

# Efficacy of Latanoprostene Bunod 0.024% Compared With Timolol 0.5% in Lowering Intraocular Pressure Over 24 Hours



JOHN H.K. LIU, JOHN R. SLIGHT, JASON L. VITTITOW, BALDO SCASELLATI SFORZOLINI, AND ROBERT N. WEINREB

- **PURPOSE:** To compare the diurnal and nocturnal effects of latanoprostene bunod 0.024% solution with timolol maleate 0.5% solution on intraocular pressure (IOP) and ocular perfusion pressure.
- **DESIGN:** Prospective, open-label randomized crossover trial.
- **METHODS:** Twenty-five patients (aged 43–82 years) with ocular hypertension or early primary open-angle glaucoma were enrolled. Baseline IOP and blood pressure were measured in a sleep laboratory every 2 hours in the sitting and supine positions during the 16-hour diurnal/wake period and in the supine position during the 8-hour nocturnal/sleep period. Subjects were randomly assigned to bilateral treatments of latanoprostene bunod at 8 PM or timolol at 8 AM and 8 PM. The second laboratory recording occurred after the 4-week treatment. Subjects were crossed over to the comparator treatment for 4 weeks before the third laboratory recording. Mean IOP and calculated ocular perfusion pressure were compared for the diurnal and nocturnal periods.
- **RESULTS:** Twenty-one subjects completed the study. Both treatments reduced diurnal sitting and supine IOP compared to baseline by 2.3–3.9 mm Hg (all  $P < .001$ ) with no statistically significant difference between the 2 treatments. Nocturnal IOP under latanoprostene bunod treatment was  $2.5 \pm 3.1$  mm Hg (mean  $\pm$  SD) less than baseline ( $P = .002$ ) and  $2.3 \pm 3.0$  mm Hg less than timolol treatment ( $P = .004$ ). Latanoprostene bunod treatment resulted in greater diurnal sitting and supine ocular perfusion pressures compared with baseline ( $P \leq .006$ ) and greater nocturnal ocular perfusion pressure compared with timolol treatment ( $P = .010$ ).
- **CONCLUSIONS:** During the nocturnal period, latanoprostene bunod caused more IOP reduction and more

increase of ocular perfusion pressure than timolol. (Am J Ophthalmol 2016;169:249–257. © 2016 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)).

**L**OWERING INTRAOCULAR PRESSURE (IOP) MAY DELAY the onset of glaucoma in ocular hypertensive patients and slow the disease progression in patients with existing glaucoma.<sup>1</sup> Whereas the highest IOP in patients with ocular hypertension and primary open-angle glaucoma frequently occur outside the diurnal/wake period,<sup>2,3</sup> currently available topical medications to treat these patients have shown variable IOP-lowering efficacies during the nocturnal/sleep period compared to their diurnal efficacies.<sup>4–10</sup> Prostaglandin analogues (including latanoprost, travoprost, and bimatoprost) applied once daily in the evening were shown to be effective in lowering IOP for 24 hours, but with less nocturnal efficacy than the diurnal efficacy.<sup>5–7,10</sup> Timolol, a  $\beta$ -adrenergic antagonist, applied in gel form once daily in the morning, had very limited IOP reduction during the nocturnal period compared to its diurnal efficacy.<sup>5,8</sup>

Latanoprostene bunod (Bausch & Lomb, Bridgewater, New Jersey, USA) is a new nitric oxide-donating prostaglandin  $F_{2\alpha}$  analogue with unique biological properties. In situ, latanoprostene bunod is rapidly metabolized to latanoprost acid, a prostaglandin agonist, and butanediol mononitrate, a nitric oxide (NO)-donating moiety.<sup>11</sup> Latanoprost acid (as the active moiety of latanoprost 0.005% [Xalatan; Pfizer, New York, NY]) is reported to reduce IOP by primarily increasing uveoscleral outflow.<sup>12,13</sup> In contrast, NO released from the NO-donating moiety of latanoprostene bunod may lower IOP by increasing the trabecular meshwork outflow.<sup>14–17</sup> Nitric oxide is also a biological messenger for other physiological functions, including vasodilation and, on systemic administration, the reduction of blood pressure.<sup>18</sup>

A recent report showed that latanoprostene bunod was well tolerated and efficacious in lowering IOP in patients with primary open-angle glaucoma or ocular hypertension.<sup>19</sup> There was a dose-dependent reduction in diurnal IOP over 28 days at concentrations of 0.006% to 0.04%, reaching a maximum effect with the 0.024% and 0.04%

AJO.com

Supplemental Material available at [AJO.com](http://AJO.com).

Accepted for publication Apr 27, 2016.

From Hamilton Glaucoma Center, Department of Ophthalmology and Shiley Eye Institute, University of California, San Diego, La Jolla, California (J.H.K.L., J.R.S., R.N.W.); and Bausch & Lomb, Bridgewater, New Jersey (J.L.V., B.S.S.).

Baldo Scasellati Sforzolini is currently affiliated with Allergan, Jersey City, New Jersey.

Inquiries to John H.K. Liu, Department of Ophthalmology, University of California, San Diego, 9500 Gilman Dr, La Jolla, CA 92093-0946; e-mail: [joliu@ucsd.edu](mailto:joliu@ucsd.edu)

doses. Statistically significantly greater IOP reductions were observed with latanoprostene bunod 0.024% and 0.04% compared with latanoprost 0.005%.<sup>19</sup> To date, IOP-lowering efficacy of latanoprostene bunod in subjects with ocular hypertension or primary open-angle glaucoma has not been reported outside the office hours. Effects of latanoprostene bunod on systemic blood pressure and calculated ocular perfusion pressure (based on mean arterial blood pressure and IOP) are also unknown outside the office hours. The present study evaluated the 24-hour effects of latanoprostene bunod 0.024%, which is considered the optimal IOP-lowering concentration during office hours,<sup>19</sup> on IOP and ocular perfusion pressure after 4 weeks of once-daily treatment in patients with ocular hypertension or primary open-angle glaucoma. These effects were compared with the treatment effects of timolol maleate 0.5% ophthalmic solution given twice daily for 4 weeks in the same patients.

---

## METHODS

THIS RANDOMIZED CROSSOVER CLINICAL TRIAL (<http://www.clinicaltrials.gov>; NCT01707381) adhered to the Declaration of Helsinki for research involving human subjects and was registered as a clinical trial. Study protocol was approved prospectively by the University of California, San Diego's Institutional Review Board of Human Research Protections Program and in accordance with the Health Insurance Portability and Accountability Act. The study was conducted from November 2012 through December 2013. Study subjects were recruited consecutively from patients with bilateral early-stage open-angle glaucoma or ocular hypertension seen at the University's Hamilton Glaucoma Center with predefined inclusion and exclusion criteria. Criteria for the diagnosis of early glaucomatous changes and ocular hypertension have been described previously.<sup>2,3</sup> Patients with open-angle glaucoma had abnormalities in optic discs or visual fields (or both). Patients with ocular hypertension had normal optic discs and visual fields. Eligible patients for this study were 40–90 years old with untreated IOP of at least 22 mm Hg in 1 eye and not higher than 36 mm Hg in both eyes, determined using Goldmann tonometer (Haag-Streit, Mason, Ohio, USA) during office hours. Subjects were fully informed about this study, and informed consents were obtained.

Each subject's medical history was reviewed. Candidates who had previous glaucoma surgery in either eye, had a history of ocular trauma, or had a sleep disorder or irregular sleep schedule were excluded. Each subject had an examination including slit-lamp biomicroscopy, gonioscopy, Goldmann applanation tonometry, and dilated funduscopy. Individuals with ocular inflammation, narrow iridocorneal angle, severe cardiovascular or diabetic condition, or use of a medication that may interact with the safety or efficacy

of an NO-donating compound were excluded. Other routine systemic medications used by the subjects were documented, and enrolled subjects with a change of systemic medication during the study period were excluded.

Either the enrolled subjects were untreated with glaucoma medication or their glaucoma medications were washed out for 4 weeks followed by a check of IOP eligibility. A washout period of 4 weeks had been used for the previous study of latanoprostene bunod and its dose–IOP response relationship.<sup>19</sup> Before the 24-hour laboratory recording, subjects were instructed to maintain a daily 8-hour regular sleep schedule for 1 week. Individual sleep schedule was verified using a wrist monitor for light exposure and arm movements (Actiwatch; Mini Mitter, Sunriver, Oregon, USA) and a wake/sleep log. Subjects were asked to abstain from alcohol for 3 days and regular coffee for 1 day before reporting to the laboratory approximately at 2 PM. Laboratory conditions and general experimental procedures have been described previously.<sup>10</sup> The 8-hour sleep time for each subject in the laboratory was adjusted close to the recorded bedtime in previous week and this 8-hour period was referred to as the nocturnal/sleep period. Clock times for the IOP measurements were also individualized accordingly. Subjects were encouraged to continue normal indoor activities in the laboratory. Food and water were available, and meal times were not regulated.

Measurements of IOP and blood pressure/heart rate were taken by experienced researchers. Intraocular pressure was measured using a calibrated pneumatonometer (Reichert, Depew, New York, USA). Topical proparacaine 0.5% was used as the local anesthetic. Every plot of IOP measurement by the pneumatonometer was evaluated according to commonly accepted standards.<sup>20</sup> Blood pressure and heart rate were measured immediately before the IOP measurements using an automated arm monitor (Accutorr Plus; Datascope, Montvale, New Jersey, USA). The cuff was mounted over the brachial artery, level with the heart, and removed after the measurement. Two readings were taken and, if the systolic or diastolic pressure differed by more than 5 mm Hg between the 2 readings, the third reading was added. The average of 2–3 readings was recorded for the systolic pressure, diastolic pressure, and heart rate at each clock time point.

Before bedtime, measurements were taken every 2 hours (eg, at 2 PM, 4 PM, 6 PM, and 8 PM). Subjects were instructed to sit for 5 minutes before the measurements of blood pressure/heart rate and IOP, and then lie in bed for 5 minutes before the supine measurements of blood pressure/heart rate and IOP. Lights in individual sleep rooms were turned off according to each individual's sleep times (between 9:30 PM and 11:30 PM). Supine measurements only were taken first at 30 minutes after the lights were turned off (eg, 10 PM) and every 2 hours later. Subjects were awakened, if needed, and the measurements were taken immediately. A dim room light was used to assist with the measurements. Some sleep disturbance due to

the measurement procedure was unavoidable. The disturbance may affect nocturnal blood pressure and IOP levels, even though the influence on IOP was probably minor.<sup>21,22</sup> However, we assumed that every 24-hour laboratory session would be similarly affected for each individual. Room lighting was restored after the 8-hour nocturnal/sleep period, and subjects were awakened. Actual sleep length for each individual was not determined. Measurements of blood pressure/heart rate and IOP were taken again first at 30 minutes after the lights were turned on (eg, at 6 AM) and every 2 hours thereafter. Timings of the measurements were documented using infrared camera recording.

After baseline 24-hour sleep laboratory data were collected, subjects were randomly assigned to receive latanoprostene bunod 0.024% ophthalmic solution in both eyes once daily at approximately 8 PM or timolol maleate 0.5% ophthalmic solution twice daily at approximately 8 AM and 8 PM. Test agents were provided by Bausch & Lomb (Bridgewater, New Jersey, USA). The first treatment period lasted for 4 weeks before the second 24-hour sleep laboratory recording. Subjects were then crossed over to the alternate therapy for 4 weeks before the third 24-hour sleep laboratory recording. During the second and third laboratory recordings, subjects self-administered the test agent under supervision.

Per the study protocol, IOP data from 1 eligible eye of each subject were used for data analyses. If both eyes were eligible, the eye with a higher baseline IOP (Goldmann tonometer) prior to the first 24-hour laboratory recording was chosen for analysis. The right eye was chosen if both eyes had the same IOP value. Mean arterial blood pressure was calculated as the diastolic pressure plus one third of the difference between the systolic and the diastolic pressures. Ocular perfusion pressure in the sitting and supine body positions were calculated, using formulas based on the mean arterial blood pressure and IOP, adjusted for the height of the eye over the heart<sup>23-27</sup>:

Sitting ocular perfusion pressure =  $95/140 \times$  mean arterial blood pressure – IOP

Supine ocular perfusion pressure =  $115/130 \times$  mean arterial blood pressure – IOP

Means of IOP, mean arterial blood pressure, ocular perfusion pressure, and heart rate were calculated for the 16-hour diurnal/wake period (8 readings) and the 8-hour nocturnal/sleep period (4 readings). For data presentation, laboratory data were aligned as if each subject had a nocturnal/sleep period from 9:30 PM to 5:30 AM. Statistical comparisons of study parameters were performed among the baseline, the latanoprostene bunod treatment, and the timolol treatment using the 1-way repeated-measures analysis of variance.<sup>5,8</sup> The criterion for statistical significance was  $P < .05$ . Post hoc Bonferroni *t* test was used for all 3 possible paired comparisons. Normal distribution of test data was confirmed using the Kolmogorov-Smirnov test. Comparison of IOP at a single clock time point was not

**TABLE 1.** Adverse Events During 4-Week Treatment With Latanoprostene Bunod 0.024% and Timolol 0.5%

	Latanoprostene Bunod 0.024% (N = 46 Eyes or 23 Subjects)	Timolol 0.5% (N = 46 Eyes or 23 Subjects)
Ocular		
Punctate keratitis	1	3
Instillation site erythema	1	0
Instillation site irritation	0	1
Nonocular		
Dizziness	0	1
Dyspnea	0	1
Nausea	1	1
Hyperhidrosis	1	0
Blood pressure decreased	0	1
Heart rate decreased	0	2

Adverse events were coded with Medical Dictionary for Regulatory Activities version 13.0. Multiple occurrences for an eye or a subject under the same treatment were counted only once.

performed because its value in assessing IOP-lowering therapy is limited.<sup>28</sup>

Subjects were instructed to report significant or unusual ocular and systemic reactions to the test agents during the study period. An eye examination was performed after each 24-hour laboratory recording and when adverse events of test agent had occurred. The severity of an adverse event was evaluated by a glaucoma specialist and could lead to patient withdrawal from the study.

## RESULTS

TWENTY-FIVE PATIENTS, 18 FEMALE AND 7 MALE, WITH AN age of  $60.3 \pm 10.6$  years (mean  $\pm$  standard deviation; range, 43–82 years) were enrolled. There were 20 white (4 Hispanic ethnicity), 4 black, and 1 American Indian patients. Twenty-one patients had a diagnosis of ocular hypertension and 4 patients had primary open-angle glaucoma. Nineteen patients were not using any glaucoma medication at enrollment. Six patients were being treated with a glaucoma medication(s) at enrollment: 4 with latanoprost, 1 with bimatoprost, and 1 with latanoprost and timolol. Treated patients underwent 4-week washout. The mean of the last office-hour Goldmann IOP reading before the first laboratory recording was  $23.2 \pm 1.6$  mm Hg (range, 21–28 mm Hg) for all the enrolled subjects under no glaucoma medication. The mean central corneal thickness was  $556.3 \pm 27.9$   $\mu$ m (range, 511–598  $\mu$ m).

The first (baseline) 24-hour laboratory recordings were obtained from all 25 enrolled subjects, but only 21 subjects

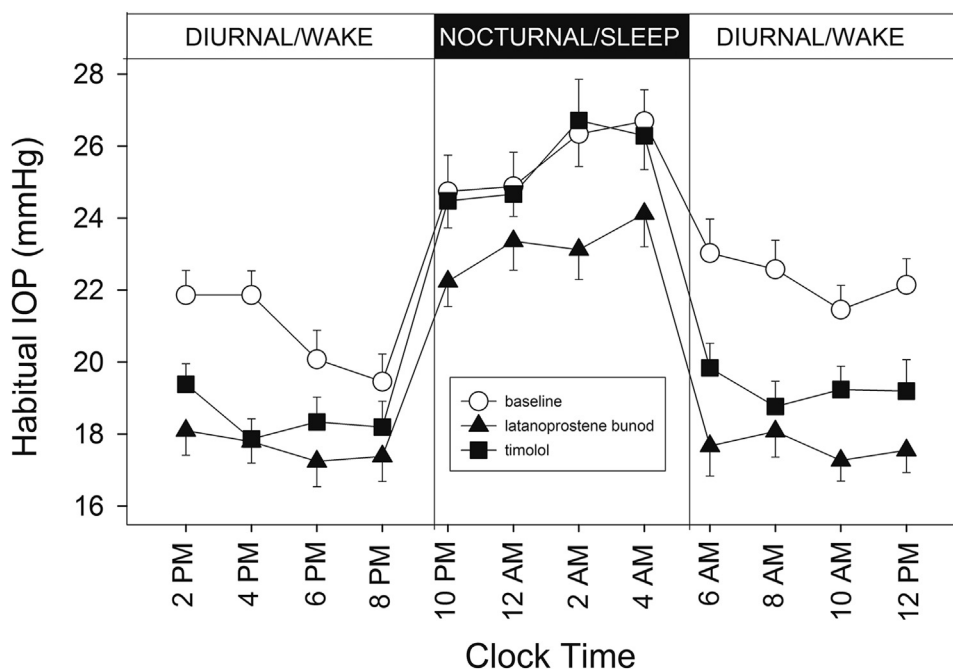


FIGURE 1. Profiles of 24-hour habitual intraocular pressure (IOP). Measurements were obtained from 21 subjects sitting during the diurnal/wake period and supine during the nocturnal/sleep period. Open circles represent the baseline, solid triangles represent after 4-week treatment with latanoprostene bunod 0.024% once daily, and solid squares represent after 4-week treatment with timolol 0.5% solution twice daily. Error bars represent standard error of the mean.

completed the entire study protocol that involved 2 additional 24-hour laboratory recordings (Supplemental Figure; Supplemental Material available at [AJO.com](#)). One subject who was under the treatment with latanoprostene bunod missed the scheduled second 24-hour laboratory recording and was withdrawn administratively. Three subjects withdrew from the study before the second laboratory recordings; 2 subjects had significant bradycardia under the timolol treatment and 1 subject had nausea and hyperhidrosis under the latanoprostene bunod treatment. The recorded adverse events from all enrolled subjects during the study period are summarized in Table 1.

Figure 1 shows the 24-hour profiles of habitual IOP, sitting during the diurnal/wake period and supine during the nocturnal/sleep period, for the 21 subjects who completed the study. Coincidentally with postural changes, IOP increased during the transition from the diurnal to the nocturnal period and IOP decreased during the transition from the nocturnal to the diurnal period. Mean IOP under the latanoprostene bunod treatment was consistently observed to be the lowest among the 3 experimental conditions during the 16-hour diurnal period. During the 8-hour nocturnal period, mean baseline IOP and mean IOP under the timolol treatment were similar. In contrast, mean IOP under the latanoprostene bunod treatment was notably lower than the baseline IOP as well as IOP under the timolol treatment. Figure 2 presents the 24-hour supine

IOP profiles for the baseline, the latanoprostene bunod treatment, and the timolol treatment. For supine IOP during the diurnal period, IOP under the latanoprostene bunod treatment was also the lowest among the 3 experimental conditions. Profiles of 24-hour ocular perfusion pressure for the habitual body positions and for the supine position are presented as Figures 3 and 4, respectively. For most time points, ocular perfusion pressures after the latanoprostene bunod treatment were the highest.

Table 2 summarizes IOP, mean arterial blood pressure, ocular perfusion pressure, and heart rate under the 3 experimental conditions. During the diurnal/wake period, both sitting and supine IOP levels under either test agent treatment were significantly lower than the baselines in the range of 2.3–3.9 mm Hg ( $P < .001$ ). However, the 1.1–1.2 mm Hg IOP difference between the 2 treatments was not statistically significant. During the nocturnal/sleep period, the supine IOP under the latanoprostene bunod treatment was significantly lower than the baseline by  $2.5 \pm 3.1$  mm Hg ( $P = .002$ ) and the timolol treatment by  $2.3 \pm 3.0$  mm Hg ( $P = .004$ ). No IOP difference appeared during the nocturnal period between the baseline and the timolol treatment. Considering the latanoprostene bunod treatment only, the diurnal IOP reduction was larger than the nocturnal IOP reduction; the difference was  $1.5 \pm 3.0$  mm Hg ( $P = .039$ , paired  $t$  test) for the habitual body positions (diurnal  $3.9 \pm 2.7$  mm Hg vs nocturnal  $2.5 \pm 3.1$  mm Hg) and  $1.0 \pm 2.5$  mm Hg ( $P = .077$ , paired

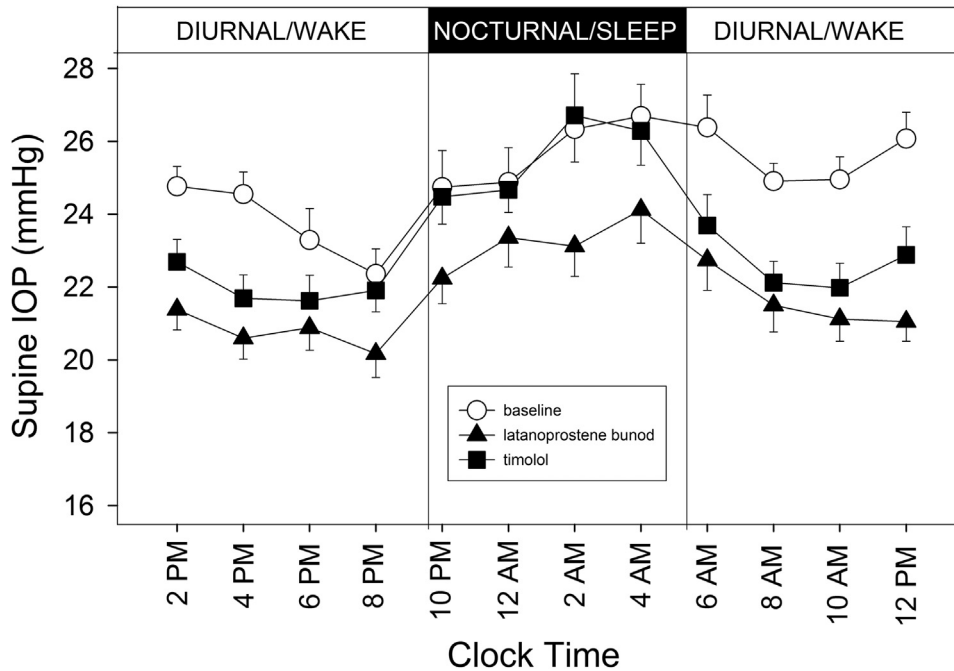


FIGURE 2. Profiles of 24-hour supine intraocular pressure (IOP). Open circles represent the baseline, solid triangles represent after 4-week treatment with latanoprostene bunod 0.024% once daily, and solid squares represent after 4-week treatment with timolol 0.5% solution twice daily from the same 21 subjects as in Figure 1. Error bars represent standard error of the mean.

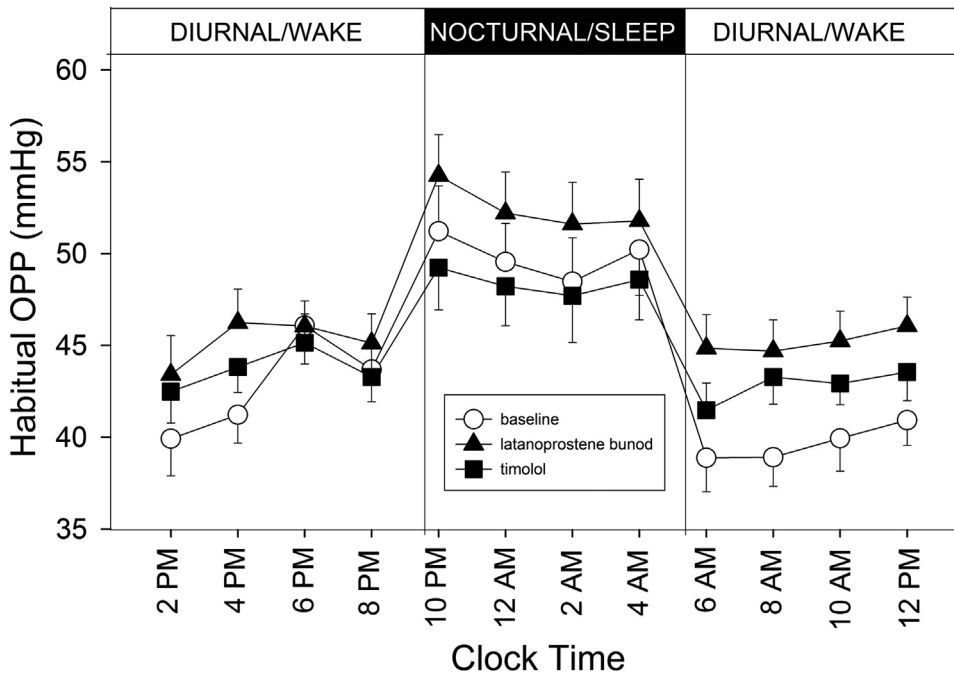


FIGURE 3. Profiles of 24-hour habitual ocular perfusion pressure (OPP). Calculations were performed with sitting data during the diurnal/wake period and supine data during the nocturnal/sleep period. Open circles represent the baseline, solid triangles represent after 4-week treatment with latanoprostene bunod 0.024% once daily, and solid squares represent after 4-week treatment with timolol 0.5% solution twice daily. Error bars represent standard error of the mean (N = 21).



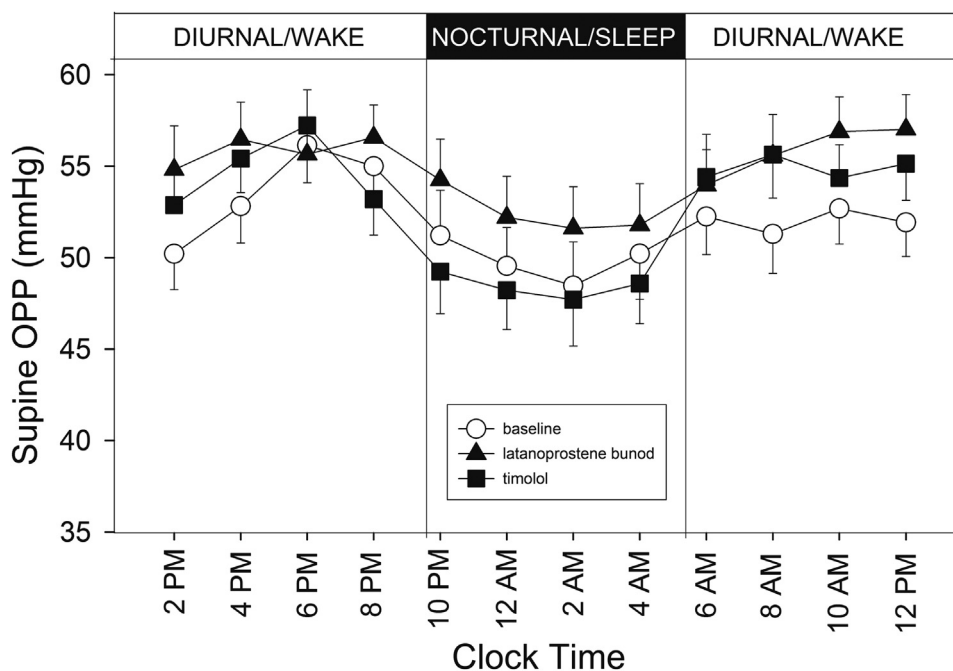


FIGURE 4. Profiles of 24-hour supine ocular perfusion pressure (OPP). Open circles represent the baseline, solid triangles represent after 4-week treatment with latanoprostene bunod 0.024% once daily, and solid squares represent after 4-week treatment with timolol 0.5% solution twice daily. Error bars represent standard error of the mean (N = 21).

*t* test) for the supine position (diurnal  $3.5 \pm 2.6$  mm Hg vs nocturnal  $2.5 \pm 3.1$  mm Hg).

Mean arterial blood pressure showed no significant change due to either treatment of test agent for the diurnal sitting, diurnal supine, and nocturnal supine readings. Under the latanoprostene bunod treatment, diurnal sitting and diurnal supine ocular perfusion pressures were greater than baseline ( $P < .001$  and  $P = .006$ , respectively). However, no significant change in ocular perfusion pressure was observed with latanoprostene bunod during the nocturnal period as compared to baseline. Under the timolol treatment, no significant change in ocular perfusion pressure from the baseline was observed for the diurnal sitting, diurnal supine, and nocturnal supine readings. Considering the 2 test agents, the nocturnal level of supine ocular perfusion pressure under the latanoprostene bunod treatment was greater than the nocturnal supine ocular perfusion pressure under the timolol treatment ( $P = .010$ ). There was no significant change in the heart rate under the latanoprostene bunod treatment. Under the timolol treatment, diurnal sitting or diurnal supine heart rate was significantly less than the heart rates under the other 2 experimental conditions (ranged from  $P < .001$  to  $P = .002$ ).

## DISCUSSION

THERE WAS A SIGNIFICANT IOP REDUCTION WITH THE latanoprostene bunod treatment during the diurnal/wake

period and during the nocturnal/sleep period compared to baseline. The nocturnal IOP-lowering effect of latanoprostene bunod appeared less than the effect during the diurnal period. Posture was not a factor for the relatively smaller nocturnal IOP-lowering effect, since both the 24-hour supine IOP profile and the 24-hour habitual IOP profile showed comparable diurnal vs nocturnal IOP reductions from the baselines. These results for latanoprostene bunod were similar to the reported observations for other prostaglandin analogues.<sup>5,6,10</sup> Based on pharmacokinetics data from nonhuman primates,<sup>11</sup> the difference in the diurnal and nocturnal IOP-lowering effects was unlikely related to the bioavailability of latanoprostene bunod given once daily in the evening.

Low ocular perfusion pressure has been proposed as a risk factor for glaucomatous damages.<sup>25-27</sup> Alteration of ocular perfusion pressure can occur by changes in mean arterial blood pressure and/or IOP. Although the mean arterial blood pressure did not change significantly under either test agent of latanoprostene bunod or timolol over the 24-hour period, the latanoprostene bunod treatment increased the diurnal ocular perfusion pressure over the baseline owing to a significant IOP reduction during the diurnal period. Treatment with timolol showed no significant effect on diurnal ocular perfusion pressure, probably because of a relatively smaller IOP reduction. Results also showed a greater nocturnal ocular perfusion pressure under the latanoprostene bunod treatment compared to the timolol treatment, reflecting the smaller effect of timolol

**TABLE 2.** Comparisons of Intraocular Pressure, Mean Arterial Blood Pressure, Ocular Perfusion Pressure, and Heart Rate Among Baseline, Latanoprostene Bunod 0.024% Treatment, and Timolol 0.5% Treatment

	Baseline	Latanoprostene Bunod	Timolol	Latanoprostene Bunod vs Baseline	Timolol vs Baseline	Latanoprostene Bunod vs Timolol
<b>Diurnal/wake sitting</b>						
Intraocular pressure (mm Hg)	21.6 ± 2.8	17.6 ± 2.5	18.9 ± 2.4	<i>P</i> < .001	<i>P</i> < .001	Not significant
Mean arterial blood pressure (mm Hg)	92.5 ± 10.3	92.6 ± 10.5	91.5 ± 9.7	Not significant	Not significant	Not significant
Ocular perfusion pressure (mm Hg)	41.2 ± 6.8	45.2 ± 6.8	43.2 ± 5.7	<i>P</i> < .001	Not significant	Not significant
Heart rate (beats/min)	69.6 ± 9.2	69.9 ± 9.8	66.2 ± 8.7	Not significant	<i>P</i> = .001	<i>P</i> < .001
<b>Diurnal/wake supine</b>						
Intraocular pressure (mm Hg)	24.7 ± 2.4	21.2 ± 2.3	22.3 ± 2.5	<i>P</i> < .001	<i>P</i> < .001	Not significant
Mean arterial blood pressure (mm Hg)	87.6 ± 9.4	87.1 ± 8.7	87.2 ± 9.2	Not significant	Not significant	Not significant
Ocular perfusion pressure (mm Hg)	52.8 ± 8.0	55.9 ± 7.8	54.8 ± 7.5	<i>P</i> = .006	Not significant	Not significant
Heart rate (beats/min)	66.2 ± 8.5	66.2 ± 9.0	63.5 ± 8.6	Not significant	<i>P</i> = .002	<i>P</i> = .002
<b>Nocturnal/sleep supine</b>						
Intraocular pressure (mm Hg)	25.7 ± 3.8	23.2 ± 3.4	25.6 ± 3.2	<i>P</i> = .002	Not significant	<i>P</i> = .004
Mean arterial blood pressure (mm Hg)	85.4 ± 11.8	85.5 ± 10.6	83.6 ± 11.1	Not significant	Not significant	Not significant
Ocular perfusion pressure (mm Hg)	49.9 ± 10.1	52.5 ± 9.5	48.4 ± 9.4	Not significant	Not significant	<i>P</i> = .010
Heart rate (beats/min)	64.3 ± 8.0	65.0 ± 7.7	62.4 ± 8.4	Not significant	Not significant	Not significant

Values are mean ± standard deviation (N = 21).

*P* values determined using 1-way repeated-measures analysis of variance and post hoc Bonferroni *t* test.

“Not significant” indicates *P* > .05.

on IOP lowering combined with some reduction in mean arterial blood pressure. The latanoprostene bunod treatment is expected to be more beneficial than the timolol treatment if one considers the difference in ocular perfusion pressure during the day and at night.

Latanoprostene bunod is a new monotherapy consisting of a prostaglandin F<sub>2α</sub> analogue with an NO-donating moiety that releases NO in situ. Results from the present study indicate that latanoprostene bunod eye drops did not lead to a change in systemic blood pressure or heart rate. The present study is not sensitive enough to determine the effect of increased NO in ocular tissues.<sup>11,19,29</sup> Owing to the small sample size and the associated statistical power, the present study was not intended and cannot be used to determine whether or not the diurnal and nocturnal IOP-lowering effects of latanoprostene bunod were greater than the effects of other prostaglandin analogues.<sup>5,6,10</sup> To answer the latter question, a direct comparison of IOP reductions over 24 hours by the treatments of latanoprostene bunod and another prostaglandin analogue in the same group of patients may be needed.

Experimental subjects in the present study were given timolol 0.5% solution twice daily as the comparator, which was different from our previous studies that involved subjects treated with timolol 0.5% gel form once daily in the morning.<sup>5,8</sup> Results showed very limited IOP lowering at night under the treatment with timolol 0.5% solution twice daily, consistent with a previous report by others.<sup>30</sup> Since the bioavailability of timolol solution after the 8 AM dose and after the 8 PM dose should not be very

different, the absence of nocturnal IOP-lowering efficacy in the present study cannot be explained by pharmacokinetic factors. The lack of IOP-lowering effect from dosing timolol prior to sleep in patients with glaucoma or ocular hypertension should be a concern.

We observed no statistically significant difference in sitting IOP, supine IOP, sitting ocular perfusion pressure, or supine ocular perfusion pressure between the latanoprostene bunod and timolol treatments during the diurnal/wake period. This was likely owing to the small sample size with inadequate statistical power (commonly required at 0.80) to detect a significant difference. The final number of 21 participants in the present study provided a statistical power of 0.65 for the observed mean sitting IOP difference of 1.2 mm Hg and a statistical power of 0.39 for the observed mean supine IOP difference of 1.1 mm Hg between the 2 treatments. The corresponding statistical powers for the differences in mean sitting and mean supine ocular perfusion pressures between the 2 treatments were 0.55 and 0.09, respectively. In a recent randomized double-masked controlled multicenter study, significantly greater IOP-lowering effect was observed with the latanoprostene bunod treatment compared to the timolol treatment at 8 AM, 12 PM, and 4 PM based on data from the final number of 387 participants with open-angle glaucoma or ocular hypertension.<sup>31</sup>

In summary, treatment with latanoprostene bunod 0.024% once daily resulted in IOP lowering during the diurnal/wake period as well as during the nocturnal/sleep period. Treatment with latanoprostene bunod showed a greater nocturnal IOP-lowering efficacy compared to

treatment with timolol 0.5% solution twice daily. Latanoprostene bunod treatment significantly increased diurnal ocular perfusion pressure from the baseline. Ocular

perfusion pressure during the nocturnal period was higher under latanoprostene bunod treatment than under timolol treatment.

FUNDING/SUPPORT: THE STUDY WAS SUPPORTED BY BAUSCH & LOMB, BRIDGEWATER, NEW JERSEY, USA. THE SPONSOR participated in the study design but played no role in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. Financial disclosures: John H.K. Liu has received support for research from Aerie (Bedminster, NJ), Alcon (Fort Worth, TX), Allergan (Irvine, CA), Bausch & Lomb, and Sensimed (Lausanne, Switzerland). John R. Slight has received support for research from Bausch & Lomb. Jason L. Vittitow is an employee of Bausch & Lomb. Baldo Scassellati Sforzolini was an employee of Bausch & Lomb during the conduct of this study. Robert N. Weinreb has received support for research from Aerie, Genentech (South San Francisco, CA), Heidelberg Engineering (Heidelberg, Germany), Konan (Nagoya, Japan), and Lumenis (San Jose, CA) and is a consultant for Aerie, Alcon, Allergan, Bausch & Lomb, Carl Zeiss-Meditec (Dublin, CA), and Topcon (Tokyo, Japan). All authors attest that they meet the current ICMJE criteria for authorship.

## REFERENCES

- Weinreb RN, Aung T, Medeiros FA. The pathophysiology and treatment of glaucoma: a review. *JAMA* 2014;311(18):1901–1911.
- Liu JHK, Zhang X, Kripke DF, Weinreb RN. Twenty-four-hour intraocular pressure pattern associated with early glaucomatous changes. *Invest Ophthalmol Vis Sci* 2003;44(4):1586–1590.
- Grippo TM, Liu JHK, Zebardast N, Arnold TB, Moore GH, Weinreb RN. Twenty-four-hour pattern of intraocular pressure in untreated patients with ocular hypertension. *Invest Ophthalmol Vis Sci* 2013;54(1):512–517.
- Orzalesi N, Rossetti L, Invernizzi T, Bottoli A, Autelitano A. Effect of timolol, latanoprost, and dorzolamide on circadian IOP in glaucoma or ocular hypertension. *Invest Ophthalmol Vis Sci* 2000;41(9):2566–2573.
- Liu JHK, Kripke DF, Weinreb RN. Comparison of the nocturnal effects of once-daily timolol and latanoprost on intraocular pressure. *Am J Ophthalmol* 2004;138(3):389–395.
- Sit AJ, Weinreb RN, Crowston JG, Kripke DF, Liu JHK. Sustained effect of travoprost on diurnal and nocturnal intraocular pressure. *Am J Ophthalmol* 2006;141(6):1131–1133.
- Orzalesi N, Rossetti L, Bottoli A, Fogagnolo P. Comparison of the effects of latanoprost, travoprost, and bimatoprost on circadian intraocular pressure in patients with glaucoma or ocular hypertension. *Ophthalmology* 2006;113(2):239–246.
- Liu JHK, Medeiros FA, Slight JR, Weinreb RN. Comparing diurnal and nocturnal effects of brinzolamide and timolol on intraocular pressure in patients receiving latanoprost monotherapy. *Ophthalmology* 2009;116(3):449–454.
- Liu JHK, Medeiros FA, Slight JR, Weinreb RN. Diurnal and nocturnal effects of brimonidine monotherapy on intraocular pressure. *Ophthalmology* 2010;117(11):2075–2079.
- Tung JD, Tafreshi A, Weinreb RN, Slight JR, Medeiros FA, Liu JHK. Twenty-four-hour effects of bimatoprost 0.01% monotherapy on intraocular pressure and ocular perfusion pressure. *BMJ Open* 2012;2(4):e001106.
- Krauss AHP, Impagnatiello F, Toris CB, et al. Ocular hypotensive activity of BOL-303259-X, a nitric oxide donating prostaglandin F<sub>2</sub>α agonist, in preclinical models. *Exp Eye Res* 2011;93(3):250–255.
- Toris CB, Gabelt BT, Kaufman PL. Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. *Surv Ophthalmol* 2008;53(Suppl 1):S107–S120.
- Kaufman PL, Rasmussen CA. Advances in glaucoma treatment and management: outflow drugs. *Invest Ophthalmol Vis Sci* 2012;53(5):2495–2500.
- Nathanson JA. Nitrovasodilators as a new class of ocular hypotensive agents. *J Pharmacol Exp Ther* 1992;260(3):956–965.
- Nathanson JA, McKee M. Alterations of ocular nitric oxide synthase in human glaucoma. *Invest Ophthalmol Vis Sci* 1995;36(9):1774–1784.
- Cavet ME, Vittitow JL, Impagnatiello F, Ongini E, Bastia E. Nitric oxide (NO): an emerging target for the treatment of glaucoma. *Invest Ophthalmol Vis Sci* 2014;55(8):5005–5015.
- Cavet ME, Vollmer TR, Harrington KL, VanDerMeid K, Richardson ME. Regulation of endothelin-1-induced trabecular meshwork cell contractility by latanoprostene bunod. *Invest Ophthalmol Vis Sci* 2015;56(6):4108–4116.
- Lowenstein CJ, Dinerman JL, Synder SH. Nitric oxide: a physiologic messenger. *Ann Intern Med* 1994;120(3):227–237.
- Weinreb RN, Ong T, Sforzolini BS, Vittitow JL, Singh K, Kaufman PL, The VOYAGER Study Group. A randomized, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: the VOYAGER study. *Br J Ophthalmol* 2015;99(6):738–745.
- Liu JHK, Kripke DF, Twa MD, et al. Twenty-four-hour pattern of intraocular pressure in the aging population. *Invest Ophthalmol Vis Sci* 1999;40(12):2912–2917.
- Aptel F, Tamisier R, Pepin J-L, et al. Hourly awakening vs continuous contact lens sensor measurements of 24-hour intraocular pressure. Effect on sleep macrostructure and intraocular pressure rhythm. *JAMA Ophthalmol* 2014;132(10):1232–1238.
- Liu JHK, Mansouri K, Weinreb RN. Estimation of 24-hour intraocular pressure peak timing and variation using a contact lens sensor. *PLoS One* 2015;10(6):e0129529.
- Bill A. Physiological aspects of the circulation in the optic nerve. In: Heilmann K, Richardson KT, eds. *Glaucoma: Conceptions of a Disease, Pathogenesis, Diagnosis, Therapy*. Philadelphia: W.B. Saunders; 1978:97–103.
- Liu JHK, Gokhale PA, Loving RT, Kripke DF, Weinreb RN. Laboratory assessment of diurnal and nocturnal ocular perfusion pressures in humans. *J Ocul Pharmacol Ther* 2003;19(4):291–297.
- Caprioli J, Coleman AL. The Blood Flow in Glaucoma Discussion Group. Blood pressure, perfusion pressure, and glaucoma. *Am J Ophthalmol* 2010;149(5):704–712.



26. Quaranta L, Katsanos A, Russo A, Riva I. 24-hour intraocular pressure and ocular perfusion pressure in glaucoma. *Surv Ophthalmol* 2013;58(1):26–41.
27. Costa VP, Harris A, Anderson D, et al. Ocular perfusion pressure in glaucoma. *Acta Ophthalmol* 2014;92(4):e252–e266.
28. Realini T. Assessing the effectiveness of intraocular pressure-lowering therapy. *Ophthalmology* 2010;117(11):2045–2046.
29. Galassi F, Renieri G, Sodi A, Ucci F, Vannozzi L, Masini E. Nitric oxide proxies and ocular perfusion pressure in primary open angle glaucoma. *Br J Ophthalmol* 2004;88(6):757–760.
30. Gulati V, Fan S, Zhao M, Maslonka MA, Gangahar C, Toris CB. Diurnal and nocturnal variations in aqueous humor dynamics of patients with ocular hypertension undergoing medical therapy. *Arch Ophthalmol* 2012;130(6):677–684.
31. Weinreb RN, Scassellati Sforzolini B, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension. *Ophthalmology* 2016; 123(5):965–973.