The 24-Hour Effects of Brinzolamide/Brimonidine Fixed Combination and Timolol on Intraocular Pressure and Ocular Perfusion Pressure

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Abstract

Purpose: To determine the 24-h effects of brinzolamide/brimonidine tartrate 1%/0.2% fixed combination (BBFC) on intraocular pressure (IOP), ocular perfusion pressure (OPP), blood pressure (BP), and heart rate (HR).

Methods: Sixty subjects with open angle glaucoma (OAG) or ocular hypertension (OHTN) were admitted overnight for 24-h monitoring of IOP, BP, and HR. All subjects underwent the first, baseline 24-h study after washout of all medications, if necessary. Subjects were then randomized to receive either (1) timolol maleate 0.5% twice daily or (2) BBFC 3 times daily. After 4 weeks of treatment, all subjects completed a follow-up 24-h study visit. At each study visit, IOP, BP, and HR were measured every 2 h in the habitual position. OPP was calculated as $2/3[\text{diastolic BP} + 1/3(\text{systolic BP} - \text{diastolic BP})] - \text{IOP}$.

Results: Treatment with BBFC significantly lowered IOP during the diurnal period (-2.7 ± 0.4 mmHg; $P < 0.01$) and nocturnal period (-0.8 ± 0.3 mmHg; $P < 0.01$). Timolol similarly reduced IOP during the diurnal period, but did not lower IOP overnight. Over a 24-h period, BBFC achieved a significantly greater IOP reduction than timolol (-0.7 ± 0.4 mmHg; $P = 0.04$). BBFC failed to achieve an increase in OPP during any time period, while timolol increased OPP during the diurnal period only. A significantly greater reduction in HR occurred in the timolol group.

Conclusions: BBFC significantly lowers IOP during both the diurnal and nocturnal periods, but has no effect on OPP. Timolol only lowers IOP during the diurnal period.

Keywords: intraocular pressure, timolol, brinzolamide, brimonidine, ocular perfusion pressure, 24-hour

Introduction

GLAUCOMA TREATMENT IS CENTERED on reduction of intraocular pressure (IOP) using medications, laser, or invasive surgery.¹ Most newly diagnosed glaucoma patients are started on one or more topical drops that are designed to decrease inflow or enhance outflow of aqueous humor. Prostaglandin analogs (PGAs) are routinely utilized as first-line therapy relating to their efficacy, once a day dosing, and excellent safety profile.² If PGAs are contraindicated or fail to achieve the desired level of IOP reduction, several other medication classes may be chosen including beta-blockers, carbonic-anhydrase inhibitors (CAIs), or alpha-agonists.³ Furthermore, fixed combination medications have become increasingly popular due to enhanced efficacy and potential for improved adherence relating to easier dosing schedules.

Until recently, the only 2 U.S. FDA approved combination medications included a beta-blocker (dorzolamide hydrochloride/timolol maleate 2%/0.5% and brimonidine tartrate/timolol maleate 0.2%/0.5%). Although both medications have well-established safety and efficacy profiles, there are several patient characteristics and/or comorbidities such as reactive airway disease, chronic obstructive pulmonary disease, and bradycardia in which the use of a beta-blocker is either contraindicated or poorly tolerated.^{4,5}

Approved in 2013, brinzolamide/brimonidine tartrate 1%/0.2% fixed combination (BBFC, Simbrinza; Alcon, Ft. Worth, TX) is the first fixed combination glaucoma medication in the United States to not contain a beta-blocker. While BBFC may be better tolerated in pulmonary or cardiac conditions, the brimonidine component may have the potential to affect blood pressure (BP).⁶ Also unique to this medication is the 3 times a day dosing schedule compared to

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twice daily dosing for beta-blocker containing combinations. Initial clinical studies have demonstrated the IOP-lowering efficacy and tolerance of BBFC is at least equivalent to the individual component medications.⁷⁻⁹ Although initial use of BBFC has been positive, its clinical effects have yet to be fully elucidated. In this prospective clinical trial, we determine the 24-h effects of BBFC on IOP and compare these to timolol in patients with open angle glaucoma (OAG) and ocular hypertension (OHTN). In addition, we analyze the effect of both medications on BP, heart rate (HR), and ocular perfusion pressure (OPP).

Methods

Approval for this randomized, prospective, clinical study was obtained from the Colorado Multiple Institutional Review Board before initial enrollment and the tenets of the Declaration of Helsinki were followed. At the time of enrollment, informed consent was obtained from all subjects. Before the study, a statistical power analysis suggested a sample size of 29 patients in each arm would provide 90% power to detect a difference of 1 mmHg. A total of 60 patients with OAG or OHTN were recruited during their regularly scheduled examination at the University of Colorado Health Eye Center, Aurora, CO. Inclusion criteria included patients of either sex or any ethnicity with an existing or new diagnosis of OHTN or OAG including pigmentary and pseudoexfoliative glaucoma. Exclusion criteria included any contraindication to beta-blocker therapy, patients taking oral beta-blocker therapy, any glaucoma diagnosis other than open

angle, narrow anterior chamber angle by gonioscopy (Schaffer grade <2), intraocular surgery within 6 months or laser within 3 months, patients who smoke or have irregular sleep patterns, inability to safely discontinue ocular glaucoma medications for 6 weeks, history of allergy or intolerance to topical CAIs or alpha agonists, and women who were pregnant or planning to become pregnant.

After enrollment, subjects taking topical glaucoma medications underwent a wash out period of 4–6 weeks, depending on drug class, before starting the study. Subjects taking a PGA underwent a 6-week washout, while all other patients taking glaucoma medications underwent a 4-week washout period where all medications were discontinued before proceeding to the first baseline study visit. Subjects not on therapy were allowed to proceed to the first 24-h study session without delay. During each study session, subjects were admitted to a private room at the University of Colorado Hospital Clinical and Translational Research Center for a continuous 24-h period. The first “baseline” session was performed off all glaucoma medications. Subjects were then randomized 1:1 to treatment with either BBFC or timolol. Patients in the BBFC group were given a medication supply with instructions to instill 1 drop in each eye 3 times daily approximately every 8 h. Patients in the timolol group were similarly supplied with medication and instructed to instill 1 drop in each eye 2 times a day approximately every 12 h. After a minimum of 4 to 8 weeks of therapy, a second “follow-up” 24-h study visit was completed. During this visit, the study medication was either self-administered under supervision or administered by a study nurse at the appropriate dosing time for each patient.

TABLE 1. SUBJECT DEMOGRAPHICS AND OCULAR CHARACTERISTICS FOR THE ENTIRE COHORT AND THE 2 STUDY GROUPS

	<i>Whole sample</i>	<i>Timolol</i>	<i>BBFC</i>	<i>P</i>
Diagnosis, <i>n</i> (%)				
OAG	55 (91.7)	29 (96.7)	26 (86.7)	0.35
OHTN	5 (8.3)	1 (3.3)	4 (13.3)	
Age (years)				
Min	44	44	55	0.04
Median	70.0	72.5	68.5	
Mean $\pm$ SD	69.5 $\pm$ 8.3	70.5 $\pm$ 9.2	68.5 $\pm$ 7.3	
Max	84	83	84	0.35
Race/ethnicity, <i>n</i> (%)				
White	36 (60.0)	17 (56.7)	19 (63.3)	0.79
Hispanic	4 (6.7)	2 (6.7)	2 (6.7)	
Sex, <i>n</i> (%)				
Male	20 (33.3)	12 (40.0)	8 (26.7)	0.41
Female	40 (66.7)	18 (60.0)	22 (73.3)	
Pachymetry (μm^a)				
OD min	469	476	469	0.79
OD median	552.5	547.0	555.0	
OD max	637	628	637	
OS min	478	503	478	0.79
OS median	552.0	548.0	555.5	
OS max	692	692	649	
Lens status				
OD phakic	39/59 (66.1%)	17/29 (58.6%)	22 (73.3%)	0.28
OD pseudophakic	20/59 (33.9%)	12/29 (41.4%)	8 (26.7%)	
OS phakic	38 (63.3%)	16 (53.3%)	22 (73.3%)	0.18
OS pseudophakic	22 (36.7%)	14 (46.7%)	8 (26.7%)	

^a μm , microns.

BBFC, brinzolamide/brimonidine tartrate 1%/0.2% fixed combination; OAG, open angle glaucoma; OHTN, ocular hypertension.

For each study visit, subjects were allowed ad lib diet and activity during the diurnal period of 0600 to 2200 h, but were asked to remain supine in bed during the nocturnal period of 2200 to 0600 h. Serial measurements of IOP, BP, and HR were recorded every 2 h at each study session. During the diurnal period, measurements were performed in the upright, sitting position while those taken during the nocturnal period were done in the supine position. A total of 8 readings were performed during the diurnal period (0700, 0900, 1100, 1300, 1500, 1700, 1900, and 2100) and 4 readings in the nocturnal period (2300, 0100, 0300, and 0500) for each study visit. A Model 30 pneumatonometer (Reichert, Inc., Depew, NY) was utilized for all IOP measurements. Before each reading, proparacaine hydrochloride 0.5% was administered for topical anesthesia. Measurements with standard deviations >1.0 were discarded and remeasured. Measurements were performed on both eyes as long as the eye met inclusion criteria. HR and BP measurements were completed with a standard automated sphygmomanometer at the time of each IOP measurement.

OPP was calculated as the difference between two-thirds of the mean arterial blood pressure (MAP) and IOP ($OPP = 2/3MAP - IOP$).¹⁰

Study patient demographics were compared between study groups using Fisher exact tests for categorical variables and *t*-tests for means. The means of IOP, OPP, systolic blood pressure (SBP), diastolic blood pressure (DBP), and HR were compared between baseline and follow-up for each 2-h period, the 16-h diurnal period, the 8-h nocturnal period, and the entire 24-h period. The multiple measurements and longitudinal structure was accounted for in our analysis by the use of generalized estimating equations (GEEs), with robust standard error estimates used for statistical inference. We treated time as a continuous variable in our work and fitted smooth curves to the data via using natural cubic B-splines for time with 6 degrees of freedom. Mean IOP, OPP, and HR were determined by estimating the area under the curve for each study drug group at baseline and at follow-up and then dividing by the duration of observation. Data analysis was conducted in R version 3.2.2.¹¹ GEEs were

FIG. 1. Mean 24-h intraocular pressure profiles in habitual body positions at baseline and follow-up on treatment with timolol (left) and BBFC (right). Solid lines represent baseline measurements and dashed lines represent follow-up during treatment with study medications. Error bars represent standard error of the mean. BBFC, brinzolamide/brimonidine tartrate 1%/0.2% fixed combination.

FIG. 2. Mean 24-h ocular perfusion pressure profiles in habitual body positions at baseline and follow-up on treatment with timolol (*left*) and BBFC (*right*). *Solid lines* represent baseline measurements and *dashed lines* represent follow-up during treatment with study medications. *Error bars* represent standard error of the mean. BBFC, brinzolamide/brimonidine tartrate 1%/0.2% fixed combination.

glaucoma medication to not contain a beta-blocker. Clinicians and patients have much anticipated a topical therapy with the efficacy and convenience of fixed combination without the risks and/or contraindications of beta-blocker use in patients with cardiac arrhythmias, reactive airway disease, among other comorbidities.⁵ Our results show that BBFC produces a statistically significant IOP reduction throughout a 24-h period in the habitual position. The 24-h IOP-lowering effect of BBFC was significantly greater than that of timolol. The effect of BBFC was less during the nocturnal period compared to the diurnal period but remained significant while timolol failed to achieve a mean reduction in IOP during the nocturnal period.

Although this trial is the first to analyze the 24-h effects of BBFC, prior studies have described the medication's effect on IOP during daytime hours. In 2 randomized, double masked, multicenter trials, BBFC was found to significantly lower IOP 24.1–34.9% with peak IOP reduction of 32%–34%.^{9,13,14} When compared to its individual component medications, BBFC achieved greater IOP reductions with similar safety and tolerability. While our diurnal IOP reductions did not reach this

magnitude, this is likely the result of the lower mean baseline IOP in our study population, which was only 19.7 mmHg in the diurnal period compared to 25.9–26.4 mmHg in previous studies. In addition, previous studies only measured IOP during a narrow time period during office hours.

The 24-h effects of the individual components of BBFC have been previously described. Using a similar protocol, Liu et al. studied the 24-h effects of brimonidine 0.1% monotherapy in 15 OAG and OHTN patients.¹⁵ Despite significant IOP reduction during the diurnal period, there was no significant effect observed overnight in the supine position. In a separate study of OHTN patients, brimonidine failed to lower IOP overnight in the supine position.¹⁶ Contrary to these reports, a later study by Quaranta et al. showed brimonidine achieved a significant IOP reduction at all time points throughout a 24-h period.¹⁷ To our knowledge, the 24-h effects of brinzolamide as monotherapy have not been studied. However, in patients receiving latanoprost monotherapy, the addition of brinzolamide 1% resulted in a significant reduction in IOP during both the diurnal and

TABLE 3. MEAN OCULAR PERFUSION PRESSURE FOR EACH STUDY VISIT AND DIFFERENCES BETWEEN VISITS AND STUDY GROUPS DURING THE DIURNAL, NOCTURNAL, AND ENTIRE 24-H PERIOD

	Timolol			BBFC			BBFC versus timolol		
	Baseline	Follow-up	Follow-up versus baseline	Baseline	Follow-up	Follow-up versus baseline	Baseline	Follow-up	Follow-up versus baseline
Diurnal	39.5±0.9	40.7±0.8	1.2±0.6; <i>P</i> =0.04	41.4±1.4	42.4±1.1	1.0±0.6; <i>P</i> =0.12	1.9±1.6; <i>P</i> =0.24	1.7±1.3; <i>P</i> =0.20	-0.2±0.9; <i>P</i> =0.79
Nocturnal	34.6±1.0	33.5±1.0	-1.1±0.7; <i>P</i> =0.11	34.6±1.7	34.6±1.5	-0.1±0.8; <i>P</i> =0.93	0.0±1.9; <i>P</i> =0.99	1.1±1.8; <i>P</i> =0.54	1.1±1.1; <i>P</i> =0.31
24-Hour	38.1±0.8	38.5±0.8	0.3±0.5; <i>P</i> =0.49	39.4±1.4	40.0±1.1	0.6±0.6; <i>P</i> =0.30	1.3±1.6; <i>P</i> =0.42	1.6±1.4; <i>P</i> =0.26	0.3±0.8; <i>P</i> =0.74

BBFC, brinzolamide/brimonidine tartrate 1%/0.2% fixed combination.

TABLE 4. MEAN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE FOR EACH STUDY VISIT AND DIFFERENCES BETWEEN VISITS AND STUDY GROUPS DURING THE DIURNAL, NOCTURNAL, AND ENTIRE 24-H PERIOD

	Timolol			BBFC			BBFC versus timolol		
	Baseline	Follow-up	Follow-up versus Baseline	Baseline	Follow-up	Follow-up versus Baseline	Baseline	Follow-up	Follow-up versus Baseline
Systolic blood pressure									
Diurnal	122.8±1.8	122.2±2.0	-0.7±1.5; <i>P</i> =0.66	131.1±2.8	126.9±2.8	-4.2±1.4; <i>P</i> <0.01	8.2±3.3; <i>P</i> =0.01	4.7±3.5; <i>P</i> =0.17	-3.5±2.1; <i>P</i> =0.09
Nocturnal	116.8±2.1	116.9±2.2	0.1±1.5; <i>P</i> =0.93	121.5±3.3	119.2±2.6	-2.2±1.6; <i>P</i> =0.16	4.7±3.9; <i>P</i> =0.22	2.4±3.4; <i>P</i> =0.49	-2.4±2.2; <i>P</i> =0.28
24-Hour	121.1±1.7	120.3±2.0	-0.8±1.2; <i>P</i> =0.53	128.1±2.9	124.6±2.6	-3.4±0.4; <i>P</i> =0.01	7.0±3.4; <i>P</i> =0.04	4.3±3.3; <i>P</i> =0.19	-2.6±1.9; <i>P</i> =0.15
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	Timolol			BBFC			BBFC versus timolol		
	Baseline	Follow-up	Follow-up versus baseline	Baseline	Follow-up	Follow-up versus baseline	Baseline	Follow-up	Follow-up versus baseline
Diastolic blood pressure									
Diurnal	70.8±1.2	69.2±1.1	-1.6±0.9; <i>P</i> =0.06	72.0±1.7	70.3±1.4	-1.7±0.8; <i>P</i> =0.04	1.2±2.1; <i>P</i> =0.56	1.1±1.7; <i>P</i> =0.52	-0.1±1.2; <i>P</i> =0.94
Nocturnal	67.7±1.4	66.5±1.4	-1.2±1.0; <i>P</i> =0.24	66.2±2.1	65.5±1.9	-0.7±1.0; <i>P</i> =0.50	-1.5±2.5; <i>P</i> =0.55	-1.0±2.4; <i>P</i> =0.68	0.5±1.5; <i>P</i> =0.72
24-Hour	69.8±1.2	68.2±1.1	-1.6±0.7; <i>P</i> =0.03	70.1±1.7	68.7±1.4	-1.4±0.7; <i>P</i> =0.06	0.3±2.1; <i>P</i> =0.89	0.5±1.8; <i>P</i> =0.76	0.2±1.0; <i>P</i> =0.81

BBFC, brinzolamide/brimonidine tartrate 1%/0.2% fixed combination.

FIG. 3. Mean 24-h heart rate profiles at baseline and follow-up on treatment with timolol (*left*) and BBFC (*right*). *Solid lines* represent baseline measurements and *dashed lines* represent follow-up during treatment with study medications. *Error bars* represent standard error of the mean. BBFC, brinzolamide/brimonidine tartrate 1%/0.2% fixed combination.

nocturnal periods.¹⁸ For comparison, the other commercially available CAI (dorzolamide 2%) has also been shown to significantly lower IOP as monotherapy during both the diurnal and nocturnal period in the habitual position.¹⁷ Based on these previous studies, it is possible that the nocturnal efficacy of BBFC is largely due to effects of the CAI component, however, the lack of a single component control in this study precludes any conclusions being made on the relative contributions from each component.

Our study supports previous literature demonstrating a relative lack of IOP-lowering effect by timolol overnight. While most studies agree on the efficacy of timolol during the day, there is some conflicting data on the nocturnal effects in the literature. In one study of 18 patients, once daily timolol 0.5% was found to be equally efficacious to latanoprost in IOP reduction during the diurnal period but produced no significant effect overnight.¹⁹ In a recent study by Oddone et al., twice daily timolol 0.5% produced a 1.1 mmHg IOP reduction overnight, but this did not reach statistical significance ($P=0.06$).²⁰ In contrast, a study by Quaranta et al. comparing the 24-h effects of twice daily

timolol 0.5% solution and once daily timolol 0.1% gel in primary open angle glaucoma (POAG) patients found that both formulations achieved a significant 3.0 mmHg reduction in IOP overnight in the supine position.²¹ Variation in patient population, drug formulation, and dosing, or study design may account for these conflicting data, but there is significant data, when combined with this study, to conclude that any effect on IOP by timolol in the nocturnal period is minimal.

In addition to the effects of BBFC and timolol on IOP over a 24-h period, both of these medications demonstrated unique effects on other systemic parameters like HR and BP. As predicted, the nonspecific beta-blockade of timolol resulted in a significant decrease in HR compared to baseline. The BBFC group also demonstrated a small but significant decrease in HR, however, the change was significantly less compared to timolol. This small but statistically significant effect of BBFC on HR is of interest considering one advantage of this fixed-combination medication was the avoidance of the systemic effects of beta-blockers like bradycardia. It is unclear whether this small magnitude of change is clinically relevant.

Although the effect of BBFC on HR was significantly less than timolol, the medication demonstrated a statistically significant hypotensive effect on BP. Both study medications demonstrated a small (1.4–1.6 mmHg) mean reduction in DBP that, while of borderline statistical significance, is not likely clinically significant. For SBP, the BBFC group demonstrated a greater reduction (–3.4 mmHg) in pressure compared to timolol (–0.8 mmHg), however, the difference between the groups did not reach significance. The mild systemic hypotensive effect of BBFC is likely attributed to the alpha 2-agonist component, brimonidine, which has been shown to lower BP in previous studies.^{6,17} Both phase III trials of BBFC demonstrated similar levels of SBP reduction in the brimonidine and BBFC groups.^{13,14}

In addition to IOP, some population-based studies have also identified OPP as a risk factor for glaucoma.^{22,23} This has prompted increased interest in the effects of glaucoma medications on OPP with a desire for medications that may increase it. In this study, we show that BBFC failed to have a significant impact on OPP. By comparison, the timolol group showed a significant increase in OPP during the diurnal period only. Despite the greater IOP-lowering efficacy of BBFC over 24 h, the change in OPP at any time point during treatment was similar between the 2 study drugs. The lack of OPP effect of BBFC may be a result of the observed systemic hypotensive effects.

We acknowledge a few limitations in our study. First, our use of timolol as a comparator to BBFC prevents drawing conclusions about the potential additional efficacy of the fixed combination compared to its individual components. Timolol was chosen to be consistent with FDA recommendations of its use in new medication trials. Second, the open-label study design has the potential to introduce bias, however, nurses measuring IOP were not involved with data analysis. We further randomized patients into treatment arms to minimize this potential. The allowance of an ad lib diet may have resulted in large fluid volume intake at certain periods, which may have resulted in transiently elevated IOP as suggested in previous studies. We consider these to be random and rare enough occurrences to not significantly alter the outcomes of this study.

In conclusion, both BBFC and timolol significantly lower IOP during the diurnal period in patients with POAG and OHTN. During the nocturnal period, the effect is lessened but remains significant for BBFC, while timolol fails to reduce IOP overnight. Over the entire 24-h period in the habitual position, the IOP reduction of BBFC was significantly greater than timolol. Neither medication achieved an increase in OPP over a 24-h period.

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