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ORIGINAL RESEARCH

Comparing the efficacy of the monocular trial treatment paradigm with multiple measurements of intraocular pressure before and after treatment initiation in primary open-angle glaucoma

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Abstract: The monocular trial has been proposed as a test to help control for diurnal fluctuations in eye pressure when assessing medication effectiveness. We undertook a prospective study to determine the sensitivity and specificity of the monocular trial as a test for determining the effectiveness of a glaucoma medication. The efficacy of the monocular trial was compared to the diagnostic paradigm of repeated pre- and post-treatment measurements in determining whether an intraocular pressure (IOP)-lowering drug is effective. Forty-two patients with newly diagnosed open-angle glaucoma completed five visits: visit 1 for determining eligibility, obtaining consent, and measuring IOP, visit 2 for a second pressure measurement, and visit 3 for a third pressure reading. The new medication was then started in one eye. IOP measurements were made at weeks 4 and 6. The gold standard IOP change was defined as the difference in mean between the pre- and post-medication visits. A medication was deemed effective if this difference was at least 15%. The monocular trial pressure change was defined as the IOP change in the treated eye between the visit immediately before and immediately after the medication addition, corrected by subtracting the pressure change in the untreated eye. All 42 patients completed the full protocol with good compliance. Twenty-five of 42 (60%) medication additions were considered effective by the gold standard method, and 25/42 (60%) by the monocular trial method. However, the two methods agreed in only 26 patients (17 Yes/Yes, 9 No/No). The calculated sensitivity was low (0.68), with a specificity of 0.53. The monocular trial can give useful clues as to whether a medication is effective, but should not be the only information used in making this determination. To obtain the most valid results, multiple pressure checks should be done before and after starting a new medication.

Keywords: applanation tonometry, visual field, eye, vision, glaucoma, pharmacology

Background

Glaucoma is a slowly progressive optic neuropathy with potential causative mechanisms related and unrelated to ocular hypertension.[1,2,3] The only proven therapy for slowing glaucomatous visual field loss and therefore the only modifiable disease risk factor is through lowering of the intraocular pressure (IOP).[4,5] Topical pressure-lowering medications are often successful at lowering the pressure to an acceptable level.[6]

Determining the effectiveness of IOP-lowering medications is important because glaucoma drugs are not equally effective in every patient, a problem for which few predictive parameters are available.[4,7] Also, once initiated, IOP-lowering medications are often used throughout the lifetime of a patient.[4,8,9] These drugs are costly, impact quality of life, and may have side effects.[4,8–11] Therefore, it is incumbent on the clinician

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to carefully assess medication effectiveness; if a drug is found to be ineffective it should be discontinued. Effectiveness is determined by comparing the intraocular pressure before starting a drug to the intraocular pressure after starting a drug.[9] This sounds simple, but in clinical practice pressure changes can be very difficult to assess because of daily fluctuations in eye pressure.[12] There is a ±1–2 mmHg degree of uncertainty in an individual eye pressure measurement, and a ±3–6 mmHg variation in an individual's eye pressure during the day, known as diurnal fluctuation.[12–16] Considering these two types of variation added together, without making any medication changes, the pressure may be 18 mmHg on one day and 13 mmHg at another time point the next day because of normal variation and measurement inaccuracies. Similarly, the pressure may be 18 mmHg on one day and then 18 mmHg the next week after starting a medication. This lack of change would suggest that the medication was not effective, when in reality, had the pressure been as high as 22 without the drops, the medication could well have been effective. Finally, the expected change in the IOP with the addition of a new medication ranges from 2–10 mmHg depending on the initial pressure and on whether initial or adjunctive medications are being added. This small pressure change is in the same range as the sum of diurnal fluctuation and measurement variability in IOP. These examples show that any given measurement of IOP can be significantly altered by several different uncontrollable mechanisms, which results in the difficulty of determining medication effectiveness in the clinical setting.

To determine the effectiveness of a medication against the background of measurement error and diurnal fluctuation, it has been suggested that a monocular trial be used. Monocular trials have been used in ophthalmology for many years, but only recently has the term appeared in the literature on pressure assessment, and the monocular trial has not previously been tested against other techniques for determining medication effectiveness other than prostaglandins.[17,18] With a monocular trial, the pressure is taken in each eye before starting the new medication (ie, 23 right eyes [OD], 25 left eyes [OS]), the drug is started in only one eye (OD, for example), and then the pressure is measured in each eye several weeks later. If the pressure in the treated eye decreases in relation to the pressure in the untreated eye and decreases >15% from the baseline pressure, the medication is deemed effective.[19] There are several assumptions made with this technique.[20] One is that the two eyes are closely correlated in their pressure fluctuation, and another is that there is no crossover effect from the medication.[20,21] A recently published study of glaucoma patients agrees with this first assumption,[22] in contrast to a prior study of healthy patients which suggested that the eyes are not correlated with respect to IOP fluctuation.[23] With regards to the second assumption, there is published evidence that certain drugs, beta blockers in particular, do have a contralateral effect.[20,24] Considering these issues, our current knowledge of IOP variability suggests that a monocular trial may not be the best means of determining medication effectiveness. Thus, we have performed a prospective clinical data collection to further investigate the efficacy of the monocular trial in determining if a particular glaucoma medication will be effective in comparison with the gold standard method of IOP measurement and treatment.

Methods and participants

The study was a prospective clinical data collection study approved by the Institutional Review Board of the University of Missouri-Kansas City. All patients signed a written consent to participate and the study was performed in compliance with the Declaration of Helsinki.[25]

Patients were required to have raised IOP such that the clinician felt that additional pressure-lowering medication was warranted. Abnormal visual fields and/or optic discs were acceptable but not necessary for enrollment. All forms of raised IOP were acceptable including primary open-angle glaucoma, pseudoexfoliation, pigmentary dispersion, and chronic angle-closure glaucoma. Conditions being treated with other medications (steroids, nonsteroidal anti-inflammatory drugs) such as uveitic glaucoma and postoperative pressure elevations were excluded, as pressure elevations in these disease states may change over a short time and interfere with true assessment of IOP change. IOP had to be below 32 mmHg as higher pressures may necessitate more rapid intervention or the addition of multiple medications at one visit. The patient must have had no clinically apparent corneal edema or central corneal scarring which might interfere with applanation tonometry. Systemic medical conditions and medication use (such as preoperative beta-blockers) guided the choice of appropriate pressure-lowering drops but were not exclusion criteria for the study.

Each patient completed five visits over the course of the study with a total time frame of 3–6 months. Visit #1 consisted of determining eligibility, obtaining consent, and measuring IOP with Goldmann applanation tonometry. Visit #2 consisted of a second IOP measurement 1–21 days later. Visit #3 consisted of a third IOP measurement and initiation of pressure-lowering medication 1–21 days after visit #2. Patients in this study used any one of the following

medications: beta blocker, brimonidine, dorzolamide, or a prostaglandin. Visit #4 occurred 21–35 days after visit #3 and consisted of an IOP measurement, the first after starting medication. Visit #5 occurred 1–21 days after the previous visit and consisted of an IOP measurement, the second after initiating medical therapy. At this point, if the medication was deemed effective it was continued and a final visit 2–3 months later for IOP measurement was completed.

The goal of the present study was to identify if using a monocular trial of a pressure-lowering medication is an accurate determination of whether that medication is effectively lowering the IOP, when compared to multiple measurements of IOP before and after treatment initiation.[26]

Results

In all, 42 patients completed the full protocol with good compliance. Mean IOP measurements for the treated eye at each visit are displayed in Figure 1 (panel A: visits 1–3; panel B: visits 4–5). In the treated eye, mean IOP was reduced from 21 mmHg before initiation of medication down to 16 mmHg after starting medication, resulting in an overall reduction of 5 mmHg, a 24% reduction in IOP. Thus, given this IOP reduction of >15%, medical intervention was deemed effective. Of the medication additions, 25/42 (60%) were considered effective by the gold standard method of multiple measurements of IOP before and after treatment initiation, and 25/42 (60%) by the monocular trial method. However, the two methods agreed in only 26 patients (17 Yes/Yes, 9 No/No; Figure 1C). The calculated sensitivity was low at 0.68, with a specificity of 0.53. While Figure 1 shows individual values for all subjects, the individual data sets comparing success of medical intervention (Figure 1C) are summarized in Figure 2.

Discussion

In our study, 42 patients with elevated eye pressure were treated with a pressure-lowering medication with pressure data recorded on three premedication visits and two post-medication visits.

Of the 42 patients who completed our treatment protocol, the medication addition was considered effective in 25 when measured by monocular trial. The gold standard was deemed effective in 25/42 patients. The two methods agreed in only 26 patients. Thus, with a low sensitivity of 0.68 and a specificity of 0.53, it appears that the monocular trial is less effective than the gold standard of multiple pre- and post- treatment measurements. However, the monocular trial disagreed with the gold standard 38% of the time, thus the monocular trial can be deemed an unreliable measure of medication effectiveness. Therefore, the gold standard of multiple measurements of IOP before and after treatment initiation may need to be reevaluated with respect to reliable numbers for data points acquired before and after treatment. Perhaps a more statistically powerful method of treatment would be one in which more data points could be created, taking into account several pre- and post-treatment IOP measurements and to standardize treatments and measurements to specific times of day. However, we would note that in clinical practice, this many visits and measurements may be difficult or even impractical to achieve.

Despite the fact that only two prospective studies of the monocular trial,[20,26] both with reasonably inconclusive results, have been published, it is still frequently used in the practice of treating glaucoma.[26] According to a study of 26 subjects in 2009 by Realini, the monocular trial is not superior to the gold standard.[26] Another more recent study, published by Bhorade et al in 2010 found the monocular trial not to be an adequate method of determining a medication's response to treatment with topical prostaglandins.[20] Realini's study found the monocular trial to be an inadequate predictor of long-term IOP reduction by prostaglandins.[26] Bhorade's study also found the monocular trial to be an inadequate method of determining the patient's response to pressure lowering with prostaglandins.[20]

Like these previous two studies, our study agrees that the monocular trial provides a lower statistical reliability than the gold standard of multiple measurements of IOP before and after treatment initiation, and overall is not a reliable measure of effectiveness.[20,26] Our study included data on 42 patients, while Realini[26] evaluated 26 subjects and Bhorade et al[20] evaluated 206. While our study evaluated only the short-term effect of the monocular trial in determining the efficacy of a given pressure-lowering medication (ie, over the course of 2–3 months after initiating a pressure-lowering medication), Realini[26] also measured long-term results which consisted of following pressure measurements for 6 months after the addition of the pressure-lowering medication.[26] His results at 6 months showed the monocular trial to again be a poor predictor of long-term IOP reduction.[26] While our study included patients using any class of first line pressure-lowering medication, Realini[26] and Bhorade et al[20] only tested one medication, topical prostaglandins (specifically latanoprost in Realini).[26] We feel that our results are more reflective of the way in which medication additions are carried out in general clinical practice, as patients may be using any one of various medication options, instead of just prostaglandins.

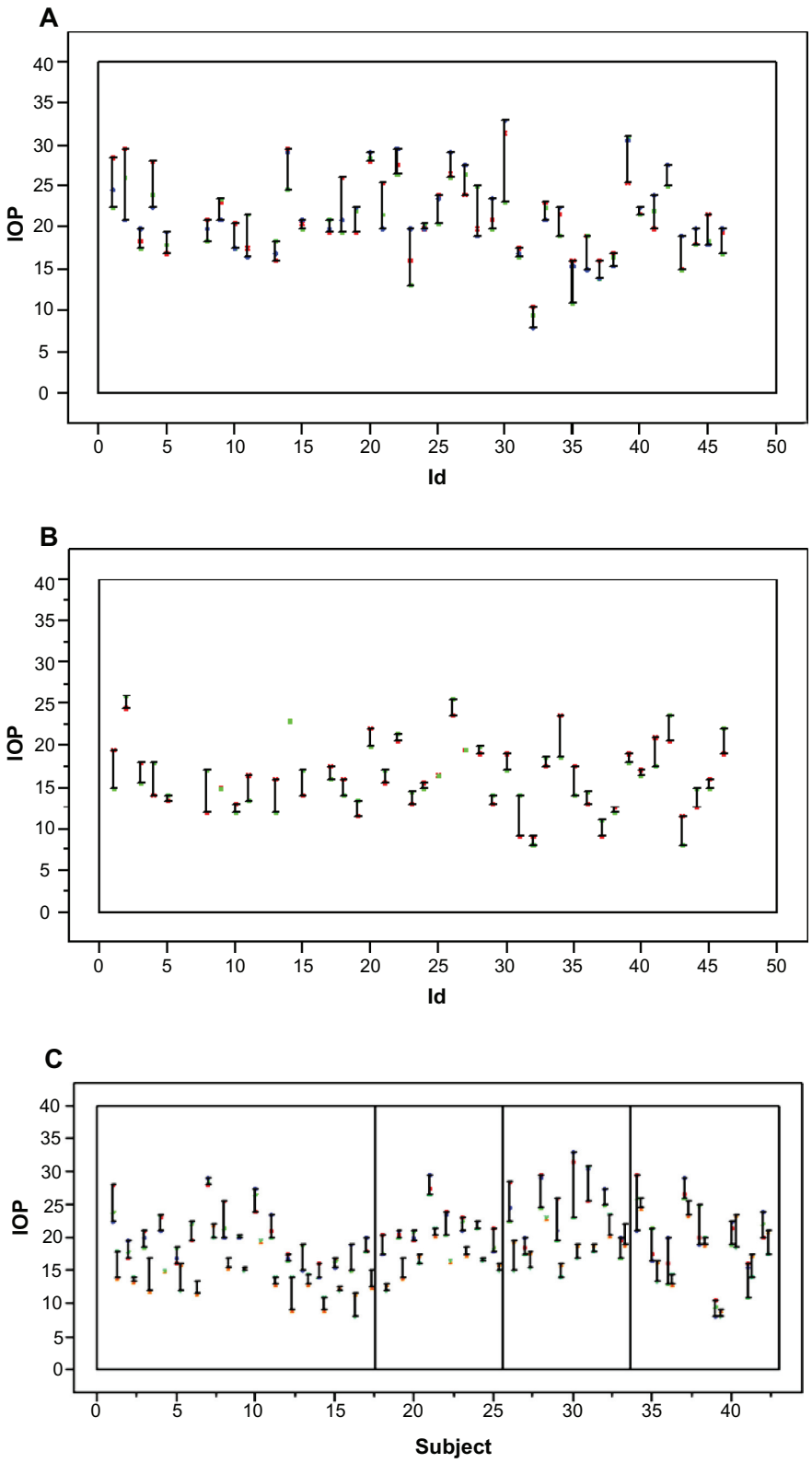

Figure 1 Panel A. Intraocular pressure readings for each subject on visits 1–3. Red x, pressure on the first visit; green square, pressure on the second visit; blue circle, pressure on the third visit. Y-axis indicates intraocular pressure in mmHg and x-axis indicates the subject's identification number. **Panel B.** Intraocular pressure readings for each subject on visits 4–5. Red x, pressure on the fourth visit; green square, pressure on the fifth visit. Y-axis indicates intraocular pressure in mmHg and x-axis indicates the subject's identification number. **Panel C.** A comparison of the efficacy of the monocular trial (MT) with the gold standard of multiple measurements of intraocular pressure before and after treatment initiation in each subject. Subpanel #1 shows that the monocular trial and the gold standard agreed on the efficacy in 17 subjects. In eight subjects, the gold standard was effective whereas the monocular trial was not (subpanel #2). In another eight subjects the monocular trial was deemed effective whereas the gold standard was not (subpanel #3). In nine subjects, neither the gold standard nor the monocular trial was deemed effective (subpanel #4).

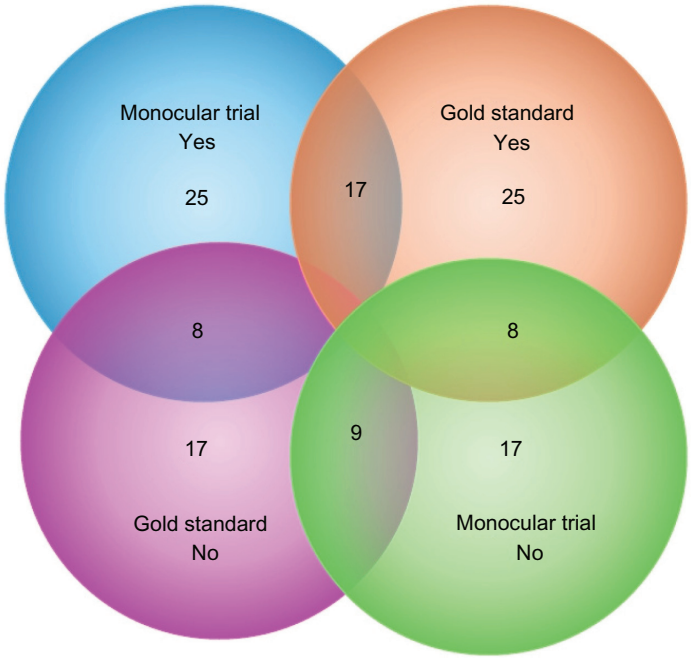

Figure 2 Agreement between monocular trial and gold standard of multiple measurements of intraocular pressure before and after treatment initiation with regards to efficacy. This chart shows that the monocular trial was deemed effective in 25/42 patients (blue circle) and the gold standard was deemed effective in 25/42 patients (red circle). These two methods agreed in 17 patients (the area in between the blue and red circles).

Overall, we concur with previous studies that the monocular trial is less effective than measuring an unadjusted pressure in each eye in response to treatment. However, the monocular trial has a practical advantage over the gold standard in that it requires fewer clinic visits and is thus more feasible. Therefore, for a subset of patients, such as individuals unable to attend multiple pre- and post-medication follow-ups, the monocular trial can provide clues as to whether a given pressure-lowering medication is effective; however, it remains less effective than the gold standard of multiple measurements before and after medication initiation.

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Disclosure

The authors have no financial or conflicting interests to declare.

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