Tonometric Changes of Latanoprost-Induced Intraocular Pressure Reduction after Photorefractive Keratectomy

Ciro Tamburrelli, Agostino Salvatore Vaiano, Tommaso Salgarello, Carmela Grazia Caputo, and Luigi Scullica

PURPOSE. To assess whether tonometric measurements of the drop in intraocular pressure (IOP) induced by 0.005% latanoprost are modified after photorefractive keratectomy (PRK).

METHODS. Data from 24 randomly selected eyes of 24 patients (12 men and 12 women, mean age ± SD: 31.7 ± 6.2 years) who were undergoing bilateral PRK for myopia (−6.38 ± 2.26 D) were obtained. Objective refraction, central corneal thickness (CCT), anterior radius of corneal curvature (R), and IOP measurements at baseline and 24 hours after 1 drop of 0.005% latanoprost, were performed before and 6 months after PRK. All measured IOPs were recalculated by a correction factor for CCT and R and expressed as true IOP (IOPT) measurements.

RESULTS. The mean CCT ± SD was 544.58 ± 36.03 and 465.21 ± 38.59 μm, and the anterior radius of corneal curvature was 7.73 ± 0.26 and 8.33 ± 0.37 mm, before and after PRK, respectively. The mean IOP at baseline was 15.8 ± 2.92 and 12.23 ± 2.37 mm Hg, and after latanoprost administration was 12.54 ± 1.97 and 10.19 ± 1.47 mm Hg, before and after PRK, respectively. The mean IOPT at baseline was 15.46 ± 1.08 and 16.18 ± 2.31 mm Hg, and after latanoprost administration was 11.85 ± 1.56 and 12.96 ± 1.71 mm Hg, before and after PRK, respectively. The mean IOP and IOPT reductions after latanoprost administration were, respectively, 3.25 ± 1.66 and 3.61 ± 1.7 mg Hg before PRK, and 2.03 ± 1.42 and 3.22 ± 1.79 mg Hg after PRK. Pre- and postoperative IOPT reduction significantly differed (P < 0.001), but not IOP.

CONCLUSIONS. The effect of hypotensive drugs on IOP readings may be underestimated because of measurement errors due to CCT reduction and R increase after PRK for myopia. Misdiagnosis of reduced pharmacologic efficacy may be avoided if the measured IOP is corrected by a proper nomogram. (Invest Ophthalmol Vis Sci. 2004;45:846–850) DOI:10.1167/iovs.03-0625

Elevated intraocular pressure (IOP) is known to be a prominent risk factor for development of optic nerve damage in glaucoma.1 Clinical introduction of optical and ultrasonic pachymeters has suggested that central corneal thickness (CCT) could directly affect evaluation of IOP, as measured by applanation tonometry.2–4 Central corneal thickness assessment has indicated a significant variability within the general population,5 greater than Goldmann and Schmidt6 supposed when they first described applanation tonometry and assumed a standard corneal thickness of 500 μm. Ehlers et al.7 and later Whitacre et al.8 reported that applanation tonometry provides accurate readings only at 520 μm CCT and estimated that IOP measurement errors of more than ± 5 mm Hg may occur within the normal CCT range. Therefore, CCT cannot be ignored in glaucoma diagnosis and management. Several studies have pointed out the risk of misdiagnosis by underestimation of IOP in patients with normal tension glaucoma who have thin corneas8–10 and overestimation in normal subjects with thick corneas.11,12

Photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) have become popular surgical options for treatment of refractive errors, mainly of myopia. Myopic PRK and LASIK flatten and reduce CCT proportionally to the extent of myopia.13–15 Increasing evidence has shown that IOP readings are reduced after PRK and LASIK.14–16 Consequently, the reliability of IOP measurements in patients with myopia who have undergone refractive photoablation has been questioned, and even clinically significant IOP increases may be overlooked.

Although the relationship between CCT and IOP has been reported frequently, to date no studies have been conducted to investigate CCT’s influence on the assessment of the reduction of IOP induced by hypotensive drugs. The purpose of this study was to determine whether measurements of the pharmacologically induced IOP decreases are modified after excimer laser change in CCT.

MATERIALS AND METHODS

Subjects

In this prospective study, data from 24 randomly selected eyes of 24 consecutive patients (12 men and 12 women, mean age ± SD: 31.7 ± 6.2 years, range: 22–45) who were undergoing bilateral PRK treatment for myopia were obtained. All patients were healthy and had no evidence of external corneal disease, ocular hypertension, or glaucoma. They were evaluated before and 6 months after the surgical procedure. In both conditions, routine ophthalmic examinations were performed, including objective refraction evaluation by autorefractometer (model AR-600; Nidek, Aichi, Japan), IOP measurements by non-contact tonometer (model TX-10; Canon Ltd., Tokyo, Japan), mean anterior radius of corneal curvature assessment (Keratron Scout; Optikon, Rome, Italy), and central corneal pachymetry by ultrasonic pachymeter (Altair 606 AN; Optikon). IOP measurements were always performed between 9 and 10 AM, and the mean of three consecutive readings was considered for the statistical analysis. IOPs with standard deviations among measurements exceeding 0.4 mm Hg were rejected.

The design and performance of the experimental procedures were clearly formulated in an experimental protocol, adhering to the tenets of the Declaration of Helsinki, which was approved by the institutional ethics review board. A written informed consent was obtained from each patient before his or her inclusion in the study and after the goals and methods of the study and the potential side effects and discomfort

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that the instillation of the topical hypotensive drug may entail were adequately explained.

After recording of the baseline IOP, 1 drop of 0.005% latanoprost (Xalatan; Pharmacia Upjohn, Uppsala, Sweden) was instilled in the selected patient’s eye. A second IOP measurement was performed 24 hours later by a second examiner masked to all previous data who used the same mode of administration. At the 6-month visit, after the ophthalmic evaluation, 1 drop of 0.005% latanoprost was placed in the patient’s eye, and a second IOP measurement was assessed 24 hours later by a different examiner masked to all previous IOP readings. Care was taken to avoid latanoprost instillation at least in the 2 hours before or after administration of artificial tears.

According to a recent study,19 all pre- and postoperative IOPs were recalculated and expressed as true IOP (IOPT) measurements, using the following mathematical formula

\[ \delta = \delta_2 - \delta_1 \] (1)

This formula considers the deformation of the apex of the anterior cornea (\( \delta \)) during applanation tonometry as the result of two opposed deformations: the intraocular (\( \delta_1 \)) and the applanating (\( \delta_2 \)) pressures.

The deformation \( \delta_2 \) may be determined by the equation20

\[ \delta_2 = \frac{aw}{Et} \left( \frac{R - t/2}{2} \right) \sqrt{1 - \nu^2} \] (2)

where \( a \) is the corneal geometry constant, \( W \) is the applanating weight, \( R \) is the radius of curvature of the anterior cornea, \( t \) is the CCT, \( \nu \) is Poisson’s ratio of the cornea, and \( E \) is the modulus of elasticity of the cornea.

According to Orrsengo and Pye,19 a constant corneal Poisson’s ratio of 0.49 was used.21,22 The modulus of elasticity was estimated from the formula \( E = 0.0229 \cdot \text{IOPT} \). The deformation \( \delta_1 \) may be determined by the equation20

\[ \delta_1 = \frac{w}{2Et} \left( \frac{R - t/2}{2} \right) \sqrt{1 - \nu^2} \] (3)

where \( w \) is actual IOP.

Substituting equations 2 and 3 for equation 1 gives the equation for the deformation \( \delta \) as

\[ \delta = \frac{aw}{Et} \left( \frac{R - t/2}{2} \right) \sqrt{1 - \nu^2} - \frac{w}{2Et} \left( \frac{R - t/2}{2} \right) \sqrt{1 - \nu^2} \] (4)

To determine the coefficient \( a \), the calculation of a parameter \( \lambda \) is needed. It may be estimated by using the equation20

\[ \lambda = \frac{12(1 - \nu^2)}{\left( \frac{R - t/2}{2} \right)^3} \] (5)

Table 1. Determination of the Coefficient \( a \) in Equation 2 Using the Parameter \( \lambda \) Given by Equation 520

<table>
<thead>
<tr>
<th>( \lambda )</th>
<th>( a )</th>
</tr>
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<tbody>
<tr>
<td>1.0</td>
<td>0.337</td>
</tr>
<tr>
<td>1.2</td>
<td>0.331</td>
</tr>
<tr>
<td>1.4</td>
<td>0.286</td>
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</table>

In a limited range of parameter \( \lambda \), each column displays the parameter \( \lambda \) and the corresponding coefficient \( a \).

where \( r \) is the radius of the circle applanated by the tonometer (standard applanated circle radius: 1.55 mm). Applying the value of \( \lambda \) in Table 1,20 the relative coefficient \( a \) is obtained.

Absolute IOP and IOPT differences before and after latanoprost instillation, as well as the corresponding percent reductions were also calculated before and after surgery.

**Statistical Analysis**

A paired Student’s \( t \)-test was used to compare the IOPs and the relative IOPTs at baseline and after latanoprost instillation before PRK with the corresponding IOPs and IOPTs at baseline and after latanoprost instillation after excimer laser treatment.

The IOPs and IOPTs at baseline were also compared with the corresponding IOPs and IOPTs 24 hours after administration of latanoprost by paired Student’s \( t \)-test, both before and after surgery.

A paired Student’s \( t \)-test was also used to compare preoperative absolute and percent reductions in IOP and IOPT after administration of latanoprost with the corresponding postoperative values.

**Results**

Demographic and clinical data from the study population are inserted in Table 2. Results are expressed as the mean ± SD with the range in parentheses. Refractive error expressed as spherical equivalent (mean ± SD) was –6.38 ± 2.26 (–1.75 to –9.25) and –0.04 ± 0.29 (–0.75 to +0.37) D, the anterior corneal curvature was 7.75 ± 0.26 (7.45–8.29) and 8.33 ± 0.37 (7.93–9.21) mm, and the mean CCT was 544.58 ± 36.03 (482–625) and 463.21 ± 58.59 (376–544) μm, before and after PRK, respectively. The mean CCT postoperative reduction was 81.37 ± 34.46 μm (15–141).

Tonometric results, expressed as IOP and IOPT measurements, in the different study conditions are reported in Table 3. The IOP at baseline was 15.80 ± 2.92 (10.80–21.20) and 12.23 ± 2.57 (8.40–17.00) mm Hg before and after PRK, respectively. After latanoprost administration the mean IOP was 12.54 ± 1.97 (8.70–16.40) and 10.19 ± 1.47 (7.30–12.80) mm Hg before and after PRK, respectively. The mean IOPT at baseline was 15.46 ± 1.08 (14.17–17.10) and 16.18 ± 2.31 (13.36–20.36) mm Hg before and after PRK, respectively. After latanoprost administration the mean IOPT was 11.85 ± 1.56 (9.11–13.81) and 12.96 ± 1.71 (10.74–15.65) mm Hg before and after PRK, respectively.

The IOP reduction after latanoprost administration was 3.25 ± 1.66 (1.00–6.70) and 2.03 ± 1.42 (0.30–4.70) mm Hg, before and after PRK, respectively. The mean IOPT reduction after latanoprost administration was 3.61 ± 1.70 (2.00–7.29) and 3.22 ± 1.79 (0.38–5.98) mm Hg, before and after PRK, respectively. Percent IOP and IOPT reductions after latanoprost instillation were 19.86% ± 8.05% (2.50–38.24) and 23.40% ± 9.42% (13.33–44.45), and 15.54% ± 8.99% (2.68–32.17) and 19.18% ± 9.64% (2.61–32.20), before and after PRK, respectively.

The mean modulus of elasticity was 0.32 ± 0.10 and 0.33 ± 0.12, before and after PRK respectively. The pre- and postoperative values did not differ significantly.

After photoablation, the IOP at baseline and after latanoprost administration were significantly \((P < 0.001)\) lower than...
TABLE 2. Demographic and Clinical Data

<table>
<thead>
<tr>
<th>Sex (M/F)</th>
<th>12/12</th>
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</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>31.7 ± 6.2 (22–45)</td>
</tr>
<tr>
<td>Refractive error (D)</td>
<td>Preoperative -6.38 ± 2.26 (-1.75 to -9.25)</td>
</tr>
<tr>
<td></td>
<td>Postoperative -0.04 ± 0.29 (-0.75 to 0.37)</td>
</tr>
<tr>
<td>Anterior radius of corneal curvature (mm)</td>
<td>Preoperative 7.73 ± 0.26 (7.45–8.29)</td>
</tr>
<tr>
<td></td>
<td>Postoperative 8.33 ± 0.37 (7.93–9.21)</td>
</tr>
<tr>
<td>Central corneal thickness (μm)</td>
<td>Preoperative 544.58 ± 36.03 (482–625)</td>
</tr>
<tr>
<td></td>
<td>Postoperative 463.21 ± 38.59 (376–544)</td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± SD, with the range in parentheses. D, diopter spherical equivalent.

before excimer laser treatment, whereas no statistically significant difference was found for the IOPT values.

IOP response to latanoprost showed statistically significant (P < 0.001) IOP and IOPT reductions both before and after surgery.

The IOP but not IOPT reduction was significantly (P < 0.001) lower after the CCT decrease induced by PRK. Similar to absolute values, the percent reductions were statistically different (P < 0.03) only for the IOP values between the pre- and postoperative conditions.

DISCUSSION

The correlation between IOP, as measured by applanation tonometry, and CCT has been analyzed in several studies. Ehlers et al. found that the difference between actual IOP as measured by an electronic manometer and IOPT applanation readings was linearly correlated with CCT, and applanation tonometry provided accurate measurements only at the CCT of 520 μm. Under- and overestimate of IOP measurements may occur with thinner or thicker corneas, respectively, with an average error of 0.7 mm Hg per 10-μm deviation from the CCT “normal” value of 520 μm. Sources of error in applanation tonometry measurements may originate from discrepancy between the assumptions of the Imbert-Fick law and anatomy as well as physical properties of the cornea. An external force against a fluid-filled sphere equals the internal pressure multiplied by the area flattened by the external force, if the sphere is perfectly spherical, dry, flexible, and infinitely thin. The cornea fails to satisfy any of the aforementioned conditions, because it is aspherical, wet, and neither perfectly flexible nor infinitely thin. The moisture creates surface tension, whereas a lack of flexibility requires force that is independent of the internal pressure to bend the cornea.

Noncontact tonometry was the preferred IOP measuring method in our study, because it has been demonstrated to be reproducible, when the mean of three measurements is used rather than a single reading, and accurate, when compared with the Goldmann tonometer. Moreover, recent studies evaluating noncontact tonometry found it to be less influenced by corneal thickness than is Goldmann tonometry. Thicker corneas tended to give higher IOP readings by the latter method than by the noncontact method. Other investigators, conversely, reported that the reliability of tonometers decreases with increasing corneal thickness, in which case higher readings were found, especially with a noncontact tonometer.

Finally, this device avoids those corneal epithelial alterations related to application of the Goldmann tonometer that may affect the CCT estimate.

According to other studies on decreased IOP measurements after PRK and LASIK, in our study population we found a significant (P < 0.001) baseline decrease in IOP after excimer laser treatment. A decreased corneal resistance to the applanation tonometer because of reduction of corneal stromal thickness or corneal structural alteration after photoablation of Bowman’s membrane might account, at least in part, for the postoperative reduction in IOP.

Indeed, a careful evaluation of the IOPTs obtained correcting the measured IOP by an applanation tonometry correction factor for various combinations of CCT and anterior radius of corneal curvature did not provide a statistically significant difference between the pre- and postoperative baseline IOPTs, stressing the importance of evaluating IOPT more than IOP, mainly in patients that underwent refractive surgery.

However, to date, no study has evaluated the role of CCT in IOP changes after the administration of ocular hypotensive drugs. Thus, we decided to use latanoprost to investigate whether the variations in CCT due to excimer laser treatment influence tonometric measurements caused by pharmacologic IOP reduction.

We chose latanoprost because some investigators have hypothesized that the shock wave from excimer laser applications may affect the trabecular meshwork or the ciliary processes, and it has been demonstrated that latanoprost decreases IOP by increasing uveoscleral outflow, and total outflow facility, with no action on trabecular outflow facility. Latanoprost has been shown to be a remarkable, potent ocular hypotensive agent in several animals, as well as in normotensive, hypertensive, and glaucomatous human eyes. Previous studies have reported 17% and 19% lowering of IOP in normal subjects at 6 hours and 5 days of treatment, respectively.

In our sample of myopic normotensive eyes, the baseline IOP measurements were reduced by 3.25 ± 1.66 (19.86% ± 8.05%) and 2.03 ± 1.43 (15.54% ± 8.99%) mm Hg 1 day after its topical administration, before and after corneal excimer laser treatment, respectively. This study indicates that the postoperative 1-day latanoprost IOP reduction was statistically lower than before laser treatment (P < 0.001). Changes in drug

TABLE 3. IOP and IOPT Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline IOP (mmHg)</th>
<th>IOP after Latanoprost (mmHg)</th>
<th>IOP Drop (mmHg)</th>
<th>%IOP Reduction</th>
<th>Baseline IOPT (mmHg)</th>
<th>IOPT after Latanoprost (mmHg)</th>
<th>IOPT Drop (mmHg)</th>
<th>%IOPT Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before PRK</td>
<td>15.80 ± 2.92 (10.80–21.20)</td>
<td>12.54 ± 1.97 (8.70–16.40)</td>
<td>3.25 ± 1.66 (1.00–6.70)</td>
<td>19.86 ± 8.05 (5.20–38.24)</td>
<td>15.46 ± 1.08 (14.17–17.10)</td>
<td>11.85 ± 1.56 (9.11–13.81)</td>
<td>3.61 ± 1.70 (2.00–7.29)</td>
<td>32.40 ± 9.42 (13.33–44.45)</td>
</tr>
<tr>
<td>After PRK</td>
<td>12.23 ± 2.37 (8.40–17.00)</td>
<td>10.19 ± 1.47 (7.30–12.80)</td>
<td>2.03 ± 1.42 (0.30–4.70)</td>
<td>15.54 ± 8.99 (2.68–52.17)</td>
<td>16.18 ± 2.31 (13.36–20.36)</td>
<td>12.96 ± 1.71 (10.74–15.65)</td>
<td>3.22 ± 1.79 (0.38–5.98)</td>
<td>21.62 ± 9.64 (6.21–32.20)</td>
</tr>
<tr>
<td>Mean difference</td>
<td>5.57 ± 2.68</td>
<td>2.34 ± 1.64</td>
<td>1.22 ± 1.71</td>
<td>4.33 ± 9.21</td>
<td>-0.72 ± 2.30</td>
<td>-1.11 ± 1.56</td>
<td>0.38 ± 2.35</td>
<td>4.22 ± 11.53</td>
</tr>
</tbody>
</table>

Data are provided for baseline and 24 hours after latanoprost administration, with the corresponding absolute and percent reduction before and after PRK. Data are the mean ± SD, with the range in parentheses.
bioavailability and/or IOP assessment errors related to corneal modifications may explain these findings.

Latanoprost is a lipophilic prodrug absorbed through the cornea where it is hydrolyzed to its active form. All the drug that enters the aqueous humor has been hydrolyzed to the free acid. Experimental studies after PRK have shown a raised corneal permeability with higher concentration of only hydrophilic drugs, whereas the permeability of lipophilic agents was scarcely affected. Accordingly, a nearly unaltered tralist, so modifying corneal structure and its in free acid. Experimental studies after PRK have shown a corneal permeability of latanoprost may be assumed. However, to minimize the influence of the photoablation on the drug bioavailability, we measured the pharmacologic IOP reduction 6 months after PRK, because a confocal microscopic study showed that, after this period, the corneal epithelium has fully restored its preoperative thickness, and stromal and wound repair have gradually occurred.

True IOP measurements showed a reduction by 3.61 ± 1.70 (23.40% ± 9.42%) and 3.22 ± 1.79 (19.18% ± 9.64%) mm Hg from baseline 1 day after topical administration of latanoprost, before and after corneal excimer laser treatment, respectively. These data indicate that, when CCT and the anterior radius of corneal curvature are considered as correction factor for IOP measurements, the postoperative 1-day latanoprost IOPT reduction is not statistically different from the preoperative one. Therefore, we may assume that measurement errors due to changes in CCT and anterior radius of corneal curvature may account, at least in part, for the lower decrease in IOP induced by 1-day of latanoprost administration after excimer laser treat-

ment. According to the mathematical formula (equation 1, see the Methods section), in our series we pharmacologically decreased \( w \) before and after both \( t \) reduction and \( R \) increase induced by PRK. The pharmacologic decrease in \( w \) appeared to be lower after PRK, because the first term in equation 4 in the Methods section decreased less than the second one, because \( a \) is proportionally reduced when \( t \) decreases and \( R \) increases.

These corneal parameter changes reflect structural variations of the stroma. In non-surgically treated corneal stroma, the collagen fibers form approximately 300 to 500 lamellae that run parallel to the corneal surface from limbus to limbus. The lamellae are in tension, because there is a force pushing on them from underneath (actual IOP), and restrained from relative sliding by biomechanical properties of stromal collagen which account for interlamellar cohesive and adhesive strength. Finally, intrinsic elastic properties of lamellae and interlamellar space may contribute to IOP measurements and account, at least in part, for all reported data regarding applapation tonometry and CCT. After myopic laser refractive surgery a series of lamellae is severed and photoablated centrally, so modifying corneal structure and its influence on the measured IOP.

In contrast, equation 4 relates the deformation \( \delta \) of the corneal apex not only to the applanating pressure \( W \), IOP \( w \), and corneal anatomy (\( R \) and \( t \)), but also to the biomechanical properties of the cornea (\( E \) and \( v \)). Nevertheless, no significant changes in \( E \) have been found in this study.

In conclusion, besides the well-known IOP underestimate after excimer laser treatment for myopia, we detected an underestimate of the non-contact-tonometry measurements of the pharmacologic IOP reduction after PRK. This estimate may be corrected if an appropriate nomogram considering both reduced CCT and increased \( R \) due to PRK is used. The correction of IOP readings may prevent misdiagnosis of reduced pharmacologic efficacy and avoid the need for further treat-