Corneal hypoesthesia is a common side effect after corneal refractive surgeries. Numerous reports have documented significant effects of refractive surgeries on corneal sensation due to the amputation of superficial nerve fibers in surgeries, including LASIK, photorefractive keratectomy, laser epithelial keratomileusis, and femtosecond laser-assisted LASIK (femto-LASIK).

Small incision lenticule extraction (SMILE) is an all-in-one procedure that avoids the creation of flaps, which theoretically allows for less amputation of superficial corneal nerve fibers than other surgery techniques. Therefore, the decrease of corneal sensation after SMILE is expected to be less significant than that of other refractive surgery techniques.

In the current study, we compared the time-dependent changes and recovery patterns of corneal sensation after SMILE and femto-LASIK for myopia. We also investigated whether postoperative corneal sensation was correlated with preoperative spherical equivalent and corneal ablation depth.

PATIENTS AND METHODS

Participants
Seventy-one consecutive patients who underwent SMILE or femto-LASIK for myopia at the Fudan University Eye and ENT Hospital (Shanghai, People’s Republic of China) were recruited.

RESULTS: All tested areas within the cap or flap demonstrated corneal hypoesthesia immediately after both surgeries. SMILE-treated eyes showed less compromised corneal sensation than femto-LASIK–treated eyes at all postoperative visits in the central, inferior, nasal, and temporal areas at the 1-week and 1-month visits. In the SMILE group, the inferior, nasal, and temporal quadrants recovered faster than other areas. In the femto-LASIK group, the sensation over the flap did not recover to preoperative levels by postoperative 6 months. There was no correlation between postoperative corneal sensation, preoperative spherical equivalent, and ablation depth in both groups.

CONCLUSIONS: The impairment of corneal sensation was less significant in the SMILE group than in the femto-LASIK group and was independent of preoperative spherical equivalent or ablation depth.

between June 2010 and February 2012. All patients underwent bilateral SMILE or femto-LASIK procedures, and 1 eye of each patient was randomly chosen for inclusion in the statistical analysis of the current study. The inclusion criteria were older than 18 years, normal ophthalmic examination (with the exception of refractive error), a stable refractive error, and a calculated residual corneal stromal bed thickness greater than 280 µm.

The same surgeon (XZ) performed all surgical procedures. Informed written consent was obtained from all patients after detailed discussions. The Ethical Committee of the Fudan University EENT Hospital Review Board approved the study protocol and the study was conducted in accordance with the tenets of the Declaration of Helsinki.

**Surgical Techniques**

The VisuMax femtosecond laser system (Carl Zeiss Meditec, Oberkochen, Germany) was used to make surgical refractive corrections in the SMILE group. The energy was set at a repetition rate of 500 kHz and a pulse energy of 130 nJ. The surgical procedure has been described by Sekundo et al. The intended thickness of the upper tissue arcade was 100 µm. The intended diameter of the cap was 7.5 mm, which was 1 mm larger than the diameter of the refractive lenticule (6.5 mm). The side cuts made for access to the lenticule were set 90° apart at a circumferential width of 4.5 mm. The refractive lenticule of the intrastromal corneal tissue was dissected through the side-cut incision and manually removed using forceps.

In the femto-LASIK group, flaps were created with a 500-kHz (pulse energy of 185 nJ) VisuMax femtosecond laser. The created flaps had diameters of 8.5 mm, standard 90° hinges, and 90° side-cut angles. The target flap thickness was 90 µm. The hinges were set to a superior orientation with a hinge width of 4.0 mm. Stromal tissue ablation was performed with the Mel-80 (Carl Zeiss Meditec) excimer laser with a repetition rate of 250 kHz and a pulse energy of 150 nJ, using a tissue-saving function. The procedure was performed under topical anesthesia in all cases.

Patients wore bandage soft contact lenses (ACUVE OASYS, Inc., Jacksonville, FL) until the day after the operation. Postoperative topical medication regimens were identical for both groups and consisted of the administration of an ophthalmic solution of levofloxacin four times per day in both eyes for 7 days, a 0.1% fluorometholone solution eight to one times per day (tapering for a period of 20 days) in both eyes, and a nonpreservative tear supplement (Carboxymethyl cellulose Sodium Eye Drops; Allergan, Inc., Irvine, CA) four times per day in both eyes for 1 month.

**Corneal Sensation Esthesiometer**

Corneal sensation was measured with a Cochet-Bonnet esthesiometer (Luneau, Paris, France), which consists of a nylon monofilament that is 60 mm long and has a diameter of 0.12 mm. The instrument was pushed perpendicular to the corneal surface until a small bend was observed between the instrument and the cornea. Corneal sensation was tested three times with each filament length and the length of the filament was sequentially reduced from 60 mm in 5-mm steps. Two positive responses among three attempts were considered positive. The longest filament length that resulted in a positive response was considered the corneal threshold. Full recovery was defined as recovery to the preoperative corneal sensation scores. All of the measurements were performed under slit-lamp examination by the same observer (ML), who was blind to the patient and postoperative time.

Corneal sensation was measured in five areas of each cornea: the central cornea and four peripheral quadrants (superior, inferior, temporal, nasal) of the cap (Figure 1A) or flap (Figure 1B). Corneal sensation was evaluated in all of the patients prior to surgery and 1 week and 1, 3, and 6 months after surgery.

**Statistical Analysis**

Data were analyzed using the SAS 9.3 statistical software (SAS Institute, Inc., Cary, NC). Continuous variables were expressed as the mean ± standard deviation, whereas categorical variables were expressed as frequency and percentage for description. The independent Student’s t test or Mann–Whitney U test was used for comparison of continuous variables and Pearson chi-square test was used for categorical variables at the baseline. A mixed model was constructed to compare the corneal sensation between the SMILE and femto-LASIK groups by taking preoperative spherical equivalent at baseline as the selected covariate and different times for measurements as the repeated factor. Analysis by Proc Mixed Procedure statistical software (SAS Institute, Inc., Cary, NC) was then performed. Least-squares means of corneal sensation in each visit were calculated. Multiple comparisons were adopted with the corneal sensation before surgery as the control group. Bonferroni-based adjustment was made for multiple comparison to control the family type I error at a level of 0.05. Associations between corneal sensation and clinical parameters (preoperative spherical equivalent, ablation depth) were examined by Spearman’s rank correlation test and expressed as the Spearman correlation. Statistical significance level was set at .05.
RESULTS

The patients’ demographic and baseline ophthalmologic data are summarized in Table 1. The analysis included 38 eyes of 38 patients in the SMILE group and 33 eyes of 33 patients in the femto-LASIK group. The two groups were comparable with regard to age, sex, central corneal thickness, surgical ablation depth, and preoperative corrected distance visual acuity. The differences in preoperative and treated spherical equivalent between the two groups were statistically significant.

Comparison of mean ± standard deviation values of corneal sensation between the SMILE and femto-LASIK groups at all visits are shown in Table 2. There were no significant differences in the mean preoperative corneal sensation in the five test areas (P = .9942, .9125, .6066, .3056, and .5760 for central, superior, inferior, temporal, and nasal areas, respectively).

At the central area, corneal sensation significantly decreased at the 1-week and 1-, 3-, and 6-month visits after surgery in both groups (all P < .0001). Additionally, the SMILE-treated eyes showed better central corneal sensation than in the femto-LASIK–treated eyes at all postoperative follow-up visits (P = .0274, .0353, .0136, and .0330 for 1 week and 1, 3, and 6 months after surgery, respectively) (Figure 2A).

The corneal sensation in the superior quadrant had not returned to preoperative levels by postoperative 6 months in both groups (Figure 2B). Yet, unlike other tested areas, corneal sensation in the superior quadrant was less compromised in the femto-LASIK–treated versus SMILE-treated eyes at postoperative 1 week (P < .0001) and 1 (P < .0001) and 3 (P = .0190) months. At the postoperative 6-month visit, there was no difference between the two groups in this quadrant (P = .2526) (Figure 2B).

### TABLE 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SMILE (n = 38)</th>
<th>Femto-LASIK (n = 33)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>Age, y (mean ± SD)</td>
<td>28.2 ± 7.04</td>
<td>27.3 ± 6.6</td>
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<td>Male/female</td>
<td>10/28</td>
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<td>Preoperative SE (D)</td>
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<td>Treated SE (D)</td>
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<tr>
<td>Mean</td>
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<tr>
<td>Range</td>
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<tr>
<td>Corneal thickness (µm)</td>
<td>544.7 ± 30.3</td>
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<td>Ablation depth (mean ± SD, µm)</td>
<td>131.5 ± 22.9</td>
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<td>Range</td>
<td>77 to 165</td>
<td>51 to 168</td>
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<tr>
<td>CDVA (logMAR)</td>
<td>-0.02 ± 0.05</td>
<td>-0.00 ± 0.07</td>
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</table>

**SMILE** = small incision lenticule extraction; **femto-LASIK** = femtosecond laser-assisted LASIK; **SD** = standard deviation; **SE** = spherical equivalent; **D** = diopters; **CDVA** = corrected distance visual acuity

*Independent Student’s t test or Mann–Whitney U test.

*Chi-square test.
The inferior, nasal, and temporal areas in the SMILE group demonstrated decreased corneal sensation at postoperative 1 week (all \( P < .0001 \)) and 1 (all \( P < .0001 \)) and 3 (\( P < .0001, < .0001, = .0025 \), respectively) months, but returned to preoperative levels at 6 months (\( P = .1405, .1915, \text{ and } .0629 \), respectively). In the femto-LASIK group, all three areas showed decreased corneal sensation at postoperative visits (all \( P < .0001 \), except \( P = .0033 \) for the temporal area at 6 months). In addition, the SMILE group showed significantly better
corneal sensation in the nasal and inferior quadrants compared to the femto-LASIK group at the postoperative visits (Figures 2C-2E). At both 1 week and 1 month postoperatively, corneal sensation in the temporal quadrants of the SMILE-treated eyes was better than in the femto-LASIK group \((P < .0001\) and \(=.0002\), respectively), but no statistical difference was found between the two groups at the postoperative 3- and 6-month visits \((P = .1982\) and .2398, respectively) (Figure 2D).

Differences of the corneal sensation in various areas were compared at each visit with multiple comparisons tests. At all postoperative visits for the SMILE group, inferior, temporal, and nasal areas showed better corneal sensation than the central and superior areas. At the 1-week and 1-month visits, the superior area showed the most compromised sensation in the whole cornea (Figure 3A). In the femto-LASIK group, the central area showed the most compromised sensation of the whole cornea throughout the follow-up and the superior area showed the best corneal sensation throughout the postoperative visits except at the 6-month visit (Figure 3B).

The Spearman correlation test showed that the postoperative corneal sensation values were not correlated with the preoperative spherical equivalent (all \(P > .05\)) or the ablation depth (all \(P > .05\)) at postoperative visits.

**DISCUSSION**

Corneal sensation is mediated by corneal nerve fibers that originate from the long ciliary nerves (which penetrate the cornea in the anterior one-third of the stroma). The long ciliary nerves then run forward in a radial fashion from the periphery of the cornea toward its center. Reduction in corneal sensation after corneal refractive surgeries is an inescapable consequence owing to the amputation of superficial corneal nerve fibers when making the flap with the subsequent laser ablation. The SMILE technique is an all-in-one procedure in which both the cap and the refractive lenticule are created using a femtosecond laser without creation of corneal flap. However, in femto-LASIK procedures, both flap cutting and laser ablation contribute to the corneal denervation. Therefore, it may be expected for SMILE to have superiority over that of the flap procedures on structural integrity of the cornea and corneal nerve fibers.9

Results of multiple tested areas differed between the two surgical procedures. Wei and Wang9 reported that all five tested areas in the SMILE-treated eyes had better corneal sensitivity than the respective values in the femto-LASIK–treated eyes at postoperative visits (1 week and 1 and 3 months).9 Our results are partly consistent with theirs. In our study, the central, inferior, and nasal areas showed better corneal sensation in the SMILE-treated eyes than in the femto-LASIK–treated eyes at postoperative visits. In the first 3 months after surgery, the SMILE-treated eyes showed better corneal sensation in the temporal area than those in the femto-LASIK–treated eyes, but there was no statistical difference between the two groups following those postoperative 3 months. On the contrary, the superior area in the SMILE-treated eyes demonstrated worse corneal sensation than in the femto-LASIK–treated eyes within the postoperative 3 months, which was not surprising in that, during the SMILE procedure, the side cuts made for accessing the lenticule were set in superior position where the superficial nerve fibers were completely severed. In the femto-LASIK–treated eyes, the nerves located at the position of the hinge were preserved.
Recovery time for corneal sensation varies for different refractive surgical procedures. Previous studies have shown that the central corneal sensation recovers to the preoperative values between approximately 1 and 3 months after photorefractive keratectomy, 11 3 months for low-moderate myopia, 6 months for high myopia after laser epithelial keratomileusis, 12 and approximately 3 to 16 months for myopia after LASIK. 13 Barequet et al. 7 found that the central corneal sensation recovered to preoperative levels 6 months after femto-LASIK, whereas Mian et al. 6, 8 considered that the central corneal sensation did not recover by the 12-month postoperative period. Wei and Wang 9 reported that corneal sensation in the five tested areas had recovered to preoperative levels 3 months after SMILE surgery but did not recover by 6 months after femto-LASIK. Our study showed that all areas (except the nasal, temporal, and inferior) in the SMILE group did not return to the preoperative levels by postoperative 6 months, although there was a strong trend close to normal. In the femto-LASIK group, all areas on the cornea did not return to preoperative levels at the postoperative 6-month visit.

Slight differences were noted for corneal sensation in different areas of the cornea. The pattern of recovery was generally characterized by earliest recovery in the regions of the inferior, nasal, and temporal cornea and latest recovery in the superior cornea in SMILE-treated eyes; the earliest took place in the hinge and the latest was found in the central cornea in femto-LASIK–treated eyes. Our results were consistent with other reports. 13, 14 Nassaralla et al. 14 and Chuck et al. 15 found that the region of the hinge recovered earliest and the central cornea recovered latest after LASIK. It was expected that the latest recovery took place in the superior cornea in SMILE-treated eyes and the earliest took place in the hinge in femto-LASIK–treated eyes because it corresponds well with the severing of the nerve fibers during surgeries. As for the different recovery pattern in other tested areas (inferior, central, nasal, temporal), we hypothesize that it may be attributed to two reasons: distribution of corneal sub-basal nerve fibers and corneal sub-basal nerve regeneration pattern. Patel et al. 16 found that the sub-basal nerve plexus appeared to radiate toward a whorl-like complex and the mean nerve density was significantly higher in the infero-central whorl region compared to the central area. Additionally, the corneal nerves usually regenerated from the peripheral cornea outside of the cap or flap to the denervated cap or flap center. 17

In our study, the degree of sensation loss was found to be independent of preoperative spherical equivalent or ablation depth, which is compatible with other studies finding that mean spherical equivalent refraction did not have a statistically significant effect on postoperative corneal sensitivity in LASIK-treated patients. 15, 18 In contrast, some studies 12, 19 found that central corneal sensation correlated significantly with the ablation depth, considering that a deeper lamellar ablation indicated a larger volume of corneal stroma through which nerves must regenerate, subsequently delaying the recovery process of corneal sensation. Additionally, Lee et al. 2 found that the regeneration of corneal nerves correlated with the recovery of corneal sensation by in vivo confocal microscopy examinations of corneal nerves. Yet, we were unable to determine why the decrease of corneal sensation was not correlated with operative ablation depth or preoperative spherical equivalent. It is possible that other factors besides sub-basal nerve density, such as nerve growth factor, may also contribute to the recovery of corneal sensation. 20 Future studies are necessary to analyze postoperative tear components and identify relevant biomarkers to facilitate corneal recovery.

Ours is the first study to statistically analyze the recovery differences among five tested areas within the caps after SMILE. Yet it was limited because it was not a randomized design. Another limitation was that it did not employ the same cap/flap diameters (7.5 mm for SMILE and 8.5 mm for femto-LASIK) or the same cap/flap thickness (100 μm for SMILE and 90 μm for femto-LASIK), which may bias the study results. Future studies are desirable to elucidate whether these different surgical parameters play a role on the postoperative corneal sensation recovery.

Our data showed that corneal sensation in the five tested areas was impaired after SMILE. The central and superior regions of the cornea needed 6 months or more for a full recovery. SMILE-treated eyes showed faster recovery than femto-LASIK–treated eyes. No direct correlation was found between the postoperative corneal sensation and ablation depth or treated spherical equivalent. Further studies with a prospective randomized design are desirable to elucidate the impact of SMILE surgery on postoperative corneal sensation.

AUTHOR CONTRIBUTIONS
Conception and design (ML, LG, XZ); data collection (ML, YS); analysis and interpretation of data (ML, ZZ, MCK); writing the manuscript (ML, ZZ, YS); critical revision of the manuscript (ML, ZZ, MCK, LG, XZ); administrative, technical, or material support (XZ); supervision (XZ)

REFERENCES


