

The Utility of the Monocular Trial

Data from the Ocular Hypertension Treatment Study

Anjali M. Bhorade, MD, MSCI,¹ Bradley S. Wilson, MA,¹ Mae O. Gordon, PhD,¹ Paul Palmberg, MD, PhD,² Robert N. Weinreb, MD,³ Eydie Miller, MD,⁴ Robert T. Chang, MD,⁵ Michael A. Kass, MD,¹ for the Ocular Hypertension Treatment Study Group

Objective: To determine whether adjusting the intraocular pressure (IOP) change of the trial eye for the IOP change of the fellow eye (i.e., monocular trial) is a better assessment of medication response than testing each eye independently.

Design: Analysis of data from a prospective, randomized, clinical trial.

Participants: Two hundred six participants with ocular hypertension randomized to the observation group and later started on a topical prostaglandin analog (PGA).

Methods: Participants were started on a topical PGA in 1 eye and returned in approximately 1 month to determine medication response. The IOP response of the trial eye was determined by the IOP change between baseline and 1 month in the trial eye alone (unadjusted method) and by adjusting for the IOP change in the fellow eye between the same visits (adjusted method). Our "gold standard" for medication response was the IOP change in the trial eye between up to 3 pre- and 3 posttreatment visits on the same medication. Pearson correlation was used to compare the gold standard with the unadjusted and adjusted methods. In addition, symmetry of IOP response between trial and fellow eyes to the same medication was determined by correlating the trial eye IOP change between up to 3 pre- and 3 posttreatment visits to the fellow eye IOP change between the same visits.

Main Outcome Measures: Correlations of IOP change of the trial eye using the gold standard to the IOP change of the trial eye using the unadjusted and adjusted methods.

Results: The correlations of IOP change using the gold standard to the IOP change using the unadjusted and adjusted methods were $r = 0.40$ and $r = 0.41$, respectively. The correlation of IOP change of both eyes between the same pre- and posttreatment visits was $r = 0.81$.

Conclusions: The monocular trial (i.e., adjusted method) appears equivalent to testing each eye independently (i.e., unadjusted method); however, neither method is adequate to determine medication response to topical PGAs. Both eyes have a similar IOP response to the same PGA. Further studies to understand IOP fluctuation are necessary to improve current methods of assessing medication response.

Financial Disclosure(s): Proprietary or commercial disclosure may be found after the references. *Ophthalmology* 2010;117:2047–2054 © 2010 by the American Academy of Ophthalmology.

The monocular therapeutic trial has been used by clinicians for decades to determine medication response to topical glaucoma medications and is currently recommended by the Preferred Practice Pattern Guidelines of the American Academy of Ophthalmology.¹ The purpose of this trial, also known as the 1-eyed or unocular trial, is to determine IOP-lowering response and side effects of topical ocular hypotensive medications in patients with glaucoma or ocular hypertension.^{1–5} In the traditional monocular trial, a topical ocular hypotensive medication is instituted in 1 eye, usually the eye with the higher intraocular pressure (IOP), and the untreated fellow eye serves as a control for natural, or nontherapeutic, variability of IOP. The patient typically returns in 4 to 8 weeks and the therapeutic response to the medication started in the trial eye is determined by subtracting the change in IOP of the fellow eye from the change in IOP of the trial eye between the 2 visits. If the therapeutic response to the medication in the trial eye seems to be

adequate, after adjusting for the change in IOP in the fellow eye, the medication is prescribed for use in both eyes.

Recent studies report varying results and contradictory conclusions regarding the utility of the monocular trial.^{6–13} Although some of these studies support the continued use of the monocular trial, others recommend abandoning the monocular trial and using bilateral simultaneous trials of the same medication. Such opposing recommendations stem from different study questions, study designs, and methods of analysis.¹⁴ Despite such controversy, it is widely agreed that multiple pre- and posttreatment measurements on different days best estimate IOP response to a topical medication.^{8,10–12,14–18} This method, however, may not always be practical for every patient. Thus, the question remains of whether or not it is better to adjust IOP of the trial eye based on the change in IOP of the fellow eye when assessing IOP response to a topical medication between 2 visits.

The Ocular Hypertension Treatment Study (OHTS) dataset provides >200 medication trials using a topical prostaglandin analog (PGA) conducted in a well-defined protocol. The purpose of this analysis is to (1) determine whether or not it is better to adjust IOP of the trial eye based on IOP change in the fellow eye (i.e., the monocular trial) to assess medication response and (2) determine whether IOP response to a medication in 1 eye is similar to the IOP response to the same medication in the fellow eye in participants undergoing a topical PGA medication trial in the OHTS.

Patients and Methods

The Ocular Hypertension Treatment Study

The OHTS is a multicenter, randomized, clinical study that assessed whether topical ocular hypotensive medications reduce or delay the onset of primary open-angle glaucoma in ocular hypertension participants.¹⁹ Each of the 22 participating clinical centers received approval of the study by their corresponding institutional review boards. Details of the study protocol are described elsewhere,²⁰ and can be viewed online (available at: <https://vrcc.wustl.edu/mop/ohmop.pdf>; accessed August 4, 2009).²¹ Between February 1994 and October 1996, patients aged 40 to 80 years with no evidence of glaucomatous optic nerve damage on examination, optic disc photography, or visual field testing were recruited for the study. Qualifying IOP ranged from 24 to 32 mmHg in 1 eye and 21 to 32 mmHg in the fellow eye and was calculated from 2 consecutive measurements taken on 2 visits. Eligible participants returned for a baseline randomization visit and were randomized to either treatment with a topical ocular hypotensive medication or close observation.

All IOP measurements were performed by trained and certified OHTS examiners using a calibrated Goldmann applanation tonometer. One operator performed the measurement while the second operator viewed and recorded the result. At each visit, IOP was measured twice and a third measurement taken if the first 2 measurements differed by >2 mmHg. The visit IOP was defined as the mean of 2 or the median of 3 IOP measurements taken at that visit. Follow-up visits were scheduled within 2 hours of the time of day as the baseline visit whenever possible.

At the randomization visit, participants in the medication group underwent a medication trial consisting mainly of topical β -blockers. After June 2002, participants in the observation group were offered topical medications after results from the OHTS primary outcome manuscript demonstrated that treatment of ocular hypertensive participants delayed or prevented the onset of primary open-angle glaucoma.¹⁹ Many of these participants were recalled to initiate medication treatment at an extra visit outside their regularly scheduled 6-month follow-up visit. These participants were started on a topical ocular hypotensive medication (mainly topical PGAs) in the eye with the higher IOP (i.e., the trial eye). If both eyes had equal IOPs, the trial eye was chosen randomly. Participants returned approximately 4 to 6 weeks later to determine IOP response to the topical medication. If, however, their regularly scheduled follow-up visit was within a reasonable time frame (e.g., 2–3 months) and their ocular disease was stable, participants were allowed to return for medication assessment at their regularly scheduled visit. If treatment goals for the trial eye were met, then the medication was also started in the fellow eye and the participant returned at their next regularly scheduled 6-month visit and every 6 months thereafter.

The treatment goals included an IOP reduction of $\geq 20\%$ from the average IOP of the qualifying and baseline randomization visits and IOP ≤ 24 mmHg. An IOP <18 mmHg was not required. If the participant did not meet treatment goals, the medication was either discontinued and another medication started or an additional medication was added until treatment goals were reached. Medications were chosen at the discretion of the clinician as long as they were commercially available in the United States.

Statistical Design and Methods

For this report, data were analyzed only from participants in the observation group who later started a PGA because this afforded the opportunity to (1) obtain a mean baseline IOP from multiple pretreatment visits (these visits were not available for the group originally randomized to medication), (2) reduce effects from regression to the mean which may be more prominent at the randomization visit for the medication group, and (3) avoid possible contralateral effects from topical β -blocker medications.

A set criterion for a successful medication trial was developed to exclude trials in which (1) participants were lost to follow-up after the medication trial was initiated, (2) the trial eye was started on >1 medication simultaneously, (3) the trial and fellow eyes were started on a medication simultaneously, (4) the fellow eye was not started on the same medication as the trial eye, or (5) the trial eye was started on an additional medication with known contralateral effect (e.g., β -blocker) while the fellow eye was started on the initial medication. If >1 monocular trial was performed on a participant, only the first completed trial that met the inclusion criteria was used in this analysis. There were 301 medication trials in the observation group using a topical PGA that were manually reviewed for inclusion criteria with 98% agreement between 2 reviewers (AB and RC).

For this analysis, IOP measurements in the trial and fellow eyes were assessed at up to 3 visits before a baseline visit (i.e., pretreatment visits), a baseline visit, a 1-month visit, and up to 3 visits after the 1-month visit (i.e., posttreatment visits). For the purposes of this report, the visit during which medication was initiated is referred to as the “baseline visit” and the visit at which medication efficacy was assessed is referred to as the “1-month visit.” The 3 pretreatment visits were obtained within 30 months before the baseline visit and occurred approximately 6, 12, and 18 months before the baseline visit. The 3 posttreatment visits occurred within 30 months after the baseline visit and occurred approximately 6, 12, and 18 months after the baseline visit. Posttreatment visits were excluded from this analysis if the participant was not using the trial medication appropriately, started on an additional medication, or switched to another medication during this period.

We compared IOP response to a topical PGA started in the trial eye using the unadjusted and adjusted methods to our “gold standard” to determine which method better estimates medication response. The unadjusted IOP change of the trial eye was calculated by the change in IOP of the trial eye between the baseline and 1-month visits. The adjusted IOP change of the trial eye was calculated by subtracting the change in IOP of the fellow eye between the baseline and 1-month visits from the change in IOP of the trial eye between the same visits [(baseline IOP of trial eye – 1 month IOP of trial eye) – (baseline IOP of fellow eye – 1 month IOP of fellow eye)]. For example, if the baseline IOPs of both eyes were 24 mmHg and the 1-month IOPs of the trial and fellow eyes were 20 and 23 mmHg, respectively, then the unadjusted IOP change of the trial eye would be 4 mmHg (24 – 20) and the adjusted IOP change of the trial eye would be 3 mmHg [(24 – 20) – (24 – 23)]. The fellow eye IOP decreased by 1 mmHg and the monocular trial assumes that this change is due to nontherapeutic fluctuation and is symmetric between eyes. Hence by this assumption, the trial eye likely

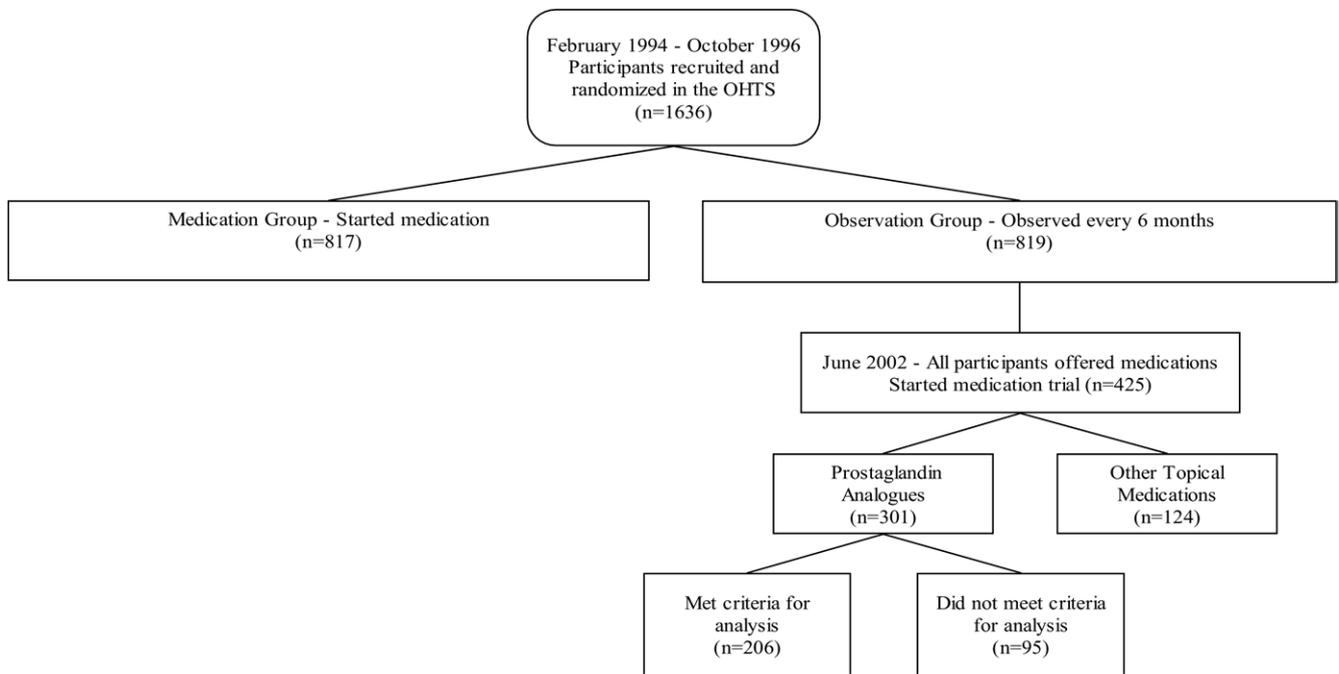


Figure 1. Flow diagram of participants included in the analysis. OHTS = Ocular Hypertension Treatment Study.

decreased 3 mmHg owing to medication and 1 mmHg owing to nontherapeutic fluctuation. We defined the “gold standard” for determining IOP response in this analysis as the difference between the mean IOP of up to 3 pretreatment and 3 posttreatment visits. Data were also analyzed in participants who had exactly 3 pre- and 3 posttreatment visits. The baseline and 1-month visits were not included in the gold standard calculation to reduce inflated correlations, which may occur if the same visits were included in both the gold standard and unadjusted and adjusted methods.

Descriptive statistics (means and standard deviations) are reported for IOP measurements at the baseline, 1-month, and pre- and posttreatment visits for trial and fellow eyes. The IOP response to a medication started in the trial eye is reported using the unadjusted, adjusted, and gold standard methods. Pearson correlation coefficients (total and partial) were performed to assess the association of IOP change using the unadjusted and adjusted methods to the IOP change using the gold standard adjusting for age, race, gender, and central corneal thickness. A multivariate regression analysis was performed to determine significant predictors of the mean IOP of up to 3 posttreatment visits in the trial eye after adjusting for covariates.

We analyzed whether both eyes have a similar IOP response to the same medication by comparing the IOP change of the trial eye between the mean of up to 3 pre- and 3 posttreatment visits to the IOP change of the fellow eye between the same visits. We used the same pre- and posttreatment visits for both eyes to reduce asymmetric effects from non-therapeutic variability of IOP which may occur between different visits for both eyes.¹⁸ All data were analyzed using SAS software version 9.1 (SAS Inc., Cary, NC).

Results

We report data from 206 PGA trials completed after June 2002 in patients originally randomized to the observation group (Fig 1). Baseline demographic characteristics of these participants are re-

ported in Table 1. For purposes of this report, Caucasians, Hispanics, Asians, and Native Americans are classified as “Other.” Of the 206 participants included in the analysis, the percent of participants with exactly 1, 2, and 3 pretreatment visits were 1.5%, 1.9%, and 96.6%, respectively, and the percent of participants with exactly 1, 2, and 3 posttreatment visits were 9.2%, 10.2%, and 80.6%, respectively. The mean number of months from the base-

Table 1. Baseline Characteristics of Participants Included in This Analysis

Characteristic	Mean ± Standard Deviation or Percent (n = 206)
Age (y)	206 61.8±9.1
Gender	
Male	76 36.9%
Female	130 63.1%
Race	
African American	60 29.1%
Other	146 70.9%
Educational status	
High school or lower	76 37.1%
Some college or higher	129 62.9%
Marital status	
Married	134 65.0%
Not married	72 35.0%
High blood pressure	
Yes	105 51.0%
No	101 49.0%
Heart disease	
Yes	27 13.1%
No	179 86.9%
Mean central corneal thickness of trial eye (µm)	206 577.2±34.5
Mean central corneal thickness of fellow eye (µm)	206 577.6±35.0

Table 2. Mean Intraocular Pressure (IOP) of Trial and Fellow Eyes and IOP Change Using the Unadjusted, Adjusted, and Gold Standard Methods

Eye	Baseline IOP (mmHg) ± SD	1 Month IOP (mmHg) ± SD	Mean of Pretreatment IOPs (mmHg) ± SD	Mean of Posttreatment IOPs (mmHg) ± SD	Unadjusted IOP Change between Baseline and 1 Month (mmHg) ± SD	Adjusted IOP Change between Baseline and 1 Month (mmHg) ± SD	Gold Standard IOP Change between Pre- and Posttreatment Visits (mmHg) ± SD
Trial eye (n = 206)	24.6±3.4	17.7±3.3	23.7±3.1	18.1±2.7	6.9±4.1	6.7±4.4	5.6±3.4
Fellow eye (n = 206)	22.8±3.1	22.6±4.2	22.7±2.8	17.7±2.8	0.2±3.5	N/A	4.9±3.1

SD = standard deviation.

line visit to the 1 month visit was 1.7±1.7 months (median, 1.1). The mean number of months from the baseline visit to the first, second, and third pretreatment visits were 5.7±1.7, 11.8± 1.9, and 18.1±2.5 months, respectively, and the mean number of months from the baseline visit to the first, second, and third posttreatment visits were 6.3±3.1, 12.1±3.3, and 19.1±3.6 months, respectively. The baseline and 1-month visits were completed within 2 hours of the same time of day in 71.6% of participants.

Table 2 describes the mean IOP of trial and fellow eyes at the baseline, 1-month, and pre- and posttreatment visits and the IOP change between visits using the unadjusted, adjusted, and gold standard methods. The Pearson correlations of trial eye IOP change between the gold standard and unadjusted and adjusted methods were $r = 0.40$ and $r = 0.41$, respectively (Figs 2 and 3). These correlations remained similar after analyzing only those participants with all 3 pre- and 3 posttreatment visits (n = 161; $r = 0.39$, unadjusted method; $r = 0.42$, adjusted method). Partial correlations adjusting for baseline age, gender, race, and central corneal thickness were $r = 0.36$ for the unadjusted and $r = 0.39$ for the adjusted analyses ($P < 0.0001$) when compared with the gold standard. In a multivariable regression analysis, the mean IOP of up to 3 posttreatment visits was associated with the 1-month unadjusted IOP ($r = 0.52$; $P < 0.0001$) and the 1 month adjusted IOP ($r = 0.40$; $P < 0.0001$) after adjusting for baseline age, gender, race, and central corneal thickness.

The Pearson correlation coefficient of IOP change of the trial eye between the mean of up to 3 pre- and 3 posttreatment visits to the IOP change of the fellow eye between the same visits was $r = 0.81$ (n = 206; Fig 4). This correlation increased slightly ($r =$

0.83) when using the mean IOP of participants with all 3 pre- and 3 posttreatment visits (n = 161).

Discussion

We believe that the OHTS dataset contains the largest number of medication trials conducted in a clinical trial to date. Although there were >800 medication trials conducted, we analyzed the 206 prostaglandin trials in participants originally randomized to the observation group to take advantage of the multiple pre- and posttreatment IOPs, reduce effects from regression to the mean from the baseline randomization visit, and avoid contralateral effects, which may occur with topical β -blocker medications. The results from our analysis suggest that adjusting IOP of the trial eye for IOP change of the fellow eye (i.e., monocular trial) is equivalent to using the unadjusted IOP of the trial eye when compared with a “gold standard” and that neither the adjusted or unadjusted method is adequate to determine medication response to topical PGAs. Our findings also imply that IOP response to a medication in 1 eye is similar to IOP response to the same medication in the fellow eye.

Earlier studies assessed dose response diurnal curves of 1 eye to different concentrations of pilocarpine while using the fellow eye as a control for nontherapeutic diurnal vari-

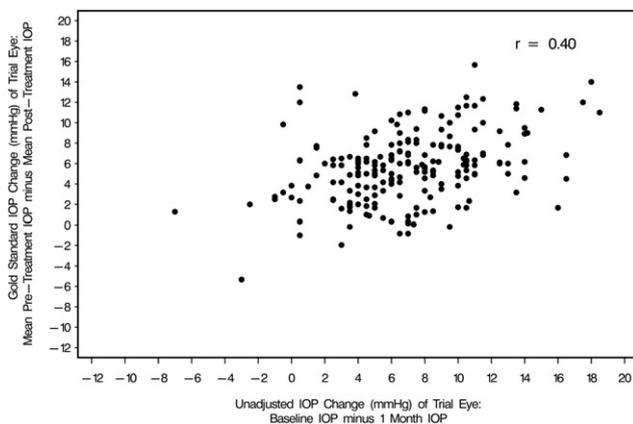


Figure 2. Scatterplot of the intraocular pressure (IOP) change of the trial eye using the gold standard versus the unadjusted method.

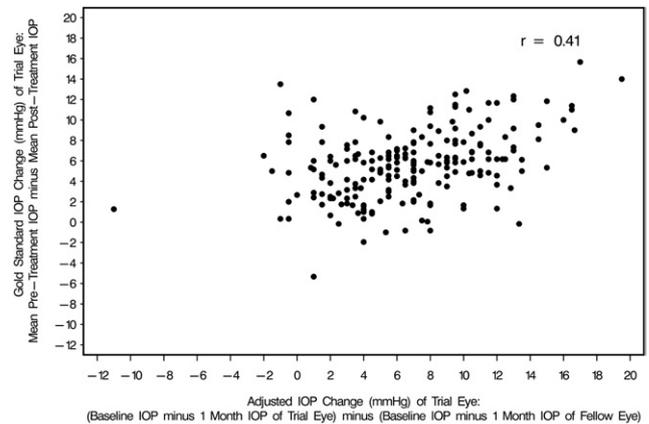


Figure 3. Scatterplot of the intraocular pressure (IOP) change of the trial eye using the gold standard versus the adjusted method.

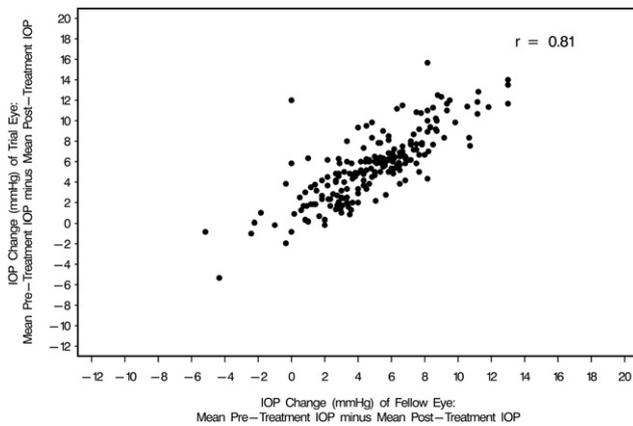


Figure 4. Scatterplot of the intraocular pressure (IOP) change of trial and fellow eyes between up to 3 pre- and 3 posttreatment visits on the same topical prostaglandin analog medication.

ability of IOP (Invest Ophthalmol Vis Sci 1963;2:289).²² This design was later extrapolated to the classic monocular trial, which assesses medication response in the trial eye while using the fellow eye as a control for nontherapeutic variability of IOP between visits. Several underlying assumptions of the trial include symmetric nontherapeutic variability of IOP between eyes, similar baseline IOPs of the 2 eyes, absence of a significant contralateral effect from the medication, and symmetric IOP response between eyes to the same medication.⁴

In 1993, Wilensky et al²³ reported asymmetric diurnal IOP curves between both eyes and cautioned against using the fellow eye as a control when assessing medication response. Over a decade later, Realini et al also challenged the use of the monocular trial sparking a debate which led to further studies to assess the validity and predictive accuracy of the monocular trial.^{6–13} These studies, however, differ in their questions of interest and methods of analysis, resulting in conflicting conclusions regarding the clinical utility of the monocular trial.¹⁴ To determine whether the classic monocular trial is useful, we need to understand the important questions at hand, the appropriate methods of analysis, and the caveats of interpreting the results.

Is It Better to Adjust the Intraocular Pressure or Not to Adjust the Intraocular Pressure to Determine Medication Response?

The essential component to determine the usefulness of the monocular trial is to assess whether or not adjusting IOP of the trial eye better estimates medication response. Many prior studies, however, analyzed the separate question of whether IOP response in 1 eye predicts IOP response in the second eye.^{7–10} Dayanir et al⁹ adjusted the IOP change in the trial eye for the IOP change in the fellow eye and correlated it to the IOP change in the fellow eye between baseline and posttreatment visits ($r = 0.54$ glaucoma and OHTN patients); however, they did not compare whether this is better or not than not adjusting IOP of the trial eye. Chaudhary et al⁸ compared initial unadjusted and adjusted

IOP change in the trial eye with the unadjusted and adjusted IOP change in the fellow eye between pre- and posttreatment visits and conclude that it is better to adjust the IOP ($r = 0.39$) than not adjust the IOP ($r = 0.22$) to determine fellow eye IOP response. The correlation for the adjusted IOP analysis, however, may be artificially inflated owing to the same IOPs (trial and fellow eye at posttreatment visit) appearing on both sides of the statistical equation.²⁴

Takahashi et al¹⁰ reported on 41 normal participants who underwent a 1-week PGA trial in the right eye followed by the same trial in their left eye after a 2-month washout period. The correlation of right eye IOP change to left eye IOP change between baseline and posttreatment visits was similar whether using the adjusted ($r = 0.31$) or unadjusted ($r = 0.32$) IOPs. This study, however, was conducted in normal participants with mean baseline IOPs ranging between 12.7 ± 2.3 and 14.0 ± 2.3 mmHg and may not accurately reflect medication trials conducted in patients with elevated IOP, particularly given the greater variability of IOP in glaucoma patients.

Our post hoc analysis of PGA trials conducted in the OHTS differs from most previous studies. We used multiple pre- and posttreatment visits (not including visits during the medication trial) to estimate the “true” medication response in the trial eye. We then compared our “gold standard” with the IOP response of the trial eye between the baseline and 1-month visits during the medication trial using the unadjusted and adjusted methods. We agree with Leffler et al¹¹ that the main question is how best to estimate true medication response in the trial eye and not the prediction of medication response in the fellow eye. However, our results from a multivariable regression analysis differ from Leffler et al, who found the best predictors of posttreatment IOP of the trial eye to be the baseline IOP of the trial eye and the unadjusted rather than the adjusted IOP of the trial eye. Our results suggest that the unadjusted and adjusted IOPs of the trial eye similarly predicted the posttreatment IOP of the trial eye.

There is only 1 other study to date that used multiple pre- and posttreatment visits and compared unadjusted and adjusted methods with a “gold standard” to analyze the utility of the monocular trial.⁶ Realini⁶ recently conducted a prospective, randomized, investigator-masked study of 26 ocular hypertensive or open-angle glaucoma patients undergoing a PGA trial. Effects from diurnal variation were strictly controlled and effects from regression to the mean were reduced by random selection of the eye undergoing the trial and a lower mean baseline IOP. The analysis design and results of his study were similar to ours and suggest fairly equivalent results between the unadjusted ($r^2 = 0.325$; $r = 0.57$) and adjusted ($r^2 = 0.279$; $r = 0.53$) methods. Removal of a visit which overlapped between the “long-term” (i.e., gold standard) and “short-term” (i.e., unadjusted or adjusted method) analysis reduced the correlations to those more comparable with ours ($r = 0.31$ unadjusted method and $r = 0.41$ adjusted method). Although the benefits of a prospective study cannot be underestimated, our post hoc analysis provides a greater number of medication trials conducted over a greater number of visits and over a longer time period than Realini’s study. In

addition, our study population reflects patients with a higher mean baseline IOP and includes those of African American descent.

Do Both Eyes Respond Similarly to the Same Topical Medication?

Most prior studies correlate IOP change of the trial eye to the IOP change of the fellow eye and report poor to moderate correlations.^{7–10} These results, however, may not accurately reflect the symmetry of IOP response between the 2 eyes of an individual patient. In a separate analysis from the OHTS, untreated participants displayed a moderate amount of variability of IOP within the same eye between visits ($r = 0.50$ to $r = 0.65$) and a better, but not perfect, concordance of IOP between both eyes at the same visit ($r = 0.65$ to $r = 0.76$).¹⁸ Correlating IOP measurements between different eyes on different pre- and posttreatment visits will likely result in low correlations and lead to erroneous conclusions of asymmetric IOP response between eyes to the same topical medication.

We believe the best analysis to determine whether both eyes respond similarly to the same topical medication is to compare the IOP change of both eyes between the same pre- and posttreatment visits. Using the same pre- and posttreatment visits likely reduces the amount of nontherapeutic variability of IOP which may occur between eyes on different visits. We used multiple pre- and posttreatment visits to reduce the variability of IOP between visits and improve our estimation of true IOP response. We found a strong correlation ($r = 0.81$) of IOP response between both eyes. Similar strong correlations ($r = 0.84$) between the 2 eyes using the same baseline and posttreatment visits were reported in another study.¹² Thus, a separate assessment of medication response in the second eye may not be necessary for patients with similar baseline IOPs and disease status in both eyes.

What Are the Factors Affecting Assessment of Medication Response?

A surprising finding in our study was the moderately poor correlations of both the unadjusted and adjusted methods compared with our gold standard, implying that neither method accurately determines medication response. To improve the accuracy of our current methods, we need to understand the factors that affect assessment of medication response.

Variability of Intraocular Pressure Between Visits. In the OHTS, 13% of untreated participants had a difference of IOP $>20\%$ within the same eye between 2 consecutive visits over a 60-month period.¹⁸ If these patients underwent a medication trial, they might be misclassified as either having a response or not having a response to the medication owing to their nontherapeutic variability of IOP. Results from the same analysis suggest that IOP was more similar between the 2 eyes at the same visit than was IOP for the same eye between visits. Although these findings imply that the monocular trial may be better than testing each eye independently, our current analysis does not support that conclusion. A better understanding of factors con-

tributing to variability of IOP within the same eye and between fellow eyes is vital to improving our current assessment of medication response.

Regression to the Mean. Clinicians often start a topical ocular hypotensive medication when a patient's IOP is elevated and in the eye with the higher IOP. A lower IOP at the subsequent visit may be due to regression to the mean as well as to the medication response. In our analysis, the IOP at the visit the medication was initiated (i.e., baseline visit) was approximately 1 mmHg higher than the mean IOP of up to 3 visits before the baseline visit (i.e., pretreatment visits). In addition, IOP in the trial eye was almost 2 mmHg higher than the fellow eye at the baseline visit, but was only 1 mmHg higher at the visits before the baseline visit. These differences reflect regression to the mean and may partially explain the greater IOP-lowering of the trial eye between the baseline and 1-month visits compared with the multiple pre- and posttreatment visits. Interestingly, in an analysis of untreated observation participants in the OHTS, we found a mean IOP-lowering of 0.6 mmHg between the randomization visit and the first follow-up visit likely due to regression to the mean.¹⁸ In the current analysis, we did not use data from medication trials conducted at the baseline randomization visit to reduce effects from regression to the mean. Although random selection of an eye starting a medication may reduce regression to the mean, this may not be appropriate for all clinical situations. A method to correct for effects from regression to the mean would be useful to improve the accuracy in assessing medication response.

Consistency of Time of Day. In the analysis of observation participants in the OHTS, there was a stronger correlation of untreated IOP measured within 2 hours of the time of day between visits ($r = 0.56$) than when measured >2 hours of the time of day ($r = 0.39$).¹⁸ This implies that patients returning for their posttreatment visit at a time of day >2 hours from their baseline visit may have an inaccurate assessment of medication response. Although the OHTS did not perform diurnal IOP measurements, we attempted to control for time of day by scheduling visits within 2 hours of each other, as similarly done in other studies.^{8–10} The rationale behind the monocular trial is using the fellow eye as a control for diurnal variation. The assumption that both eyes have symmetric diurnal variation, however, is controversial.^{15,16,23,25–28} Although consistency of time of day is important to consider when determining medication response, it may not always be practical in the clinical setting.

Contralateral Effect. One of the main assumptions of the classic monocular trial is absence of a significant contralateral effect in the fellow eye from a topical medication instilled in the trial eye. Similar to prior studies, we used only topical PGAs in our analysis to avoid contralateral effects from topical β -blocker medications.^{6,9,10} In clinical practice, however, patients may undergo trials using topical β -blockers. The estimated mean contralateral effect of 1.5 mmHg from topical β -blockers may or may not be negligible in a monocular trial, depending on the amount of IOP-lowering from the medication.²⁹

Measurement Error. Inaccurate IOP measurements owing to an uncalibrated tonometer, the examiner, or patient-

related factors (e.g., ocular squeezing) may affect accurate assessment of medication response. The order of IOP measurement between right and left eyes may also affect IOP measurement with the first eye measuring a higher IOP than the second eye.¹⁸ In the OHTS, we reduced measurement error and bias by frequently checking tonometer calibration and multiple IOP measurements using 1 examiner rotating the tonometer dial and a second examiner reading the dial. Although many factors affecting measurement error and bias in clinical practice cannot be controlled, efforts to improve amenable factors may increase the accuracy of assessment of medication response.

Patient Compliance. An important, and often underestimated, component of accurate assessment of medication response is patient compliance. Poor patient compliance with topical medications may result from many factors including confusion of directions (e.g., correct eye, frequency) and forgetting to or inappropriately instilling the medication daily. Daily instillation of the medication was performed by the investigator in a prior study, but is likely not feasible in clinical practice.¹⁰ Thus, methods to improve patient compliance may lead to more accurate estimates of medication response.

What Is the Best Method to Assess Medication Response?

The best “gold standard” method that we are currently aware of is assessment of medication response through averaging multiple pre- and posttreatment visits.^{6,8,10–12,14–18} Multiple visits reduce the contribution of nontherapeutic variability of IOP between visits (i.e., regression to the mean, diurnal variation) and factors which affect IOP at each visit (i.e., measurement error, patient compliance) resulting in a more accurate estimate of medication response than from 1 pre- and 1 posttreatment visit. Multiple visits, however, may not be practical in certain clinical situations (e.g., patients with elevated IOP who are functionally monocular or noncompliant with multiple visits). In such scenarios, clinicians may need to rely on the unadjusted or adjusted methods to assess medication response over 2 visits.

Although the unadjusted and adjusted methods seem to be equivalent in estimating medication response, they may benefit different patients in clinical practice. The unadjusted method tests each eye independently and may be implemented through bilateral simultaneous trials. Such trials may be easier for patients to comprehend, resulting in better patient compliance and estimation of medication response than monocular trials. In addition, bilateral simultaneous trials may more accurately assess medication response for medications with a contralateral effect, such as topical β -blockers. Our results in this highly selected group of OHTS participants suggest that both eyes respond similarly to the same medication. Patients with asymmetric IOPs or disease between eyes, however, may not respond similarly and may benefit from bilateral simultaneous trials over a classic monocular trial. However, patients with a large amount of variability of IOP between visits may benefit from the classic monocular trial by using the fellow eye as a control for nontherapeutic variability of IOP.¹⁸ Monocular

trials may also facilitate easier identification of ocular side effects. Furthermore, patients at risk for a systemic reaction (e.g., sulfa allergy, asthma) may have milder effects with half the medication dose in a monocular trial. We believe that if medication efficacy must be assessed between 2 visits, the choice of whether to use the classic monocular trial or bilateral simultaneous trials should be individualized to patient and clinician preferences.

The standardized protocol, strict treatment goals, and multiple IOP measurements using a 2-operator system were implemented to improve the accuracy of IOP measurements in the OHTS. Data from the OHTS, however, may not reflect clinical practice, which may have even greater variability of IOP (owing to measurement error, diurnal variation, etc.) during assessment of medication trials. Intraocular pressure measurements were obtained at single time points in a day and may not accurately reflect time points throughout a 24-hour period. Participants in the OHTS were started on medications in the eye with the higher IOP, which may introduce bias from regression to the mean. In addition, the results from our analysis reflect initial medication trials conducted in patients with ocular hypertension and may be different in patients with glaucoma or patients treated with >1 topical ocular hypotensive medication.

In conclusion, the monocular trial and bilateral simultaneous trials are equivalent for estimating medication response. Both methods, however, are inaccurate compared with assessing medication response from multiple pre- and posttreatment visits. Further studies are needed to better understand factors that influence IOP measurement and thus assessment of medication response between visits. Knowledge gained from such studies may help to improve our current methods or develop a new method to more accurately assess IOP response to ocular hypotensive medications.

References

1. American Academy of Ophthalmology Glaucoma Panel. Preferred Practice Pattern. Primary Open-Angle Glaucoma. San Francisco, CA: American Academy of Ophthalmology; 2005: 13. Available at: <http://one.aao.org/CE/PracticeGuidelines/PPP.aspx?sid=ca9ec1b5-2567-4e85-96f6-b6540e5ac5a1>. Accessed August 4, 2009.
2. Hoskins HD Jr. The management of elevated intraocular pressure with normal optic discs and visual fields. II. An approach to early therapy. *Surv Ophthalmol* 1977;21:479, 489–93.
3. Drance SM. The unioocular therapeutic trial in management of elevated intraocular pressure. *Surv Ophthalmol* 1980;25: 203–5.
4. Smith J, Wandel T. Rationale for the one-eye therapeutic trial. *Ann Ophthalmol* 1986;18:8.
5. Stamper RL, Lieberman MF, Drake MV. *Becker-Shaffer's Diagnosis and Therapy of the Glaucomas*. 7th ed. St. Louis: Mosby; 1999:424.
6. Realini TD. A prospective, randomized, investigator-masked evaluation of the monocular trial in ocular hypertension or open-angle glaucoma. *Ophthalmology* 2009;116:1237–42.
7. Realini T, Fechtner RD, Atreides SP, Gollance S. The unioocular drug trial and second-eye response to glaucoma medications. *Ophthalmology* 2004;111:421–6.

8. Chaudhary O, Adelman RA, Shields MB. Predicting response to glaucoma therapy in one eye based on response in the fellow eye: the monocular trial. *Arch Ophthalmol* 2008;126:1216–20.
9. Dayanir V, Cakmak H, Berkit I. The one-eye trial and fellow eye response to prostaglandin analogues. *Clin Experiment Ophthalmol* 2008;36:136–41.
10. Takahashi M, Higashide T, Sakurai M, Sugiyama K. Discrepancy of the intraocular pressure response between fellow eyes in one-eye trials versus bilateral treatment: verification with normal subjects. *J Glaucoma* 2008;17:169–74.
11. Leffler CT, Amini L. Interpretation of unioocular and binocular trials of glaucoma medications: an observational case series. *BMC Ophthalmol* [serial online] 2007;7:17. Available at: <http://www.biomedcentral.com/1471-2415/7/17>. Accessed December 3, 2009.
12. Realini T, Vickers WR. Symmetry of fellow-eye intraocular pressure response to topical glaucoma medications. *Ophthalmology* 2005;112:599–602.
13. Realini T, Barber L, Burton D. Frequency of asymmetric intraocular pressure fluctuations among patients with and without glaucoma. *Ophthalmology* 2002;109:1367–71.
14. Bhorade AM. The monocular trial controversy: a critical review. *Curr Opin Ophthalmol* 2009;20:104–9.
15. Liu JH, Sit AJ, Weinreb RN. Variation of 24-hour intraocular pressure in healthy individuals: right eye versus left eye. *Ophthalmology* 2005;112:1670–5.
16. Sit AJ, Liu JH, Weinreb RN. Asymmetry of right versus left intraocular pressures over 24 hours in glaucoma patients. *Ophthalmology* 2006;113:425–30.
17. Piltz-Seymour J, Jampel H. The one-eye drug trial revisited. *Ophthalmology* 2004;111:419–20.
18. Bhorade AM, Gordon MO, Wilson B, et al. Ocular Hypertension Treatment Study Group. Variability of intraocular pressure measurements in observation participants in the Ocular Hypertension Treatment Study. *Ophthalmology* 2009;116:717–24.
19. Kass MA, Heuer DK, Higginbotham EJ, et al. Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open angle glaucoma. *Arch Ophthalmol* 2002;120:701–13.
20. Gordon MO, Kass MA, Ocular Hypertension Treatment Study Group. The Ocular Hypertension Treatment Study: design and baseline description of the participants. *Arch Ophthalmol* 1999;117:573–83.
21. Ocular Hypertension Treatment Study (OHTS). Manual of Procedures. Version 3. September 24, 2001: 2-4 to 2-37. Available at: <https://vrcc.wustl.edu/mop/ohtsmop.pdf>. Accessed September 22, 2008.
22. Drance SM, Nash PA. The dose response of human intraocular pressure to pilocarpine. *Can J Ophthalmol* 1971;6:9–13.
23. Wilensky JT, Gieser DK, Dietsche ML, et al. Individual variability in the diurnal intraocular pressure curves. *Ophthalmology* 1993;100:940–4.
24. Leffler CT. Studies of monocular trials of glaucoma medications: conflicting results explained by varying methods [letter]. *Arch Ophthalmol* 2009;127:707–8; author reply 708.
25. Katavisto M. The diurnal variations of ocular tension in glaucoma. *Acta Ophthalmol Suppl* 1964;78:1–130.
26. Kitazawa Y, Horie T. Diurnal variation of intraocular pressure in primary open-angle glaucoma. *Am J Ophthalmol* 1975;79:557–66.
27. Dinn RB, Zimmerman MB, Shuba LM, et al. Concordance of diurnal intraocular pressure between fellow eyes in primary open-angle glaucoma. *Ophthalmology* 2007;114:915–20.
28. Shuba LM, Doan AP, Maley MK, et al. Diurnal fluctuation and concordance of intraocular pressure in glaucoma suspects and normal tension glaucoma patients. *J Glaucoma* 2007;16:307–12.
29. Piltz J, Gross R, Shin DH, et al. Ocular Hypertension Treatment Study Group. Contralateral effect of topical beta-adrenergic antagonists in initial one-eyed trials in the Ocular Hypertension Treatment Study. *Am J Ophthalmol* 2000;130:441–53.

Footnotes and Financial Disclosures

Originally received: August 18, 2009.

Final revision: February 17, 2010.

Accepted: February 17, 2010.

Available online: August 12, 2010.

Manuscript no. 2009-1118.

¹ Department of Ophthalmology & Visual Sciences, Washington University School of Medicine, St. Louis, Missouri.

² Department of Ophthalmology, University of Miami, Miami, Florida.

³ Department of Ophthalmology, University of California, San Diego, La Jolla, California.

⁴ Department of Ophthalmology, University of Pennsylvania, Philadelphia, Pennsylvania.

⁵ Department of Ophthalmology, Stanford University, Stanford, California.

Financial Disclosure(s):

The authors have made the following disclosures:

Michael Kass – Paid Consultant - Pfizer Pharmaceuticals, Alcon Incorporated, Allergan Incorporated, and Merck & Co. Incorporated.

Paul Palmberg – Paid Consultant - Pfizer Pharmaceuticals

Robert N. Weinreb – Paid Consultant - Pfizer Pharmaceuticals

Eydie Miller – Paid Consultant - Allergan Incorporated

The funding organizations had no role in the design or conduct of this research.

Supported by grants from the National Eye Institute, and the National Center on Minority Health and Health Disparities, National Institutes of Health, Bethesda, MD (EY09341, EY09307, and Core Grant EY02687); Merck Research Laboratories, White House Station, New Jersey; and an unrestricted grant from Research to Prevent Blindness, New York, New York.

Correspondence:

Mae O. Gordon, PhD, OHTS Coordinating Center, Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, Box 8203, 660 South Euclid, St. Louis, MO 63110. E-mail: mae@vrcc.wustl.edu.