# Peak pressures: Crossover study of timolol and latanoprost

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PURPOSE. *To compare the diurnal efficacy and action on peak intraocular pressures (IOP) of 0.005% latanoprost and 0.5% timolol as primary therapy in 60 eyes having dark brown irides with primary open angle glaucoma (POAG).*

METHODS. *A prospective, comparative, observer-masked, crossover, interventional trial including the mean of both eyes of 30 patients with POAG who were randomly started on either latanoprost once daily or timolol twice daily. Three months after treatment with one drug, the second drug was substituted. A masked observer carried out diurnal assessments of IOP before the start of therapy and at 3 and 7 months. The fourth month was the washout period for the first drug.*

RESULTS. *The average baseline IOP was 23.36 ± 2.14 mm Hg, which was reduced by 8.8 ± 2.2 mmHg with latanoprost (p<0.01) and by 6.75 ± 1.9 mm Hg with timolol (p=0.01). The reduction was greater for latanoprost (p<0.005). The average peak IOP at baseline was 27.6 ± 2.22 mmHg. The effective fall in IOP at the time of new peaks in subsequent diurnal recordings of IOP compared to the baseline diurnal curve was 8.9 mm Hg with latanoprost (p<0.005) and 5.77 mm Hg with timolol (p<0.01). This difference in IOP reduction between the two drugs was statistically significant (p<0.01). Latanoprost had a lower efficacy in peak IOP reduction in eyes with evening peak of IOP than in those with morning peak (p<0.005). The efficacy of timolol was lower overall compared to latanoprost, but was similar in all circadian rhythms. The shift in timing of IOP peak was greater with latanoprost compared to timolol (4.34 hours vs –0.72 hours, p<0.01). A total of 90% of patients on latanoprost and 33.3% on timolol achieved a reduction of >30% in baseline mean IOP. The average of the trough IOP recorded in each of the individual baseline IOP curves was 19.05 ± 2.05 mm Hg.*

CONCLUSIONS. *Greater mean and peak IOP reduction was achieved with latanoprost compared to timolol. Dampening of the circadian rhythm was better with latanoprost. Latanoprost appears to be more effective than timolol at all points in time with greater efficacy in eyes with morning peaks compared to evening peaks. (Eur J Ophthalmol 2003; 13: 546-52)*

KEY WORDS. *Primary open angle glaucoma, Diurnal variation, Latanoprost, Timolol*

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## INTRODUCTION

Latanoprost (Xalatan, Pharmacia & Upjohn), a phenyl substituted prostaglandin analogue, has been studied extensively for its intraocular pressure (IOP) lowering efficacy and side effects. In a pooled data analysis, Hedman and Alm found latanoprost to be more effective than timolol when morning, noon, and afternoon IOP were averaged to determine the diurnal IOP (1). Orzalesi et al (2) reported a uniform cir-

cadian reduction in IOP with latanoprost as compared to timolol.

No long-term, crossover study has evaluated latanoprost and timolol with respect to their circadian efficacy and action in peak pressure control especially in patients with dark brown irides. The aim of the present study was to compare the effect of latanoprost once at night and timolol twice a day on different circadian rhythms, in a masked, crossover study.

## METHODS

The study was designed as a prospective, comparative, observer-masked, crossover, interventional trial comparing the efficacy and side effects of timolol (Glucomol, Allergan) and latanoprost (Xalatan) as monotherapy in eyes with dark brown irides with newly diagnosed primary open angle glaucoma (POAG).

Consecutive adult patients with bilateral, untreated POAG were included in the study after giving proper informed consent. All patients had a baseline IOP of more than 21 mmHg without any antiglaucoma medication on more than two occasions, optic nerve head and visual field changes commensurate with the diagnosis of glaucoma, and an open angle on gonioscopy.

Exclusion criteria included prior medical laser or surgical intervention for the control of IOP, any previous ocular surgery, any other intraocular disorder, or any condition preventing reliable applanation tonometry. Patients with known hypersensitivity to any component of the drugs to be used, who were unable to adhere to the follow-up protocol, or with systemic or ocular problems contraindicating the use of either of the two study drugs were also excluded. Patients with a baseline IOP of more than 35 mmHg were also excluded from the study.

At the time of enrolment, a complete medical and ocular history was taken and any concurrent medical therapies were recorded. A detailed systemic examination was carried out including evaluation of the cardiovascular, neurologic, and respiratory systems. A comprehensive ocular examination was performed, including best-corrected visual acuity, slit-lamp examination, gonioscopic examination using Zeiss 4 mirror, biomicroscopic fundus evaluation, recording of IOP every 3 hours from 7 am to 10 pm on a single day

using Goldmann applanation tonometer, and full threshold automated perimetry on the 30-2 program of Humphrey field analyzer.

The patients were then randomized into two parallel study groups: one group received latanoprost 0.005% at 10 pm once daily and the other group received timolol maleate 0.5% at 8 am and 8 pm. Follow-up examination was carried out at 3 weeks, 6 weeks, and 3 months after the start of therapy. Best-corrected visual acuity, IOP recording, and fundus evaluation was done at each follow-up visit. After 3 months, the second medication was substituted for the first; i.e., patients in the latanoprost group were started on timolol and vice versa. The first month of treatment with the second drug (i.e., the fourth month of the trial) was deemed as the washout period for the first drug used during the first 3 months of therapy. Further follow-up was done 3 weeks, 6 weeks, and 3 months after the washout period.

An applanation diurnal IOP and full threshold automated perimetry was carried out before the start of therapy and at 3 months and 7 months after enrollment in the study. Although 60 eyes of 30 patients were evaluated, a mean of the pressure of both the eyes was taken as the IOP for analysis. The times of the diurnal recording of IOP were 7 am, 10 am, 1 pm, 4 pm, 7 pm, and 10 pm; on all occasions the IOP was recorded by applanation tonometry in the sitting position by a masked observer. For the 10 pm diurnal pressure recording, the patients were advised to use the latanoprost drops after the pressure recording was over, in a separate waiting room. The 8 pm timolol drops were instilled in the waiting room in patients waiting for the 10 pm pressure recording. This was done to maintain the masking of the observer. In the 3-week and 6-week follow-ups on treatment with either drug, the IOP recording was done at 10 am in all cases.

At each of the follow-up visits, a masked observer carried out the patient's ocular and systemic evaluation. Ocular examination was carried out under slit-lamp biomicroscopy to rule out uveitis, iris color changes, or eyelash changes. The patients were also asked in detail about any adverse ocular and systemic events occurring during the course of the treatment. A repeat systemic examination with heart rate and blood pressure measurement was done at each follow-up visit. The efficacy of each drug was evaluated with

respect to dampening of the diurnal variation in IOP, effect on the different types of circadian cycles, and correlation of the drug efficacy with the height of the baseline peak IOP. The efficacy of each drug was also evaluated with respect to age, sex, and the presence or absence of diabetes and hypertension.

Peak pressure was defined as the highest pressure recorded in each individual circadian rhythm. Trough pressure was defined as the lowest pressure recorded in each individual circadian rhythm.

A change in the timing of the peak pressures at 3 and 7 months was recorded in each individual circadian rhythm. It was considered negative if the peak IOP in the circadian rhythm on treatment was earlier compared to the timing of the baseline peak and positive if it occurred later.

Each of the baseline circadian rhythms was classified as morning type, noon type, or evening type depending on the timing of the peak pressures recorded in that diurnal curve, as follows: morning type-peak pressures at 7 am or 10 am; noon type-peak pressures at 1 pm or 4 pm; evening type-peak pressures at 7 pm or 10 pm.

Statistical analysis was carried out on STATA Intercoled version 6.0 (Stata Corporation, College Station, Houston, TX) using Student *t*-test and one-way analysis of variance.

## RESULTS

Thirty patients (mean pressure of both the eyes) were enrolled in the study over an enrollment period of 3 months. All patients completed the study period of 7 months. The mean age of the patients was 59.65 ± 7.95 years, with a range of 44 to 76 years. There were 16 men and 14 women. The prevalence of diabetes mellitus was 10% and hypertension was 23.3%. Both diseases were controlled by oral medication. None of the patients was on oral beta-blockers for control of elevated blood pressure. The average cup:disc ratio was 0.73 ± 1.1.

Figure 1 depicts the baseline diurnal IOP, as well as the IOP on latanoprost and on timolol. Both the drugs significantly reduced IOP in comparison with baseline at all points on the diurnal curve. Latanoprost was significantly more effective in lowering IOP than timolol at 7 am, 1 pm, 4 pm, and 7 pm. At 10 am, pa-
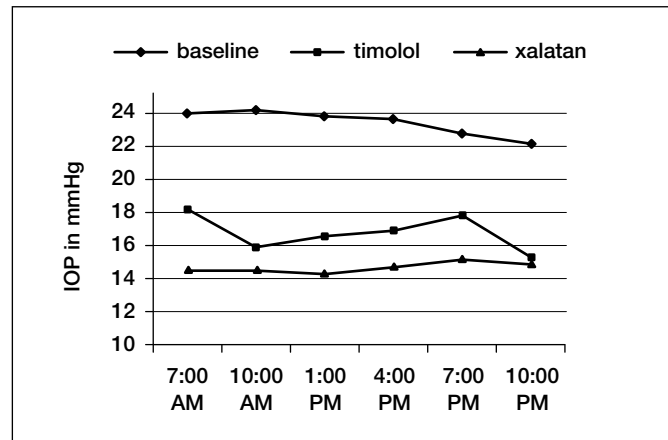


**Fig. 1 -** *Graph shows mean circadian measurements of intraocular pressure at baseline and after 3 months on latanoprost and timolol in 30 patients.*

tients on latanoprost had lower IOP compared to those on timolol, but the difference was not significant (p=0.1).

The average of the peak pressures recorded in the 30 individual baseline IOP curves was 27.6 ± 2.22 mmHg. The average of the peak pressures in each individual circadian rhythm after treatment with latanoprost for 3 months was 18.7 ± 2.71 mmHg and 21.8 ± 2.37 mmHg with timolol after 3 months of treatment. The peak IOP reduction was greater for latanoprost compared to timolol (p=0.01). In each of the individual circadian rhythms, the effect of the drugs was evaluated at the same time in the subsequent circadian rhythms when the peak pressures were recorded in the baseline curve. The average peak was reduced to 14.41 ± 2.78 mmHg on latanoprost (p<0.005) and to 18.97 ± 2.55 mmHg on timolol (p<0.005).

The average of the trough IOP recorded in each of the individual baseline IOP curves was 19.05 ± 2.05 mmHg. The average of the trough IOP recorded at any point of time on each of the diurnal curves was 12.02 ± 1.87 mmHg with latanoprost (p<0.001) and 12.9 ± 1.59 mmHg with timolol (p<0.001). The average IOP recorded at the same time as the baseline trough decreased to 14.93 ± 2.43 mmHg on latanoprost (p<0.001) and to 15.1 ± 2.91 mmHg on timolol (p<0.001).

The mean baseline IOP was 23.26 ± 2.14 mmHg and was decreased to 14.58 ± 1.63 mmHg (37% reduction) with latanoprost (p<0.01) and to 16.67 ± 1.42 mmHg (29.1% reduction) with timolol (p=0.01) (Tab. I).

**TABLE I -** DIURNAL VARIATION OF INTRAOCULAR PRESSURE (IOP) AT BASELINE AND AFTER 3 MONTHS OF THERAPY WITH LATANOPROST AND TIMOLOL IN 30 PATIENTS

| Time of IOP recording | Baseline | Latanoprost Fall in IOP mmHg ( %) | Timolol Fall in IOP mmHg (%) |
|---|---|---|---|
| 7 am | 24.02 ± 1.36 | 9.65 (40.17) | 5.91 (24.6) |
| 10 am | 24.10 ± 1.49 | 9.69 (40.21) | 8.23 (34.17) |
| 1 pm | 23.73 ± 1.59 | 9.53 (40.16) | 7.68 (31.87) |
| 4 pm | 23.57 ± 1.60 | 8.92 (37.84) | 6.73 (28.61) |
| 7 pm | 22.72 ± 1.94 | 7.71 (33.93) | 5.27 (23.18) |
| 10 pm | 22.05 ± 1.59 | 7.12 (32.29) | 6.95 (31.52) |
| Mean | 23.36 ± 1.62 | 8.84 (37.35) | 6.75 (29.11) |

peak (40.3%) was statistically significant ($p < 0.001$).

In each of the individual diurnal curves, the change in time of the IOP peak on therapy with both the drugs was compared to the time of the peak IOP on the baseline diurnal curve of the same patient. The average of this shift in the time of the peak pressures was recorded for both the drugs used (Tab. III). The results showed that with timolol, there was no significant timeshift of the peak IOP as compared to baseline in the three types of circadian rhythms, and overall the peak IOP was recorded 0.72 ± 0.3 hours earlier than that recorded in the baseline curve. Latanoprost caused the peak IOP to occur 4.34 ± 1.89 hours later in the day, especially for those with a morning or afternoon peak.

**TABLE II -** MEAN CHANGE IN INTRAOCULAR PRESSURE (IOP) ON THERAPY IN 30 PATIENTS WITH DIFFERENT CIRCADIAN RHYTHMS

| Circadian rhythm | Fall in IOP cf. baseline IOP, mmHg | | | % Change in IOP cf. baseline IOP | | |
|---|---|---|---|---|---|---|
| | Latanoprost | Timolol | p Value | Latanoprost | Timolol | p Value |
| *Morning peak:* 7 and 10 am (15 eyes) | 10.56 ± 2.81 | 5.83 ± 2.21 | <0.001 | 40.3 ± 12.5 | 21.94 ± 7.3 | <0.001 |
| *Afternoon peak:* 1 and 4 pm (6 eyes) | 9.42 ± 3.12 | 5.92 ± 2.64 | <0.001 | 36.4 ± 10.4 | 22.5 ± 8.26 | <0.001 |
| *Evening peak:* 7 and 10 pm (9 eyes) | 7.7 ± 4.22 | 5.56 ± 2.63 | <0.001 | 28.6 ± 13.4 | 20.3 ± 8.0 | <0.001 |
| Total (30 eyes) | 9.1 ± 0.49 | 5.77 ± 0.31 | <0.001 | 35.1 ± 1.7 | 21.24 ± 1.0 | <0.001 |

The circadian rhythm recorded on baseline evaluation was found to fall into one of the following three categories: those with peaks in the morning (15 eyes, 50%), noon (6 eyes, 20%), or evening (9 eyes, 30%). The fall in IOP after the use of latanoprost or timolol at the same point in time as the peak of the baseline diurnal curve was analyzed in each of the three types of patterns seen (Tab. II). Timolol was found to have a similar drop in IOP in all the three types of circadian rhythms, whereas latanoprost showed a percentage drop in IOP of 40.3% (±12.5) in those with a morning peak, 36.4% (±10.4) for afternoon peaks, and 28.6% (±13.4) in eyes having a peak at night. This difference in the efficacy of latanoprost on patients with a night peak (28.6%) as compared to patients with a morning

**TABLE III -** TIMESHIFT IN HOURS OF BASELINE PEAK INTRAOCULAR PRESSURE AFTER TREATMENT IN 30 PATIENTS

| Circadian rhythm | Change in time of peak pressure, hours | | |
|---|---|---|---|
| | Latanoprost | Timolol | p Value |
| *Morning peak:* (15 eyes) | +7.23 ± 2.1 | -0.66 ± 1.3 | <0.001 |
| *Afternoon peak:* (6 eyes) | + 3.33 ± 2.0 | -1.5 ± 4.5 | <0.001 |
| *Evening peak:* (9 eyes) | + 0.21 ± 1.4 | -0.3 ± 1.44 | 0.03 |
| Total (30 eyes) | +4.34 ± 1.89 | -0.72 ± 0.3 | <0.001 |

+ = Peak occurs later; - = Peak occurs earlier

On comparing the efficacy of latanoprost and timolol for different age groups of patients, timolol was significantly more effective in the older age group (>60 years) in the reduction of peak IOP (p<0.01). Latanoprost was found to be more effective in blunting the peak IOP in patients between the ages of 40 and 60 years (p<0.01). Changes in mean or trough IOP were not significantly different between timolol and latanoprost. Timolol appeared to be more effective clinically in patients without hypertension, although the result did not reach significant levels (p=0.07). The sex of the patient, the presence or absence of diabetes, and the height of the baseline peak, trough, and mean IOP did not affect the pressure reduction achieved with either drug. The effect of the two drugs was similar regardless of which was used first or second in the study.

The percentage of patients who achieved a mean IOP of 15 mm Hg or less was 53.3% on latanoprost and 18.3% on timolol (p<0.001) (Fig. 2). A pressure reduction of 30% or more from baseline was observed in 90% of patients on latanoprost compared to 33.3% on timolol (p<0.001) (Tab. IV).

No significant adverse effects were observed during the study period. Four patients on latanoprost complained of mild brow ache during the study period and two patients reported foreign body sensation after instilling timolol drops. None of the side effects were significant enough to result in discontinuation of therapy. There was no significant change in pulse rate or blood pressure compared to baseline with any of the medications used in our study. No significant change was noted in the color or pattern of the iris or the ocular adnexa in any of the patients on treatment.

## DISCUSSION

There are many glaucoma medications that can lower IOP significantly, and the challenge lies in their appropriate use for the individual patient. In glaucoma it is essential that IOP should be controlled around the clock. Large fluctuations of IOP (3, 4) or an uncontrolled single IOP peak may cause more damage than a steadily raised IOP.

The efficacy of latanoprost has been compared to that of timolol in multiple studies, but to our knowledge, there has been no long-term crossover study
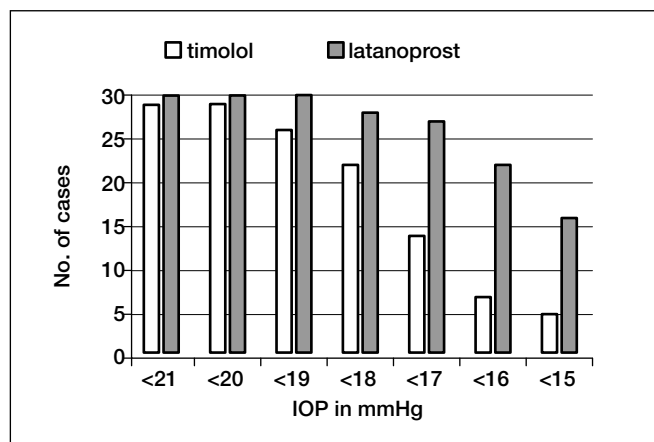


**Fig. 2 -** *Mean intraocular pressures after 3 months of therapy with latanoprost and timolol in 30 eyes.*

**TABLE IV -** PERCENTAGE REDUCTION IN INTRAOCULAR PRESSURE (IOP) AFTER 3 MONTHS OF THERAPY WITH LATANOPROST AND TIMOLOL IN 30 PATIENTS

| % Reduction in IOP from baseline | Latanoprost N (%) | Timolol N (%) |
|---|---|---|
| >40 | 9 (30) | 1 (3.3) |
| 40-35 | 10 (33.3) | 5 (16.7) |
| 35-30 | 8 (26.7) | 4 (13.3) |
| 30-25 | 2 (6.7) | 9 (30) |
| 25-20 | 1 (3.3) | 8 (26.7) |
| 20-15 | 0 (0) | 2 (6.7) |
| <15 | 0 (0) | 1 (3.3) |
| Total | 30 (100) | 30 (100) |

regarding their effect on peak IOP. The current study was undertaken to evaluate and compare the efficacy of latanoprost with that of timolol in the same group of eyes with dark brown irides. The two eye drops have a different viscosity and different administration regimens that made masking difficult. As the same patients were tested with both drugs, confounding factors were minimized.

Our study noted the highest IOP recorded at any point of time on the diurnal curve at baseline, on latanoprost, and on timolol. The reduction of this peak IOP was significantly more with latanoprost as compared to timolol. The trough IOP was also lower with latanoprost compared to timolol; however, this reduction was less than the effect on peak pressures with la-

tanoprost. There was greater dampening of the circadian rhythm of IOP with latanoprost, largely due to the differences in effectiveness at the time of the peak pressures. Orzalesi et al (2) and Racz et al (5) have also noted that latanoprost leads to a more uniform circadian rhythm. This lower fluctuation in IOP has also been shown in a previous study to show a lower rate of progression in visual field damage (6). Orzalesi et al (2) found that timolol was less effective at 3 am, a point in time we did not study, as waking up a patient for the IOP recordings introduces many nonphysiologic variabilities and results in nonphysiologic IOP recordings.

We found 50% of eyes to have a morning peak, 30% an afternoon peak, and 20% a night peak. The patients with POAG seen by Orzalesi et al all had a baseline peak in the morning (3 am–noon) (2), unlike our study. Katavisto (7) described patients with different types of diurnal variations.

Our study also evaluated the effect of these two commonly prescribed medications in patients with different diurnal rhythms. Latanoprost used at night was less effective in the control of baseline peaks that occurred in the evening (7–10 pm). A baseline circadian rhythm would help to identify patients like these, who could then be administered latanoprost in the morning instead of the usual administration at night. Timolol was equally effective in all types of circadian rhythms and appeared to work around the clock, albeit to a lesser extent.

It is important to schedule the follow-up of patients with glaucoma about the time that the highest IOP is expected, as recordings at trough level would give the patient and the ophthalmologist a false sense of security. We studied the change in timing of the highest recorded IOP with latanoprost and timolol. The time shift of peak IOP in eyes on timolol was insignificant in all types of circadian rhythms. On latanoprost the peak IOP in eyes with morning and afternoon baseline peaks were shifted 3 to 7 hours later in the day. This could be due to its waning effectiveness with time and should be used in scheduling follow-up visits.

Previous studies have shown that patients with IOP consistently below 15 mm Hg had a higher chance of remaining stable (8). However, as different patients have different baseline pressures and different target pressures, it may be reasonable to lower the IOP by at least 30% of baseline pressures to prevent pro-

gression of field loss (9). The effect of latanoprost on mean IOP was clinically more significant than that of timolol in our study in lowering the IOP below 15 mm Hg and also causing a reduction of more than 30% from baseline. This result is similar to previous studies carried out on white and Asian eyes (1, 2, 5, 10-13). Hedman and Alm (1) reported a mean fall of 7.7 ± 0.1 mmHg in a meta-analysis, as compared to a mean fall of 8.7 ± 2.2 mmHg in our study from similar baseline IOP. Aung et al (10) found a fall of 8.8 ± 1.1 mmHg after 2 weeks' use of latanoprost in pigmented eyes with angle closure glaucoma.

For reasons that are not clear, latanoprost was found to be more effective in patients 40 to 60 years of age. Timolol was more effective in patients older than 60 years. To our knowledge, this difference in effect has not been documented previously.

Owing to the use of multiple tests of statistical significance, a correction factor like Bonferroni was considered. Although Bonferroni correction may help reduce alpha error, it significantly increases the chances of beta error. Its use in medical literature is controversial (14). The p value as obtained is mentioned on the charts and the Bonferroni correction is easily deducible by a simple multiplication for the interested reader. We believe that it is best to leave the results as obtained with a description of the method used to arrive at them. However, the alpha value may be higher than indicated due to multiple measurements.

In conclusion, latanoprost was clinically more effective than timolol because it dampened the circadian rhythm of IOP, and lowered the IOP to a greater extent. Follow-up of patients on latanoprost should be scheduled, keeping in mind the baseline circadian rhythm and the fact that peak IOP on latanoprost are likely to occur a few hours later in the day. In patients with a nighttime IOP peak, one could consider changing the timing of the drug instillation so as to control the peak pressure more effectively.

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