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Comparison of Brimonidine/Latanoprost and Timolol/Dorzolamide: Two Randomized, Double-Masked, Parallel Clinical Trials

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ABSTRACT

Two double-masked, randomized, parallel, multicenter trials of similar design were conducted to compare the IOP-lowering efficacy of dual therapy with brimonidine 0.2% and latanoprost 0.005% with the fixed combination of timolol 0.5%/dorzolamide 2% in patients with glaucoma or ocular hypertension. The combination of brimonidine and latanoprost produced significantly greater mean IOP reductions at each visit in both trials. In study 1, the mean reduction at peak drug effect after 6 weeks was 9.2 mm Hg (34.7%) with brimonidine and latanoprost and 6.7 mm Hg (26.1%) with timolol/dorzolamide (*P*=.024); respective reductions at week 12 were 9.0 mm Hg (33.9%) and 6.5 mm Hg (25.3%) (*P*=.044). At the month 1 visit in study 2, the mean peak IOP reduction was 10.6 mm Hg (39.0%) with dual therapy and 6.3 mm Hg (25.1%) with the fixed combination (*P*=.001). After 3 months, reductions were 9.1 mm Hg (33.4%) and 6.6 mm Hg (26.3%) (*P*=.047). In these studies, the combination of brimonidine and latanoprost provided IOP control superior to that of the fixed combination of timolol/dorzolamide.

Keywords: brimonidine; latanoprost; fixed combination; timolol; dorzolamide

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INTRODUCTION

Therapy for glaucoma centers on lowering intraocular pressure (IOP) to a level at which the progression of damage is halted and the visual field is preserved. Monotherapy is the ideal, but many patients eventually require more than a single medication.

Timolol has been the most prescribed first-line ocular hypotensive agent; however, topical beta blockers often lose efficacy over time, necessitating add-on drugs.[1] A fixed combination of timolol 0.5% and the topical carbonic anhydrase inhibitor (CAI) dorzolamide 2% was introduced in 1998 and has lowered IOP more than did monotherapy with either component. The combination may be less effective than therapy with dorzolamide 2% three times daily and timolol 0.5% twice daily given concomitantly.[2]

Brimonidine, a highly selective alpha-2 agonist, has provided IOP lowering at least equivalent to that of timolol in numerous clinical trials, with a favorable safety and tolerability profile.[3,4] Moreover, while particularly effective as adjunctive therapy,[5-8] brimonidine is also safe and effective as monotherapy or replacement therapy.[3,9]

The prostaglandin $F_{2\alpha}$ prodrug latanoprost has also lowered IOP significantly, either as monotherapy or adjunctive therapy, and in large multicenter trials was at least as effective as monotherapy with timolol.[10-12] In a retrospective study,[13] the addition of latanoprost to ongoing ocular hypotensive treatment reduced IOP by at least 20% in 56% of patients.

The addition of brimonidine to ongoing latanoprost therapy produced a further IOP reduction of 5.9 mm Hg (32.2%) in a recent open-label trial.[5] Results were similar when brimonidine was added to latanoprost used adjunctively with nonselective beta blockers and with nonselective beta blockers and CAIs.[5]

We conducted two clinical trials with similar designs to compare dual therapy with brimonidine and latanoprost and the fixed combination of timolol/dorzolamide in patients with glaucoma or ocular hypertension.

PATIENTS AND METHODS

These multicenter, randomized, double-masked, parallel-design trials enrolled patients older than 18 years of age whose IOP was controlled with any combination of two ocular hypotensive agents or who were using monotherapy and needed a second agent. A best-corrected Snellen visual acuity of 20/100 or better in the study eye(s) was required, as well as an untreated baseline IOP between 22 and 35 mm Hg following a washout of all IOP-lowering medications. Study 2 enrolled only patients with open-angle glaucoma or ocular hypertension; study 1 also included patients with pigmentary and pseudoexfoliative glaucoma. Study 2 patients fulfilled the inclusion criteria in both eyes; study 1 patients could enroll with only one qualifying eye.

Reasons for exclusion from both studies were active ocular disease (other than glaucoma or ocular hypertension); poor general health; IOP uncontrolled on two ocular hypotensive agents; ocular abnormalities preventing reliable applanation tonometry; contraindications to any study medications or their components; pregnancy or nursing; and failure to use a reliable form of birth control throughout the study (women of childbearing potential).

In each study, after an initial screening visit to determine eligibility, patients underwent a washout of their ocular hypotensive medication(s): 2 weeks for alpha-adrenoreceptor agonists and epinephrine-related agents and 4 weeks for all other agents, except for a 3-day washout from CAIs and pilocarpine in study 1. Patients returned for a baseline visit after completing the washout period.

At baseline and each follow-up visit, patients underwent a complete ophthalmic examination that included slit-lamp biomicroscopy, visual acuity, and measurement of IOP by Goldmann applanation tonometry. In study 1, visits were scheduled at 7 AM + 1 hour at baseline, week 6, and week 12. IOP was measured before the morning instillation of study medication, and patients returned for another IOP measurement 2 hours after instillation, at peak effect for brimonidine and timolol. In study 2, visits were scheduled at baseline, week 2, month 1, and month 2 between 9 and 11 AM, approximately 2 hours after the morning instillation. At the final visit, the physicians completed a "clinical success" questionnaire for each patient.

Following the baseline visit, patients were randomized to treatment with either brimonidine 0.2% plus latanoprost 0.005% or the fixed combination of timolol 0.5% and dorzolamide 2% and were instructed in the use of their medications, which were dispensed in masked bottles. Regimens varied slightly. In study 1, patients instilled either brimonidine twice daily (AM and PM) and latanoprost once daily (PM) with vehicle solution once daily (AM), or timolol/dorzolamide twice daily with vehicle twice daily. In study 2, patients instilled brimonidine twice daily and latanoprost once daily in the evening. Patients assigned to timolol/dorzolamide instilled the active drops twice daily, with vehicle once daily (PM) to maintain masking.

At each follow-up visit, study 2 patients completed a quality-of-life questionnaire that rated shortness of breath, ability to climb stairs, mood, and participation in social activities since the previous visit, as well as the level of satisfaction, eyedrop comfort, and whether or not discomfort from their eyedrops prohibited the performance of daily activities.

The primary outcome measure in both studies was the mean reduction in IOP from baseline at peak drug effect. Secondary outcome measures included patient satisfaction and clinical success. Defined as the opinion of the masked investigators at the final visit, clinical success was based on IOP lowering, patient satisfaction with the regimen, the physician's willingness to continue the patient on the regimen, and incidence of adverse events. Patients were questioned about adverse events at each visit, and any relationship to the study medications was noted.

Prior to the start of each study, approval was obtained from each site's institutional review board. Patients gave written informed consent prior to enrollment.

Statistical Analysis

Within-group continuous variables were analyzed by means of paired-sample *t* tests. Independent-sample *t* tests were used to evaluate between-group differences in continuous data. The χ^2 or Fisher's exact test was applied to nominal data. All tests of continuous data were one-tailed, with the *a priori* significance level set at alpha=.05. In study 1 for patients with both eyes eligible, one eye was randomly selected for analysis; for patients with only one eligible eye, that eye provided data. Because study 2 enrolled only patients who met inclusion criteria in both eyes, the mean IOP in both eyes was used in data analysis.

RESULTS

Patients

Study 1 enrolled 40 patients at five sites; study 2 enrolled 23 patients at three sites. The majority of patients in each study were white and female and had open-angle glaucoma. Demographic variables did not differ significantly between groups in either study (Table).

Patient Demographics

	Study 1			Study 2		
	Brimonidine/ Latanoprost (n=22)	Timolol/ Dorzolamide (n=18)	*P* Value	Brimonidine/ Latanoprost (n=12)	Timolol Dorzolamide (n=11)	*P* Value
Age, y*	62.1 (±11.4)	65.2 (±13.9)	.452	62.3 (±12.3)	58.5 (±10.8)	.451
Race, % (no.)						
White	81.8 (18)	77.8 (14)	.751	58.3 (7)	72.7 (8)	.469
Black	13.6 (3)	16.7 (3)		41.8 (5)	27.3 (3)	
Hispanic	4.6 (1)	5.6 (1)		0	0	
Iris color, % (no.)						
Brown	63.6 (14)	44.4 (8)	.225	66.6 (8)	81.8 (9)	.408
Blue	22.7 (5)	16.7 (3)		8.4 (1)	9.1 (1)	
Green	13.7 (3)	38.9 (7)		16.6 (2)	0	
Hazel	0	0		8.4 (1)	9.1 (1)	
Sex, % (no.)			.324			.221
Male	54.5 (12)	38.9 (7)		41.7 (5)	18.2 (2)	
Female	45.5 (10)	61.1 (11)		58.3 (7)	81.8 (9)	
Diagnosis, % (no.)			.267			
POAG	77.2 (17)	61.1 (11)		91.7 (11)	72.7 (8)	.231
OHT	13.6 (3)	33.3 (6)		8.3 (1)	27.3 (3)	
POAG/OHT	4.6 (1)	0		0	0	
POAG/PXF	4.6 (1)	0		0	0	
PDS	0	5.6 (1)		0	0	

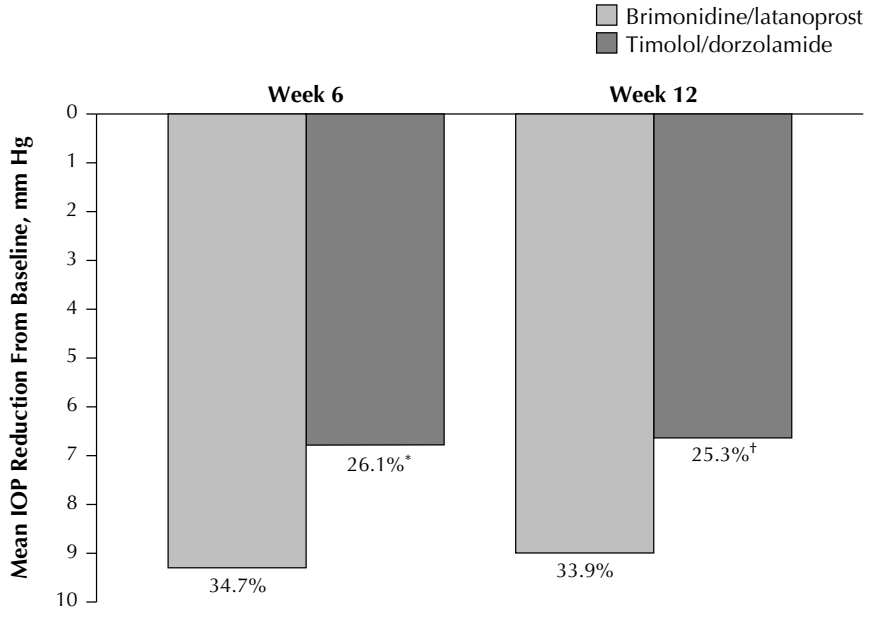
*Mean ±SD

POAG=primary open-angle glaucoma; OHT=ocular hypertension; PXF=pseudoexfoliative glaucoma; PDS=pigment dispersion syndrome.

IOP Lowering

In study 1, the mean (± SD) IOP at baseline was 26.4±5.0 mm Hg in the brimonidine/latanoprost group and 25.6±2.9 mm Hg in the timolol/dorzolamide group (*P*=.291). Throughout the study, the mean reduction in IOP was consistently larger with brimonidine/latanoprost therapy than with the fixed combination (Fig 1): 9.2±3.6 mm Hg (34.7%) with brimonidine/latanoprost and 6.7±3.5 mm Hg (26.1%) with timolol/dorzolamide at 6 weeks (*P*=.024); 9.0±4.5 mm Hg (33.9%) and 6.5±3.6 mm Hg (25.3%) at 12 weeks (*P*=.044).

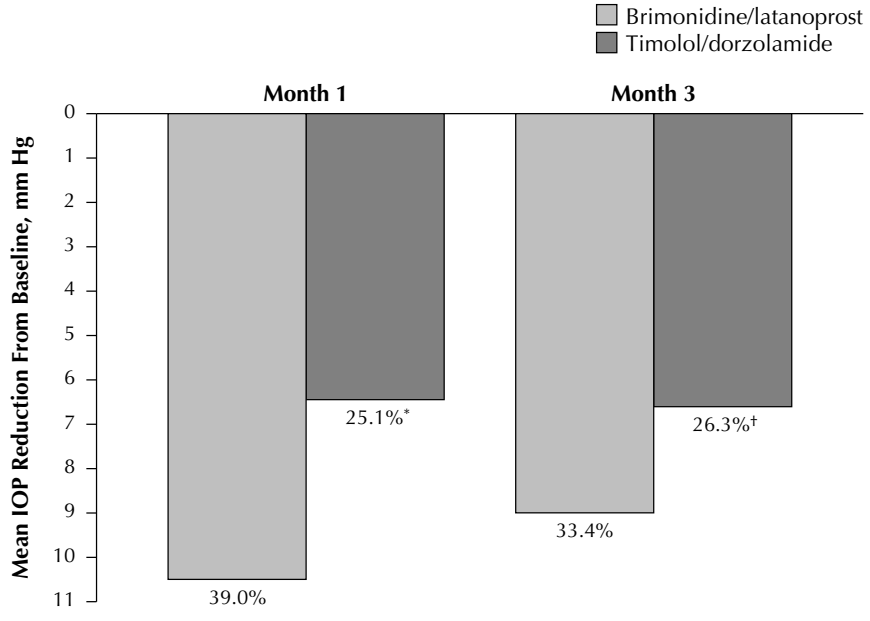
Fig 1. Mean IOP reduction (peak drug effect) at each visit in study 1.



*P=.024.
†P=.044.

In study 2, mean IOP at baseline was 27.2±4.4 mm Hg in the brimonidine/latanoprost group and 25.1±4.1 mm Hg in the timolol/dorzolamide group (*P*=.127). Respective mean IOP reductions were 10.6±3.5 mm Hg (39.0%) and 6.3±1.8 mm Hg after 1 month of treatment (25.1%; *P*=.001), and 9.1±4.0 mm Hg (33.4%) and 6.6± 2.2 mm Hg (26.3%) at the 3-month visit (*P*=.047; Fig 2).

Fig 2. Mean IOP reduction (peak drug effect) at each visit in study 2.



*P=.001.
†P=.047.

Adverse Events

Both regimens were safe and well tolerated, and few patients in either study discontinued treatment because of adverse events. In study 1, in the brimonidine/latanoprost group, one patient withdrew because of dry eyes and another because of chest pain unrelated to the study medications. Three discontinuations in the timolol/dorzolamide group were due to dry mouth (n=1), allergy (n=1), and nausea with lack of appetite (n=1); these adverse events were considered treatment related.

In study 2, one patient instilling timolol/dorzolamide left prematurely because of palpitations unrelated to treatment.

Quality of Life and Patient Satisfaction

In study 1, 88.9% (17/19) of brimonidine/latanoprost patients who completed the study were satisfied with their medications, compared with 76.9% (8/13) of timolol/dorzolamide completers (1 brimonidine/latanoprost patient and 2 timolol/dorzolamide patients did not answer the question) (P=.372). Respective percentages in study 2 were 91.7% (11/12) and 90.9% (10/11) (P=.949).

Quality of life, assessed through a questionnaire administered in study 2, seemed to remain stable in this short-term study. No significant between-group differences were noted in any measure recorded. At the 1-month visit, shortness of breath increased in 1 of 12 brimonidine/latanoprost patients and in none of the 10 timolol/dorzolamide patients, although 1 patient in the latter group complained of increased difficulty climbing stairs. The entire brimonidine/latanoprost cohort reported that the drops were comfortable, while 2 timolol/dorzolamide patients noted discomfort with the medications. At the month 3 visit, 1 timolol/dorzolamide patient cited a decreased ability to participate in social activities, and another reported that the study medications were uncomfortable. Both groups in their entirety indicated no change in shortness of breath, ability to climb stairs, or any other variable.

Clinical Success

In study 1, masked investigator-assigned rates of clinical success were 89.5% (17/19) with brimonidine/latanoprost and 61.5% (8/13) with timolol/dorzolamide (P=.060). Respective rates in study 2 were 75% (9/12) and 70% (7/10) (P=.793).

DISCUSSION

The present study demonstrates the powerful IOP lowering provided by the combination of brimonidine and latanoprost and supports previous research.[5] The mean IOP reduction was considerably greater than that achieved with timolol/dorzolamide, and this difference was statistically significant at each visit.

Current therapy for glaucoma focuses on reducing IOP to a level at which the progression of glaucomatous damage is halted, and recent studies have illustrated the importance of lowering IOP to prevent optic-nerve damage.[14,15] In the Advanced Glaucoma Intervention Study,[14] patients with low mean IOP had less progression of damage. In the present studies, mean IOP reductions from baseline ranged from 9.0 to 10.6 mm Hg with brimonidine/latanoprost and from 6.3 to 6.7 mm Hg with timolol/dorzolamide. Dual therapy with brimonidine twice daily and latanoprost once daily was 2.5 to 4.3 mm Hg superior to twice-daily use of the timolol/dorzolamide fixed combination in reducing IOP, a difference that is likely to be clinically relevant.

The present results agree with an earlier evaluation[16] in which the addition of brimonidine to established latanoprost monotherapy produced a greater mean IOP reduction than did the addition of timolol (4.5 mm Hg [22%] vs 3.4 mm Hg [18%]). The present results are also consistent with data from a large (n=554) community-based assessment of brimonidine used adjunctively with a variety of ongoing regimens.[5] In that study, the addition of brimonidine to latanoprost significantly reduced IOP by a further 5.9 mm Hg (32.2%), even in patients already using multiple medications. Similar reductions occurred when brimonidine was added to latanoprost used adjunctively with nonselective beta blockers, with or without additional ocular hypotensive agents.

Each of our short-term studies noted high rates of patient satisfaction, with no significant between-group differences, and clinical success. Both regimens were safe and well tolerated, and few patients discontinued because of adverse events.

CONCLUSIONS

Dual therapy with brimonidine and latanoprost provides IOP lowering superior to that with the fixed combination of timolol and dorzolamide. The difference in mean IOP reduction between these regimens was substantial (from 2.5–4.3 mm Hg) and likely to have clinical relevance. Both treatments were safe and well tolerated. The combination of brimonidine and latanoprost may lower IOP more effectively than the fixed combination of timolol/dorzolamide in patients requiring more than a single medication for control.

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