Single vs Multiple Intraocular Pressure Measurements in Glaucoma Surgical Trials

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IMPORTANCE Little is known about the necessity of multiple same-day intraocular pressure (IOP) measurements in describing the effect of IOP-lowering surgical procedures, and such evidence could affect surgical trial recruitment and retention of participants.

OBJECTIVE To determine whether a single IOP measurement might adequately approximate the mean of several measurements in glaucoma surgical trials.

DESIGN, SETTING, AND PARTICIPANTS A prospective, multicenter, interventional cohort from the prerandomization phase of a randomized clinical trial evaluating use of a supraciliary implant for treatment of IOP was conducted at multiple ophthalmology clinics. A total of 609 patients (609 eyes) with primary open-angle glaucoma and cataract were included.

INTERVENTIONS One IOP measurement was made while patients were receiving their usual medications to lower IOP, and 3 IOP measurements were made at 8 AM, 12 PM, and 4 PM after patients underwent washout of all IOP-lowering eyedrops.

MAIN OUTCOMES AND MEASURES The proportion of eyes in which the increase in IOP after washout, using the mean of the 3 measurements, differed by more than 0.5, 1.0, 1.5, or 2.0 mm Hg from the increase in IOP after washout using only 1 of the postwashout measurements. A proportion of 10% or less at the 1.5-mm Hg cutoff was considered clinically acceptable. The hypothesis was formulated after data collection but before the data were examined.

RESULTS The mean (SD) IOP before washout was 18.5 (4.0) mm Hg. The mean increase in IOP after washout, using the mean of the 3 measurements, was 5.3 (4.2) mm Hg. The percentage of eyes in which the increase in IOP using a single postwashout IOP differed from the increase in IOP using the mean of 3 measurements by more than 0.5 mm Hg from the increase in IOP after washout using only 1 of the postwashout measurements. A proportion of 10% or less at the 1.5-mm Hg cutoff was considered clinically acceptable. The hypothesis was formulated after data collection but before the data were examined.

CONCLUSIONS AND RELEVANCE Although eliminating multiple IOP measurements would simplify the conduct of surgical trials in glaucoma, our data show that using a single IOP measurement after washout does not adequately approximate the mean of multiple IOP measurements.
ntraocular pressure (IOP) is a key outcome variable in studies of glaucoma therapy. The IOP fluctuates by 2 to 6 mm Hg during a 24-hour period in healthy individuals and even more in some patients with glaucoma. For the purposes of clinical trials, it is unclear which IOP factor (mean, peak, fluctuation, or an upper threshold) is most appropriate as an end point. At the recommendation of the World Glaucoma Association, many clinical studies on the medical and surgical lowering of IOP have used multiple IOP measurements during the day to arrive at a mean IOP, which is thought to better reflect the true level. Multiple diurnal measurements are clearly necessary for characterizing the short-term effect of IOP-lowering eyedrops because the effect of the medications varies with the duration after instillation. However, the same may not be true for IOP-lowering surgical procedures, which are believed to narrow the range of diurnal IOP fluctuation more than medicines. If multiple measurements throughout the day were not necessary for surgical trials in glaucoma, it would decrease a clinical trial participant’s time commitment and inconvenience, making recruitment and retention easier and reducing costs.

We had access to diurnal IOP measurements from many individuals that were obtained during the prerandomization phase of a phase 3 randomized clinical trial evaluating use of a stent for reduction of IOP (CyPass supraciliary Micro-Stent; the COMPASS trial). Our goal was to examine to what extent one of the 3 IOP measurements in a patient’s diurnal curve could be used to approximate the mean of the 3 diurnal measurements. If the differences were small in a large group of individuals, it might be practical to use a single office-measured IOP in future glaucoma surgical trials, which would facilitate patient recruitment and make such studies easier and less expensive.

Methods

Study Design

Prerandomization data were analyzed from the COMPASS study (ClinicalTrials.gov NCT01085537), a randomized, double-masked, comparative trial of the CyPass supraciliary Micro-Stent (Transcend Medical Inc), a supraciliary implant designed to treat open-angle glaucoma (OAG). All patients provided written informed consent at the initial screening visit before study enrollment and subsequent medication washout. The COMPASS study protocol was approved prospectively by the institutional review boards at each of the 27 participating sites, adhered to the tenets of the Declaration of Helsinki, and was compliant with the Health Insurance Portability and Accountability Act. The study is being conducted in the United States. The data analysis performed in the present study was approved by the institutional review board of Johns Hopkins Medicine.

Eligibility Criteria

At the screening visit, the diagnosis of glaucoma was based on glaucomatous optic neuropathy detected by direct ophthalmoscopy and/or a glaucomatous visual field defect tested with the Humphrey automated perimeter (Carl Zeiss Meditec) using a testing algorithm (Swedish Interactive Testing Algorithm Standard 24-2). Participants had to meet the following inclusion criteria: age 45 years or older, diagnosis of mild to moderate primary OAG with mean deviation scores between −12.0 and 0 dB, mean diurnal IOP of 21 to 33 mm Hg when not receiving medication, and presence of an operable age-related cataract. Exclusion criteria included use of more than 3 ocular hypotensive medications (fixed combinations counted as 2 medications), presence of grade 1 or 2 angle closure according to the Shaffer classification, secondary OAG, and uveitic and neovascular glaucoma or any other discernible congenital anomalies of the anterior chamber and angle, including presence of other ocular abnormalities, judged as significant by discretion of the investigator. If both eyes qualified for the study, a random number generator was used to designate the study eye.

IOP Measurements

All individuals under consideration for inclusion in the study underwent a single IOP measurement at a screening visit while they were receiving their usual glaucoma medication regimen. This measurement could have occurred at any time of day. Patients then discontinued their IOP-lowering medication for a minimum of 5 days for carbonic anhydrase inhibitors, 14 days for α-adrenergic agonists, and 28 days for all other medications. At a baseline visit after complete medication washout, IOP measurements were taken at 8 AM, 12 PM, and 4 PM. We defined the mean postwashout IOP as the mean of these 3 IOP measurements. The mean postwashout IOP was used as the baseline IOP for purposes of qualifying for the COMPASS study and will be used for future comparisons with posttreatment IOP measurements in the clinical trial. A total of 619 participants had diurnal IOP measurements; 10 of these patients were excluded because they did not adhere to the washout instructions (Supplement [eFigure]).

All IOP measurements were performed by 2 trained individuals using Goldmann applanation tonometry while the participants were seated upright. One individual performed the measurement and the other read the scale. The IOP was measured twice at each time of day. If the 2 measurements differed by 2 mm Hg or less, the mean was used as the IOP. If the 2 measurements differed by more than 2 mm Hg, a third IOP was taken and the median value was used.

Outcomes

The change in IOP was defined as the postwashout IOP minus the prewashout IOP. We calculated the change in IOP for each eye using 5 definitions for single postwashout IOP: (1) the 8 AM measurement, (2) the 12 PM measurement, (3) the 4 PM measurement, (4) the measurement closest in time to the prewashout measurement (referred to as the time-matched IOP), and (5) a random selection of either the 8 AM, 12 PM, or 4 PM measurement as the postwashout IOP. For each definition, we determined in what proportion of eyes the change in IOP after washout differed by more than 0.5, 1.0, 1.5, and 2.0 mm Hg from the change in IOP using the mean postwashout measurements. A proportion of 10% or less at the 1.5-mm Hg cutoff was considered clinically acceptable.
Table 1. Number of Eyes With the Highest and Lowest IOP at Each Time Point After Washout

<table>
<thead>
<tr>
<th>Time of Day</th>
<th>Time of Highest Single Postwashout IOP, No. (%)</th>
<th>Time of Lowest Single Postwashout IOP, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8 AM</td>
<td>12 PM</td>
</tr>
<tr>
<td>8 AM</td>
<td>280 (46.0)</td>
<td>44 (7.2)b</td>
</tr>
<tr>
<td>12 PM</td>
<td>118 (19.4)</td>
<td>26 (4.3)d</td>
</tr>
<tr>
<td>4 PM</td>
<td>110 (18.1)</td>
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</table>

Abbreviation: IOP, intraocular pressure.

The 8 AM IOP and 4 PM IOP were identical.

The 12 PM IOP and 4 PM IOP were identical.

The 8 AM IOP and 12 PM IOP were identical.

The 12 PM IOP and 1 PM IOP were identical.

Results

The 609 participants had a mean (SD) age of 70.2 (8.2) years and 55.5% were women (338). A diurnal IOP trend was noted, with IOP decreasing from morning to afternoon. The mean IOP before washout was 18.5 (4.0) mm Hg. The mean IOP after washout was 24.6 (4.4) mm Hg at 8 AM, 23.7 (3.8) mm Hg at 12 PM, and 23.2 (3.9) mm Hg at 4 PM. The mean of the 8 AM, 12 PM, and 4 PM measurements was 23.8 (3.6) mm Hg. The mean increase in IOP after washout, using the mean of the 3 measurements, was 5.3 (4.2) mm Hg. There were significant differences between all pairs of times (P < .001). Table 1 reports the number of eyes with the highest and lowest IOPs by time of day. Of 609 total eyes, 280 (46.0%) had the highest IOP at 8 AM, 118 (19.4%) at 12 PM, and 110 (18.1%) at 4 PM; 245 eyes (40.2%) had the lowest IOP at 4 PM, followed by 142 (23.3%) at 12 PM and 108 (17.7%) at 8 AM. There were 183 eyes (30.0%) that had the same IOP at 2 time points and 16 eyes (2.6%) that had the same IOP at all 3 time points. The intraclass correlation coefficient of the 3 postwashout IOPs was 0.72, indicating that there is fair agreement among the values.

Figure 1 summarizes the differences in the increase in IOP with washout when only one of the single postwashout IOPs is used compared with the mean of the 3 postwashout IOPs. The difference in the increase in IOP after washout using a single postwashout IOP compared with using the mean of the 3 measurements was 0.75 (1.9), −0.13 (1.5), and −0.62 (1.8) mm Hg for 8 AM, 12 PM, and 4 PM, respectively. The increase in IOP after washout was greater when only the 8 AM postwashout IOP was used than when the mean of the 3 time points was used, as depicted in Figure 1A by the shift of the curve to the right of 0. The increase in IOP after washout was lower when either the 12 PM or 4 PM IOP was used instead of the mean of the 3 measurements, as depicted in Figure 1B and C by the shift of the curve to the left of 0. The mean increases in IOP when the randomly selected or time-matched postwashout IOP was used were 0.02 (1.8) mm Hg and 0.31 (1.8) mm Hg greater, respectively, than when the mean of the 3 postwashout IOPs was used (Figure 1D and E). The SD of the increase in IOP after washout was greatest at 8 AM and smallest at 12 PM.

The mean absolute differences between using a single postwashout IOP measurement and the mean postwashout IOPs in calculating the increase in IOP with washout are reported in Table 2. The mean increase in IOP with washout differed least from the increase calculated using the mean postwashout IOPs when the 12 PM single postwashout IOP was used (1.08 [1.02] mm Hg; P < .001).

Figure 2 depicts the percentage of eyes in which the increase in IOP with washout when calculated using a single postwashout IOP measurement differed from the increase when calculated using the mean postwashout IOPs by more than 0.5, 1.0, 1.5, and 2.0 mm Hg. In general, the increase in IOP with washout when using only the 12 PM postwashout IOP had the lowest proportion of eyes differing from the increase calculated using the mean; by logistic regression, it was less likely to exceed any of the chosen cutoffs compared with the 8 AM, 4 PM, random, and time-matched postwashout IOPs (P < .001). The proportions at 8 AM and 4 PM were similar, resulting in mean percentages of 71.5%, 46.5%, 34.5%, and 22.5% of eyes exceeding cutoffs of 0.5, 1.0, 1.5, and 2.0 mm Hg, respectively. Although inferior to the 12 PM IOP, using a randomly chosen postwashout IOP compared with the mean postwashout IOP was less likely to exceed 1.5 mm Hg than when the 8 AM (P = .001) and 4 PM (P = .02) IOPs were used. The IOPs that were time matched at 8 AM (n = 246), 12 PM (n = 277), and 4 PM (n = 86) did not differ significantly from one another in the closeness with which they approximated the mean of the 8 AM, 12 PM, and 4 PM measurements.

Figure 3 shows the influence of participant variables on the proportion of eyes with a difference greater than 1.5 mm Hg in the increase in IOP after washout between a single postwashout IOP vs the mean postwashout IOP. We chose 1.5 mm Hg as the clinically acceptable cutoff because the repeatability coefficients of 2 to 3 successive Goldmann application tonometry measurements from our data were 1.43 mm Hg (95% CI, 1.36-1.52) for the prewashout measurements and 1.41 mm Hg (95% CI, 1.34-1.50) for the postwashout measurements. The difference in the increase calculated with washout between the 12 PM postwashout IOP and the mean postwash-
Figure 1. Histograms of Differences Between Intraocular Pressure (IOP) Changes After Washout

Each single postwashout IOP was compared with the mean of the 8 AM, 12 PM, and 4 PM IOPs in 609 patients.

Discussion

This study examined the value of measuring a single IOP vs multiple IOPs for glaucoma clinical studies, in particular, sur-
gical trials. We undertook the study with the hypothesis that a single IOP measurement might approximate the mean of several measurements, realizing that reducing the number of measurements would inevitably result in some loss of information, but that the extent of lost precision might be small compared with the savings in time, inconvenience, and cost to investigators and patients. We determined a priori that we would consider a single measurement as a substitute for 3 diurnal measurements if less than 10% of eyes had values that differed by more than 1.5 mm Hg between a single measurement and the mean of the diurnal measurements.

We collected a large data set prospectively in a standardized, rigorous, masked fashion. Contrary to our hypothesis, we found that a proportion of eyes exceeded by more than 10% what we defined as a clinically significant difference of greater than 1.5 mm Hg between using 1 postwashout IOP measurement and the mean of 3 measurements throughout the day.

We found that at a difference cutoff of 1.5 mm Hg between a single postwashout IOP and the mean postwashout IOP, 35.1%, 25.6%, 34.2%, 30.0%, and 31.4% of eyes exceeded that difference at the 8 AM, 12 PM, 4 PM, random-time, and time-matched measurements, respectively. The proportion of eyes at 12 PM was significantly less than those at all other times, and the proportion of eyes at a random time was still significantly less than that at 8 AM and 4 PM.

Therefore, if one could make only 1 determination, using a single IOP measurement at 12 PM would be closest to the mean diurnal IOP with the least variability, and using a single random IOP measurement would be the second-best option. However, because for all single measurements more than 10% of the eyes had a difference greater than 1.5 mm Hg, we conclude that single IOP measurements do not adequately approximate multiple diurnal IOP measurements.

We made the assumptions that the mean of 3 IOP measurements would most closely approximate the level of IOP throughout the day and night influencing the optic nerve in glaucoma and that deviation from this criterion standard is undesirable. In the absence of data demonstrating a relationship between this mean and the propensity for worsening of glaucoma, this remains an assumption.

<table>
<thead>
<tr>
<th>Table 2. Mean Absolute Difference in the Change in IOP With Washout Using Single Postwashout IOP vs Mean of 3 Postwashout IOPs in 609 Patientsa</th>
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<tbody>
<tr>
<td>Single Postwashout IOP</td>
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<tr>
<td>8 AM</td>
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<td>12 PM</td>
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<td>4 PM</td>
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<tr>
<td>Random</td>
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<td>Time-matchedb</td>
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Abbreviation: IOP, intraocular pressure.

a The difference was regardless of whether the change was greater or less when using the single value instead of the mean of 3 values.

b Prewashout IOP measurement times were matched to postwashout IOP measurement times as follows: before 10 AM was matched with 8 AM, between 10 AM and 2 PM was matched with 12 PM, and after 2 PM was matched with 4 PM.

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We made the assumptions that the mean of 3 IOP measurements would most closely approximate the level of IOP throughout the day and night influencing the optic nerve in glaucoma and that deviation from this criterion standard is undesirable. In the absence of data demonstrating a relationship between this mean and the propensity for worsening of glaucoma, this remains an assumption.

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Figure 2. Percentage of Eyes in Which Differences Between Intraocular Pressure (IOP) Changes After Washout Exceeded Cutoffs

The percentage of eyes in which the calculated change in IOP after washout using a single postwashout measurement differed from the change in IOP after washout using the mean of the 3 postwashout IOPs by greater than 0.5, 1.0, 1.5, and 2.0 mm Hg in 609 patients.
Similar to other investigations that have described IOP variations during the day in patients with untreated OAG, we found that the mean IOP was highest in the morning and lowest in the afternoon. Although the most eyes at 8 AM had the highest IOP (280 [46.0%]), many eyes did not fit this diurnal trend. The substantial amount of diurnal curve variation among individuals with OAG is consistent with findings from other studies. Drance found that, although 46.4% of 138 untreated eyes with OAG had IOP peaks at 6 AM, the other eyes had IOP peaks distributed throughout the day until 10 PM. In a more recent study, Saccà et al found that 65.2% of 95 washed-out eyes with primary OAG had IOPs that peaked at 8 AM and declined through the day to 4 PM, and the remaining eyes followed various diurnal curves. Other studies have shown this same predominant IOP pattern in individuals with treated OAG, normal-tension glaucoma, ocular hypertension, and healthy individuals serving as controls. However, recent evidence has indicated that patients with treated primary OAG and healthy individuals may manifest no reproducible diurnal IOP pattern from day to day, leaving still no agreement as to the predominant diurnal IOP pattern or the time of peak IOP.

We studied the risk factors contributing to a larger disparity between single IOP measurements and the mean postwashout IOP. We found that, for every 1-mm Hg increase in mean postwashout IOP, an eye was 1.1 times more likely to deviate more than 1.5 mm Hg from an increase in IOP after washout using the mean postwashout IOP. From this we can infer that, as baseline IOP level increases, IOP fluctuation increases. A previous prospective study found that daily IOP fluctuations were directly proportional to IOP level when comparing the diurnal curves of normal OAG with those of normal tension. Therefore, our results support the idea that IOP fluctuation increases with increased mean IOP.

There are several limitations to the present study. The COMPASS study had well-defined inclusion criteria; therefore, our results may be generalizable only to the population eligible for the trial. As a retrospective analysis, only diurnal measurements from one day were available because the screening visit required a single measurement. Furthermore, the diurnal IOP measurements available from the COMPASS study included only 3 measurements spanning 8 hours (8 AM to 4 PM); other studies have used 12-hour or 24-hour IOP measurements as a more complete characterization of IOP fluctuation.

Conclusions

Because the COMPASS study was ongoing at the time of our analysis, we were limited to the prerandomization data. It may be possible that only a single IOP measurement is needed after surgery if the operation results in decreased IOP fluctuation. We look forward to evaluating data on diurnal IOP variation after surgery when the COMPASS trial is complete. Further research is needed to determine whether single IOP measurements might have applicability for postsurgical IOP characterization, as well as to address the clinical usefulness of single-day multiple diurnal IOP measurements.


**Mycobacterium chelonae Keratitis in a 3-Decade-Old Corneal Graft**

Kailun Jiang, MD; Seymour Brownstein, MD; Baldwin Toye, MD; Andre Ali-Ridha, MD; George Mintsioulis, MD

A. A 47-year-old man with a right corneal graft transplanted 27 years previously for treatment of a traumatic scar showing deep infiltrates along the sutures (arrowheads). Histopathologic examination revealed minimal inflammation and large, mostly intralamellar clusters (B-F, arrowheads; hematoxylin-eosin; original magnifications ×25 [B] and ×400 [C]) consisting of Gram-positive rods (D, original magnification ×1600) with focal beading (E, arrowhead; original magnification ×1600) and acid-fast positivity (F, original magnification ×1600) consistent with *Mycobacterium chelonae*, which was cultured. G, Electron microscopy showing microorganisms aligned longitudinally, replacing stroma, following the collagen lamellar orientation.