Evaluation of brimonidine-timolol fixed combination in patients of primary open-angle glaucoma

Sachin R Joshi, Pramod B Akat, Jaiprakash B Ramanand, Sunita J Ramanand, Vitthal B Karande, Suyog S Jain

The aim of present study was to compare the efficacy and safety of fixed combination of brimonidine and timolol with individual components used as monotherapy in patients of primary open angle glaucoma. Patients were randomly assigned to receive brimonidine or timolol or brimonidine-timolol fixed combination, with 30 patients in each group. The mean reduction in intraocular pressure in brimonidine, timolol, and brimonidine-timolol group were 4.29 ± 1.97 mm Hg, 4.34 ± 1.21 mm Hg, and 5.54 ± 1.87 mm Hg respectively at 2 weeks and 4.86 ± 1.16 mm Hg, 5.42 ± 1.50 mm Hg, and 7.36 ± 2.58 mm Hg respectively at 6 weeks. When values of mean reduction in intraocular pressure were compared between brimonidine-timolol fixed combination with brimonidine and timolol, it was found to be statistically significant ($P < 0.05$) at 2 weeks and highly significant (0.001) at 6 weeks. The overall frequency of adverse effects was similar in all three groups.

Key words: Brimonidine, combination, glaucoma, intraocular pressure, timolol

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Department of Pharmacology, Government Medical College, Miraj, Maharashtra, India

Correspondence to: Dr. Pramod B. Akat, Department of Pharmacology, Government Medical College, Miraj - 416 410, Maharashtra, India. E-mail: dr_akat@rediffmail.com

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Glaucoma is among the leading causes of blindness in the developing world and a major health problem in the developed world. Elevated intraocular pressure (IOP) is the most important known risk factor for the progression of visual field loss in patients with glaucoma. Despite the substantial IOP lowering effect possible with monotherapy, many patients may need to use two or more medications to reach a target IOP sufficiently low to halt further visual deterioration.[1,2] In the Ocular Hypertension Treatment Study, by year 5, almost 40% of the patients required two or more medications to achieve their target IOP.[1] In the medical arm of the Collaborative Initial Glaucoma Treatment Study, more than 75% of the patients required two or more medications after 2 years.[2] Therefore this study was undertaken to compare the efficacy and safety of a fixed combination of 0.2% brimonidine tartarate and 0.5%

Table 1: Effect of brimonidine, timolol, and brimonidine-timolol fixed combination on intraocular pressure

Parameters	Brimonidine IOP in mm Hg Mean±S.D	Timolol IOP in mm Hg Mean±S.D	Brimonidine-Timolol IOP in mm Hg Mean±S.D
Baseline	25±1.38	25.27±1.22	25.50±1.28
After 2 weeks	20.71±0.98	20.93±1.14	19.96±1.23*
After 4 weeks	20.21±0.96	20.33±1.36	19.25±1.58*
After 6 weeks	20.14±1.35	19.85±1.58	18.14±2.16**

*P<0.05, **P<0.001 occurred when comparisonis made between mean reduction in intraocular pressure from baseline of brimonidine, timolol and brimonidine-timolol fixed combination

Table 2: Effect of brimonidine, timolol, and brimonidine-timolol fixed combination on blood pressure and heart rate

Parameters	Brimonidine		Timolol		Brimonidine-Timolol	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Systolic BP in mm Hg Mean±S.D	136.67±5.05	136.57±4.64*	138.33±5.90	138.74±5.74*	137.40±5.80	137.42±6.25*
Diastolic BP in mm Hg Mean±S.D	85.13±2.61	84.86±2.69*	85.33±2.61	84.88±2.30*	86.13±2.67	85.64±2.56*
Heart rate beats/min	75.43±2.41	75.43±2.22*	75±2.9	70.67±1.96**	74.23±2.83	70.17±1.22**

*P>0.05, **P<0.05 when comparison is made between before treatment and after treatment

timolol maleate compared to the effect of either component administered as monotherapy in patients of POAG.

Materials and Methods

This was a prospective, open, randomized, comparative controlled clinical trial. A total of 90 patients were enrolled into the study as per selection criteria. Patients of either sex with 18 year of age or more diagnosed as unilateral primary open-angle glaucoma with IOP of 22 mmHg and above with open anterior chamber angle, characteristic optic disk cupping and/or visual field loss, Snellens's visual acuity of 6/60 or better were included in the study. They were either newly diagnosed patients or those who had discontinued topical antiglaucoma therapy voluntarily for more than 4 weeks. Following categories of patients were excluded from the study: patients having anterior synechiae, clinically dry eye syndrome, active ocular infection, inflammation and significant ocular trauma, patients taking other systemic or ocular medications that could have substantial effect on intraocular pressure, patients of bronchial asthma or other reactive airway disease, severe heart failure, sinus bradycardia, hypotension, and diabetes mellitus, patients with history of ocular surgery in last 3 months, patients with only one sighted eye, patients using contact lenses, patients with corneal abnormalities, patients with history of herpetic keratitis, corneal ulcer in the last 1 year, and female patients of child bearing age group not using medically approved contraceptives.

Patients of primary open-angle glaucoma were randomly assigned to receive brimonidine tartarate (0.2%) three times daily topically or timolol maleate (0.5%) twice daily topically or brimonidine (0.2%) and timolol (0.5%) fixed combination ophthalmic solution twice daily topically, with 30 patients in each group. At each visit thorough ocular examination of the patient including intraocular pressure recording, visual acuity, direct ophthalmoscopy, and slit lamp examination was performed. The intraocular pressure was recorded with Goldman applanation tonometry. Systolic blood pressure, diastolic blood pressure, and heart rate were also recorded during each visit. After enrollment into the study follow-up was done after 2 weeks, 4 weeks, and 6 weeks.

The primary efficacy end point was the change from baseline intraocular pressure. Patients who did not complete full 6 weeks therapy as per study regulations were not included for statistical analysis. Safety was assessed in terms of ocular and systemic adverse effects both subjective and objective. Subjective symptoms such as itching, stinging, dry mouth and headache, were assessed by questioning the patient at each visit. Objective signs were obtained by examining the patient in detail by ocular and clinical examinations. Quantitative data were analyzed by paired t test and unpaired t test while qualitative data of frequency of adverse events were analyzed by the Chi-square test. A P value < 0.05 was taken as significant.

Results

The results are shown in Tables 1 and 2.

Discussion

In the present study, we have observed that brimonidine, timolol, and brimonidine-timolol-fixed combination are effective agents in reducing intraocular pressure throughout the study period when measured at 2nd, 4th, and 6th weeks. When efficacy of brimonidine-timolol fixed combination was compared with individual drugs used, we found that brimonidine-timolol fixed combination was more effective in reducing IOP compared to the individual drugs used alone [Table 1]. In a randomized study it was found that a decrease from baseline IOP was 7.6 mm Hg with fixed brimonidine-timolol, 5.5 mm Hg with brimonidine, and 6.2 mm Hg with timolol.[3] In another short-term 3-week study found that the mean IOP was significantly reduced by an average of 5.44 ± 1.98 mmHg compared with baseline value with the use of the fixed combination.[4] Thus the results of our study are in congruence with these studies further supporting the additive IOP lowering effect of the brimonidine–timolol fixed combination. Data from the Early Manifest Glaucoma Trial have shown that even 1 mm Hg of additional IOP lowering reduces the risk of glaucoma progression by 10%.[5] Thus more IOP lowering effect of the fixed combination should prove beneficial for preserving the patient vision.

No serious adverse effect necessitating stoppage of the therapy was encountered in any of the patient receiving brimonidine-timolol fixed combination. There was no significant effect of brimonidine-timolol fixed combination, brimonidine, and timolol on mean systolic blood pressure and mean diastolic blood pressure but the mean heart rate was significantly reduced more with brimonidine-timolol combination compared to brimonidine and no significant reduction compared with timolol [Table 2].

Apart from the more IOP lowering effect the brimonidine - timolol fixed combination has other two advantages. First, as benzalkonium is most commonly used in ophthalmic medications as a preservative and as the treatment of the glaucoma is life long, it may have dose-related harmful effects on the corneal surface.[6] Use of the combination product twice daily results in a daily ocular exposure to preservative that is one third of that associated with the use of both

component drugs given separately. Second, when more than one drug is administered topically in the eye, the first drug may be diluted due to application of the second drug. As the formulation allows the delivery of 2 ocular drugs in a single drop it also ensures full exposure to both medications by preventing dilution of the first drug by application of a second drop before the first has been absorbed.

Thus based on the results of our study, it can be concluded that brimonidine-timolol fixed combination is more effective to lower IOP and safe compared to the individual agents used for the treatment of primary open angle glaucoma.

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