ORIGINAL RESEARCH

Effect of travoprost on 24-hour intraocular pressure in normal tension glaucoma

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Purpose: The effect of travoprost 0.004% on 24-hour intraocular pressure (IOP) was examined in patients with normal tension glaucoma (NTG).

Subjects and methods: This study included 17 patients with newly diagnosed unilateral NTG. IOP was measured at three-hour intervals over 24 hours by Goldman applanation tonometer in patients taking topical travoprost 0.004% and was compared retrospectively with 24-hour IOP data in untreated eyes.

Results: IOP values were significantly reduced at individual time points after treatment ($P < 0.01$). Mean 24-hour IOP, maximum 24-hour IOP, minimum 24-hour IOP, and 24-hour IOP fluctuations at baseline (mean $\pm$ SD) were 12.9 ± 2.2 mmHg, 15.4 ± 2.7 mmHg, 10.5 ± 2.2 mmHg, and 4.9 ± 1.2 mmHg, respectively, and were significantly reduced to 10.3 ± 2.0 mmHg, 12.4 ± 2.5 mmHg, 8.5 ± 1.9 mmHg (all $P < 0.001$), and 3.9 ± 1.5 mmHg ($P < 0.05$), respectively, after treatment. The rate of IOP reduction greater than 20% was 58.8% (10 eyes) for maximum 24-hour IOP and 53.0% (nine eyes) for mean 24-hour IOP.

Conclusion: Travoprost reduced IOP throughout the 24-hour study period, with over half of the eyes examined showing IOP reduction exceeding 20%.

Keywords: 24-hour intraocular pressure, fluctuation, normal tension glaucoma, travoprost, Travatan Z

Introduction

Elevated intraocular pressure (IOP) is a primary risk factor for the development of glaucoma. However, some patients develop glaucomatous damage to the optic nerve in the absence of elevated IOP, known as normal tension glaucoma (NTG). The importance of lowering IOP to reduce the progression of glaucomatous damage was demonstrated by the Collaborative Normal Tension Glaucoma (CNTG) study group which showed that lowering IOP by 30% from baseline reduces the risk of progression of visual field loss in NTG patients. However, 12% of treated patients progressed during five years of follow-up versus 35% of an untreated group.[1,2]

The Early Manifest Glaucoma Trial (EMGT) indicated that IOP fluctuation is not a risk factor for the progression of glaucoma.[3] However, some reports have shown that circadian IOP, diurnal IOP fluctuation, and maximum diurnal IOP are also important factors influencing the progression of glaucoma.[4-6] IOP fluctuation remains a controversial issue that has not yet been resolved. However, present management of NTG involves achieving the best possible reduction in IOP over a 24-hour period.

Once patients begin to use antiglaucoma eye drops, their IOP curve is altered, and estimation of maximum IOP becomes difficult. Wilensky et al[7] conducted a

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study of 24-hour IOP measured with a home tonometer in patients with well-controlled IOP and found that a half of the maximum IOP measurements were obtained outside of clinic hours. This study shows the importance of measuring IOP throughout a 24-hour period.[7,8]

Prostaglandin analogs can strongly reduce IOP compared with beta-blockers or carbonic anhydrase inhibitors.[9,10] Latanoprost 0.005% and bimatoprost 0.03%, both prostaglandin analogs, are effective in reducing IOP in NTG patients.[10–13] Another prostaglandin analog, travoprost 0.004%, has been shown to be equivalent in the reduction of IOP in primary open angle glaucoma and ocular hypertension.[9,14–16] However, only two reports have investigated the effect of travoprost on NTG.[17,18] Suh et al[17] reported the effect of travoprost on clinic IOP measurements in patients with NTG over a 12-month period, and Ang et al[18] reported the effect of travoprost on daytime IOP in NTG patients. Neither group measured changes in IOP overnight in NTG patients. To the best of our knowledge, the present study is the first to evaluate the effect of travoprost 0.004% on 24-hour IOP in NTG patients.

Subjects and methods

The study group comprised 17 newly diagnosed patients with unilateral NTG treated with travoprost 0.004% in one eye for one to two months. The patients were admitted to Osaka City University Hospital between January 2008 and October 2008 to evaluate their 24-hour IOP whilst receiving topical travoprost 0.004%.

All patients agreed to undergo 24-hour IOP measurements and signed informed consent forms in accordance with the Declaration of Helsinki. A complete slit examination, gonioscopic evaluation, and dilated fundus examination were performed by glaucoma specialists in the clinic. Visual acuity, visual field tests (Humphrey 30-2 or 24-2 SITA program, Humphrey Field Analyzer, Carl Zeiss Meditec, Dublin, CA), and measurement of central corneal thickness by specular microscope (SP-3000P, Topcon, Tokyo) were also conducted. A diagnosis of NTG was made if criteria were fulfilled for glaucomatous optic disc change, the presence of visual field defects typical of glaucoma, and both clinic and untreated 24-hour IOP were <21 mmHg. Patients with congenital, secondary, or narrow angle glaucoma, ocular inflammation, a severe corneal disorder, or a history of ocular surgery were excluded.

During hospitalization, IOP was measured in patients in the sitting position with a Goldmann applanation tonometer at three-hour intervals from midnight to 9:00 am by the same doctor. Patients self-administered travoprost 0.004% to the treated eye at night in their usual manner. For nighttime measurements, patients were gently awakened and walked 10–20 meters to the tonometer. Immediately after IOP measurement, patients returned to their beds. Mean 24-hour IOP was determined as the mean of the eight IOP measurements recorded. Fluctuation in 24-hour IOP was calculated as the difference between maximum 24-hour IOP and minimum 24-hour IOP. Clinic IOP was measured between 10:00 am and 6:00 pm at approximately the same time for each patient.

We used Travatan Z™ ophthalmic solution 0.004% (Alcon Japan Limited, Tokyo), which is the prostaglandin analog product without benzalkonium chloride (BAK) and which has a similar IOP reduction efficacy and safety profile as does travoprost with BAK.[19] Each patient's 24-hour IOP data following administration of travoprost were retrospectively compared with their 24-hour IOP data obtained in the same manner from the same untreated eye at one to two months prior to treatment.

Statistical analysis

Values are shown as means ± standard deviation (SD). We used the paired t-test to analyze the differences between IOP at individual time points before and after treatment for both eyes, maximum 24-hour IOP, minimum 24-hour IOP, clinic IOP, and 24-hour IOP fluctuation before and after treatment in the treated eye. Paired t-tests and *post hoc* testing (Bonferroni correction) were used to analyze differences between the different time points of each IOP curve (treated eye and fellow eye before and after treatment). A *P* value of <0.05 was considered statistically significant.

Results
Patients

We included 17 newly diagnosed unilateral NTG patients in the present study (right eye, n = 6; left eye, n = 11). The patients comprised nine men and eight women with a mean age of 63.1 ± 14.3 (range 31–81) years. Average central corneal thickness for both eyes was 515.8 ± 34.6 μM. Mean deviation was −7.3 ± 3.3 dB (range −3.3–15.0) in the treated eyes. Data for 24-hour IOP in both eyes are shown in Table 1. At all individual time points, IOP was significantly decreased after travoprost treatment in the treated eye (*P* < 0.01, Figure 1). There were no significant reductions in IOP at each time point in untreated fellow eyes (*P* > 0.05, Figure 2).

Multiple comparisons between IOP curves

Before treatment, there was a significant difference in IOP curves between 9:00 am and 12 pm, 12 pm and 9:00 pm,

Table I Mean baseline and post-treatment IOP values

	Treated eye		Untreated fellow eye	
	Baseline	Travoprost	Before	After
9:00 am	12.6 ± 2.5	10.4 ± 1.9	11.9 ± 2.2	12.4 ± 2.4
12:00 pm	14.5 ± 2.6	11.0 ± 2.3	13.5 ± 2.5	13.5 ± 2.9
3:00 pm	13.4 ± 2.7	10.4 ± 2.2	12.5 ± 2.6	12.5 ± 2.7
6:00 pm	13.7 ± 2.6	10.3 ± 2.0	12.7 ± 2.4	12.8 ± 2.4
9:00 pm	12.0 ± 2.4	9.4 ± 2.6	11.5 ± 2.0	11.4 ± 2.7
12:00 am	12.2 ± 3.2	10.41 ± 2.9	11.8 ± 2.3	11.9 ± 2.9
3:00 am	12.5 ± 3.4	10.3 ± 2.8	12.1 ± 2.6	11.3 ± 2.8
6:00 am	12.8 ± 2.2	10.5 ± 2.4	12.2 ± 2.6	11.5 ± 2.7

Values indicate mean mmHg ± SD.
Abbreviations: IOP, intraocular pressure; SD, standard deviation.

12:00 pm and 12:00 am, and 12:00 pm and 3:00 am in the treated eye, and between 12:00 pm and 9:00 pm and 12:00 pm and 12:00 am in the untreated eye. After treatment, there was no significant difference in IOP curves between these times in the treated eyes. However, there was a significant difference in IOP curves between 12:00 pm and 12:00 am, 12:00 pm and 3:00 am, and 12:00 pm and 6:00 am in the untreated eye.

Clinic IOP was reduced by 24.3% (from 14.8 ± 2.7 mmHg to 11.2 ± 2.4 mmHg, $P < 0.001$). Mean 24-hour IOP was reduced by 20.2% (from 12.9 ± 2.2 mmHg to 10.3 ± 2.0 mmHg, $P < 0.001$). Maximum 24-hour IOP decreased 19.5% (from 15.4 ± 2.7 mmHg to 12.4 ± 2.5 mmHg, $P < 0.001$), and minimum 24-hour IOP was reduced by 19.0% (from 10.5 ± 2.2 mmHg to 8.5 ± 1.9 mmHg, $P < 0.001$). Fluctuation in 24-hour IOP was flattened by 20.4% (from 4.9 ± 1.2 mmHg to 3.9 ± 1.5 mmHg, $P < 0.05$, Table 2).

The percentage reduction of each parameter in the treated eye is shown in Table 3. The rate of >30% reduction in maximum 24-hour IOP was 23.5% and in mean 24-hour

IOP was 11.8%. The rate of >20% reduction was 58.8% in maximum 24-hour IOP and 53.0% in mean 24-hour IOP. Categorization as a travoprost nonresponder (TNR), defined as a mean 24-hour IOP reduction <10%, occurred in two eyes (11.8%). No serious treatment-related adverse events were observed in this study, and any adverse events that did occur were mild and controllable.

Discussion

The present study is the first to show the effect of travoprost on 24-hour IOP in NTG patients. In this study, the rate of IOP reduction was 20.2% for mean 24-hour IOP, 19.5% for maximum 24-hour IOP, and 20.4% for 24-hour IOP fluctuation. The results of this study indicate that travoprost can reduce IOP throughout a 24-hour period and flatten the IOP curve.

In the present study, travoprost reduced clinic IOP by 24.3%. In previous studies, IOP reduction by latanoprost 0.005% and bimatoprost 0.03% in NTG has been reported to be in the range of 12.7% to 20% and 16% to 21.6%, respectively.[10,13,20,21] Travoprost 0.004% has been reported to have similar results (16.7% to 25.1%).[17,18] Our results are in accordance with the results of these previous studies.

Ang et al[18] published the only report showing the effect of travoprost on daytime IOP in NTG. These authors reported a mean IOP reduction of 16.1%, a maximum IOP reduction of 13.5%, a 43% rate of >20% IOP reduction, and a 30% rate of <10% IOP reduction (considered as TNR) in both mean and maximum IOP. These findings are considerably worse than our results. We suspect that this disparity may be due to measurement of daytime IOP only and that maximum and minimum IOP may have changed outside of daytime hours in the earlier study.[7,8] Another possible explanation
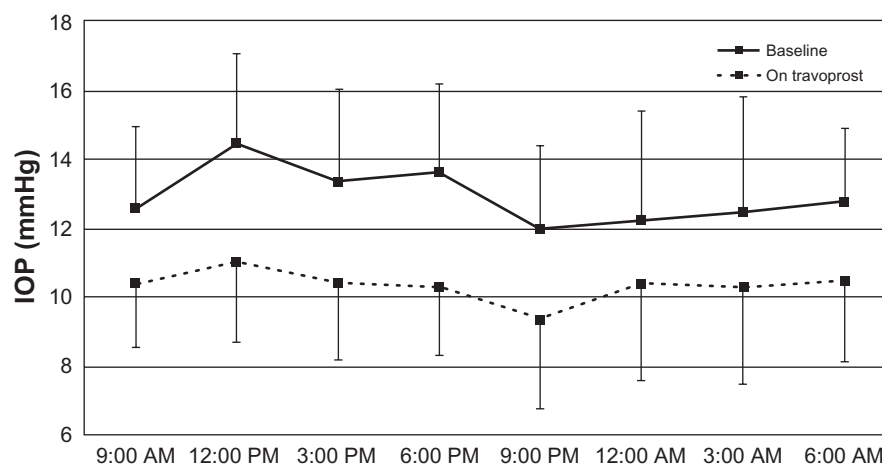

Figure I IOP measurements from the travoprost-treated eye over 24 hours. There is a significant reduction in IOP at each time point ($P < 0.01$). The 24-hour IOP curve also shifted toward a lower IOP.
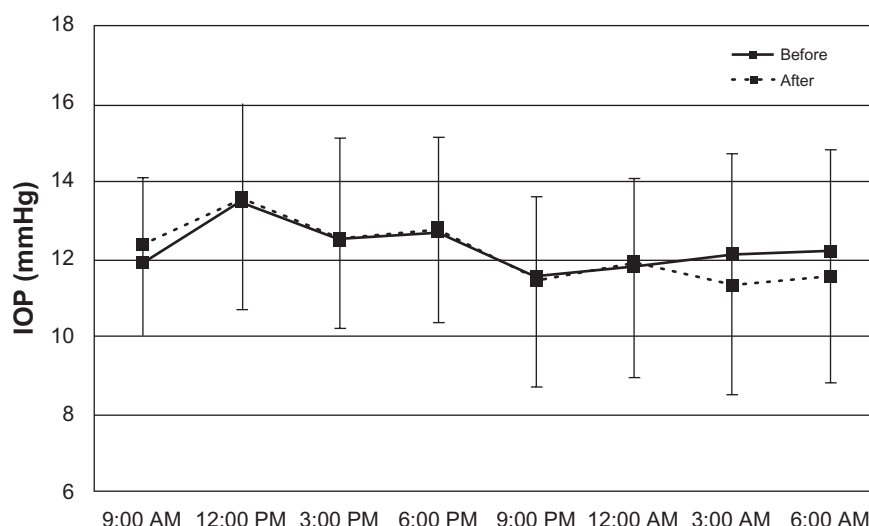**Abbreviation:** IOP, intraocular pressure.

Figure 2 IOP measurements from the fellow eye over 24 hours. There is no significant IOP reduction at each time point ($P > 0.05$).
Abbreviation: IOP, intraocular pressure.

is that the earlier investigators included both eyes in their study, which may have led to a TNR double-counting error. Additionally, 96% of their patients were Caucasians. Netland et al[22] reported that travoprost is more effective in blacks than nonblacks, so patient race might influence this result. Furthermore, Suh et al[17] reported the effect of travoprost 0.004% during 12 months of treatment and noted that IOP reduction was evident at one month; however, a slight increase in IOP occurred between nine and 12 months. Almost all of our data were obtained within a one- to two-month period after the beginning of travoprost treatment, whereas the data from the study by Ang et al were obtained at six months.[18]

Achievement of an IOP reduction greater than 30% as recommended by the CNTG study group is very difficult using a single, topical antiglaucoma eye drop.[10–13,17,18,20,21] In our study, the rates of 30% IOP reduction are 23.5% for maximum 24-hour IOP and 11.8% for mean 24-hour IOP. When a topical combination therapy is needed to achieve the target reduction in IOP, travoprost without BAK is a superior option because preservatives such as BAK can induce conjunctival inflammation and affect success rates for filtering surgery.[23,24]

However, reduction of IOP alone is considered to be insufficient for the management of NTG. Hemodynamic factors such as ocular perfusion pressure (OPP) are also reported to be important.[25–27] Among the topical antiglaucoma eye drops, the prostaglandin F2-alpha analogs (travoprost, latanoprost, and bimatoprost) and dorzolamide increase OPP, whereas timolol, a beta-blocker, and brimonidine do not.[28–30] Therefore, to investigate the effect of eye drops, both the reduction in IOP and the hemodynamic effects of the medication should be evaluated.

The present study suggests that travoprost reduces IOP throughout a 24-hour period in NTG patients, and an IOP reduction greater than 20% was observed in over half of the eyes examined. However, our study reported short-term results in a small group of patients in whom IOP was measured during only one 24-hour period, and we compared these results retrospectively with untreated 24-hour IOP measurements made one to two months earlier, prior to the started of travoprost. Further long-term, large-scale, prospective studies are needed to compare our findings with the effects of other prostaglandin analogs on 24-hour IOP in NTG.

Table 2 Changes in IOP and percentage change from baseline in the treated eye

	Travoprost	Baseline	IOP reduction (%)	P value
Clinic IOP	11.2 ± 2.4	14.8 ± 2.7	24.3%	<0.001
Mean 24-hour IOP	10.3 ± 2.0	12.9 ± 2.2	20.2%	<0.001
Maximum 24-hour IOP	12.4 ± 2.5	15.4 ± 2.7	19.5%	<0.001
Minimum 24-hour IOP	8.5 ± 1.9	10.5 ± 2.2	19.0%	<0.001
24-hour IOP fluctuation	3.9 ± 1.5	4.9 ± 1.2	20.4%	<0.05

Values indicate mean mmHg ± SD.
Abbreviations: IOP, intraocular pressure; SD, standard deviation.

Table 3 Distribution of percentage change from baseline in the treated eye

	≧30%	20%–29.9%	10%–19.9%	0%–9.9%
Clinic IOP	23.5%	41.2%	23.5%	11.8%
Mean 24-hour IOP	11.8%	41.2%	35.3%	11.8%
Maximum 24-hour IOP	23.5%	35.3%	17.6%	23.5%
Minimum 24-hour IOP	23.5%	17.6%	29.4%	29.4%

Abbreviation: IOP, intraocular pressure.

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