COMPARISON OF IOP LOWERING Efficacy
BRIMONIDINE-TIMOLOL VERSUS DORZOLAMIDE-TIMOLOL
FIXED COMBINATION THERAPY

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OBJECTIVE: Fixed combinations of 0.2% brimondine-0.5% timolol are used to lower intraocular pressure (IOP). The objective of this study was to evaluate the IOP-lowering efficacy and ocular tolerability of brimonidine-timolol compared with dorzolamide-timolol when used as monotherapy or as adjunctive therapy to a prostaglandin analog (PGA) in patients with glaucoma or ocular hypertension.

STUDY DESIGN AND METHODS: Polled data analysis of two randomized, 3 months, parallel-group studies angle glaucoma or ocular hypertension who were in need of lower IOP received topical brimonidine-timolol BID or dorzolamide-timolol BID as monotherapy (n=101) or as adjunctive therapy to a PGA (latanoprost, bimatoprost or travoprost) (n=79).

MAIN OUTCOME MEASURES: IOP was measured at 10a.m. (peak effect) at baseline and at months 1 and 3. Tolerability/comfort was evaluated using a patient questionnaire.

RESULT: There were no statistically significant between-group differences in patient demographics. Most patients were the mean age was 68 years. There were
also no statically significant differences between treatment groups in baseline IOP. At month 3, the mean (SD) reduction from baseline IOP for patient's on fixed-combination monotherapy was 7.7 (4.2) mmHg (32.3%) with brimonidine-timolol versus 6.7 (5.0) mmHg (26.1%) with dorzolamide-timolol (p=0.040). The Mean reduction from PGA-treated baseline IOP for patients on fixed-combination adjunctive therapy was 6.9 (4.8) mmHg (29.3%) with brimonidine-timolol versus 5.2 (3.7) mmHg (23.5%) with dorzolamide-timolol (p=0.213). Patients on brimonidine-timolol reported less burning (p<0.001), stinging (p<0.001) than patients on dorzolamide-timolol.

**CONCLUSION:** Fixed-combination brimonidine-timolol provided the same or greater IPO lowering compared with fixed-combination dorzolamide-timolol. Both fixed-combination medications were safe and well-tolerated. Brimonidine-timolol received higher ratings of ocular comfort than dorzolamide-timolol. The duration of the studies was 3 months, and additional studies will be needed to compare the efficacy and tolerability of brimonidine-timolol and dorzolamide-timolol during long-term treatment.

**INTRODUCTION:** A primary goal of medical therapy in glaucoma and ocular hypertension (OHT) is to reduce intraocular pressure (IOP) to a level sufficiently low to prevent disease progression¹. While IOP lowering is ideally achieved with monotherapy, many patients are not adequately controlled on a single IOP-lowering agent. When multiple medications are required, the use of a fixed combination of two IOP-lowering medications offers several advantages over the concomitant use of the individual components. In addition to the convenience of a single bottle, which may
improve patient compliance\(^2\), fixed combinations of IOP-lowering medications also reduce the likelihood of drug dilution caused by the instillation of multiple eye drops, minimize ocular exposure to preservatives\(^3\), and may lead to a decrease in costs and patient copayments for the medications\(^4\).

The fixed combination of dorzolamide 2% and timolol 0.5% (MISOPT) has been available for many years and is widely used in glaucoma therapy. The active components include dorzolamide, a carbonic anhydrase inhibitor, and timolol, a nonselective B-blocker, both of which reduce IOP by suppressing aqueous production\(^5\). In recent years, a fixed combination of brimonidine 0.2% and timolol 0.5% (Combigan) has also received approval for IOP lowering in glaucoma and OHT. The brimonidine component is an alphadrenergic agonist that reduces IOP by increasing uveoscleral aqueous production\(^6\).

The fixed combinations of dorzolamide-timolol and brimonidine-timolol have only direct head-to-head comparison of dorzolamide-timolol and brimonidine-timolol published to date was a crossover study in 30 patients reported by Arcieri et al\(^7\). Dorzolamide-timolol and brimonidine-timolol provided similar IOP lowering, though the treatment was only over a 4-week period\(^7\). Two independent studies have compared dorzolamide-timolol fixed-combination therapy with concomitant brimonidine and timolol therapy\(^8,9\). In each of these studies, the nonfixed combination of brimonidine and timolol was more effective than fixed-combination dorzolamide-timolol in reducing IOP at peak 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
Due to their efficacy, safety profile, and closing regimen, the once-daily prostaglandin analogs (PGAs) bimatoprost, latanoprost and travoprost remain the most commonly prescribed first-line medications for the treatment of glaucoma and OHT. Although monotherapy is ideal, many patients require more than one medication to achieve their target pressure. Over 20% of PGA patients, for example, may be required to add another IOP-lowering medications to their treatment regimen within a year of initiating treatment. As most IOP-lowering medications outside of the PGA class are typically used adjunctive to a PGA, it is important to evaluate the IOP-lowering effect of these agents not only in isolation but also in the adjunctive setting. The efficacy of the dorzolamide-timolol and brimonidine-timolol fixed combinations used as adjunctive therapy to a PGA has not been well-studied. Prospective open-label studies have suggested that both dorzolamide-timolol and brimonidine-timolol effectively reduce IOP when added to a PGA.

Both IOP-lowering efficacy and tolerability are primary considerations when choosing medication for treatment of glaucoma and OHT. The purpose of the present study was to evaluate the comparative efficacy and ocular tolerability of fixed-combination brimonidine-timolol compared with fixed-combination dorzolamide-timolol when used as monotherapy or as adjunctive therapy to a PGA in patients with glaucoma or OHT.

**METHODS:**

Two randomized, parallel-group clinical comparison trials with identical protocols were carried out at two sites (outpatients settings in both private) and the data were
pooled for analysis. All patients who participated provided written informed consent prior to the initiation of study-related procedures.

Patient eligibility was determined at screening during a routine, scheduled office visit. Patients at least 18 years old with a diagnosis of open-angle glaucoma (OAG) or OHT who were in need of lower IOP in each eye were potentially eligible for the study. Patients could be untreated or currently on IOP-lowering therapy. The need for lower IOP was based on the opinion of the investigator. Primary exclusion criteria included current enrollment in a clinical trial with an investigational drug; history of ophthalmic disease other than glaucoma; closed-angle glaucoma; any known contraindication to B-blockers, a-agonists, or carbonic anhydrase inhibitors, asthma or chronic obstructive pulmonary disease; uncontrolled diabetes; clinically significant heart disease, second-or third-degree atrioventricular block, or sinus bradycardia; use of a monoamine oxidase inhibitor; and previous sensitivity or allergic reaction to brimonidine or dorzolamide. Eligible patients on current treatment with a once-daily PGA were continued on the PGA. All other IOP-lowering medications were discontinued and washed out for a period of 4 weeks prior to the baseline visit.

At the baseline visit, patients were randomized in a 1:1 ratio to treatment with topical fixed-combination brimonidine 0.2%-timolol 0.5% or fixed combination dorzolamide 2%-timolol 0.5% alone or as adjunctive therapy to a PGA. Patients were instructed to instill one drop of their study medication in each eye twice daily between 7 and 8 a.m. and between 7 and 8 p.m. patients on concurrent PGA therapy were instructed to wait at least 10 minutes between instillation of the study drug and the PGA. The investigators were masked to the treatment assignment.
Bottles of study medication were supplied to patients in identical masked cartons labeled with the patient randomization number. Patients were instructed not to disclose the name of their study medication to other patients or to the investigator or office staff.

Study visits were scheduled at baseline (day 0), month 1, and month 3. The primary efficacy outcome measure was mean change from baseline IOP at each follow-up visit. Intraocular pressure was measured using Goldman applanation at 10 a.m. (peak study drug effect, approximately 2 hours after the morning dose of study medication) at each visit. Patients self-administered their study drug approximately 2 hours prior to the visit and were contacted either the day prior to or the morning of the study visits to be reminded to put in their medication at the appropriate time. Safety outcome measures included adverse events and comfort/tolerability.

A tolerability and comfort questionnaire was administered at month 1. Patients were asked to rate the severity of stinging in their eyes, burning (other than stinging) in their eyes, and unusual taste they experienced with the study medication on a 5-point scale with 0=none, 1=very minimal, 2=mild, 3=moderate and 4=severe. Patients were asked to rate the overall comfort of using the study medication on a 3-point scale of 1=uncomfortable, 0=comfortable, and 1=very comfortable. For each question, patients were asked to base their answers on their impressions over the last 7 days of study medication use.

Analyses of IOP were based on the worse eye (the of 180 patients at with the high IOP at baseline) for the intent-to-treat patient population (all randomized patients)
with no imputation for missing values. If both eyes, rather than the IOP of the worse eye, was used for analysis at each time point. Analyses were performed for the subgroup of patients who received study medication as adjunctive therapy to a PGA. Analysis of variance (ANOVA) was used to test between-group differences in mean IOP at baseline and analysis of covariance (ANCOVA) with baseline IOP as the covariate was used to test between group-differences in mean IOP at follow-up visits. Results were qualitatively similar when ANOVA rather than ANCOVA was used for these analyses. Other continuous variables were analyzed using t-tests. Categorical variables were analyzed using the chi-square test.

All statistical tests were two-tailed with the a level for significance set at 0.05.

**RESULTS:**

**PATIENT CHARACTERISTICS AND DISPOSITION:**

A total ten sites were randomized and prospectively evaluated on study medication for 3 months in two studies with identical protocols. Study 1 was conducted at a single site and enrolled 100 patients, while study 2 was at other centre and enrolled 80 patients. Baseline patients. Baseline characteristics of the pooled patient population are listed in Table 1. There were no statistically significant between-group differences in patient demographics. Most patients were Indians and were diagnosed with OAG. Approximately 56% of the patients received the fixed combination as monotherapy. Most of these patients used the fixed combination in replacement of previous therapy, but 15 patients (28%) in the brimonidine-timolol monotherapy group and 16 patients (34%) in the dorzolamide-timolol monotherapy group were
naïve to IOP-lowering medication. The fixed combination was used as adjunctive therapy to a PGA in 44% of the patients. Among the patients who the fixed combination of as adjunctive therapy, the proportion of patients on bimatoprost, latanoprost and travoprost was similar between treatment groups (p=0.540).

The study completion rate was 89.4% (161/180). In the brimonidine-timolol group, 12 patients exited the study early because of adverse events (n=10) withdrawal of consent (n=1) and loss to follow-up (n=1). In the dorzolamide-timolol group, seven patients discontinued prior to month 3 because of adverse events (n=6) and protocol violations (n=1). No patients in either treatment group discontinued from the study due to insufficient IOP lowering.

**IOP-LOWERING EFFICIENCY:**

There were no statistically significant differences in the baseline mean IOP between the brimonidine-timolol treatment groups. For patients who used the study medication as monotheapy, the mean (SD) IOP as baseline was 23.0 (4.4) mmHg in the brimonidine-timolol group verses 23.6 (4.5) mmHg in the dorzolamide-timolol group (p=0.522; Figure 1A). For patients who used the study medication as adjunctive therapy to a PGA, the baseline mean IOP on the PGA was 21.9 (4.3) mmHg in the brimonidine-timolol group (p=0.277; Figure 1B).

Among patients treated with fixed-combination monotherapy, the mean IOP was similar between treatment groups at month 1 (Figure 1A). At month 3, however, the mean IOP was significantly lower with brimonidine-timolol than with dorzolamide-
timolol (Figure 1A). The mean IOP at a month 3 was 15.6 (3.8) mmHg with brimonidine-timolol versus 17.2 (3.2) mmHg with dorzolamide-timolol (p=0.040). The mean reduction from baseline IOP was also significantly greater with brimonidine-timolol than with dorzolamide-timolol at month 3 (Figure 2A). After 3 months of fixed-combination monotherapy, the mean (SD) decrease from baseline IOP was 7.7 (4.2) mmHg (32.3%) with brimonidine-timolol versus 6.7 (5.0) mmHg (26.1%) with dorzolamide-timolol (p=0.040).

For patients who used the fixed combination as adjunctive therapy to a PGA, the differences between treatment groups in mean IOP were not statistically significant at any visit (Figure 1B). At month 3, the mean IOP was 15.3 (3.3) with brimonidine-timolol versus 16.1 (3.7) mmHg with dorzolamide-timolol (p=0.213). The mean additional reduction from baseline IOP on the PGA was 6.9 (4.8) mmHg (29.3%) for brimonidine-timolol and 5.2 (3.7) mmHg (23.5%) for dorzolamide-timolol after 3 months of adjunctive therapy (p=0.213; Figure 2B).

**SAFETY AND TOLERABILITY:**

There were no significant differences between treatment groups in the incidence of any particular treatment-related adverse event or in overall, treatment-related adverse events were reported for 13 patients in the brimonidine-timolol group and six patients in the dorzolamide-timolol group (p=0.160). The most common treatment-related adverse events were headache, dry-mouth/throat and fatigue (Table 2), with headache reported in four patients in the brimonidine-timolol group and one patient in the dorzolamide-timolol group (p=0.368), and dry mouth/throat reported in five
patients in the brimonidine-timolol group and no patients in the dorzolamide-timolol group (p=0.059). The rate of discontinuations due to adverse events (treatment-related or unrelated) was also similar in the two treatment groups (ten patients, 11.0%, in the brimonidine-timolol group and six patients, 6.7%, in the dorzolamide-timolol group, p=0.317). The most common adverse effects that led to discontinuation were headache, fatigue, allergic conjunctivitis/allergic reaction, burning/stinging, and dry mouth.

Brimonidine-timolol patients reported less stinging, burning and unusual taste compared with dorzolamide-timolol patients on the comfort and tolerability questionnaire. Mean scores for each of these symptoms were lower in the brimonidine-timolol group that in dorzolamide-timolol group (p<0.001), and fewer patients in the brimonidine-timolol group than in the dorzolamide-timolol group reported moderate or severe stinging, burning and unusual taste (p<=0.015). The percentage of patients who rated symptoms as moderate or severe in the brimonidine-timolol and dorzolamide-timolol groups, respectively, was 8.2% and 31.4% for stinging (p<0.001), 7.1% and 19.8% for burning (p=0.015), and 4.7% versus 18.6% for unusual taste (p=0.005).

Overall comfort scores were higher with brimonidine-timolol than with dorzolamide-timolol (p=0.014). The overall comfort of the study medication was rated as very comfortable by 41.2% (35/85) of patients in the brimonidine-timolol group and 20.9% (18/86) in the dorzolamide-timolol group (p=0.005).
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OHT: Ocular Hyper Tension, OAG: Open-Angle Glaucoma, PGA Prostaglandin Analog

<sup>a</sup>Ocular Hyper Tension in one eye and angle glaucoma in the fellow eye

<sup>b</sup>p-value for ‘yes’ vs. ‘no’
Figure 1: Mean Intraocular pressure (IOP) at each study visit for patients using the fixed combination as (A) monotherapy or (B) adjunctive therapy to a prostaglandin analog (PGA). Error bars represent standard error of the mean (SEM). *p=0.040 vs. dorzolamide-timolol
Figure 2. Mean change from baseline IOP at each follow-up study visit for patients using the fixed combination as (A) monotherapy of (B) adjunctive therapy to a PGA. Error bars represent standard error of the mean (SEM). P = 0.040 vs. dorzolamide-timolol.
**DISCUSSION:**

This study was designed to compare the efficacy, safety, and ocular tolerability of brimonidine-timolol with dorzolamide-timolol both in patients who used the fixed combination as monotherapy and in those who used the fixed combination adjunctive to a PGA. Each of the two fixed-combination agents provided substantial IOP lowering in both patient populations. In addition, few adverse events in each of the treatment arms resulted in the need for discontinuation of medication and early study exit.

Overall, the magnitude of IOP lowering in patients treated with fixed brimonidine-timolol was similar to or greater than that observed in patients treated with fixed dorzolamide-timolol. Among patients who were given the fixed combination as monotherapy, there was a statistically significant lower mean IOP and a greater mean reduction from baseline IOP with brimonidine-timolol than with dorzolamide-timolol at month 3. Among patients who used the fixed combination as adjunctive therapy to PGA, the mean IOP and the mean additional reduction from baseline IOP on the PGA were similar with each fixed combination at month 3.

In the present study, the IOP-lowering effect of brimonidine-timolol was the same as or greater than that of dorzolamide-timolol. These findings are similar to those observed in prior reports of non-fixed combinations of the individual components when each was dosed twice daily. Controlled studies of adjunctive therapies have typically found greater IOP lowering at peak effect with brimonidine than with dorzolamide added to timolol, while at trough effect, brimonidine and dorzolamide
provided similar additional IOP lowering. Though a prior head-to-head clinical comparison of brimonidine-timolol and dorzolamide-timolol found no significant difference in IOP lowering between the fixed combinations, no measurements were taken at peak drug effect.

Based on the patient questionnaire in the current study, brimonidine-timolol produced less burning, stinging, unusual taste than dorzolamide-timolol and was rated as more comfortable by patients. These findings are also consistent with results from previous studies. Ocular burning/stinging was more common with dorzolamide-timolol than with brimonidine-timolol in a head-to-head comparison study of the 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 30-40 seconds after eye drop instillation. 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. The finding of greater ocular comfort with the brimonidine-timolol fixed combination may have clinical significance, since in some cases, ocular discomfort upon instillation of eye drops may limit patient compliance with treatment. Future studies are needed to evaluate the relationship between ocular comfort upon instillation of topical medications and compliance.

Numerous clinical trials have demonstrated the importance of IOP lowering in minimizing glaucomatous progressions. Most recently, the Canadian Glaucoma Study demonstrated that every 1mm Hg rise in IOP was associated with a 19%
increase ion the risk of progression. Therefore, the primary consideration in selecting a medical regimen in glaucoma and OHT remains achieving maximum IOP lowering to a target IOP. For patients on a PGA who need additional IOP lowering, the number of additional bottles of medication ideally should be limited as the addition of a third or fourth IOP-lowering mechanism to a medication regimen is often unsuccessful for reasons of efficacy, safety or compliance. In patients on a PGA therapy requiring further IOP reduction, the addition of a fixed-combination therapy may provide significant IOP lowering while adding only one bottle and two drops to the patient’s daily regimen. In this study, both the brimonidine-timolol fixed combination and the dorzolamide-timolol fixed combination provided substantial additional IOP lowering (29.3% with brimonidine-timolol and 23.5% with dorzolamide-timolol) when used as adjunctive therapy in patients on a PGA. Based on the distribution of patients in this study between monotherapy and adjunctive therapy, this study may have been underpowered to detect differences in the adjunctive patient populations.

**LIMITATIONS:**

The limitations of this study include its relatively short duration (3 months) and the measurement of IOP at only a single timepoint (peak drug effect) at each visit. Further studies should evaluate long-term efficacy and tolerability and use additional timepoints. As the tolerability and comfort questionnaire was administered only at month 1, the test-retest reliability of the questionnaire was not evaluated. Further, the questionnaire may not have captured all of the ocular surface or systemic side-effects associated with the study medications. Ocular allergy, which is sometimes
associated with brimonidine treatment and less frequently with brimonidine-timolol treatment, was not queried because it typically represents a delayed response. In addition, patient compliance with medications was not directly assessed. It is unclear if differences in IOP, which were more prominent at month 3 than at month 1, may be partially attributed to reduced compliance and are in any way related to the differences reported in patient ocular comfort associated with the instillation of the study medications.
CONCLUSIONS:

Both brimonidine-timolol and dorzolamide-timolol effectively lowered IOP when added to an ongoing PGA or used as monotherapy in patients with glaucoma or OHT. Better overall ocular comfort was reported in those patients on the brimonidine-timolol combination.
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17. Chan K, Testa M, McCluskey P Okular comfort of combination glaucoma therapies: brimonidine 0.2% timolol 0.5% compared with dorzolamide 2% timolol o.5% J Ocul Pharmacel then 2007;23:372-6.

