Comparison of the Effects of Bimatoprost and Timolol on Intraocular Pressure and Pulsatile Ocular Blood Flow in Patients with Primary Open-Angle Glaucoma: A Prospective, Open-Label, Randomized, Two-Arm, Parallel-Group Study

Michele Vetrugno, MD, Nicola Cardascia, MD, Francesco Cantatore, MD, and Carlo Sborgia, MD

Departments of Ophthalmology and Otorhinolaryngology, University of Bari, and the Glaucoma Research Centre, Department of Ophthalmology, University Hospital of Bari, Bari, Italy

ABSTRACT

Background: The current objective of antiglaucomatous therapy is to reduce intraocular pressure (IOP), and thus to preserve visual function. Many ophthalmologists believe this objective is best achieved by methods that improve ocular blood flow to the optic nerve head. Beta-blockers are effective ocular hypotensive agents, but they can reduce choroidal blood flow. Bimatoprost, a new prostamide analogue, has been shown to have a better IOP-lowering effect compared with the nonselective beta-adrenergic receptor blocker timolol maleate, but little is known about its effects on the vascular bed of the eye.

Objective: The aim of this study was to compare the effects of bimatoprost and timolol on IOP and choroidal blood flow (as measured using pulsatile ocular blood flow [pOBF]) in patients with primary open-angle glaucoma (POAG).

Methods: This prospective, open-label, randomized, 2-arm, parallel-group study was conducted at the Glaucoma Research Centre, Department of Ophthalmology, University Hospital of Bari, Bari, Italy. Patients with POAG having well-controlled IOP (<16 mm Hg) on monotherapy with timolol 0.5% ophthalmic solution (2 drops per affected eye BID) for ≥ 12 months but with a progressive decrease in pOBF during the same time period were randomly allocated to 1 of 2 treatment groups. One group continued monotherapy with timolol, 2 drops per affected eye BID. The other group was switched (without washout) to bimatoprost 0.3% ophthalmic solution (2 drops per affected eye QD [9 PM]). Treatment was given for 180 days. IOP and pOBF were assessed at the diagnostic visit (pre-timolol), baseline (day 0), and treatment days 15, 30, 60, 90, and 180. Primary adverse effects (AEs) (ie, conjunctival hyperemia, conjunctival papillae, stinging, burning, foreign body sensation, and pigmentation of peri-orbital skin) were monitored throughout the study.

Results: Thirty-eight patients were enrolled (22 men, 16 women; mean [SD] age, 51.7 [4.8] years; 19 patients per treatment group; 38 eligible eyes). At 180-day follow-up in the timolol group, the IOP and the pOBF remained unchanged compared with baseline. In the bimatoprost group the IOP remained unchanged and the pOBF was decreased by 38.9% compared with baseline ($P < 0.01$). All AEs were mild to moderate and included conjunctival hyperemia and ocular itching (5 patients [26.3%] in the bimatoprost group) and pigmentation of periorbital skin (2 patients [40.0%] in the bimatoprost group). The incidence of each AE was higher in the bimatoprost group than in the timolol group ($P = 0.008$).

Conclusions: In this population of patients with POAG, bimatoprost was associated with increased pOBF, and the reduction in pOBF associated with timolol was corrected after patients were switched to bimatoprost. Bimatoprost was associated with increased choroidal blood flow, beyond the levels recorded before timolol treatment. The decreased IOP level achieved in the timolol group seemed to be improved further by bimatoprost. Considering the potential efficacy of bimatoprost on IOP and pOBF, we suggest that this new drug may represent a clinical advance in the medical treatment of POAG. (*Curr Ther Res Clin Exp.* 2004;65:444–454) Copyright © 2004 Excerpta Medica, Inc.

Key words: bimatoprost, timolol, pulsatile ocular blood flow, intraocular pressure, primary open-angle glaucoma.

INTRODUCTION

The current objective of antiglaucomatous therapy is to reduce intraocular pressure (IOP) and thus to preserve visual function. Many ophthalmologists believe this objective is best achieved by methods that improve ocular blood flow to the optic nerve head.^{1,2} Thus, drugs effective in lowering IOP should be investigated with regard to their effect on ocular hemodynamics.³

Studies on the pharmacologic mechanism of action of the new prostamide analogue bimatoprost have reported that this drug acts on the prostaglandin F_{α_2} vascular receptor, with selectivity for the F prostaglandin receptor,^{4–7} to reduce IOP, lowering the tonographic resistance to outflow.^{8,9} Bimatoprost has been associated with greater decreases and diurnal control compared with other molecules, with mild adverse effects (AEs).^{10–13} A previous study showed that although selective and nonselective beta-blockers reduce IOP, the effect of the 2 treatments on the ocular blood flow, as measured by pulsatile ocular blood flow (pOBF), differs: with nonselective beta-blockers, the pOBF decreased significantly, whereas with selective beta-blockers it remained stable.¹⁴ Considering the importance of ocular blood flow in the pathogenesis of glaucoma, and with no information in this regard available on bimatoprost (according to a MEDLINE search [key terms: *ocular blood flow*, *bimatoprost*, and *glaucoma*; years: 1989–2004]), we compared the effects of bimatoprost and timolol ophthalmic solutions on IOP and pOBF in patients with primary open-angle glaucoma (POAG).

PATIENTS AND METHODS

This prospective, open-label, randomized, 2-arm, parallel-group study was conducted at the Glaucoma Research Centre, Department of Ophthalmology, University Hospital of Bari, Bari, Italy. The independent ethics committee at the hospital approved the study.

Inclusion and Exclusion Criteria

At an initial study visit (pre-timolol), consecutive patients with POAG were recruited from those regularly attending the Glaucoma Research Centre. The diagnostic criteria for POAG were glaucomatous visual field anomalies, pathologic optic disc cupping or notching, and open drainage angle. At this visit, patients were prescribed a 12-month, prestudy treatment regimen of topical timolol 0.5% ophthalmic solution (2 drops per affected eye BID). At the end of 12 months (baseline visit), patients became eligible for the study if they had well-controlled IOP (<16 mm Hg) on the timolol regimen.

To avoid the influence of ocular and general factors that could affect pOBF measurements, additional, restrictive inclusion criteria were as follows: refraction ± 3 D, ocular hypotension obtained only by means of timolol use, and a reduction of pOBF $>10\%$ from the pre-timolol visit. Stringent systemic inclusion criteria were as follows: age 40 to 60 years, nonsmoking status, systolic brachial pressure 120 to 140 mm Hg, diastolic brachial pressure 70 to 90 mm Hg, heart rate 66 to 80 bpm, body mass index within normal range for sex and age, and unremarkable hemorheologic test results (hematocrit, hemoglobin concentration, iron level, white blood cell count, platelet count).

Patients were excluded from the study if they had any cardiovascular abnormalities (eg, atherosclerosis, carotid stenosis) or were using systemic vasoactive therapy (eg, aspirin, calcium antagonists, nitroglycerin derivatives, oral beta-blockers). Patients with types of glaucoma other than POAG were also excluded.

Written informed consent was obtained from all eligible patients before study entry.

Study Drug Administration

At the baseline visit (day 0), eligible patients were randomly assigned, using a computer-generated randomization code list, to 1 of 2 treatment groups. One group continued therapy with timolol (2 drops per affected eye BID). The other group was switched, without washout, from timolol to bimatoprost 0.3% ophthalmic solution (2 drops per affected eye QD [9 PM]).

Efficacy Assessments

IOP and pOBF were measured on the morning (9 AM) of each study visit (pre-timolol, baseline, and treatment days 15, 30, 60, 90, and 180). Measurements were taken after patients had been seated for 5 minutes. pOBF was measured using a tonograph (Langham Ophthalmic Technologies, Timonium, Maryland).

To minimize evaluation bias, all of the examinations were carried out by the same investigator (M.V.).

Tolerability Assessment

Primary AEs (ie, conjunctival hyperemia, conjunctival papillae, stinging, burning, foreign body sensation, and pigmentation of periorbital skin) were monitored throughout the study.

Statistical Analysis

The mean (SD) values for IOP and pOBF were calculated before and after treatment. Within-group variations were evaluated using the Bonferroni adjustment, and between-group variations, using the unpaired *t* test. The Pearson correlation coefficient was calculated to determine the correlation between IOP and pOBF at each time point. $P < 0.05$ was considered significant (2-tailed test).

RESULTS

Study Population

Forty-seven patients were screened for the study; 9 were ineligible (2 could not return for follow-up, 5 had brachial systolic pressure >140 mm Hg, and 2 had brachial systolic and diastolic pressures >140 and >90 mm Hg, respectively). Therefore, 38 patients were included in the study (22 men, 16 women; mean [SD] age, 51.7 [4.8] years; 19 patients per treatment group; 38 eligible eyes). Baseline characteristics of the patients are shown in **Table I**. Patients had statistically similar values of IOP and pOBF before prestudy timolol and at baseline (**Table II**).

Table I. Baseline demographic and clinical characteristics of patients to undergo therapy for primary open-angle glaucoma (N = 38).*

Characteristic	Timolol (n = 19)	Bimatoprost (n = 19)
Age, mean (SD), y	51.2 (4.12)	52.1 (5.01)
Sex, no. (%)		
Male	10 (52.6)	12 (63.2)
Female	9 (47.4)	7 (36.8)
Brachial systolic pressure, mean (SD), mm Hg	129.8 (8.1)	132.3 (7.1)
Heart rate, mean (SD), bpm	81.7 (4.9)	83.1 (5.1)
No. eyes qualified for study	38	38
Refraction, mean (SD), D	0.68 (0.98)	0.71 (0.84)
IOP, mean (SD), mm Hg	16.75 (2.38)	17.0 (1.69)
Cup-disk ratio, mean (SD)	0.43 (0.08)	0.44 (0.07)

IOP = intraocular pressure.

*No significant between-group differences were found.

Table II. Intraocular pressure (IOP; mm Hg) and pulsatile ocular blood flow (pOBF; $\mu\text{L}/\text{min}$) in patients undergoing therapy for primary open-angle glaucoma (N = 38). Values are mean (SD) unless otherwise specified.

Variable/ Time Point	Timolol (n = 19)	Bimatoprost (n = 19)	Between-Group Difference, %	P*
IOP				
Pre-timolol	22.63 (1.41)	23.13 (1.55)	–	0.510
Baseline	16.75 (2.38)	17.00 (1.69)	0.52	0.810
15 d	15.88 (1.46)	14.25 (2.18)	10.98	0.130
30 d	16.35 (1.99)	14.28 (2.12)	13.61	0.058
60 d	15.50 (1.93)	13.88 (1.25)	10.89	0.065
90 d	16.13 (1.36)	14.13 (1.13)	13.18	<0.007
180 d	15.75 (1.67)	13.50 (1.31)	14.62	<0.010
Δ vs pre-timolol	–6.88 (1.13)	–9.63 (1.85)	–	–
% Δ	–30.40 (15.67)	–41.63 (18.55)	–	–
P vs pre-timolol	NS	NS	–	–
pOBF				
Pre-timolol	1133.75 (88.02)	1114.25 (120.60)	–	0.720
Baseline	841.38 (80.59)	785.00 (87.28)	3.76	0.200
15 d	838.13 (80.97)	1092.00 (296.84)	–39.50	0.035
30 d	856.25 (70.50)	1078.38 (116.76)	–35.61	<0.001
60 d	846.25 (65.29)	1138.75 (158.81)	–44.49	<0.001
90 d	855.00 (70.31)	1187.88 (103.10)	–49.70	<0.001
180 d	853.13 (70.05)	1242.00 (296.13)	–56.82	<0.003
Δ vs pre-timolol	–280.62 (103.11)	127.75 (319.63)	–	–
% Δ	–24.41 (7.61)	12.63 (28.36)	–	–
P vs pre-timolol	NS	<0.01	–	–

*Between-group difference (unpaired *t* test).

Efficacy

Figure 1 shows the mean (SD) values for IOP in the 2 treatment groups from the pre-timolol visit through follow-up at day 180. All patients had a good response to prestudy treatment with timolol in terms of a decreased IOP at baseline, with a significant reduction in IOP compared with the untreated (pre-timolol) levels (both groups, $P < 0.001$). The group of patients that was switched to bimatoprost showed no significant change in IOP from pre-timolol levels throughout the study. However, at day 180, the bimatoprost group had a significantly lower IOP compared with baseline ($P < 0.01$).

Figure 2 shows the mean (SD) pOBF values of the 2 treatment groups from the pre-timolol visit through day 180. At baseline, both groups showed significant mean (SD) reductions from the pre-timolol visit in pOBF (timolol group, 292.37 [100.59] $\mu\text{L}/\text{min}$; mean [SD] percentage change, -25.53% [7.50%]; $P < 0.001$; bimatoprost group, 329.25 [109.52] $\mu\text{L}/\text{min}$; mean [SD] percentage change, -28.36% [13.79%]; $P < 0.05$). Although the decrease in pOBF from the pre-timolol level was statistically significant in the timolol group, no significant change was seen during the follow-up period. In the bimatoprost group, however, the pOBF value returned to pre-timolol levels by day 15 ($P < 0.05$) and further increased throughout the follow-up period (each visit, $P < 0.01$ vs pre-timolol). A comparison between the groups showed statistically significant differences after 15 days of therapy (each visit, $P \leq 0.035$) (Table II). After 180 days of therapy, patients switched from timolol to bimatoprost had

Figure 1. Intraocular pressure (IOP) in patients undergoing treatment for primary open-angle glaucoma (N = 38). * $P < 0.001$ versus pre-timolol; † $P < 0.007$ versus timolol; ‡ $P < 0.01$ versus timolol.

Figure 2. Pulsatile ocular blood flow (pOBF) in patients undergoing treatment for primary open-angle glaucoma (N = 38). * $P < 0.001$ versus pre-timolol; † $P < 0.05$ versus pre-timolol; ‡ $P = 0.035$ versus bimatoprost; § $P < 0.01$ versus pre-timolol; ¶ $P < 0.001$ versus bimatoprost; †† $P < 0.003$ versus bimatoprost.

a significantly higher pOBF value compared with the timolol group (between-group difference, 56.8%; $P < 0.003$).

As shown in Table III, no correlation between IOP and pOBF was found at any time point in either treatment group.

Tolerability

No serious AEs were observed in either treatment group. Five patients (26.3%) in the bimatoprost group experienced both conjunctival hyperemia and ocular itching, both of which resolved spontaneously after 3 weeks. Pigmentation of periorbital skin developed in 2 patients in the bimatoprost group (40.0%). The between-group difference in the incidence of each AE was significant ($P = 0.008$ [Fisher exact test]).

DISCUSSION

Bimatoprost is a new prostamide analogue that has been shown to have good IOP-lowering efficacy and to be generally well tolerated.¹⁵ Nevertheless, IOP control should not be the sole aim of modern antiglaucomatous therapy. A powerful hypotensive agent that also enhances blood flow to the eye and provides

Table III. Linear correlation between intraocular pressure and pulsatile ocular blood flow in patients undergoing therapy for primary open-angle glaucoma (N = 38).

Time Point	Timolol (n = 19)		Bimatoprost (n = 19)	
	<i>r</i> *	<i>p</i> †	<i>r</i> *	<i>p</i> †
Pre-timolol	0.64	0.12	−0.08	0.85
Baseline	0.19	0.65	0.21	0.62
15 d	−0.02	0.95	0.11	0.78
30 d	0.14	0.73	0.26	0.54
60 d	0.11	0.79	0.50	0.21
90 d	0.05	0.90	−0.43	0.28
180 d	−0.20	0.62	0.58	0.13

*Pearson correlation coefficient.

†Unpaired *t* test.

neuroprotection would be the ideal glaucoma therapy, especially because it is now recognized that visual field loss continues in some patients despite successful medical or surgical reduction of IOP.¹⁶

pOBF measurement may provide an indirect estimation of optic nerve blood flow.^{17–19} pOBF is estimated from the ocular pulse, which is proportional to perfusion pressure and inversely correlated with vascular resistance. Although this pulse mostly reflects choroidal blood flow, the choroidal system is also the main contributor to optic nerve blood flow, accounting for 90% of choroidal circulation and for only 10% of retinal circulation.^{20,21} Choroidal circulation is affected differently by various hypotensive medications, with a direct effect on optic nerve head perfusion. Therefore, antiglaucomatous treatments can influence the long-term tropism of the optic nerve head.²² It has been shown that pOBF values are decreased in patients with POAG.²³

Several studies have demonstrated the efficacy of bimatoprost in reducing IOP, but according to our MEDLINE search, this is the first study of its effect on choroidal perfusion. We used a study design similar to one used in a previous study that evaluated the effect of brimonidine,²⁴ travoprost, and latanoprost²⁵ on pOBF.

This study showed that treatment with bimatoprost may have a beneficial effect on pOBF: after 180 days of therapy, patients switched from timolol to bimatoprost had a significantly higher pOBF value compared with the timolol group ($P < 0.003$). Compared with pre-timolol pOBF values, the net increase achieved was 12.6%. In patients treated with timolol, pOBF decreased by 24.4% compared with pretreatment. Furthermore, although IOP in the timolol group was reduced 30.4% compared with pretreatment, the bimatoprost group showed an additional 11.2% decrease in IOP compared with the timolol group.

Several studies correlate the improvements in pOBF and IOP reduction.²⁶ However, our results did not confirm this correlation. This finding seems to indicate that the enhancing effect of bimatoprost on ocular blood flow is independent of its efficacy in lowering IOP. We believe that stopping the timolol treatment improved ocular blood flow by interrupting the beta-blocker-induced vasoactive effect, and that subsequent flow variations might be related to capillary autoregulation, which is known to exist in the retina and hypothesized to exist in the choroid.²⁷

Unfortunately, our data are not adequate to make conclusions regarding tolerability and the effects of bimatoprost on ocular blood flow, because all of the patients enrolled in this study had normal hemorheologic values. For this reason, and because some patients may have vasculopathy and other systemic diseases, it may not be accurate to extrapolate our results to the general patient population. Our results suggest that bimatoprost may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years.¹⁵

CONCLUSIONS

In this population of patients with POAG, bimatoprost was associated with increased pOBF, and the reduction in pOBF associated with timolol was corrected after patients were switched to bimatoprost. Bimatoprost was associated with increased choroidal blood flow, beyond the levels recorded before timolol treatment. The decreased IOP level achieved in the timolol group seemed to be improved further by bimatoprost. Considering the potential efficacy of bimatoprost on IOP and pOBF, we suggest that this new drug may represent a clinical advance in the medical treatment of POAG.

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Address correspondence to: Michele Vetrugno, MD, Università degli Studi di Bari, Policlinico di Bari, p.zza G Cesare 11, Bari 70124, Italy. E-mail: m.vetrugno@oftalmo.uniba.it