Intraocular Pressure Changes and Relationship With Corneal Biomechanics After SMILE and FS-LASIK

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PURPOSE. The purpose of this article was to evaluate intraocular pressure (IOP) changes and investigate the relationship with corneal biomechanics after small-incision lenticule extraction (SMILE) and femtosecond laser-assisted laser in situ keratomileusis (FS-LASIK).

METHODS. A total of 193 eyes of 193 patients who underwent SMILE and FS-LASIK procedures were included in this retrospective study. Data were collected preoperatively and postoperatively, including Goldmann-correlated IOP (IOPg), corneal-compensated IOP (IOPcc), corneal hysteresis (CH), and corneal resistance factor (CRF) by ocular response analyzer, noncontact intraocular pressure (IOPNCT) by noncontact tonometer, and Ehlers, Shah, Dresden, Kohlhaas, Orssengo/Pye by the Pentacam corrected system. Changes in both groups and differences between groups were evaluated. Multiple linear regression models were constructed to explore factors influencing IOP changes.

RESULTS. In SMILE, the IOPg, IOPcc, IOPNCT, and Kohlhaas decreased significantly at 1 month postoperatively (P < 0.01), whereas with the Ehlers formula they significantly increased (P < 0.01). IOPs decreased at 3 and 6 months compared with all preoperative values except Ehlers values (P < 0.01), but there was no significant difference between 3 and 6 months (P > 0.05). In FS-LASIK, the IOPg, IOPcc, and IOPNCT decreased significantly at 1 month (P < 0.01), whereas in the Ehlers and Shah formulas they significantly increased (P < 0.01). Compared with preoperative values, the IOPs decreased at 3 and 6 months except in the Ehlers and Shah formulas (P < 0.01). Only IOPg and IOPcc differed between 3 and 6 months (P < 0.05). The Ehlers and Shah formulas were closer to the preoperative IOP for both groups, with variation approximately 1 mm Hg at 6 months postoperatively. Preoperative IOP, postoperative corneal resistance factor, corneal hysteresis, and flat keratometry were enrolled into the regression equations.

CONCLUSIONS. IOP underestimation after SMILE or FS-LASIK was related to corneal biomechanics as well as preoperative IOP and flat keratometry. IOP after SMILE seem to remain more stable. Accordingly, the Ehlers and Shah formulas were closer to the preoperative IOP. It may be useful to estimate future IOP with the best-fit models after surgery.

Keywords: intraocular pressure, small-incision lenticule extraction, femtosecond laser-assisted laser in situ keratomileusis, corneal biomechanics

Corneal refractive surgery, such as femtosecond laser-assisted laser in situ keratomileusis (FS-LASIK) and small-incision lenticule extraction (SMILE), has emerged as having good efficacy, predictability, safety, and stability for surgical correction of low, moderate, and high myopia. However, the central corneal thickness (CCT), the corneal curvature, and corneal biomechanics change after corneal refractive surgery, which may affect intraocular pressure (IOP) measurements.

Meanwhile, myopia is a risk factor for open-angle glaucoma, and the routine application of steroids postoperatively will increase the risk of elevated IOP after corneal refractive surgery, even causing steroid-induced glaucoma. In addition, elevated IOP is recognized as the most important risk factor for progressive glaucomatous damage. Therefore, the accurate evaluation of IOP is a great concern for clinicians.

Previous studies have showed IOP changes after some refractive surgeries, including photorefractive keratectomy, laser-assisted subepithelial keratectomy, laser in situ keratomileusis (LASIK), epipolis laser in situ keratomileusis, and FS-LASIK. Up to now, there has been no study regarding IOP change after SMILE, especially a comparison of IOPs between SMILE and FS-LASIK. We therefore decided to conduct a new retrospective study to evaluate IOP changes and the relationship with corneal biomechanics after both surgeries.

METHODS

Patients

The institutional review board at Tianjin Eye Hospital, Tianjin Medical University, approved this study protocol, which adhered to the tenets of the Declaration of Helsinki. All patients provided informed consent for surgery.

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Intraocular Pressure Changes After SMILE and FS-LASIK

This was a retrospective study performed at Tianjin Eye Hospital, and patients with myopia or myopic astigmatism who underwent SMILE or FS-LASIK were enrolled. Inclusion criteria were (1) patients older than 18 years; (2) absence of corneal, ocular, or systemic diseases; (3) refractive dioptr maintained stable the past 2 years (change of ± 0.50 diopter); (4) patients who wore soft contact lenses were off contact lenses for at least 2 weeks and off rigid contact lenses for at least 4 weeks; (5) preoperative noncontact intraocular pressure (IOP\textsubscript{NCT}) less than 21 mm Hg; (6) no family history of glaucoma; (7) accurate value in softer eyes and patients after refractive surgery. From a total of 193 eyes, 97 eyes of 97 patients underwent SMILE and 96 eyes of 96 patients underwent FS-LASIK.

Measures

Patients underwent preoperative measurements of uncorrected distance visual acuity; corrected distance visual acuity; manifest and cycloplegic refractions; IOP\textsubscript{NCT}, Goldmann-corrected IOP (IOPg), and corneal-compensated IOP (IOPcc) measured by an Ocular Response Analyzer (ORA), corneal tomography, and Pentacam-corrected IOPs by the Scheimpflug tomography system (Pentacam; Oculus GmbH, Wetzlar, Germany). Patients were followed up at 1, 3, and 6 months after surgery.

Ocular Response Analyzer

The ORA (Reichert, Inc., Depew, NY, USA) was used to measure corneal biomechanics and IOPs. Measured parameters are produced by the dynamic bidirectional applatonator based on the two pressure measurements at application, P1 in the inward direction and P2 in the outward direction. The four parameters included (1) corneal hysteresis (CH), with \( CH = a[P1-P2]^{10} \) representing the ability of the cornea to absorb or dampen the applied force; (2) corneal resistance factor (CRF), with \( CRF = a[P1-0.7P2] + d \) described as the whole corneal resistance cumulative effect; (3) IOPg, with \( IOPg = a[P1-P2]/2 + c \), which were highly correlated with IOPcc; (4) IOPcc, with \( IOPcc = b[P2-0.43P1] + e \), which compensated for corneal properties in estimating IOP, producing a more accurate value in softer eyes and patients after refractive surgery, which a, b, c, d, and e are calibration and regression constants. For each studied eye, three records were reserved with the signal core higher than 3.5, and the average values were calculated.

Noncontact Tonometer

The noncontact tonometer (TX-F; Canon, Tokyo, Japan) was used to measure IOP avoiding contact and thus reducing the risk of infection. Some research suggested that IOP\textsubscript{NCT} had good repeatability and precision. This tonometer records three readings and then calculates the average value automatically.

Pentacam Scheimpflug Images

The rotating Scheimpflug camera identified 25,000 true parameters included (1) corneal hysteresis (CH), with \( CH = a[P1-P2]^{10} \) representing the ability of the cornea to absorb or dampen the applied force; (2) corneal resistance factor (CRF), with \( CRF = a[P1-0.7P2] + d \) described as the whole corneal resistance cumulative effect; (3) IOPg, with \( IOPg = a[P1-P2]/2 + c \), which were highly correlated with IOPcc; (4) IOPcc, with \( IOPcc = b[P2-0.43P1] + e \), which compensated for corneal properties in estimating IOP, producing a more accurate value in softer eyes and patients after refractive surgery, which a, b, c, d, and e are calibration and regression constants. For each studied eye, three records were reserved with the signal core higher than 3.5, and the average values were calculated.

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Pentacam Scheimpflug Images

The rotating Scheimpflug camera identified 25,000 true elevation points to measure corneal thickness and curvature. It also had five IOP correction formulas to correct IOP. This applied for measurements with the application tonometer as well as the NCT. When IOP\textsubscript{NCT} data were input into Pentacam, Ehlers, Shah, Dresden, Kohlhaas, and Orsengo/Pye formulas, corrected IOPs were generated. The following descriptions explain the calculation of IOP change for the correction formula: (1) Ehlers: \( IOP\text{change} = 0.071 \times (545 - \text{corneal thickness}_{\text{measured}}^{31}) \); (2) Shah: \( IOP\text{change} = 0.050 \times (550 - \text{corneal thickness}_{\text{measured}}^{32}) \); (3) Dresden: \( IOP\text{change} = 0.040 \times (550 - \text{corneal thickness}_{\text{measured}}^{32}) \); (4) Kohlhaas: \( IOP\text{change} = (540 - \text{corneal thickness}_{\text{measured}}^{31})/71 + (45 - K)/2.7 + 0.75^{24} \); (5) Orsengo/Pye: \( IOP\text{change} = IOP_{\text{measured}}/K_{25} \). These formulas can correct the effects of corneal thickness and corneal curvature on IOP.

Surgical Procedures

All surgical procedures were performed by the same surgeon (Y.W.). After routine irrigation of the conjunctival sac and periocular sterilization, topical anesthesia was applied with two to three drops of oxybuprocaine hydrochloride (benoxyl; Santen, Inc., Osaka, Japan) twice before surgery, 5 minutes apart.

SMILE Procedure

SMILE was performed using only the femtosecond laser platform (Visumax; Carl Zeiss Meditec AG, Jena, Germany), with typical pulse energy of approximately 140 to 150 nJ and a pulse repetition rate of 500 kHz. Four sequential cleavages were created to make an intrastromal lenticule and a small incision. The laser scanning order was, first, the posterior surface of the refractive lenticule, then the lenticule border, then the anterior surface of the lenticule and, finally, the side-cutting of the 3-mm width incision at the 12:00 location of the cornea. The lenticule diameter was 6.5 mm, and the side-cut angle was 90°. The corneal cap thickness was 110 μm, and its diameter was 7.5 mm. A basement of 10 to 15 μm above the lenticule was added to remove the lenticule successfully.

FS-LASIK Procedure

In the FS-LASIK group, flap creation was performed using the same femtosecond laser with pulse energy at 165 to 175 nJ. Flap diameter was 8.0 mm, and the thickness was 100 to 110 μm. The flap hinge was positioned nasally. After lifting the flap, ablation of the stromal bed was performed by an excimer laser system (Allegretto; WaveLight Laser Technologie AG, Erlangen, Germany). Finally, the corneal flap was repositioned.

Patients of both groups were medicated with topical 0.5% levofloxacin (Cravit; Santen, Inc.) eye drops four times daily for 2 days, and 0.1% fluorometholone (FML; Flumetholon; Santen, Inc.) twice before surgery, 5 minutes apart. Patients were medicated with topical 0.5% fluorometholone (FML; Flumetholon; Santen, Inc.) four times daily for 2 weeks and then tapered down to once every 2 weeks.

Statistical Analysis

Statistical analysis was performed using SPSS (version 20.0; IBM Corp., Chicago, IL, USA). In this study, changes were expressed by the Δ symbol and calculated as preoperative value minus 6-month postoperative value; the thickness of the tissue removed was expressed as lenticule thickness (LT) in the SMILE group and as ablation depth (AD) in the FS-LASIK group. Furthermore, because SMILE uses a unique corneal cutting algorithm, the LT was based on the algebraic sum of spherical power and astigmatic power. In the FS-LASIK group, the spherical equivalent was calculated.

The normality of all data samples were checked with the Kolmogorov–Smirnov test. The means of all of the IOPs at each examination point were compared by repeated-measures analysis of variance, and the further pairwise comparison used least-significant difference. The Greenhouse Geisser correction was applied to degrees of freedom if sphericity was violated. The comparison of IOP...
changes between two groups were performed using independent *t*-tests. The Pearson correlation coefficient (*r*) was used to evaluate the correlations between variables. Multiple linear regressions were used to explore factors influencing IOP changes in both groups. *P* values less than 0.05 were considered statistically significant.

**RESULTS**

Table 1 shows the preoperative baseline characteristics of patients by group. In the SMILE and FS-LASIK groups, 97 and 96 eyes completed postoperative examinations at 1 and 3 months, respectively; 44 and 38 of these eyes completed the 6-month follow-up. There were no significant differences between preoperative baseline characteristics.

**Change in the IOP Measurement Values and Corneal Parameters Over Time**

Table 2 shows IOPs, CH, CRE, CCT, flat keratometry (Kf), steep keratometry (Ks), and mean keratometry (Km) changes after SMILE and FS-LASIK. In SMILE, the IOPg, IOPcc, IOPnc, and Kohlhaas decreased significantly at 1 month postoperatively (*P < 0.01*), whereas in the Ehlers formula, they significantly increased (*P < 0.01*). All of the IOPs showed severe decreases at the 3- and 6-month follow-ups except for those in Ehlers (*P < 0.01*), but there were no significant differences between 3 and 6 months (*P > 0.05*). CH, CRE, CCT, Kf, Ks, and Km decreased significantly at 1, 3, and 6 months when compared

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<th>Pre- vs. Post-3M</th>
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1M, 1 month; 3M, 3 months; 6M, 6 months.

* *Significant difference at *P* < 0.05.*
with preoperative values (P < 0.01). CH and CRF showed no significant differences between 1, 3, and 6 months (P > 0.05).

In FS-LASIK, the IOPg, IOPcc, and IOPNCT decreased significantly at 1 month (P < 0.01), whereas in the Ehlers and Shah formulas they significantly increased (P < 0.01). All of the IOPs decreased sharply at the 3- and 6-month follow-up except in the Ehlers and Shah formulas (P < 0.01) when compared with preoperative values. Only IOPg and IOPcc differed between 3 and 6 months (P < 0.05). CH, CRF, CCT, Kf, Ks, and Km decreased significantly at 1, 3, and 6 months when compared with preoperative values (P < 0.01). CH and CRF showed no significant differences between 1 and 3 months (P > 0.05; Table 2).

**Between-Group Comparisons**

Table 3 shows IOP variation per removed or ablated tissue (ΔIOP/AD or ΔAD) between two groups, only ΔIOPg/AD and ΔIOPcc/AD in FS-LASIK were higher than ΔIOPg/AD and ΔIOPcc/AD in SMILE at the 6-month follow-up (P < 0.05). The Figure shows the ΔIOP at 1, 3, and 6 months postoperatively, and only ΔIOPg in FS-LASIK was higher than SMILE at the 6-month follow-up (P < 0.05). Similarly, ΔCRF, ΔCH, ΔKf, ΔKs, and ΔKm per removed or ablated tissue in FS-LASIK were higher than in SMILE (0.05 ± 0.02 vs. 0.04 ± 0.01, 0.03 ± 0.02 vs. 0.02 ± 0.01, 0.05 ± 0.02 vs. 0.04 ± 0.01, 0.06 ± 0.02 vs. 0.04 ± 0.01, 0.05 ± 0.02 vs. 0.04 ± 0.01; P = 0.001, 0.009, 0.001, <0.001, <0.001; respectively).

**Correlation Analysis**

Table 4 shows the correlations between the ΔIOPg, ΔIOPcc, ΔIOPNCT, and the pre-IOP, ΔCCT, ΔCRF, ΔCH, ΔKm, respectively. The ΔIOP in the FS-LASIK group had more influencing factors and correlated with ΔCH and ΔCRF. In SMILE, the ΔIOPg, ΔIOPcc, and ΔIOPNCT correlated with the pre-IOP (r = 0.532, 0.478, 0.512, respectively, P < 0.01). Although in FS-LASIK, the ΔIOPg, ΔIOPcc, and ΔIOPNCT correlated with the pre-IOP (r = 0.780, 0.664, 0.614, respectively, P < 0.01).

**Regression Analysis of ΔIOPNCT and Influencing Factors**

Table 2 shows that IOPNCT was stable at 3 months after SMILE and FS-LASIK, so patients’ completed 3-month follow-ups were analyzed. Considering that IOPNCT was common in clinical examinations, a multiple linear regression analysis of ΔIOPNCT was created to analyze the relationships between possible preoperative influencing factors (pre-IOP, pre-CCT, Kf, Ks, CRF, CH, and spherical power and astigmatic power/spherical equivalent) and intraoperative parameters (IT or AD) as well as postoperative influencing factors (post-CCT, Km, Kf, Ks, CRF, CH) and variations after surgery (ΔCCT, ΔKm, ΔKf, ΔKs, ΔCRF, ΔCH).

Multiple linear regression models were constructed to explore the factors influencing ΔIOPNCT in both groups. Preoperative IOP and postoperative CRF, CH, and Kf were enrolled into regression equations in both groups. Table 5 shows the definite regression coefficients between ΔIOPNCT and influencing factors.
and the influencing factors. It is possible to obtain the following two regression equations to evaluate $\Delta IOP_{NCT}$ after SMILE,

$$\Delta IOP_{NCT} = -5.412 + 0.768 IOP_{pre} - 1.892 CRF_{post} + 1.345 CH_{post};$$

$$R^2 = 0.520, R^2_{adjusted} = 0.505;$$

and after FS-LASIK,

$$\Delta IOP_{NCT} = 8.612 + 0.681 IOP_{pre} - 1.362 CRF_{post} + 0.881 CH_{post} - 0.327 Kf_{post};$$

$$R^2 = 0.571, R^2_{adjusted} = 0.552.$$  

The actual postoperative IOP may be evaluated by the measured IOP plus the $\Delta IOP$.

**DISCUSSION**

IOP measurement values decreased after both SMILE and FS-LASIK, which was consistent with previous research results. In this study, corneal biomechanical method ORA combined with NCT were used to investigate the relationship between corneal biomechanics and IOP change. Both tonometers estimated IOP by directing a pulse of air at the cornea, causing it to flatten and allowing an electro-optical collimation detector to evaluate corneal curvature. Both SMILE and FS-LASIK surgeries used a myopic ablation profile to remove tissue from the cornea to correct refractive error. After the surgery, CCT, corneal curvature, and corneal biomechanics decreased significantly, and the corneal structure also changed. These corneal changes altered postsurgical measurement of IOP. The corneal biomechanic parameters from ORA could present CH and CRF, with CH representing the viscoelastic property of the cornea and CRF the corneal elasticity with a strong positive correlation for CCT. The decrease of CH and CRF then indicates the decrease of cornea stiffness. When the IOP was measured, the cornea was more likely to be flattened, so these values were lower and underestimated the real IOP. Some studies suggested that there were no clinical symptoms of low IOP after surgery, based on animal experiments but also on clinical observation. This IOP reduction was an illusion and what really changed were the influencing factors of IOP measurement.

In this study, IOP measurement values remained stable at 3 months after SMILE, with CH and CRF also restored at 1 month. Moreover, CCT remained stable at 3 months and corneal curvature kept changing. Although some studies showed that the corneal curvature and CCT were related to IOP reduction, Liu and Roberts reported that differences in corneal biomechanics between individuals may contribute more than corneal thickness or curvature to IOP measurement errors, which was consistent with this study. After surgery, patients needed routine application of 0.1% FML to prevent inflammation and refractive regression for 2 months. In a comparative study, 6 weeks of FML treatment resulted in an IOP increase greater than 5 mm Hg in 8.3% of cases, although topical FML was thought to have less effect on IOP than other steroid agents. All of these possible influencing factors, especially corneal biomechanics, regained stability, and after stopping FML medication, IOP measurement values were stable again. Regarding IOP changes in FS-LASIK, most IOP measurement values remained stable at 3 months except IOPg and IOPcc. Similarly, CCT, Kf, Ks, and Km also did not regain its stability at 3 months except in corneal biomechanics. When compared with SMILE, FS-LASIK induced more keratocyte apoptosis, proliferation, and inflammation, so IOP values after FS-LASIK seemed less stable, which may be a result of corneal structure variation.

In both groups, the low IOP readings after surgery resulted in a delayed diagnosis of glaucoma or recognition of ocular hypertensive patients, so it was very important to measure postoperative IOP or the change of IOP in an accurate way. Interestingly, the decrease in postoperative 6-month IOP in the current study was significant when measured using NCT (approximately 5 mm Hg) and IOPg (approximately 6 mm Hg) when compared with IOPcc (approximately 3 mm Hg) and Pentacam (approximately 2 mm Hg). This finding is supported by the hypothesis that IOPcc is less influenced by corneal properties, such as CCT, and does not decrease significantly following LASIK and epipolaris laser in situ keratomileusis. Furthermore, among all of the $\Delta IOP$ after SMILE, $\Delta$Shah was smallest (0.83 mm Hg), followed by $\Delta$Ehlers (~0.87 mm Hg). After FS-LASIK, $\Delta$Shah was the smallest (0.35 mm Hg) and $\Delta$Ehlers second (~1.43 mm Hg). The comparison between $\Delta$Ehlers and $\Delta$Shah showed no significant difference. Accord-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>Unstandardized Coefficients</th>
<th>Standardized Coefficients</th>
<th>$r$ Value</th>
<th>$P$ Value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>SMILE</td>
<td>-5.412</td>
<td>-5.583</td>
<td>0.001</td>
<td>-8.412, -2.413</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FS-LASIK</td>
<td>8.612</td>
<td>2.261</td>
<td>0.026</td>
<td>1.045, 16.178</td>
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<tr>
<td></td>
<td>SMILE</td>
<td>0.768</td>
<td>0.850</td>
<td>0.000</td>
<td>0.613, 0.924</td>
<td></td>
</tr>
<tr>
<td></td>
<td>FS-LASIK</td>
<td>0.681</td>
<td>0.734</td>
<td>0.000</td>
<td>0.540, 0.821</td>
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</tr>
<tr>
<td>post-CRF</td>
<td>SMILE</td>
<td>-1.892</td>
<td>-1.118</td>
<td>0.000</td>
<td>-2.446, -1.337</td>
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</tr>
<tr>
<td></td>
<td>FS-LASIK</td>
<td>-1.362</td>
<td>-0.736</td>
<td>0.000</td>
<td>-1.913, -0.812</td>
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<tr>
<td>post-CH</td>
<td>SMILE</td>
<td>1.345</td>
<td>1.697</td>
<td>0.000</td>
<td>0.770, 1.921</td>
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<td></td>
<td>FS-LASIK</td>
<td>0.881</td>
<td>0.415</td>
<td>0.007</td>
<td>0.249, 1.513</td>
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</tr>
<tr>
<td>post-Kf</td>
<td>SMILE</td>
<td>-0.327</td>
<td>-0.245</td>
<td>0.003</td>
<td>-0.536, -0.118</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval.
Intraocular Pressure Changes After SMILE and FS-LASIK

In summary, IOP measurement underestimation after SMILE and FS-LASIK was related to corneal biomechanics as well as to preoperative IOP and K. IOP after SMILE seemed to remain more stable than FS-LASIK. Accordingly, the Ehlers and Shah formulas were closer to the preoperative values, with IOP variation approximately 1 mm Hg at 6 months postoperatively. The best-fit models for IOP change may be useful to evaluate the long-term postoperative IOP after SMILE and FS-LASIK. Further investigations on accurate IOP measurements are required.

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