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# Comparison of intraocular pressure lowering effect of once daily morning vs evening dosing of latanoprost/timolol maleate combination

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PURPOSE. *To compare intraocular pressure (IOP) reduction profiles of latanoprost-timolol maleate fixed combination (LTFC) administered in the morning or evening in primary open angle glaucoma (POAG).*

METHODS. *A prospective, randomized study including 60 eyes of 30 patients with POAG was carried out. Patients were randomized to treatment with LTFC at 8 PM (Group 1) or at 8 AM (Group 2). After therapy of 4 weeks, IOP was measured at 2 AM, 6 AM,10 AM, 2 PM, 6 PM, and 10 PM and compared with baseline values and latanoprost therapy alone.*

RESULTS. *Mean diurnal baseline IOPs and IOPs after treatment with latanoprost and LTFC were 23.6±2.6, 16.7±2.3, and 15.5±2.2 mmHg in Group 1 and 23.1±2.6, 16.9±2.4, and 15.7±2.4 mmHg in Group 2. LTFC lowered IOP more than latanoprost at all time points in both groups ($p<0.001$) (except 6 AM in Group 2). The mean IOP range after LTFC therapy was lower than the baseline in Group 1 whereas it was not different in Group 2. IOP at 10 AM was significantly higher than the other time points at baseline measurements in both groups ($p<0.01$) but after treatment there was no difference ($p>0.05$). According to IOP reduction from baseline, there was a statistically significant difference between groups in favor of Group 1 at 6 AM, 10 AM, and mean diurnal measurement ($p<0.01$).*

CONCLUSIONS. *Both morning and evening dosing of LTFC were effective in lowering diurnal IOP in patients with POAG. However, evening dosing of LTFC seemed to be more effective in controlling IOP especially in the morning and avoiding the fluctuations with lower range of IOP. (Eur J Ophthalmol 2008; 18: 60-5)*

KEY WORDS. *Fixed combination, Glaucoma, Intraocular pressure, Latanoprost/timolol*

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## INTRODUCTION

High intraocular pressure (IOP) is considered to be the most important risk factor for progressive damage in primary open angle glaucoma (POAG) and its reduction continues to be the reasonable way of treating the disease. Adjunctive therapy, combination of medications, is important to many POAG patients in order to control the IOP at a level that will help to maintain vision and to retard or prevent additional damage to the optic nerve, when a single medication does not adequately lower IOP.

One of these fixed-combination products is 0.005% latanoprost–0.5% timolol maleate fixed combination (LTFC) (Xalacom, Pfizer, New York, NY, USA), which has become available in many countries recently. The β-adrenergic receptor antagonist timolol maleate, one of the components of Xalacom, lowers IOP by reducing the production of aqueous humor (1). Timolol is administered twice daily in standard practice; however, its IOP lowering effect has been reported to last for at least 24 hours (1, 2). In some studies it has been suggested that β-blockers do not lower the production of aqueous humor during sleep and when administered in the evening, IOP does not decrease during the night and these patients are less protected

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during the critical nighttime period (3, 4). Timolol also has been shown to provide excellent additivity of IOP lowering effect with other ocular hypotensives like latanoprost (5), the other component of Xalacom, which is the first prostaglandin $F_{2\alpha}$ analogue to be commercially available and lowers the IOP by facilitating uveoscleral outflow of aqueous humor (6). Latanoprost monotherapy reduces IOP by 32%. The maximal IOP reducing effect of latanoprost has been reported to be 8–12 hours after administration, but it has also been reported to have maximal IOP lowering effect later, at 12 to 18 hours (7). Administered once daily, it leads to a reduction in IOP through the night comparable to its daytime effect (4, 8). In some studies it has been demonstrated that nighttime dosing of latanoprost provides lower daytime IOPs compared with morning dosing while other studies have reported no difference in response to therapy in patients who received latanoprost in the morning vs in the evening (9-12). It has been shown that, as monotherapy, latanoprost is more effective than timolol maleate 0.5% (5). Furthermore, the efficacy of LTFC given once daily provided greater IOP lowering than either monotherapy alone (9, 13).

Timolol has been shown to have no effect on aqueous humor production at night (14). As the daytime aqueous humor flow is more than the nighttime values, it seems more reasonable to give timolol in the morning (15). But it is also known that nighttime dosing of latanoprost provides lower daytime IOPs compared with morning dosing (10, 11). Because of these findings, the administration time of LTFC, in the morning or in the evening, should be researched.

The purpose of this study was to compare the efficacy (IOP lowering effect) of the LTFC once daily morning vs evening dosing in patients with POAG.

## PATIENTS AND METHODS

This study was designed as a prospective, single-center, randomized, and investigator masked study, to compare the IOP lowering effect of once daily morning vs evening dosing of the LTFC.

All patients enrolled in this study agreed to participate and met the inclusion and exclusion criteria and signed an informed consent agreement before any procedures were performed. The study was performed in accordance with the ethical principles as described in the Declaration of Helsinki.

All patients in this study had to demonstrate a clinical diagnosis of POAG and were required to have a baseline IOP of at least 21 mmHg before treatment, typical glaucomatous visual field loss determined by automated static threshold perimetry (Humphrey 30-2, Humphrey Field Analyzer, Humphrey Instruments, San Leandro, CA), glaucomatous optic nerve head changes, and normal appearing open angles. All patients needed to have a visual acuity better than 20/200 in either eye.

Exclusion criteria were any condition preventing reliable applanation tonometry, inadequate visualization of the fundus, conjunctivitis, keratitis, uveitis, progressive retinal or optic nerve disease other than glaucoma, intraocular surgery or laser surgery, or severe ocular trauma at any time. Patients who had a risk of visual field or visual acuity worsening, had a cup-disc ratio of 0.8 or worse, were unwilling to accept a risk of iris color or eyelash changes, were at risk for uveitis or cystoid macular edema, had a history of ocular herpes simplex, or had a history of hypersensitivity to any components of the preparations used in this study were excluded from the study. A severe medical or psychiatric condition, inability to adhere to a treatment, reactive airway disease, second or third degree atrioventricular block, congestive heart failure, concomitant use of systemic beta-blockers, history of bronchial asthma, or pregnancy or nursing were also considered reasons for exclusion from the study.

At all visits Snellen visual acuity measurements and slit-lamp biomicroscopy were performed and the diurnal IOP was measured; patients also had gonioscopy, funduscopy, and automated full-threshold perimetry by Humphrey Field Analyzer. Patients were admitted to the hospital in the morning and the 24-hour diurnal IOP measurements were performed at 2 AM, 6 AM,10 AM, 2 PM, 6 PM, and 10 PM. At each visit, local and systemic adverse effects occurring during the treatment were recorded.

Patients with POAG were enrolled in the study and underwent a run-in with 0.005% latanoprost (Xalatan, Pfizer, New York, NY, USA) once every evening at 8 PM. Those not reaching target IOP determined according to the patients' ophthalmologic findings and/or with progression of the disease were randomly assigned to receive LTFC once daily every evening at 8 PM or every morning at 8 AM. Four weeks after treatment all measurements were performed again.

During the study, the investigators, masked to the treatment regimen, measured the IOP with the same calibrated Goldmann applanation tonometer. Although IOP mea-

surements were performed for both eyes, for statistical analysis we justified the use of both eyes from the same subject and we used the average of right and left eyes for each patient.

Statistical analysis was performed using SPSS 13.0 for Windows (SPSS Inc.). To compare the IOPs between two groups at each time point and for the diurnal curve (average of the all time points) and also to compare the IOP reduction from baseline after LTFC therapy, Mann-Whitney *U* test was used. Analysis of variance test (ANOVA) was used to compare the IOPs between time points in each group and to compare the IOPs between baseline and after therapy with latanoprost and LTFC within the groups. A Bonferroni correction was used to adjust the p value at individual time points over the 24-hour diurnal curve. To compare the IOPs after latanoprost and LTFC administration, Wilcoxon test was used in both groups. Statistical analysis of between-group differences in sex was performed using the chi-square test. Age and central corneal thickness were compared using the Mann-Whitney *U* test. The significance level was set at 5% and a two-way analysis was used for all tests.

All patients enrolled in this study signed informed consent agreement and the study was performed in accordance with the ethical principles as described in the Declaration of Helsinki.

## RESULTS

Fifty patients with POAG were enrolled in the study and 30 of these patients, treated inadequately with latanoprost, were evaluated. Thirty eyes of 15 patients received LTFC at 8 PM (Group 1) and 30 eyes of the other 15 patients received LTFC at 8 AM (Group 2). There were eight women and seven men in Group 1 and seven women and eight men in Group 2 (p=0.715). The mean age of the patients was 66.4±10.2 years (range 45–80) and 62.3±8.1 years (range 49–75) in Groups 1 and 2, respectively (p=0.229). Mean central corneal thickness was 539.9±21.2 mm in Group 1 and 534.9±17.6 mm in Group 2 (p=0.646).

The mean baseline IOPs and standard deviations for patients included in this trial were shown in Table I. When the IOPs in two groups were compared to each other, at each time point and for the diurnal curve, there was no statistical difference between the groups, according to baseline IOPs, IOPs after treatment with latanoprost, and

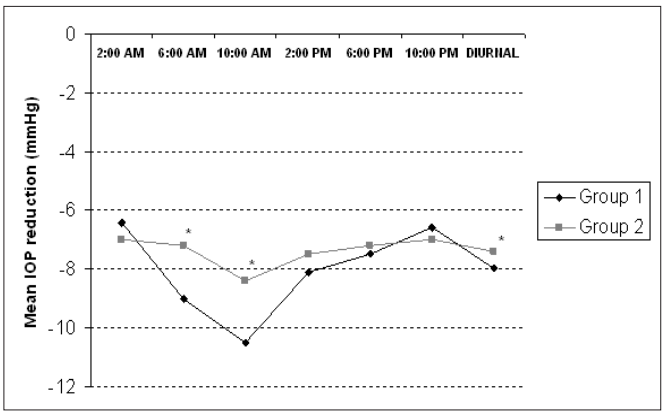


**Fig. 1 -** *Mean intraocular pressure reduction levels from baseline: comparison of 0.005% latanoprost–0.05% timolol maleate fixed combination dosed at 8 pm (Group 1) vs 8 am (Group 2). *Statistically significant difference between groups (p<0.01).*

treatment with LTFC (p>0.05). After LTFC therapy, the greatest differences between groups were seen at 6 and 10 AM and the IOPs in Group 1 were manifestly lower than the IOPs in Group 2 at these time points, but this was not statistically significant (p=0.210 and p=0.092, respectively).

Both latanoprost and LTFC therapy dosed at 8 PM (Group 1) reduced the IOP from baseline statistically significantly at each time point and for the diurnal curve (p<0.001). LTFC administration also lowered the IOP more than latanoprost at all time points (p<0.001), but only at time point 2 AM p value was 0.039 (p<0.05). When range of the IOP was taken into consideration, it was seen that the mean range in LTFC therapy (4.3±1.2 mmHg) was lower than the baseline (5.9±2.5 mmHg) in Group 1 (p=0.027). Latanoprost therapy dosed at 8 PM and LTFC therapy dosed at 8 AM (Group 2) again provided a statistical reduction in IOP from baseline for the diurnal curve (p<0.001). LTFC administration also lowered the IOP more than latanoprost in Group 2 at all time points (p<0.001) except 6 AM (p=0.276). Although mean IOP range was also lower than baseline (5.4±2.8 mmHg) in LTFC (4.3±2.5 mmHg) therapy, this was not statistically significant in Group 2 (p=0.087). The range of diurnal IOP seemed to be lower in LTFC therapy dosed at 8 PM.

When IOPs between all time points were compared within groups, it was seen that IOP at 10 AM was significantly higher than the other time points at baseline measurements in both groups (p<0.01). After treatment, diurnal IOP measurements were not statistically different between time points (p>0.05).

After LTFC therapy IOP reduction from baseline at 2 AM, 6

**TABLE I -** MEAN BASELINE DIURNAL INTRAOCULAR PRESSURE LEVELS (mean±SD mmHg) OF PATIENTS RECEIVING 0.005% LATANOPROST –0.05% TIMOLOL MALEATE FIXED COMBINATION AT 8 PM (Group 1) AND AT 8 AM (Group 2)

| Time | Group 1 | Group 2 | p value |
|---|---|---|---|
| 2 am | 22.3±4.1 | 22.0±2.8 | 0.917 |
| 6 am | 23.9±2.7 | 23.4±3.1 | 0.349 |
| 10 am | 25.9±3.2 | 25.1±2.5 | 0.261 |
| 2 pm | 23.5±3.0 | 23.4±3.1 | 0.786 |
| 6 pm | 23.3±2.9 | 22.6±3.4 | 0.349 |
| 10 pm | 22.5±2.8 | 22.3±3.2 | 0.617 |
| Diurnal | 23.6±2.6 | 23.1±2.6 | 0.455 |
| Mean range | 5.9±2.5 | 5.4±2.8 | 0.489 |

**TABLE II -** MEAN INTRAOCULAR PRESSURE REDUCTION LEVELS (mean±SD mmHg) OF PATIENTS RECEIVING 0.005% LATANOPROST –0.05% TIMOLOL MALEATE FIXED COMBINATION AT 8 PM (Group 1) AND 8 AM (Group 2)

| Time | Group 1 | Group 2 | p value |
|---|---|---|---|
| 2 am | –6.4±1.8 | –7.0±1.0 | 0.614 |
| 6 am | –9.0±1.4 | –7.2±0.5 | <0.001 |
| 10 am | –10.5±1.3 | –8.4±0.7 | <0.001 |
| 2 pm | –8.1±1.0 | –7.5±0.8 | 0.069 |
| 6 pm | –7.5±1.0 | –7.2±1.9 | 0.983 |
| 10 pm | –6.6±1.2 | –7.0±1.0 | 0.241 |
| Diurnal | –8.1±0.8 | –7.4±0.6 | 0.011 |

AM, 10 AM, 2 PM, 6 PM, and 10 PM and diurnal curve were as follows, respectively: in Group 1-29.1%, 37.7%, 40.5%, 34.5%, 32.2%, 29.3%, and 34.3%; and in Group 2-31.8%, 30.8%, 33.5%, 32.1%, 32.3%, 31.8%, and 32.0% (Fig. 1). There was a statistically significant difference between groups at 6 AM ($p<0.001$), 10 AM ($p<0.001$), and mean diurnal measurement ($p=0.011$) (Tab. II).

There were no reported serious ocular or systemic adverse events in either group.

## DISCUSSION

Glaucoma is a 24-hour disease and any medication administered must be effective all night and day. From the studies mentioned above (1, 2, 4, 5, 7-13), it is clearly seen that timolol maleate has maximum effect when administered in the morning, whereas latanoprost has maximum effect when administered in the evening. So the question is: When should LTFC be instilled to have its maximum effect—in the morning or in the evening?

Morning dosing of the LTFC has been evaluated in several studies (16). A single dose of LTFC administered in the morning has been shown to provide maximal IOP reduction of 12.4 mmHg after 6.4 hours with a reduction in IOP levels still evident 48 hours after administration (17). Also, a greater IOP reduction was seen during the daytime compared with night (18). Stewart and associates (19) have noted that the LTFC was more effective at 6–12 hours after dosing. In another study maximal effect of the LTFC has been noted to be 6–7 hours after administration (17). Morning administration of the LTFC was timed to provide peak aqueous suppression during the daytime, when aqueous formation is great. In regulatory trials it was shown that morning dosing of the fixed combination therapy reduced the IOP further compared with latanoprost therapy alone by 1.1 (9), 1.2 (13) mmHg and with timolol maleate alone by 1.9 (13), 2.9 (9) mmHg. It was seen that the IOP pattern corresponds to the pattern of each drug, with the effect of timolol first setting in and then the effect of latanoprost with a long-lasting, rather than stable reduction of IOP (17). In addition, the morning administration of LTFC therapy has been said to enhance patient compliance and reduce the risk of nocturnal arterial hypotension that is sometimes associated with the nighttime use of β-blockers. Konstas et al (20) demonstrated a mean reduction of 7.5 mmHg with LTFC dosed in the evening compared with baseline over the 24-hour diurnal curve. In Stewart et al's (19) study, LTFC dosed in the evening had a trend towards greater efficacy for the fixed combination 4–12 hours after dosing.

Konstas et al (11) have evaluated the efficacy and safety of concomitant latanoprost and timolol maleate, dosed either each evening or morning, and found that both dosing regimens reduced the IOP significantly at each time point and for the diurnal curve, when compared with timolol maleate twice daily dosing. They have also found that morning dosing of concomitant timolol maleate and latanoprost therapy was generally statistically equal to evening dosing. However, a trend has been observed for morning dosing to provide better nighttime pressure control and evening dosing to provide greater daytime pressure control. The difference was significant at 6 AM with

the evening-dosed group demonstrating a lower pressure. The range of diurnal pressure control was statistically better with latanoprost alone or LTFC dosed in the evening vs morning (11, 21).

In regulatory trials there has been relative lack of efficacy of the fixed combination over latanoprost alone, but this has not been explained completely. However, it was mentioned partly to be caused by once daily dosing of timolol maleate and instillation of LTFC in the morning whereas latanoprost alone was administered in the evening (9, 16, 19, 20).

In this study, evening dosing of latanoprost was used first and then the therapy was changed to LTFC administered in the morning or in the evening. A direct 24-hour diurnal IOP comparison between morning and evening administration of LTFC was performed to be helpful in addressing the issue of its preferred instillation time.

After evening dosing of LTFC diurnal IOP was decreased 8.1 mmHg from baseline and 1.2 mmHg from latanoprost therapy, and after morning dosing, IOP was decreased 7.4 and 1.2 mmHg from baseline and latanoprost therapy, respectively. After LTFC therapy, the greatest differences between groups were seen at 6 AM (1.3 mmHg) and 10 AM (1.3 mmHg) and the IOPs were manifestly lower at these time points when LTFC was administered in the evening. Furthermore, IOP reduction from baseline was significantly lower at 6 AM (1.8 mmHg), 10 AM (2.1 mmHg), and diurnal measurements (0.7 mmHg) after evening administration of LTFC than morning administration.

The pattern of the daily IOP cycle has classically been described as having the peak IOP in the morning hours (22). In our study, baseline IOPs at 10 AM were higher than the other time points in both groups, considering that any medication must have its maximum effect around 10 AM. After treatment, as mentioned above, the greatest IOP reductions from baseline in both groups were around 10 AM, where IOPs were maximum and moreover evening dosing was more effective than the morning dosing.

The reported mean amplitude of the daily fluctuation ranges approximately between 3 and 6 mmHg (22, 23). In our study the mean range of the IOP showed a trend to be lower with the LTFC therapy. This also seemed to be lower and statistically significant in the evening dosing, showing that the evening dosing of LTFC may also avoid IOP fluctuations.

In conclusion, both morning and evening dosing of LTFC was effective in lowering diurnal IOP in patients with POAG, with 0.7 mmHg greater effect of the latter. It is also found that evening dosing of LTFC controls IOP around 10 AM better than the morning dosing. Although morning dosing is preferred by many patients and ophthalmologists, these results suggest that additional studies are needed to determine whether evening dosing of LTFC is more effective in controlling IOP.

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