Predicting Response to Glaucoma Therapy in One Eye Based on Response in the Fellow Eye

The Monocular Trial

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Objective: To evaluate whether the change in intraocular pressure (IOP) observed in one eye after starting a glaucoma medication regimen is predictive of the change in IOP due to the same medication in the fellow eye.

Methods: A retrospective medical record review of 22 patients with primary open-angle glaucoma (POAG) and 27 glaucoma suspects who underwent monocular drug trials before the drug was added to the second eye. The absolute change in IOP from baseline and the relative change (change in treated eye minus change in fellow eye) in the first eye treated were compared with the second eye after binocular treatment.

Results: The absolute and relative decreases in IOP of the first eye were poorly correlated with those of the second eye in patients with POAG ($r^2<0.001; P=0.97$ and $r^2=0.040; P=0.38$, respectively). However, they were well correlated in glaucoma suspects ($r^2=0.348; P=0.001$ and $r^2=0.396; P<0.001$, respectively).

Conclusions: The change in IOP of one eye due to a medication may be predictive of the subsequent response of the fellow eye to the same medication in glaucoma suspects, but not in patients with POAG. Using the fellow eye as a control may confer a more accurate portrayal of the true therapeutic effects of a medicine, although further study is needed to support both of these findings.

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The monocular drug trial for management of glaucoma may be applied in 2 ways: (1) to assess the efficacy of a drug in the first eye treated and (2) to predict the response to a drug in the second eye treated. The first practice is based on the assumption that spontaneous fluctuations in intraocular pressure (IOP) are sufficiently symmetrical to allow one eye to be used as a control for the fellow eye, while the second assumes that both eyes respond in a similar manner to the same medication.

The validity of these 2 assumptions has been challenged, casting doubt on the usefulness of the monocular trial. The first assumption, that spontaneous pressure fluctuations between fellow eyes are sufficiently symmetrical to allow use of the untreated eye as a control for the treated eye, has not been supported by some studies that have shown significant asymmetric IOP variations in patients with and without glaucoma, although other studies have shown better concordance between eyes.

The second assumption, that the response of one eye to a medication will be matched by a symmetric response in the fellow eye, can be tested in 2 ways. One is to compare the absolute changes in IOP of the 2 eyes from baseline, while the other is to compare the relative changes in IOP (ie, corrected for corresponding change in the fellow eye) of the first and second eyes treated. Realini and colleagues reported that the absolute response of the first eye treated during a monocular trial is not a good predictor of the second eye's response, although they found that fellow eyes respond symmetrically when treated simultaneously.

These investigators used the absolute rather than the relative IOP change because of their previous findings of asymmetry in spontaneous IOP fluctuations between fellow eyes; this led them to conclude that the fellow eye cannot be used as a control.

To our knowledge, no studies have been published that study whether the relative IOP changes of the first and second eyes treated as part of a monocular trial are correlated and whether the correlation is influenced by a diagnosis of glaucoma suspect vs established primary open-angle glaucoma (POAG). We report herein the findings of a study to further evaluate these questions regarding the monocular drug trial.
This is a retrospective observational study of patients with POAG and glaucoma suspects aged 18 years and older who underwent a monocular trial for glaucoma therapy. The study was designed to look for any possible differences between the eyes of glaucoma suspects and those of patients with POAG, in part because the latter might be more influenced by prior medical and surgical therapy. In each patient, a topical glaucoma medication was administered to 1 eye for 1 to 2 months, followed by administration of the same medication to the fellow eye. Intraocular pressure measurements were documented before and after treatment of each eye. All IOP measurements were taken by experienced practitioners with a Goldmann applanation tonometer. Patients were typically seen within 2 hours of prior visits, and no time difference exceeded 4 hours. Exclusion criteria included any other change in medication or dosage of medication during the trial or any other event that might have altered the IOP in either eye. The Human Investigations Committee at the Yale School of Medicine approved this study.

Data gathered included demographic information and glaucoma status (ie, glaucoma suspect vs POAG), history of prior ocular surgery, current medications, and all pertinent IOPs. Glaucoma suspects were defined as patients with an IOP consistently greater than 21 mm Hg but with normal optic discs and visual fields, or with optic discs suspicious for glaucomatous damage. Patients with POAG had documented glaucomatous optic nerve damage with no evidence of a secondary mechanism for the glaucoma. The absolute IOP response of the first and second eye treated was determined by calculating the change in IOP from the baseline directly prior to treatment. The relative IOP response of the first and second eye treated was determined by subtracting the change in IOP of the fellow eye from the change in IOP of the newly treated eye during the same time period. Patients who had a decrease in IOP of 2 mm Hg or more in the monocular phase were included in the binocular phase of the study. The data on the other patients, ie, patients with poor responses, were not recorded because many were not treated in the fellow eye. The responses of the left and right eyes to therapy were also compared for the entire study.

Linear regression analysis was performed using the coefficient of determination, $r^2$, to look for statistical correlation between both the absolute and relative responses of the first and second eyes to treatment. Statistical significance was determined for $P$ values less than .05.

Population subsets were analyzed separately to determine if IOP response was influenced by glaucoma status (glaucoma suspect vs POAG), different medications used in the trial, concurrent use of systemic $\beta$-blockers, and history of ocular procedures.

## METHODS

Forty-nine patients met the eligibility criteria and were included in this study. Twenty-six of the patients were women (53%), 29 were white (59%), and the mean age was 64 years. A total of 27 patients had a diagnosis of glaucoma suspect and 22 had POAG. Prostaglandin analogs (59.2% [29]) and $\beta$-adrenergic antagonists (22.4% [11]) were the most common drugs chosen for the monocular drug trial (Table 1).

The eye treated first in the monocular drug trial had the higher baseline IOP in 27 patients and the lower baseline IOP in 8, while pressures were equal in the remaining 14. Nine of 22 patients (41%) with POAG were already taking a glaucoma medication at the time of the monocular trial, compared with 6 of 27 (22%) in the glaucoma suspect group.

The results of the monocular trial in the overall population are shown in Table 2. There was poor correlation between the absolute change in IOP of the first eye treated and the second eye treated ($r^2=0.047; P=.14$). Correlation using relative changes: $r^2=0.151; P=.006$. Relative change was calculated by subtracting the change in IOP of the fellow eye from that of the treated eye.

The results of the monocular trial when controlling for POAG vs glaucoma suspect are shown in Table 3. In the 27 patients with a diagnosis of glaucoma suspect, there was a strong correlation between absolute response in IOP of the first and second eyes treated ($r^2=0.348; P=.001$) (Figure 1) and an even stronger correlation between relative IOP responses ($r^2=0.396; P<.001$) (Figure 2). In the 22 patients with POAG, the first and second eyes treated were poorly correlated when using either absolute ($r^2<0.001; P=.97$) (Figure 3) or relative changes in IOP ($r^2=0.040; P=.38$) (Figure 4).

In the subset of 29 patients who received a prostaglandin analog in the monocular drug trial, there was no statistically significant correlation between the absolute change in IOP of the first and second eyes treated ($r^2=0.037; P=.32$), although there was a significant correlation when using the relative IOP response ($r^2=0.145; P=.04$). Of the 11 patients receiving a $\beta$-adrenergic antagonist in the monocular trial, there was no statisti-
cally significant correlation when using the absolute IOP change ($r^2=0.096; P=.35$). While the relative IOP change showed better correlation than the absolute change, it did not reach statistical significance ($r^2=0.289; P=.38$). In the 11 patients with prior ocular laser or incisional surgery, a poor correlation was found between the absolute first and second eye responses ($r^2=0.134; P=.27$), while relative changes had a strong correlation ($r^2=0.429; P=.03)$. In 38 patients who had not undergone an ocular procedure, no statistically significant correlation was found for absolute changes in IOP ($r^2=0.032; P=.29$), although there was significant correlation when using relative changes ($r^2=0.090; P=.07$).

When comparing the absolute IOP responses of the right and left eyes from the baseline to the end of the study, the mean (SD) pressures of the right eyes decreased 3.1 (5.5) mm Hg and left eyes decreased 4.3 (7.2) mm Hg, which was strongly correlated ($r^2=0.399; P<.001$). The line of best fit was $IOP_{left} = 0.82 (IOP_{right}) - 1.76$ mm Hg.

**COMMENT**

In theory, the primary benefit of a monocular trial in the medical management of glaucoma is to assess the efficacy of a topical drug by delivering it in one eye and using the fellow eye as a control for spontaneous IOP fluctuations. A secondary benefit may be to predict the response to the drug in the fellow eye on the basis of the response to that drug in the first treated eye. Recent studies, however, have challenged whether spontaneous variations in IOP are symmetrical enough to allow the fellow eye to serve as a valid control.
eye to act as a control for the treated eye\textsuperscript{1-4} and whether the response in IOP of the first eye during the monocular trial is a good predictor of the future response of the second eye to the same medication.\textsuperscript{7}

Realini et al\textsuperscript{1} reported that asymmetric fluctuations in IOP between fellow eyes (defined as at least a 3-mm Hg difference in IOP change over 2 consecutive visits) occurred in 16.3% of visits by patients with glaucoma. Liu et al\textsuperscript{2} measured the IOPs every 2 hours for 24 hours in a sleep laboratory of healthy individuals and found only moderate symmetry between the right and left eyes at a single measurement ($r^2$ varied from 0.311 to 0.741 depending on the time of day). A follow-up study by the same group\textsuperscript{3} found similarly moderate correlation in patients with glaucoma ($r^2$ varied from 0.416 to 0.536). Wilensky et al\textsuperscript{4} observed similar results by obtaining IOP measurements 5 times per day for 5 days with a home tonometer and noted that 33% of patients with ocular hypertension and 36% of patients with POAG had IOP curves of different shapes in the left and right eyes.

Dinn et al\textsuperscript{5} found that asymmetric spontaneous changes in IOP occurred between 5% and 22% of measurements in patients with POAG and between 6% and 13% of measurements in glaucoma suspects,\textsuperscript{6} depending on the time of day. Although their data are similar to that of Realini et al,\textsuperscript{1} the authors believe that symmetric, spontaneous IOP fluctuations between eyes occur with sufficient frequency to allow one eye to serve as a control for the fellow eye in a monocular trial. This question has yet to be resolved.

Realini et al\textsuperscript{7} also found the first eye treated to be a poor predictor of the response of the second eye treated with the same topical glaucoma medication and advocated for rejection of the monocular trial. Based on their previous findings, ie, that one eye is not a good control for the response of the fellow eye,\textsuperscript{1} they used absolute rather than relative IOP changes. They also observed that when medication is given in both eyes at the same time, absolute IOP changes in the left and right eye are well correlated.\textsuperscript{8} It is not entirely clear why spontaneous variations in therapeutic responses between fellow eyes in monocular trials would show poor correlation while therapeutic responses to simultaneous treatment show good correlation between eyes. In the present study, we attempted to shed some light on this question.

Our results are in agreement with those of Realini et al\textsuperscript{7} to the extent that we did not find correlation of first and second eye responses using absolute IOP changes in the combined POAG and glaucoma suspect population ($r^2$=.047; $P=.14$ in our study vs $r^2=.0171; P=.35$ in Realini et al), although the correlation was significant in our study when using relative changes ($r^2=.151; P=.006$). In addition, when controlling for glaucoma suspect vs POAG, we did find significant correlations using both absolute and relative IOP changes in the suspect subset, while neither absolute nor relative changes correlated in our patients with POAG. It would appear, therefore, that the patient’s glaucoma status, ie, glaucoma suspect vs POAG, may influence the ability of the first eye’s response to predict the second eye’s response, whereas the method of IOP calculation, ie, absolute vs relative, is of secondary importance.

The influence of glaucoma status in our study is likely due to the reported effects of glaucoma on IOP asymmetry.\textsuperscript{9,10} Although an unknown percentage of our glaucoma suspects undoubtedly had premanifest glaucoma, all of the patients with POAG had established glaucoma, which may have influenced the observed differences between the 2 study groups. Other investigators, however, have found asymmetric IOP variations to be similar between patients with POAG and glaucoma suspects\textsuperscript{9,10} and between patients with glaucoma and healthy subjects.\textsuperscript{3,10} Another possibility is that, because a greater percentage of patients with POAG were already taking a glaucoma medication prior to initiation of the monocular trial than the glaucoma suspect group, the additional medication could have contributed to asymmetric fluctuations between eyes owing to variable times since last instillation and inconsistency in patient compliance. Further study is needed, therefore, to confirm our findings.

Although our study focused primarily on the ability of the first eye’s response to predict the subsequent response of the fellow eye to the same medication, it also provides an indirect implication regarding the symmetry of spontaneous IOP fluctuation between fellow eyes, which is the most important issue in a monocular trial. Presumably, the therapeutic component of IOP change between fellow eyes is approximately equal, as supported by Realini and Vickery,\textsuperscript{8} leaving asymmetry of spontaneous variations as the main source of discrepancy between first and second eye responses in the trial. If patients with asymmetric spontaneous pressure fluctuations at a given time were exerting more influence than those with symmetric fluctuations, then using one eye to adjust for change in the fellow eye would result in poorer correlation between first and second eye responses. Our observation of a stronger correlation in both population subsets when using relative rather than absolute IOP changes suggests that there may be sufficient symmetry in spontaneous IOP fluctuations between eyes to allow use of the fellow eye as a control when attempting to isolate the therapeutic effect of a drug. This may explain the poorer correlation between eyes in studies that evaluate only absolute IOP change, especially when the 2 eyes.
are compared at different time periods, as in the study by Realini et al.\(^7\)

An additional question raised by our study is why the patients with POAG had significantly more pronounced absolute IOP responses in the first eye treated than in the second. One explanation is that the second eyes treated had lower mean baseline IOPs, which could have resulted from a crossover effect when treating the first eye with a β-blocker.\(^{11,13}\) or simply that the eye with the higher pressure was selected for initial treatment. Another explanation might be the need for sufficient time for the medication to exert its full effect in each eye. This possibility is supported by the observation that the absolute change in IOP between right and left eyes from baseline to the end of the study was strongly correlated.

Other variables that were evaluated for possible influence on the outcome of our study included types of medications and history of ocular surgery. Not surprisingly, the drugs most commonly chosen in the monocular trials were prostaglandins (59.2% [29]) and β-blockers (22.4% [11]). The type of topical medication did not appear to influence the correlation of responses between first and second eyes treated, except for a weakly positive correlation in the prostaglandin group when using relative IOP change. Only 11 patients had a history of unilateral or bilateral ocular laser or incisional surgery, and this group had positive correlations between the first and second eyes treated when using relative but not absolute IOP change.

Limitations of our study include the retrospective, observational design, which introduced selection bias, because the monocular trial was performed on the eye with the higher IOP in most patients. The IOP of the treated eye on the day of the monocular trial may have been on average closer to the peak of the diurnal curve than to the mean, which would influence regression to the mean. In addition, a single measurement at each time point was used to calculate IOP changes, which is insufficient for making definite conclusions about the total diurnal curve.

Limiting the study population to those who had an acceptable response in the first eye and including only patients in whom a monocular trial was followed by binocular therapy may have excluded some patients with asymmetric glaucoma, leading to better correlation between eyes than might occur in clinical practice. In addition, excluding patients who had medication changes during the trial may have skewed the patients toward those with less advanced disease, which might have improved the overall correlation.

The monocular trial has long been a common practice in the management of glaucoma, and it was disappointing to many clinicians when we learned that it may not be as useful as we originally believed. Realini and his colleagues deserve credit for bringing this to our attention. However, rather than completely abandoning the practice, we believe that it may still have clinical value if certain caveats are recognized. First, several investigators have suggested that the correlation of spontaneous IOP fluctuations between eyes may be enhanced by multiple pressure readings over time.\(^{1,11}\)\(^{11}\) The monocular trial may also be more reliable in assessing the benefit of a drug if the IOP reduction in the treated eye is at least 4 mm Hg greater than that in the fellow eye, because 3 mm Hg was the definition of asymmetric fluctuations used by Realini et al.\(^1\) It remains to be seen whether a medication that lowered IOP in the monocular trial proves to be successful in the long term.

Some observations from the present study may also be applicable to improving the usefulness of the monocular trial. First, glaucoma suspects had a statistically significant correlation between responses of first and second eyes treated, while patients with POAG did not, suggesting that the monocular trial may be more useful in the former group. We also found that the response of the first eye may be a better predictor of the second eye’s response when using a prostaglandin than with a β-blocker. Finally, we found that correlation of the first and second eyes treated is enhanced by using the relative IOP change in which the fellow eye is used as a control for the change in the treated eye. While the latter observation clearly requires confirmation by additional studies, we hope that investigators will continue to evaluate ways to maximize the benefit of the monocular trial.

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REFERENCES