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Research Article

A comparative study on safety and efficacy of travoprost and brimonidine/timolol fixed combination in patients of primary open-angle glaucoma

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ABSTRACT

Background: The purpose of this study was to compare and evaluate the clinical efficacy of topically applied travoprost 0.004% eye drops versus brimonidine/timolol fixed combination eye drops in the management of primary open-angle glaucoma.
Methods: In this prospective, randomized study, 65 patients received either travoprost eye drops once daily in the morning (n=33) or brimonidine/timolol fixed combination eye drops twice daily (n=32). Intra ocular pressure (IOP) was assessed at 2, 4, 8, and 12 weeks. The primary outcome measure was mean reduction in IOP.
Results: The baseline mean IOP values were similar between two groups. Mean reduction of IOP in the right eye for brimonidine/timolol fixed combination group was 9±2.9 mmHg, whereas in the left eye it was 10.9±2.8 mmHg. In the travoprost group, the reduction in IOP of the right eye was 7.8±2.9 mmHg (p=0.0002) and 7.5±3.4 mmHg (p=0.0001) in the left eye. The mean reduction of IOP for the brimonidine/timolol group was 9.95 mmHg and for the travoprost group it was 7.6 mmHg (p<0.0001) in both the eyes.
Conclusions: The fixed combination brimonidine/timolol twice daily demonstrated superior mean IOP lowering efficacy compared to travoprost 0.004% in patients with open-angle glaucoma.

Keywords: Open-angle glaucoma, Intra ocular pressure, Timolol, Travoprost, Brimonidine

INTRODUCTION

Glaucoma is the "silent thief of sight." It is the second leading cause of blindness globally,[1] accounts for 12.3% of total blindness.[2] The estimated number of people with vision loss from glaucoma range from 5.2 to 6.7 million.[3] If left undiagnosed and untreated there is slow progressive degeneration of retinal ganglion cells and the optic nerve axons, leading to irreversible blindness.

Prevalence of glaucoma varies between 1% and 4% in people over 40, and they increase with age. The incidence rate is estimated to be 0.1% per year.[4] Several randomized controlled trials have determined that reduction in IOP can delay glaucomatous nerve or field damage.[5-7] Normal intraocular pressure ranges from 10 to 2 mmHg. Data from the Early Manifest Glaucoma Trial have shown that an additional 1 mmHg of IOP lowering reduces the risk of glaucoma progression by 10%.[7] Lowering of IOP remains

the most readily modifiable risk factor in development of glaucoma.[8] To maximize convenience and compliance with therapy, fixed combinations, containing drugs of two classes have been developed.[9] Monotherapy is frequently not sufficient for reaching the preset target IOP; therefore, many patients require more than one medication to achieve adequate IOP reduction.

Several fixed drug combinations of commonly used IOP-lowering medications have been developed and available in the market worldwide. Most fixed drug combinations contain timolol maleate, as it can be dosed either once or twice daily and can be combined with prostaglandin analogues (PGAs), adrenergic agonists, and carbonic anhydrase inhibitors.

Compared to concomitant dosing with individual constituents, these combinations offer the convenience of fewer drops per day, fewer bottles to handle the patients, reduced exposure to preservatives, and elimination of the washout effect of multiple drops.

Ocular hypotensive drugs are used on a long term basis and constitute the definitive treatment in the majority of cases. Some of the drugs are prostagladin analogue such as latanoprost, travoprost, bimatoprost act by increasing uveoscleral outflow possibly by increasing the permeability of tissues in ciliary muscle or by an action on episcleral vessels. Since the introduction of PGAs, many ophthalmologists prefer these agents as first-line treatment.[10] Travoprost has been shown to have a greater IOP lowering effect than latanoprost.[11,12] Side effects are thickening and elongation of eyelashes. Hyper pigmentation of the iris and periocular skin. Topical beta-adrenergic receptor antagonists such as timolol, levobunolol, and betaxolol lower IOP by reducing aqueous formation. This probably results from down regulation of adenylyl cyclase due to β_2 receptor blockade in the ciliary epithelium and a secondary effect due to reduction in ocular blood flow.[13] α-adrenergic agonists like apraclonidine decreases aqueous production by primary α_2 and subsidiary α_1 action in the ciliary body. Brimonidine acts via decreasing synthesis of aqueous humor and increasing the uveoscleral outflow. The drug binds to presynaptic receptors and reduces the amount of neurotransmitter release from sympathetic nerve stimulation and thereby lowers IOP. By binding postsynaptic α-$_2$ receptor, the drug stimulates G_i pathway, inhibit the activity of adenylate cyclase and reduces cellular cyclic adenosine monophosphate production thereby reducing aqueous humor production.[14] Sympathomimetics like Epinephrine decrease aqueous humor production through vasoconstriction of ciliary body blood vessels. Carbonic anhydrase inhibitors such as dorzolamide, brinzolamide, and acetazolamide lower secretion of aqueous humor by inhibiting carbonic anhydrase in the ciliary body.[13,14] Miotic agents like pilocarpine works by contraction of the ciliary muscle, tightening the trabecular meshwork and allowing increased outflow of the aqueous humor.[15] Physostigmine (0.1%) is used only to supplement pilocarpine.

METHODS

All the cases studied were attending the outpatient Department of Ophthalmology at Peoples College of Medical Science and Research Centre Bhanpur Bhopal. Study duration was 1½ years. While selecting the cases for the study special care was taken to include only newly diagnosed cases of primary open-angle glaucoma (POAG).

Necessary approval were taken (CTRI/2011/11/002105). Informed consent from the patient was obtained after explaining to them the details of the study. Inclusion criteria were followed to include the subjects for the study - age 40 years or more, patients with POAG, the intraocular pressure in each eye >21 mmHg, Best corrected visual acuity 6/24 or better. Exclusion criteria were - progressive and significant visual fields loss in last 1 year, patients with corneal abnormalities or any other corneal conditions that prevent applanation tonometry (as elicited by history given by the patients.), patients with ocular infection, inflammation, and advanced cataract, patients of bronchial asthma and cardiac disease.

Seventy cases of POAG were selected and divided equally into two groups based on simple random sampling. One group was treated with 0.004% of travoprost eye drops once a day in the morning and the other with fixed combination of brimonidine/timolol eye drops twice a day.

A detailed history was taken, and detail ocular examination was done for all the 70 patients. The physical examination of all these 70 patients included a thorough examination of their general and systemic conditions. The intraocular pressure was measured at baseline, 2, 4, 8, and 12 weeks of visit using applanation tonometer. Two readings were taken to establish the final IOP. The visual field defect was documented by perimetry and visual acuity by Snellen's chart both at the commencement and at the end of the study. Total 5 patients did not come for follow-up and the study was completed in 65 patients.

33 patients (11 females and 22 males) with POAG on travoprost once a day for 3 months and another 32 patients (10 females and 22 males) (Figure 1) of POAG were treated with fixed combination of brimonidine/timolol eye drops twice daily. Ocular improvement and efficacy of the drug were assessed by a follow-up study done 2, 4, 8, and 12 weeks. The peak prevalence age in the travoprost group was between 41-50 years and 51-60 years in brimonidine + timolol group (Figure 2).

The data collected were tabulated and analyzed using descriptive statistical tools mean, standard deviation, and comparison between the groups by using Student's t-test.

RESULTS

Mean reduction of IOP in the right eye for brimonidine/

timolol fixed combination group was 9 ±2.9 mmHg, whereas in the travoprost group the reduction in IOP of the right eye was 7.8±2.9 mmHg (p=0.0002) and in the left eye it was 10.9±2.8 mmHg for brimonidine/timolol and 7.5±3.4 mmHg for travoprost (p=0.0001). The mean reduction of IOP for travoprost group it was 7.6 mmHg (p=0.0001) and for the brimonidine/timolol group was 9.95 mmHg in both the eyes.

Both treatment regimens were well tolerated during the study. The patients in the travoprost group had a higher incidence of ocular irritation (30%), pigmentation of skin (33%), thickening of eyelashes (39%), and hyperemia (36%) when compared to the brimonidine/timolol group which showed only ocular irritation (21%) and foreign body sensations (28%) (Figure 3).

DISCUSSION

This prospective, randomized, open labelled, study was conducted on 65 patients of POAG; 33 patients were on travoprost eye drops administered once a day, and the other 32 patients were on brimonidine/timolol eye drops administered twice a day. The reduction of IOP with brimonidine/timolol was from 27.9 to 18.98 mmHg and for travoprost it was from 26.6 to 18.99 mmHg. The mean overall reduction in IOP for brimonidine/timolol was 9.95 mmHg, whereas for travoprost; it was 7.6 mmHg (p=0.0002). The difference in reduction of IOP was statistically significant. The reduction in IOP with brimonidine/timolol combination was more consistent (Figures 4 and 5), Travoprost showed an inconsistent reduction. This inconsistency may be attributed to noncompliance. There were some reasons for noncompliance with travoprost in this study: (i) adverse effects, which are more with travoprost, (ii) cost of travoprost. The results of this study correlate with those of

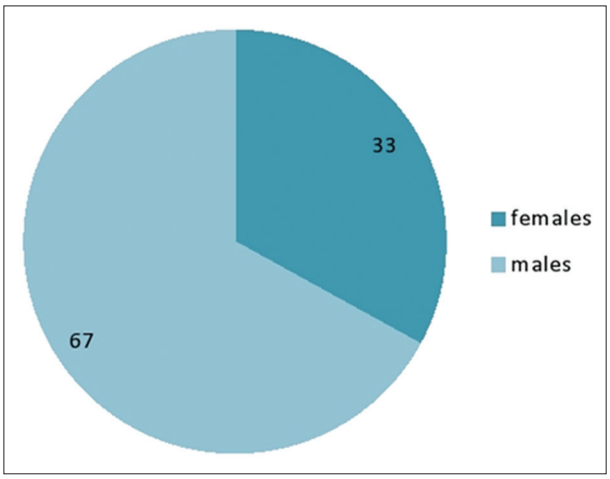

Figure 1: The sex distribution in both the travoprost group and brimonidine + timolol group.

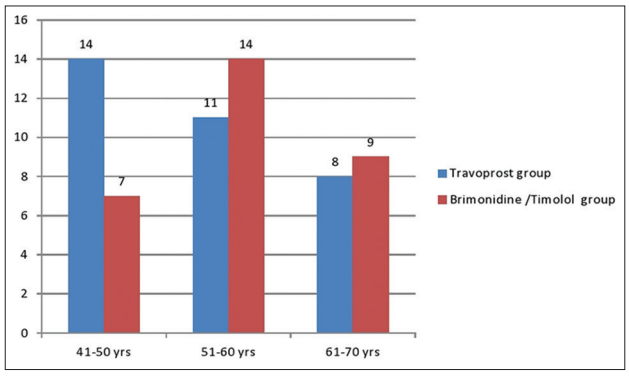

Figure 2: The age distribution in the brimonidine/ timolol and the travoprost group.

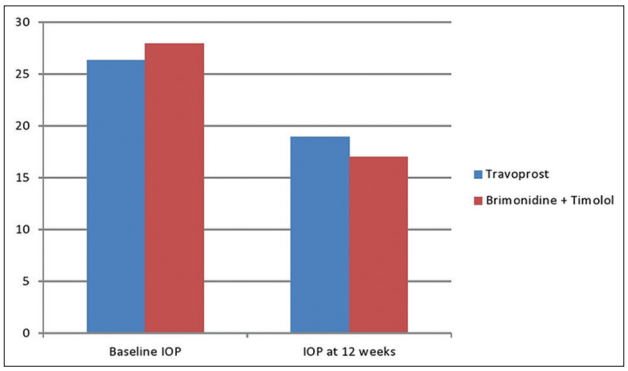

Figure 3: The comparative overall reduction in intra ocular pressure from baseline to the last visit between the two groups in the left eye.

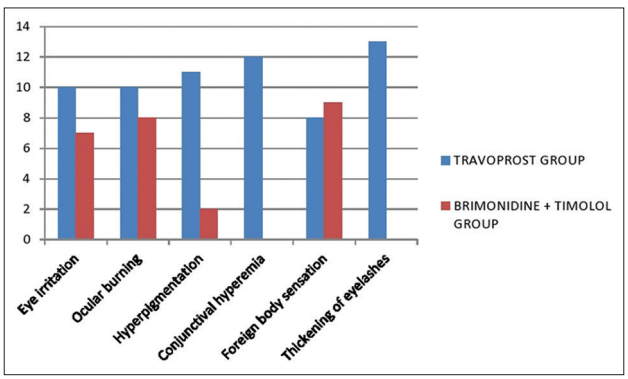

Figure 4: Adverse effects observed in the two groups.

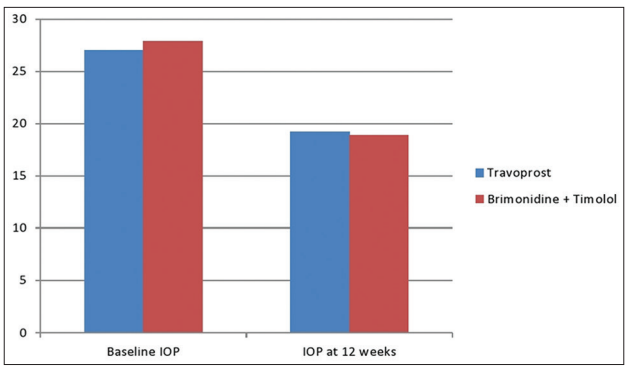

Figure 5: The comparative overall reduction in intra ocular pressure from baseline to the last visit between the two groups in the right eye.

other studies comparing the two drugs.

Safety evaluation was another important object of this study. There were no serious side-effects observed in this study. Both the drugs were well tolerated. Travoprost had a higher incidence of adverse effects. Ocular irritation (30%), pigmentation of eyelashes (36%), change of iris color (25%), thickening of eyelashes (39%), and hyperpigmentation (33%) when compared to the brimonidine/timolol group which showed only ocular irritation (21%).

There was no ocular pain with brimonidine/timolol combination therapy, in contrast to the travoprost group where 10% of the patients suffered from ocular pain and conjunctival hyperemia (36%). While this effect may lessen over time,[12] it may represent a cosmetic concern to the patient, that may lead to poor treatment adherence and thus poor outcomes.[16] In general, PGAs have few systemic adverse events and local ones are mainly transitory or reversible, supporting their use as first-line therapy. Beta-blockers on the other side have a greater risk of systemic adverse events, but fewer local and cosmetic side-effects.[16-18] Of note, adherence to treatment may depend on side-effects, but also on the frequency of instillation of the drops and the presence of preservative agents, the latter inducing a local reaction, that can have a negative effect on surgery, making the rate of success lower.[19]

When medical therapy has been chosen as initial treatment for open-angle glaucoma prostaglandins are generally considered first-line therapy. Most[20,21] but not all[22] meta-analyses have found prostaglandins to be more effective than beta blockers, carbonic anhydrase inhibitors, and alpha adrenergic agonists for the treatment of open-angle glaucoma. Beta blockers may be more appropriate as initial therapy for those patients who cannot afford a topical prostaglandin. Combining drops from different classes (i.e. beta blocker plus prostaglandin, or beta blocker plus carbonic anhydrase inhibitor) can cause a greater reduction in the intraocular pressure than monotherapy, and several drugs are available as fixed combination products. Adding a second medication is reasonable if initial monotherapy is not effective.

CONCLUSION

Glaucoma requires long term therapy, failing which there is a gradual loss of vision. Loss of vision becomes a handicap for glaucoma patients, who commonly belong to the elderly age group. Treatment also has a negative impact on the cost-factor which is one of the important factors of noncompliance. Hence, combination therapy with brimonidine/timolol combination therapy would be economically effective, and compliance would also be better with these drugs in a developing country like India. Clinical trials assessing the efficacy of a fixed combination of brimonidine 0.2% and timolol 0.5% (contribution of elements studies) showed mean IOP reductions were greater with the fixed combination than when the individual agents were used alone.[23] The advantage of the fixed combination, ease and convenience of instillation, might result in better patient compliance, thus leading to the higher success rate with this treatment. These efficacy studies including our study support the versatility of brimonidine as an effective ocular hypotensive agent in patients with glaucoma.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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