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Comparison of Efficacy and Safety of Latanoprost versus Fixed Combination of Tafluprost and Timolol in Patients with Primary Open-Angle Glaucoma

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Abstract

Background: Glaucoma is a progressive disease that requires lifelong treatment to maintain visual function. Elevated intraocular pressure (IOP) is considered the most important treatable risk factor for disease development and progression. The present prospective study was initiated to compare the IOP lowering efficacy and safety of the preservative-free (PF) fixed combination of 0.0015% tafluprost and 0.5% timolol maleate (FCTT) administered once daily versus 0.005% latanoprost (LT) once daily.

Materials and Methods: One hundred newly diagnosed patients with primary open-angle glaucoma (POAG) who fulfilled the inclusion/exclusion criteria were enrolled and randomized into two groups. The first LP group was prescribed 0.005% latanoprost eye drops once daily, whereas the second FCTT group was prescribed a PF fixed combination of 0.0015% tafluprost and 0.5% timolol once daily. In both groups, IOP was recorded at baseline, at the end of the fourth, eighth, and twelfth weeks, and six months after, and any adverse effects were assessed. The primary efficacy endpoint, absolute mean IOP reduction six months after LP or FCTT treatment from baseline IOP, was statistically significant for both treatment groups (P<0.0001). However, the IOP-lowering efficacy of latanoprost was superior to FCTT. In the LP group, IOP decreased from 26.32±2.0 mmHg at baseline to 18.4±1.57 mmHg six months after treatment with a mean reduction of 8.60±1.57 mmHg (31.8%). In the FCTT group, IOP decreased from 26.23±1.97 mmHg at baseline to 17.49±1.28 mmHg six months after treatment, with a mean reduction of 6.51±1.28 mmHg (27.1%). Latanoprost caused a greater reduction in mean IOP than FCTT in the second follow-up visit (P<0.05), the third follow-up visit (P<0.05), and the difference was much greater in the fourth follow-up visit (P<0.0001)

Conclusion: The absolute mean IOP reduction from baseline at six months is statistically significant in LP or FCTT treatment. Compared to FCTT, 0.005% latanoprost administered once daily has a more significant IOP-lowering effect and safety for up to six months.**(International Journal of Biomedicine. 2024;14(4):621-625.)**

Keywords: primary open-angle glaucoma • latanoprost • tafluprost • timolol • fixed combination • intraocular pressure

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Abbreviations

IOP, intraocular pressure; **LT**, latanoprost; **LTFC**, latanoprost plus timolol fixed combination; **OHT**, ocular hypertension; **POAG,** primary open-angle glaucoma; **PGs,** prostaglandins; **PGA**, prostaglandin analogs; **PF**, preservative-free; **TAF/TIM**, Tafluprost/Timolol.

Introduction

Glaucoma is a leading global cause of blindness.[1,2] An estimated 76 million people worldwide are currently diagnosed with open-angle glaucoma or angle closure glaucoma, and this number has been projected to reach 112 million by the year 2040.[1,2] Elevated intraocular pressure (IOP) is considered the most important treatable risk factor for disease development and progression.[2-7]

Glaucoma is a progressive disease that requires lifelong treatment to maintain visual function. A primary treatment for primary open-angle glaucoma is topical medication to reduce

IOP. It is commonly recommended to initiate the treatment with monotherapy in glaucoma guidelines, and sometimes, the addition of a second drug should be considered when the initial monotherapy has not succeeded in reaching the target IOP.[2] Topical prostaglandins (PGs), with their potent ocular hypotensive effect (mainly due to increased uveoscleral outflow), are an important treatment option for glaucoma.[8] Latanoprost, a PGF2α analog, is an FDA-approved eye drop in the glaucoma treatment by IOP reduction. Tafluprost is another PGF2α analog with the same mechanism.[9] When IOP is insufficiently controlled using topical monotherapy, combination therapies containing a prostaglandin analog (PGA) and beta-blocker are frequently prescribed.[10-17] A fixed combination of 0.0015% tafluprost and 0.5% timolol maleate (FCTT) provides favorable control of IOP with a good safety profile.[18-20]

The present prospective study was initiated to compare the IOP lowering efficacy and safety of a fixed combination of 0.0015% tafluprost and 0.5% timolol maleate (FCTT) administered once daily versus monotherapy with 0.005% latanoprost (LT) once daily.

Materials and Methods

This prospective study was conducted in the Clinic of Ophthalmology at the University Clinical Center of Kosovo.

Patients

Eligible patients for the study were 30 years or older and diagnosed as having unilateral or bilateral primary open-angle glaucoma (POAG). They were expected to visit the clinic according to the observation schedule determined in the study protocol and provide written informed consent. The exclusion criteria included any corneal abnormalities or other diseases that could interfere with accurate IOP measurement with a Goldmann applanation tonometer (GAT); a history of corneal refractive surgery; corrected visual acuity of 0.6; advanced visual field defects; active extraocular disease, or ocular or eyelid inflammatory or infectious diseases; a history of anterior or intraocular surgery; a history of glaucoma surgery, including laser treatment; allergy to the ingredients used in this study; pregnancy, lactation, possibly pregnancy, a wish to become pregnant during the study period or unable to conduct appropriate contraception during the study; scheduled medications or therapies prohibited during the study period; contraindications to beta-blockers, such as bronchial asthma or poorly controlled cardiac failure; anyone the principal or other investigators considered ineligible for enrollment.

During the study period, the patients were prohibited from using anti-glaucoma eye drops other than the study drugs, oral or intravenous IOP-lowering agents, or corticosteroid drugs. Ocular laser surgery and invasive surgery were also prohibited.

Procedures

This study was designed as a prospective, single-arm, open-label trial. During the study period, each patient routinely underwent a comprehensive clinical examination that included measuring IOP with a calibrated GAT, slit-lamp biomicroscopy, fundoscopy, blood pressure determination, and heart rate measurement. Visual acuity tests were conducted at the time of enrollment and the end of the study. During the six months, patients were instructed to administer one drop of study medication once daily at approximately 9 PM. Patients with unilateral disease were treated only in the affected eye.

During the treatment period, scheduled visits were performed at baseline and the end of weeks 4, 8, 12, and 6 months of treatment. IOP was calculated at 9 AM. A deviation of ±30 minutes from the measurement time was permitted.

The study included 100 POAG patients who were grouped into two groups. The first LP group (n=51) was prescribed 0.005% latanoprost eye drops once daily, whereas the second FCTT group (n=49) was prescribed the preservative-free (PF) fixed combination of 0.0015% tafluprost and 0.5% timolol once daily. The primary efficacy endpoint was absolute mean IOP change six months after LP or FCTT treatment from baseline IOP. Adverse events are defined as any undesirable medical event.

Statistical analysis

Statistical analysis was performed using the statistical software package SPSS version 22.0 (SPSS Inc, Armonk, NY: IBM Corp). Baseline characteristics were summarized as frequencies and percentages for categorical variables and mean (M) ± standard deviation (SD) for continuous variables. The Friedman test, a nonparametric repeated measures ANOVA, was used to assess the change from baseline for multiple follow-up time points within a study, and the Wilcoxon signed-rank test was used for pairwise comparisons between the baseline measurement and each follow-up time point to identify where the significant change occurred. The Mann-Whitney U Test was used to compare the differences between the two independent groups. A probability value of $P<0.05$ was considered statistically significant.

Results

The clinical characteristics of patients included in the study are presented in Table 1.

Table 1.
General characteristics of the patients.

Variable	PT group n=51	FCTT group n=49
Gender		
Female	31 (60.8%)	27 (55.1%)
Male	20 (39.2%)	22 (44.9%)
Age, year	74.8±11.0	69.7±10.7
Place of residence		
Village	31 (60.8%)	8 (16.3%)
Town	20 (39.2%)	41 (83.7%)
Cup/Disc ratio	0.45±0.11	0.44±0.13
Baseline IOP, mmHg	26.32±2.00	26.23±1.97

The primary efficacy endpoint, absolute mean IOP change six months after LP or FCTT treatment from baseline

IOP, was statistically significant for study participants in both groups (P<0.0001). The mean reduction in IOP from baseline was also statistically significant at each interim study visit (P<0.0001) in both groups (Table 2). However, the IOP-lowering efficacy of latanoprost was superior to FCTT. In the LP group, IOP decreased from 26.32±2.0 mmHg at baseline to 18.40±1.57 mmHg six months after treatment with a mean reduction of 8.60±1.57 mmHg (31.8%). In the FCTT group, IOP decreased from 26.23±1.97 mmHg at baseline to 17.49±1.28 mmHg six months after treatment, with a mean reduction of 6.51±1.28 mmHg (27.1%). Latanoprost caused a greater reduction in mean IOP than FCTT in the second follow-up visit (P<0.05), the third follow-up visit (P<0.05), and the difference was much greater in the fourth follow-up visit (P<0.0001) (Table 3).

Table 2.

Change in IOP from baseline at the first, second, third, and fourth follow-up in study groups.

	IOP (mmHg)	*P*-value*	IOP reduction from baseline (mmHg)	MPR (%)	*P*-value^
	LT group				
Baseline	26.32±2.00		-	-	
First follow-up	20.71±1.86		5.61±2.09	21.1	<0.0001
Second follow-up	19.21±1.62	<0.0001	7.79±1.62	28.9	<0.0001
Third follow-up	18.73±1.59		8.27±1.59	30.6	<0.0001
Fourth follow-up	18.40±1.57		8.60±1.57	31.8	<0.0001
	FCTT group				
Baseline	26.23±1.97		-	-	
First follow-up	20.36±1.90		3.64±1.90	15.2	<0.0001
Second follow-up	18.57±1.83	<0.0001	5.43±1.83	22.6	<0.0001
Third follow-up	18.13±1.68		5.87±1.68	24.4	<0.0001
Fourth follow-up	17.49±1.28		6.51±1.28	27.1	<0.0001

**Friedman test; ^ Wilcoxon signed-rank test; MPR, mean percentage reduction in IOP from baseline*

Table 3.

Comparison of mean IOP reduction in the study groups by Mann-Whitney U test.

Visit	LT group	FCTT group	Mann-Whitney U test	*P*-value
Baseline	26.32±2.00	26.23±1.97	U'=5124.0	0.759
First follow-up	20.71±1.86	20.36±1.90	U'=5477.0	0.241
Second follow-up	19.21±1.62	18.57±1.83	U'=5948.5	0.020
Third follow-up	18.73±1.59	18.13±1.68	U'=5888.0	0.029
Fourth follow-up	18.40±1.57	17.49±1.28	U'=6839.0	<0.0001

Adverse reactions occurred in more subjects in the FCTT group (Table 4) than in the LP group (Table 4).

Table 4.

Adverse effects of LT and TTFC (n/%)

Adverse effects	LT group n=51	FCTT group n=49
Blurred vision	1 (2.0)	2 (4.1)
Burning	1 (2.0)	3 (6.1)
Conjunctival hyperemia	2 (3.9)	3 (6.1)
Dry eye	2 (3.9)	3 (6.1)
Headache	2 (3.9)	1 (2.0)

Discussion

Fixed combinations of PGA and timolol are widely used in treating glaucoma because they have several advantages. The simplified dosing regimen of fixed combinations improves patient compliance.[21] Fixed combinations reduce ocular exposure to preservatives.[22,23] Preservative-free (PF) glaucoma medications are generally better tolerated than preservative eye drops.[24]

In the present study, we evaluated and compared the IOP-lowering efficacy and safety of the PF fixed combination of 0.0015% tafluprost and 0.5% timolol maleate (FCTT) administered once daily versus 0.005% latanoprost (LT) once daily. The primary efficacy endpoint, absolute mean IOP reduction six months after LP or FCTT treatment from baseline IOP, was statistically significant for both treatment groups (P<0.0001). However, the IOP-lowering efficacy of latanoprost was superior to FCTT. In the LP group, IOP decreased from 26.32±2.0 mmHg at baseline to 18.40±1.57 mmHg six months after treatment with a mean reduction of 8.60±1.57 mmHg (31.8%). In the FCTT group, IOP decreased from 26.23±1.97 mmHg at baseline to 17.49±1.28 mmHg six months after treatment, with a mean reduction of 6.51±1.28 mmHg (27.1%).

The results of Hollo et al.[20] show that the capacity to reduce IOP in patients with open-angle glaucoma or ocular hypertension with the medications is approximately 32–36% from the mean baseline pressures of around 24–29 mmHg.

In a combined analysis of the two TAF/TIM phase III studies,[20,25] an analogous linear relationship between the baseline IOP and level of IOP reduction was seen, and IOP decreases up to 40% and beyond were achieved when the baseline IOP was 31 mmHg or higher. Such pressure reductions would be very beneficial in treating glaucoma with high IOP. Moreover, the results of Pfeiffer et al.[25] suggest that the superiority of TAF/TIM over the underlying monotherapies (0015% tafluprost once daily and 0.5% timolol twice daily) was more pronounced in patients with a high baseline IOP. These results indicate that baseline IOP has a distinct role in interpreting study results and needs to be considered when choosing the correct treatment option.

Several fixed-combination (FC) therapies are currently available for the treatment of glaucoma. In a multicenter study by Shoji et al.,[26] the ocular hypotensive effect of travoprost plus timolol (TTFC) and latanoprost plus timolol fixed combinations (LTFC) in patients with normal-tension

glaucoma (NTG) pre-treated for 12 weeks with dorzolamide plus timolol fixed combination (DTFC) and achieving a mean baseline IOP of 14.8±3.3 mmHg, was compared. The mean reduction in IOP at 12 weeks was significantly greater in the TTFC group than in the LTFC group (-2.4±2.3 mm Hg vs. -1.1±2.3 mm Hg; *P*=0.021). The tolerability profiles of both treatments were similar.

Latanoprost/timolol (LTFC) is a commonly used FC. Xing et al.[27] conducted a meta-analysis of 16 trials to compare the IOP-lowering effects of LTFC with other FCs for patients with POAG and ocular hypertension (OHT). LTFC was as effective as travoprost/timolol FC and dorzolamide/timolol FC, but worse than bimatoprost/timolol FC in controlling mean IOP and IOP fluctuation for POAG or OHT patients.

Li et al.[28] conducted a systematic review and network meta-analysis to assess the comparative effectiveness of first-line medical treatments in patients with POAG or ocular hypertension. The meta-analysis included 114 RCTs with data from 20 275 participants. The mean reductions (95% credible intervals) in IOP (mmHg) at 3 months ordered from the most to least effective drugs were as follows: bimatoprost 5.61 (4.94; 6.29), latanoprost 4.85 (4.24; 5.46), travoprost 4.83 (4.12; 5.54), levobunolol 4.51 (3.85; 5.24), tafluprost 4.37 (2.94; 5.83), timolol 3.70 (3.16; 4.24), brimonidine 3.59 (2.89; 4.29), carteolol 3.44 (2.42; 4.46), levobetaxolol 2.56 (1.52; 3.62), apraclonidine 2.52 (0.94; 4.11), dorzolamide 2.49 (1.85; 3.13), brinzolamide 2.42 (1.62; 3.23), betaxolol 2.24 (1.59; 2.88), and unoprostone 1.91 (1.15; 2.67). Bimatoprost, latanoprost, and travoprost were among the most efficacious drugs.

Conclusion

The absolute mean IOP reduction from baseline at six months is statistically significant in LP or FCTT treatment. Compared to FCTT, 0.005% latanoprost administered once daily has a more significant IOP-lowering effect and safety for up to six months.

Ethical Considerations

The study was conducted in accordance with the ethical principles of the WMA Declaration of Helsinki (1964, ed. 2013) and approved by the Ethics Committee of the University Clinical Center of Kosovo (Ref. Nr.11389 dated 10.28. 2022). Written informed consent was obtained from all participants.

Competing Interests

The authors declare that they have no competing interests.

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