

The Uniocular Trial Myth

Debunking the dogma underlying the monocular drug trial.

BY TONY REALINI, MD

Assessing the effectiveness of IOP-lowering therapy is made difficult by the dynamic nature of IOP, which changes spontaneously over time in both normal and glaucomatous eyes. Therein arises the challenge: when starting IOP-lowering therapy in a glaucomatous eye, how do we know if the treatment is successful? Is the observed drop in IOP therapeutic or spontaneous?

The uniocular therapeutic drug trial has been developed to address this clinical dilemma. After administering an appropriate course of uniocular therapy, the differences in IOP from baseline for the treated and untreated fellow eye are calculated. The change in the treated eye

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represents both spontaneous and therapeutic components, whereas the change in the untreated eye represents a spontaneous change in IOP. The inter-eye difference is assumed to represent the therapeutic change.

The simple and elegant uniocular trial has been embraced by the clinical community, advocated in textbooks,^{2,3} and strongly recommended by the crafters of the AAO's *Preferred Practice Patterns: Primary Open-Angle Glaucoma*.⁴ Nevertheless, the uniocular drug trial is based upon several assumptions, some of which may be false and thus render this type of trial invalid. This article reviews data contradicting the usefulness of the uniocular trial.

THE ASSUMPTIONS

No. 1: Spontaneous IOP Fluctuation Between Fellow-Eye Pairs Is Symmetric Over Time

In the uniocular trial, the IOP variation in the untreated eye essentially serves as the control for the IOP of the treated eye. For the uniocular trial to be effective, the spontaneous fluctuation in fellow-eye pairs must be equal, or physicians cannot infer (and correct for) the spontaneous component for the observed change in IOP in the treated eye. An example would be a patient with an IOP of 20 mm Hg in both eyes. After 6 weeks of treatment with a topical drug in his right eye, the patient's IOP measures 14 mm Hg OD and 17 mm Hg OS. We assume that the spontaneous 3-mm Hg decrease in the patient's left eye also occurred in his right, thus leaving a 4-mm Hg therapeutic change in his right eye that is attributable to

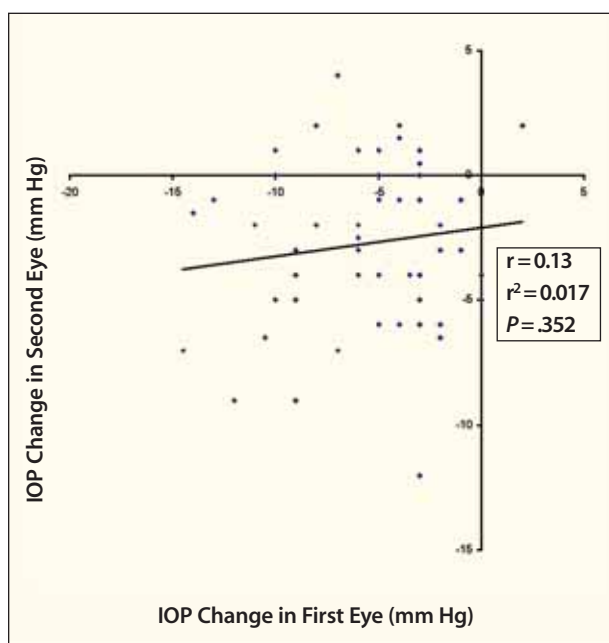


Figure 1. This graph depicts the correlation between uniocular trial IOP response and subsequent fellow-eye IOP response found in one study.¹ (Adapted and reprinted with permission from Realini T, Fechtner RD, Atreides SP, Gollance S. The uniocular drug trial and second-eye response to glaucoma medications. *Ophthalmology*. 2004;111:421-426.)

TABLE 1. CHARACTERISTICS OF ASYMMETRIC IOP FLUCTUATIONS IN NORMAL SUBJECTS AND GLAUCOMA PATIENTS*

	Normal Subjects (n = 42)	Glaucoma Patients (n = 38)
Number of Patients in Whom Fluctuations Were Observed	21 (50%)	24 (63%)
Frequency	One in seven visits	One in six visits
Mean Absolute Magnitude	3.7 mm Hg	4.0 mm Hg
Mean Relative Magnitude	24.5%	22.6%

*Data from Realini et al.⁵

the drug. Clinical data, however, suggest that IOP variation in fellow-eye pairs is not as symmetric as the uniocular trial requires. In 2002, my colleagues and I reported that asymmetric IOP fluctuations between fellow-eye pairs are common in both normal subjects and glaucoma patients.⁵ This retrospective study identified (1) 38 glaucoma patients whose IOP-lowering regimen was the same in both eyes and unchanged over at least five regularly scheduled, consecutive visits and (2) 42 normal subjects who underwent no IOP-altering events (intraocular surgery or use of systemic medications such as beta-blockers or steroids) for at least five regularly scheduled, consecutive visits. We examined subjects' IOP behavior during these visits and looked for episodes of asymmetric IOP fluctuations. We defined these fluctuations as IOP changes of at least 3 mm Hg (to exceed the widely accepted Goldmann measurement error of +2 mm Hg) in one eye relative to the fellow eye and representing at least a 15% change from baseline (to eliminate inclusion of relatively small changes in eyes with high IOPs). We specifically chose 15% as our threshold, because a spontaneous 15% IOP change in one eye could easily mimic or mask a clinically meaningful therapeutic IOP change if the spontaneous fluctuation occurred simultaneously with the initiation of IOP-lowering therapy.

We found that 50% of normal subjects and 63% of glaucoma patients (the difference was not significant) exhibited at least one asymmetric IOP fluctuation during the study period, and we suspected that these numbers would have been higher if we had observed the subjects for longer periods of time. Overall, asymmetric IOP fluctuations in glaucoma patients occurred in one out of every six visits. The average asymmetric IOP fluctuation was 4 mm Hg and represented a 22.6% change from baseline (the values for normal subjects were similar) (Table 1).

Other data support our finding that fellow eyes exhibit some independence in IOP variation. Wilensky et al⁶ re-

ported that 36% of glaucoma patients (compared with only 6% of normal subjects) have significantly different diurnal IOP curves between fellow-eye pairs. They concluded, "The frequent difference between the two eyes noted in our patients suggests that caution must be used in relying on one eye as a control for its fellow eye, as is sometimes done when evaluating drug treatment by unilateral administration." Similarly, Katavisto⁷ found that as many as 50% of glaucoma patients may have different diurnal IOP curves between fellow eyes. If this information is applied to the earlier example, it is likely that the patient's right eye experienced a spontaneous fluctuation in IOP that was different from the 3-mm Hg decrease observed in his left eye. Perhaps the IOP of the patient's right eye spontaneously decreased by 7 mm Hg, and there was no drug effect. Maybe the pressure in his right eye spontaneously rose 5 mm Hg, and the drug lowered the IOP by 12 mm Hg. We have no way of knowing with any degree of certainty what the spontaneous change in the patient's treated eye was. We therefore cannot calculate the therapeutic effect of the drug, and the uniocular trial is of no help.

No. 2: An IOP-Lowering Intervention in One Eye Does Not Alter the IOP of the Fellow Eye

In the uniocular trial, we infer the pure, spontaneous component of IOP fluctuation from the untreated fellow eye and assume that the drug applied to one eye does not change the IOP of its fellow. The contralateral, or crossover, effect of various IOP-lowering medications has been well established, however. Zimmerman et al⁸ first reported the existence of a crossover effect with timolol, and, in a recent *post hoc* analysis of data from the Ocular Hypertension Treatment Study,⁹ the magnitude of the beta-blocker crossover effect in the fellow eye was on the order of 1.5 mm Hg. Obviously, using the uniocular trial to assess the efficacy of a beta-blocker would underestimate the agent's true efficacy, and the practitioner might advise

DISCUSSION

By Theodore Krupin, MD, and John W. Yang, MD

Tony Realini, MD, shares a number of useful observations regarding diurnal IOP fluctuation as it relates to the uniocular drug trial for glaucoma therapy. He states that many of the trial's assumptions are "flawed" and argues that the one-eye trial should be "abandoned." We disagree with his conclusion and view the one-eye trial as a valuable tool that must be interpreted within the limitations relating to all IOP determinations.

CHALLENGES

IOP is a dynamic measurement manifesting diurnal variation that is influenced by aqueous humor dynamics. Glaucomatous eyes with reduced outflow facility experience large diurnal IOP fluctuations that can vary from day to day and possibly seasonally. These variations make ascertaining a medication's true pressure-lowering effectiveness challenging. The intent of the one-eye trial is to assess the benefit of a medication in a given person while taking into account both spontaneous IOP variations and the wide response to IOP-lowering medication among patients (because some drugs are ineffective for an individual).¹

Several circumstances can influence the interpretation of a one-eye trial:

- (1) Asymmetry of pretreatment IOPs requires an adjustment for a greater expected magnitude of a medication-induced decrease in IOP in the higher-pressure eye;
- (2) A crossover effect may occur in the fellow eye when the trial is instituted (Dr. Realini's assumption No. 2). This effect appears to be most prominent with the beta-blocker family of medications (approximately 1.5 mm Hg) and needs to be factored into the overall decision-making process on the efficacy of the trial; and
- (3) As Dr. Realini notes, asymmetry of the diurnal IOP curve occurs in one of six visits (his assumption No. 1) and presents an unknown to the interpretation of the trial. We do not believe, however, that this limitation is sufficient to throw out the baby with the bath water, as the adage goes. Like all measurements, IOP demonstrates a regression toward the mean. Obtaining several IOP measurements after initiating treatment is useful in determining spontaneous IOP fluctuations and the subsequent efficacy of medical treatment.

BENEFITS

The one-eye trial is beneficial when the practitioner is adding medications, because it is difficult to determine the interaction of aqueous humor dynamics and the IOP response to multiple drugs. The physician faces similar complexity when considering the elimination of therapy. We often encounter patients in whom the requirement for their current therapy is questionable. A "reverse" one-eye trial (eg, stopping a medication in one eye) is informative.

Additionally, despite the suggestion that fellow (untreated) eyes will respond similarly to the trial-treated eyes, we believe that the trial's real value lies in its ability to determine a medication's effectiveness in the first treated eye. Differences in aqueous humor dynamics between a patient's eyes can produce different responses to medications, even if the eyes have symmetric IOPs. We therefore do not assume that, because a medication lowers IOP by a certain amount in one eye, the fellow eye will necessarily respond in the same manner.

CONCLUSION

Glaucoma is more than an elevated IOP, and glaucoma control is more than just lowering IOP. Although reducing IOP is the only proven glaucoma treatment, monitoring glaucoma stability or progression depends on an examination of the optic nerve and retinal nerve fiber layer (structural damage) and of visual field loss (functional damage). Dr. Realini's observations should be viewed as limitations to one-eye trials, not as proof that they are useless. The uniocular trial's basic premise remains the most efficient and effective way to determine the IOP-lowering efficacy of medications in the clinical setting.

Theodore Krupin, MD, is Clinical Professor, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago. Dr. Krupin may be reached at (312) 474-1000; krupin@northwestern.edu.

John W. Yang, MD, is Instructor, Department of Ophthalmology, Feinberg School of Medicine, Northwestern University, Chicago. Dr. Yang may be reached at (312) 475-1000; johnnyang@yahoo.com.

1. Smith J, Wandel T. Rationale for the one-eye therapeutic trial. *Ann Ophthalmol*. 1986;18:8.

discontinuing the drug due to flawed assessment methodology, despite the agent's clinically relevant efficacy.

No. 3: Fellow-Eye Pairs Respond Similarly to the Same IOP-Lowering Therapy

After a successful uniocular trial, we administer the drug in the fellow eye. We do not usually assess agents' IOP-lowering efficacy in second eyes but instead assume that the effect will be similar to that in the first eye. For a uniocular drug trial to accurately predict the fellow eye's IOP response, the therapeutic response to the drug must be symmetric between fellow-eye pairs. The uniocular trial assumes that the individual, not the eye, is the unit of responsiveness to a given medication. Both eyes, therefore, must respond similarly to a given medication, an assumption that a colleague and I recently validated in a retrospective series.¹⁰

"Because IOP is a dynamic variable ..., we cannot gauge a therapeutic IOP-lowering effect based on one pretreatment IOP and one on-treatment IOP reading."

IMPACT ON THE UNIOCLULAR TRIAL

What does it mean for the validity of the uniocular trial that two of its three underlying assumptions may be false? My colleagues and I recently reported that the uniocular trial does not predict the fellow eye's IOP response to topical IOP-lowering therapy.¹ We examined our experience with uniocular trials in the past and correlated the IOP reduction observed in the first treated eye with that seen after starting the same medication in the patient's fellow eye. All 52 study subjects had bilateral glaucoma. We found essentially no correlation between the fellow-eye IOP responses (Pearson correlation coefficient $r^2 = 0.017$, $P = .352$) (Figure 1).

At first glance, these results seem to contradict those described earlier¹⁰ that showed a strong correlation between fellow-eye pairs. The difference is that fellow eyes were treated sequentially in the study showing a poor correlation between fellow-eye pairs versus simultaneously in the other study. The difference in outcomes relates to treatment regimens. When treated simultaneously, both eyes are assessed during the same time interval, so they are subjected to the same nontherapeutic factors driving spontaneous IOP changes (whatever they may be). In this setting, asymmetric IOP fluctuations

are only expected in one of six visits, as described earlier. When treated sequentially, first-treated eyes are assessed at one time and second-treated eyes at another. It is possible—even reasonable—to assume that the nontherapeutic forces driving spontaneous IOP fluctuations differ between these two time points. The uniocular trial therefore fails to predict an IOP reduction in the eyes treated second because of unpredictable variability in spontaneous IOP fluctuations over time.

Simply put, because IOP is a dynamic variable subject to spontaneous fluctuations, we cannot gauge a therapeutic IOP-lowering effect based on one pretreatment IOP and one on-treatment IOP reading. There is too much noise, and, contrary to the uniocular trial's assumptions, we cannot separate the signal from the noise. Because the uniocular trial is flawed and does not deliver the data we think it does, we should abandon its use. Instead, we should treat glaucoma as the chronic disease that it is and assess broader endpoints than a single IOP reading after each therapeutic adjustment. A better approach is to collect several pretreatment IOP readings to establish a reliable baseline (often advocated) and then to collect several on-treatment readings to establish treatment efficacy (seemingly never advocated). We should probably stop asking, "Have I lowered this patient's IOP?" and start asking, "Have I lowered the IOP range within which this patient's eye fluctuates?" This approach requires more visits but provides necessary information for assessing therapeutic efficacy. □

Tony Realini, MD, is Associate Professor of Ophthalmology at West Virginia University Eye Institute in Morgantown, West Virginia. Dr. Realini may be reached at (304) 598-6925; hypotony@yahoo.com.

1. Realini T, Fechtner RD, Atreides SP, Gollance S. The uniocular drug trial and second-eye response to glaucoma medications. *Ophthalmology*. 2004;111:421-426.
2. Stamper RL, Lieberman MF, Drake MV. Medical treatment of glaucoma: general principles. In: Stamper RL, Lieberman MF, Drake MV, eds. *Diagnosis and Therapy of the Glaucomas*. St. Louis: Mosby; 1999: 424.
3. Ritch R, Shields MB, Krupin T. Chronic open-angle glaucoma: treatment overview. In: Ritch R, Shields MB, Krupin T, eds. *The Glaucomas*. St. Louis: Mosby; 1996: 1512.
4. American Academy of Ophthalmology. *Preferred Practice Patterns: Primary Open-Angle Glaucoma*. San Francisco, CA: American Academy of Ophthalmology; 2000: 11.
5. Realini T, Barber L, Burton D. Frequency of asymmetric intraocular pressure fluctuations among patients with and without glaucoma. *Ophthalmology*. 2002;109:1367-1371.
6. Wilensky JT, Gieser DK, Dietsche ML, et al. Individual variability in the diurnal intraocular pressure curve. *Ophthalmology*. 1993;100:940-944.
7. Katavisto M. The diurnal variations of ocular tension in glaucoma. *Acta Ophthalmol (Copenh)*. 1964;46:78(suppl):1-130.
8. Zimmerman TJ, Kaufman HE. Timolol. A beta-adrenergic blocking agent for the treatment of glaucoma. *Arch Ophthalmol*. 1977;95:601-604.
9. Piltz J, Gross R, Shin DH, et al. Contralateral effect of topical beta-adrenergic antagonists in initial one-eyed trials in the ocular hypertension treatment study. *Am J Ophthalmol*. 2000;130:441-453.
10. Vicker WR, Realini T. Symmetry of fellow-eye intraocular pressure responses to topical glaucoma therapy. Poster presented at: The ARVO Annual Meeting; April, 29, 2004; Fort Lauderdale, FL.