigmatism, and stability of spherical equivalent refraction (CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity).

include thin preoperative corneas, treatment of high myopia, thin residual stromal beds, preoperative topographic changes of keratoconus or forme fruste keratoconus in the affected or contralateral eye, or a family history of keratoconus.[11] In 2008, Randleman et al. proposed a risk factor score system to identify those people at risk of ectasia progression after LASIK. This system takes into account topography pattern, residual stromal bed, age, central corneal thickness and preoperative spherical equivalent. Those with 4 or more points on the scale were

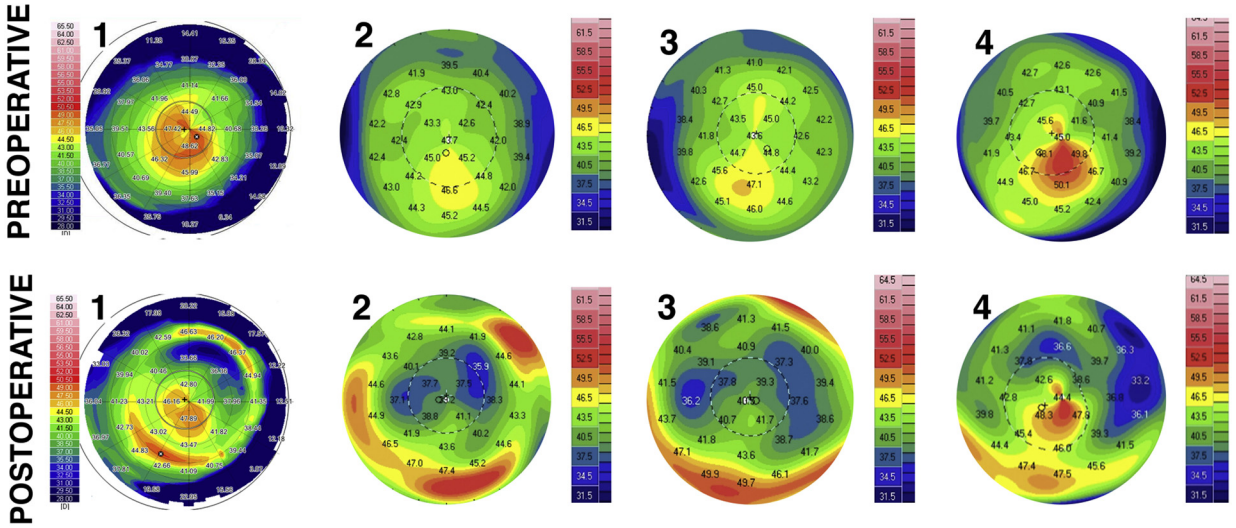

Figure 2. Four representative preoperative tangential maps of the anterior corneal surface and their corresponding postoperative maps at 18 to 24 months. Patient 1 (Sirius, CSO, Italy) and patients 2, 3, and 4 (Pentacam HR, Oculus, Inc). Inferior steepening and skewed axis are evident and consistent with early keratoconus.

considered to be at high risk with 96% sensitivity and 91% specificity.[10] All patients included in our study were classified as being at high risk; therefore, conventional LASIK was not an option.

Refractive lenticule extraction was introduced during the 2006 American Academy of Ophthalmology (AAO) Meeting in Las Vegas, Nevada, USA. Sekundo and Blum presented the very first cases of corneal refractive correction using a prototype of the Visumax femtosecond laser (Carl Zeiss Meditec AG).[13] This new procedure, which did not require an excimer laser, was named femtosecond lenticule extraction. A further refinement of the technique through a small incision, called small incision lenticule extraction, was developed by Sekundo and Blum between 2008 and 2009 and published by their group in 2011. The results are very similar to those obtained with LASIK for the correction of myopia and myopic astigmatism with similar efficacy and safety indices.[8]

On the other hand, CXL is the only conservative treatment currently available to stop or reduce progression by improving the biomechanical rigidity of the corneal stroma.[14] This technique consists of exposure to UVA irradiation at 370 nm, in the presence of stromal riboflavin (vitamin B2, a chromophore) and a UVA-blocking agent. It combines the principles of chemical nonenzymatic CXL with the photo-oxidative CXL, in which riboflavin is the photosensitizer. The reactive oxygen species induce the formation of covalent bonds that bridge the amino and carbonyl groups of collagen.[15] It has been reported that, in experimental studies, the intact epithelium did not limit the UVA transmittance but did reduce the effectiveness of CXL by preventing stromal penetration.[16] Wollensak et al.[15] were the first to describe the clinical effect of CXL on 22 eyes with keratoconus during a 2- to 4-year follow-up period. All eyes experienced an arrest in KCN progression. Recently, Wittig-Silva et al. published their results of a randomized controlled clinical trial that clearly demonstrated the sustained improvement in Kmax, UCVA, and CDVA (with spectacles/eyeglasses) after CXL, whereas eyes in the control group demonstrated further progression.[17]

The original Dresden protocol for CXL required the epithelium to be removed to allow proper penetration of the riboflavin into the corneal stroma,[18] because riboflavin is a macromolecule with inadequate corneal penetration.[7] De-epithelization is a potential risk factor for infection; it is associated with intense postoperative pain and slows down recovery, thereby delaying the return of the patient to normal activities.[19] Given these inconvenient side effects, several methods to deliver riboflavin to the corneal stroma have been developed, including modified riboflavin solutions that allow penetration into the stroma, drug delivery by iontophoresis, and femtosecond-generated intrastromal pockets that bypass the epithelium, thus overcoming epi-off disadvantages.[20] Intrastromal CXL has been shown to increase corneal rigidity, although in animal models the biomechanical effect was observed to be less when compared with standard CXL, but whether this difference is clinically significant is still uncertain.[15,21] Recently, the use of intracorneal ring channels to deliver riboflavin into the stroma has been described,[22] and an ex vivo model of intrastromal lamellar corneal tissue removal and CXL may increase significantly the rigidity of human corneas.[23]

Cohesive tensile strength, tangential tensile strength, and shear strength are greater in the anterior cornea,

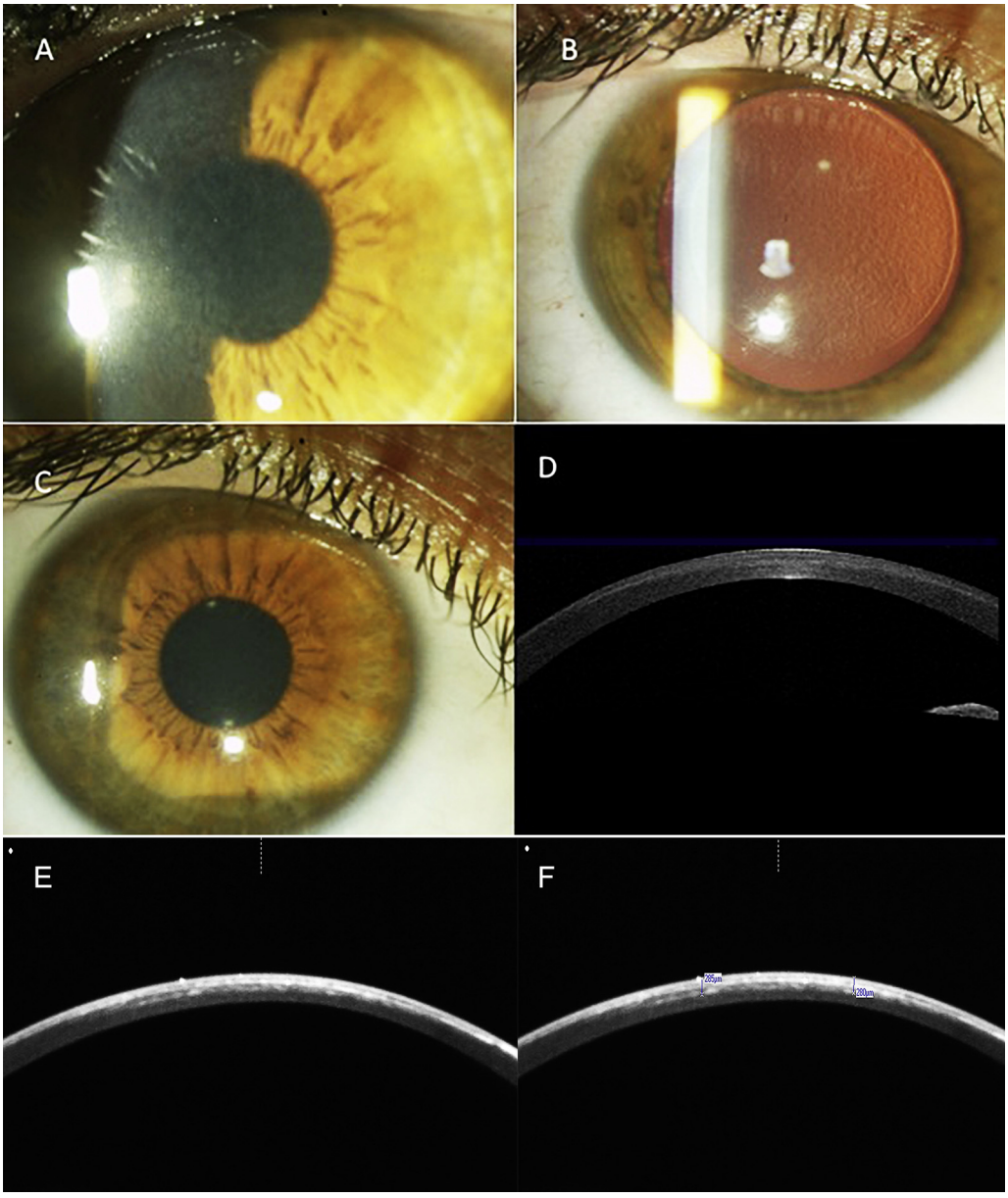

Figure 3. *A, B*: Corneal haze after 1 month of treatment. *C*: Corneal haze has disappeared after 3 months. *D*: Anterior-segment optical coherence tomogram at 1 month postsurgery demonstrates demarcation crosslinking line. *E, F*: Demarcation crosslinking line at 280 µm depth, as seen in high-resolution Scheimpflug camera (Pentacam HR, Oculus, Inc).

and hence it is thought that most biomechanical stability is due to the anterior cornea.[24,25] In small-incision lenticule extraction, the Bowman layer is fractured along only a small peripheral incision, so the effective stromal bed in biomechanical terms could be even greater than that for PRK.[8] This phenomenon has been mathematically modeled and published by Reinstein et al.[26] Also, Sinha-Roy et al. found, through a computational modeling study, that small-incision lenticule extraction may present less biomechanical risk to the residual stromal bed of susceptible corneas and that deeper corrections in the stroma may be possible compared to those achieved with LASIK, without added risk of ectasia.[27]

Therefore, using small-incision lenticule extraction to correct the refractive myopic and astigmatic error while minimizing biomechanical weakening, and combining this technique with intrastromal CXL to increase stability while overcoming the potential side effects of epithelial removal, appeared to be an ideal therapeutic approach to treat refractive error in mild keratoconic patients.

Recently, several case series have reported the use of simultaneous CXL and topography-guided

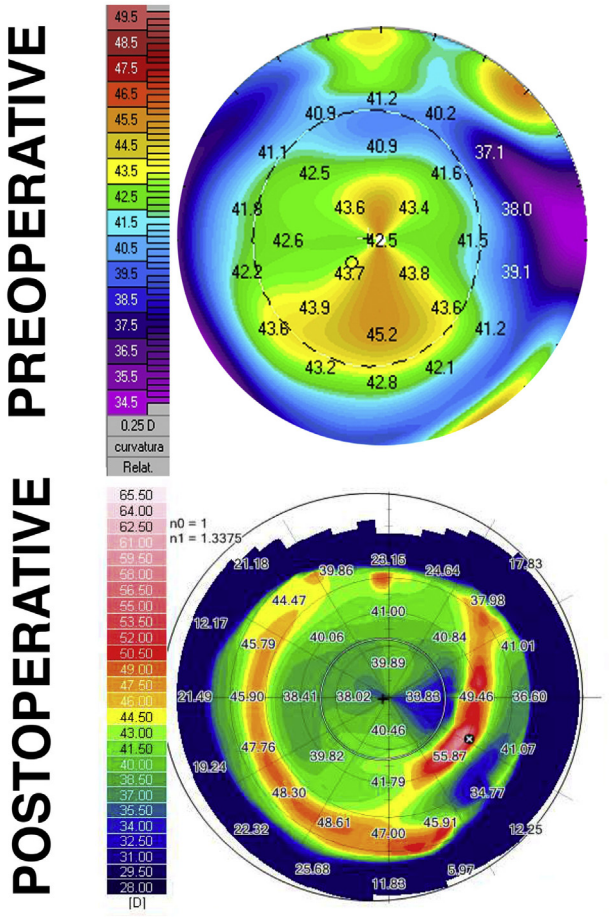

Figure 4. Comparison of preoperative (Pentacam HR, Oculus, Inc) and postoperative (Sirius, CSO, Italy) tangential maps of the anterior corneal surface of 1 patient with incomplete removal of the lenticule.

photorefractive keratectomy, with encouraging results.[5,28,29] The depth of the ablation, however, is of concern, and pain is a major drawback. Intraocular phakic or pseudophakic IOLs are also a treatment option, especially when dealing with high refractive errors.[30] This technique can also be combined either with intracorneal rings to improve corneal regularity or with CXL to improve stability.[31] Although these procedures have shown encouraging results, they are intraocular, so the risk of complications such as endophthalmitis or toxic anterior segment syndrome is always present.[32,33] Furthermore, in the case of progression, the resulting refractive error may be difficult to treat.

Perhaps the combination of small-incision lenticule extraction and intrastromal CXL can best be compared with the method used in the Athens protocol, published by Kanellopoulos et al.[34] In that protocol, the authors combined PRK and epi-off CXL. Accordingly, we named our method the AZTEC protocol. Nevertheless, several differences need to be considered. The Athens protocol is aimed at treating advanced keratoconic disease with topography-guided ablation, which theoretically redistributes corneal strain through stromal remodeling. Its goal is thus to improve CDVA. On the other hand, the Aztec protocol aims to achieve spectacle independence in patients with early keratoconus, in whom visual spectacle correction is still satisfactory but wearing glasses or contact lenses is intolerable. Being a sub-Bowman procedure, further weakening is less likely to occur than with PRK; in addition, because the epithelium is not removed, the risk of infection and pain is greatly reduced. Finally, there is some concern that crosslinking may cause progressive flattening with time. In our series, this was not significant over the 24-month follow-up period, which could possibly be accounted for by the decreased effect with intrastromal CXL, although, as stated earlier, it may still be enough to achieve stability.[15,21]

In conclusion, the Aztec protocol seems to be an efficient, predictable, and stable means of treating early keratoconus, providing spectacle independence and potentially improving biomechanical stability. The results are encouraging at 2 years; however, they must be interpreted cautiously, as the study sample is small, and consequently the results must be confirmed by other investigators.

WHAT WAS KNOWN

- Most corneal refractive surgery procedures are contraindicated in keratoconus patients because of the high risk of ectasia progression, thus affecting visual quality.
- Crosslinking has been shown to be effective in stopping or halting ectasia progression.
- Conceptual and computational studies have suggested that small-incision lenticule extraction could have structural stability advantages over comparable flap-based refractive surgery procedures.

WHAT THIS PAPER ADDS

- A combination of small-incision lenticule extraction and CXL (Aztec protocol) could improve simultaneously both visual and biomechanical qualities in patients with keratoconus or corneas at risk.
- The technique offers refractive correction and, potentially, improvement in corneal stability in early or mild keratoconus by combining small-incision lenticule extraction and intrastromal crosslinking.
- Simultaneous small-incision lenticule extraction and CXL could be an effective and stable alternative, improving patient quality of life, where other refractive procedures might be contraindicated or should be avoided.

REFERENCES

1. Rabinowitz YS. Keratoconus. Surv Ophthalmol 1998; 42:297–319. Available at: http://www.keratoconus.com/resources/Major+Review-Keratoconus.pdf. Accessed September 12, 2015
2. Davidson AE, Hayes S, Hardcastle AJ, Tuft SJ. The pathogenesis of keratoconus. Eye 2014; 28:189–195. Available at: http://www.nature.com/eye/journal/v28/n2/pdf/eye2013278a.pdf. Accessed September 12, 2015
3. Ormonde S. Refractive surgery for keratoconus. Clin Exp Optom 2013; 96:173–182. Available at: http://onlinelibrary.wiley.com/doi/10.1111/cxo.12051/pdf. Accessed September 12, 2015
4. Alio JL, Vega-Estrada A, Esperanza S, Barraquer RI, Teus MA, Murta J. Intrastromal corneal ring segments: how successful is the surgical treatment of keratoconus? Middle East Afr J Ophthalmol 2014; 21:3–9. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3959038/?report=printable. Accessed September 12, 2015
5. Assaf A, Kotb A. Simultaneous corneal crosslinking and surface ablation combined with phakic intraocular lens implantation for managing keratoconus. Int Ophthalmol 2015; 35:411–419
6. Jaimes M, Xacur-García F, Alvarez-Melloni D, Graue-Hernández EO, Ramirez-Luquín T, Navas A. Refractive lens exchange with toric intraocular lenses in keratoconus. J Refract Surg 2011; 27:658–664
7. Chan E, Snibson GR. Current status of corneal collagen crosslinking for keratoconus: a review. Clin Exp Optom 2013; 96:155–164. Available at: http://onlinelibrary.wiley.com/doi/10.1111/cxo.12020/pdf. Accessed September 12, 2015
8. Sekundo W, Gertnere J, Bertelmann T, Solomatin I. One-year refractive results, contrast sensitivity, high-order aberrations and complications after myopic small-incision lenticule extraction (ReLEx SMILE). Graefes Arch Clin Exp Ophthalmol 2014; 252:837–843
9. Spoerl E, Mrochen M, Sliney D, Trokel S, Seiler T. Safety of UVA–riboflavin crosslinking of the cornea. Cornea 2007; 26:385–389
10. Randleman JB, Trattler WB, Stulting RD. Validation of the Ectasia Risk Score System for preoperative laser in situ keratomileusis screening. Am J Ophthalmol 2008; 145:813–818
11. Santhiago MR, Smadja D, Gomes BF, Mello GR, Monteiro MLR, Wilson SE, Randleman BJ. Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal preoperative topography. Am J Ophthalmol 2014; 158:87–95
12. Navas A, Ariza E, Haber A, Fermón S, Velázquez R, Suárez R. Bilateral keratectasia after photorefractive keratectomy. J Refract Surg 2007; 23:941–943
13. Sekundo W, Kunert KS, Blum M. Small incision corneal refractive surgery using the small-incision lenticule extraction (SMILE) procedure for the correction of myopia and myopic astigmatism: results of a 6 month prospective study. Br J Ophthalmol 2011; 95:335–339
14. Gaster RN, Caiado Canedo AL, Rabinowitz YS. Corneal collagen crosslinking for keratoconus and post-LASIK ectasia. Int Ophthalmol Clin 2013; 53:79–90
15. Wollensak G, Hammer CM, Spörl E, Klenke J, Skerl K, Zhang Y, Sel S. Biomechanical efficacy of collagen crosslinking in porcine cornea using a femtosecond laser pocket. Cornea 2014; 33:300–305
16. Daxer A, Mahmoud HA, Venkateswaran RS. Corneal cross linking and visual rehabilitation in keratoconus in one session without epithelial debridement: new technique. Cornea 2010; 29:1176–1179
17. Wittig-Silva C, Chan E, Islam FMA, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen crosslinking in progressive keratoconus; three-year results. Ophthalmology 2014; 121:812–821
18. Wollensak G, Spoerl E, Seiler T. Riboflavin/ultraviolet-A–induced collagen crosslinking for the treatment of keratoconus. Am J Ophthalmol 2003; 135:620–627. Available at: http://grmc.ca/assets/files/collagen_crosslinking_2003_wollensak.pdf. Accessed September 12, 2015
19. O'Brart DPS. Corneal collagen cross linking: a review. J Optom 2014; 7:113–124. Available at: http://www.journalofoptometry.org/en/pdf/S1888429613000824/S300/. Accessed September 12, 2015
20. Cummings AB, McQuaid R, Mrochen M. Newer protocols and future in collagen crosslinking. Indian J Ophthalmol 2013; 61:425–428. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3775079/?report=printable. Accessed September 12, 2015
21. Kanellopoulos AJ. Collagen crosslinking in early keratoconus with riboflavin in a femtosecond laser-created pocket: initial clinical results. J Refract Surg 2009; 25:1034–1037
22. Kılıç A, Kamburoglu G, Akıncı A. Riboflavin injection into the corneal channel for combined collagen crosslinking and intrastromal corneal ring segment implantation. J Cataract Refract Surg 2012; 38:878–883
23. Kanellopoulos AJ, Kontos MA, Chen S, Asimellis G. Corneal collagen crosslinking combined with simulation of femtosecond laser–assisted refractive lens extraction: an ex vivo biomechanical effect evaluation. Cornea 2015; 34:550–556
24. Randleman JB, Dawson DG, Grossniklaus HE, McCarey BE, Edelhauser HF. Depth-dependent cohesive tensile strength in human donor corneas: implications for refractive surgery. J Refract Surg 2008; 24:S85–S89
25. Petsche SJ, Chernyak D, Martiz J, Levenston ME, Pinsky PM. Depth-dependent transverse shear properties of the human corneal stroma. Invest Ophthalmol Vis Sci 2012; 53:873–880. Available at: http://iovs.arvojournals.org/article.aspx?articleid=2188338. Accessed September 12, 2015
26. Reinstein DZ, Archer TJ, Randleman JB. Mathematical model to compare the relative tensile strength of the cornea after PRK, LASIK, and small-incision lenticule extraction. J Refract Surg 2013; 29:454–460. Available at: http://www.choeye.co.kr/webi_board/upFile/mathematical_model_to_compare_the_reletive_tensile_strength_of_the_cornea_after_PRK_Lasik_Smile.pdf. Accessed September 12, 2015
27. Sinha Roy A, Dupps WJ Jr, Roberts CJ. Comparison of biomechanical effects of small-incision lenticule extraction and laser in situ keratomileusis: finite-element analysis. J Cataract Refract Surg 2014; 40:971–980
28. Lin DTC, Holland S, Tan JCH, Moloney G. Clinical results of topography-based customized ablations in highly aberrated eyes and keratoconus/ectasia with crosslinking. J Refract Surg 2012; 28(11 Suppl):S841–S848
29. Kremer I, Aizenman I, Lichter H, Shayer S, Levinger S. Simultaneous wavefront-guided photorefractive keratectomy and corneal collagen crosslinking after intrastromal corneal ring segment implantation for keratoconus. J Cataract Refract Surg 2012; 38:1802–1807
30. Gomez-Bastar A, Jaimes M, Graue-Hernández EO, Ramirez-Luquin T, Ramirez-Miranda A, Navas A. Long-term refractive outcomes of posterior chamber phakic (spheric and toric implantable collamer lens) intraocular lens implantation. Int Ophthalmol 2014; 34:583–590
31. Navas A, Ramirez-Miranda A, Graue-Hernandez EO, Gomez-Bastar A, Ramirez-Luquin T. Intracorneal ring segments and phakic intraocular lens [letter]. J Refract Surg 2011; 27:555–556. reply by H Cakir, CA Utiene, 556. Available at: http://www.healio.com/ophthalmology/journals/jrs/2011-8-27-8/%7Ba68db

fc9-52aa-4eea-bc81-94d9cb647469%7D/intracorneal-ring-segments-and-phakic-intraocular-lens. Accessed September 12, 2015
32. Espinosa-Mattar Z, Gomez-Bastar A, Graue-Hernández EO, Navas A. DSAEK for implantable collamer lens dislocation and corneal decompensation 6 years after implantation. Ophthalmic Surg Lasers Imaging 2012; 43:e68–e72
33. Navas A, Tapia-Herrera G, Jaimes M, Graue-Hernández EO, Gomez-Bastar A, Ramirez-Luquín T, Ramirez-Miranda A. Implantable collamer lenses after intracorneal ring segments for keratoconus. Int Ophthalmol 2012; 32:423–429
34. Kanellopoulos AJ, Asimellis G. Epithelial remodeling after partial topography-guided normalization and high-fluence short-duration crosslinking (Athens protocol): results up to 1 year. J Cataract Refract Surg 2014; 40:1597–1602

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