
Research Article

Safety and Efficacy for the combination of Brimonidine and Timolol in patients for the treatment of Glaucoma

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Abstract:

Introduction: Glaucoma is a prevalent neurodegenerative disorder of the eye which can be characterised by increased intraocular pressure which leads to chronic, degenerative optic neuropathy. Fixed dose combination of Brimonidine 0.2%w/v and Timolol 0.5%w/v per ml can be used for the treatment of glaucoma due to elevated intraocular pressure (IOP).

Methodology: Of total 150 enrolled patients, 125 patients completed the study and of 125 patients the clinical trial was conducted on 227 eyes. All the patients were asked to use the study fixed dose combination of Brimonidine 0.2%w/v and Timolol 0.5%w/v per ml twice a day. Efficacy assessment was done at visit 2 (day 10), visit 3 (day 20) and visit 4 (day 30) by analysing the reduction in the IOP as compared to baseline and safety assessment was done by recording and analysing the adverse events through the study.

Results: At baseline the mean IOP was 27.659 which was decreased by 22.193% to 21.520 at visit 2 (V2), at visit 3 (V3) it was further decreased by 25.207% to 20.687 and at visit 4 (V4) the mean IOP was further decreased by 25.446% to 20.621.0. At V1 all 227 patients were having IOP>21 but at V2, V3 and V4; 134 (59.03%), 136 (59.91%) and 162 (71.36%) patients were having their IOP in the normal range i.e. IOP≤21.

Conclusion: Fixed dose combination of Brimonidine 0.2%w/v and Timolol 0.5%w/v per ml is safe as well as efficacious for the treatment of glaucoma due to elevated IOP.

Keywords: Brimonidine, Timolol, glaucoma, efficacy, safety

Introduction

Glaucoma is a common visual disorder and second leading cause of blindness in the world after cataract. Glaucoma is characterised by increased intraocular pressure which leads to chronic, degenerative optic neuropathy that can be differentiated from other forms of developed optic neuropathy by the distinguishing appearance of the optic nerve. The neuro-retinal rim of the optic nerve in glaucoma becomes progressively thinner by enlarging the optic nerve cup. This phenomenon is known as optic nerve cupping. Therefore, it causes the loss of retinal ganglion cell axons, supporting glia and vasculature. The remaining neuro-retinal rim of the optic nerve retains its normal pink colour. In other optic neuropathies, the optic nerve tissue loses its pink colour and optic nerve cupping does not develop. Glaucoma patients typically lose peripheral vision and if not treated, may lose all vision.^{1,2}

The most common types of glaucoma are open-angled and closed-angled, together they are major cause of irreversible vision loss. Worldwide, more than 65 million people suffering from glaucoma of which 12 to 15 million are in India. Higher intraocular pressure (IOP) i.e. >21 mmHg is a major and

modifiable risk factor for loss of vision. The risk of blindness depends on the elevated IOP, severity of disease, increased age, racial background, hypertension, hyperopia, myopia, thin cornea, positive family history and diabetes. Patients with glaucoma are reported to have reduced levels of physical, emotional and social well-being, poorer quality of life, and utilize more health care resources.^{3,4,5,6}

Pharmacological management is the most common preliminary intervention in reducing the IOP, although surgery and laser trabeculoplasty are frequently used to slow the disease development. For visual field protection, surgical treatment has no advantage over pharmacological management. Several agents are easily available and the leading choice of drug depends on the degree of pressure reduction which needs to be achieved.^{7,8,9} Pharmacological agents used to reduce the IOP include α_2 adrenergic agonists, prostaglandin analogs, carbonic anhydrase inhibitors, cholinergic agonists, hyperosmotic agents and β -blockers.^{7,10} Several drug combination are available for the treatment of glaucoma. Most of these combinations contains Timolol, as β -blockers are still considered to be a first line therapy in glaucoma or ocular hypertension. Fixed-dose combinations

(FDC) therapy is more efficacious than its individual components. It provides simplified treatment regimens and enhances patient compliance. An FDC containing Brimonidine and Timolol used to reduce the elevated IOP in glaucoma or ocular hypertension. Combination which contains Brimonidine have less visual disturbances, ocular allergic reactions and taste alterations compared to the product which contains single ingredient.^{7,11,12}

Brimonidine is a selective α -2-adrenergic receptor agonist that shows up to 1780-fold selectivity for α -2 over α -1-adrenergic receptors.^{13,14} After topical instillation, Brimonidine reduces the IOP within 1 hour, and the peak effect occurs at 2 to 3 hours after dosing.^{13,15} Brimonidine has a dual mechanism of lowering IOP, as it stimulates aqueous humor outflow through the uveoscleral pathway and reduces aqueous humor production.^{13,16} The main effect of short term Brimonidine treatment is inhibition of aqueous humor production, whereas the main effect of chronic treatment is stimulation of aqueous humor outflow through the uveoscleral pathway.^{13,17}

Timolol, the first β -adrenergic blocking agent available for ophthalmic solutions. It was introduced in market in 1978 and has since become the standard β - blocker in ophthalmology. It mainly blocks the action of the sympathetic (adrenergic) nervous system. In addition, Timolol causes a reduction of the intraocular pressure and this effect may result from a reduction in production of the liquid aqueous humor within the eye. The precise mechanism of this effect is not known. The reduction in intraocular pressure reduces the risk of damage to the optic nerve and loss of vision in patients with glaucoma.^{18,19} This phase IV study was conducted to evaluate the safety and efficacy for the FDC of Brimonidine and Timolol in the treatment of glaucoma or ocular hypertension.

Methodology

10 Ophthalmologists were selected all over the India for conducting the Phase IV clinical trial. Total 150 patients were recruited for the study out of which 125 patients completed the study. 25 patients were lost to follow-up. And of 125 patients total 227 eyes data was collected to test the efficacy and safety of the formulation.

Inclusion and exclusion criteria

Glaucoma patients with increased intraocular pressure (IOP > 21) of both the sexes including male and female of age 18 – 65, willing to sign the informed consent form and patients who can adhere to the protocol were recruited for the clinical trial. Patients known, or thought to be hypersensitivity to study drugs or any excipient of the study drug combination, pregnant or lactating woman or Patients who cannot adhere to the Protocol i.e. mentally ill and patients with Psychological problem were excluded from the study.

Study Intervention

Study drug combination eye drops used was the combination of Brimonidine Tartrate 0.2% w/v and Timolol Maleate 0.5% w/v per ml. Patients were asked to instil one drop of study drug combination eye drops two times daily with

approximately 12 hours apart from the previous dose for a study period of 30 days.

Study procedure

The study duration was decided to keep 30 days. Patients who were perfectly fitting into the inclusion and exclusion criteria were recruited for the clinical trial after giving them brief information about the clinical trial and getting their sign on the informed consent form. On case report form detailed medical history and current medical examination report of the patient was recorded. Investigators holding post-graduate degree in ophthalmology were selected for conducting the study. Patients were asked to instil one drop of Study drug combination eye drops two times daily with approximately 12 hours apart from the previous dose for a study period of 30 days. Patients were asked to maintain a diary to record any adverse events occurring during the clinical trial duration. Four visits were planned for all the patients recruited in this study – baseline visit (V1) on day 1 before treating patient with the study medication, evaluation visit (V2) on day 10, reevaluation visit (V3) on day 20 and conclusion visit (V3) on day 30. Adverse events occurring and IOP were noted during each visit along with medical history and physical examination to record the safety and efficacy. Investigators were asked to discontinue the study drug in case of severe adverse event.

Concomitant therapy

In clinical trial duration of 30 days all the patients were not allowed to take any pharmacological intervention for the treatment of glaucoma or elevated IOP.

Efficacy assessment

IOP was measured at baseline, day 10, day 20 and day 30. Efficacy assessment was done by analysing the reduction in mean IOP and also by calculating the percentage decrease in mean IOP at V2, V3 and V4 as compared to baseline.

Safety assessment

Patients were asked for any adverse event and if present were noted in the case record form (CRF) and adverse event reporting form during each post-dose visit. These adverse events were classified into serious and non-serious adverse events. Naranjo's scale of probability was used to classify the adverse events as drug related or nondrug related. Adverse events were followed up and also treated if necessary by the investigators till their resolution.

Regulatory and Ethical matters

The said combination is available and is classified in schedule H drugs in India, i.e. it should be sold in presence of prescription of registered medical practitioners only. All the patients participated in the study have read and voluntarily signed the informed consent form (ICF). This clinical trial was conducted in accordance with schedule Y.

Results

IOP data of total 227 eyes of 125 patients were collected and

for efficacy assessment the mean IOP at visit 1, 2, 3 and 4 were calculated. At visit 1 i.e. at baseline the mean IOP was 27.659 which was reduced to 22.520 at visit 2, further reduced to 21.520 at visit 3 and 20.621 at visit 4. So at visit 2, 3 and 4 there was reduction of 22.1953 %, 25.207 % and 25.446 % as compared to baseline mean IOP, considering baseline mean IOP as 100 %. The reduction in mean IOP at visit 1 to 4 and percentage reduction in mean IOP at visit 2, 3 and 4 as compared to baseline is graphically presented in figure 1 and 2 respectively.

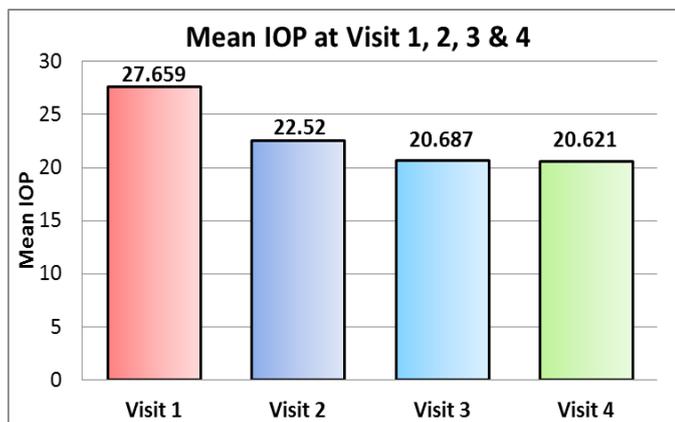


Fig. 1 Mean IOP at visit 1, 2, 3 and 4

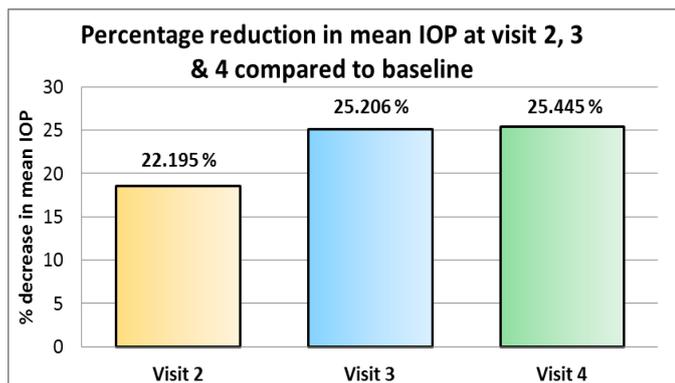


Fig. 2 Percentage reduction in mean IOP at visit 2, 3 and 4 as compared to baseline

At visit 1 all the 100 % patients were having IOP more than 21. At visit 2, out of 227, 134 i.e. 59.03 % of patients were having IOP in the normal range i.e. IOP ≤ 21. At visit 3 and 4 the number was increased to 136 (59.91 %) and 162 (71.36 %). So at the end of the clinical trial duration of 30 days 71.36 % patients elevated IOP get back to the normal range of IOP which was 12 to 21.

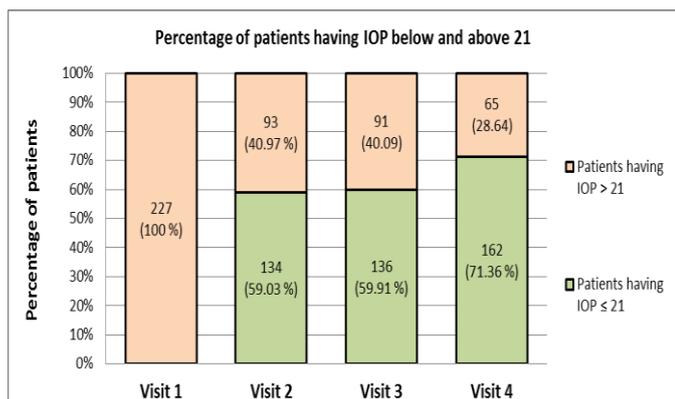


Fig. 3. Percentage of patients having IOP > 21 or ≤ 21 mmHg at visit 1, 2, 3 and 4

At baseline 227 patients recruited having IOP > 21 and after initiating the clinical trial at visit 2, 3 and 4, 134 (59.03 %), 136 (59.03 %) and 162 (71.36 %) of patients had IOP ≤ 21 mmHg which was in the normal range.

Safety analysis

In this phase IV clinical trial 227 eyes of 125 patients were examined. All the adverse events experienced by the patient or observed by the investigator were recorded on the case report form. The list of adverse events with the number of patients is mentioned in table 1.

Table 1 Adverse Events and their Incidence

Sr no.	Adverse events	Number of patients	Percentage of population
1	Mild irritation	28	12.33 %
2	Mild ocular burning sensation	7	3.08 %
3	Mild itching	9	3.96 %
4	Mild redness in the eye	60	26.43 %
5	Blurring of the vision	4	1.76 %
	Total	79	34.80 %

Discussion

Glaucoma is characterised by increased intraocular pressure which leads to chronic, degenerative optic neuropathy that can be differentiated from other forms of developed optic neuropathy by the distinguishing appearance of the optic nerve.¹ This clinical trial was conducted to test the safety and efficacy of the study drug combination eye drops for the treatment of glaucoma by decreasing the elevated IOP to normal. To test the efficacy of the product IOP was measured at baseline followed by all the visits and decrease in elevated IOP was analysed. And to test the safety, adverse events experienced by the patients or observed by the investigator were recorded on the case report form and adverse event reporting form by the investigator and then all the data is compiled and further analysis is done which is shown in the table 1.

Mean IOP at baseline before treating patients with the study medication was 27.659 which was decreased to 22.52 at visit 2 i.e. at visit 2 the mean IOP was decreased by 22.195 %. At visit 3, the mean IOP was further decreased to 20.687 i.e. there was reduction of 25.207 % in the mean IOP as compared to baseline. At visit 4, the mean IOP was further reduced to 20.621 i.e. there was 25.446 % reduction in the IOP as compared to the baseline. At visit 1, total 227 eyes were suffering from the elevated IOP i.e. IOP > 21. At Visit 2, 3

and 4; 59.03 %, 59.91 % and 71.36 % of patients were having IOP in the normal range respectively. So at the end of the clinical trial 71.36 % of patients were having IOP in the normal range.

Mark B Sherwood et al had conducted a prospective, 12 months, phase II, randomized, double masked, parallel group study for comparing the efficacy and safety for the fixed dose combination of 0.2 % Brimonidine and 0.5 % Timolol per ml, 0.2 % Brimonidine per ml and 0.5 % Timolol per ml ocular drops for the treatment of glaucoma due to elevated intraocular pressure. The study was conducted for the duration of 12 month. The patients of either sex having age more than 18 years or older who requires bilateral treatment for glaucoma or ocular hypertension having IOP after washout at baseline between 22-24 mm Hg, with no more than 5 mm Hg difference in both the eyes and a best correlated visual acuity of 20/100. Washout period was kept 4 days for parasympathomimetics and carbonic anhydrase inhibitors, 2 weeks for sympathomimetics and α agonists and 4 weeks for β blockers (alone or in combination) and topical prostaglandin analogues. The mean decrease in IOP from the from the baseline in the group of the patients treated by the combination of 0.2 % Brimonidine and 0.5 % Timolol per ml was ranging from the minimum 4.4 to maximum 7.6 mm Hg. In the group of patients treated by 0.2 % Brimonidine, the IOP reduction was ranging from minimum 2.7 to maximum 5.5 and in the group of patients treated by 0.5 % Timolol was minimum 3.9 to maximum 6.2. The reduction in mean IOP as compared to baseline was significantly better in the group of patients treated by the combination of brimonidine and timolol as compared to the patients treated by Brimonidine or Timolol.²⁰

Conclusion:

Fixed dose combination of 0.2 % w/v Brimonidine and 0.5 % w/v Timolol per ml ocular drops provides optimum relief from the elevated IOP and is safe for the use in the management of glaucoma.

Acknowledgement:

We would like to acknowledge Dr. Purvi Bhagat (Gujarat), Dr. Rajesh Parekh (Karnataka), Dr. P Sharada Rao (Karnataka), Dr. Deepali Yadav (Maharashtra), Dr. Milankumar Panchal (Gujarat), Dr. Chintan Dholakia (Gujarat), Dr. Susheel Deshmukh (Maharashtra), Dr. Pradeep Kumar Verma (Odisha), Dr. Chandana Misra (Bhubaneswar), Dr. Chandana Misra (Odisha), Dr. Ashok Kumar Nanda (Odisha) who were the co-investigators in this study.

Disclosure:

This study was conducted as a part of Pharmacovigilance activity for Brimopress T Eye Drops marketed by Centaur Pharmaceuticals Pvt. Ltd. in accordance with Pharmacovigilance Program of India (PvPI).

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