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ORIGINAL RESEARCH

Short-Term Effects of Brimonidine/Timolol and Dorzolamide/Timolol on Ocular Perfusion Pressure and Blood Flow in Glaucoma

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ABSTRACT

Introduction: To examine the comparative short-term effects of brimonidine/timolol and dorzolamide/timolol on ocular perfusion pressure and retrobulbar blood flow in patients with primary open angle glaucoma (OAG). ***Methods:*** In a prospective, randomized, double-blind, crossover study, intraocular pressure (IOP), blood pressure (BP), ocular perfusion pressure (OPP), and retrobulbar hemodynamics were assessed in 15 patients with OAG (mean age 68.1 years, eight women) with well controlled IOP. IOP was measured by Goldman applanation tonometery and color Doppler imaging was utilized to assess the retrobulbar blood vessels before and 1 month after treatment with topical brimonidine/timolol and dorzolamide/timolol. Statistical analysis was performed by Friedman two-way analysis of variance by ranks and post-hoc Wilcoxon signed rank test for multiple comparisons with Holm's sequential Bonferroni procedure. P values <0.05 were considered statistically significant. ***Results:*** The Friedman test and subsequent post-hoc analysis indicated that IOP, BP, OPP, and retrobulbar blood flow velocities did not significantly differ between brimonidine/timolol and dorzolamide/timolol after 1-month treatment administration in patients with OAG and well controlled IOP. ***Conclusion:*** In this cohort of patients with OAG, short-term treatment with brimonidine/timolol and dorzolamide/timolol results in similar effects on OPP and retrobulbar blood flow velocities.

Keywords: glaucoma; intraocular pressure; ocular blood flow; ocular perfusion pressure; gretrobulbar hemodynamics; therapy

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INTRODUCTION

Primary open angle glaucoma (OAG) is a multifactorial optic neuropathy characterized by progressive retinal ganglion cell death and visual field loss. Despite being a leading cause of impaired vision worldwide, the risk factors for OAG have not been fully defined. Elevated intraocular pressure (IOP) is the only currently treatable risk factor for OAG, although a high percentage of individuals with elevated IOP do not develop glaucoma.[1] In addition, many patients experience glaucoma progression despite significantly reduced IOP, suggesting other factors contribute to OAG disease onset and progression.[2-3]

Over the past several decades, dozens of studies have linked abnormalities in ocular perfusion pressure (OPP) and blood flow to glaucomatous optic neuropathy.[4] Specifically, blood flow deficiencies of the retinal, choroidal, and retrobulbar circulations have been reported in patients with OAG.[4] In large population-based trials, reduced OPP has been linked to both the prevalence and incidence of glaucoma.[5-8] Systemic and local vascular abnormalities have also been linked to OAG, including arterial hypertension, nocturnal hypotension, optic disc hemorrhage, migraine, and aging of the vasculature.[9] Mechanistically, reduced ocular perfusion may be secondary to IOP elevation or represent a primary insult in glaucoma, including the presence of vasospasm and/or faulty vascular autoregulation. At the 2009 World Glaucoma Association meeting[10] a consensus was agreed that vascular dysregulation may contribute to the pathogenesis of glaucoma, and that low OPP is an independent risk factor for OAG. Although a wealth of pilot research has shown that vascular parameters are associated with glaucoma, their exact relationship to glaucoma progression remains insufficiently investigated.

The physiological mechanisms of OAG therapies that reduce IOP differ, as do their potential to influence vascular smooth muscle.[11] It is, therefore, important to consider how glaucoma treatments may impact OPP and blood flow in addition to IOP reduction.

Dorzolamide/timolol contains a carbonic anhydrase inhibitor (dorzolamide) and a beta-blocking agent (timolol). Dorzolamide/timolol has been previously demonstrated to produce increases in ocular blood flow in addition to IOP reduction.[12] Brimonidine/timolol contains an alpha$_2$-adrenergic receptor agonist (brimonidine) and a beta-blocking agent (timolol). The hemodynamic effects of brimonidine/timolol are currently not sufficiently established in the literature.

The purpose of this investigation was to examine differences in short-term treatment of dorzolamide/timolol versus brimonidine/timolol in terms of OPP and retrobulbar blood flow in patients with OAG.

MATERIALS AND METHODS

This investigation was conducted at the Glaucoma Research and Diagnostic Center in conjunction with the Department of Ophthalmology and Division of Biostatistics at the Indiana University School of Medicine, Indianapolis, IN, USA. All experimental procedures conformed to the tenets of the Declaration of Helsinki and were approved by the institutional review board at Indiana University School of Medicine. Subjects signed informed consent prior to entry into the study. The study was registered with ClinicalTrials.gov (NCT 00811850) under the title Comparing Effects of Two Fixed Combinations Ophthalmic Solutions on Ocular Blood Flow.

A total of 15 established patients with documented OAG and well controlled IOP

participated over a period of 10 weeks in a prospective, double-blind, randomized crossover study. All participants were referred by the Departments of Ophthalmology at Indiana University and Wishard Hospitals.

Inclusion criteria included: age 30 years or older; previously documented OAG in at least one eye, defined as characteristic glaucomatous visual field loss and optic nerve head damage; best corrected visual acuity of at least 20/40; and baseline IOP well controlled below 22 mmHg.

Exclusion criteria included: history of acute angle closure or a narrow, occludable anterior chamber angle by gonioscopy; history of chronic or recurrent inflammatory eye diseases (eg, scleritis, uveitis); history or signs of intraocular trauma; any abnormality preventing reliable applanation tonometry; current use of any ophthalmic or systemic medications that may interfere with the investigation; and severe, unstable, or uncontrolled cardiovascular, renal, or pulmonary disease.

All subjects discontinued all hypotensive therapies and underwent a 3-week washout and timolol (twice daily) run prior to baseline evaluations. For each visit, IOP, blood pressure, radial pulse, OPP, and color Doppler imaging (CDI) of retrobulbar blood vessels were performed. Subjects were randomized to topical brimonidine/timolol (Combigan®, brimonidine tartrate 0.2%/timolol maleate 0.5% ophthalmic solution; Allergan, Inc., Irvine, CA, USA) or dorzolamide/timolol (Cosopt®, dorzolamide hydrochloride/timolol maleate ophthalmic solution; Merck & Co., Inc., Whitehouse Station, NJ, USA) twice daily and measurements were repeated after 1 month. A second 2-week timolol washout of the first study medication was followed by a second baseline examination and a crossover of study medications for an additional 1-month treatment period and final evaluation. Compliance of drug administration was based upon self-reporting.

All examinations were performed on one qualified study eye chosen at random by randomization chart. All measurements were performed in the same order, at the same time of day, and by the same examiner for each patient.

Measurements

Brachial artery systolic and diastolic blood pressure (SBP and DBP, respectively) and pulse were assessed after a 5-minute rest period using a calibrated automated sphygmomanometer at the beginning and end of each study visit. IOP was assessed using Goldmann applanation tonometry. OPPs were calculated as two-thirds mean arterial pressure minus IOP.

CDI of the retrobulbar blood vessels was conducted using Philips High Definition Ima (HDI) 5000 Sono computed tomography (CT) Ultrasound System with the microvascular small parts clinical option (Philips Medical Systems, Bothell, WA, USA) with a 7.5 MHz linear probe as described in detail previously.[13-16] Samples of pulsed Doppler signal from within a 0.2 x 0.2 mm sample area were analyzed to calculate blood flow velocities in the retrobulbar vasculature. CDI measurements were taken in the ophthalmic arteries (OA), central retinal arteries (CRA), and nasal and temporal short posterior ciliary arteries (NPCA and TPCA, respectively). In each vessel, peak systolic and end diastolic velocities (PSV and EDV, respectively) were determined and Pourcelot's vascular resistive index (RI) was calculated (RI=[PSV-EDV]/PSV). These techniques have been previously shown to yield reproducible measurements of retrobulbar blood flow velocities and peripheral vascular resistance.[13-16]

Statistical Analysis

Statistical analyses were performed using the SPSS statistical software package (version 18.0, SPSS Inc, Chicago, IL) for Microsoft Windows. The Friedman two-way analysis of variance by ranks and post-hoc Wilcoxon signed rank test for multiple comparisons were used to compare retrobulbar hemodynamic variables before and after dorzolamide/timolol or brimonidine/timolol administration (four conditions). Holm's sequential Bonferroni adjusted significance levels were used to control the number of multiple paired comparisons, and to reduce type I errors. Given that six pairwise comparisons were performed, the adjusted cutoff *P* values were 0.017, 0.02, 0.025, 0.033, 0.05, and 0.1, in ascending order. Data are presented as mean ± SD or median (range). *P* values <0.05 were considered statistically significant.

RESULTS

All 15 patients (mean age 68.1 years, eight women) completed all study visits. Baseline IOP values were obtained under timolol washout treatment with initial IOP values of 13.33-13.73 mmHg (3.09-3.20). No statistically significant differences in OPP, mean arterial pressure, and heart rate were found between the four studied conditions (Friedman test; *P*=0.516, 0.880, 0.992, and 0.114, respectively).

The Friedman test indicated that the mean ranks for CDI-assessed PSV, EDV, and RI in the CRA, NPCA, and TPCA did not significantly differ before and after dorzolamide/timolol or brimonidine/timolol administration (Tables 1 and 2, Figures 1 and 2). A difference was noted in the sum of ranks of OA EDV between the four experimented conditions (Table 1); however, post-hoc analysis revealed no difference between the two drugs (*Z* score=1.19, *P*=0.233).

When comparing treatments to individual baselines, both dorzolamide/timolol and brimonidine/timolol tended to increase PSV and EDV in the NPCA and TPCA, with a significant increase for dorzolamide/timolol in both blood vessels (Table 3), although the changes were not statistically significant after conservative adjustment for multiple comparisons (paired comparison with Holm's sequential Bonferroni correction). The differences between the two drugs were also not statistically significant with Holm's sequentially rejective Bonferroni correction procedure.

DISCUSSION

Primary OAG continues to be enigmatic in some patients, with continued progression of the disease, despite significantly lowered IOP. Vascular considerations in patients with OAG continue to be actively discussed,[10] with ever-increasing data to support their relevance in optic neuropathy. It is, therefore, important to establish the hemodynamic profile of glaucoma treatments, in addition to their effects on IOP. To the best of the authors' knowledge, this is the first study to report results on the effects of brimonidine/timolol on retrobulbar blood flow in patients with OAG.

To significantly impact ocular blood flow, topical OAG medications must penetrate the anterior surface of the eye, reach critical concentrations, and exert a physiological effect on the vascular tissue. Each of the different classes of OAG therapies maintain the potential to interact with vascular smooth muscle.[11] Topical medications may have a direct vascular interaction in ocular tissues, or may increase OPP by lowering IOP; thus, producing a

Table 1. Friedman comparison before and after brimonidine/timolol or dorzolamide/timolol administration. Color Doppler imaging measurements were taken in the OA and CRA. In each vessel, PSV and EDV were determined and Pourcelot's vascular RI.

Artery/measurement		Experiment	Mean (SD)	Median (range)	*Z* score (*P* value)
OA	PSV (cm/s)	Pre-brimonidine/timolol	23.66 (10.98)	20.60 (8.30-50.70)	3.67 (0.299)
		Post-brimonidine/timolol	24.50 (11.25)	22.10 (8.20-48.80)	
		Pre-dorzolamide/timolol	21.40 (8.28)	19.30 (7.50-39.50)	
		Post-dorzolamide/timolol	22.09 (8.25)	22.10 (6.70-38.70)	
	EDV (cm/s)	Pre-brimonidine/timolol	5.16 (2.04)	5.30 (1.60-8.40)	9.98 (0.019)
		Post-brimonidine/timolol	5.83 (2.49)	5.30 (1.60-12.20)	
		Pre-dorzolamide/timolol	4.49 (1.46)	4.60 (1.60-6.60)	
		Post-dorzolamide/timolol	5.18 (2.33)	5.30 (1.20-9.40)	
	RI	Pre-brimonidine/timolol	0.77 (0.09)	0.79 (0.50-0.87)	3.96 (0.265)
		Post-brimonidine/timolol	0.75 (0.08)	0.76 (0.53-0.84)	
		Pre-dorzolamide/timolol	0.77 (0.07)	0.77 (0.63-0.85)	
		Post-dorzolamide/timolol	0.77 (0.06)	0.78 (0.58-0.84)	
CRA	PSV (cm/s)	Pre-brimonidine/timolol	8.75 (2.40)	8.80 (4.50-13.50)	1.69 (0.640)
		Post-brimonidine/timolol	8.86 (2.19)	8.80 (6.00-13.30)	
		Pre-dorzolamide/timolol	8.29 (2.48)	8.30 (3.50-13.30)	
		Post-dorzolamide/timolol	8.81 (2.54)	8.00 (4.10-13.80)	
	EDV (cm/s)	Pre-brimonidine/timolol	2.56 (1.05)	2.30 (1.30-5.30)	6.07 (0.108)
		Post-brimonidine/timolol	2.73 (0.65)	2.80 (1.80-4.00)	
		Pre-dorzolamide/timolol	2.45 (0.82)	2.30 (1.00-4.00)	
		Post-dorzolamide/timolol	2.75 (0.78)	2.80 (1.10-4.00)	
	RI	Pre-brimonidine/timolol	0.71 (0.06)	0.74 (0.54-0.77)	3.83 (0.281)
		Post-brimonidine/timolol	0.70 (0.06)	0.71 (0.60-0.80)	
		Pre-dorzolamide/timolol	0.70 (0.06)	0.71 (0.56-0.80)	
		Post-dorzolamide/timolol	0.68 (0.05)	0.68 (0.60-0.80)	

CRA=central retinal artery; EDV=end diastolic velocity; OA=ophthalmic artery; PSV=peak systolic velocity; RI=resistive index.

net effect on the ocular circulation and possibly influencing OAG pathology.

Aqueous humor secretion depends on the production of bicarbonate (HCO3-) in a reaction catalyzed by carbonic anhydrase II,[17] an isoenzyme found in the nonpigmented ciliary epithelium. Chemically, carbonic anhydrase catalyzes carbon dioxide (CO_2) interconversion to carbonic acid (H_2CO_3), which freely dissociates into HCO_3- and protons. A blockade of carbonic anhydrase in local tissues reduces IOP but may also increase tissue CO_2 concentrations and/or lower tissue pH, resulting in vascular dilation and increased blood flow.[12,18] This may explain the physiological mechanism by which dorzolamide/timolol has been consistently shown to increase blood flow in ocular tissues in numerous clinical trials.[12]

To the best of the authors' knowledge, there has been no prior published study that has reported on the ocular blood flow effects of

Table 2. Friedman comparison before and after brimonidine/timolol or dorzolamide/timolol administration. Color Doppler imaging measurements were taken in the NPCA and TPCA. In each vessel, PSV and EDV were determined and Pourcelot's vascular RI.

Artery/measurement		Experiment	Mean (SD)	Median (range)	*Z* score (*P* value)
TPCA	PSV (cm/s)	Pre-brimonidine/timolol	8.47 (1.71)	8.30 (5.80-11.50)	5.26 (0.154)
		Post-brimonidine/timolol	8.52 (1.57)	8.50 (5.50-11.30)	
		Pre-dorzolamide/timolol	8.05 (1.45)	8.00 (5.00-10.30)	
		Post-dorzolamide/timolol	8.84 (1.75)	8.80 (4.50-12.00)	
	EDV (cm/s)	Pre-brimonidine/timolol	2.56 (0.62)	2.30 (2.00-3.80)	6.42 (0.093)
		Post-brimonidine/timolol	2.73 (0.67)	2.80 (1.80-4.30)	
		Pre-dorzolamide/timolol	2.38 (0.71)	2.00 (1.80-4.50)	
		Post-dorzolamide/timolol	2.87 (0.95)	2.80 (1.50-5.00)	
	RI	Pre-brimonidine/timolol	0.69 (0.08)	0.70 (0.49-0.81)	1.99 (0.574)
		Post-brimonidine/timolol	0.67 (0.08)	0.70 (0.48-0.78)	
		Pre-dorzolamide/timolol	0.70 (0.08)	0.71 (0.53-0.80)	
		Post-dorzolamide/timolol	0.68 (0.08)	0.67 (0.54-0.83)	
NPCA	PSV (cm/s)	Pre-brimonidine/timolol	7.81 (2.08)	7.50 (5.00-12.30)	6.94 (0.074)
		Post-brimonidine/timolol	8.61 (2.33)	7.50 (6.30-14.00)	
		Pre-dorzolamide/timolol	7.61 (2.28)	7.10 (4.00-11.50)	
		Post-dorzolamide/timolol	8.02 (2.51)	7.80 (4.30-12.30)	
	EDV (cm/s)	Pre-brimonidine/timolol	2.41 (0.62)	2.30 (1.50-3.50)	6.38 (0.095)
		Post-brimonidine/timolol	2.63 (0.71)	2.30 (2.00-4.50)	
		Pre-dorzolamide/timolol	2.39 (0.63)	2.30 (1.50-3.50)	
		Post-dorzolamide/timolol	2.61 (0.63)	2.50 (1.50-3.80)	
	RI	Pre-brimonidine/timolol	0.69 (0.05)	0.67 (0.60-0.77)	5.16 (0.160)
		Post-brimonidine/timolol	0.68 (0.04)	0.67 (0.60-0.75)	
		Pre-dorzolamide/timolol	0.68 (0.05)	0.68 (0.56-0.75)	
		Post-dorzolamide/timolol	0.67 (0.06)	0.68 (0.57-0.76)	

EDV=end diastolic velocity; NPCA=nasal short posterior ciliary artery; PSV=peak systolic velocity; RI=resistive index; TPCA=temporal short posterior ciliary artery.

brimonidine/timolol combination in patients with OAG. In the current investigation, the authors examined how brimonidine/timolol combination may differ from dorzolamide/timolol combination, an established[12,19,20] concomitant therapy, in terms of OPP and retrobulbar blood flow in IOP-controlled OAG patients. In this short-duration investigation, both dorzolamide/timolol and brimonidine/timolol tended to increase blood flow velocities in both short posterior ciliary arteries, with a statistically significant increase for dorzolamide/timolol in both blood vessels compared to baseline. This is in agreement with the majority of previous trials involving dorzolamide/timolol.[12] In the current analysis, both dorzolamide/timolol and brimonidine/timolol increased blood flow velocities, thereby resulting in no statistically significant difference between treatments. In other comparative trials of dorzolamide/timolol, retinal blood flow was found to increase in the superficial retinal

Figure 1. Color Doppler imaging measurements taken in the TPCA. In each vessel, PSV and EDV were determined and Pourcelot's vascular RI. Changes in TPCA PSV (A), EDV (B), and RI (C) following 2-week treatment with brimonidine/timolol and dorzolamide/timolol. The fluctuations are not statistically significant. EDV=end diastolic velocity; PSV=peak systolic velocity; RI=resistive index; TPCA=temporal short posterior ciliary artery.

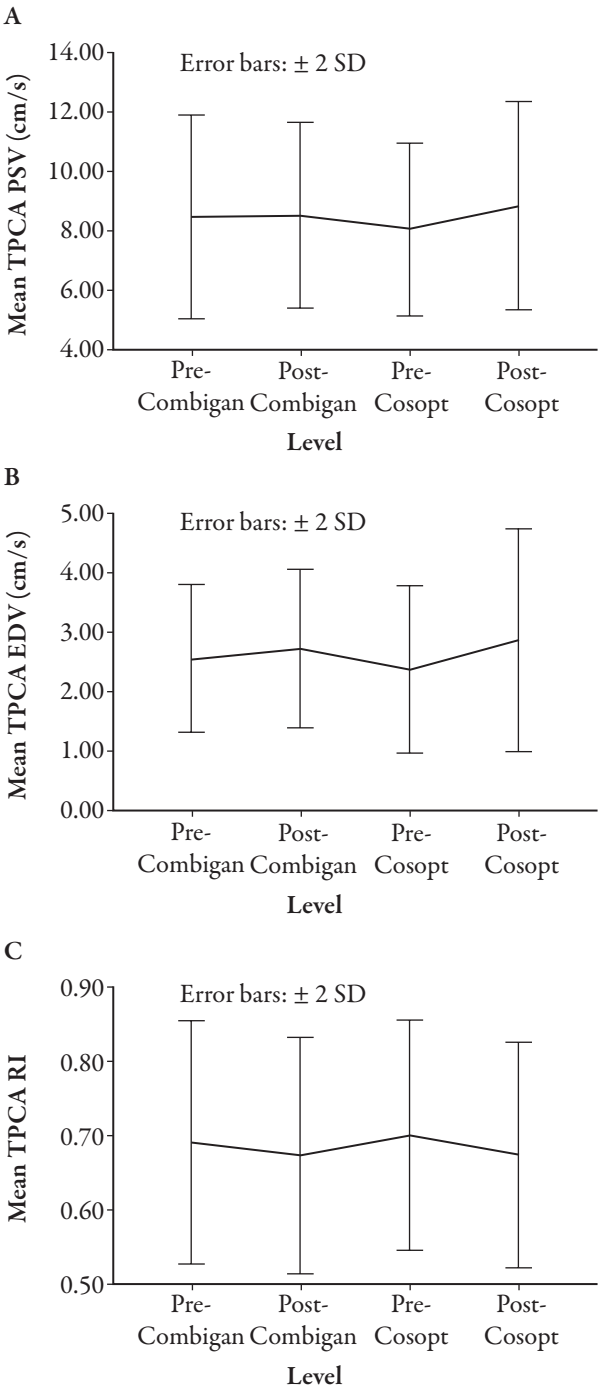

Figure 2. Color Doppler imaging measurements were taken in the NPCA. In each vessel, PSV and EDV were determined and Pourcelot's vascular RI. Changes in NPCA PSV (A), EDV (B), and RI (C) following 2-week treatment with brimonidine/timolol and dorzolamide/timolol. The fluctuations are not statistically significant. EDV=end diastolic velocity; NPCA=nasal short posterior ciliary artery; PSV=peak systolic velocity; RI=resistive index.

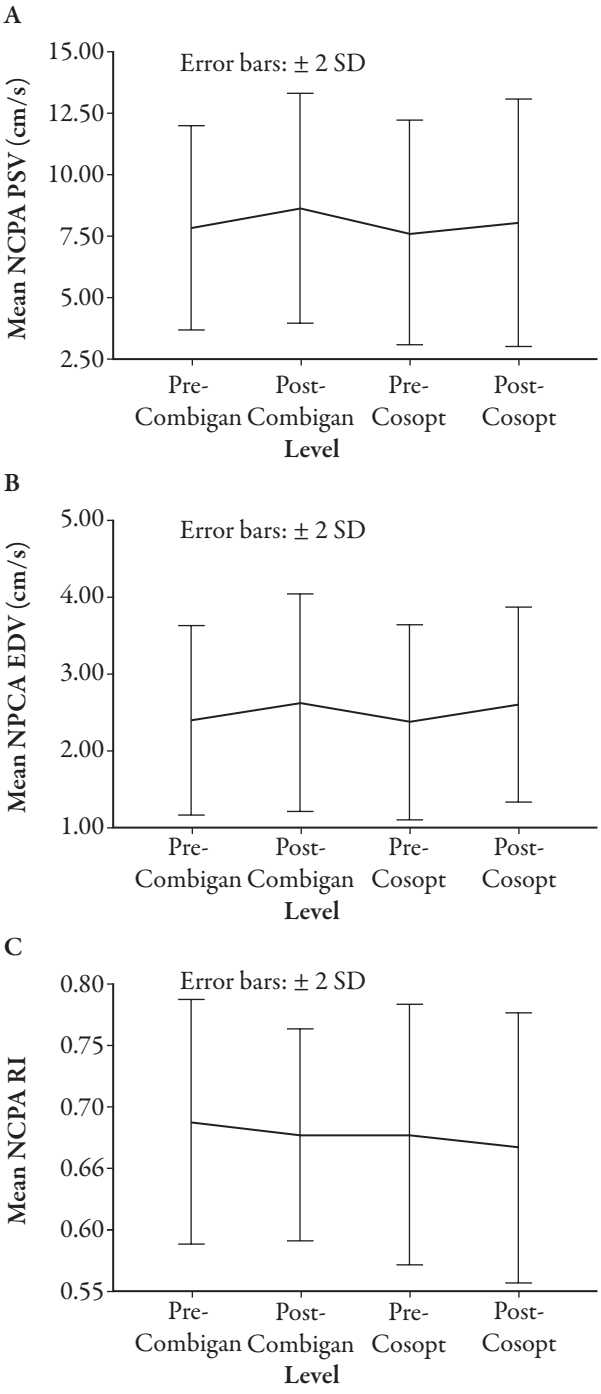

Table 3. Results of Wilcoxon signed rank multiple comparisons expressed in *P* values. Color Doppler imaging measurements were taken in the OA, CRA, NPCA, and TPCA. In each vessel, PSV and EDV were determined and Pourcelot's vascular RI.

	TPCA		NPCA	
Comparison	**PSV**	**EDV**	**PSV**	**EDV**
Pre-brimonidine/timolol vs. post-brimonidine/timolol	0.779	0.103	0.155	0.167
Pre-dorzolamide/timolol vs. post-dorzolamide/timolol	0.025	0.031	0.035	0.020
Pre-brimonidine/timolol vs. pre-dorzolamide/timolol	0.271	0.171	0.571	0.889
Pre-brimonidine/timolol vs. post-dorzolamide/timolol	0.257	0.278	0.675	0.104
Pre-dorzolamide/timolol vs. post-brimonidine/timolol	0.306	0.049	0.099	0.235
Post-brimonidine/timolol vs. post-dorzolamide/timolol	0.572	0.683	0.243	0.968

CRA=central retinal artery; EDV=end diastolic velocity; NPCA=nasal short posterior ciliary artery; OA=ophthalmic artery; PSV=peak systolic velocity; RI=resistive index; TPCA=temporal short posterior ciliary artery.
Dorzolamide/timolol significantly increased TPCA and NPCA PSV and EDV; however, none of the observed differences were statistically significant based on Holm's sequential Bonferroni adjusted significance levels.

vasculature in both glaucomatous and healthy patients following 8 months of treatment, but with no effect on the retrobulbar blood vessels.[19] Another study also found neither dorzolamide nor latanoprost had any statistically significantly effect on retrobulbar blood flow, but did find dorzolamide significantly decreased arteriovenous passage time in the superior retina, while latanoprost did not.[21] Similar findings have been previously reported with dorzolamide/timolol compared to timolol monotherapy.[22] As retinal microcirculation was not measured in the current study, it remains unknown if dorzolamide/timolol and brimonidine/timolol may differ in their effects on retinal capillary blood flow.

Previous investigations of brimonidine (monotherapy) did not find any significant alterations in blood flow velocities or RI in the retrobulbar vessels after 2 weeks[23] and 3 months[24] of treatment. The findings in the present study are in agreement with these prior studies suggesting no significant influence of brimonidine/timolol on the retrobulbar blood vessels, although a positive trend was found compared to timolol baseline values. One study, which investigated the ocular hemodynamic effects of brimonidine/timolol versus placebo in patients with ocular hypertension, reported a significant decrease of CRA RI that the authors suggested may be explained by a concurrent decrease in IOP, whereas placebo showed no significant changes after 3 months.[25] The authors of this study acknowledged that the short-duration administration may be insufficient to elicit potential differing effects between brimonidine/timolol and dorzolamide/timolol, and that well controlled IOP glaucoma patients may not be representative of high pressure OAG patients. Additional research into the possible effects of brimonidine/timolol on other ocular vascular beds, including the retinal microcirculation, is suggested before a definitive conclusion can be reached.

In this study's group of patients with OAG there were also no statistically significant differences between brimonidine/timolol versus dorzolamide/timolol when comparing the mean change between treatments from baseline in the effects on blood pressure or calculated OPPs. A similar effect on IOP was observed between treatments in the current investigation, though the study was not designed for evaluating IOP-lowering efficacy.

While brimonidine and timolol have previously been shown to significantly decrease SBP, DBP, and diastolic perfusion pressure in a study by Quaranta et al.,[26] no significant effects were observed between treatments or from baseline in terms of blood pressure or OPPs. Results from the current study are similar to Liu, who previously reported brimonidine twice daily caused no changes in OPPs.[27] The differences between the findings of the present study and the results from Quaranta et al.[26] and Liu et al.[27] may be due to the dosing regimen, treatment duration (4 weeks in the current investigation and in the Liu et al. study,[27] 6 weeks in the Quaranta et al. study[26]), specific measurement timepoints, patient populations (current study established OAG compared to normal tension glaucoma,[27] and newly diagnosed[26]), and/or coadministration of brimonidine with timolol. There is currently insufficient agreement to conclude that brimonidine/timolol influences blood pressure or OPP based upon these combined investigations. The results of the present study suggest brimonidine/timolol does not negatively impact OPP in established IOP-controlled glaucoma patients.

The current study had several limitations. First, the study duration was only 1 month for each therapy and may not reflect the long-term effects of chronic glaucoma management under either treatment. Second, due to the study duration, changes in visual field or optic nerve structure for either treatment were not evaluated. While the current study group had well controlled IOP, the results of this study may not be fully applicable to low-pressure glaucoma patients. Retinal capillary blood flow or diurnal fluctuations in IOP, OPP, or blood flow for these therapies was also not assessed, which recent research has indicated may be linked to glaucoma progression.[28] Future studies that monitor risk factor fluctuations throughout the 24-hour period may reveal differences not seen in the present study. Although adequate based upon similar studies of dorzolamide, a larger patient sample may further differentiate results. Finally, each imaging technology has inherit limitations; within the current investigation, CDI evaluated blood flow velocities and calculated vascular resistance but did not analyze direct flow assessments due to a lack of blood vessel diameter.[13-16]

CONCLUSION

In summary, both brimonidine/timolol and dorzolamide/timolol therapies tended to increase OPP and retrobulbar blood flow, with no statistically significant differences between treatments after 1 month in patients with OAG and well controlled IOP.

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