·Clinical Research·

Short term effects of small incision lenticule extraction surgery on corneal endothelium

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Abstract

• AIM: To assess the effects of small incision lenticule extraction (SMILE) surgery on the corneal endothelium at 1d to 1mo postoperatively.

• METHODS: A retrospective, observational study was conducted on 47 patients (47 eyes) who received SMILE surgery. Patients were grouped according to contact lens wear condition. The corneal endothelium was examined preoperatively and at 1d, 1wk and 1mo postoperatively. The corneal endothelium was analyzed for endothelial cell density (ECD), percentage of hexagonal cells, and coefficient of variation (CV) of cell size.

• RESULTS: There were no significant decrease in the ECD, percentage of hexagonal cells or increase in CV at 1d, 1wk and 1mo postoperatively (P>0.05). However, there was a small increase of ECD by 2.88% in contact lens wearers (78.26±113.62 cell/mm², P<0.05).

• CONCLUSION: SMILE has no significant adverse effects on the corneal ECD and morphology during 1mo follow-up time.

• **KEYWORDS:** myopia; corneal endothelium; refractive surgery
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INTRODUCTION

Since first described by Pallikaris *et al* [1], laser *in situ* keratomileusis (LASIK) has become a widely used procedure to correct myopia. It combines the creation of a corneal flap using a microkeratome or femtosecond laser and ablation of the underlying corneal stroma using an excimer laser. Recently, refractive lenticule extraction (ReLEx®) has been introduced as an innovative refractive procedure without the use of excimer laser [2-4]. Small incision lenticule extraction (SMILE) is a variation of ReLEx® performed entirely through a small incision rather than by creating and lifting a hinged flap. SMILE is considered a promising new, flapless, minimally invasive, precise, refractive procedure to correct myopia[4-9]. Corneal clarity and function depend on an intact and healthy corneal endothelium, and surgical procedures of the cornea should not adversely affect this non-regenerative cell layer [10]. Previous studies have shown that there were no significant impairment on corneal endothelium in short and long-term follow-up time points (1mo to 9y) after LASIK, femtosecond LASIK, photorefractive keratectomy (PRK) and ReLEx® [10-13]. When compared with these surgeries, features of SMILE such as deep ablation depth (120 μm cap in SMILE *vs* 85-110 μm flap in femtosecond LASIK), bigger laser energy and frequency (180 nJ and 500 kHz femtosecond laser for SMILE *vs* 130 nJ and 500 kHz femtosecond laser for femtosecond LASIK, 400Hz excimer laser for femtosecond LASIK, LASIK and PRK stromal ablation) and more laser scan (two layer laser scan in SMILE *vs* one layer of laser scan in LASIK and PRK) may increase the risk of endothelial damage. Therefore, the short term effects of SMILE surgery on corneal endothelial cells need further investigation.

Corneal endothelial density and morphology may be influenced by long term contact lens wear, which is attributed to the contact lens inducing hypoxia in many studies. Refractive surgery stops the usage of contact lens in myopes, theoretically improving the oxygen transmission in the cornea.

In this study, we evaluated the effects of SMILE surgery on corneal endothelium cell density (ECD), percentage of hexagonal cells, and coefficient of variation (CV) of cell size in contact lens wearer and non-contact lens wearer to evaluate the number and morphology of endothelial cells at 1d, 1wk and 1mo postoperatively. The decrease in ECD, percentage of hexagonal cells, and increase in CV are considered to be indicative of endothelial damage.

SUBJECTS AND METHODS

Consecutive patients undergoing SMILE between March and May 2013 were enrolled in this retrospective observational study. All patients were treated at Zhongshan Ophthalmic Center. All patients aged 18y or older, had topography examination, anterior segment microscopy confirmed by slit lamp, and fundus confirmed by dilated funduscopy. The patients did not have glaucoma, ocular hypertension, a history of ocular disease, trauma, prior surgery, systemic disease, and pregnant or using systemic corticosteroids. Patients were grouped according to contact lens history, a patient was considered a contact lens wearer (CL group) only if he or she had a history of contact lens used for at least 16h per week one year before surgery[14].

All patients were appropriately informed before their participation in the study and gave their written informed consent in accordance with institutional guidelines according to the Declaration of Helsinki. The ethics committee in Zhongshan Ophthalmic Center, Sun Yat-sen University, approved this study.

All operations were performed by the same surgeon (Liu Q) using the VisuMax® femtosecond laser system (Carl Zeiss Meditec AG, Jena, Germany) with a laser frequency of 500 kHz and laser energy of 180 nJ. After application of topical anesthesia, standard sterile draping, and insertion of the speculum, the patient's eye was centered and docked with the curved interface cone before application of suction fixation. The laser was then activated for photo-dissection in the following sequence: first, the posterior surface of the refractive lenticule (spiral in), then the lenticule border was created; the anterior surface of the refractive lenticule (spiral out) was then formed and extended beyond the posterior lenticule diameter by 0.5 mm to form the anterior cap and was followed by a 3-mm incision width. Femtosecond laser parameters were 120 μm cap thickness, 7.3 mm cap diameter, and 6.3 mm optical zone of lenticule, the energy for the cap and lenticule creation was 180 nJ. After the suction was released, a spatula (S02710 Geuder) was inserted under the cap near the hinge, and the cap was separated. The edge of the refractive lenticule was separated from the stromal bed, and the posterior border of the lenticule was gently separated with the spatula. The lenticule was then grasped with a non-toothed serrated forceps through the small incision[15].

Table 1 Demographic data $\bar{x} \pm s$

Parameters	NCL group (n=30)	CL group (n=17)	^aP
Age (a)	25.53 ± 4.17	24.18±4.49	0.303
CCT (μm)	549.23±24.20	553.41±29.32	0.601
MSRE (D)	-5.37±1.65	-6.23±1.96	0.114
RCT (μm)	327.67±28.63	323.12±35.27	0.633
ECD (cells/mm^2)	2908.18±259.99	2863.24±224.45	0.536
Hex (%)	58.26±9.70	59.81±11.05	0.633
CV (%)	31.61±3.65	31.91±3.45	0.776

CCT: Center corneal thickness; MSRE: Manifest spherical refractive equivalent; RCT: Residual corneal thickness; ECD: Endothelial cell density; Hex: Percentage of hexagonal cells; CV: Coefficient of variation of cell size. ^aP: Student's t-test.

After surgery, topical levofloxacin eye drops (Santen Pharmaceutical Co., Ltd., Tokyo, Japan) were administered four times daily during the first 2wk. Tobramycin and dexamethasone eye drops (TobraDex, Alcon, Rijksweg, Belgium) and loteprednoletabonate ophthalmic suspension (Lotemax, Bausch &Lomb, Rochester, NY, USA) were administered four times daily during the first and second week, respectively.

Endothelial microscopy was performed preoperatively and 1d, 1wk and 1mo postoperatively using a noncontact specular microscope (Topcon SP-3000P, Topcon Corporation, Tokyo, Japan). The measurement was taken three times from the central cornea for each eye, and the mean value was used for analysis.

Residual bed thickness was calculated by postoperative corneal thickness measured by a Pentacam rotating Scheimpflug camera (Oculus, Wetzlar, Germany) with minus cap thickness of 120 μm.

Statistical Analysis Statistical analysis was performed using SPSS 18.0 for Windows (SPSS Inc, Chicago, IL, USA). General linear model, repeated measures and LSD-tests were used to test the difference of ECD, percentage of hexagonal cells, and CV pre- and postoperatively. Statistical significance was set at P<0.05.

RESULTS

There were 47 patients enrolled, 30 were non-contact lens wearers (NCL group) (18 males and 12 females), 17 were CL group (5 males and 12 females). Demographic data from NCL and CL groups are shown in Table 1. Only data from right eyes were used for analysis.

In corneal refractive surgery, corneal endothelial cell density is overestimated after surgery because the image is minimized depending on the change in corneal thickness and keratometry. An equation was used to calculate the ECD in each time point postoperatively, which is described in detail by Nawa *et al*[16].

An uncorrected visual acuity (logarithm of the minimum angle of resolution, logMAR) of 20/20 or better was observed in 70%, 96% and 96% of contact lens wearer at 1d, 1wk and 1mo postoperatively, respectively. On the other hand, 69%, 96% and 97% of non-contact lens wearer had an uncorrected visual acuity (logMAR) of 20/20 or better at 1d, 1wk and 1mo postoperatively, respectively. The mean ECD, percentage of hexagonal cells, and CV preoperatively and at 1d, 1wk and 1mo postoperative follow-up time points from CL and NCL groups are shown in Figure 1. No statistically significant changes were found in percentage of hexagonal cells and CV preoperatively, and at 1d, 1wk and 1mo postoperatively (general linear modal, repeated measurement, P>0.05) in both CL and NCL groups. ECD in NCL groups showed a small increase by 0.70% at 1mo postoperatively, which is not statistically significant. However, an increase in ECD by 2.88% was found in CL group 1mo postoperatively (general linear modal, repeated measurement, P<0.05).

DISCUSSION

As a new surgical technique, SMILE uses an all-in-one femtosecond laser system that requires only a small incision (2-4 mm) without the need for lifting a flap, which means the incision may heal relatively quickly and more corneal nerves are preserved. Also, there may be beneficial biomechanical effects caused by the preserved corneal integrity. The SMILE technique must be used safely because the corneal endothelium cannot regenerate after birth, and any endothelial cell loss or damage after SMILE would lower the procedure's acceptance and application.

Many studies have been performed to evaluate the influence of refractive surgery on the corneal endothelium. Tomita *et al*[11] studied and compared the corneal endothelial changes after LASIK with the use of femtosecond lasers for flap creation, and concluded that both IntraLase FS60 (Abott Medical Optics, Santa Ana, California, USA) and ZiemerFemto LDV (Ziemer Ophthalmic Systems, Port, Switzerland) did not impair the corneal endothelium at 3mo postoperatively. Klingler *et al* [10] investigated the endothelium at 3 and 5y after LASIK using the femtosecond laser or mechanical microkeratome, the authors found no significant damage in either type of LASIK surgery. Kamiya *et al* [13] first reported corneal endothelial cell density changes after ReLEx® and the result showed that ECD didn't have a significant decrease 6mo postoperatively. Most recently, Zhang *et al* [14] reported that SMILE surgery is safe for corneal endothelium. In our study, we compared the ECD, percentage of hexagonal cells, and CV of cell size before SMILE surgery to 1d and up to 1mo after surgery and found that these parameters did not have a statistically significant change at 1d, 1wk, or 1mo postoperatively. Interestingly, a 2.88% increase in ECD was observed 1mo postoperatively in CL group. Previous studies have also reported the same results and proposed that after refractive surgery, patients would have a thinner cornea, which could allow oxygen to diffuse across the corneal endothelium more easily, thereby improving its health [17]. Sheng and Bullimore [18] considered that stopping the use of contact lenses may be related to this increase in central ECD as peripheral cells reposition to the central area. Wiffen *et al*[19] also reported that contact lens wear may cause a mild redistribution of endothelial cells from the central to the peripheral cornea and a reversal of this redistribution can happen after discontinuing contact lens wear after refractive surgery. As endothelial nutrition and oxygen are mainly supplied by aqueous humor, and endothelial repair is limited to enlargement and sliding of existing cells, with little capacity for cell division, we considered this increase of ECD

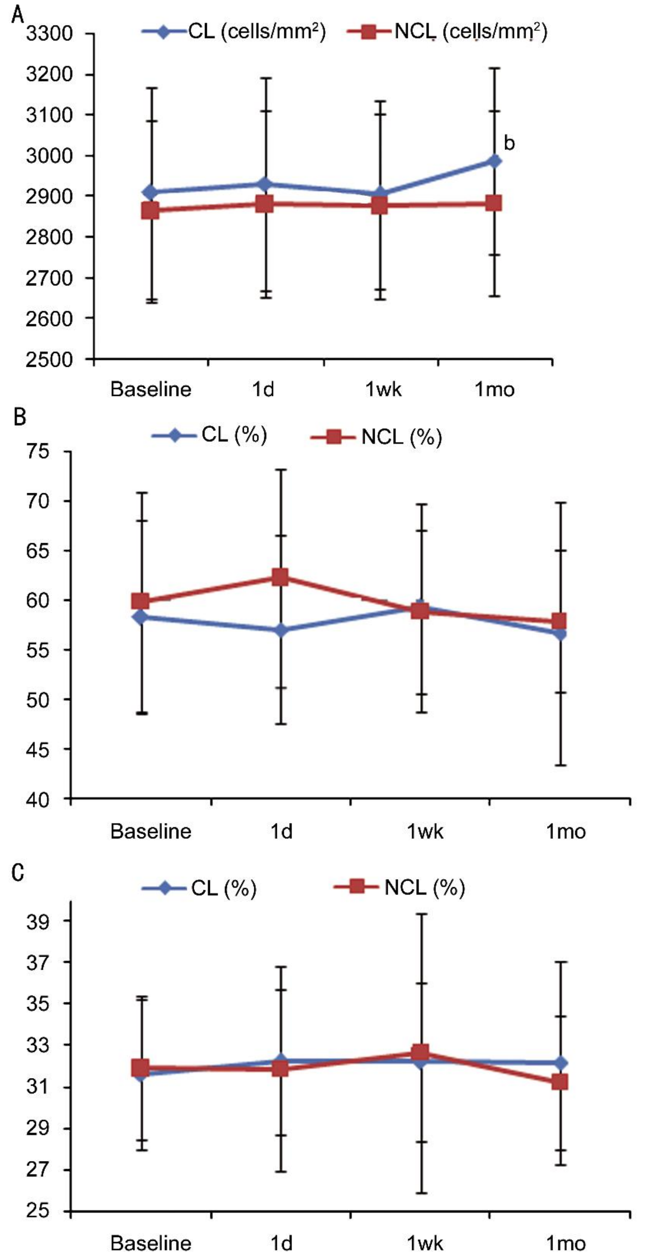

Figure 1 Comparison of ECD, percentage of hexagonal cells and CV between CL and NCL groups at 1-month follow up
A: Corneal endothelium cell density; B: Percentage of hexagonal cells; C: Coefficient of variation. ^bP<0.001 *vs* NCL group.

in our study attributable to discontinuation of contact lens use before surgery and reestablishment of a normal endothelial pattern by cell migration from the peripheral to central cornea. Contact lens wearers may benefit from refractive surgery to halt anoxia of the cornea.

A limitation of our study was that our follow-up time started at 1d postoperatively, thus the effects of femtosecond laser on endothelium within hours or even minutes after surgery have not been looked into. LASIK and PRK have been reported to have an acute damage on endothelium and represent endothelial cell edema which may happen a few minutes after surgery and then reverses at day 1 postoperation [20-21]. Whether SMILE also have this acute damage on the endothelium should be studied in the future.

Further studies should also analyze the peripheral endothelial cell density and morphology causing damage to the endothelium that may be masked upon discontinued use of contact lens, which can cause a redistribution of endothelial cell from peripheral to central area [19]. In conclusion, after 1-month follow-up in 47 eyes, we found no significant decrease in ECD, percentage of hexagonal cells, and no significant increase of CV after SMILE surgery. SMILE appears to have no apparent adverse effect on the corneal endothelium.

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