·Clinical Research·

Intraocular pressure-lowering effects of commonly used fixed combination drugs with timolol in the management of primary open angle glaucoma

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Abstract

• AIM: To evaluate intraocular pressure (IOP)-lowering effect and ocular tolerability of brimonidine/timolol, dorzolamide/timolol and latanoprost/timolol fixed combination therapies in the management of primary open angle glaucoma.

• METHODS: Each drug was administered for two months, after which a circadian tonometric curve was recorded using a Goldmann applanation tonometer. Ocular discomfort (conjunctival hyperemia, burning or stinging, foreign body sensation, itching, ocular pain) of each eye was assessed by the subject on a standardized ocular discomfort scale.

• RESULTS: Among the three study groups, there were no significant differences in the mean baseline IOP measurements, mean 2nd mo IOP measurements, and mean (%) change of IOPs from baseline. Among the three study groups, there were no significant differences in the mean IOP measurements obtained at circadian tonometric curves at baseline and at two months controls. In sum brimonidine/timolol, dorzolamide/timolol and latanoprost/timolol fixed combination therapies showed similar effects on IOP levels.

• CONCLUSION: Brimonidine/timolol, dorzolamide/timolol and latanoprost/timolol fixed combination therapies showed similar lowering efficacies on IOP levels whereas there was no any difference between each other.

• KEYWORDS: intraocular pressure; primary open angle glaucoma; brimonidine/timolol; dorzolamide/timolol; latanoprost/timolol

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INTRODUCTION

Glaucoma has been established as the second leading cause of world blindness, which may affect 60.5 million people worldwide in 2010, and 79.6 million in 2020, and approximately 74% of glaucoma patients have primary open-angle glaucoma (POAG)[1]. The treatment of glaucoma focuses mainly on lowering intraocular pressure (IOP) [2]. During the last decades, effective interventions have been developed to slow down that process, and there is ongoing development of methods to detect glaucoma earlier, to monitor progression more reliably and to treat glaucoma more effectively. A recent meta-analysis of the IOP-lowering effect of glaucoma drugs showed a maximum mean IOP reduction of 33% from baseline IOP in the case of monotherapy [3]. However, many patients require more than one medication to achieve adequate IOP reduction [4,5].

More recently, to maximize patient medication adherence and quality of life, several fixed combinations of commonly used IOP-lowering medications have been developed [6]. Current commercially available, fixed combination drugs mostly include the topical beta-blocker 0.5% timolol combined with a prostaglandin analogue, an alpha-adrenoceptor agonist or a topical carbonic anhydrase inhibitor [7,8]. More and more clinical trials are published to evaluate the efficacy of these fixed combination options. However, the non-consistent results of these studies made it difficult to draw conclusions of the degree of reduction of IOP that can be achieved with different fixed combination drugs.

The aim of the present study was to evaluate IOP-lowering effect and ocular tolerability of brimonidine/timolol, dorzolamide/timolol and latanoprost/timolol fixed combination therapies in the management of primary open angle glaucoma.

SUBJECTS AND METHODS

Study Design The study design of this study was a

prospective clinical trial. This study was approved by the local Institutional Review Board (27012009/01) and carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects. Adult patients (>35y) admitted to the Department of Ophtalmology of our university between February 2009 and July 2009 and diagnosed with POAG constituted the study group.

POAG was defined as an untreated IOP of more than 21 mm Hg in at least one eye measured on two consecutive occasions separated by an interval of at least 2h but no more than 4wk. Also, glaucomatous changes in the visual field or optic disc or defects in the retinal nerve fiber layer were evaluated.

Exclusion criteria included a baseline untreated IOP of more than 30 mm Hg confirmed on 2 occasions within 1wk; angle-closure glaucoma; corneal abnormalities preventing reliable IOP measurement, including photorefractive keratectomy; previous filtration surgery; a life-threatening or debilitating disease limiting the patient's ability to participate in the trial; secondary causes of high IOP, such as the use of corticosteroids, iridocyclitis, or ocular trauma; conditions for which the trial drugs are contraindicated; having only 1 eye or pregnancy. Significant wake-sleep rhythm disturbances and the regular use of hypnotic drugs as reported by the patients were also considered the reasons for exclusion.

Using hardware random number generators, patients were randomized to receive 1 of the following treatment sequences: Group 1: Fixed combination of 0.2% brimonidine tartrate and 0.5% timolol maleate (Combigan®, Abdi Ibrahim, Turkey); Group 2: Fixed combination of 2% dorzolamide hydrochloride and 0.5% timolol maleate (Cosopt®, MSD Pharm. Ind., Turkey); Group 3: Fixed combination of 0.005% latanoprost and 0.5% timolol maleate (Xalacom®, Pfizer, Turkey). Participants were instructed to instill the eye drops according to the study protocol, twice daily for Group 1 and 2 (8 a.m. and 8 p.m.) and once daily for Group 3 (8 a.m.). Each trial drug was administered for two months, after which a circadian tonometric curve was recorded.

Methods Intraocular pressure was measured at 08:30 a.m., 10:30 a.m., 12:00 p.m., 13:30 p.m., 15:30 p.m., and 17:30 p.m. at baseline and at two months controls using a Goldmann applanation tonometer. All measurements were taken by a single well-trained evaluator who was masked to the treatment assignment. Ocular discomfort (conjunctival hyperemia, burning or stinging, foreign body sensation, itching, ocular pain) of each eye was assessed by the subject on a standardized ocular discomfort scale ranging from 0 to 5, and was recorded by study staff 5min after the first application of the drug and at the two months controls [9].

Statistical Analysis Data were analyzed using the Statistical Package for Social Sciences (SPSS) software (version 10.0 for Windows). All differences associated with a chance probability of 0.05 or less were considered statistically significant. When Type I error (α) of 0.05, type II error (β) of 0.20 (1-β=0.80) and deviation of 0.05 were considered, each group must have at least 17 individuals by power analysis. Continuous variables are presented as mean ±standard deviation (SD). Normality distribution was confirmed by Kolmogorov Smirnov test. One-way analysis of variance (ANOVA) test was used to compare groups of independent continuous variables, and Bonferroni post-hoc-analysis was used for multiple comparison tests. The distribution of categorical variables in both groups was compared using Pearson chi-square test.

RESULTS

A total of 111 eyes of 61 patients who were diagnosed with POAG were included in the study. One patient in Group 1 was removed from the study due to daytime somnolence. Treatment was discontinued due to allergic reactions in two patients, one from Group 2 and one from Group 3. Due to these changes, data were available for 34 eyes of 18 patients (10 females, 8 males, mean age 56.17±7.49) in Group 1, 34 eyes of 20 patients (11 females, 9 males, mean age 56.05± 7.82) in Group 2, and 38 eyes of 20 patients (9 females, 11 males, mean age 58.60±6.06) in Group 3. The age range of the patients differed from 37y to 70y. The studied groups did not differ from each other in terms of gender and age (P >0.05 and P>0.05, respectively).

There were no significant differences between the mean central corneal thickness measurements in the three study groups. Mean central corneal thickness was 540.06±23.27 μm for Group 1, 535.94±25.37 μm for Group 2, and 544.29± 33.57 μm for Group 3. Changes in intraocular pressure among study groups were shown in Table 1. Among the three study groups, there were no significant differences in the mean baseline IOP measurements, mean 2nd mo IOP measurements, and mean (%) change of IOPs from baseline (Table 1). Significant differences were observed between the mean baseline IOP measurements, mean 2nd mo IOP measurements in all three groups (P<0.001).

Mean IOPs measured at 08:30 a.m., 10:30 a.m., 12:00 p.m., 13:30 p.m., 15:30 p.m., and 17:30 p.m. at baseline and at two months controls were shown in Table 2. Among the three study groups, there were no significant differences in the circadian tonometric curves obtained at baseline and at two months controls (P>0.05).

All drugs were generally well tolerated throughout the study period, and few side effects were noted. As mentioned above, one patient in Group 1 withdrew from the study due to daytime somnolence. Allergic reaction was the reason for discontinuation in two patients, one from Group 2 and one from Group 3. There were other systemic side effects in either group during the study period. Patients in Group 1 reported less conjunctival hyperemia compared with patients

Table 1 Changes in intraocular pressure among study groups

	Group 1	Group 2	Group 3	*P*
Baseline IOP	22.38±2.07	23.12±3.01	22.64±2.81	>0.05
2nd mo IOP	14.32±1.98	14.51±2.14	14.62±1.84	>0.05
Mean (%) change from baseline	8.06±1.08 (36.01%)	8.61±1.14 (37.24%)	8.02±1.05 (35.42%)	>0.05
P	<0.001	<0.001	<0.001	

IOP: Intraocular pressure; Values are given as mean±SD.

Table 2 Goldmann tonometer intraocular pressure readings

	Group 1		Group 2		Group 3	
	Baseline IOP	2nd mo IOP	Baseline IOP	2nd mo IOP	Baseline IOP	2nd mo IOP
08:30 a.m.	23.03±2.87	14.41±1.69	23.25±2.38	14.44±2.23	23.37±2.70	14.84±2.33
10:30 a.m.	22.94±2.00	14.47±3.30	23.15±2.41	14.47±2.30	23.26±1.83	15.11±1.93
12:00 p.m.	22.12±2.40	14.21±2.03	22.94±1.94	14.76±1.92	22.55±2.72	14.37±1.98
13:30 p.m.	21.94±2.39	14.44±1.58	23.38±2.50	14.65±2.17	22.97±2.28	14.34±2.12
15:30 p.m	22.09±2.04	14.00±1.89	23.00±3.03	14.44±1.99	21.92±1.81	14.29±2.03
17:30 p.m.	22.21±2.27	14.41±1.48	23.09±2.07	14.32±2.14	22.61±2.18	14.37±1.72
P	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05

IOP: Intraocular pressure; Values are given as mean±SD.

Table 3 Reported side effects among groups

Symptoms	Group 1	Group 2	Group 3	*P*
Conjunctival hyperemia				
5th min	0.06±0.14	0.29±0.21	0.79±0.71	*P* (1 *vs* 2)=0.032[1] *P* (1 *vs* 3)=0.017[1] *P* (2 *vs* 3)=0.021[1]
2nd mo	0.12±0.15	0.56±0.61	1±1.02	*P* (1 *vs* 2)=0.032[1] *P* (1 *vs* 3)<0.001[1] *P* (2 *vs* 3)=0.033[1]
Burning or stinging				
5th min	0.94±0.73	0.88±0.69	0.53±0.34	*P* (1 *vs* 2) >0.05 *P* (1 *vs* 3) =0.044[1] *P* (2 *vs* 3) >0.05
2nd mo	0.71±0.81	0.58±0.43	0.42±0.53	*P* >0.05
Foreign body sensation				
5th min	0.56±0.41	0.76±0.52	0.45±0.42	*P* >0.05
2nd mo	0.65±0.43	1.08±0.87	0.53±0.67	*P* (1 *vs* 2) =0.041[1] *P* (1 *vs* 3) >0.05 *P* (2 *vs* 3) >0.05
Itching				
5th min	0.38±0.27	0.56±0.39	0.26±0.37	*P* (1 *vs* 2) >0.05 *P* (1 *vs* 3) >0.05 *P* (2 *vs* 3)=0.035[1]
2nd mo	0.35±0.31	0.5±0.35	0.42±0.38	*P* >0.05
Ocular pain				
5th min	0.29±0.19	0.29±0.11	0.42±0.51	*P* >0.05
2nd mo	0.23±0.18	0.31±0.23	0.19±0.17	*P* >0.05
Mean score				
5th min	0.44±0.51	0.55±0.32	0.49±0.51	*P* >0.05
2nd mo	0.41±0.39	0.60±0.71	0.51±0.65	*P* >0.05

[1]Values are given as mean±SD.

in Group 2 and patients with Group 3 on the comfort and tolerability questionnaire both at 5th min. and at two months controls (Table 3). Similarly, Group 2 patients reported less hyperemia compared with patients in Group 3 at both visits. Patients in Group 1 reported more burning or stinging compared with patients in Group 3 at the 5th min. Patients in Group 3 reported less itching compared with patients in Group 2 at the 5th min. Patients in Group 1 reported less foreign body sensation compared with patients in Group 2 at the 2nd mo controls (Table 3).

DISCUSSION

This study compared the efficacy and safety of brimonidine/timolol, dorzolamide/timolol and latanoprost/timolol fixed combination therapies in the management of POAG. Each of the groups showed significant reductions from baseline mean IOP at 2mo; however, the group results were similar at each visit time during each stage of the study.

Current therapy for glaucoma focuses on reducing IOP to a level at which the progression of glaucomatous damage is halted, and recent studies have illustrated the importance of lowering IOP to prevent optic-nerve damage. In the Advanced Glaucoma Intervention Study (AGIS), patients with low mean IOP had less progression of damage. The results of the AGIS showed that visual field progression was prevented only in the eyes that had IOP lower than 18 mm Hg at all clinic visits during the study. In line with these findings, 5y data from the Collaborative Initial Glaucoma Treatment Study (CIGTS) showed the importance of lowering IOP aggressively from baseline to prevent visual field damage[10,11]. These two studies demonstrated that the target pressures required to prevent visual field progression are lower than previously thought.

Combinations of two IOP-lowering agents with different mechanisms of action are often used to treat glaucoma patients whose target pressures cannot be achieved with monotherapy. Efficacy, safety, and compliance are the most important aspects of these multi-drug therapies. Fixed combination agents require instillation of fewer drops per day than the concomitant use of the two drugs separately, and thus may increase patient compliance with therapy.

Two studies have compared dorzolamide/timolol and brimonidine/timolol in reported similar IOP lowering, though the treatment was only over a 4wk period [12,13]. Two independent studies have compared dorzolamide/timolol fixed combination therapy with brimonidine/timolol fixed combination therapy [14,15]. In each of these studies, the fixed combination of brimonidine and timolol was more effective than fixed combination dorzolamide/timolol in reducing IOP, and the treatments were comparable in efficacy during trough periods in medication dosing. Both treatments were well-tolerated, but burning, stinging, and taste perversion were more common with dorzolamide/timolol than with concomitant brimonidine and timolol in each study [14,15]. Arcieri *et al* [16]. compared dorzolamide/timolol and brimonidine/timolol in 30 patients and reported similar IOP lowering, though the treatment was only over a 4wk period. In the present study, the IOP-lowering effect of brimonidine/timolol was the same as that of dorzolamide/timolol.

Pajic *et al* [17] compared the efficacy dorzolamid and latanoprost when added to a topical β-blocker for at least 4y in patients with POAG. Dorzolamide/timolol fixed combination and latanoprost/timolol fixed combination significantly reduced mean IOP over time (from 22.6±3.0 to 13.8±1.9 mm Hg and from 22.3±4.0 to 14.7±1.9 mm Hg, respectively). Both treatments significantly and similarly reduced IOP as compared with baseline [17]. In a double-masked, randomized, crossover study, comparing the effect of latanoprost/timolol and brimonidine/timolol fixed combination on intraocular pressure with POAG. Both drugs were equally effective in reducing IOP (-35.0%±10.0%; -33.6%±8.8%, respectively)[18].

A significant difference was observed between groups in success rates (defined as reduction in IOP ⩾3 mm Hg); latanoprost 70%, brimonidine 58%, dorzolamide 40%. A multicenter European study evaluated IOP in 325 patients with POAG on latanoprost/timolol given in the morning or the concomitant brimonidine/timolol given twice daily [19]. At baseline, mean diurnal IOP was 26.4 mm Hg for the latanoprost/timolol group and 26.5 mm Hg for the concomitant brimonidine/timolol group. After 6mo, mean diurnal IOP was significantly lower in the latanoprost/timolol group (16.9 mm Hg) when compared with the brimonidine/timolol group (18.2 mm Hg).

Based on the patient questionnaire in the current study, brimonidine/timolol produced less conjunctival hyperemia than the other fixed combinations. In a paired-eye study of discomfort associated with eye drop instillation in normal subjects, mean scores of ocular discomfort were significantly higher with dorzolamide/timolol than with brimonidine/timolol at 30-40s after eye drop instillation [9]. In an open-label study, 92% of patients who were switched from dorzolamide/timolol monotherapy to brimonidine/timolol monotherapy reported improved ocular comfort with the brimonidine/timolol fixed combination [20]. The main limitation of this study includes its relatively short duration (2mo) and further studies should to evaluate the long-term efficacy and tolerability. Secondly, the questionnaire for side effects may not have captured all of the ocular surface or systemic side-effects associated with the study medications. Thirdly, patient compliance with medications was not directly assessed. Finally, some details of history and factors that may influence the outcome may not be completely documented. Due to these restrictions, associations should be interpreted with caution.

In conclusion, single-agent therapy is always the first strategy used in patients with glaucoma. No second agent is added until monotherapy with different classes of agents has been attempted and has failed. The second step in the treatment algorithm is two-agent combination therapy, and fixed combinations are good choices for this purpose. More recently, to maximize patient medication adherence, several fixed combinations of commonly used IOP-lowering therapies have been developed. However, the non-consistent results of these studies made it difficult to draw conclusions of the degree of reduction of IOP that can be achieved with

different fixed-combination drugs. Further clinical studies and combination therapies are needed to evaluate the degree of reduction of IOP.

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