Comparative study to assess efficacy and safety of brinzolamide 1% and timolol 0.5% fixed combination eye drops versus dorzolamide 2% and timolol 0.5% fixed combination eye drops in management of open-angle glaucoma

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ABSTRACT

Aim and Objective: To compare the efficacy and safety of brinzolamide 1% and timolol 0.5% fixed combination eye drops versus dorzolamide 2% and timolol 0.5% fixed combination eye drops in the treatment of primary open-angle glaucoma. Design: Prospective, randomized, comparative, interventional study. Setting: Tertiary eye care centre. Material and Method: The present study was a comparative study carried out on patients visiting OPD of Ophthalmology Department and diagnosed with primary open-angle glaucoma. Group 1 (n=30 BT) received brinzolamide 1% and timolol 0.5% fixed combination eye drops, and Group 2 (N=30 DT) patients received dorzolamide 2% and timolol 0.5% fixed combination eye drops. A complete ophthalmic examination was performed, including Goldmann applanation tonometry. IOP was measured twice daily (9 AM and 4 PM). The patients were evaluated at 2, 4, 8, and 12 weeks. IOP was measured at follow-up. Side effects and tolerability of both drugs were assessed, and patient preference for drugs was noted. Results: Mean reduction in morning IOP was significantly more in Group 1 than in Group 2 at 8 weeks and 12 weeks (p < 0.05). Mean reduction in evening IOP was significantly more in Group 1 than in Group 2 at all follow-ups (p < 0.05). Conclusion: Brinzolamide 1% + timolol 0.5% fixed drug combination is more preferred and effective in lowering IOP than dorzolamide 2% + timolol 0.5% fixed drug combination in patients of primary open-angle glaucoma.

Keywords: Brinzolamide, dorzolamide, open-angle glaucoma, timolol

Introduction

Glaucoma is a group of progressive ocular neuropathies marked by the degeneration of retinal ganglion cells, which leads to abnormalities in the optic nerve head and irreversible vision loss. Increased intraocular pressure (IOP) is one of the most significant and modifiable risk factors for glaucoma. Hence, the main aim of glaucoma management involves effective control of IOP and various anti-glaucoma agents can be used for this purpose. Beta blockers, alpha agonists blockers, alpha agonists, prostaglandin analogs (PGA), sympathomimetic drugs and carbonic anhydrase inhibitors (CAIs) are some of the major classes of anti-glaucoma drugs that are commercially available.
Numerous studies have compared the action of different anti-glaucoma agents either singly or in combination. When treating primary open-angle glaucoma, PGAs, beta blockers and CAIs are widely used as first-line agents (POAG). This occurs by either increasing tissue permeability or by acting on episcleral vessels, which are responsible for increasing the outflow from the uveoscleral system. Latanoprost, travoprost, bimatoprost and tafluprost are currently available PGA medications. Carbonic anhydrase inhibitors decrease aqueous secretion by limiting the generation of bicarbonate ions in the ciliary epithelium. Commerially available topical CAIs include dorzolamide and brinzolamide. Among beta blockers, the most commonly used drug is timolol maleate0.5%. Due to the fact that these drugs reduce IOP in different ways, they are often given in combination with one another.

Fixed dose combination of hypotensive medications reduces IOP and slow progression of visual field defects, simplifies treatment regimens and increases treatment adherence of the patients.

The purpose of this study was to assess the efficacy and safety of brinzolamide1% and timololo0.5% fixed combination eye drops vs dorzolamide2% and timololo0.5% fixed combination eye drops in the treatment of open-angle glaucoma. Since glaucoma is the disease which can lead to irreversible loss of sight, newer research studies are continuously being conducted in this field to curb the disease effectively at an early stage, not only the ophthalmologists but primary care physicians should also be having knowledge of drugs which can be used as monotherapy or as fixed combinations so that patient can receive treatment at the earliest which is the most important factor in curbing permanent visual damage due to this disease.

**Material and Methods**

The current study was planned as a 12-week prospective, comparative, randomized, interventional trial in individuals with primary open-angle glaucoma, evaluating the efficacy and safety of topical brinzolamide1% + timololo0.5% with topical dorzolamide2% + timololo0.5%. The study was approved by the institutional ethics committee, and it was carried out in accordance with the Helsinki Declaration. Before the study began, all patients provided signed informed consent.

**Patient selection**

All consecutive patients presenting to the Ophthalmic Outpatient Department at Saraswathi Institute of Medical Sciences, Hapur, between December 2019 and December 2020, were screened for POAG. Inclusion criteria included patients with age ≥18 years who were willing to participate and follow up, with newly diagnosed POAG with baseline IOP >21 mmHg and not on any prior systemic or topical medications. All patients were subjected to a thorough eye examination inclusive of visual acuity assessment, refraction, slit-lamp examination, dilated fundoscopy (using tropicamide1%), automated perimetry (Humphrey field analyser program 30-2 equipped with StatPac, Carl Zeiss Meditec AG, Jena Germany) and IOP measurement (calibrated Goldmann applanation tonometry). Three different measurements were taken at each time point, and the mean was derived for further analysis. POAG was defined as a visual field defect or glaucomatous changes to the optic nerve head (neural rim loss, disc asymmetry, blood vessel abnormalities and peripapillary atrophy) in the presence of a high IOP (>21 mmHg). All eligible patients were required to have an IOP between 22 mmHg and 36 mmHg; the right eye of all patients was enrolled in the study and the left eye was taken as control and was instilled lubricating eye drops. Sixty eyes (right eye) from 60 patients who met the criteria were randomly allocated into two groups using a computer randomised program. One group (n = 30) was administered topical Brinzox T (brinzolamide1% + timololo0.5%) (Ajanta Pharma, India) two times a day, and the other group (n = 30) was advised topical Dorzox T (dorzolamide2% + timololo0.5%) (Cipla Ltd., India) two times per day at 7:00 am and 7:00 pm. The left eye of all patients was administered preservative-free lubricant eye drops two times a day. The patients were instructed how to instil the medications. Patients with an IOP greater than 36 mmHg in the affected eye, best-corrected visual acuity of less than 0.6 log MAR, cup–disc ratio greater than 0.8, gonioscopy-measured angle less than grade 2 (Shaffer classification), severe central visual field loss, a history of chronic and recurrent inflammatory eye disease, the presence of ocular surface disease or any other ophthalmic pathology (retinal disease, etc.), or any other abnormality limiting reliable applanation tonometry, ocular trauma, laser procedure or intraocular surgery within 6 months, secondary, ocular hypertension and glaucoma with normal intraocular pressure were excluded from the study. Pregnant or lactating women and patients with severe unstable or uncontrolled cardiovascular, hepatic or renal diseases, bronchial asthma or chronic pulmonary diseases; or hypersensitivity to any components of the study medications were also excluded.

**Follow-up**

The patients were followed up at 2, 4, 8 and 12 weeks, and IOP was again recorded at this visit at 9 am and 4 pm with the same applanation tonometer (used preoperatively) by a single observer to avoid inter-observer bias. This observer was blinded for the type of drug administered to avoid intra-observer bias. Effectiveness of the drugs was calculated in terms of mmHg fall in mean IOP. An adverse event was defined as any unfavourable occurrence in a subject, whereas a major adverse event was defined as a potentially lethal, life-threatening, or sight-threatening occurrence. Flare, if present, was graded as none (0–2 cells), mild (3–5 cells), moderate (6–20 cells) or severe (>20 cells) based on the number of anterior chamber cells in a 2-mm slit. At each follow-up, the following symptoms were noted: conjunctival hyperaemia, foreign body sensation, blurred vision, dry eye sensation, stinging, pruritus, eyelash changes, iris pigmentation, superficial keratitis, follicular conjunctivitis, herpetic reactivation, taste anomalies and headache.
Statistical analysis
The data were collected and entered into a Microsoft Excel spreadsheet. SPSS version 23 was used to conduct the statistical analysis. For comparing categorical and continuous data, appropriate statistical tests were used. Statistical significance was defined as a P value of less than 0.05.

Results

Demographic characteristics
Sixty eyes of 60 patients were included in the study and divided into two groups of 30 each. The mean age of patients was 44 ± 8.39 years and 42.3 ± 9.02 years, respectively, in Groups 1 and 2, respectively. Group 1’s gender distribution (17 males, 13 females) is comparable to Group 2’s (14 females, 16 males) Figure 1. In terms of sex, diagnosis, visual acuity, gonioscopy values and horizontal and vertical cup–disc ratio, there was no statistical difference between the therapy groups. No patient was lost to follow-up.

Mean IOP value
Baseline IOP in Group 1 was 25.3 ± 1.6; it reduced to 18.36 ± 1.37 (2 weeks), 16.83 ± 1.46 (4 weeks), 16.06 ± 1.53 (8 weeks) and 15.7 ± 1.51 (12 weeks). Mean IOP in Group 2 was 25.13 ± 0.94 mmHg at baseline. It reduced to 18.73 ± 1.1 at 2 weeks, 17.36 ± 0.76 at 4 weeks, 17.2 ± 0.84 at 8 weeks and 16.73 ± 0.82 at 12 weeks Table 1.

Baseline IOP in Group 1 and Group 2 was 25.76 ± 1.71 mmHg and 25.1 ± 0.96 mmHg, respectively. IOP decreased over follow-up as shown in Table 2. It was 15.76 ± 1.56 mmHg and 16.96 ± 0.88 mmHg in Group 1 and Group 2, respectively, at 12 weeks.

We observed that mean reduction in IOP in Group 1 at 2 weeks was 6.94 ± 1.21 mmHg. Reduction increased over next follow-ups. It was 8.47 ± 1.43 mmHg at 4 weeks, 9.24 ± 1.51 at 8 weeks and 9.6 ± 1.55 mmHg at 12 weeks. In Group 2, the reduction was 6.4 ± 1.3 mmHg (2 weeks), 7.77 ± 0.88 mmHg (4 weeks), 7.93 ± 0.99 mmHg (8 weeks) and 8.4 ± 0.84 mmHg (12 weeks). On analysis, we found that a reduction in mean IOP was more in Group 1 than in Group 2 at all follow-ups, but reduction was statistically significant between two groups at 8 weeks and 12 weeks Table 3.

Reduction in mean evening IOP from baseline in Group 1 was 7.43 ± 1.43 mmHg at 2 weeks, 9.00 ± 1.52 mmHg at 4 weeks, 9.6 ± 1.71 mmHg at 8 weeks and 10.0 ± 1.57 mmHg at 12 weeks. In Group 2, mean reduction was 6.37 ± 1.1 mmHg at 2 weeks, 7.57 ± 0.92 mmHg at 4 weeks, 7.74 ± 0.98 mmHg at 8 weeks and 8.14 ± 0.85 mmHg at 12 weeks. Thus, we can conclude that mean reduction in evening IOP was significantly more in Group 1 than in Group 2 at all follow-ups (p < 0.05) Table 4.

Adverse effects
In our study, 25 (83.33 percent) patients in Group 1 (BT) and 17 (56.67 percent) patients in Group 2 (DT) had perfect ocular comfort with no ocular side effects (p < 0.05) Ocular discomfort and ocular pain were observed more in Group 2 (DT) patients. No anterior segment inflammation, blurred vision, eyelash changes, iris pigmentation, superficial keratitis, follicular conjunctivitis, herpetic reactivation and taste abnormalities were seen in any patient. Patients preferred Brinzox T eye drops over Dorzox T eye drops.

Discussion
Elevated IOP is the most important modifiable risk factor of glaucoma, and a lot of present-day research focuses on

### Table 1: Comparison of mean morning IOP (mmHg) in both the groups over follow-up
| Group | Baseline | 2 weeks  | 4 weeks  | 8 weeks | 12 weeks |
|-------|----------|----------|----------|---------|----------|
| Group 1 | 25.3±1.6 | 18.36±1.37 | 16.83±1.46 | 16.06±1.53 | 15.7±1.51 |
| Group 2 | 25.13±0.94 | 18.73±1.1 | 17.36±0.76 | 17.2±0.84 | 16.73±0.82 |

### Table 2: Comparison of mean evening IOP in both the groups over follow-up
| Group | Baseline | 2 weeks  | 4 weeks  | 8 weeks  | 12 weeks  |
|-------|----------|----------|----------|----------|-----------|
| Group 1 | 25.76±1.71 | 18.33±1.49 | 16.76±1.50 | 16.16±1.74 | 15.76±1.56 |
| Group 2 | 25.1±0.96  | 18.73±0.86 | 17.53±0.89 | 17.36±0.99 | 16.96±0.88 |

### Table 3: Reduction in mean morning IOP compared to baseline
| Group | 2 weeks  | 4 weeks  | 8 weeks  | 12 weeks  |
|-------|----------|----------|----------|-----------|
| Group 1 | 6.94±1.21 | 8.47±1.43 | 9.24±1.51 | 9.6±1.55  |
| Group 2 | 6.4±1.3   | 7.77±0.88 | 7.93±0.99 | 8.4±0.84  |
| P      | 0.10      | 0.02      | 0.002     | 0.004     |

### Table 4: Reduction in mean evening IOP compared to baseline
| Group | 2 weeks  | 4 weeks  | 8 weeks  | 12 weeks  |
|-------|----------|----------|----------|-----------|
| Group 1 | 7.43±1.43 | 9.00±1.52 | 9.6±1.71  | 10.0±1.57 |
| Group 2 | 6.37±1.1  | 7.57±0.92 | 7.74±0.98 | 8.14±0.85 |

Figure 1: Distribution of patients according to group and sex
modalities that aid in lowering the IOP. In the present times, topical pharmacotherapy with currently available anti-glaucoma agents remains the primary mode of management of patients for POAG.\textsuperscript{15,17} This study compared the efficacy and safety of brinzolamide1% and timolol0.5% fixed combination eye drops to dorzolamide2% and timolol0.5% fixed combination eye drops in the treatment of primary open-angle glaucoma. During the 8-week and 12-week periods of our study, the mean reduction in morning IOP was significantly greater in Group 1 (BT) than in Group 2 (DT). At all follow-ups, Group 1 (BT) had a substantially greater drop in evening IOP than Group 2 (DT) (p < 0.05).

Manni et al.\textsuperscript{18} studied 437 patients with open-angle glaucoma and ocular hypertension and found that the reduction in IOP ranged between 7.2 and 9.2 mmHg in the BT group and 7.4 to 8.9 mmHg in the DT group, which is comparable to our study. Sczigin A\v{c}ay et al.\textsuperscript{19} noted that IOP reduction in the brinzolamide group was 6.42 to 9.74 mmHg (26.09–37.46%) and dorzolamide group had reductions from 8.16 to 12.41 mmHg (31.19–41.44%) (P > 0.05). Holló et al.\textsuperscript{20} also observed IOP reduction of 30–33% in the brinzolamide group and found that both drugs are equally effective. Similar findings were made by Cheng et al.\textsuperscript{21} who observed a similar reduction in IOP in BT (33%) and DT (30%) groups.

When tested brinzolamide and dorzolamide alone, they show equal efficacy. The difference in the structure of brinzolamide and dorzolamide may have an effect on efficacy when combined with timolol. Different synergy of the drugs in fixed dose combination could lead to difference in the outcome.

Dorzolamide is formulated at acidic pH (5.65), and brinzolamide has a pH of 7.2. Difference in pH between brinzolamide and dorzolamide may affect the compliance of the patients to the treatment, which may in turn affect the efficacy.\textsuperscript{22–28} A recently published review of literature suggests ample evidence with the use of dorzolamide–timolol fixed combination as initial therapy to promptly lower significantly high IOP in the presence of significant damage and particularly so in glaucoma with alarming 24-h IOP characteristics.\textsuperscript{29} A recent study conducted by Dixit et al.\textsuperscript{24} also showed >30% reduction in IOP with fixed combination of brinzolamide and timolol eye drops and no side effects, thereby supporting this drug as primary monotherapy in treatment of POAG. Similarly, although our study suggests that both brinzolamide–timolol fixed combination and dorzolamide–timolol fixed combination can be used as an effective primary therapy in POAG cases, BT may be preferred over DT due to its superior efficacy. Besides, both brinzolamide–timolol and dorzolamide–timolol had a relatively low frequency of manageable adverse effects following treatment. Although brinzolamide–timolol had marginally lesser side effects, the role of preservatives used in both medications on these side effects needs to be explored further.

It is reported that glaucoma patients can have their peak IOP outside office hours.\textsuperscript{27} A retrospective review by Hughes et al.\textsuperscript{24} also showed that the peak diurnal IOP was on average 4.9 mmHg higher than the maximum IOP conventionally measured in a clinic. In the same study comparing 24-h IOP monitoring with the conventional office-hour IOP measurements, the implementation of 24-h IOP monitoring even resulted in a change of clinical management in 79.3% of the patients. Clinicians/primary care physicians may thus choose different anti-glaucoma therapy according to the distinct circadian rhythm in each glucomatous subtype or as reflected by the individual IOP profile. Certain limitations of our study include relatively short duration and limited sample size. Although early results support convincing results in our study, larger, long-term studies are needed to assess the clinical effects, and particularly the safety, of these medications. Also, caution is to be exercised while extrapolating the results of the present study to other types of glaucoma due to variable pathophysiology and to other brands of same active chemicals due to their variable efficacy. While we tried to minimize the false positive results by taking fellow eyes as controls, crossover studies or paired-eye comparisons are recommended for obtaining accurate results.

### Conclusion

Fixed drug combination of brinzolamide and timolol has higher efficacy in terms of IOP reduction and better preference when compared with dorzolamide and timolol fixed drug combination in patients of primary open-angle glaucoma.

### Ethical clearance

This ethical approval for this study was obtained from the ethical Committee of Saraswati Institute of Medical Sciences, Hapur, Uttar Pradesh, India, with the No. SIMS/FMT/ETHI/22/19 dated 04/12/19.

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The study was carried out at Saraswati Institute Of Medical Sciences, Hapur, and no extra financial support was required.

### Conflicts of interest

There are no conflicts of interest.

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