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CLINICAL STUDY

24-h IOP control with latanoprost, travoprost, and bimatoprost in subjects with exfoliation syndrome and ocular hypertension

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Abstract

Purpose **To compare the 24-h IOP reductions induced by latanoprost, travoprost, and bimatoprost in eyes with exfoliation syndrome (XFS) associated with ocular hypertension (OH).**

Methods **This was a prospective, randomized, single masked, and parallel design study with 15 patients in each treatment group. After washout of any previous medications, each patient underwent a baseline 24-h IOP curve testing at 0600, 0900, 1200, 1500, 1800, 2100, and at 2400 (midnight) hours. Patients were then randomized to receive latanoprost, travoprost, or bimatoprost once a day for 3 months. The 24-h curve testing was repeated at first week, and first and third months.**

Results **Maximal and minimal IOP was recorded at 0600 and 1800–2100 hours. There was no significant difference among treatment groups at any time-point except for the first week. At the first week, the travoprost group had significantly lower IOP levels than the latanoprost and bimatoprost groups. All medicines significantly lowered 24-h IOP from baseline ($P = 0.001$ for each). Although there was no significant difference in IOP reduction among groups at first week and first month, bimatoprost reduced the 24-h IOP (7.9 ± 1.4) more than travoprost (6.6 ± 0.5) at the end of the third month ($P = 0.003$). The mean 24-h range of IOP was lowest with travoprost in all visits, and between-group differences was significant for travoprost *vs* latanoprost ($P = 0.007$) and travoprost *vs* bimatoprost ($P = 0.001$) at the third month.**

Conclusion **Latanoprost, travoprost, and bimatoprost were effective in reducing the 24-h IOP in patients with XFS and OH, and more research is required with a larger study.**

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Introduction

It has recently been pointed out that fluctuations in IOP seem to be an important risk factor for the progression of glaucoma.[1,2] Konstas *et al*[3,4] have shown that the diurnal range of IOP is greater in both the treated and untreated patients with exfoliative glaucoma (XFG) than in the treated and untreated patients with primary open-angle glaucoma (POAG). This may be a reason for worse prognosis for medical therapy and progressive visual field defects in XFG than those in POAG.[3–6]

Different antiglaucoma drugs can have different effects on 24-h variation of the IOP. It would be useful to detect this effect of the drugs, especially in XFG. Previous studies clearly demonstrated that topical administration of latanoprost 0.005% once daily provided a steady reduction of the IOP during both the day and night in POAG and XFG.[7–13] To the best of our knowledge, no information is available regarding 24-h curve testing or the mean range of IOP with the newer medication such as travoprost or bimatoprost in patients with exfoliation syndrome (XFS) together with

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elevated IOP. The purpose of this study was to compare the effects of three PG analogues on the 24-h IOP curve in eyes with XFS and ocular hypertension (OH).

Materials and methods

The patients were recruited from the Department of Glaucoma at the Inonu University Hospital. The local Medical Ethics Committee gave approval for the study, and informed consent form had been signed by all patients. A total of 45 consecutive patients who had XFS with elevated IOP were entered into this prospective, randomized, and unmasked study. XFS was diagnosed by observing the exfoliation material on the anterior lens surface, or both on the papillary border and on the anterior lens surface. Inclusion and exclusion criteria are listed in Table 1.

Patients already on medical treatment underwent a 4-week washout period before their admission. During hospitalization for 24 h, patients were allowed to follow on their regular lifestyle and received normal meals without any restrictions. IOP measurements were taken at 0600, 0900, 1200, 1500, 1800, 2100, and 2400 (midnight) hours. The baseline 24-h IOP curve was recorded at first. Then, the eligible eye in patients with clinically unilateral XFS, or the better eye in patients with both eyes eligible was randomized to receive one of the three medications: latanoprost 0.005% (Xalatan, Pfizer), travoprost 0.004% (Travatan, Alcon), or bimatoprost 0.03 % (Lumigan, Allergan). The other eye was also treated with the same medication in the patients with OH in both eyes. Patients were instructed to instill the eye drop once daily (2200 hours) for all the three drugs, and on proper drop spacing and nasolacrimal occlusion. They were followed up for 3 months. The patients were readmitted, and 24-h IOP measurements were repeated in the first week, first month, and at the end of the third month. A total of four 24-h tonometric curves were therefore obtained for each patient, one baseline and three different treatment curves. All measurements were completed by the same investigator using the same Goldman applanation tonometer with the patient sitting near a slit-lamp. Automated visual field test (24/2 SitaFast Humphrey) was performed at baseline and at the end of the study.

Main outcome measures were 24-h mean IOP, the mean change from untreated baseline, and the mean 24-h range (average of the highest time-point minus the lowest time-point for each individual). Data were collected as arithmetic mean $\pm$ SE. The SPSS software was used for all statistical analysis (SPSS, Chicago, IL, USA). Comparisons among the three groups were performed using a repeated-measures analysis of variance (ANOVA) with treatment (latanoprost, travoprost, or bimatoprost) as the independent variable. If the overall treatment effect was not significant ($P>0.05$), it was concluded that no difference existed between treatment means. If the overall treatment effect was significant ($P\leqslant 0.05$), pairwise comparisons of treatment means were performed using pair wise *t*-test, with the significance of each set at the 0.05 level. Friedman variance analysis was used for comparison within each group. When P was significant ($P\leqslant 0.05$), further comparison between two measurements was carried out using Wilcoxon signed rank tests. $P<0.05$ was considered as statistically significant. The mean 24-h range was also analysed by a paired *t* test within an ANOVA.

Table 1 Inclusion and exclusion criteria for the study

Inclusion criteria
Age over 50 years
Exfoliation syndrome in one or both eyes
Elevated IOP greater than 21 mmHg without glaucoma
Open angle by gonioscopy
Exclusion criteria
Absence of exfoliation material on the lens surface in the eye to be treated
Glaucomatous damage in the optic nerve head
Glaucomatous defects in visual field
Known allergy to any of the study medication
Previous intraocular or laser surgery
Previous angle-closure glaucoma attack
Patients on systemic beta blocker agents

Results

A total of 45 patients with XFS and OHT were prospectively enrolled. Following enrolment at baseline, the patients were randomized to three treatment groups: latanoprost 0.005% ($n=15$), travoprost 0.004% ($n=15$), and bimatoprost 0.03% ($n=15$). There was no difference among treatment groups with regard to age, gender, baseline IOP, and baseline visual acuity as shown in Table 2. All subjects completed the study.

Efficacy results with regard to IOP

The 24-h mean IOP measurements among groups were not statistically significant at baseline and each study visit except for the first week (Figure 1). Mean 0900 hours IOP measurements at baseline was significantly different between groups when travoprost was compared with either latanoprost (travoprost *vs* latanoprost, $P=0.007$) or bimatoprost (travoprost *vs* bimatoprost, $P=0.006$).

At the first week measurement, the travoprost group has significantly lower IOP levels than the latanoprost group at 0600 hours ($P=0.009$) and 0900 hours

Table 2 Patient demographics at baseline

Groups	*Mean age (range)*	*Gender ratio (F/M)*	*Visual acuity (mean BCVA)*	*24-h mean IOP (mmHg)*
Latanoprost ($n=15$)	61.6±9.7 (50–73)	8/7	0.8±0.15 (0.5–1.0)	23.2±1.8
Travoprost ($n=15$)	62±7.6 (50–74)	9/6	0.8±0.12 (0.5–1.0)	21.7±2.1
Bimatoprost ($n=15$)	62.4±8.2 (50–75)	8/7	0.8±0.16 (0.5–1.0)	23.3±3.4

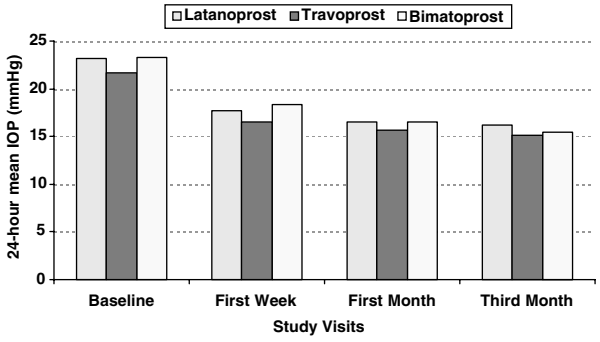

Figure 1 Mean 24-h IOP results with three medications at each study visits.

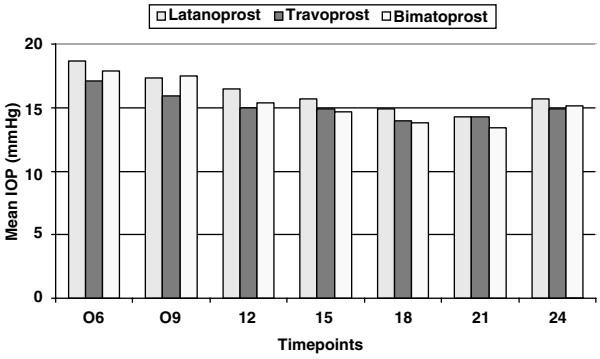

Figure 2 Mean 24-h IOP results with three medications at every time-point at the end of the third month.

($P=0.003$), and the bimatoprost group at 0900 hours ($P=0.004$) and 1500 hours ($P=0.006$).

At the first and third month, the travoprost treatment group has lower mean IOP levels than the latanoprost and bimatoprost groups at every time-point measured, although the between-group differences did not reach statistical significance (Figures 1 and 2).

By month 3, latanoprost, travoprost, and bimatoprost significantly lowered IOP from baseline ($P=0.001$ for all) (Figures 1 and 2). Maximum IOP measurement was recorded at 0600 hours in all the three groups at every visit in both the untreated (baseline) and the treated period. The most common time of minimal IOP was 1800 and 2100 hours for all study medications (Figure 2).

The mean 24-h range of IOP was lowest with travoprost in all study visits, and between-group differences was significant at the end of the third month (travoprost *vs* latanoprost, $P=0.007$; travoprost *vs* bimatoprost, $P=0.001$) (Figure 3).

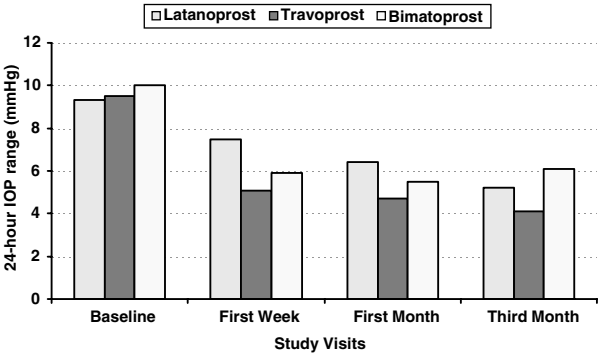

Figure 3 Mean 24-h IOP range with three medications at each study visit.

Efficacy results with regard to IOP reduction from baseline

Generally, all three study medicines have similar reductions in 24-h IOP at every time-point measured. The estimated 24-h mean IOP reductions and the percentage of these reductions for each treatment group at each follow-up study visit are shown in Figure 4.

Although there was no statistically significant difference in the estimated 24-h mean IOP reduction among the three study groups at the first week and first month, bimatoprost reduced the 24-h IOP more than travoprost at the end of the third month ($P=0.003$). The between-group differences reached statistical significance at 0900 hours (bimatoprost *vs* travoprost, $P=0.014$; bimatoprost *vs* latanoprost, $P=0.015$), and at 1200 hours (bimatoprost *vs* travoprost, $P=0.005$) in the third month. Latanoprost also reduced IOP more efficiently than travoprost ($P=0.008$) at 0900 hours in the third month.

Mean IOP reductions within each group among all study visits were statistically significant. In all study groups, 24-h mean IOP reduction between the first week and first month and between the first week and third month were statistically significant. In only travoprost group, 24-h mean IOP change between the first and third month was also significant ($P=0.002$).

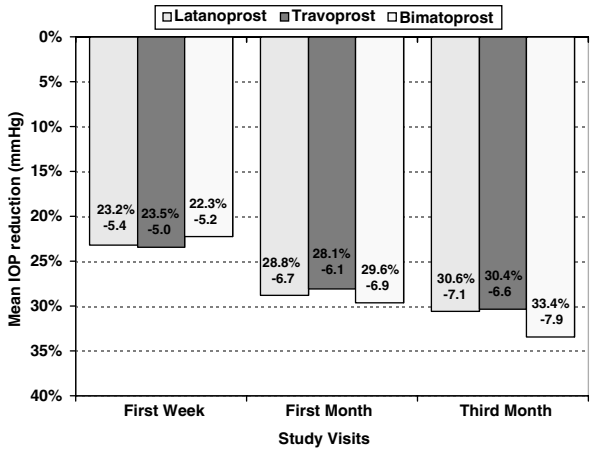

Figure 4 Percentage of 24-h mean IOP reductions from baseline in three treatment groups at each study visit.

Discussion

We present a clinically relevant study evaluating the 24-h IOP efficacy of latanoprost, travoprost, and bimatoprost specifically in patients with XFS and OH. To the best of our knowledge, this is a novel comparison to determine if there is a clinically meaningful IOP difference among three prostaglandins in patients with XFS and OH. We think it is of clinical value with the inclusion of a seven time-points IOP curve (almost a 24-h curve with readings between 0600 and 2400 hours). This study also evaluated the effects of three PG analogues at night, for which little information exists.[14] We documented the immediate 24-h IOP response at 1 week, as well as the longer term comparisons (1 and 3 months) with these three medications.

However, the parallel design and the numbers employed (15 patients in each group) are weak points for this study. To evaluate the IOP, ANOVA test among the three groups and *t*-test within the ANOVA for pair-wise comparison were used as a stronger test. A rationale for excluding patients with glaucomatous damage is to get a pure and homogenous population for each group. We do not include safety data, because observational side effects of these three drugs have been well known for years.

By 3 months, we found no significant differences in efficacy among the three medications with regard to IOP. At the third month, however, IOP reduction from baseline with bimatoprost was significantly greater than that with travoprost (Figure 4), and travoprost has significantly narrow range of IOP than the other two medications (Figure 3). The baseline IOP was lower in the travoprost group than in the latanoprost and bimatoprost treatment groups (21.7 mmHg *vs* 23.2 and 23.3 mmHg, respectively). Although statistically not significant, this IOP difference of 1.5 mmHg may be clinically important. For this reason, the comparisons of mean IOP values may be relatively meaningless, and we focused on IOP reduction from the untreated baseline and range of IOP. The difference between travoprost and latanoprost or bimatoprost efficacy after 1 week highlights the quicker hypotensive action of travoprost. This study confirmed that the efficacy with PGs improves slightly over time, and at 3 months, these drugs may reach maximum efficacy.

IOP has been thought to be typically lowest during the night, and peaks in the early morning, from about 0700 to 1000 hours, or during the day, both in normal and glaucoma subjects.[15] Some individuals also have a nocturnal spike in IOP.[16] A single IOP measurement does not reflect the dynamic equilibrium of IOP during the 24-h cycle. There is often poor correlation between a single IOP reading and the peak, or fluctuation of 24-h IOP. Since glaucoma is a 24-h disease, it is logical that we should aim to determine and control the IOP throughout the 24-h cycle. Studies evaluating 24-h IOP control are superior to studies that only include 1–3 daytime IOP measurement, and may provide a more complete picture of the efficacy of all glaucoma treatment options.[17]

Our 24-h IOP curves do not include the entire nocturnal sleep period. There was a gap between 2400 (midnight) and 0600 hours in the morning. Sleep studies, however, have shown that IOP peaks in glaucoma patients just after patients wake up. Mosaed *et al*[18] found the peak IOP occurred at the end of the nocturnal sleep period in both glaucoma patients and control subjects. In patients with POAG and XFG, the 24-h IOP findings are in accordance with most publications in the relevant literature in that the highest IOP values are generally found in the morning.[3,4,13,14,19,20] Konstas *et al*[3,14] reported that the most common time of maximal IOP for both POAG and XFG is 1000 hours. In our study subjects with XFS and OH, the evening and night time sitting IOP measurement were generally lower, and this is in accordance with most studies in the literature with POAG and XFG patients like Konstas *et al*'s[4] study. We found IOP spike at 0600 hours, and there was no rise of IOP at night (between 1800 and 2400 hours). However, there was a real IOP difference between the 0600 and 0900 hours time-points. The most common time of minimal IOP was 2000 hours in Parrish *et al*'s[20] study, 0200 hours in Konstas *et al*'s[14,19] study, and 6 hours in the present study.

Konstas *et al*[3] previously documented that there were significant differences in the diurnal curve of IOP during the nontreatment phase in the patients who had XFG compared with age- and sex-matched patients who had POAG. They evaluated the 24-h response with timolol 0.5% and showed that despite a greater initial IOP reduction in subjects with XFG, they still had a higher

mean IOP and a greater fluctuation in diurnal IOP curve than subjects with POAG.[4]

Prostaglandin analogues are potent ocular hypotensive agents and were almost chosen as a first-line therapy in POAG. However, there are limited data with respect to the efficacy of this medication in controlling 24-h IOP variation in XFG or XFS with elevated IOP. The study by Konstas *et al*[7] suggests that latanoprost provides statistically lower morning IOP and more favourable diurnal IOP range than timolol maleate in the treatment of XFG. To date, there is no comparative study evaluating the efficacy of the newer prostaglandins such as travoprost and bimatoprost in XFS eyes. In this prospective study, we investigated the efficacy of these drugs on the 24-h IOP variation in eyes with XFS and OH.

The similar ocular hypotensive effects of latanoprost, travoprost, and bimatoprost in this study are consistent with most previous studies[14,19–21] in patient with POAG or OH. Parrish *et al*[20] performed a first randomized, parallel-group, and controlled trial simultaneously comparing the IOP lowering efficacy and safety of latanoprost, bimatoprost, and travoprost in patients with POAG or OH. Over 12 weeks, they found no significant differences in efficacy among the three medications. Although their study populations and the number of time-points for IOP measurement (they included four time-points) differ from those of the present study, they reported a similar diurnal mean IOP of 16.7, 16.8, and 16.4 mmHg, and mean IOP reduction levels of 7.0, 6.2, and 7.3 mmHg at week 12 for those treated with latanoprost, travoprost, and bimatoprost, respectively.

The relevant literature comprising 24-h IOP studies are more pertinent as a comparison measure than studies that only included 3–4 time-points. In a current crossover trial, Konstas *et al*[14] evaluated latanoprost *vs* bimatoprost in only POAG patients. This study showed that both treatments provided a statistical reduction in IOP from untreated baseline at each individual time-point and for the diurnal curve. When treatment groups were compared directly, there was a greater reduction with bimatoprost for the diurnal curve. Walters *et al*,[21] in a randomized, multicentre, prospective, and parallel-group study in patients with POAG or OH, measured IOP eight times over a 24-h period for 28 days. They showed that the 24-h mean IOP was significantly lower with bimatoprost than with latanoprost ($P = 0.003$). In their study, the mean IOP reduction from baseline with bimatoprost (9.3 mmHg, 40.3%) was also significantly greater than the mean IOP reduction with latanoprost (7.4 mmHg, 33.3%) at 1000 hours (peak drug effect) on day 28. Their results are not consistent with the 3-month results of the present study with regard to mean IOP reduction (Figure 1). In our study, the mean pressure-lowering effect of bimatoprost (7.9 mmHg, 33.4%) and latanoprost (7.1 mmHg, 30.6%) are less than that reported in the study by Walters *et al*.[21]

Lack of variation has been shown in several studies to be important in helping to prevent long-term progressive VF loss with glaucoma.[1,2,22] We additionally evaluated the mean range of IOP as Konstas *et al*'s[14] study. The untreated mean range of IOP is approximately 7 mmHg in previous reports. In the present study, we found 9.3, 9.5, and 10 mmHg range of 24-h IOP levels at untreated baseline in latanoprost, travoprost, and bimatoprost treatment groups, respectively. Prostaglandins generally obtain a narrow range of 24-h IOP. In their study, Konstas *et al*[14] demonstrated that latanoprost provided a mean range of 4.0 mmHg, and bimatoprost showed a better mean range of 3.5 mmHg. In our study population with XFS and OH, the range of 24-h IOP was 5.2 mmHg for latanoprost, 4.1 mmHg for travoprost, and 6.1 mmHg for bimatoprost. Travoprost showed significantly lower mean range IOP in this study. The further reduction in mean range of IOP with travoprost was consistent with the lower mean IOP levels than latanoprost and bimatoprost at every time-points measured. Our results on mean range of IOP at baseline and study visits were not consistent with Konstas *et al*'s[14] study. It was more difficult to explain in our study the increase in fluctuation with bimatoprost only between the first and the third month. The differences might be because of the different study populations (XFS and OH *vs* POAG) or different baseline IOP ranges (for bimatoprost, 10.0 ± 1.7 in this study *vs* 7.0 ± 2.6 in Konstas *et al*'s study[14]). There may be some alternative explanations for this finding (e.g. worse compliance, or more side effects with bimatoprost). This topic requires further elucidation with a crossover study.

In conclusion, this 3-month study demonstrates that latanoprost, bimatoprost, and travoprost have similar IOP-lowering effect in patients with XFS and OH. Although the results suggest a trend toward greater IOP-lowering efficacy with bimatoprost, the differences were only significant between bimatoprost and travoprost at the end of the third month. This may be because of the parallel design and the small sample.

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