The Efficacy of a Monocular Drug Trial in Normal-Tension Glaucoma

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Purpose: To evaluate the efficacy of a monocular drug trial in eyes with normal-tension glaucoma (NTG).

Methods: This prospective study enrolled 74 patients with NTG. The monocular drug trial was started using latanoprost 0.005% for one week. If the intraocular pressure (IOP) reduction was greater than 15%, the same medication was administered to both eyes for one month. The unadjusted change and adjusted change (the change in the treated eye minus the change in the contralateral eye) in IOP were evaluated, and the predictors of IOP response were analyzed by multivariate linear regression.

Results: Among the initial 74 patients, 31 (41.9%) were included; others were excluded because they did not meet the requisite conditions. The most significant predictors of IOP response in the initial eye and subsequent eye were the baseline IOPs in both eyes ($\beta = 0.907, 0.771$, respectively). The adjusted change in IOP of the initial eye had greater association ($\beta = 0.589$) with the IOP after monocular trial in the initial eye than that of unadjusted IOP change ($\beta = 0.279$). The adjusted change in IOP also had greater predictability ($\beta = 0.348$) for IOP after monocular trial in the subsequent eye than that of the unadjusted IOP change ($\beta = 0.090$).

Conclusions: Although the monocular trial in NTG patients had limited efficacy due to its stringent conditions, it was useful for evaluating the IOP response in the initial eye and for predicting the IOP response in the subsequent eye.

Key Words: Latanoprost, Low tension glaucoma, Monocular drug trial, Normal-tension glaucoma

Decreasing the intraocular pressure (IOP) is the main goal of glaucoma treatment. The Early Manifest Glaucoma Trial showed that glaucoma progression decreased by 10% with the reduction of each mmHg of IOP [1]. According to the Collaborative Normal Tension Glaucoma Study Group, an IOP reduction of 30% slowed the progression of normal-tension glaucoma (NTG) [2].

Evaluation of the IOP reduction after glaucoma treatment is important for clinical decision-making. A monocular drug trial is one of the clinical methods used to evaluate the amount of IOP reduction after treatment and to predict the drug response in the contralateral eye. In a monocular drug trial, instillation of a drug is carried out for only one eye initially. After a period of time to allow the drug to exert sufficient effect, the amount of IOP reduction in the treated eye is compared to the changes in IOP of the contralateral eye; the untreated eye serves as a control to assess the efficacy of the drug. By comparing the IOP changes of the two eyes, one can determine the net effect of treatment based on diurnal variation and visit-to-visit variation of the IOP. After evaluating the effects, the drug can then be instilled in the contralateral eye or can be changed.

Various studies have been performed to evaluate the efficacy of monocular drug trials [3-9]. However, studies have shown mixed results. Retrospective study design, use of beta-blockers, and/or not measuring diurnal variations in IOP may cause inconsistent study findings. In addition, there is a paucity of prospective clinical trials that have evaluated the usefulness of monocular drug trials in eyes.
with NTG, which is the most common type of glaucoma in some Asian countries [10,11]. Therefore, this study was performed prospectively to evaluate the efficacy of a monocular drug trial using latanoprost 0.005% with measurement of the diurnal variation of IOP in eyes with NTG.

Materials and Methods

This study was approved by the Institutional Review Board and adhered to the tenets of the Declaration of Helsinki. All participants provided written informed consent. Among the individuals that visited our clinic between February 2008 and March 2010, those diagnosed with NTG with no history of glaucoma treatment were enrolled.

Ocular examinations including visual acuity, slit lamp examination, IOP measurements with a Goldmann applanation tonometer, refractive error measurements with an autorefractokeratometer (RK-F1; Canon, Tokyo, Japan), corneal thickness measurements obtained by specular microscope (Topcon SP-2000P; Topcon America Corp, Paramus, NJ, USA), gonioscopic examination, retinal nerve fiber layer and stereo disc photos, and visual field examination (Humphrey Automated Perimetry 30-2 SITA program) were performed on all eyes. Glaucomatous disc change (i.e., diffuse or localized rim thinning, rim notches, increased cupping, or disc hemorrhage) was evaluated based on stereo disc photographs (Zeiss FF450 fundus camera; Carl Zeiss Meditec, Dublin, CA, USA), and retinal nerve fiber layer defect (i.e., increased clarity of vascular light reflexes in diffuse atrophy, dark slits or wedges along the arcuate bundle) was assessed by red-free fundus photography (Zeiss FF450 fundus camera; Carl Zeiss Meditec) performed by a single examiner. NTG was identified by glaucomatous optic disc changes and corresponding retinal nerve fiber layer defects with (perimetric glaucoma) or without (preperimetric glaucoma) corresponding visual field changes, coincident with an IOP <21 mmHg at any point during the IOP measurements. Eyes with ocular diseases other than NTG or with refractive errors outside the range of ±6 diopters were excluded. The baseline IOP was measured at 10:00, 12:00, 14:00, and 16:00 on the same day by one examiner (YHH) to confirm the range of IOP <21 mmHg during at any time of the day. Among the four IOP measurements, one IOP was selected as a baseline measure according to patient convenience (i.e., if the patient wanted to make follow-up visits at 10:00, the IOP of the 10:00 before treatment was considered as a baseline IOP). Only patients with similar IOPs (≤2 mmHg IOP differences) in both eyes were included. After evaluating the baseline IOP, the patients were instructed to use latanoprost 0.005% in only one eye. The initial eye was the eye with the higher IOP or more severe visual field defects in those cases with similar IOP levels in both eyes.

After the treatment of one eye for one week (monocular phase), the IOP changes in both eyes were evaluated using unadjusted (absolute) IOP change and adjusted (relative) IOP change [6]. The unadjusted IOP change was defined as the difference between the baseline IOP and the IOP after treatment. The adjusted IOP change was defined as the difference between the unadjusted IOP change and IOP change of the contralateral eye during the treatment period. If the amount of IOP reduction was greater than 15% [12] with the adjusted changes, the same medication was started in the contralateral eye. After the treatment of both eyes with the same drug for one month (binocular phase), the unadjusted and adjusted IOP reductions of the initial eye and subsequent eye were calculated. At each visit during the treatment phase, participants were instructed to visit at the same time of day as for the baseline IOP measurements. Any patients who did not visit at the indicated time or day were excluded. All of the IOP measurements were performed by the same examiner (YHH) who was blinded to whether the individual was enrolled in the monocular phase or binocular phase and to which eye was initially treated.

When considering the initial eye as B, the subsequent eye as A, the baseline visit as 1, visit after the monocular phase as 2, and visit after the binocular phase as 3, unadjusted and adjusted IOP changes were identified as follows: unadjusted IOP change in the initial eye (B2 – B1), adjusted IOP change in the initial eye (B2 – B1) – (A2 – A1), unadjusted IOP change in the subsequent eye (A3 – (A1 + A2) / 2), and adjusted IOP change in the subsequent eye (A3 – [A1 + A2] / 2) – (B3 – B2). As previous studies have recommended measuring multiple baseline IOPs, the average of A1 and A2 was considered as the baseline IOP of the subsequent eye during the binocular phase [8,9]. Distributions of all variables were examined for normality using the Kolmogorov Smirnov 1-sample test. The baseline IOP, spherical equivalent (spherical refractive error +1/2 cylindrical refractive error in the negative form), visual field indices, and central corneal thickness of the initial eye and subsequent eye were compared by paired t-test or Wilcoxon signed rank test. Because the purpose of the present study was to evaluate the predictive value of baseline IOP, unadjusted IOP change, and adjusted IOP change, multivariate linear regression analysis was performed to determine the predictors of IOP response in both eyes. To evaluate the predictors of the initial eye, B3 was considered as the dependent variable, and B1, B2 – B1, and (B2 – B1) – (A2 – A1) were considered as independent variables. On the other hand, A3 was set as the dependent variable for evaluation of predictors of the subsequent eye, and (A1 + A2) / 2, B2 – B1, and (B2 – B1) – (A2 – A1) were considered as independent variables. The clinical value of significance was set at $p < 0.05$ for all analyses.
Seventy-four Korean NTG patients with no history of glaucoma medication usage were considered during the study period. Among them, 31 patients (41.9%) were included in the study. Others were excluded due to asymmetric diurnal variation in baseline IOP (5 patients, 6.8%), insufficient response to the drug (7 patients, 9.5%), missing more than 25% of total doses based on the patient’s own admission (8 patients, 10.8%), administration of eye drops to the wrong eye or both eyes in the monocular phase (2 patients, 2.7%), cessation of eye drops owing to side effects such as conjunctival injection and stinging sensation (3 patients, 4.1%), not measuring IOP by the same examiner (1 patient, 1.3%), and failure to measure the IOP at the indicated time or day during the monocular or binocular treatment phases (17 patients, 23.0%).

The characteristics of the 31 patients are listed in Table 1. Among the 31 patients, 19 were male (61.3%) and 12 were female (38.7%). The mean age of the patients was 55.13 ± 12.99 years (range, 22 to 82 years). There were no significant differences in spherical equivalent or central corneal thickness between the initial eye and subsequent eye; whereas, visual field indices of the initial eye were worse than those of the subsequent eye (Table 1). The baseline IOP values of both eyes are shown in Table 2. The difference between the two eyes was equal to or less than 2 mmHg at each of the four measurements. The IOP of the initial eye was equal to or greater than that of the contralateral eye (paired t-test) (Table 2).

The Kolmogorov-Smirnov test showed that all of the IOP variables used in this study fulfilled the requirements for parametric statistics (p > 0.05). The effect of multicollinearity was not significant (variance influence factors of all variables were less than 10). The amount of IOP reduction at each treatment phase is listed in Table 3, and predictors of IOP response in the initial eye and subsequent eye are listed in Table 4. The most significant predictors for IOP response in the initial eye and subsequent eye were baseline IOPs in both eyes (β = 0.907, 0.771, respectively); eyes with a higher baseline IOP had greater IOP response. The adjusted IOP change in the initial eye had greater association (β = 0.589) with the IOP after a monocular trial in the initial eye than that of unadjusted IOP change (β = 0.279). The adjusted IOP change of the initial eye also had greater predictability (β = 0.348) for IOP after a monocular trial in the subsequent eye than that of unadjusted IOP change (β = 0.090).

### Table 1. Patient characteristics

|                        | Mean ± SD (n = 31) | p-value |
|------------------------|--------------------|---------|
| Age (yr)               | 55.13 ± 12.99      |         |
| Female / male (%)      | 12 / 19 (38.7 / 61.3) | 0.427*  |
| Refractive error (diopter) |                  |         |
| Initial eye            | -1.76 ± 1.95       |         |
| Subsequent eye         | -1.67 ± 1.99       |         |
| Central corneal thickness (µm) |              | 0.156†  |
| Initial eye            | 533.29 ± 28.22     |         |
| Subsequent eye         | 535.87 ± 26.10     |         |
| MD (dB)                |                    | <0.001† |
| Initial eye            | -3.95 ± 2.33       |         |
| Subsequent eye         | -3.12 ± 1.73       |         |
| PSD (dB)               |                    | <0.001† |
| Initial eye            | 4.10 ± 2.51        |         |
| Subsequent eye         | 3.05 ± 1.44        |         |

MD = mean deviation, PSD = pattern standard deviation.
*Paired t-test between initial eye and subsequent eye; †Wilcoxon signed rank test between initial eye and subsequent eye.

### Table 2. Baseline intraocular pressure of the initial eye and the subsequent eye

| Time   | Initial eye (n = 31) | Subsequent eye (n = 31) | p-value* |
|--------|----------------------|-------------------------|----------|
| 10:00  | 15.96 ± 2.82         | 15.32 ± 2.68            | 0.003    |
| 12:00  | 16.00 ± 2.70         | 15.69 ± 2.71            | 0.118    |
| 14:00  | 15.92 ± 2.64         | 15.27 ± 2.63            | 0.004    |
| 16:00  | 16.54 ± 2.82         | 15.71 ± 2.54            | 0.001    |

Values are presented as mean ± SD (mmHg).
*Paired t-test.
The American Academy of Ophthalmology’s Preferred Practice Pattern for Primary Open-Angle Glaucoma recommends the use of a monocular drug trial when starting a new topical glaucoma medication [13]. However, the efficacy of a monocular drug trial in the clinical setting continues to be debated. Smith and Wandel [14] described the ideal situations for a monocular drug trial: “1) Both eyes have the same IOP at the beginning of the trial. 2) Both eyes have the same diurnal IOP curve; 3) medication applied to one eye does not influence the IOP of the other eye, to a degree sufficient to influence the IOP of the other eye, to influence judgment of therapeutic efficacy.” Therefore, to evaluate the efficacy of a monocular drug trial, pretreatment diurnal IOP measurement is needed to achieve patient-specific information about symmetry and variability. To minimize the contralateral effect of topical medication, beta-blockers, known to have contralateral effects, should be avoided [15].

In the present prospective study, only eyes with NTG and no history of previous glaucoma treatment were included. Further, only latanoprost 0.005% was used for the treatment, and baseline IOPs at four different time points were recorded to identify symmetric diurnal IOP changes.

Lastly, both unadjusted and adjusted IOP changes were estimated at a similar time of day during the monocular and binocular treatment phases. According to the present study, the adjusted change in the IOP of the initial eye had greater association with the IOP after a monocular trial in the initial eye, as well as greater predictability for IOP after a monocular trial in the subsequent eye, compared to that of the unadjusted IOP change. These results highlight the efficacy of a monocular drug trial in eyes with NTG. This is the first prospective study demonstrating the efficacy of a monocular drug trial in eyes with NTG.

The Ocular Hypertension Treatment Study (OHTS) reported that the variability of IOP measurements within the same eye was greater than the variability of IOP measurements between the eyes [16]. That is, the contralateral eye can serve as a better control for IOP variability than the same eye treated, and therefore adjusted IOP changes can diminish the variability of IOP measurements more than can unadjusted IOP changes. The results of the OHTS may explain why adjusted IOP changes had greater predictability than unadjusted IOP changes for the evaluation of IOP response in our study.

Previous studies evaluated the efficacy of a monocular drug trial with various types of glaucoma and different methods. A retrospective study by Dayanir et al. [4] re-

### Table 3. The amount of IOP reduction after the monocular trial

| Phase (n = 31) | IOP (mmHg) |
|---------------|------------|
| Baseline IOP of the initial eye (at visit 1): B1 | 16.23 ± 2.69 |
| Monocular (at visit 2) | |
| Unadjusted IOP change of the initial eye: (B2 – B1) | -3.94 ± 1.95 |
| Adjusted IOP change of the initial eye: (B2 – B1) – (A2 – A1) | -3.55 ± 1.63 |
| Baseline IOP of the subsequent eye (at visit 1 & 2): (A1 + A2) / 2 | 15.32 ± 2.60 |
| Binocular (at visit 3) | |
| Unadjusted IOP change of the subsequent eye: A3 – (A1 + A2) / 2 | -3.13 ± 2.04 |
| Adjusted IOP change of the subsequent eye: (A3 – [A1 + A2] / 2) – (B3 – B2) | -2.81 ± 1.83 |

Values are presented as mean ± SD.
IOP = intraocular pressure; B = initial eye; A = subsequent eye; 1 = baseline visit; 2 = visit after the monocular phase; 3 = visit after the binocular phase.

### Table 4. Predictors of intraocular pressure response in the initial eye and the subsequent eye

| | Initial eye (R² = 0.637) | Subsequent eye (R² = 0.514) |
|-----------------|---------------------------|-----------------------------|
| | Standardized β | p-value* | Standardized β | p-value* |
| Baseline IOP (B1 and [A1 + A2] / 2) | 0.907 | <0.001 | 0.771 | <0.001 |
| Unadjusted IOP change in the initial eye (B2 – B1) | 0.279 | 0.252 | 0.090 | 0.730 |
| Adjusted IOP change in the initial eye ([B2 – B1] – [A2 – A1]) | 0.589 | <0.001 | 0.348 | 0.015 |

IOP = intraocular pressure; B = initial eye; A = subsequent eye; 1 = baseline visit; 2 = visit after the monocular phase.
*Multivariate linear regression.

### Discussion

The American Academy of Ophthalmology’s Preferred Practice Pattern for Primary Open-Angle Glaucoma recommends the use of a monocular drug trial when starting a new topical glaucoma medication [13]. However, the efficacy of a monocular drug trial in the clinical setting continues to be debated. Smith and Wandel [14] described the ideal situations for a monocular drug trial: “1) Both eyes have the same IOP at the beginning of the trial. 2) Both eyes have the same diurnal IOP curve; 3) medication applied to one eye does not influence the IOP of the other eye, to a degree sufficient to influence the IOP of the other eye, to influence judgment of therapeutic efficacy.” Therefore, to evaluate the efficacy of a monocular drug trial, pretreatment diurnal IOP measurement is needed to achieve patient-specific information about symmetry and variability. To minimize the contralateral effect of topical medication, beta-blockers, known to have contralateral effects, should be avoided [15].

In the present prospective study, only eyes with NTG and no history of previous glaucoma treatment were included. Further, only latanoprost 0.005% was used for the treatment, and baseline IOPs at four different time points were recorded to identify symmetric diurnal IOP changes.
ported that there was a significant correlation of the IOP response in the initial eye (adjusted IOP change) and that of the subsequent eye (unadjusted IOP change) in patients with high tension glaucoma, whereas this relationship was not significant in patients with normal tension glaucoma. Another retrospective study documented that a correlation between the two eyes was higher when using adjusted IOP changes [5]. Chaudhary et al. [6] retrospectively analyzed the correlation of unadjusted and adjusted IOP changes in eyes with primary open-angle glaucoma and suspected glaucoma, and the correlation was stronger when using adjusted changes. The results of these studies are in line with the present study in terms of adjusting IOP change.

On the other hand, in normal individuals, the contralateral eyes did not respond symmetrically to a monocular drug trial according to the unadjusted IOP change or the adjusted IOP change [7]. Another study reported that the best predictors of post-treatment IOP of the trial eye and the contralateral eye were the baseline IOP and unadjusted IOP change, not the adjusted IOP change [8]. Their study also demonstrated that monocular and binocular trials had similar predictive value. Recently, Realini [9] performed a prospective, randomized evaluation of the monocular drug trial in patients with ocular hypertension or open-angle glaucoma. According to the analysis, neither the unadjusted IOP change in the initial eye nor the adjusted IOP change in the initial eye showed a significant correlation with long-term (unadjusted) IOP change in the subsequent eye. The differences between these studies and the present study may be attributed to the differences in methodology or diagnosis of the participants.

There are controversies with regard to the statistical methodology used in the analysis of monocular trials [17]. Based on the definition of adjusted IOP change in previous studies, analyzing correlations between the adjusted IOP of the eye initially treated [(B2 – B1) – (A2 – A1)] and the adjusted IOP of the subsequent eye [(A3 – A2) – (B3 – B2)] could have artificial effects because both values include ‘B2 – A2’ or ‘minus A2.’ To exclude this artificial effect, we performed multivariate analysis as described in Leffler and Amini’s methods [8], and used (A1 + A2) / 2 as the baseline IOP of the subsequent eye, as suggested by previous studies [8,9]. However, measuring the baseline IOP of the initial eye one time only and a relatively small number of patients remain limitations of the present study.

From a practical point of view, it may be difficult to meet the stringent conditions of the monocular drug trial applied in our study. In the present study, a large number of patients were excluded because they did not meet the requisite criteria. We think that to evaluate the efficacy of something, its conditions should be stringently upheld. To date, no study has met all the criteria of the monocular trial, which is why we excluded many patients who did not meet our conditions. Our high exclusion rate may be a limitation of the monocular trial and an explanation of why the monocular trial is not universally being performed despite being recommended [13].

In the present study, among the 74 NTG patients, 7 (9.5%) exhibited an insufficient response (less than 15% of IOP reduction). According to the study results of the Latanoprost Study Group, the percentage of non-responders to latanoprost was 10%. However, it is difficult to compare the rate of that study with ours because they evaluated only unadjusted IOP, and the baseline IOP (24.4 ± 0.3 mmHg) observed was higher than in our study [12]. In the present study, we excluded eyes with an adjusted IOP reduction less than 15% after one week of administering the eye drops in one eye. Camras et al. [12] also used this cut-off value to evaluate the percentage of non-responders. When considering if a portion of non-responders would be converted to responders as the treatment period continues, as in the Latanoprost Study Group, a study protocol with a longer monocular phase would be better. However, we are not sure whether it would affect the study results because only 7 patients (9.5%) were excluded owing to insufficient IOP reduction during the monocular trial, and the IOP changes after one week were reported as minimal [18,19].

In conclusion, although the monocular trial in NTG patients had limited efficacy due to its stringent conditions, it seems to be a useful method for evaluating IOP response in the initial eye and for predicting IOP response in the subsequent eye.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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