OPEN ACCESS

ISSN: 2676-7473

RBMS.2021;26(1):e3

ORIGINAL RESEARCH

Refractive outcomes of small incision lenticule extraction with accelerated cross-linking (ReLEx SMILE Xtra) in patients with thin cornea

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Date Received: July, 2020 *Date Accepted: August, 2020* *Online Publication: February 28, 2021*

Abstract

Objective: To study the safety and clinical outcomes of ReLEx SMILE with accelerated cross-linking in eyes with thin cornea.
Materials and Methods: Fifty-four thin cornea with corrected distance visual acuity 20/25 or better, stable refraction of at least 1 year, age 21 years or older, and residual corneal thickness of greater than 400 mm before performing collagen crosslinking were studied. Following the removal of lenticule, 0.25% riboflavin in saline was injected into the interface and allowed to diffuse for 60 seconds. Finally, eye was exposed to UV-A radiation of 45mW/cm2 for 75 seconds through the cap. Total energy delivered was 3.4 J/cm2.
Results: 54 eyes of 27 patients with mean age of 25.22 ± 2.67 years were treated. Mean follow-up was 6 months. Mean spherical equivalent (SE) was −5.58 ± 1.22D preoperatively and -0.111 ± 0.636D postoperatively. The mean central corneal thickness (CCT) and keratometry changed from 498.39 ± 11.79 µm to 417.85 ± 12.82 µm and 45.47 ± 0.68 D to 41.13 ± 1.13D, respectively. Mean uncorrected visual acuity (UCVA) was 20/25 or better in all eyes. No eyes lost lines of corrected distant visual acuity (CDVA). There were no complications like haze, keratitis, ectasia, or regression.
Conclusion: Based on the initial clinical outcome it appears that SMILE Xtra may be a safe. 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 (CXL) are a promising treatment option for patients for whom conventional laser refractive surgery is contraindicated.

Keywords: Cross-linking, Refractive Lenticule extraction, SMILE techniques

Introduction

Small-incision lenticule extraction (SMILE) is a lately expanded corneal refractive method that has been appeared to be effective, safe and predictable in myopic eyes.[1-3] corneal refractive surgery in thin corneas or borderline topography is a very difficult decision for surgeons, with the most dreaded inconvenience being postoperative ectasia or return of refraction.[4,5] Corneal collagen crosslinking (CXL) has been demonstrated to be an efficient method to reinforcement and consolidation the cornea in type of ectasia after corneal refractive surgery.[6,7] Another novel utilization of CXL is the mix of this system with, laser-assisted in situ keratomileusis (LASIK) and photorefractive keratectomy(PRK) [8,9] that has better and safety outcomes in patients with borderline topography and thin cornea for corneal refractive surgery.[9]

A ReLEx® SMILE laser eye surgery is a flapless and one-step, one laser only procedure that creation of a lenticule by femtosecond laser and pulled out from small incision. This method has notable benefits over LASIK with CXL method, as there are fewer complications such as dry eye, induction of aberrations, decreased biomechanical stability and no flap related complications.[10] The combination of these ReLEx SMILE with collagen cross-linking is to prevent the occurrence of ectasia in high-risk cornea. The main purpose of this study was to evaluate the efficacy and safety of surgery during the follow -up period.

Materials and Methods

The tenets of the Declaration of Helsinki were followed. Before starting the study, we obtained ethical approval from the Iran University of Medical Sciences. The procedure and complications of the surgery were explained to the patients and all patients signed up with full consent to participate in the study.

Inclusion criteria included: Age greater than or equal to 21 years, spherical myopia ≥-3.00 diopters (D) and myopic astigmatism -4.75 D≤, minimum corneal thickness > 480 µm. Prior to surgery, a thorough pre-surgically ocular examination was accomplished to confidence no past or present ocular pathology except refractive errors.

Exclusion criteria included: patients with corneal thickness < 480 µm, keratoconus, hyperopic and hyperopic astigmatism, history of riboflavin allergy, past history of chemical injury and herpes infection, concurrent eye infection, long-term use of oral or topical steroids and pregnancy.

All patients underwent complete ophthalmologic examinations before surgery, including uncorrected visual acuity (UCVA) and best corrected distant visual acuity(CDVA) by ETDRS charts at 4 m, manifest and cycloplegic refraction by automated kerato refractometry (KR1; Topcon , Tokyo, Japan), applanation tonometry, fundus examination, slit lamp biomicroscopy, topography (Orbscan IIz, Baush & Lomb), contrast sensitivity(CS) by CVS-IOOO. We examined the patients on day 1 and 2, 4 and 6 months post-operatively.

In postoperative examinations UCVA, CDVA, contrast sensitivity, efficacy index, corneal thickness, safety index, and the predictability of the correction, topography were performed.

Surgical Technique

All surgeries were performed by the same trained surgeon (F.D). In the primary stage, patients underwent ReLEx SMILE was accomplished utilizing standard surgical techniques. Visumax femtosecond laser system (Carl Zeiss Meditec, Jena) was utilized to make a refractive lenticule with cap diameter 7–7.5 mm, thickness of 110 μm and optical zone 6 to 6.5 mm, with a transition zone of 0.1mm, spot and tracking distance, 2.0–3.0 μm, cut energy, 1.4 μJ then the cut refractive lenticule removed from through a 2mm superior incision at 10 o'clock position (for right eye) and 12 o'clock position (for left eye),. Following the removal of lenticule, 0.25% riboflavin in saline (VibeX Xtra, Avedro) was injected into the interface and allowed to diffuse for 60 seconds. Finally, eye was exposed to UV-A radiation of 45mW/cm2 for 75 seconds through the cap with total energy delivered 3.4 J/cm2 utilizing the CXL-365 vario system (Schwind eye-tech-solutions GmbH & Co. Kleinostheim, Germany). No complications were observed during surgery. Postoperative medical and pharmaceutical care included topical levofloxacin 0.3% (Oftaquix, Bausch and Lomb, Milan, Italy) 4 times for 3 days, betamethasone 0.1% eye drops

(Betasonit, Sina Darou Company, Tehran, Iran) 4 weeks, and lubricants 4–6 times for 4 weeks or more.

Statistical Analysis: After data collection, data analysis before surgery and 2, 4 and 6 month's post-surgery and according to the objectives of the study. We used a parametric one-way repeated measure ANOVA test to assess the statistically significant changes in the outcomes overtime at 0.05 significance level. We used the Stata Version 15 statistical program (Stata- Corp, College Station, TX, USA) to the statistical analysis.

Results

The investigation included 54 eyes from 27 patients of both sexes. Demographic and preoperative baseline data are summarized in table 1.

Table 1: Preoperative data of 27 patients (n = 54 eyes) who underwent SMILE Xtra.

Preoperative parameters	Mean ± SD
Mean age	25.22 (2.67), Range (21-30)
Female (%)	18 (0.66)
UCVA (Log MAR)	0.95 (0.16)
BCVA (LogMAR)	0.06 (0.07)
SE (D)	-5.58 (1.22)
K	45.47 (0.68)
CCT	498.39 (11.79)
Cylinder	-2.63 (0.93)
Sphere	-4.27 (1.50)

UCVA: Uncorrected Visual Acuity, BCVA: Best Corrected Visual Acuity SE: spherical equivalent, *K*: keratometry, CCT: central corneal thickness

In the first days after the surgery, all corneas were clear and all patients were comfortable and did not report symptoms. We didn't see any side effects like keratitis, ectasia, deep lamellar keratitis and epithelial ingrowth the entire 6 months follow-up period. After one month of surgery, four eyes of two patients were created late mild haze and a decease CDVA by two line which later recovered within four months after application topical steroids.

Visual Acuity, Safety, Efficacy, Stability and Predictability: Table 2 shows the visual acuity during the follow-up period. After 6 months follow-up, all (100%) eyes were 20/25 or better, 21 eyes (38.8%) had no change in CDVA, 31 eyes (57.4%) more than gained 1 line. Four eyes lost 2 line at one month follow-up, which improved to 20/20 visual acuity at 4 months. From month 2 onwards, UCVA, BCVA, and SE variables showed stability. Generally mean safety index (postoperative CDVA/preoperative CDVA) was 1.03 and mean efficacy index (postoperative UDVA/ preoperative CDVA) was 1.09 at the last follow-up visit. High levels of predictability were observed after surgery, with 30 eyes 55% at ±0.25 and 38 eyes 70% at ±0.50 after 6 months of surgery. (Figure 1)

Table 2: Visual acuity and refraction during the complete postoperative follow-up

Parameters Mean ± SD	2 Months	4 Months	6 Months	P-value
UCVA (LogMAR)	0.026 ± 0.068	0.056 ± 0.050	0.054 ± 0.050	
P-value	Pre. Versus 2 m P=0.00	2 mo versus 4 m P=0.018	4 mo versus 6 m P=0.98	0.01
BCAV (LogMAR)	0.006 ± 0.036	-0.006 ± 0.036	-0.006 ± 0.036	
P-value	Pre. Versus 2 m P=0.00	2 mo versus 4 m P=0.19	4 mo versus 6 m P=0.99	0.14
Residual SE (D)	-0.056 ± 0.627	0.083 ± 0.622	-0.111 ± 0.636	
P-value	Pre. Versus 2 m P=0.00	2 mo versus 4 m P=0.48	4 mo versus 6 m P=0.89	0.26
Cylinder	-0.810 ± 0.431	-0.852 ± 0.375	-0.852 ± 0.375	
P-value	Pre. Versus 2 m P=0.00	2 mo versus 4 m P=0.85	4 mo versus 6 m P=0.99	0.82
Spher	0.458 ± 0.576	0.361 ± 0.608	0.347 ± 0.625	0.56
P-value	Pre. Versus 2 m P=0.00	2 mo versus 4 m P=0.63	4 mo versus 6 m P=0.99	

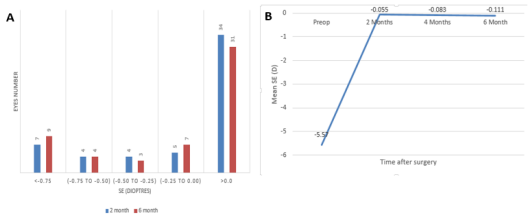

Figure1: Changes and stability of spherical equivalent and stigmatism over time (A). Time course of manifest spherical equivalent refraction (SEQ) after small-incision lenticule extraction (SMILE) and combined SMILE with cross-linking (SMILE Xtra). (B)

Keratometry and Central Corneal Thickness: Table 3 shows keratometric and pachymetric changes over the follow-up period that the changes were not statistically significant.

Table3: Changes in keratometry and central corneal thickness over time.

Parameters Mean ± SD	2 Months	4 Months	6 Months	P-value
Keratometry (Orbscan II)	41.143 ± 1.133	41.124 ± 1.158	41.130 ± 1.130	0.99
P-value	Pre. Versus 2 m P=0.00	2 mo versus 4 m P=0.99	4 mo versus 6 m P=0.99	
CCT	415.24 ± 11.60	417.63 ± 13.03	417.85 ± 12.82	0.49
P-value	Pre. Versus 2 m P=0.00	2 mo versus 4 m P=0.58	4 mo versus 6 m P=0.99	

Contrast Sensitivity

Although there was a drop in the contrast for all spatial frequencies, it remained in the normal acceptable range and showed a trend towards recovery in all subjects at the end of the mean follow-up. In all postoperative visits P value was <0.05 for all spatial frequencies. (Figure 2)

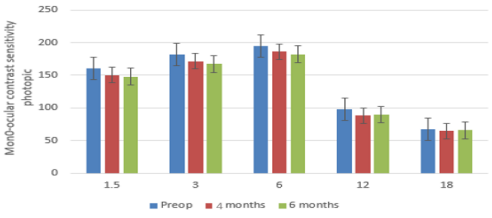

Figure 2.Mono-ocular contrast sensitivity during 6 months follow up

Discussion

SMILE surgery has theoretical advantages such as minimal effect on corneal strength, flapless as a result, no flap complications. SMILE additionally is viewed as a more tissue

saving technique when contrasted with LASIK (In SMILE per diopter 13 microns and 17 microns LASIK). As a result, SMILE is a more appropriate option for treating thinner corners, high myopia, and those with abnormal topography. [11-14]

However, there have been reports of corneal ectasia following SMILE surgery.[15-19]

PRK and LASIK weaken the cornea by 14% to 33%, which can increase the risk of ectasia for this reason; this possibility can be minimized by methods such as combining with CXL. 20, 21

Past studies have reported the combination of LASIK or PRK with CXL as effective and safe. 22 This will increase the number of patients eligible for surgery.

In this study, we used a new method of combining SMILE with CXL to minimize side effects and increase efficacy. In 2009, Kanellopoulos et al 23 demonstrated, using a femtosecond laser, which created corneal pocket in the stroma of patients with mild keratoconus and riboflavin injection, it increased wound healing and efficacy and minimized complications such as infection. He proposed an option to the regular CXL with the benefit of not removing the epithelium subsequently having quicker healing, better comfort, also, less possibility of infection. Combining SMILE procedure (SMILE Xtra) with CXL has utilized a similar idea. Preliminary results published of SMILE Xtra demonstrate the method to be effective and safe on the short courses. There are not many articles in the literature covering this technique, and they all need long-term follow-up .[24- 26]

One of the benefits of the SMILE Xtra is that CXL is performed for the underlying stroma and the overlying cap; where LASIK Xtra, just under stromal done because it may cause wrinkles flap and flap displacement problem to be touched.

Treating thin or borderline topography corneas with CXL as prophylaxis must be different from therapeutic protocols. The goal is to stabilize the cornea with the least amount of energy. Excessive energy causes interfere with vision and haze, however, if energy is low, it cannot stabilize and create strong connections in the stroma. For the treatment of ectasia, there are long-term follow-up for CXL protocols that have confirm to be effective and safe.[27] Although, in order to prophylaxis for the treatment of high-risk eyes, there is still no standard protocol with different regimens. In LASIK Xtra method, various researchers have utilized 30 mW/cm2 for various lengths with a total energy of 1.8 to 5.4 J/cm2, and each one of those various regimens confirm to be effective and safe. [9, 28] Also, for the prophylaxis treatment in keratoconus, the minimum amount of energy to strengthen the cornea is yet unbeknown. In our study, eye was exposed to UV-A radiation of 45mW/cm2 for 75 seconds through the cap with total energy delivered 3.4 J/cm2 utilizing the CXL-365 vario system (Schwind eye-tech-solutions GmbH & Co. Kleinostheim, Germany). It is easy to cross-link because of the cap and epithelium remains intact .We suggested that a high concentration of 45mW / cm2 would permit adequate radiation to reach the stroma to be effective for cross-linking, because the epithelium can absorb a significant amount of UV-A radiation.[29]

With a prophylactic system, we planned for accomplishing an ideal energy, which is neither excessively high as is utilized for ectasia (>5.4 J/cm2) nor too low to be in any way successful.

We used the most elevated fluency of the method and saw our routine as safe as it didn't outcome in epithelial defects, punctate keratitis, endothelial toxicity or deep lamellar keratitis.

We utilized VibeX Xtra 0.25% in saline, which is prescribed for intrastromal usage as it quickly accomplishes high condensations in the stroma. Since it is without dextran, the dissemination into more profound layers is accomplished as right on time as 60 seconds after usage. This aides in particular position of riboflavin in the stroma with the goal that it assimilates and actuates UVA light and accomplishes cross-connecting without representing a danger to the basic essential structures because of any wanderer radiation. We watched the topographic and refractive constancy of the strategy to be superb and all around kept up at six months. None of the patients' eyes had clinical or topographic, regression, or evidence of postoperative ectasia. There was no decrease in CDVA in any of them and they did not need glasses during the follow-up period. Drop in CS and dry eye was insignificant, with close to

recovery of both transient issues during follow-up.

Preliminary outcomes recommend that it is safe to combine CXL with SMILE for future utilizations to prevent keratoconus .Limitations of this study include: lack of equipment for examine the changes in biomechanics and impact of the excessive cross-connecting on keratocytes with confocal microscopy, small number of patients participating in the project and its short-term follow-up.

In conclusion, combining SMILE Xtra with CXL is a promising method to keep ectasia in patients with thin cornea and borderline topography. With at risk for ectasia. It is a simple and safe strategy that can be proposed to patients undergoing SMILE who are at risk for ectasia.

Acknowledgments:

Special thanks to the management and staff of Bina Afrin eye Clinic

Conflict of interest

Authors declare no conflict of interest.

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