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A comparison of travoprost, latanoprost, and the fixed combination of dorzolamide and timolol in patients with pseudoexfoliation glaucoma

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PURPOSE. *To compare the intraocular pressure (IOP) lowering effect and safety of latanoprost, travoprost given every evening, and the fixed combination dorzolamide + timolol (DTFC) given twice daily in pseudoexfoliation glaucoma (PXG).*

METHODS. *This randomized, prospective, investigator-masked study has been conducted with 50 PXG patients. Patients were assigned to one of three groups: travoprost 0.004%, fixed combination of dorzolamide 2%+timolol 0.5%, or latanoprost 0.005% for 6 months. At baseline and 0.5, 1, 2, 3, 4, 5, and 6 months of therapy, IOP (8 am, 10 am, 4 pm), blood pressures, and pulse rates were measured, and ophthalmologic examination was performed. The side effects were recorded at each visit.*

RESULTS. *Forty-two of the 50 patients initially enrolled completed this study. Withdrawn patients included one (latanoprost) for lack of efficacy, five (three travoprost, one latanoprost, one DTFC) for adverse events, and two (one latanoprost, one DTFC) for loss of follow-up. Each of the three drugs considerably reduced the IOP in PXG cases throughout the 6 months. Mean IOP reduction at 6 months was –9.3±2.9 mmHg in the travoprost group, -8.2±1.2 mmHg in the latanoprost group, and 11.5±3.3 mmHg in the DTFC group. Comparing the groups, DTFC is more effective than latanoprost and travoprost in lowering IOP ($p<0.05$). There was no difference between travoprost and latanoprost. The most common treatment-related adverse event was conjunctival hyperemia. Intensity of ocular hyperemia was greater in the travoprost group compared with the latanoprost and DTFC groups ($p<0.05$). There were no significant effects on systemic safety parameters.*

CONCLUSIONS. *The results demonstrated that DTFC is more effective in reducing IOP than latanoprost and travoprost. Latanoprost and travoprost had similar ocular hypotensive effects in patients with PXG. All three drugs were well tolerated; there were fewer ocular side effects attributable in the latanoprost group. (Eur J Ophthalmol 2006; 16: 73-80)*

KEY WORDS. *Dorzolamide, Glaucoma, Latanoprost, Pseudoexfoliation, Timolol, Travoprost*

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INTRODUCTION

Pseudoexfoliation syndrome is the most common identifiable cause of glaucoma. Pseudoexfoliation glaucoma (PXG) is clinically and histopathologically different from primary open angle glaucoma (POAG). The level of intraocular pressure (IOP) and diurnal variation of IOP in untreated newly diagnosed patients with PXG were higher than those in patients with POAG. PXG has a more serious clinical course than POAG. PXG may progress faster and may result in irreversible blindness more often. Surgical intervention is more frequently needed (1-4).

Dorzolamide + timolol fixed combination was found

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to be as effective as the concomitant administration of its components in reducing IOP (5). This combination has simplified the therapy for patients needing these two medications. Latanoprost is an ester prodrug analogue of prostaglandin F 2α, which is widely used clinically as an ophthalmic solution.

The persistent IOP-lowering effect of the drug is created by increasing the uveascleral outflow of aqueous humor rather than altering the conventional trabeculocanalicular aqueous outflow (6, 7). Travoprost is also an esterified prostaglandin F2α analogue, which may be useful as a monotherapy for glaucoma or as an adjunct to other ocular hypotensive agents (8-10).

Several studies have been compared with dorzolamide + timolol fixed combination and latanoprost in patients with POAG (5).

However, the efficacy of IOP and side effects of new glaucoma medications in patients with PXG may differ from that of patients with POAG (4, 11). There are few studies evaluating the efficacy and side effects of the new glaucoma medications in PXG.

More recently, Konstas and Kozobolis demonstrated that latanoprost and dorzolamide + timolol fixed combination had effects in reducing the IOP in patients with PXG (12). The efficacy and side effects of travoprost have not yet been presented in patients with PXG.

The purpose of the present study is to compare the IOP-lowering efficacy and safety of latanoprost, travoprost, and DTFC in patients with PXG followed for a 6-month period.

PATIENTS AND METHODS

Patients

This study was conducted with 50 randomized patients with PXG, treated and followed at Kocaeli University Faculty of Medicine, Ophthalmology Department. This was a randomized, investigator-masked, clinical, prospective study conducted in accordance with the ethical principles set forth in the Declaration of Helsinki. The patients were divided into three groups: 18 patients in the travoprost group, 16 patients in the latanoprost group, and 16 patients in the timolol-dorzolamide fix combination group. All the patients enrolled in the study were diagnosed with PXG. The diagnosis of PXG was made according to deposition of pseudoexfoliation material on the anterior lens capsule and at the pupillary border accompanied by glaucomatous optic neuropathy, visual field damage, and an IOP of more than 22 mmHg without treatment. Patients who were taking glaucoma medication underwent a washout period of 3 weeks for b antagonists and prostaglandins, 2 weeks for a and ab agonists, 5 days for miotics, and 5 days for oral or topical carbonic anhydrase inhibitors. Patients with an IOP grater than 36 mmHg were excluded due to potential risk.

Other factors for exclusion included a cup-to-disc ratio greater than 0.8 in either eye, a history of ocular infection or ocular inflammation within the past 3 months, chronic and recurrent inflammatory eye disease, history of ocular trauma within the past 6 months,

TABLE I - DEMOGRAPHIC AND BASELINE CHARECTERISTICS OF STUDY PATIENTS

	Travoprost, n=18	**Latanoprost, n=16**	**Timolol and dorzolamide, n=16**
Sex, n (%)			
Female	9 (50)	7 (43.7)	9 (56.2)
Male	9 (50)	9 (56.2)	7 (43.7)
Age, mean ± SD	65.8±8	67.0±8	66.7±8
Iris color			
Brown	16	15	14
Blue	1	-	1
Green	1	1	1
Cup-to-disk ratio, mean ± SD	0.4±0.2	0.3±0.2	0.3±0.1
Washout required/Yes, n (%)	9 (50)	8 (50)	5 (31.2)
Mean ± SD baseline intraocular pressure	25.3±3	23.5±1	25.5±3

intraocular surgery within the past 6 months, a history of progressive retinal disease or a history of severe ocular pathology in either eye that would preclude the administration of a topical b blocker or prostaglandin, a history of severe or serious hypersensitivity to prostaglandins or systemic b blockers, a history of severe unstable or uncontrolled cardiovascular, hepatic, or renal disease, bronchial asthma, or severe chronic obstructive pulmonary disease that would preclude the safe administration of a topical b blocker. In addition, patients who were under medication of any glucocorticoid or topical nonsteroidal anti-inflammatory agents were excluded.

The study visits included one visit for baseline data and on therapy visits at week 2 and at months 1, 2, 3, 4, 5, and 6. IOP measurements were performed at 8:00 am, 10:00 am, and 4:00 pm. Prerandomization baseline data included ocular and medical his-

TABLE II - DIFFERENCES IN INTRAOCULAR PRESSURE (IOP) AND MEAN DIURNAL IOP, BASELINE TO MONTH 6

		Travoprost	Latanoprost	DTFC	p*	p†	p‡
	Baseline mean IOP	25.4±3.0	23.8±1.7	25.7±3.9			
2-week	Mean diurnal IOP	16.1±3.2	16±2.5	14.3±2.6	0.992	0.224	0.299
	Mean reduction	-9.2±3.1	-7.8±1.9	-11.3±3.6	0.434	0.156	0.011*
1-month	Mean diurnal IOP	15.9±2.5	16.6±2.3	13.6±2.4	0.696	0.048*	0.008*
	Mean reduction	-9.4±2.9	-7.1±2.6	-12±3.2	0.112	0.065	0.000*
2-month	Mean diurnal IOP	16.5±3.1	16±2.2	14.2±1.7	0.852	0.052	0.181
	Mean reduction	-8.8±3	-7.8±2.4	-11.4±3	0.606	0.054	0.006*
3-month	Mean diurnal IOP	16±2.4	15.8±1.9	14.5±1.8	0.980	0.152	0.239
	Mean reduction	-9.4±3.1	-8±1.4	-11.2±3.5	0.420	0.226	0.018*
4-month	Mean diurnal IOP	16±2.7	16.9±1.5	14.1±1.4	0.502	0.042*	0.003*
	Mean reduction	-9.3±2.9	-6.8±1.7	-11.5±3.4	0.072	0.098	0.000*
5-month	Mean diurnal IOP	16±2.8	16.7±2.9	14.2±1.6	0.735	0.151	0.036*
	Mean reduction	-9.4±2.9	-7.1±2.9	-11.5±3.5	0.153	0.187	0.003*
6-month	Mean diurnal IOP	16±2.8	14.3±1.9	14.1±1.6	0.866	0.060	0.198
	Mean reduction	-9.3±2.9	-8.2±1.2	-11.5±3.3	0.522	0.049*	0.007*

Group1 = Travoprost, group 2 = Latanoprost, group 3 = Dorzolamide and timolol fixed combination (DTFC)
* Compared with Latanoprost and Travoprost
† Compared with Travoprost and DTFC
‡ Compared with Latanoprost and DTFC

tory, slit lamp biomicroscopy examination, dilated fundus examination, cup-to-disc ratio, gonioscopy, best-corrected visual acuity (Snellen scale), IOP measurement, evaluation of ocular hyperemia, inflammatory cells and aqueous flare, resting pulse rate, and blood pressure.

The patients underwent IOP measurements at 8.00 am, 10.00 am and 4.00 pm on the same day. One of the results of these measurements was required to be between the range of 22 to 36 mmHg. Patients were divided into three groups. The first group was the travoprost group, the second group was the latanoprost group, and the third group was the DTFC group. Although both eyes could have met these criteria, only one eye of each patient was included in the study.

Examinations for the study visits were performed as follows: IOP is measured at 8:00 am, 10:00 am, and 4:00 pm measurements. Besides IOP, conjunctival hyperemia, visual acuity, biomicroscopy, resting pulse, and blood pressure were also evaluated at the second week, and months 1, 2, 3, 4, 5, and 6. Iris and eyelash photography was taken on the first day, third month, and sixth month.

The IOP measurement was determined by the same examiner with a recently calibrated Goldmann applanation tonometer. IOP was measured at least twice in each eye, and if the difference between the readings was greater than 2 mmHg, a third reading was taken. IOP was reported as either the mean of two readings or median of three readings.

Conjunctival hyperemia assessment was made by the same observer in ambient light before IOP measurements and instillation of fluorescein. Conjunctival hyperemia scale was 0 = none/trace, 1 = mild, 2 = moderate, 3 = severe. Photographs of each eye were taken to assess any change in iris pigmentation or eyelash characteristics. Iris color classifications were brown, blue, green, or hazel.

Mean outcome measures and analyses

Fisher least significant difference procedure was used to compare the treatment groups.

Continuous variables were tested for treatment group differences using one-way analysis of variance (ANOVA) with treatment. If the overall treatment effect was significant ($p<0.05$), the comparison of treatment means was performed using Tukey tests; categorical variables were analyzed using Pearson χ^2 test. Within the treatment groups IOP changes were tested with paired t test.

RESULTS

Patients

The demographic characteristics of the treatment groups are presented in Table I. There were no statistically significant differences between the treatment groups in age distribution, sex, iris color, ocular diagnosis, or cup-to-disc ratio.

Baseline IOP values

The results of the patients who underwent washout of other IOP-lowering agents were similar between the treatment groups. Of the 50 patients, 42 (84%) completed the 6-month study.

A similar percentage of patients in each treatment

TABLE III - ADVERSE EVENTS REPORTED DURING THE STUDY

	Travoprost	**Latanoprost**	**DTFC**
Conjunctival hyperemia	7 (38.8)*	1 (6.2)	2 (12.5)
Mild	1 (5)	1 (6.2)	2 (12.5)
Moderate	3 (16.6)	-	-
Severe	3 (16.6)	-	-
Allergic conjunctivitis	-	-	1 (6.2)
Taste disturbance	-	-	1 (6.2)
Headache	1 (5)	1 (6.2)	-
Visual acuity decrease	1 (5)	1 (6.2)	1 (6.2)

*$p<0.05$
DTFC = Dorzolamide and timolol fixed combination

group discontinued the study: 1 (latanoprost) for lack of efficacy, 5 (3 travoprost, 1 latanoprost, 1 dorzolamide + timolol) for adverse events, and 2 (1 latanoprost, 1 DTFC) for loss of follow-up.

Intraocular pressure

IOP reductions from the baseline produced by all three medications at each time point were statistically significant at each measurement time ($p<0.05$). At all follow-up timepoints, mean diurnal IOP reductions ranged from -8.8 to -9.4 mmHg for travoprost, -6.8 to -8.2 for latanoprost, and -11.0 to -12.0 for DTFC. At the end of 6 months, mean diurnal IOP was 16.0 ± 2.8 mmHg in the travoprost group, 14.3 ± 1.9 mmHg in the latanoprost group, and 14.1 ± 1.6 mmHg in the DTFC group.

At the end of 6 months, mean diurnal IOP decrease from baseline was -9.3 ± 2.9 mmHg in the travoprost group, -8.2 ± 1.2 mmHg in the latanoprost group, and 11.5 ± 3.3 mmHg in the DTFC group; the differences between groups were statistically significant for DTFC vs latanoprost and DTFC vs travoprost ($p<0.05$) but there was no difference between travoprost and latanoprost (Tab. II, Fig. 1).

Side effects

The most common treatment-related adverse event reported was conjunctival hyperemia: 38.8% of the travoprost patients, 12.5% of the DTFC group patients, and 6.2% of the latanoprost patients ($p<0.05$). In the travoprost group, 3 patients (16.6%) had severe hyperemia, 3 (16.6%) had moderate hyperemia, and 1 (5%) had mild hyperemia. Three patients with severe hyperemia were excluded from the study in the travoprost group. Both of the patients in the DTFC group had mild hyperemia, and the patient in latanoprost group had mild hyperemia. The patients with conjunctival hyperemia were complaining of itching and burning. One patient in the DTFC group was withdrawn owing to ocular irritation and allergic conjunctivitis. Two patients in the DTFC group reported taste disturbances. One patient was complaining of headache in the latanoprost group. We did not observe any other complaints during the study. At the end of 6 months visual acuity decreased 2 lines in one patient in the travoprost group and one patient in the DTFC group, and 1 line in one patient in the latanoprost group (Tab. III).

There was no clinically significant difference according to changes in inflammatory cells and aqueous flare,

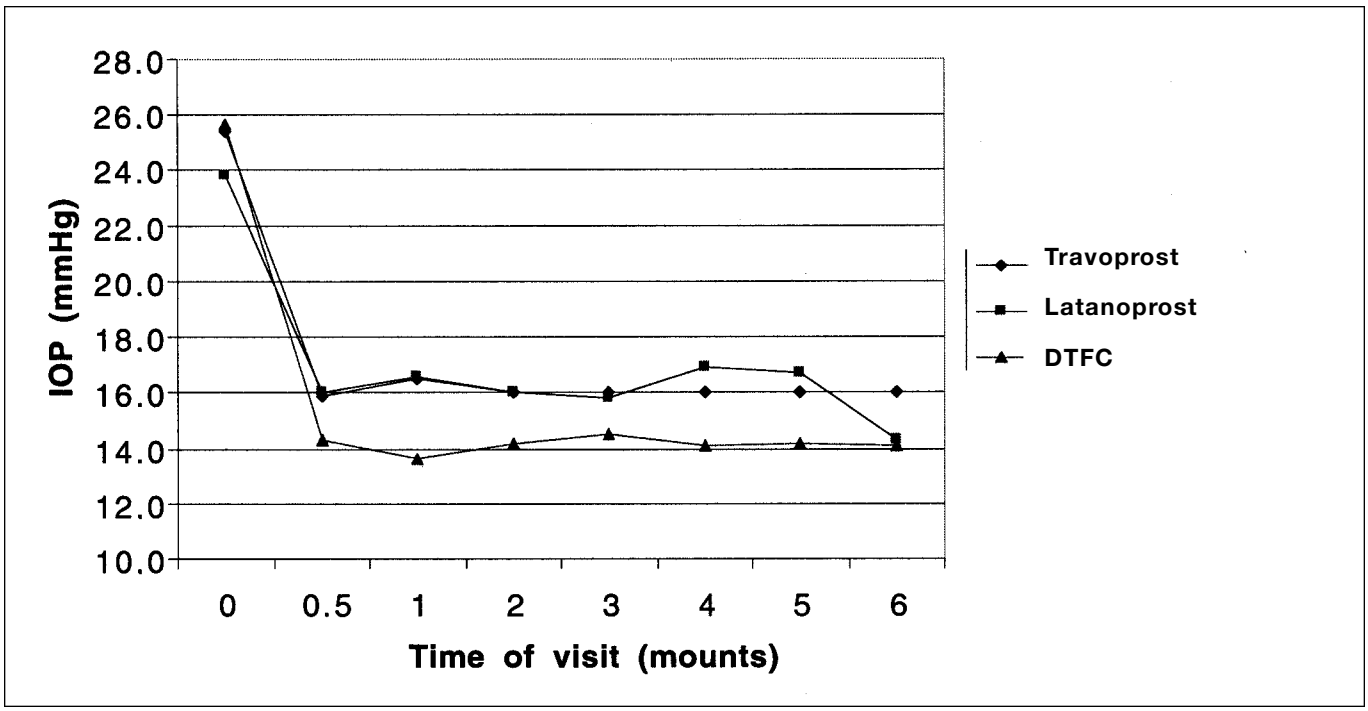

Fig. 1 - *Mean intraocular pressure (IOP) by measurement times at baseline and month 6.*

fundus parameters, cup-to-disc ratio, iris pigmentation, eyelash characteristics including length, thickness, density, and color, pulse rate, and systolic and diastolic blood pressure.

DISCUSSION

In this study we evaluated the effects and side effects of three different topical glaucoma drugs in patients with PXG during a 6-month period. All of the three drugs significantly reduced the baseline IOP at each time point. DTFC reduced the mean IOP from baseline significantly more than latanoprost and travoprost. No significant difference was found between travoprost and latanoprost in lowering IOP.

We found that mean diurnal IOP lowering effect of travoprost monotherapy in patients with PXG at 6 months was –9.3±2.9 mmHg (36.5%). There is no other study investigating the effects of travoprost on patients with PXG, so we evaluated our results comparing the studies done on patients with ocular hypertension and patients with POAG. In one of these studies, patients with POAG and patients with ocular hypertension were treated for 12 months with travoprost once daily and mean decrease from baseline was 7.1 mmHg (28%) (8). In the study carried out by Franzco (13), it was 8–8.9 mmHg (31–34%). Although it is known that response to conventional medical therapy is low in patients with PXG, this study provided evidence for the IOP-lowering effect of travoprost during the 6-month period. Travoprost can be chosen as a first-line therapy in patients with PXG.

In this study, the mean diurnal decrease of IOP was -8.2±1.2 mmHg (34%) in the latanoprost group at the end of 6 months. Konstas and Kozobolis (12) found that the mean decrease of IOP was 40.2% in patients with PXG. Hedman and Alm (14) found that mean IOP decrease was 31% after 6 months latanoprost therapy in POAG and ocular hypertensive cases. In a similar study, IOP decrease was found to be 33.7% by Watson and Stjernschantz (15). The equivalent ocular hypotensive effects of latanoprost and travoprost in this study are consistent with previous studies (8, 16). In this study, the mean baseline IOP in the latanoprost group was lower than in the travoprost group and the DTFC group but this did not reach the level of statistical significance. This difference might affect the level of IOP reduction with latanoprost.

We found that mean diurnal IOP lowering effect of DTFC in patients with PXG at 6 months was -11.5±3.3 mmHg. Previous studies have shown that DTFC combination decreased IOP between 20% and 27% from the baseline in patients with POAG (5, 17, 18).We found slightly greater mean IOP reductions for DTFC compared to latanoprost or travoprost in patients with PXG. In another study comparing latanoprost to DTFC in patients with PXG, Konstas and Kozobolis (12), in a 2-month crossover study in newly diagnosed previously untreated patients with PXG, found that IOP lowering effects were not different between those treated with latanoprost or DTFC. However, when they compared the mean maximum IOP decrease values of each drug, they found that lowering effect of DTFC was higher than latanoprost. In previous studies, the timolol-dorzolamide fixed combination has been shown to be equal in efficacy to latanoprost monotherapy in POAG (15, 16, 19-23). Medical treatment of PXG is more difficult than in POAG; IOP is usually higher at the time of diagnosis, and diurnal fluctuations are also higher. It has been shown that response to medical therapy is weaker than it is in POAG (1-3). In this study, we observed that these three drugs could be used effectively in patients with PXG; in addition, the results found greater IOP-lowering efficacy with DTFC than latanoprost and travoprost.

Common beliefs in the therapy of PXG may be revised by the new studies that show the effectiveness of the new treatments.

In this study, DTFC twice daily provided better IOP control than travoprost and latanoprost once daily. For patients with PXG, diurnal fluctuation of IOP is higher than in patients with POAG (2). Because damage to the optic nerve might be associated with fluctuations in IOP (24), a drug that consistently controls IOP in the day and night may be an important choice for the medical treatment of PXS glaucoma. The daytime fluctuations of the present study allowed comparison of IOP fluctuations between treatments groups because IOP levels most commonly peak in the morning hours (25). Konstas et al (26) reported that the 24-hour diurnal IOP was lowered more effectively with DTFC compared to latanoprost in POAG.

All three drugs were well tolerated with very few discontinuations for adverse effects. The most frequent

side effect was conjunctival hyperemia with itching and burning. Hyperemia was higher in the travoprost group. We observed that severe hyperemia appeared in the early period of the treatment during the first week. Orengo-Nania et al (9) reported the travoprost hyperemia rate as 35.9%. Netland et al (8) found hyperemia rates of 50% in the travoprost group, 28% in the latanoprost group, and 14% in the timolol group in a 12-month study. They reported not having seen any severe hyperemia in the same study. Latanoprost also was reported to cause less discomfort than DTFC (22). Only one case of headache was noted in a patient receiving latanoprost therapy. There is only one study reporting three patients who had headache during latanoprost treatment (27). The side effects seen in the present study were similar to those seen in previously published clinical trials about POAG.

In conclusion, 6-month results showed that all three drugs could be a choice in PXG treatment. In addition, DTFC is significantly better than either latanoprost or travoprost in lowering IOP in PXG. All drugs were well tolerated, but there were less ocular side effects attributable to the latanoprost group. Further studies that evaluate 24-hour IOP control and long-term use of these drugs are needed to determine the efficacy and side effects.

The authors have no commercial or proprietary interest in this study.

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