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The Monocular Trial: Does Response to Glaucoma Therapy in One Eye Predict Response in the Fellow Eye?

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Does Response to Glaucoma Therapy in One Eye Predict Response in the Fellow Eye?

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Purpose: To study if the intraocular pressure (IOP) change observed after starting a glaucoma medication in one eye is predictive of the change in IOP observed in the fellow eye once the same medication is used in both eyes.

Methods: In a retrospective study, 55 patients with glaucoma underwent monocular drug trials with various medications before the drug was added to the second eye. The change in IOP of the first treated eye during monocular therapy was compared with the IOP change of the second eye during binocular therapy. Relative changes in IOP of each eye were calculated by subtracting the change in IOP of the fellow eye from the treated eye.

Results: The IOP of the first eye decreased 5.8 ± 6.1 mmHg (mean ± standard deviation) during monocular therapy and the IOP of the second eye decreased 3.4 ± 5.7 mmHg during binocular therapy. The absolute IOP changes in the first and second eyes were poorly correlated ($r = 0.095$, $p = 0.49$). When relative changes in IOP were used, the first eye decreased 6.3 ± 5.3 mmHg and the second eye 4.2 ± 4.5 mmHg. The relative changes were well correlated ($r = 0.404$, $p = 0.002$). Excellent correlation was noted in the subset of glaucoma suspect patients when using absolute IOP changes ($r = 0.590$, $p = 0.001$).

Conclusions: The data supports that the absolute response of one eye to a medication is predictive of the future response of the fellow eye to the same medication in patients with glaucoma suspect, but not in the overall glaucoma population. If one uses one eye as a control when assessing the efficacy of a drug in the fellow eye, then the response of one eye to a glaucoma medication is predictive of the response of the fellow eye.

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Introduction

Glaucoma is one of the leading causes of blindness in the world and elevated intraocular pressure (IOP) is the only proven risk factor.[1] Pharmacotherapy and surgery form the basis of treatment as the risk of progression of visual field loss decreases 10% for each millimeter of mercury reduction in IOP.[2] Other factors may also be at play as some patients develop glaucomatous damage even with normal pressures while others live comfortably with elevated pressures without any evidence of damage. Once the decision has been made to start pharmacotherapy, the patient is usually started on a monocular drug trial to test the efficacy of a drug. However, recent evidence has led some researchers to question the validity of the monocular drug trial and advocate for fundamentally altering the treatment strategy.[3] This thesis will examine the latest evidence on the subject and will attempt to answer some of the questions regarding the basis of the monocular drug trial.

Before we look at the monocular drug trial, let us first examine the factors influencing intraocular pressure. Roughly, the IOP is dependent upon the production of aqueous humor versus the outflow through the trabecular meshwork. Elevations in IOP are often the result of impedance in the outflow tract as there is not a known auto-regulatory mechanism to maintain normal pressures. Intraocular pressure in each eye is not constant, but instead varies throughout the day because of variables that cause both short and long-term fluctuations in IOP. Factors influencing short-term changes in IOP include breath holding and straining. The intake of food and water causing a change blood osmolarity has also been proposed as a mechanism for short-term changes in IOP.[4]

Long-term variations of IOP have been well studied. Intraocular pressure varies in a 24 hour pattern, commonly referred to as each eye's "spontaneous diurnal variation." These variations are described as spontaneous because of the high variability and unpredictability of pattern noted. Diurnal variations in IOP were first observed by Sidler-Huguenin in 1898 when he found the IOPs of 10 patients with glaucoma were highest at night before sleeping and within an hour of awaking in the morning.[5] These seemingly rhythmic variations in IOP led researchers to look for correlations with systemic processes. Weitzman et al. pointed out a correlation between the plasma cortisol level and IOP.[6] Vascular tone changes affecting aqueous production and outflow have been postulated to influence rhythmic changes in IOP.[7, 8] Despite many hypotheses that have been proposed for the basis of the pressure cycle, further research is required to fully explain the cause for the diurnal variations.

Spontaneous IOP changes can frequently be quite large. In a study by Drance, 404 eyes of patients without ocular disease had a mean IOP fluctuation of 3.7 mmHg over 24 hours.[9] Another study by de Venecia and Davis found a similar diurnal IOP fluctuation of 4.9 mmHg in healthy individuals in a single day.[10] Glaucomatous individuals, on the other hand, have a magnitude of diurnal variation of more than double compared to healthy patients. Katavisto found the variation to be 11.1 mmHg in individuals with primary open angle glaucoma (POAG).[5] A more recent study by Asrani et al. found that the diurnal variation is approximately 10 mmHg.[11] These variations present a problem for ophthalmologists due to their large magnitude. One can not know if an individual's IOP is normal or abnormal based on a single measurement because an elevated reading could

be attributed to a fluctuation of the diurnal cycle or actually be pathologically elevated requiring treatment.

Researchers have attempted to characterize the diurnal pattern. Katavisto found the peak of the diurnal cycle most commonly occurred at 6 a.m. in treatment naïve patients and 8 a.m. in previously treated patients.[5] This corresponds nicely with previously discussed findings relating IOP with cortisol level. Recently, Zeimer stated that diurnal rhythms fit into 4 common patterns: 1) a 24 hour cycle with an IOP peak in the morning; 2) a 24 hour cycle with an IOP peak in the afternoon; 3) "flat" curves without significant pressure variation; and 4) "erratic" curves that do not follow a daily pattern.[1] Wilensky et al. found that most patients had rhythmic diurnal variations in IOP with pressure peaks in the morning.[12] Only 22% of patients with ocular hypertension and 16% of patients with POAG had an erratic diurnal rhythm. It is important to learn about the pattern of variation because as we will see, there are significant implications regarding treatment and interpretation of disease progression. One of the most intimately involved consequences relates to the monocular drug trial.

What is the monocular drug trial?

Since spontaneous fluctuations of intraocular pressure in patients are substantial, it is important for ophthalmologists to differentiate spontaneous changes in IOP from effects of pharmacotherapy. For this reason, it has become standard practice for ophthalmologists to institute a monocular trial of a glaucoma medication in order to determine if a drug is efficacious.[13] First, baseline IOPs of both eyes are determined before any medications are administered. The patient is instructed to take a glaucoma

medication in one eye, usually the eye with higher pressure.[14] After a period of time thought to be enough for the medication to take effect (usually 1 – 2 months), the patient is seen again in the clinic to determine if the drug was successful in reducing the IOP in the treated eye. If the clinician decides that the medication is efficacious, the patient is instructed to start taking the drug binocularly. If the drug is not successful, the medication is discontinued and the monocular trial is repeated with another drug.

Since spontaneous changes in IOP are thought to occur equally in both eyes, the untreated eye acts as a control for the treated eye during the monocular trial. Changes in IOP of the untreated eye are presumably due only to spontaneous effects while changes in the treated eye are from both spontaneous and therapeutic effects. If the change in IOP in the untreated eye is subtracted from the change in the IOP of the treated eye, one can eliminate the spontaneous variations and isolate for the therapeutic effects of the medication.

As an example, let us take a patient whose left and right eye IOPs were 24 mmHg prior to the initiation of the drug trial in the left eye. If at the second clinic visit, the IOP of the left eye was 16 mmHg while the IOP of the right eye was 22 mmHg, then spontaneous changes in IOP theoretically contributed a decrease of 2 mmHg (24 - 22 = 2) while the therapeutic effect of the medication was a decrease of 6 mmHg (24 – 16 – 2 = 6). The medication would be determined to be efficacious based on these results and therapy would be instituted binocularly.

However, interpreting the trial can easily become more complicated. Let us take another patient whose initial IOPs were 24 mmHg in both eyes before treatment is initiated in the left eye. However in this patient, at the second clinic visit the left eye's

IOP is 26 while the right eye's IOP is 32. Using the same calculations as before, spontaneous changes in IOP would account for an increase of 8 mmHg in both eyes over this time period and the therapeutic effect of the medication would be a decrease in IOP of 6 mmHg in the left eye. In this situation, it is uncertain whether or not this medication would be viewed as a success. The IOP decrease calculated to be secondary to the medication is significant; however with an absolute increase in IOP of both eyes, an ophthalmologist would be hesitant to deem this drug as efficacious since the overall goal is to achieve a decrease in IOP. In clinical practice at some institutions, the medication in this example might still be deemed a successful trial. However, other researchers have treated the quandary presented both ways.[15]

The debate over the monocular drug trial has centered on the trial's two main assumptions. First, can one eye serve as a control for the fellow eye during the monocular drug trial? Second, will the response to therapy in one eye will be matched by a similar response in the fellow eye, i.e. if a medication is successful in reducing the IOP in the first eye, will it also decrease the IOP in the second eye in a similar way? We will now examine these assumptions in detail.

Can one eye serve as a control for the fellow eye during the monocular drug trial?

Since spontaneous diurnal variations of IOP in the eyes can often be quite large, this question is particularly important to answer. Theoretically, the treated eye during the monocular drug trial should be affected equally by the variables influencing IOP as the fellow eye except for the therapeutic effects of the drug. If one eye can serve as the control for the fellow eye, the therapeutic effects of a medication can be easily

differentiated from the natural diurnal spontaneous changes that occur by subtracting out the spontaneous change in IOP from both eyes. If not, the large spontaneous fluctuations in IOP can dwarf any effects from pharmacotherapy.

Two major questions have been raised when addressing this assumption. First, when a topical glaucoma drug is added to one eye, is there any effect of the drug in the fellow untreated eye? Secondly, are the spontaneous diurnal variations between the left and right eye symmetric enough to allow one eye to serve as a true control for the other?

The idea that a drug applied to one eye can cause a change in IOP of the fellow eye is known as the "crossover effect". Zimmerman and Kaufman first came across the effect when they studied the responses of 30 glaucoma patients to topical beta adrenergic antagonists.[16] They noted a significant IOP decrease in the untreated eye 5 hours after the monocular administration of 0.5% timolol maleate. They attributed this crossover effect to possibly "rubbing of the eyes after application of treatment, systemic absorption, or a centrally mediated effect." Since this time, studies have clarified that topical beta blockers are absorbed systemically, possibly through the nasolacrimal mucosa and travel via the bloodstream to cause effects in the contralateral eye.[17, 18] Others have suggested a centrally mediated effect on IOP.[19]

Piltz et al. performed an extensive analysis of 817 patients receiving topical beta adrenergic antagonists during the Ocular Hypertensive Treatment Study.[20] They found the mean IOP of the treated eye dropped 5.9 mmHg while the fellow untreated eye decreased 1.5 mmHg. Both of these values were statistically significant when compared to the control group receiving placebo and this effect was noted among both selective and

non-selective beta blockers. Others have shown similar, but less, crossover effect in healthy individuals.[21]

Topical prostaglandin medications are metabolized quicker and have less systemic effects compared to beta blockers. Alm and Stjernschantz found that the blood pressure in patients given topical timolol was lower than patients given topical latanoprost.[22] The implication is perhaps there is less of a crossover effect in patients given prostaglandin analogs than with beta adrenergic antagonists. However, no confirmatory studies have been performed. This is one of the hypotheses that will be addressed in this thesis.

Any crossover effect would result in the underestimation of the therapeutic effect in the monocular drug trial since the drug would have some efficacy in both eyes. In some cases, medications would incorrectly be deemed ineffective when not much relative improvement is noted. This is one of the limitations of the monocular drug trial and must be taken into account when clinicians are evaluating whether a drug is efficacious.

The second question of whether the IOP of fellow eyes vary symmetrically is more complex. In a healthy individual, the intraocular pressures in the left and right eye are often assumed to be almost equal. In fact, Lee et al. have found that asymmetry in the IOPs of the left and right eye is a useful sign in diagnosing primary open angle glaucoma in patients without elevated intraocular pressures.[23]

However, even in healthy patients the intraocular pressures in the left and right eye are not always equal. Liu et al. measured the IOP of 91 healthy individuals every 2 hours for 24 hours in a sleep laboratory.[24] They compared the IOP of the left and right eye and tried to determine if the IOPs were correlated at a single measurement. The

coefficient of determination (r^2) varied from .311 to .741 during different times of the day. In other words, only 31% to 74% of the fluctuation of IOP in one eye at a single measurement can be explained by the IOP of the fellow eye. Liu et al. further found that there was a significant difference in the mean IOP of the left and right eye over 24 hours. However, the authors attributed this to possibly effects from repeated tonometry, order of measurement, or the predominance of right-handedness of patients rather than to represent a fundamental difference in the IOPs of the fellow eyes.

In a similar study by Sit et al., 41 subjects with primary open angle glaucoma had their IOPs measured in a sleep lab over 24 hours.[25] They found the coefficient of determination to be .416 to .536 for left and right eye IOP pairs which represents moderate correlation. These two studies illustrate that at a single IOP measurement (for example, during a clinic visit), the IOP of the left and right eyes are frequently dissimilar in both healthy and glaucomatous patients.

While the IOPs of the left and right eye are only moderately correlated at a single measurement, one eye can still serve as a control for the fellow eye if the IOPs fluctuate symmetrically over time. Realini et al. addressed this question in a study published in 2002 when they examined if IOP fluctuations in the left and right eye were symmetric across two consecutive visits.[26] They defined the change in IOPs of a patient to be symmetric if the change in IOP of the left eye was less than 3 mmHg different than the change in IOP of the right eye. They found that 50% of healthy individuals and 63% of glaucomatous patients had at least one visit where there was an asymmetric change. In total, 13.7% of visits of healthy individuals and 16.3% of visits of glaucomatous patients had asymmetric changes in IOP from the previous visit. There was not a statistically

significant difference in the frequency of asymmetric visits between the two groups. However, the frequency that asymmetric IOP changes occur is significant. Not only are the IOPs frequently different at a single point of time, but often they seem to vary independently.

At first glance, Realini et al.'s use of 3 mmHg as the cutoff between a symmetric and an asymmetric change seems arbitrary. However, others have used a similar cutoff based on upon the published variability of the equipment and technician. Sudesh et al. found that the variability of IOP measurements on the same eye by different observers using an applanation tonometer was 3 mmHg or less 80% of the time.[27] Others have found less than a 3 mmHg variation in repeated measurements on the same patient by the same examiner more than 90% of the time.[28, 29] A study by dos Santos et al. found that measurements taken with Goldmann applanation tonometry had less variation than measurements taken with Perkins hand-held applanation tonometry.[30] A study by Wittenberg found that the standard deviation of repeated pneumatonometry readings was 1.75 mmHg.[31] Since a high percentage of readings usually fall within 3 mmHg, this is usually taken as the acceptable cutoff for determining asymmetry between IOP measurements. Any change above 3 mmHg, therefore, is considered a significant change and not attributed to intraobserver or interobserver variability. A cut-off of 15% change in IOP has been also used to represent a significant IOP fluctuation.[26]

The literature suggests that the IOP in the left and right eye are frequently not equal and may vary independently of each other. These conclusions have been based on finding asymmetry of IOPs in the left and right eye on a single measurement or in the change between two consecutive measurements. The problem with drawing conclusions

based on a single IOP reading at a point in time is that one can not be sure where this reading lies on an individual's IOP curve. If both eyes of an individual had the same diurnal IOP curve but lied on different points of the curve at a certain point of time, the two eyes would have unequal IOPs and be falsely asymmetric under the single IOP measurement methodology. Perhaps the reason why the IOP readings in the studies quoted above were not equal is that fellow eyes were at different points of the diurnal curve and one eye was measured at the peak and the fellow eye at the trough. In other words, one can not make conclusions about the symmetry of the IOPs of the left and right eye, or even the peak or mean IOP of the diurnal curve based on a single measurement. Others have thought a better strategy is to look for symmetry by plotting diurnal curves by taking multiple measurements over the course of a day. These data are not usually available since IOP is usually measured once during an office visit.

Liu et al. fit curves to the averaged 24 hour data of the left and right eye and found significant similarities in the diurnal curves' shape and amplitude.[24] The pressure curve acrophase (the time that the overall pressure curve is equal to the mean IOP) was 8:22 a.m. (SD = 394 min) for the right eye of a younger group of patients and 7:43 a.m. (SD = 375 min) for the left eye. A similar finding was seen in an older group: left eye acrophase was 7:37 a.m. (SD = 334 min) and right eye 8:19 a.m. (SD = 301 min). Of note, large standard deviations in the range of 5 to 6 hours indicate that perhaps many dissimilarities exist between *individual* diurnal pressure curves even though the overall pressure curves are similar. Since each patient's IOP is evaluated independently in clinical practice, it is dubious to make conclusions based on averaged IOP data as in this study.

Wilensky et al. showed that this was in fact true when they looked at the type of diurnal variation cycle that each eye follows.[12] They mapped diurnal pressure curves in 176 patients with primary open angle glaucoma and 55 patients with ocular hypertension (OHT) by measuring IOP 5 times per day over a period of 5 days. Each eye was characterized to a type of diurnal pressure curve to which it fit best as defined previously by Zeimer et al. (see above).[1] They found that 33% of the patients with OHT and 36% of patients with POAG had different types of pressure curves in the left and right eyes! This was a significant difference from the control group where only 6% of the patients had different diurnal pressure curves in the left and right eyes ($p = 0.05$ and $p = 0.03$ respectively). In fact, when diurnal pressure curves were remapped on the same eyes months later, only 28% of eyes of OHT patients and 44% of eyes of POAG patients had the same curve as before. So, not only do a significant number of left and right eyes follow different diurnal curves at one point in time, but even the same eye may have a different curve when measured at a later date. This does not support the practice of ophthalmologists who draw conclusions about the diurnal curve by taking IOP measurements over many successive clinical visits. This is a significant finding which needs to be confirmed with further studies.

Sit et al. tried another method to determine if the left and right eye diurnal pressure curves were related.[25] They tried to fit the 24 hour IOP data to statistical models to see if the IOP of one eye could be predicted based on the IOP of the fellow eye. This drives to the heart of the monocular drug trial, because even if the diurnal curves are not symmetric, if the IOP of one eye can be predicted by the IOP of the fellow eye, then reasonable conclusions can be made using the IOP of just a single eye. The first model

they assessed was the "symmetric model" which assumed that if the IOP of the left eye increased by 1 mmHg, the right eye's IOP should also increase by 1 mmHg. This is the assumption that is used in clinical practice, i.e. if the IOP of the left eye increases from 24 mmHg to 26 mmHg, the right eye should also have a 2 mmHg increase over the same time period. Using this model, if the IOP predicted was greater than 3 mmHg different than the actual IOP then it was considered an inaccurate prediction. In the symmetric model, 14% (SD = 12%) of the predictions were inaccurate. This is similar to the results reported above by Realini et al. which reported that 16.3% of glaucomatous patients' IOP measurements had greater than a 3 mmHg difference in IOP change between the left and right eye.[26]

The second model they tried was the "best fit model" using least-squares linear regression analysis. This method utilizes many IOP readings to create a differential equation that approximates the relationship between the IOP of the left and right eye. If given the IOP of one eye, one can use the equation to estimate what the IOP should be in the fellow eye. Only 8.5% (SD = 10.6%) of the predicted measurements were greater than 3 mmHg different than the actual IOP measurements with the best fit model which is an improvement over the symmetric model. However, these results must be taken with a grain of salt. The 8.5% of inaccurate predictions only reflects the quality of the model of fitting the given data that it was based on. It is unknown whether the model can predict future IOP values with the same accuracy. Wilensky et al. presented evidence (see above) that showed that one can not assume the relationship between the left and right eye is stable over time because a significant proportion of diurnal curves may have

shifted.[12] A study examining the accuracy of the best fit model in predicting future IOP values still needs to be performed.

A problem with using multiple measurements during clinic visits to create a diurnal pressure curve is that one can not be certain that the IOP maximum is found unless a continuous IOP measurement device is developed and used over a 24 hour period. In fact, the pressure peak is often missed in clinical practice. Wilensky et al. found that in patients who had IOPs measured less than 21 mmHg and yet still had evidence of progression of disease, more than 50% were found to have pressure spikes of greater than 22 mmHg when their full diurnal curves were measured.[32] They also found in 50% of these patients, the IOP peak noted was either before 8 a.m. or after 5 p.m. In a follow up study, Wilensky et al. found that 48% of all ocular hypertensive patients and 43% of all primary open angle glaucoma patients had IOP peaks outside of normal office hours.[12] In fact, in patients who develop glaucomatous damage even with pressures in the normal range, it has been postulated that perhaps these patients did have elevated nighttime IOP spikes that were not picked up on routine clinic measurements.[11] Thus, important pressure peak determinations may be missed when only performing routine IOP measurements during clinic visits.

Another important value when assessing pressures is the fluctuation of IOPs over the course of a day. One study found that the range of IOPs is more predictive of glaucomatous damage than the mean or peak IOP.[11] As a result, there has been an effort to develop methods to minimize the daily variation of IOP. Some glaucoma medications such as pilocarpine, carbonic anhydrase antagonists, and alpha-2 adrenergic agonists have short durations of action and wear off before the next dose is administered which would

result in a large range of IOP fluctuation. In contrast, medications with longer durations of action such as prostaglandins have been shown to reduce the range of IOPs and thus, be more effective at preventing glaucomatous damage.[33]

Others have looked at the effects of laser or ocular surgery on IOP. Glaucoma procedures altering the trabecular meshwork may result in a different diurnal curve. Agarwal et al. noted that in 40 eyes with POAG which had undergone argon laser trabeculoplasty, the mean IOP decreased from 25.8 mmHg to 17.8 mmHg and the average range from 7.9 mmHg to 3.2 mmHg.[34] However, as with any studies looking at the change in the range of IOPs after an intervention that lowers the mean IOP, it is unclear what implications to draw because the range of IOPs should also decrease with a lower mean IOP.

The purpose of first administering the drug in one eye (i.e. the monocular drug trial) is to allow the clinician to differentiate the spontaneous variations of IOP from the therapeutic variations by having one eye serve as a control for the fellow eye. However as we have seen, many studies have cast doubt on this crucial assumption. A single IOP measurement is insufficient in predicting IOP because of the significant independent diurnal variation between eyes. Multiple measurements can be used to learn more about diurnal variations; however it is important to map each eye's diurnal curve instead of finding the mean IOP because the range of IOPs also has significance. Further research is needed to determine if the diurnal cycles of the left and right eye are symmetric and are stable over time. If one can predict the IOP of one eye using the fellow eye's IOP diurnal curve, then the monocular trial can still be reliably used. This debate continues to be unresolved and plays prominently in the discussion about the monocular drug trial.

Is the response to the therapy in one eye matched by a similar response in the fellow eye?

In order for the monocular trial to guide therapy, a success in one eye must be accompanied by a symmetric decrease in IOP when the drug is administered to the fellow eye. Realini et al. tested this second assumption in their 2004 paper by measuring the IOP response of the treated eye during the monocular drug trial versus the IOP response of the fellow eye during binocular treatment.[15] However, citing the significant asymmetric spontaneous diurnal fluctuations in IOP discussed above, they did not use the untreated eye as a control for the treated eye during the monocular phase, nor did they use the originally treated eye as a control for the second eye during the binocular phase. They instead compared absolute changes in IOP of the eyes in question. The first eye IOP decreased 5.7 mmHg (SD = 3.8) during monocular therapy and the second eye decreased 2.8 mmHg (SD = 3.3) during binocular therapy. The changes in IOP were very poorly correlated ($r^2 = 0.0174$, $p = 0.35$). Because of evidence showing little cross-over effect in topical prostaglandin use, the subset of the patient population who only received prostaglandin analogs were analyzed separately. Again, little correlation was seen ($r^2 = 0.024$, $p = 0.449$). Neither the type of glaucoma nor a history of surgery improved the correlation between the change of IOP in the first eye during monocular therapy and the second eye during binocular therapy.

The results from Realini et al. were surprising. They postulated that perhaps, fellow eyes actually have asymmetric therapeutic responses to medication due to asymmetries in aqueous production or outflow. A more likely explanation is that large spontaneous changes confounded each data measurement. This study is subject to the problems associated with using only one reading of IOP instead of mapping the entire

diurnal curve. The measurements quite possibly could have been made at different points on the diurnal curve (meaning differences in IOP noted were due to spontaneous changes instead of therapeutic changes), or perhaps on different diurnal curves entirely. Inability to control for spontaneous variation between fellow eyes is a major flaw in the study design and is resulting from their decision to not use the fellow eye as a control.

Another limitation of Realini et al.'s results is based on that fact that in clinical practice as well as in this trial, the eye chosen for treatment is the eye with the higher IOP.[14] The IOP must be sufficiently high for a clinician to decide to start pharmacotherapy. A selection bias is introduced because it is more likely that the IOP at the last measurement before therapy is initiated is closer to the peak of the diurnal curve than at the mean. However, at the second visit when the monocular drug trial is assessed, there is no tendency of the IOP to be a certain part of the curve and instead, the IOP measured should be close to the mean IOP. If this is the case, not only would the therapeutic benefit of the medication be seen at the second visit, but in general, the pressures would be moving on average from the peak of the diurnal curve to the mean. This phenomenon is referred to as "regression to the mean" and may be contributing to the asymmetries in the IOP change observed by the authors. Again, it would be averted by mapping the full diurnal curve instead of making conclusions based on a single measurement. In fact, in Realini et al.'s study, the average change in IOP seen in the first eye was 5.7 mmHg and 2.8 mmHg in the fellow eye which is a difference of only 2.9 mmHg. This is less than the 3 mmHg accepted standard allowed for spontaneous variation of IOP (discussed above).[30] In other words, the 2.9 mmHg difference noted could completely be explained by regression to the mean. Realini et al. contends that this

effect should occur equally in both eyes to balance out. The second eye's IOP would also have to be sufficiently high to warrant pharmacotherapy. If the second eye's IOP is not sufficiently high to warrant treatment, the patient would be maintained on monocular therapy and not included in the trial. Although there are significant questions raised by the paper, no confirmatory studies have been performed.

In light of their findings that a monocular trial of a drug did not predict fellow eye response, Realini et al. performed a follow-up study published in 2005 where they administered medication to both eyes at the same time.[3] They compared absolute changes in IOP before and after treatment and found extremely high correlation ($r^2 = 0.7$, $p < 0.0001$). There was less than a 2 mmHg difference in IOP between the left and right eye in 67% of patients. As a result, they conclude that the monocular drug trial fails because of asymmetric spontaneous changes between fellow eyes and not because of asymmetric therapeutic changes. They propose that instead of using the monocular drug trial to test the efficacy of a medication, the drug should be started in both eyes at the same time and each eye be assessed independently for response to the medication. However, they do not address the conflicting results between this study and their previous study. In both studies, they used a single IOP measurement to determine baseline and post-treatment IOP and therefore did not account for spontaneous diurnal fluctuations. Perhaps there were too many confounding variables in the first trial related to the different time periods being analyzed that that did not come into play in the second trial.

There have been significant objections raised about the assumptions that form the basis of the monocular drug trial. This has led at least one group of authors to advocate for rejection of the practice and the adoption of initiation of binocular therapy with

independent assessment of efficacy for each eye. However, conflicting findings have been published in the literature that require further study. Many of these questions will be addressed in this thesis to elucidate how IOP changes relate to the monocular drug trial.

Specific Aims

1. To study if first eye response to a medication during the monocular drug trial is predictive of second eye response if the fellow eye is not used as a control.
2. To study if first eye response to a medication during the monocular drug trial is predictive of second eye response if the fellow eye is used as a control.
3. To study if the left and right eyes differ in mean IOP.
4. To study if the left and right eyes respond differently to the same medication.
5. To study if correlation between first and second eye response is improved when controlling for type of glaucoma.
6. To study if correlation between first and second eye response is improved when controlling for type of medication used in the trial.
7. To study if correlation between first and second eye response is improved when controlling for prior history of ocular surgery.
8. To study if correlation between first and second eye response is improved when controlling for race.
9. To study if correlation between first and second eye response is improved when controlling for use of systemic beta-adrenergic antagonists.
10. To study if certain types of medications when administered monocularly cause a decrease in IOP in the fellow eye, i.e. the “crossover effect.”
11. To study where the last IOP measurement before therapy is initiated lies on the diurnal IOP curve.

Methods

The Human Investigations Committee at the Yale School of Medicine approved this retrospective, observational study. Medical records of patients seen in the Yale Eye Center were reviewed by the author to screen for eligibility. In order to be eligible, the patient had to be: 1) 18 years of age, 2) received diagnosis of glaucoma, 3) had a monocular trial of a medication followed by binocular therapy (started on a topical glaucoma medication in one eye, evaluated for response at a later clinic visit, started on the same medication binocularly, and again evaluated for response at a later visit.) Exclusion criteria included 1) change of medication or dosage of medication during the trial, 2) use of a different topical ocular medication in a single eye during the trial, and 3) use of ocular steroids during the trial.

Data was gathered by the author from medical charts and included demographic information such as age, race, and gender. Type of glaucoma, presence of other ocular diseases, history of prior ocular surgery, presence of other systemic diseases, current medications, and the date of each visit were also collected. IOP data were collected at each visit during the trial. All measurements were taken during office hours by experienced practitioners trained to make IOP measurements with a Goldmann applanation tonometer. IOP readings at 5 visits before the trial were also collected if no changes in ocular medications occurred during this time. The maximum IOP measurement was designated as the "peak IOP" and the minimum IOP as the "trough IOP".

In 47 patients, the monocular drug trial was evaluated over 3 consecutive visits (Table 1). In 8 patients, trial was evaluated over 4 consecutive visits. "Baseline IOP" is

defined as the IOP of each eye at the last measurement before treatment was initiated (time A for the first eye and time C for the second eye). Response of each eye was calculated as the change in IOP of each eye from baseline to the next visit (for the first eye: IOP at time B – IOP at time A; for the second eye: IOP at time D – IOP at time C). The IOP change of the fellow eye was also calculated for both time periods. Separate calculation was also performed using the fellow eye as a control for the treated eye. This was done by subtracting the change in IOP of the fellow eye from the change in IOP of the treated eye during the same time period.

Table 1 – Order of Visits

For 47 patients		
Visit 1	Time A	Baseline IOP determined, Treatment started in first eye
Visit 2	Time B, Time C	Response of first eye to medication determined, Treatment started in second eye.
Visit 3	Time D	Response of second eye to medication determined
For 8 patients		
Visit 1	Time A	Baseline IOP determined, Treatment started in first eye
Visit 2	Time B	Response of first eye to medication determined
Visit 3	Time C	Treatment started in the second eye
Visit 4	Time D	Response of second eye to medication determined

The left eye and the right eye were compared by examining the baseline IOP and response to therapy. Analysis of the cross-over effect was performed by looking at the change in IOP of the non-treated eye. To analyze the presence of regression to the mean, the IOPs of the previous 5 visits before the trial were compared to the baseline IOP.

Linear regression analysis was performed by the author using the Pearson correlation coefficient, r, and the coefficient of determination, r^2, to look for statistical correlation between the response of the first eye and second eye to treatment. The paired

t test was used to look for statistical difference between the IOP of the first eye versus the second eye and the also for the left eye versus the right eye. Statistical significance was determined for p values less than 0.05.

Other population subsets were separately analyzed to determine if IOP response was dependent upon the race of the patient, type of glaucoma, different medications used in the trial, concurrent use of systemic beta adrenergic antagonists, and history of prior ocular surgery.

Results

Fifty-five patients met the eligibility criteria and their charts were reviewed for this study. Demographic information is included in Table 2. Fifty-five percent of patients were female, 62% were white, and the mean age was 65. Forty-nine percent of patients had the diagnosis of glaucoma suspect and 40% had primary open-angle glaucoma. Prostaglandin analogs (58%) and beta-adrenergic antagonists (20%) were the most common drugs chosen for the monocular drug trial.

Table 2 – Demographics

Total	55	100%
Diagnosis		
Glaucoma Suspect	27	49.1%
Primary Open Angle Glaucoma	22	40%
Narrow Angle Glaucoma	2	3.6%
Traumatic Glaucoma	2	3.6%
Normal Tension Glaucoma	1	1.8%
Uveitic Glaucoma	1	1.8%
Gender		
Female	30	54.5%
Male	25	45.5%
Race		
White	34	61.8%
Black	18	32.7%
Hispanic	3	5.5%
Mean Age	64.7 yrs	(SD = 11.9)
Median Age	67 yrs	
Type of Medication used in Monocular Trial		
Prostaglandin analog	32	58.2%
Beta-adrenergic antagonist	11	20%
Alpha 2 agonist	4	7.3%
Carbonic anhydrase inhibitor/beta-adrenergic antagonist combination	4	7.3%
Carbonic anhydrase inhibitor	2	3.6%

Sympathomimetic	1	1.8%
Docosanoid	1	1.8%
Presence of ocular other ocular disease	30	54.5%
History of previous eye procedure	14	25.5%
Concurrently taking a systemic beta adrenergic antagonist	13	23.6%
Left eye was first eye treated in monocular trial	30	54.5%
Right eye was first eye treated in monocular trial	25	45.5%

SD = standard deviation

Are there differences between the right and left eye?

Overall, the baseline IOP of the right eye measured at time A was 21.4 ± 4.8 mmHg (mean ± standard deviation) and the left eye was 22.5 ± 6.8 mmHg (Table 3). This difference was not found to be statistically significant (p = 0.122). There was moderate correlation noted between the right and left eye IOPs at baseline ($r^2 = 0.365$).

Table 3 – Intraocular pressures at the baseline reading (time A)

	Right Eye	Left eye	r^2	P value for difference
All patients (n = 55)	21.4 (SD = 4.8)	22.5 (SD = 6.8)	0.365	0.122
Patients with left eye treated first in trial (n = 30)	20.9 (SD = 4.5)	24.2 (SD = 7.5)	0.496	0.002
Patients with right eye treated first in trial (n = 25)	21.9 (SD = 5.3)	20.5 (SD = 5.3)	0.428	0.121

P value for difference was determined from paired student t-test.

Since the left eye was chosen as the first eye treated in 30 of 55 patients, perhaps some differences between the eyes would be noted if the population was examined separately based on which eye was chosen to be treated first. In the 25 patients that had their right eye chosen as the first treated eye in the monocular drug trial, the average IOP

of the right eye at baseline was 21.9 ± 5.3 mmHg and the left eye was 20.5 ± 5.3 mmHg, which was not statistically significant ($p = 0.121$). In the 30 patients with left eye treated first, the baseline IOP measured at time A of the right eye was 20.9 ± 4.5 mmHg and 24.2 ± 7.5 mmHg in the left eye. There was a statistically significant difference found between these two values ($p = 0.002$). Since there was not a consistent pattern noted, the results when controlling for which eye was treated first are inconclusive.

The IOP responses of the right and left eyes were compared from baseline until the end of the study to determine if the unequal length of time that one eye was delivered a medication affected the long-term therapeutic effects of the drug. The right eye decreased 3.4 ± 5.5 mmHg and left eye decreased 4.4 ± 7.0 mmHg from the beginning to the end of the trial (Table 4). There was excellent correlation noted in IOP response between the eye ($r = 0.638$, $p < 0.0001$). This indicates that there is excellent symmetry of therapeutic response of the right and left eye to the same medication over a period of time. The line of best fit using linear regression analysis to describe the relationship between left and right eye IOP pairs was $\Delta IOP_{\text{left eye}} = 0.8161\ (\Delta IOP_{\text{right eye}}) - 1.6475$ mmHg. The excellent correlation noted above indicates that the IOP data closely fits the linear regression equation.

Table 4 – Right and left eye over the course of the study

	Left eye	Right eye
Mean IOP at baseline (time A)	22.5 (SD = 6.8)	21.4 (SD = 4.8)
Mean IOP at end of trial (time D)	18.1 (SD = 3.9)	18.0 (SD = 5.0)
Change in IOP from time A to time D	-4.4 (SD = 7.0)	-3.4 (SD = 5.5)
Pearson correlation coefficient of change of right and left eye from time A to time D	r = 0.638	p < 0.0001

Does the response of the first eye predict response of the second eye?

The eye chosen to be treated first in the monocular drug trial was the eye with the higher IOP at baseline in 31 of 55 patients. In 9 patients, the eye with lower baseline IOP was treated first and 15 patients had equal IOPs at baseline. During the monocular phase, the IOP of the first treated eye decreased 5.8 ± 6.1 mmHg, a reduction of 25%, while the fellow eye's IOP increased 0.5 ± 3.5 mmHg, an increase of 2.4% (Table 5). During the binocular phase, the mean IOP of the second eye decreased 3.4 ± 4.2 mmHg (a 16% reduction). The mean IOP of the fellow eye (the first eye treated) increased 0.9 ± 4.8 mmHg (a 5.2% increase).

Table 5 – Overall results

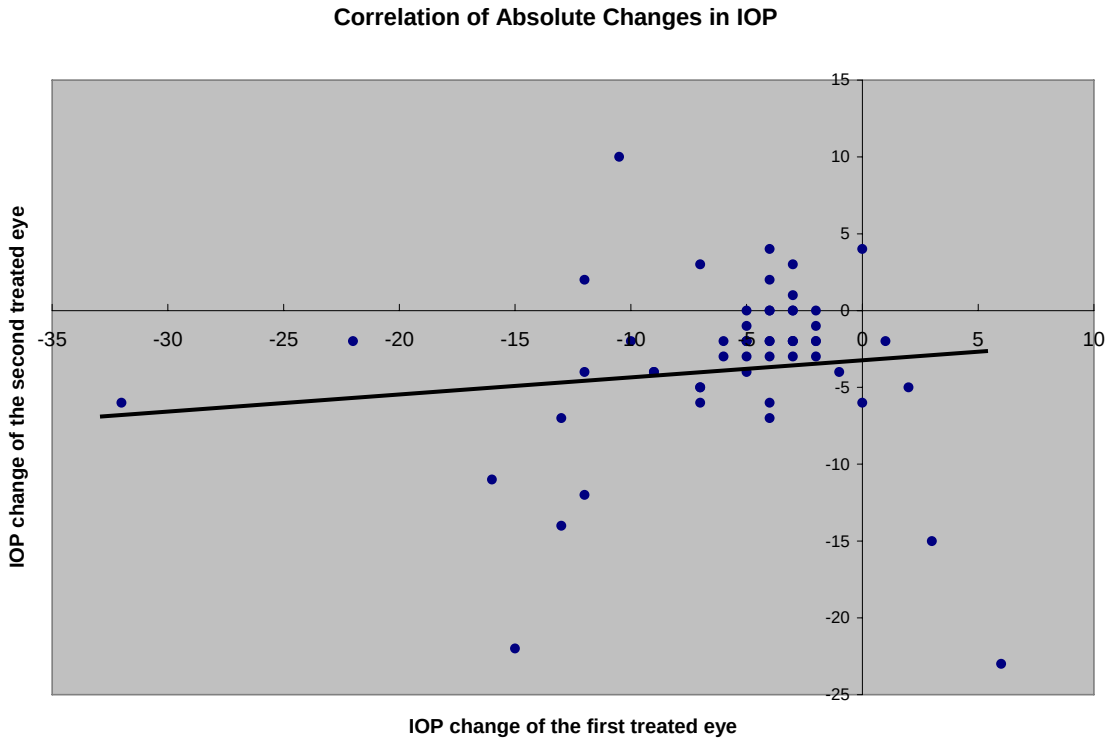
	First eye	Fellow eye
Baseline IOP	23.1 (SD = 6.6)	20.7 (SD = 4.8)
IOP at assessment (Time B)	17.4 (SD = 3.5)	21.2 (SD = 5.2)
Absolute IOP change from Time A to B	-5.8 (SD = 6.1)	0.5 (SD = 3.5)
Relative change from Time A to B	-6.3 (SD = 5.3)	
	Second eye	Fellow eye
Baseline IOP (Time C)	21.3 (SD = 5.2)	17.3 (SD = 3.4)
IOP at assessment (Time D)	18.0 (SD = 3.8)	18.1 (SD = 5.2)
Absolute IOP change from Time C to D	-3.4 (SD = 5.7)	0.9 (SD = 4.8)
Relative change from Time C to D	-4.2 (SD = 4.5)	
Correlation using absolute changes	R = 0.095	P = 0.49
Correlation using relative changes	R = 0.404	P = 0.002

First eye denotes the eye that the monocular drug trial was performed on.
Second eye denotes the eye that the drug was added to for binocular therapy.
Relative change was calculated using the fellow eye as a control.

There was poor correlation noted between the absolute changes in IOP of the first eye during monocular therapy and the second eye during binocular therapy when they were analyzed with the Pearson correlation coefficient (r = 0.095, p = 0.49) (Figure 1).

This indicates that the first eye is a poor predictor of second eye response when absolute IOP changes are used. The line of best fit of the absolute IOP change of the first and second treated eye using linear regression analysis was $\Delta IOP_{\text{second eye}} = 0.09\ (\Delta IOP_{\text{first eye}}) - 2.87$ mmHg.

Figure 1

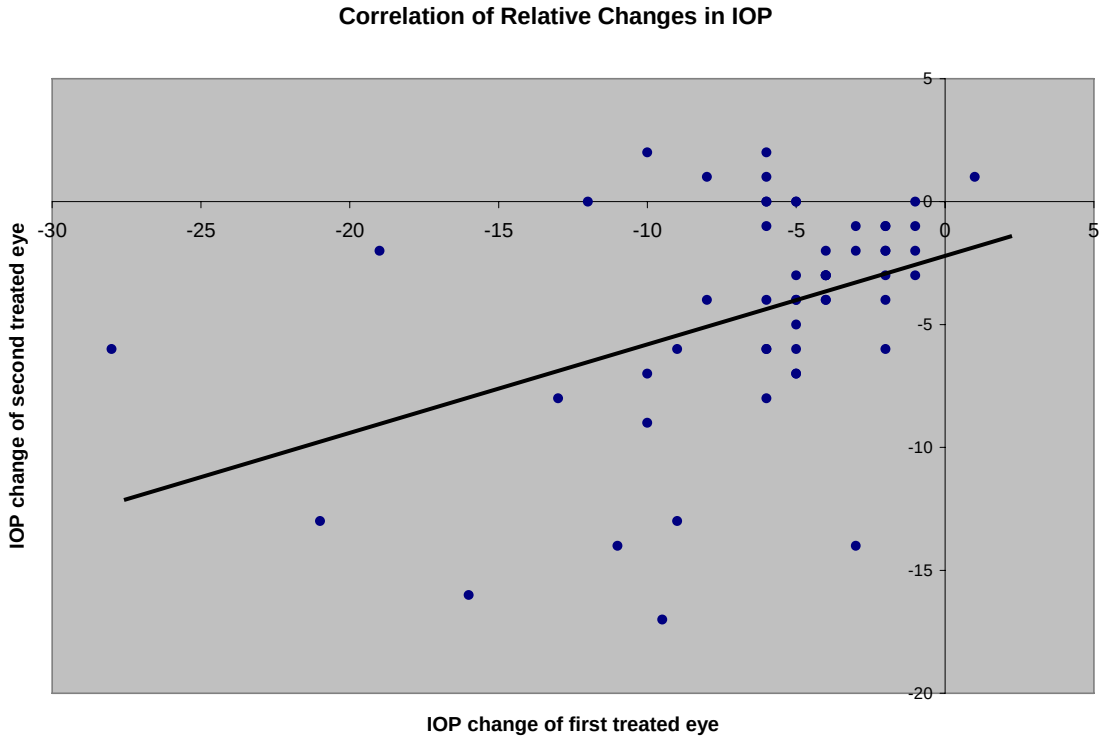


When the fellow eye is not used as a control to adjust for spontaneous changes during the monocular drug trial, there is poor correlation between the first and second eye response to the same medication ($r = 0.095$, $p = 0.49$). As you can see, the data are widely scattered around the line of best fit.

When the fellow eye was used as a control for spontaneous diurnal variations, the relative decrease in IOP of the first treated eye from time A to B was 6.3 ± 5.3 mmHg, a change of 27.2% (Table 5). When the fellow eye was used as a control for the second eye from time C to D, the relative reduction in IOP of the second eye was 4.2 ± 4.5 mmHg, a

decrease of 19.7%. There was statistically significant correlation between the relative change in IOP in the first eye during monocular therapy and the second eye during binocular therapy ($r = 0.49$, $p = 0.002$) (Figure 2). This indicates that when the fellow eye is used as a control, the first eye is an excellent predictor of second eye response. The line of best fit of the relative IOP change of the first and second treated eye using linear regression analysis was $\Delta IOP_{\text{second eye}} = 0.35\ (\Delta IOP_{\text{first eye}}) - 2.05$ mmHg. The excellent correlation indicates that the IOP data closely fits this line.

Figure 2



When the fellow eye is used as a control, better correlation is noted between the response of the first eye treated during the monocular trial and the second eye during binocular therapy ($r = 0.404$, $p = 0.002$). As you can see, there is roughly a linear relationship between first and second eye response.

Does the type of medication affect first and second eye correlation?

A subset of 32 patients who were given prostaglandin analogs in the monocular drug trial were separately analyzed because of the postulated lack of cross-over effect of this type of medication (Table 6).[22] The IOP of the first eye decreased 6.0 ± 6.7 mmHg while the fellow eye increased 0.6 ± 3.4 mmHg during monocular therapy. During binocular therapy, the IOP of the second eye decreased 3.6 ± 5.7 mmHg while the fellow eye increased 1.4 ± 5.4 mmHg. There was not a statistically significant correlation between the absolute change in IOP of the first eye during monocular therapy and the second eye during binocular therapy (r = 0.250, p = 0.168). However, statistically significant correlation was noted when the fellow eye was used as a control (r = 0.400, p = 0.023).

Table 6 – Medication class

	Beta-blockers (n=11)	Prostaglandin analogs (n=32)
IOP change of first eye (Time A to B)	-7.1 (SD = 5.8)	-6.0 (SD = 6.7)
IOP change of fellow eye (Time A to B)	-0.6 (SD = 3.1)	0.6 (SD = 3.4)
Relative change of first eye (Time A to B)	-6.5 (SD = 7.0)	-6.6 (SD = 5.4)
IOP change of second eye (Time C to D)	-3.5 (SD = 4.0)	-3.6 (SD = 5.7)
IOP change of fellow eye (Time C to D)	0.5 (SD = 1.9)	1.4 (SD = 5.4)
Relative change of second eye (Time C to D)	-3.9 (SD = 3.9)	-5.1 (SD = 4.9)
Correlation using absolute changes	R = 0.310	R = 0.250
	P = 0.350	P = 0.168
Correlation using relative changes	R = 0.538	R = 0.400
	P = 0.088	P = 0.023

Since beta-adrenergic antagonists have been found to have a significant crossover effect, the 11 patients given this type of medication were also analyzed separately.[20] The mean IOP of the first eye decreased 7.1 ± 5.8 mmHg while the fellow eye decreased 0.6 ±

3.1 mmHg during monocular therapy. During binocular therapy, the mean IOP of the second eye decreased 3.5 ± 4.0 mmHg while the fellow eye increased 0.5 ± 1.9 mmHg. There was not a statistically significant correlation when using the absolute IOP change ($r = 0.310$, $p = 0.350$). When using the relative IOP change, there was a trend noted but it was not statistically significant ($r = 0.538$, $p = 0.088$).

To examine if more of a cross-over effect existed in prostaglandin analogs than beta-blockers, the IOP change in the fellow eye was examined while the first eye was being treated. There was not a statistically significant difference found in the response of the fellow eye in these two groups ($p = 0.309$). This indicates that the statement that a cross-over effect exists in beta-blockers but not in prostaglandin analogs is not supported by this study; however as shown above, there was an improvement of correlation of first and second eye response in prostaglandin analogs than beta-blockers when the fellow eye was used as a control.

Does type of glaucoma affect first and second eye correlation?

In 22 patients with primary open angle glaucoma, the IOP change of the first eye was -6.5 ± 7.7 mmHg during monocular therapy and the second eye was -1.5 ± 4.7 mmHg during binocular therapy (Table 7). These were poorly correlated ($r = 0.008$, $p = 0.973$). Using relative changes in IOP did not significantly improve correlation ($r = 0.199$, $p = 0.375$). In 27 patients with the diagnosis of glaucoma suspect, the IOP change in the first eye was -5.4 ± 4.4 mmHg during monocular therapy and -4.1 ± 5.2 mmHg of the second eye during binocular therapy. There was a strong correlation between these

two values (r = 0.590, p = 0.001). When using relative values, this correlation was even better (r = 0.629, p = 0.0004).

Table 7 – Type of Glaucoma

	POAG (n=22)	Glaucoma Suspect (n=27)
IOP change of first eye (Time A to B)	-6.5 (SD = 7.7)	-5.4 (SD = 4.4)
IOP change of fellow eye (Time A to B)	-0.6 (SD = 3.1)	1.1 (SD = 3.1)
Relative change of first eye (Time A to B)	-5.8 (SD = 6.5)	-6.6 (SD = 4.7)
IOP change of second eye (Time C to D)	-1.5 (SD = 4.7)	-4.1 (SD = 5.2)
IOP change of fellow eye (Time C to D)	2.0 (SD = 6.1)	0.4 (SD = 3.2)
Relative change of second eye (Time C to D)	-3.4 (SD = 4.7)	-4.6 (SD = 4.0)
Correlation using absolute changes	R = 0.008	R = 0.590
	P = 0.973	P = 0.001
Correlation using relative changes	R = 0.199	R = 0.629
	P = 0.375	P = 0.0004

Does race affect first and second eye correlation?

Strong correlation was found in 34 White patients when using absolute IOP changes (r = 0.541, p = 0.001) and when using the relative IOP change (r = 0.599, p = 0.0002) (Table 8). In 21 Black and Hispanic patients, a statistically significant negative correlation was found using absolute IOP changes (r = -0.513, 0.009). When relative IOP values were used, poor correlation was found (r = 0.059, p = 0.799).

Table 8 – Race

	White (n = 34)	Black/Hispanic (n = 21)
IOP change of first eye (Time A to B)	-6.5 (SD = 6.1)	-4.7 (SD = 6.1)
IOP change of fellow eye (Time A to B)	0.0 (SD = 3.0)	1.2 (SD = 4.6)
Relative change of first eye (Time A to B)	-6.5 (SD = 5.9)	-5.9 (SD = 4.2)
IOP change of second eye (Time C to D)	-3.7 (SD = 5.2)	-2.9 (SD = 6.5)

IOP change of fellow eye (Time C to D)	0.5 (SD = 3.1)	1.4 (SD = 6.7)
Relative change of second eye (Time C to D)	-4.2 (SD = 4.2)	-4.3 (SD = 5.0)
Correlation using absolute changes	R = 0.541	R = -0.513
	P = 0.001	P = 0.009
Correlation using relative changes	R = 0.599	R = 0.059
	P = 0.0002	P = 0.799

Does history of ocular procedure affect first and second eye correlation?

Fourteen patients had undergone an ocular procedure prior to initiation of the monocular trial (Table 9). These included 2 peripheral iridotomies, 7 laser photocoagulation procedures, 7 lens removal procedures, and 1 scleral buckle procedure. In these patients, there was poor correlation between the first eye during monocular therapy and the second eye during binocular therapy ($r = -0.049$, $p = 0.868$). However, the correlation was statistically significant using relative changes ($r = 0.643$, $p = 0.013$). In 41 patients that had not undergone an ocular procedure, statistically significant correlation was not found in either absolute changes of IOP ($r = 0.180$, $p = 0.261$), or in relative changes in IOP ($r = 0.301$, $p = 0.056$).

Table 9 – History of Surgery

	History of ocular procedure (n=14)	Patients without ocular procedure history (n=41)
IOP change of first eye (Time A to B)	-5.0 (SD = 6.2)	-6.1 (SD = 6.1)
IOP change of fellow eye (Time A to B)	1.0 (SD = 5.9)	0.3 (SD = 2.6)
Relative change of first eye (Time A to B)	-6.0 (SD = 5.5)	-6.4 (SD = 5.2)
IOP change of second eye (Time C to D)	-4.0 (SD = 7.6)	-3.2 (SD = 4.9)
IOP change of fellow eye (Time C to D)	0.6 (SD = 4.0)	0.9 (SD = 5.0)
Relative change of second eye (Time C to D)	-4.6 (SD = 5.6)	-4.1 (SD = 4.1)
Correlation using absolute changes	R = -0.049	R = 0.180
	P = 0.868	P = 0.261
Correlation using relative changes	R = 0.643	R = 0.301
	P = 0.013	P = 0.056

Does concurrent systemic medication use affect first and second eye correlation?

In order to isolate the effect of systemic medications on IOP, the 13 patients who were concurrently taking systemic beta-adrenergic antagonists were analyzed independently (Table 10). There was statistically significant correlation found when using relative IOP changes ($r = 0.598$, $p = 0.031$) but not when using absolute IOP changes ($r= 0.449$, $p = 0.123$). In the 42 patients not on systemic beta-blockers, statistically significant correlation was observed using relative IOP changes ($r = 0.324$, $p = 0.036$) but not using absolute IOP changes ($r = -0.084$, $p = 0.597$). Patients on systemic beta-blockers did not have a statistically significant difference in absolute IOP response from those not on systemic beta-blockers during the monocular period ($p = 0.0865$).

Table 10 – Concurrent systemic beta-adrenergic antagonist use

	Concurrent beta-blocker (n=13)	Patients not on beta-blockers (n = 42)
IOP change of first eye (Time A to B)	-8.3 (SD = 9.0)	-5.0 (SD = 4.7)
IOP change of fellow eye (Time A to B)	0.0 (SD = 4.5)	0.6 (SD = 3.5)
Relative change of first eye (Time A to B)	-8.3 (SD = 8.3)	-5.7 (SD = 3.9)
IOP change of second eye (Time C to D)	-4.2 (SD = 4.9)	-3.2 (SD = 5.9)
IOP change of fellow eye (Time C to D)	0.0 (SD = 1.9)	1.1 (SD = 5.3)
Relative change of second eye (Time C to D)	-4.2 (SD = 4.9)	-4.2 (SD = 4.4)
Correlation using absolute changes	R = 0.449	R = -0.084
	P = 0.123	P = 0.597
Correlation using relative changes	R = 0.598	R = 0.324
	P = 0.031	P = 0.036

Where does baseline measurement of IOP fall on the diurnal curve?

Ten patients had 5 consecutive visits prior to the initiation of the monocular drug trial where no changes in medication had taken place (Table 11). In these patients, the mean IOP of the first treated eye was 23.0 ± 7.9 mmHg. During the baseline visit and the previous 5 visits, the mean IOP of the first treated eye was 20.6 ± 3.8 mmHg, the average trough IOP was 17.2 ± 4.0 mmHg, and average peak IOP was 25.0 ± 6.9 mmHg. For the second eye treated, the mean IOP at time A for these 10 patients was 19.9 ± 4.0 mmHg. The mean IOP of the second eye at time A and the previous 5 visits was 19.4 ± 3.1 mmHg, the average trough IOP was 15.8 ± 3.8 mmHg, and the average peak IOP was 23.1 ± 2.8 mmHg. For these patients, the baseline IOP at time A was intermediately between the mean and peak of the diurnal curve for the first treated eye and the baseline was approximately equal to the mean of the diurnal curve for the fellow eye.

Table 11 – Regression to the Mean

	All eyes (n = 20)	1st treated eye (n = 10)	Fellow eye (n = 10)
Mean IOP at baseline (time A)	21.5 (SD = 6.3)	23.0 (SD = 7.9)	19.9 (SD = 4.0)
Mean IOP at baseline + 5 previous visits	20.0 (SD = 3.4)	20.6 (SD = 3.8)	19.4 (SD = 3.1)
Mean trough IOP at baseline + 5 previous visits	16.5 (SD = 3.9)	17.2 (SD = 4.0)	15.8 (SD = 3.8)
Mean peak IOP at baseline + 5 previous visits	24.0 (SD = 5.2)	24.8 (SD = 6.9)	23.1 (SD = 2.8)

Only included were the 10 patients that had in 5 consecutive visits prior to initiation of the monocular drug trial did not have any change of medications.

Discussion

For many years, ophthalmologists have used a monocular trial when starting glaucoma patients on pharmacotherapy to test the efficacy of the medication. The drug is started in only one eye so that the fellow eye can be used to control for spontaneous diurnal variations in intraocular pressure, which was historically assumed to be approximately equal in both eyes. In this study, we show that when the fellow eye is used as a control, the first eye is an excellent predictor of response of the second eye. Also, when the fellow eye is not used as a control, there is sufficient symmetry in IOP changes in glaucoma suspect patients for the monocular drug trial to be a useful predictor of IOP response in the fellow eye.

Why does such a difference exist in the correlation when using absolute IOP change and relative IOP change?

Better correlation between first and second eye response is noted in the overall patient population as well as many of the subsets when the fellow eye is used as a control than when absolute intraocular pressures are compared. As has been previously reported, asymmetric diurnal variations of IOP are substantial and sufficiently skew the data so that the absolute change in IOP noted in the first eye during the monocular trial does not predict the absolute change in the second eye during binocular therapy.[15]

However, even though spontaneous variations are substantial, they can be mitigated if the fellow eye is used as a control. The better correlation noted with relative changes indicates that significant symmetry in diurnal variation exists between fellow eyes to allow an adjustment of the absolute IOP change to be closer to the true

therapeutic effect. If, however, the diurnal curves between fellow eye pairs were unrelated, adjustment using the fellow eye would instead confound the data and result in worse correlation. When examining our data, this is not the case.

Absolute IOP change in one eye does not predict future IOP change in the fellow eye because of asymmetric spontaneous diurnal variations between two eyes when comparing *different* time periods (i.e. the first eye during monocular therapy and the second eye during binocular therapy). In contrast, good correlation exists when using relative IOP changes because fellow eyes' spontaneous variations are symmetrical over the *same* time period. Since in the monocular trial, the fellow eye is used as a control only during the same time period (i.e. the second eye is a control while the first eye is treated and the first eye is a control while the second is treated), the fellow eye's diurnal variation is symmetric enough to allow the other eye to be used as a control.

Realini et al. have shown that when medication is started in both eyes at the same time, fellow eyes' absolute IOP changes are well correlated.[3] Therefore, therapeutic response with spontaneous changes over the same time period between fellow eyes are symmetrical. We supplement these findings by showing that even if a medication is administered for unequal time lengths in fellow eyes (because only one was used for the monocular phase of the trial), there is still excellent correlation noted in absolute IOP change between fellow eyes as long as a sufficient amount of time is allowed to pass for binocular administration to take effect. Therefore, the major source of variation seen when comparing the first eye treated in the monocular trial and the second eye during binocular therapy is due to spontaneous changes in different time periods being

compared. As a result, one must take the spontaneous changes of the fellow eye over the same time period into account to obtain meaningful results.

Can we use the fellow eye as a control?

Some researchers have objected to use of the fellow eye as a control stating that diurnal fluctuations in IOP may be too large in magnitude and independent in each eye for one eye to serve as a useful predictor of drug efficacy in the fellow eye. In fact, Realini et al. decided to not use the fellow eye as a control and instead compared only absolute changes of IOP.[15] As we have shown, in order for the monocular trial to be valid in the general population, one must use the IOP of the fellow eye to predict what the IOP of the treated eye would have been in the absence of treatment. Only then can a clinician isolate the therapeutic effect of the medication. If, however, the IOPs independently fluctuate, then no comparison can be made between fellow eyes and the monocular drug trial is rendered useless.

Realini et al. also called into question what response constitutes an efficacious drug.[3] They give an example that if the absolute IOPs of both eyes increase after a monocular trial, but the treated eye increases less than the fellow eye, does that constitute a successful drug? Some ophthalmologists may say yes even if the absolute IOP increased in the treated eye. However, since the overall goal is to lower IOP, this claim is perplexing. Quite possibly, a single measurement may catch one eye at the IOP peak and the other eye at the IOP trough giving the clinician a skewed perception. One may make false conclusions about the extent and asymmetry of glaucomatous damage between the eyes or about the drug's efficacy.

Thus, there is a critical question of whether one eye can be used as a control for the fellow eye. The debate can not be settled with a mathematical study, and must instead be proven with theoretical argument. We counter that even if Realini et al.'s objection is valid, any skew in comparison of IOP changes between the first and second treated eye because of asymmetric fluctuations would actually decrease the correlation observed. If fellow eyes were not the same place on their diurnal pressure curves, this would serve to scatter the data and would thus, underestimate the correlation. Yet, in spite of this scattering of data, we still note excellent correlation. Realini et al. state that intraocular pressures between eyes may be similar on average.[15] However, since Pearson correlation analysis looks for similarities at each data point for each individual and not for the population as a whole, our data shows there is strong correlation for *each* individual ($r = 0.404$, $p = 0.002$).

Multiple measurements may allow an ophthalmologist to avert this problem and get a better picture of the diurnal pressure curve. In fact, ophthalmologists often rely on IOP measurements over many visits before making a treatment decision unless the IOP is so high to warrant immediate treatment. However, in a non-emergency setting, research has not be done to determine if an individual's IOP curve can be accurately mapped if measurements are taken across multiple visits or must be during a single day. Since diurnal pressure curves in the same eye have been shown to shift over time, it is reasonable to assume the measurements need to be taken preferably over the least amount of time to reduce the possibility of shifting of the diurnal curve.[12] Given the impracticality for a patient to be in an office setting for 24 hours to check IOP, Zeimer has advocated for an individual to use a home tonometer multiple times over 24 hours

and report the readings at a future checkup in order to map the full diurnal pressure curve.[1]

If an individual's diurnal IOP curve can be mapped using multiple measurements, a monocular trial would cease to be useful. The purpose of using a monocular trial is so that the response of one eye can be compared to the response in the fellow eye in order to isolate the effect of spontaneous variations. However, since multiple IOP measurements would already fully characterize the spontaneous variations, both eyes could now be started on therapy at the same time. The patient would be instructed to take enough measurements with a home tonometer both before treatment was started; and then again when enough time had passed to make a decision about the efficacy of the medication. The ophthalmologist would then compare the before and after treatment IOP curves to make a treatment decision.

Using this method, the quandary presented above about what constitutes an efficacious drug would no longer be in question. Since IOP curves would be directly compared with each other without any adjustments from the changes observed in the fellow eye, absolute IOP measurements can now reliably be used. Only if the IOP curve is noted to be less after treatment will a drug be considered a success and continued. An ophthalmologist would be able to offer more tailored therapy and perhaps, a different medication for each eye if the case warrants.

Are there intraocular pressure differences between the left and right eye?

Lee et al. found that asymmetry between the left and right eye to be a sign of primary open angle glaucoma.[23] In order to examine the relationship between the left and

right eye, we looked at the mean pressures at baseline of the 55 glaucoma patients in our study. The mean IOP of the left eye was slightly higher than the mean IOP of the right eye (22.4 mmHg and 21.4 mmHg respectively) although they were not statistically different. Intraocular pressures in the left and right eye were moderately correlated with a Pearson correlation coefficient of 0.365. This is similar to previously published studies including Liu et al. who found a correlation of 0.311 to 0.741 in normal individuals and Sit et al. who found a correlation of 0.416 to 0.536 in glaucomatous patients.[24, 25] Since the correlation is only moderate, this illustrates that asymmetries exist between eyes during a single measurement in absence of any effects of medication. Without multiple measurements mapping each eye's diurnal curve, we are unable to say whether these differences reflect asymmetric spontaneous fluctuations (each eye on a different point of their diurnal curves) or asymmetries of average IOPs (different diurnal curves entirely).

Since the eye with higher IOP at baseline is often the one treated first in the monocular trial, we looked at if there were differences in the mean IOP between the left and right eye depending one which one was chosen for treatment. We found that there was a statistically significant difference in the mean IOP of the left and right eye in patients when the left eye was the first treated eye; however, no difference was noted when the right eye was treated first. We believe that these results reflect the subjective nature of which eye is first chosen for treatment. In fact, Liu et al. found opposite results in their study, that the average IOP of the right eye than higher than in the left eye.[24]

Realini et al. found that when medication was added to both eyes at the same time, the IOP responses of the left and right eyes were correlated.[3] However, using linear regression analysis, they found that the slope of the line of best fit of left and right IOP

change was 0.77. We compared the IOP at baseline with the IOP after a sufficient amount of time had passed after initiation of binocular therapy. We, indeed, found that the left and right eyes were extremely well correlated ($p < 0.0001$) and the slope of best fit for our data was 0.81 (Table 4). This suggests that the therapeutic responses of the left and right eyes are well correlated as long as a sufficient amount of time has passed to allow the medication to take effect. However, we did expect that the slope of the line of best fit would be closer to 1 which would indicate an equal response between eyes. IOP change can be well correlated but not equal if the ratio of IOP change between fellow eyes is consistent. In both our study and Realini et al.'s study, the right eye response was less than the left eye response. Perhaps, there are some inherent differences between the left and right eye. Studies have found various causes for slight asymmetries between IOP measurements of the left and right eye such as order of measurement and hand and eye dominance of the patient.[28, 35] In our study, the IOP of the right eye was regularly measured first. However, it is unlikely for the order of measurement to cause the larger decrease noted in the left eye over a period of time.

Is there a cross-over effect?

One of the objections to the monocular trial is that a drug applied in one eye will decrease the IOP in the fellow eye. This would result in an underestimation of the therapeutic effect of the treated eye when the fellow is used as a control. To assess this possibility, we looked at the change in IOP of one eye while the fellow eye is treated with the medication. In the population as a whole, there doesn't seem to be a cross-over effect. In fact, the average IOP of the second eye increases from 20.7 to 21.2 mmHg

while the first eye is being treated and the first eye increases from 17.3 to 18.1 mmHg when medication is added to the second eye.

Since beta-adrenergic antagonists are known to cause a cross-over effect, the subset of patients given this type of medication was examined separately. In the 11 patients given beta-blockers, the fellow eye decreased an average of 0.6 mmHg while the first eye was being treated. Previous studies have shown a decrease of 1.5 mmHg.[20] In contrast, in patients given prostaglandin analogs where studies have shown there is little cross over effect, the fellow eye actually increased an average of 0.6 mmHg.[22] The differences in IOP changes observed between patients given prostaglandins and beta-blockers were not found to be statistically significant. Differences may exist in the types of medication and be shown in a study with a larger sample size.

The increase in IOP noted in the fellow eye while the other eye is being treated is perplexing. Perhaps, there are compensatory adjustments to maintain intraocular pressure in the eye. Local or central mechanisms may serve to balance any reductions in pressure due to medication. To date, no reports have been published detailing adjustment mechanisms to maintain a range of normal intraocular pressures.

Since there was less of a cross-over effect in prostaglandin analogs compared with beta-adrenergic antagonists, one would assume that the correlation noted between first and second eye responses is better in patients given prostaglandin analogs during the monocular trial. This is exactly what we found. The only statistically significant correlation was found was in patients given prostaglandin analogs when using relative IOP changes. Perhaps correlation also existed in the group given beta-blockers, however

it was not found to be statistically significant in part due to the cross-over effect but also possibly because of the small sample size (n = 11).

Given that topical beta-blockers cross into systemic circulation and decrease IOP in the contralateral eye, we wondered what effect systemic beta-blocker use would have on the monocular trial. However, systemic beta-blockade did not affect the results of the monocular trial. Good correlation was found both in groups using and not using systemic beta-blockers when the fellow eye was used as a control but not when using absolute IOP changes. Since systemic medication probably has some influence on IOP, we assumed that the eye would be less responsive to glaucoma medications in patients given systemic beta-blockers. In contrast, we found that there was a larger decrease in IOP of the first eye in patients given systemic beta-blockers (-8.0 mmHg versus -5.0 mmHg), however, this difference was not found to be statistically significant ($p = 0.0865$). This may represent a possible multiplicative effect of the glaucoma medication when used in conjunction with a systemic beta-adrenergic antagonist or may be because of small sample size. This needs further investigation.

Is there regression to the mean?

Regression to the mean describes the possibility that at the last measurement before therapy is initiated, the IOP is more likely to be at the peak of the diurnal curve than at the average in order to warrant a therapeutic intervention. Since measurement taken at any other point in time probably has no predilection for a particular point of the IOP curve, these measurements are more likely to be at the mean IOP. Thus, a selection bias is introduced that would overestimate the IOP change in the treated eye during the

monocular trial because not only would therapeutic changes cause a reduction in IOP of the treated eye, but the eye would also be moving from the peak of its diurnal curve to the average.

In order to assess this phenomenon, the 5 previous measurements of IOP before therapy was initiated were compared with the baseline IOP reading. Based on our results, the average baseline IOP was slightly above the average IOP of the previous 5 measurements. When looking only at the first treated eye, the baseline IOP is closer to the peak IOP than the mean IOP of the previous 5 measurements. The second treated eye at baseline was approximately equal to the average of the previous 5 measurements. However, one can not completely elucidate the entire IOP curve based on measurements taken at multiple previous visits especially since all were taken during office hours. More likely, the IOP of the eye chosen for treatment at baseline is somewhere between the mean and peak of the diurnal curve. Therefore, some regression to the mean undoubtedly exists; however, this is an inherent source of bias during the monocular trial and may explain why there is not stronger correlation noted overall. In any case, even with this confounding bias, there is strong correlation seen when using the fellow eye as a control as noted above.

Does type of glaucoma affect correlation seen in the monocular trial?

We also looked at the type of glaucoma of the patient to determine if there were any differences based on the mechanism of the disease. We hypothesized that patients with primary open angle glaucoma have symmetry of trabecular meshwork impairment that would result in good correlation of response to medication of the first and second

eye. However, we found the opposite that almost no correlation existed when using absolute and relative IOP changes. Realini et al. noted similar findings when using absolute IOP changes.[15]

We had interesting results when looking at the glaucoma suspect patients. There was excellent correlation noted when using absolute IOP changes in the first and second eye response and even better correlation when using relative IOP changes. This is the first subset of patients where there was statistically significant correlation noted when using absolute changes in IOP. This means that in glaucoma suspect patients, the spontaneous variations between fellow eyes are well correlated and symmetrical over different periods of time so that the absolute change of IOP of the first eye during the monocular trial correlates with the absolute change in the second eye during binocular therapy. Realini et al. did state that they observed better correlation with the non-POAG patients, yet stated that the correlation was "abysmal" and did not detail their results.[15] It is not known whether they separately analyzed glaucoma suspect patients. The surprising results in glaucoma suspect patients mean that an ophthalmologist can continue to use the monocular drug trial to reliably determine the efficacy of a medication even when not using the fellow eye as a control.

The possible explanation for the large discrepancy of correlation between glaucoma suspect and POAG patients is multi-faceted. Glaucoma suspect patients are at the early progressions of disease. Perhaps at this stage, there are not asymmetries in aqueous inflow or outflow that may occur in advanced cases of disease. Since glaucoma suspect patients are usually on fewer medications, there is a lower possibility for

interplay with other ocular medications. There also may be long-term effects of medications in POAG patients that permanently alter the response in IOP of each eye.

These results, together with the improvement noted in correlation when the fellow eye is used as a control, convey that perhaps as the disease become more advanced, the asymmetry of spontaneous changes in IOP over different time periods increases. In this case, the fellow eye must be used as a control in POAG patients for the monocular trial to be valid, but may not be necessary in glaucoma suspect patients. Further studies must be performed to examine whether symmetry of spontaneous variation is affected by progression of disease.

Does history of ocular procedure affect first and second eye IOP response?

Patients with previous eye procedures have structural alterations that may affect the aqueous inflow and outflow. As a result, these patients may not exhibit correlation between the first and second eye response in the monocular drug trial. However, we found little difference between past-surgical and non-surgical patient groups. Correlation was noted in both groups when relative IOP changes were used.

How does race affect the monocular drug trial?

Race is one of the risk factors for the development of glaucoma. Tielsch et al. found that the prevalence of primary open-angle glaucoma was four to five times higher in African Americans as Caucasians.[36] Our results when controlling for race were puzzling. The 34 White patients exhibited excellent statistically significant correlation between first and second eye response both using absolute and relative changes.

However, the 21 minority patients had a statistically significant negative correlation when using absolute changes in IOP. This result was highly expected. When the fellow eye was used as a control, very little correlation was noted.

We are unable to find a satisfactory explanation for these results. The huge discrepancy when controlling for race points to perhaps a different mechanism of disease afflicting each population. However, more likely is that there are significant biases in the patient population used for this study. It is possible that the sample size of the study was not sufficiently large to allow for correct interpretation of results. Realini et al. did not control for race in their correlation study.[15] Further investigation needs to be performed to look if there are differences noted in glaucoma based on race. If race is an important factor, this may shed light on the lack of statistically significant correlation of the first and second eye IOP response in the general population when using absolute IOP changes.

Limitations

There are limitations to this study that prevent the generalization of results to the patient population. This was a retrospective, observational study that is subject to the same confounders of all studies of this kind. It is possible that there was a selection bias in this study. In majority of patients, the monocular trial was performed on the eye with the higher IOP. The eye with higher IOP may have been on average close to the peak of the diurnal curve rather than the mean which would skew the calculated IOP change. In addition, a single measurement at each time point was used to calculate IOP changes which, as discussed above, is insufficient for making conclusions about the total diurnal curve.

Only patients that had a monocular trial followed by binocular therapy were included in this study. In clinical practice, a patient may be maintained on monocular therapy after the drug trial if the IOP of both eyes are deemed to be acceptable. This may have led to the exclusion of subjects that had asymmetric glaucoma. As a result, better correlation may have been found that truly occurs in the general glaucoma patient population.

Patients that had medication changes during the trial were excluded from the study. This may have excluded patients that had advanced progression of disease or had co-morbidities requiring therapy. As a result, study may have been skewed towards a healthier population. We showed that better correlation was noted in glaucoma suspect patients than in primary open angle glaucoma patients. This selection bias of many patients with worse progression of disease being excluded may have improved the overall correlation.

The monocular drug trial is used in clinical practice to isolate the therapeutic effect of a medication from spontaneous diurnal variations in intra-ocular pressure. Some have questioned the validity of the trial because of magnitude of the diurnal variations. Further study is needed to determine if multiple measurements taken over a period of 24 hours can reliably characterize the normal diurnal cycle so that a monocular trial would no longer be necessary. Until this occurs, we show in this study that the monocular trial is a useful protocol to determine the efficacy of a medication. When the fellow eye is used as a control, the first eye response during the monocular drug trial is an excellent predictor of second eye response. There also may be sufficient symmetry in diurnal

variations in glaucoma suspect patients for the first eye to be a useful predictor of second eye response even if the fellow eye is not used as a control.

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