Comparison of the Effects of Latanoprost, Travoprost, and Bimatoprost on Circadian Intraocular Pressure in Patients with Glaucoma or Ocular Hypertension

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Purpose: To compare 24-hour reduction in intraocular pressure (IOP) by latanoprost 0.005%, travoprost 0.004%, and bimatoprost 0.03% in patients with primary open-angle glaucoma (POAG) or ocular hypertension (OH).

Design: Randomized, double-masked, crossover study.

Participants: Twenty-four patients with POAG and 20 with OH.

Methods: Patients were treated with latanoprost, travoprost, and bimatoprost for 1 month. The treatment sequence was randomized, and washout lasted 30 days for each trial drug. Four 24-hour tonometric curves were recorded for each patient: 1 at baseline and 1 after each treatment period.

Main Outcome Measures: Intraocular pressure was measured at 3, 6, and 9 AM; noon; 3, 6, and 9 PM; and midnight by 2 treatment-masked well-trained evaluators using a handheld electronic tonometer with the patient in supine and sitting positions and a Goldmann applanation tonometer with the patient sitting at the slit lamp. Supine systemic blood pressure was recorded at the same times. A randomized-blocks analysis of variance was used to analyze data.

Results: All 3 drugs were highly effective in reducing IOP when compared to baseline. Mean IOP reductions were similar after the 3 prostaglandin analogs, and none of the differences among treatments reached statistical significance. The drugs' effect was significantly greater during the daytime (9 AM–9 PM) than during the nighttime (midnight–6 AM) with all prostaglandin analogs. In 7 of 44 patients (16%), nocturnal IOP was significantly higher than diurnal IOP, both at baseline and under the 3 prostaglandin analogs.

Conclusions: From a clinical point of view, the overall results seem to indicate that the 3 prostaglandin analogs are powerful agents in controlling round-the-clock IOP in POAG and OH patients. *Ophthalmology 2006; 113:239–246 © 2006 by the American Academy of Ophthalmology.*

Primary open-angle glaucoma (POAG) is a severe disease causing blindness in about 7 million people worldwide.[1] From the beginning of medical treatment of the disease, the reduction of intraocular pressure (IOP) has represented the only way of slowing the progression of glaucoma.[2,3] This has long been done mainly by means of topical β-blockers,[3–6] and only recently have more powerful drugs, belonging to the class of prostaglandin analogs,[7–16] played an increasingly important role in the medical management of the disease.

The 3 new prostaglandin analogs latanoprost, travoprost, and bimatoprost have been shown to decrease IOP in POAG patients and in subjects with ocular hypertension (OH) to a greater extent than β-blockers.[17–24] Conflicting results have been reported in the Parrish and Noecker trials[25,26] when comparing effects of the prostaglandin analogs. In Noecker et al's study,[26] bimatoprost was found significantly more effective than latanoprost at 8 AM, noon, and 4 PM. On the other hand, in the Parrish et al trial[25] the 3 prostaglandin analogs were found comparable in their ability to reduce IOP. Moreover, the IOP-lowering effect has been evaluated till now only in the diurnal curve, and more data would be needed for the nighttime, also in consideration of the importance of this period for progression of POAG.[27–39] In a recent study, Konstas et al[40] compared 24-hour efficacies of bimatoprost and latanoprost in lowering IOP in POAG patients. This study found that bimatoprost was more effective than latanoprost at 6 PM.

The aim of this study was to compare the 24-hour IOP curve in a sample of POAG and OH patients treated with latanoprost, travoprost, and bimatoprost in a randomized, double-masked, crossover trial. To the best of our knowledge (after a Medline search, updated February 2005), this is the first direct comparison of the IOP-lowering effects of these 3 drugs over a 24-hour period.

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None of the authors has any proprietary interest in any of the drugs or instruments used in the trial.

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Materials and Methods

The method used to evaluate the 24-hour curves is described in detail in our previous articles.[28,33] A summary of the procedures follows. This study was carried out on patients diagnosed as having POAG or OH. To be included, glaucoma patients had to have an IOP of >21 mmHg without medication (in at least one eye and measured on 2 consecutive occasions separated by an interval of at least 2 hours but not more than 12 weeks), glaucomatous field (on the basis of at least 2 reliable Humphrey 30-2 full-threshold tests), or optic disc changes (evaluated by means of color stereophotographs) or retinal nerve fiber layer (RNFL) defects (evaluated by means of a scanning laser ophthalmoscope). Patients with OH had to have an IOP of >21 mmHg without medication (measured as above), and a normal visual field (VF), optic disc, and RNFL. The diagnosis was agreed upon by 2 of the authors (NO, LR).

Exclusion criteria included a baseline untreated IOP of >30 mmHg confirmed on 2 occasions within 1 week, angle-closure glaucoma, corneal abnormalities preventing reliable IOP measurement, previous filtration surgery, life-threatening or debilitating disease, secondary causes of elevated IOP, having a single eye, and pregnancy. Patients treated with any prostaglandin analog were not considered for inclusion in this study. Significant disturbances of wake–sleep rhythms and/or the regular assumption of hypnotic drugs reported by the patients were also considered reasons for exclusion.

The trial had a crossover design, with patients on medical treatment undergoing a 4-week washout before their baseline circadian tonometric curve was recorded. Informed consent was obtained before starting the drug washout. The study adhered to the tenets of the Declaration of Helsinki.

Patients were randomized to receive one of the following treatment sequences: (1) A, B, C; (2) A, C, B; (3) B, A, C; (4) B, C, A; (5) C, A, B; and (6) C, B, A, where A is latanoprost 0.005% (Xalatan, Pfizer, New York, New York); B, travoprost 0.004% (Travatan, Alcon, Fort Worth, TX); and C, bimatoprost 0.03% (Lumigan, Allergan, Irvine, CA). Randomization was obtained using a list of random numbers. Patients were given the masked bottles and instructed to instill the eyedrops once daily at 9 PM. Duration of treatment with each trial drug was 1 month, after which a circadian tonometric curve was recorded. All treatment periods were followed by a drug washout lasting 1 month. A total of 4 circadian tonometric curves were therefore obtained for each patient: 1 baseline and 3 different treatment curves.

To record the circadian tonometric curves, the patients were hospitalized in the morning (at 7 AM) and stayed for the following 24 hours. They were also given an ad hoc questionnaire designed to assess their reaction to hospitalization, anxiety due to measurements, quality of sleep, etc. The awake period lasted from approximately 6:30 AM to 11 PM. Intraocular pressure was measured at 3, 6, and 9 AM; noon; 3, 6, and 9 PM; and midnight. During hospitalization, drugs were administered by the study personnel according to the protocol. For the daytime measurements (9 AM–9 PM), patients were asked to go to bed and relax for about 15 minutes, after which supine IOP was measured in both eyes. Subsequently, their blood pressure (BP) was assessed, and patients were then asked to sit on the bed while ocular pressure was measured again after an average of 5 to 10 minutes from the first IOP recording. Then a third IOP value was measured at the slit lamp. The IOP measurements were made using a handheld electronic tonometer (TonoPen XL, Bio-Rad, Glendale, CA) with the patient in supine and sitting positions and a Goldmann applanation tonometer with the patient sitting at the slit lamp. All measurements were taken at each time point at least twice by 2 well-trained glaucoma specialists. If the measurements differed by >2 mmHg, a third measurement was taken. The mean of 2 or the median of 3 recordings was used for analysis.

The study outcome was the difference in IOP values between the groups. If both eyes were eligible, only one eye (chosen at random) was used for analytical purposes.

The sample size calculation was based on the assumption that a difference in mean IOP of 1.5 mmHg is clinically relevant. About 40 patients were needed given an α of 0.05, $1-\beta$ of 0.90, and standard deviation (SD) of 3 mmHg. A statistical power of 90% was chosen to reduce the risk of a false-negative result. A randomized-blocks analysis of variance (ANOVA), treatment by period, was used to analyze data. In this type of analysis, the between-subjects variance comes from the time period, whereas the within-subjects variance comes from time of measurement, type of treatment, and interactions. Analysis of proportions was performed by means of the Fisher exact test. All analyses were performed using GB-STAT software (Dynamic Microsystems Inc., Silver Spring, MD).

Results

Forty-four patients were included in the trial. Their main characteristics are shown in Table 1. All patients completed the 3 crossover phases, and no major adverse event was recorded.

Figure 1 shows the circadian Goldmann tonometer IOP curves recorded at baseline and after latanoprost, travoprost, and bimatoprost treatment: all of the drugs significantly reduced IOP at all time points. The mean (± SD) IOP values were 21.9±3.4 mmHg at baseline, 16.2±3.2 on latanoprost, 15.9±3.1 on travoprost, and 15.3±3.1 on bimatoprost. All drugs obtained mean IOPs significantly lower than those at baseline, though none of the differences in mean IOP among treatments reached statistical significance (Table 2).

Results of the randomized-blocks ANOVA are summarized in Table 3. The only significant source of variation was the time of IOP measurement ($P<0.0001$), whereas time period, type of prostaglandin analog, and interactions were not statistically significant sources of variation. Goldmann IOP recordings were used for this analysis.

The drugs' effect was significantly greater during the daytime, and in comparison with baseline, the mean diurnal (9 AM–9 PM) versus nocturnal (midnight–6 AM) reductions in IOP were, respectively, 6.7±2.8 and 3.7±3.1 mmHg for latanoprost ($P = 0.02$),

Table 1. Patients' Main Characteristics

Total	44
POAG	24
OH	20
Age (yrs) [mean (SD)]	71 (±14.2)
Gender	26 female, 18 male
IOP (mmHg) (mean at baseline ± SD)	21.9±3.4
Diurnal (9 AM–9 PM)	23.0±2.9
Nocturnal (midnight–6 AM)	19.8±3.0
Corneal thickness (μm)	554±22
Prestudy therapy	
None	12
β-blockers	24
Dorzolamide	4
Other	4
Systemic hypertension	29
Treated with β-blockers	15
Other treatments	14

SD = standard deviation.

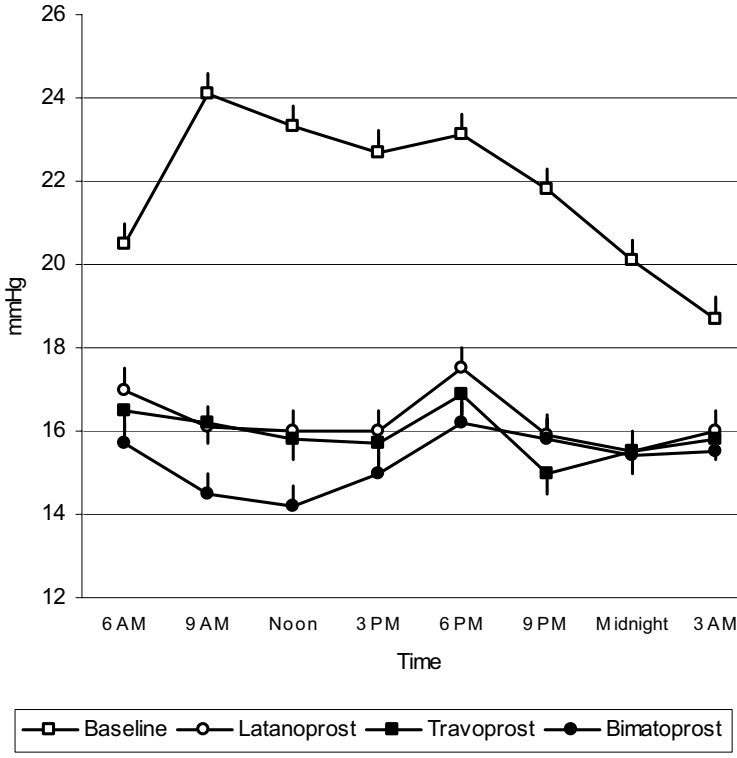

Figure 1. Goldmann tonometer intraocular pressure readings (mean, standard error of the mean).

7.1±3.2 and 3.9±2.9 mmHg for travoprost ($P = 0.03$), and 7.9±3.2 and 4.3±3.0 mmHg for bimatoprost ($P = 0.02$).

Figures 2 and 3 show supine and sitting electronic tonometer measurements, respectively. Shapes of the curves were consistent with those obtained using the Goldmann tonometer. Mean supine position IOPs were higher than Goldmann IOPs, though the difference did not reach statistical significance (Table 4).

Figure 4 shows the distribution of IOP reduction from baseline after latanoprost, travoprost, and bimatoprost. Goldmann IOP data from all 44 patients in the trial were used.

There was good agreement between the sitting Goldmann and electronic tonometer readings ($r = 0.70$), but the electronic tonometer values were higher in the case of the supine measurements. The mean supine and sitting IOP values were, respectively, 22.9±3.5 and 22.0±3.5 mmHg at baseline, 17.2±3.1 and 16.2±3.1 mmHg on latanoprost, 16.9±3.3 and 16.2±2.9 mmHg on travoprost, and 16.4±3.2 and 15.5±3.0 mmHg on bimatoprost (Table 4).

In 7 of 44 patients (5 POAG and 2 OHT [16%]), nocturnal baseline IOP was significantly higher than diurnal baseline IOP ($P = 0.02$). Although IOP was significantly lower after each treatment phase of the crossover as compared with baseline, in all 7 cases nocturnal IOP remained significantly higher during nighttime than during the day. Control for postural effect (i.e., when only TonoPen supine or Goldmann readings were used) did not change the results substantially.

Table 5 reports mean systemic BPs and perfusion pressures under the 3 prostaglandin analogs. Comparisons failed to show any significant difference among study drugs. As expected, perfusion pressures were lower during nighttime with any drugs.

The responses to the questionnaire indicated that the overall quality of the days and nights spent in the hospital for the measurement of circadian IOP curves was normal.

Discussion

The results of this crossover trial clearly indicate that all 3 of the prostaglandin analogs are very effective in reducing IOP in

Table 2. Goldmann Mean (± Standard Deviation) Intraocular Pressures (mmHg)

Time	Baseline	Latanoprost	Travoprost	Bimatoprost
6 AM	20.5±3.0	17.0±3.2	16.5±2.7	15.7±2.9
9 AM	24.1±2.8	16.1±3.0	16.2±2.9	14.5±3.1
Noon	23.3±2.9	16.0±2.9	15.8±3.0	14.2±2.8
3 PM	22.7±3.1	16.0±3.1	15.7±3.2	15.0±3.1
6 PM	23.1±3.0	17.3±2.8	16.9±2.8	16.2±3.0
9 PM	21.8±2.8	15.9±3.1	15.0±3.0	15.8±2.9
Midnight	20.1±2.6	15.5±3.0	15.5±3.0	15.4±2.8
3 AM	18.7±3.1	16.0±2.8	15.8±3.1	15.5±3.0
Total, 44 patients	21.9±3.4	16.2±3.2	15.9±3.1	15.3±3.1

Table 3. Results of Analysis of Variance

Source of Variation	df	*F* Ratio	*P* Value
Time period	2	1.27	0.3 (NS)
Treatment*	2	3.01	0.08 (NS)
Time of IOP measurement†	7	78.2	0.0001
Time period × treatment	4	1.01	0.2 (NS)
Treatment × time of IOP measurement	14	1.15	0.3 (NS)

IOP = intraocular pressure; NS = nonsignificant.
*Latanoprost, travoprost, and bimatoprost.
†Goldmann IOP data (8 time points) were used for analysis.

comparison with baseline, thus confirming the findings of previous studies.[7–26,40] The level of IOP obtained with the 3 drugs was fairly stable throughout the 24 hours, though the drugs' effect was greater during the daytime hours, when baseline IOP was significantly higher. Mean IOP-lowering effects of the 3 prostaglandin analogs were similar. As expected, given the short duration of the study, the drugs were well tolerated. There were some reports of local discomfort and minor side effects, but these were generally mild and did not prevent any of the patients from completing the trial.

In 2 previous articles, latanoprost's 24-hour effect on IOP was shown to be relatively uniform throughout the circadian cycle. Moreover, latanoprost was found to be more effective than timolol and dorzolamide in the first of these studies[33] and to be almost equivalent to the fixed combination of timolol and dorzolamide and superior to brimonidine in the second.[28] In both studies, the efficacy of latanoprost, given in the evening, was slightly but not significantly greater during the day, thus confirming the results of other trials.[41–43] In the present study, all drugs allowed achievement of stable levels of IOP over the 24 hours, though their effect was significantly greater during the day when baseline IOP was higher. The greater effect of these drugs during the daytime may be simply due to the time of administration (prostaglandin analogs are most effective in the 12–18 hours after administration), although other mechanisms have also been suggested.[44–46]

Despite the flaws limiting the value of the 24-hour circadian tonometric curve, nocturnal assessment of IOP has an important role in the management of glaucoma, as fluctuations of IOP seem to be one of the most important risk factors for the progression of the disease[47] and different ocular hypotensive drugs can have different effects on IOP over 24 hours, at least in some patients.[17,28,31,33,42–44]

It is well known that the risk of glaucoma progression is increased, at least in some cases, by the fact that IOP may be higher during the night.[29–32] A series of studies have shown that in sleep laboratory conditions glaucoma IOP peaks in the early morning,[17,30] later than normal IOP in healthy subjects.[38] In the present study, 7 of 44 (16%) patients had significantly higher IOP levels during the night both at baseline and under treatment. Furthermore, the nocturnal decrease in systemic BP may make such values even more critical by decreasing optic nerve head perfusion pressure.[31,35,36] As expected, analysis of perfusion pressures showed lower diastolic perfusion pressures during the night also in this study.

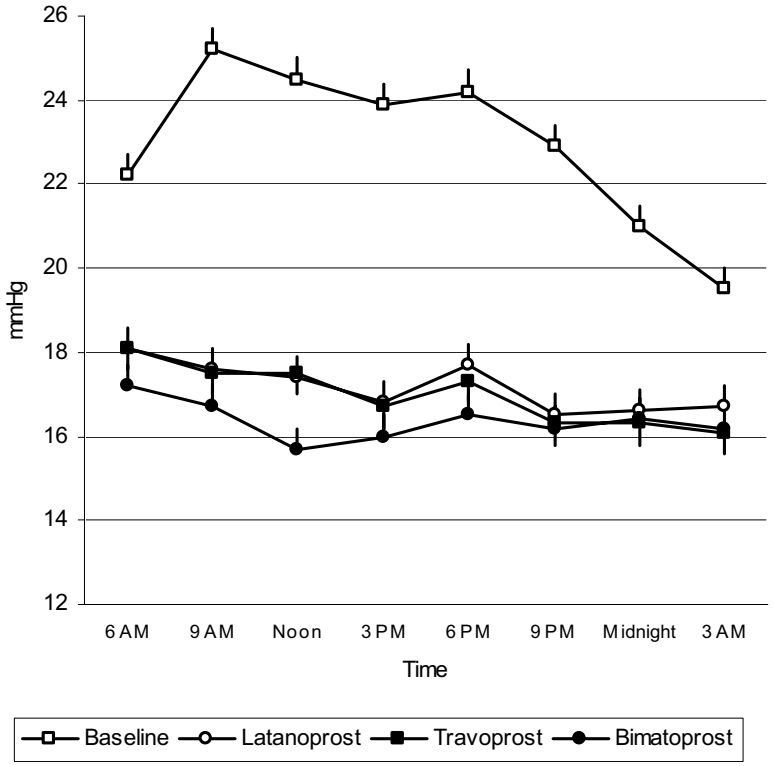

Figure 2. Supine position tonometric readings (TonoPen XL, Bio-Rad, Glendale, CA) (mean, standard error of the mean).

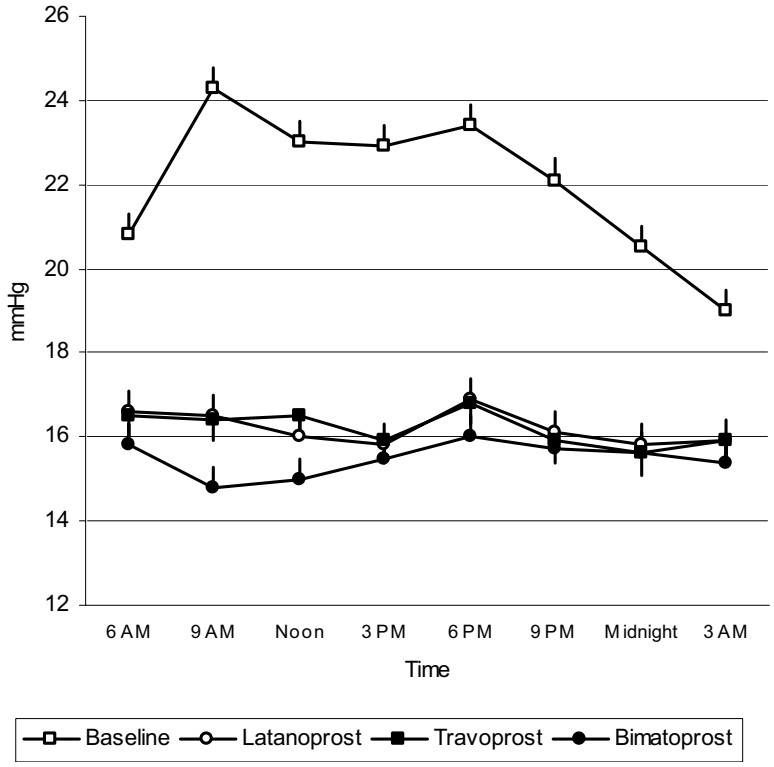

Figure 3. Sitting position tonometric readings (TonoPen XL, Bio-Rad, Glendale, CA) (mean, standard error of the mean).

There has been considerable debate as to which of the 3 prostaglandin analogs is the most potent IOP-lowering agent. Growing evidence indicates that bimatoprost is slightly more effective than the other prostaglandin analogs,[26,40,48–51] though there is still very little information on the nocturnal comparison of these drugs. The results of our study seem to show that the IOP-lowering effects of latanoprost, travoprost, and bimatoprost are similar not only during the day, but also during the critical nocturnal period. Similar findings were reported by Konstas et al,[40] though bimatoprost was found significantly superior to latanoprost, with the largest IOP difference at 6 PM.

Table 4. TonOpen Mean Intraocular Pressures (IOPs)

Time	Baseline (Mean ± SD)	Latanoprost (Mean ± SD)	Travoprost (Mean ± SD)	Bimatoprost (Mean ± SD)
		Supine IOPs		
6 AM	22.2±3.6	18.1±3.1	18.1±3.1	17.2±3.0
9 AM	25.2±3.3	17.6±2.9	17.5±2.8	16.7±2.9
Noon	24.5±3.2	17.4±3.0	17.5±3.0	15.7±3.1
3 PM	23.9±3.4	16.8±2.8	16.7±2.9	16.0±3.1
6 PM	24.2±2.9	17.7±3.1	17.3±3.1	16.5±3.0
9 PM	22.9±3.0	16.5±3.2	16.3±3.0	16.2±3.1
Midnight	21.0±2.9	16.6±3.1	16.3±3.0	16.4±3.1
3 AM	19.5±3.2	16.7±3.0	16.1±2.9	16.2±3.0
Total, 44 patients	22.9±3.5	17.2±3.1	16.9±3.3	16.4±3.2
		Sitting IOPs		
6 AM	20.8±3.2	16.6±2.9	16.5±3.2	15.8±3.1
9 AM	24.3±3.3	16.5±3.1	16.4±3.0	14.8±2.9
Noon	23.0±3.3	16.0±2.8	16.5±3.0	15.0±3.0
3 PM	22.9±2.9	15.8±3.0	15.9±2.8	15.5±2.8
6 PM	23.4±3.2	16.9±3.2	16.8±2.9	16.0±3.0
9 PM	22.1±3.4	16.1±3.0	15.9±3.1	15.7±3.1
Midnight	20.5±3.2	15.8±2.8	15.6±2.9	15.6±2.7
3 AM	19.0±3.0	15.9±3.0	15.9±3.0	15.4±3.1
Total, 44 patients	22.0±3.5	16.2±3.1	16.2±2.9	15.5±3.0

SD = standard deviation.

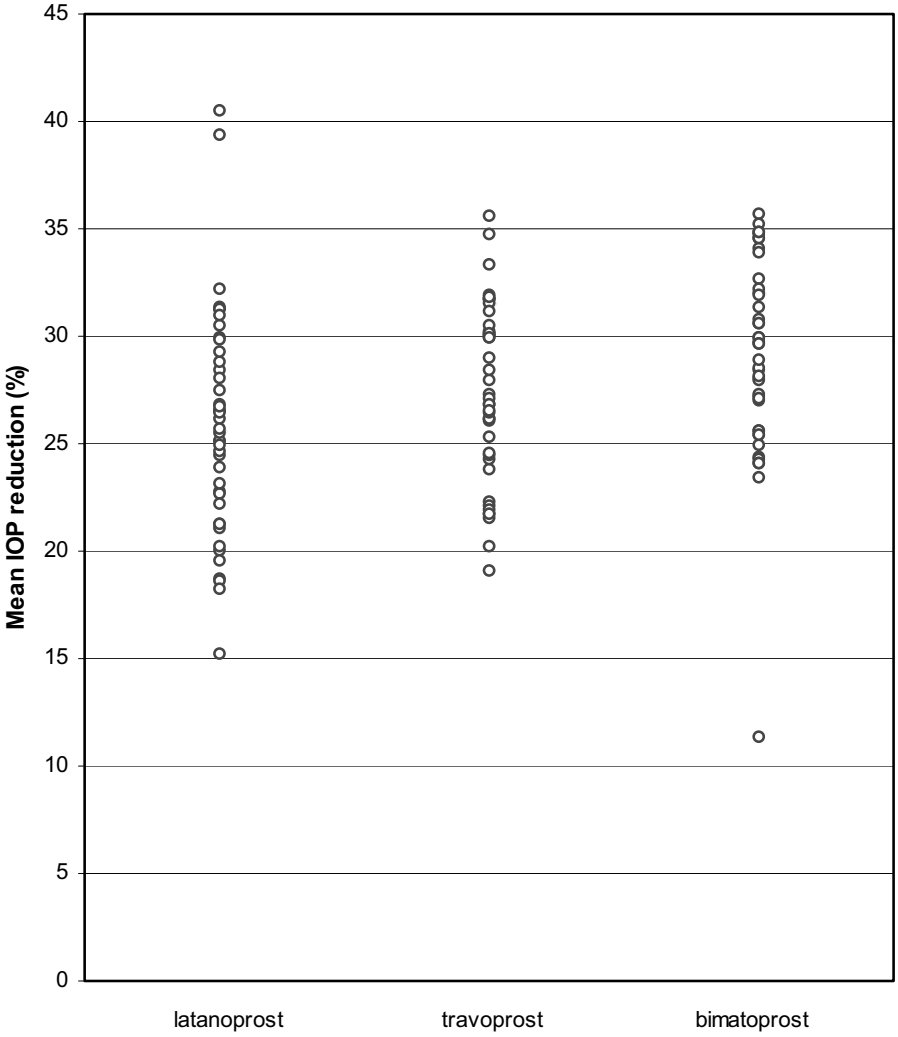

Figure 4. Distribution of intraocular pressure (IOP) reduction from baseline after latanoprost, travoprost, and bimatoprost. Data presented are percentages of mean Goldmann IOP reductions in each of the 44 patients in the 3 phases of the crossover.

As in the case of our previous studies,[28,33] the circadian curves recorded using the TonoPen and Goldmann measurements in the sitting and supine positions were similar, but as expected, the tonopen sitting values were lower than the supine values, probably because of the increase in supine venous pressure.

Any trial of this type cannot avoid some biases that must be born in mind when drawing conclusions. The most important

Table 5. Mean Systemic Blood Pressures and Perfusion Pressures under Treatment

	6 AM	9 AM	Noon	3 PM	6 PM	9 PM	Midnight	3 AM
Latanoprost								
SBP	133±18	144±18	147±21	144±22	140±18	143±21	130±18	131±19
DBP	73±8	83±8	81±9	80±7	78±7	78±9	74±6	73±7
DPP	54.9±4	65.4±5	63.6±5	62.3±6	60.3±5	61.5±4	57.4±4	56.3±5
Travoprost								
SBP	136±21	144±21	145±23	142±19	139±21	143±24	131±18	132±18
DBP	72±8	81±8	81±9	79±8	77±7	79±9	73±6	73±9
DPP	53.9±4	63.5±5	63.5±4	62.3±5	59.7±4	62.7±4	56.7±5	56.8±5
Bimatoprost								
SBP	134±18	142±19	148±22	140±20	141±20	143±23	133±19	133±19
DBP	73±8	81±7	81±8	78±7	78±7	81±8	73±5	73±6
DPP	55.8±5	64.3±5	65.3±6	62.0±6	61.5±4	64.8±5	56.6±4	56.8±5

DBP = diastolic blood pressure; DPP = diastolic perfusion pressure; SBP = systolic blood pressure.
To obtain perfusion pressures, only supine (TonOpen) intraocular pressure measurements were used.

concern is the measurement of IOP in a clinical setting: hospitalization, exposure to light during the nighttime measurements, disturbed sleep, and sudden awakenings may all affect the evaluation of IOP. We tried to limit these biases as much as possible by using a blinded crossover design that assured their even between-treatment distribution. The similarity of the curves obtained in this and in the 2 previous crossover studies[28,33] (3 baseline and 3 treatment curves) seems at least to indicate that the method is repeatable and that the mean IOP values recorded over the 24 hours were consistent.

Finally, there were cases of a thick central cornea (the average central corneal thickness of the whole sample was 554 μm, higher than the one of the general and glaucomatous populations; Table 1): as there were no exclusion criteria based on central corneal thickness, data on IOP changes might have included data from OH suspects (i.e., normals) and from normal-tension glaucomas.

In conclusion, the results of this study seem to indicate that the 3 prostaglandin analogs are effective in reducing IOP in POAG and OH patients throughout the circadian cycle, and their performance was statistically identical within the 1.5-mmHg power of the trial.

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