Brimonidine Tartrate 0.15%, Dorzolamide Hydrochloride 2%, and Brinzolamide 1% Compared as Adjunctive Therapy to Prostaglandin Analogs

Thomas E. Bournias, MD, Jerry Lai, MD

Objective: To compare the efficacy of brimonidine, dorzolamide, and brinzolamide in reducing intraocular pressure (IOP) when used as adjunctive therapy to a prostaglandin analog (PGA).

Design: Randomized, controlled, investigator-masked, single-site, parallel-group clinical trial.

Participants: One hundred twenty eyes of 120 patients with open-angle glaucoma or ocular hypertension who had inadequate IOP control after at least 6 weeks of monotherapy with a once-daily PGA (bimatoprost, latanoprost, or travoprost).

Intervention: Study eyes were assigned randomly to adjunctive treatment with thrice-daily brimonidine tartrate 0.15% (n = 41), dorzolamide hydrochloride 2% (n = 40), or brinzolamide 1% (n = 39) for 4 months.

Main Outcome Measures: Efficacy was evaluated by IOP measured at 10 AM and 4 PM at baseline, month 1, and month 4.

Results: The mean IOP at each hour at PGA-treated baseline was comparable among treatment groups. After initiation of adjunctive therapy, the mean IOP was lower and the mean change from baseline IOP was greater in the brimonidine group than in either the dorzolamide group or the brinzolamide group at 10 AM and 4 PM at months 1 and 4 ($P<0.001$). After 4 months of adjunctive treatment, the mean IOP reduction from baseline at 10 AM and 4 PM was 4.8 mmHg (21%) and 3.8 mmHg (19%) with brimonidine, 3.4 mmHg (16%) and 2.8 mmHg (14%) with dorzolamide, and 3.4 mmHg (16%) and 2.6 mmHg (13%) with brinzolamide ($P<0.001$ for brimonidine vs. dorzolamide and brinzolamide at each time point). Each of the study drugs was well tolerated, and all patients completed the study.

Conclusions: The addition of brimonidine to a PGA provided greater IOP lowering than the addition of either dorzolamide or brinzolamide. Further studies are needed to evaluate the relative long-term efficacy and tolerability of these medications as adjunctive therapy to a PGA.

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The goal of medical therapy in glaucoma and ocular hypertension (OHT) is to reduce intraocular pressure (IOP) and thus the risk of vision loss. The once-daily prostaglandin analogs (PGAs) bimatoprost, latanoprost, and travoprost provide the largest reductions in IOP and frequently are used as first-line therapy in glaucoma and OHT.[1,2] Many patients, however, need to use multiple medications to achieve sufficiently low IOP.[3,4] Among patients initiated on monotherapy with a once-daily PGA, more than 20% have an additional IOP-lowering medication added to their treatment regimen within the next year.[5]

Several classes of IOP-lowering medications are available for use as adjunctive therapy including α-adrenergic agonists, β-blockers, carbonic anhydrase inhibitors (CAIs), and cholinergic agonists. A primary consideration in choosing an adjunctive medication is its efficacy in combination with the initial therapy. A fixed combination of latanoprost and the β-blocker timolol has been shown to reduce IOP only 1 mmHg more than latanoprost alone, suggesting that β-blockers may not be particularly efficacious as adjunctive therapy to a PGA.[6] Although the cholinergic agonist pilocarpine has been shown to provide additional IOP lowering when added to latanoprost, the use of pilocarpine has declined because of its ocular side effect profile, and pilocarpine is not preferred adjunctive therapy to a PGA.[7] The medications most commonly used as adjunctive therapy to a PGA include the selective α-adrenergic agonist brimonidine and the CAIs dorzolamide and brinzolamide. Brimonidine tartrate 0.15% has been shown to provide clinically significant additional IOP lowering when used in combination with latanoprost[8,9] or travoprost.[10] Similarly, brinzolamide 1% has been shown to reduce IOP effectively when used as adjunctive therapy with latanoprost[11,12] or travoprost,[10] and dorzolamide hydrochloride 2% has been shown to reduce IOP effectively when added to ongoing latanoprost therapy.[13,14]

The comparative efficacy of brimonidine, dorzolamide, and brinzolamide used in combination with a PGA has not been well established. The purpose of the present study was

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to compare the IOP-lowering efficacy of brimonidine tartrate 0.15%, dorzolamide hydrochloride 2%, and brinzolamide 1% when used as adjunctive therapy in patients with glaucoma or OHT whose IOP was controlled inadequately with a PGA.

Patients and Methods

This was a randomized, prospective, single-center, investigator-masked, parallel-group study evaluating the efficacy of brimonidine, dorzolamide, and brinzolamide as adjunctive therapy to a PGA. The protocol was approved by the ethics committee of the Northwestern Ophthalmic Institute S.C. The study adhered to the principles of the Declaration of Helsinki and was compliant with the Health Insurance Portability and Accountability Act. All patients provided written informed consent before study entry. The study is registered with the trial identifier NCT00675207 at http://www.clinicaltrials.gov (accessed April 23, 2008).

The study involved patients who had inadequate IOP control (defined as IOP ≥18 mmHg) with monotherapy with a once-daily PGA (bimatoprost, latanoprost, or travoprost). A preliminary evaluation of patient eligibility was made at a screening visit. Patients older than 40 years who were diagnosed with unilateral or bilateral primary open-angle glaucoma or OHT were potentially eligible for the study. Primary exclusion criteria included: history of angle closure or narrow angle; previous intraocular surgery; laser trabeculoplasty within 3 months before screening; history of uveitis or intraocular inflammation; use of systemic medications that are known to affect IOP (e.g., β-blockers, corticosteroids, or angiotensin II blockers) within 3 months of study entry or during the study; intolerance of or hypersensitivity to PGAs, sulfonamides, α-agonists, or the preservative benzalkonium chloride; and women of childbearing age who were pregnant or not using contraception.

Patients who met the criteria at the screening visit began a 6-week run-in of PGA monotherapy. Patients who were receiving a PGA at screening continued the PGA dosed once daily between 8 and 10 PM, and all other patients began treatment with a PGA using the same dosing regimen. Any other IOP-lowering medication used before the screening visit was discontinued.

Patients were seen at the baseline visit 6 weeks after screening. Patients who had baseline IOP while receiving PGA monotherapy of ≥18 mmHg at 10 AM and of ≥18 mmHg at 4 PM were randomized in a 1:1:1 ratio to 1 of 3 adjunctive treatment groups: brimonidine tartrate 0.15% thrice daily preserved with purite (Alphagan P 0.15%; Allergan, Inc., Irvine, CA), dorzolamide hydrochloride 2% thrice daily (Trusopt; Merck & Co., Inc., Whitehouse Station, NJ), and brinzolamide 1% suspension thrice daily (Azopt; Alcon Laboratories, Fort Worth, TX). The randomization schedule was computer generated and stored in a locked cabinet until the study ended and all data had been collected. One eye of each patient was included in the study. If both eyes were eligible, the study eye was determined by a coin toss. The adjunctive study medications were provided to patients in their marketed bottles in identically appearing masked cartons labeled with the patient randomization number. To maintain investigator masking, patients were instructed not to reveal the identity of their study medication to the investigators or the office staff. Patients were instructed to instill the study medication at 8 AM, 4 PM, and 10 PM for 4 months. The ongoing regimen of PGA therapy for each patient was constant from screening through month 4, with bimatoprost, latanoprost, or travoprost dosed once daily in the evening between 8 PM and 10 PM.

Study visits were scheduled at baseline, month 1, and month 4. Intraocular pressure was measured using a calibrated Goldmann tonometer at 10 AM (2 hours after the adjunctive medication dose) and 4 PM (just before the adjunctive medication dose) at each study visit. A 2-person reading method was used for the IOP measurements. Intraocular pressure was measured twice (or 3 times if the measurements differed by more than 2 mmHg) at each time point, and the average value was used for analysis. The primary outcome measure was the change from baseline IOP at 10 AM and 4 PM at month 1 and 4. Secondary outcome measures included the mean IOP at 10 AM and 4 PM at each visit and the percentage of patients with IOP consistently <18 mmHg in the study eye throughout follow-up (i.e., at both 10 AM and 4 PM at months 1 and 4).

The primary safety outcome measure was adverse events. All adverse events that were reported by patients or observed by the investigator were recorded at the 1-month and 4-month study visits, as well as at any unscheduled patient-initiated visits. Compliance was determined by verifying the dosing schedule and the need for refills with the patient.

Statistical analyses of the data used the chi-square test for categorical variables and the analysis of variance for IOP. Data were analyzed for the intent-to-treat patient population. All patients were administered the correct medication according to the randomization schedule. The planned sample size was 90 patients. Assuming that there were 30 patients in each of the 3 treatment groups and that the standard deviation of the mean IOP for each group was 1.2 mmHg at a particular time point, the study would have 80% power to detect a 1-mmHg difference between groups at that timepoint.[15]

Results

Patient Baseline Characteristics and Disposition

A total of 120 patients were enrolled in the study and were randomized to adjunctive treatment with brimonidine (n = 41), dorzolamide (n = 40), or brinzolamide (n = 39). There were no significant differences among treatment groups in patient demographics (Table 1). The mean age of the patients was 65.6 years. Most of the patients (61.7%) were female; 44.2% were black, 47.5% were white, and 8.3% were Hispanic. Most (59.2%) were receiving bimatoprost PGA therapy at baseline. The study was completed by all 120 patients (100%). None of the patients had any missing data.

Efficacy

The baseline mean IOP while receiving PGA therapy was not significantly different among the 3 treatment groups at either 10 AM or 4 PM (Table 2). After 1 and 4 months of adjunctive therapy, the mean IOP was significantly lower in the brimonidine group than the dorzolamide group ($P<0.001$) or brinzolamide group ($P<0.001$) at both 10 AM and 4 PM (Table 2). The mean additional reduction in IOP from baseline on PGA therapy was significantly larger in the brimonidine group than in either the dorzolamide or the brinzolamide group at each follow-up time point ($P<0.001$; Fig 1). The IOP-lowering effects of each adjunctive therapy were sustained from month 1 to month 4.

The IOP in the study eye was less than 18 mmHg at all 4 follow-up time points (10 AM and 4 PM at months 1 and 4) for 70.7% (29/41) of brimonidine patients, 7.4% (3/40) of dorzolamide patients, and 2.6% (1/39) of brinzolamide patients ($P<0.001$ for brimonidine vs. dorzolamide and brinzolamide).

All of the study drugs were well tolerated. None of the 120 enrolled patients discontinued from the study for safety or tolerability reasons. At the end of the study, however, 1 patient (2.4%) in the brimonidine group, 2 patients (5.0%) in the dorzolamide

Table 1. Baseline Characteristics of Patients

	Adjunctive Treatment Group			
	Brimonidine Tartrate 0.15% (n = 41)	*Dorzolamide Hydrochloride 2% (n = 40)*	*Brinzolamide 1% (n = 39)*	**Among-Group P Value**
Age, yrs				0.739
Mean (SD)	64.9 (7.6)	65.6 (8.0)	66.3 (8.6)	
Range	49–80	49–82	49–88	
Gender, no. (%)				0.700
Female	25 (61.0%)	23 (57.5%)	26 (66.7%)	
Male	16 (39.0%)	17 (42.5%)	13 (33.3%)	
Race, no. (%)				0.982
Black	19 (46.3%)	17 (42.5%)	17 (43.6%)	
White	19 (46.3%)	20 (50.0%)	18 (46.2%)	
Hispanic	3 (7.3%)	3 (7.5%)	4 (10.3%)	
Prostaglandin analog therapy in study eye, no. (%)				0.996
Bimatoprost once daily	24 (58.5%)	24 (60.0%)	23 (59.0%)	
Latanoprost once daily	12 (29.3%)	12 (30.0%)	11 (28.2%)	
Travoprost once daily	5 (12.2%)	4 (10.0%)	5 (12.8%)	

SD = standard deviation.

group, and 2 patients (5.1%) in the brinzolamide group requested different therapy because of ocular discomfort.

Discussion

Patients with glaucoma frequently require more than 1 medication to achieve adequate IOP control, even when the initial therapy is a PGA. Efficacy is a primary consideration when selecting an adjunctive medication for the patient who responds well to a PGA yet still requires additional IOP lowering. For therapy to be successful, the adjunctive medication must provide a substantial reduction in IOP and be well tolerated when added to the PGA.

In this study, each of the medications tested reduced IOP when added to ongoing PGA therapy, but brimonidine 0.15% demonstrated adjunctive IOP-lowering efficacy superior to dorzolamide 2% and brinzolamide 1%. The mean changes from PGA-treated baseline IOP were significantly greater with brimonidine than with either CAI, and mean IOPs were significantly lower with adjunctive brimonidine than with adjunctive dorzolamide or brinzolamide at both 10 AM (2 hours after dosing) and 4 PM (just before dosing). Furthermore, eyes treated with adjunctive brimonidine were more than 9 times as likely as those treated with either CAI to achieve an IOP consistently less than 18 mmHg throughout follow-up.

The 1- to 2-mmHg difference in observed efficacy between brimonidine and the CAIs is likely to be clinically relevant, because at this pressure range, every 1-mmHg reduction in IOP has been shown to decrease the risk of glaucomatous progression by 10%.[16] The difference between drugs in the achievement of IOP less than 18 mmHg also may be important because patients who consistently attained pressures less than 18 mmHg in the Advanced Glaucoma Intervention Study on average had no visual field progression, whereas patients who had pressures of 18 mmHg or higher at any visit incurred visual field loss.[17] Moreover, it is important to reduce IOP to the target pressure using a minimal number of medications, because compliance

Table 2. Mean (Standard Deviation) Intraocular Pressure (mmHg) at All Time Points

	Adjunctive Treatment Group			
	Brimonidine Tartrate 0.15% (n = 41)	*Dorzolamide Hydrochloride 2% (n = 40)*	*Brinzolamide 1% (n = 39)*	**Among-Group P Value**
Baseline				
10 AM	21.9 (0.88)	21.9 (0.90)	21.9 (0.98)	0.965
4 PM	20.2 (0.88)	20.3 (0.79)	20.4 (0.67)	0.729
Month 1				
10 AM	17.0 (1.15)*	18.5 (0.88)	18.4 (0.72)	<0.001
4 PM	16.3 (0.88)*	17.6 (0.93)	17.7 (0.84)	<0.001
Month 4				
10 AM	17.1 (1.01)*	18.5 (0.85)	18.5 (0.64)	<0.001
4 PM	16.4 (0.84)*	17.5 (0.93)	17.8 (0.93)	<0.001

*$P<0.001$ for brimonidine vs. dorzolamide and brinzolamide.

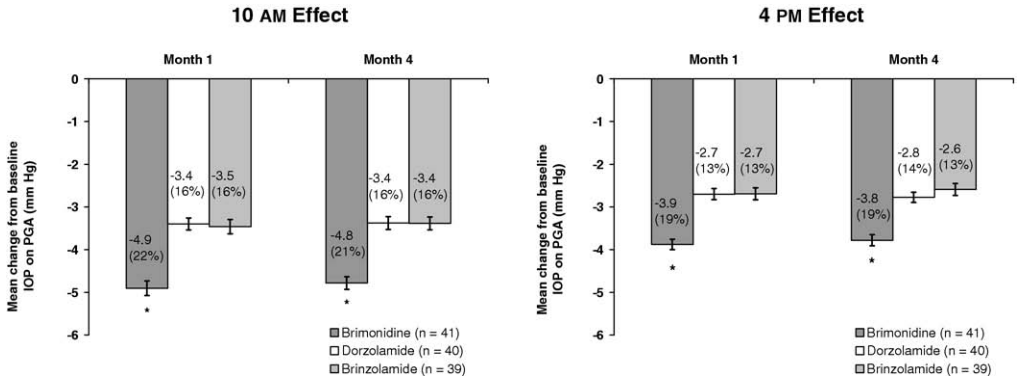

Figure 1. Bar graphs showing the mean change from baseline intraocular pressure (IOP). Error bars represent standard error of the mean (SEM). PGA = prostaglandin analog. *$P<0.001$ vs. dorzolamide and brinzolamide.

worsens when more than 2 medications are needed,[18] and addition of a third or fourth medication frequently is unsuccessful.[19] The results of this analysis of patients with pressures less than 18 mmHg at both 10 AM and 4 PM at months 1 and 4 suggest that adjunctive brimonidine is more likely to achieve low pressures consistently. If so, use of adjunctive brimonidine with a PGA may avoid the addition of a third medication, thereby improving compliance and patient outcomes.

In clinical practice, brimonidine, dorzolamide, and brinzolamide often are dosed twice daily. The prescribing information for each medication recommends thrice-daily dosing, however, and in this study, each medication was dosed 3 times daily. The additional afternoon dose is unlikely to have affected the efficacy results of the study, because the afternoon (4 PM) IOP measurement was obtained before the afternoon dose of adjunctive medication. Despite the increased drug exposure caused by use of a thrice-daily dosing schedule, each of the study medications was well tolerated, and all enrolled patients completed the study as planned.

Previous studies using the study drugs as monotherapy have suggested that brimonidine reduces IOP more effectively than dorzolamide only at peak effect (2 hours after dosing),[20,21] whereas dorzolamide and brinzolamide have comparable efficacy in reducing IOP throughout the day.[22] The efficacy of drugs used as adjunctive therapy may or may not mirror their efficacy when used as monotherapy. In

Table 3. Mean (Standard Deviation) Intraocular Pressure (mmHg) at All Time Points in Patients Stratified by Prostaglandin Analog Treatment

Prostaglandin Analog Used in Ongoing Therapy	Adjunctive Treatment Group			Among-Group P Value
	Brimonidine Tartrate 0.15%	*Dorzolamide Hydrochloride 2%*	*Brinzolamide 1%*	
Bimatoprost (n = 71)				
Baseline, 10 AM	21.9 (0.80)	21.8 (1.05)	21.9 (0.95)	0.958
Baseline, 4 PM	20.3 (0.94)	20.4 (0.77)	20.4 (0.66)	0.802
Month 1, 10 AM	17.1 (1.35)*	18.6 (0.83)	18.3 (0.65)	<0.001
Month 1, 4 PM	16.4 (0.97)*	17.6 (0.82)	17.6 (0.89)	<0.001
Month 4, 10 AM	17.3 (1.15)*	18.5 (0.72)	18.5 (0.59)	<0.001
Month 4, 4 PM	16.5 (0.93)*	17.5 (0.88)	17.7 (0.97)	<0.001
Latanoprost (n = 35)				
Baseline, 10 AM	21.8 (1.11)	22.1 (0.67)	21.6 (1.12)	0.558
Baseline, 4 PM	20.0 (0.85)	20.2 (0.94)	20.2 (0.75)	0.849
Month 1, 10 AM	16.9 (0.90)*	18.4 (0.90)	18.5 (0.82)	<0.001
Month 1, 4 PM	16.2 (0.72)*	17.4 (1.00)	17.7 (0.79)	<0.001
Month 4, 10 AM	16.9 (0.90)*	18.6 (1.00)	18.4 (0.67)	<0.001
Month 4, 4 PM	16.3 (0.75)*	17.4 (0.90)	17.7 (0.79)	<0.001
Travoprost (n = 14)				
Baseline, 10 AM	22.4 (0.55)	21.8 (0.50)	22.2 (0.84)	0.362
Baseline, 4 PM	20.6 (0.55)	20.3 (0.50)	20.6 (0.55)	0.560
Month 1, 10 AM	17.0 (0.71)	18.3 (1.25)	18.4 (0.89)	0.081
Month 1, 4 PM	16.6 (0.89)	18.0 (1.41)	17.8 (0.84)	0.128
Month 4, 10 AM	17.2 (0.45)†	18.3 (1.26)	18.8 (0.84)	0.041
Month 4, 4 PM	16.8 (0.45)	18.0 (1.41)	18.2 (1.10)	0.114

*$P \leq 0.002$ for brimonidine vs. dorzolamide and brinzolamide.
†$P = 0.006$ for brimonidine vs. brinzolamide.

the present study, dorzolamide and brinzolamide were comparable in efficacy when used as adjunctive therapy to a PGA, but brimonidine was more efficacious than either CAI, both at 2 hours after dosing and at the afternoon measurement.

Previously published studies also have demonstrated clinically significant additional IOP lowering when brimonidine, dorzolamide, or brinzolamide was added to ongoing PGA therapy.[8–14,23] Most of the previous studies evaluated the efficacy of the medications as adjunctive therapy to latanoprost.[8,9,11–14,23] In the study reported by Konstas et al,[8] brimonidine and dorzolamide similarly were effective in reducing 24-hour IOP by approximately 2.2 mmHg when added to latanoprost therapy. In contrast, in the study reported by Day and Hollander,[23] brimonidine was significantly more effective than brinzolamide in reducing diurnal IOP when added to latanoprost therapy. The mean diurnal IOP reduction was 3.3 mmHg with brimonidine and 2.1 mmHg with brinzolamide. None of the previous studies evaluated the efficacy of the study drugs when added to bimatoprost therapy, but a study recently reported by Feldman et al[10] evaluated brimonidine and brinzolamide as adjunctive therapy to travoprost. Mean IOP (measured at 4 PM) was similar in the brimonidine and brinzolamide treatment groups after 1 month but was lower in the brinzolamide group after 3 months of adjunctive therapy. The adjusted mean diurnal IOP reduction at month 3 was 2.1 mmHg with brimonidine and 2.7 mmHg with brinzolamide. Differences in the study designs might have contributed to the differences in the results observed. The peak effect of the study medications (2 hours after dosing[24,25]) was not measured in the study by Feldman et al,[10] and the authors suggested that brimonidine may lower IOP more than brinzolamide at that time. Also, the study medications were rebottled in the study by Feldman et al to facilitate masking, and to the authors' knowledge, stability of the rebottled formulations has not been demonstrated. Finally, it is possible that the relative efficacy of brimonidine, dorzolamide, and brinzolamide as adjunctive therapy with a PGA may be influenced by the particular PGA used (bimatoprost for most eyes in this study, travoprost in the study by Feldman et al,[10] and latanoprost in the studies reported by Konstas et al[8] and by Day and Hollander[23]).

A limitation of the study was that it was not designed to address the question of whether the efficacy of the adjunctive medications tested varied with the particular PGA used as ongoing therapy. In post hoc analyses, however, significant differences in efficacy were found between brimonidine and the CAIs in the subgroups of patients using bimatoprost and latanoprost (Table 3). The results were not statistically significant at most time points in the subgroup of patients taking travoprost, probably because of the small sample size (5 brimonidine patients, 4 dorzolamide patients, and 5 brinzolamide patients). A second limitation was the relatively short-term nature of the study. Finally, patients were not asked about side effects or discomfort associated with instillation of their eye drops. Although transient, side effects and discomfort have the potential to decrease patient compliance, and they may differ among the study medications.[21,22]

In summary, in this study brimonidine reduced IOP significantly more than dorzolamide or brinzolamide at both 10 AM and 4 PM when added to bimatoprost, latanoprost, or travoprost therapy. More than 9 times as many patients achieved pressures <18 mmHg with adjunctive brimonidine than with either CAI throughout the follow-up. These results suggest that brimonidine may be a more effective choice of adjunctive therapy than dorzolamide or brinzolamide for patients with open-angle glaucoma or OHT who have inadequate IOP control with a once-daily PGA.

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Correspondence:
Thomas E. Bournias, MD, 233 East Erie, Suite 614, Chicago, IL 60611.
E-mail: bournias@northwestern.edu.