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Marco Centofanti
Gianluca Manni
Daniela Gregori
Francesco Cocco
Daniele Lorenzano
Massimo G. Bucci

Comparative acute effects of brimonidine 0.2% versus dorzolamide 2% combined with beta-blockers in glaucoma

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M. Centofanti · G. Manni · D. Gregori
F. Cocco · D. Lorenzano · M.G. Bucci
Department of Ophthalmology,
University of Rome "Tor Vergata" and
G.B. Bietti Eye Foundation, Rome Italy

M. Centofanti
AFaR-CRCCS, Divisione Oculistica
Ospedale Fatebenefratelli, Isola Tiberina,
Rome, Italy

M. Centofanti (✉)
Via Bolzano,1, 000198 Rome, Italy
e-mail: mcentofanti@lycosmail.com
Tel.: +39-06-85301805
Fax: +39-06-3017436

Abstract *Purpose:* To assess the acute intraocular hypotensive efficacy of brimonidine tartrate 0.2% (a highly selective α_2-adrenergic agonist) compared with dorzolamide 2% (a topical carbonic anhydrase inhibitor) as adjunct therapy to topical β-blockers in patients with primary open-angle glaucoma. *Methods:* A randomized cross-over masked study was performed. We enrolled one eye of each of 28 patients who were on different β-blocker therapy. We measured the intraocular pressure (IOP) 2 h after the β-blocker instillation; we then randomly administered one of the two drugs and we compiled an IOP diurnal curve. One month later we repeated the same procedures with the second drug. Unpaired Mann-Whitney *U*-test was used to compare decreases in IOP between the two drugs ($P<0.05$). *Results:* Both brimonidine 0.2% and dorzolamide 2% have good ocular hypotensive efficacy, significantly lowering IOP when compared to β-blocker therapy alone, for the whole diurnal curve. Maximum mean percent IOP decrease from baseline was 22.0±15.7% (4.0± 2.9 mmHg) for dorzolamide 2% 6 h after instillation and 35.5±16.4% (7.0±4.1 mmHg) for brimonidine 0.2% 8 h after administration of the drug. When we compared the two treatments, brimonidine 0.2% showed a higher hypotensive effect than 2% dorzolamide after 4 h (28.4±16.8% vs 17.6 ±9.3%; $P=0.04$) and 8 h (35.5±16.4% vs 21.6 ±10.8%; $P=0.04$). *Conclusion:* This study indicates that 0.2% brimonidine acutely associated with β-blockers is an interesting new combination treatment useful in the management of glaucoma.

Introduction

Glaucoma, a serious worldwide public health problem causing blindness in 5.2 million people [10], is usually associated with elevated intraocular pressure (IOP); therefore, it is treated with drugs that lower IOP. Currently, β-blockers are the most common therapy, but almost half the patients on topical β-blockers require adjunctive therapy to achieve target IOP lowering, and many drugs may be added to β-blocker therapy [2, 4].

One of the drugs most frequently used in addition to β-blocker therapy, is dorzolamide. It is a well-known topical carbonic anhydrase inhibitor, generally considered to be an additive therapy rather than a first choice for glaucoma therapy, because its duration of action requires dosing three times daily and it is less effective than β-blockers [9].

Brimonidine tartrate is a highly selective α_2-adrenoceptor agonist, derived from clonidine, as aproclonidine, but less lipophilic than clonidine and more α_2-adrenergic receptor-selective than either clonodine or apraclonidine (28 times more selective than apraclonidine and 10 times more selective than clonidine) [3, 6]. Brimonidine is emerging as a potential first-line therapy for primary open-angle glaucoma, with a peak IOP-lowering efficacy comparable to that of timolol, but without the adverse

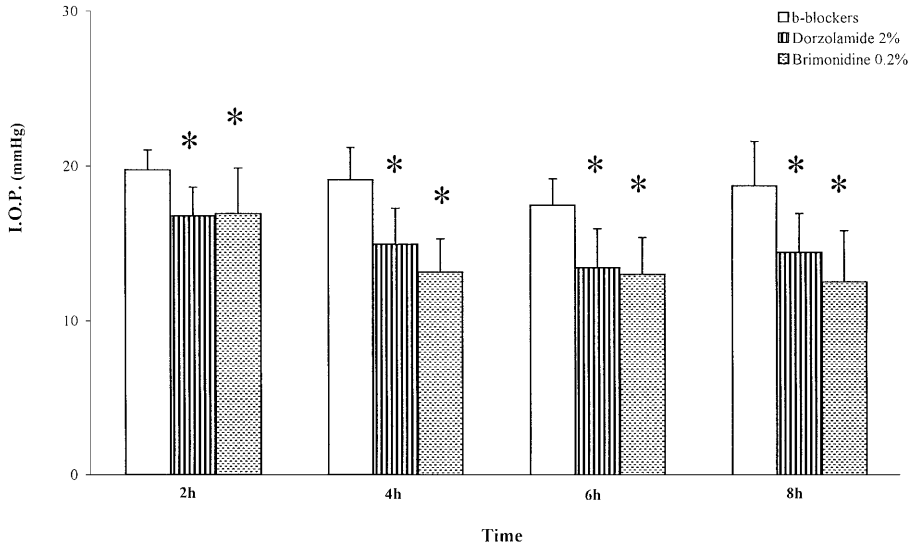

Fig. 1 Mean IOP during the diurnal curve with β-blocker therapy alone, with dorzolamide 2% and with brimonidine 0.2% (* statistically significant differences from baseline)

cardiopulmonary side effects of timolol [8]; its safety profile may also make it an excellent choice as an additive agent for patients whose IOP is not adequately managed with other therapy.

The aim of this study was to assess the acute intraocular hypotensive efficacy of 0.2% brimonidine tartrate compared to 2% dorzolamide as adjunctive therapy to topical β-blockers in patients with elevated IOP.

Materials and methods

A short-effect randomized cross-over masked comparison clinical study was performed. We enrolled 28 adult patients with advanced open-angle glaucoma diagnosis with a visual field Mean Defect ranged between –10 and –16 dB.They were receiving a non-selective β-blocker (timolol 0.50%) therapy for a minimum of 2 weeks, but they required adjunctive therapy due to worsening of the disease. Ophthalmic exclusion criteria included: any history of ocular diseases (chronic or recurrent inflammatory eye disease, ocular trauma, ocular infection, severe retinal disease, corneal abnormality preventing reliable applanation tonometry); intraocular surgery within the past 12 months or laser surgery within the past 3 months; history of hypersensitivity to any components of any of the medications used in the study; inability to discontinue contact lens wear during the study. The systemic exclusions included: severe unstable or uncontrolled systemic disease; pregnancy, lactation or childbearing potential; contraindication to α-adrenoreceptor agonist (such as depression, coronary insufficiency, Raynaud phenomenon), β-adrenoreceptor antagonist and carbonic anhydrase inhibitor therapy; chronic use of any systemic medication that may effect IOP.

We compiled a diurnal tonometric curve on each patient on β-blocker therapy (baseline). One week later (visit 1) we measured IOP 2 h after β-blocker instillation. Fifteen minutes later the patients were randomly assigned to receive, in masked fashion, one drop of either brimonidine 0.2% or dorzolamide 2% sterile ophthalmic solution instilled into each eye, and we performed tonometry at 2-h intervals. One month later (visit 2) we repeated the same measurements, this time administering 2% dorzolamide to those who had first received 0.2% brimonidine, and vice versa. Upon recruitment, each patient gave informed consent to the procedures. The research followed the tenets of the Declaration of Helsinki.

Results are presented as mean ± standard deviation. Unpaired Mann-Whitney *U*-test was used for the statistical analysis, considering $P<0.05\%$ statistically significant (Systat 5.2, Macintosh, Tolentino, USA).

Table 1 Mean IOP (mmHg, ±SD) during the diurnal curve in β-blocker therapy alone (*Baseline*), associated with dorzolamide 2% (*Group A*) and associated with brimonidine 0.2% (*Group B*)

Time	Baseline	Group A	p[a]	Group B	p[a]
2 h	19.75±1.28	16.79±1.85	0.002	16.93±2.95	0.01
4 h	19.12±2.10	15.0 ±2.29	0.0006	13.21±2.15	0.0002
6 h	17.5 ±1.69	13.5 ±2.5	0.002	13.07±2.37	0.0007
8 h	18.75±2.87	14.5 ±2.47	0.004	12.57±3.32	0.001

[a] Comparison with baseline

Results

There was no statistical significantly difference between the two eyes, so we arbitrarily enrolled the right eye (n=28) of 28 patients (17 men, 11 women) whose mean age was 65.14±15.7 years with a range of 45–87 years. Mean pretreatment IOP for all the group was 19.36±1.82 mmHg. Both brimonidine 0.2% and dorzolamide 2% have good ocular hypotensive efficacy, significantly lowering IOP compared to baseline for the whole diurnal curve.

Maximum mean percent IOP decrease from baseline was 22.15±15.7% (4.0±2.9 mmHg) for dorzolamide 2% 6 h after instillation and 35.5±16.4% (7.0±4.1 mmHg) for brimonidine 0.2% 8 h after administration of the drug. Minimum mean percent IOP decrease from baseline was 14.9±8.2% (3.0±1.4 mmHg) for dorzolamide 2% and 14.2±5.1% (2.9±1.1 mmHg) for brimonidine

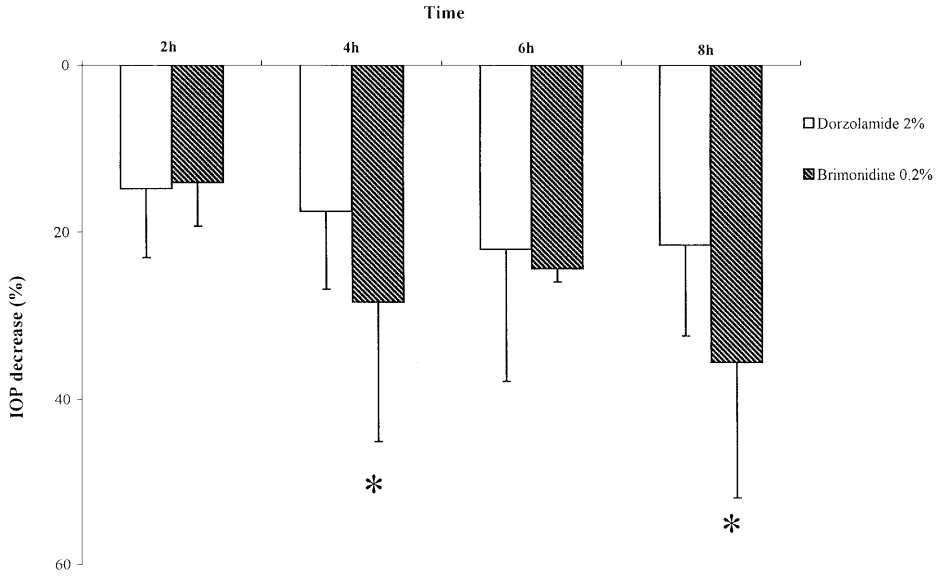

Fig. 2 Mean percent decrease in IOP from baseline during β-blocker therapy associated with dorzolamide 2% and with brimonidine 0.2% (* statistically significant difference between the two groups)

Table 2 Mean IOP decrease from baseline in β-blocker therapy associated with dorzolamide 2% (*Group A*) and with brimonidine 0.2% (*Group B*)

Time	Group A		Group B		*P*[a]
	mmHg	%	mmHg	%	
2 h	3.0±1.4	14.9±8.2	2.9±1.1	14.2±5.1	n.s.
4 h	3.5±1.9	17.6±9.3	5.6±3.3	28.4±16.8	0.04
6 h	4.0±2.9	22.1±15.7	4.4±3.1	24.4±1.6	n.s.
8 h	4.1±2.2	21.6±10.8	7.0±4.1	35.5±16.4	0.04

[a] Between-group comparison

0.2%, both 2 h after instillation. When we compared the two treatments we found that brimonidine 0.2% had a higher hypotensive effect than 2% dorzolamide after 4 h (28.4±16.8% vs 17.6±9.3%; *P*=0.04) and after 8 h (35.5±16.4% vs 21.6 ±10.8%; *P*=0.04).

Discussion

In this study both brimonidine 0.2% and dorzolamide 2% provided an equivalent significant additive IOP-lowering effect, but brimonidine 0.2% showed a higher hypotensive effect than dorzolamide 2% 4 and 8 h after instillation of the drugs. Previous studies indicated that carbonic anhydrase inhibitors are additive to other antiglaucoma therapies. They reduce IOP by decreasing aqueous humor production. Dorzolamide is the first carbonic anhydrase inhibitor to be marketed as a topical antiglaucoma agent; because the duration of action of dorzolamide requires dosing three times daily and it is a less effective IOP-lowering agent than non-selective β-blockers, dorzolamide is generally considered to be an additive therapy rather than a first choice for glaucoma [9]. Brimonidine tartrate 0.2% instilled twice daily offers long-term IOP control, appears to be generally well tolerated by patients and has a favorable ocular and systemic safety profile [8]. It has IOP-lowering characteristics similar to those of other α_2-agonists, acting by reducing aqueous humor production and increasing uveoscleral outflow [5]. Brimonidine has also been shown to facilitate rescue and attenuate degeneration of optic nerve fibres that escaped primary injury following a calibrated compressive injury to the adult rat optic nerve, suggesting a potential beneficial neuroprotective effect in the management of glaucoma beyond the lowering of IOP [1, 12]. Thus, at therapeutic doses, it does not readily cross the blood-brain barrier to cause side effects on the central nervous system, such as systemic hypotension, bradycardia or sedation, and the risk of α_1-adrenergic receptor-mediated ocular side effects such as mydriasis, vasocontriction and lid retraction is substantially reduced [2, 7]. Furthermore, brimonidine is oxidatively stable, which may account for its low reported rate of ocular allergy compared with other α_2-agonists [11].

Although a long-term study is required to confirm our observations, brimonidine has been proved to be an appropriate choice as an additive agent and an interesting new adjunct that could provide a welcome alternative to recently marketed combination treatments, useful in the management of glaucoma.

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