

## SCIENTIFIC REPORT

## Effects of the combination of bimatoprost and latanoprost on intraocular pressure in primary open angle glaucoma: a randomised clinical trial

L M Doi, L A S Melo Jr, J A Prata Jr

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**Aims:** To evaluate the effect of the combination of bimatoprost and latanoprost on intraocular pressure (IOP) in primary open angle glaucoma (POAG).

**Methods:** An open label randomised clinical trial was conducted, which included 18 glaucomatous patients (36 eyes). In the first 4 weeks, latanoprost 0.005% was prescribed for both eyes of the patients and any other antiglaucoma medication was discontinued. In the next 4 weeks (phase 1), bimatoprost 0.03% was combined with latanoprost in one randomly assigned eye (case eye) of each patient. In the next 4 weeks (phase 2), bimatoprost was discontinued in the case eyes, while bimatoprost was substituted for latanoprost in the fellow eye (control eye). The IOP was measured at the end of the first 4 weeks (baseline measurement) and weekly during phases 1 and 2.

**Results:** In the case eyes, the mean IOP increased along the first phase (1.8 mm Hg;  $p=0.006$ ) when compared to baseline measurements. The IOP returned to previous values after discontinuation of bimatoprost in phase 2. In the control eyes, the mean IOP did not change throughout the study.

**Conclusion:** The combination of bimatoprost and latanoprost in POAG increases the IOP and should not be considered as a therapeutic option.

Goldmann applanation tonometry, gonioscopy, funduscopy using a 78 dioptre lens, and automated static perimetry (Humphrey Sita 24–2, Carl Zeiss Meditec, Dublin, CA, USA) examinations were performed to select the patients.

Patients were eligible for the study if they met all of the following criteria in both eyes: (1) alterations of the optic nerve head (vertical cup to disc ratio of more than 0.5, notching, splinter haemorrhage, acquired pit) and visual field defects (defects of three or more contiguous points with a probability of less than 5% in a non-edge localisation at the pattern deviation plot) suggestive of glaucoma; (2) gonioscopy demonstrating a 360° normal appearing open angle; (3) IOP >21 mm Hg; and (4) no ocular or systemic findings that could justify an ocular hypertension.

Exclusion criteria included the presence of advanced glaucoma, IOP >30 mm Hg despite the use of antiglaucoma medications, previous intraocular surgery, patients younger than 18 years, pregnancy or lactation, inability to make return visits, and use of corticosteroids. The glaucoma was considered advanced if the patients presented an optic nerve head with vertical cup to disc ratio of more than 0.8, or visual field with defects threatening the central fixation or mean deviation (MD) <–12 dB.

### Intervention procedures

The patients were instructed to instil once daily latanoprost 0.005% (Xalatan, Pfizer) in both eyes in the evening (between 7 pm and 9 pm) for 4 weeks. Any other antiglaucoma medication was discontinued. At the end of this period, the IOP was measured and recorded as the baseline measurement (fig 1). Patients with baseline IOP measurements higher than 30 mm Hg in either eye were excluded from the study, others were entered into phase 1.

In phase 1, once daily bimatoprost 0.03% (Lumigan, Allergan), instilled in the morning (between 7 am and 9 am), was added to the prescription in one of the patient's eyes (case eyes). The patient's eye treated with a combination of bimatoprost and latanoprost was randomly assigned using a sealed envelope technique. During this 4 week phase, the patients had their IOP measured in both case and control eyes weekly. The patients would be excluded from the study if the IOP increased more than 12 mm Hg from the baseline measurement or any severe ocular complication was detected.

In phase 2, bimatoprost was discontinued from the case eyes. In the control eyes, once daily bimatoprost 0.03% in the evening (between 7 pm and 9 pm) was substituted for latanoprost. During this 4 week phase, the patients also had their IOP measured weekly.

The combination of bimatoprost and latanoprost could produce an additive intraocular pressure (IOP) lowering effect, considering the mechanisms of action of these medications. Most of their effect is on uveoscleral outflow,<sup>1–6</sup> where they act, probably, on different receptors.<sup>1–6</sup> However, one medication could also interfere with the IOP lowering effect of the other, leading to an increase in IOP, as it was observed in a case series of three glaucomatous patients.<sup>7</sup>

We are unaware of a published comparative clinical trial evaluating the combination of these medications and could find no reference to it in a Medline based search. Therefore, this clinical trial was conducted to evaluate the effect of the combination of bimatoprost and latanoprost on IOP in primary open angle glaucoma (POAG).

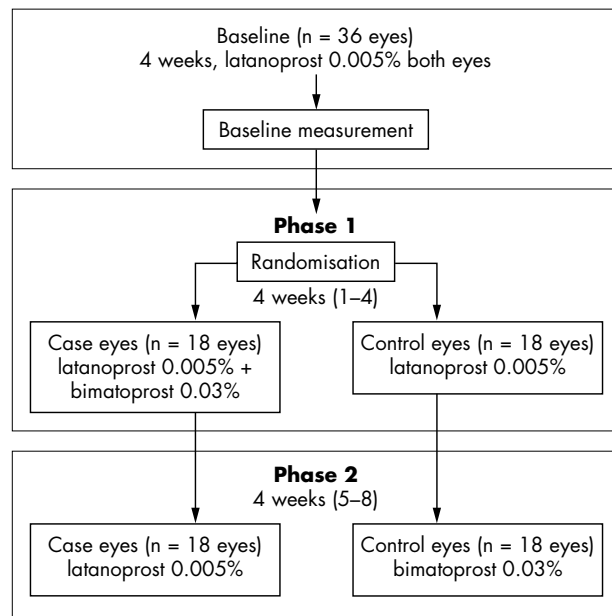
### PATIENTS AND METHODS

A 12 week open label randomised clinical trial was performed. The protocol was approved by the ethics committee of the Federal University of São Paulo and was in compliance with the Declaration of Helsinki. All patients gave their informed consent.

### Study population

This study enrolled patients with POAG who were treated at the Federal University of São Paulo. Slit lamp biomicroscopy,

**Abbreviations:** IOP, intraocular pressure; MD, mean deviation; POAG, primary open angle glaucoma

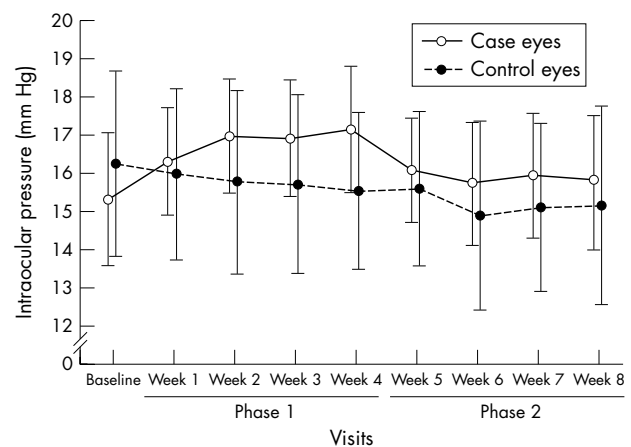


**Figure 1** Flow chart of the study.

Throughout the study, IOP measurements were performed between 10 am and 12 pm using a Goldmann applanation tonometer. The examiner was masked for the groups before measuring the IOP. In all visits, the patients were asked about the medication regimen to ensure that the prescription had been followed correctly.

### Statistical analysis

Repeated measures analysis of variance (ANOVA) was performed for the analysis of IOP data. In cases of missing IOP values, the mean IOP value of the two adjacent visits was used. To determine whether the IOP changes were different between the two groups throughout phase 1, an analysis of the interaction between visits and groups was performed.<sup>8</sup> The Dunnett test was used for post hoc multiple comparisons in the case group and the baseline IOP measurement was used as the reference value. With 18 eyes for each group and five visits (baseline—week 4), this design achieved 90% power to detect actual effect standard deviation of 0.45 mm Hg (an effect size of 1.14) within each group. The significance level was set at 0.05.



**Figure 2** Intraocular pressure (IOP) at baseline, first, and second phases. In each bar, the central mark represents the mean and the vertical bar represents 95% confidence interval.

### RESULTS

All of the 18 patients included completed the study. Five patients missed visits (two patients at week 2 and three patients at week 3). Five patients were male and 13 were female, and the mean (SD) age was 63.5 (9.7) years. Fourteen patients were white and four were black. Eleven right and seven left eyes were randomised to receive the addition of bimatoprost and latanoprost. None of the participants was using latanoprost and two patients (four eyes) were using bimatoprost at the time of enrolment.

The IOP of case and control eyes from baseline to week 8 are summarised in table 1. The interaction between group and visits (from baseline to week 4) was statistically significant ( $p = 0.009$ ; fig 2).

In the case eyes, the IOP changed from baseline to week 8 ( $p = 0.005$ ). The IOP increased from baseline to week 4 ( $p = 0.013$ ). The data from weeks 2, 3, and 4 showed statistically significant higher IOP measurements than baseline (table 1). The mean (95% confidence interval) increases in IOP from baseline to weeks 2, 3, and 4 were 1.7 mm Hg (0.2 to 3.1), 1.6 mm Hg (0.2 to 3.0) and 1.8 mm Hg (0.4 to 3.3), respectively. After phase 1, the IOP decreased to values close to the baseline measurements (fig 2). Conversely, in the control eyes, the mean IOP did not change either from baseline to week 4 ( $p = 0.669$ ), or from week 4 to week 8 ( $p = 0.459$ ). Although mild conjunctival hyperaemia was

**Table 1** Intraocular pressure (IOP) throughout the study according to group and visit

Visits	IOP (mm Hg)		p Value*	IOP (mm Hg)	
	Case eyes			Control eyes	
	Mean (SD)			Mean (SD)	
Baseline	15.3 (3.5)			16.3 (4.9)	
<b>Phase 1</b>					
Week 1	16.3 (2.9)	0.304		16.0 (4.5)	
Week 2	17.0 (3.0)	0.015		15.8 (4.9)	
Week 3	16.9 (3.1)	0.021		15.7 (4.7)	
Week 4	17.2 (3.3)	0.006		15.6 (4.1)	
<b>Phase 2</b>					
Week 5	16.1 (2.8)	0.578		15.6 (4.1)	
Week 6	15.7 (3.2)	0.978		14.9 (5.0)	
Week 7	15.9 (3.3)	0.803		15.1 (4.4)	
Week 8	15.8 (3.5)	0.954		15.2 (5.2)	

\*Dunnett test, baseline measurement used as reference.

noted in a few eyes, no patients discontinued the study because of any adverse effects of the medications.

## DISCUSSION

In this study, IOP increased in eyes treated with the combination of latanoprost and bimatoprost. Herndon *et al*<sup>7</sup> described increases in IOP of 23, 15, and 23 mm Hg in a case series of three patients using latanoprost in combination with bimatoprost; 11 mm Hg was the maximum IOP increase in our study. Differences in the type and stage of glaucoma could be related to this discrepancy. In the paper by Herndon *et al*<sup>7</sup> one patient had pigmentary glaucoma and another one had angle closure glaucoma. In our series, all patients had POAG. Since we did not include patients with advanced glaucoma, we could not determine whether IOP changes in advanced glaucoma are different from early or moderate stages of this disease.

The reason for the IOP increase with the adjunctive use of both medications could not be clarified in our study. Although bimatoprost and latanoprost could act by different receptors,<sup>1,6</sup> they share similar characteristics regarding alterations in IOP according to doses and regimens of administration. Latanoprost and bimatoprost produce a greater IOP reduction with single than multiple daily doses.<sup>9-11</sup> Proposed hypotheses for this effect are reduction of the uveoscleral outflow, increase in episcleral venous pressure of short duration, development of subsensitivity at the FP receptor or intracellular pathways, compromise in the classic pathway, and it was also speculated that a twice daily regimen presents a dose beyond the dose-response curve, resulting in a consequently lower effect.<sup>9-15</sup>

The fact that the free acid of bimatoprost is a potent FP receptor agonist<sup>16</sup> and enzymes in mammalian ocular tissues may hydrolyse bimatoprost to its free acid<sup>17</sup> could account for the increase in IOP observed with the adjunctive use of bimatoprost and latanoprost. These facts argue favourably that a common receptor for both drugs may be involved. Thus, the concurrent use of both drugs could increase the IOP by mechanisms that are proposed and result in the reduced IOP lowering effect when multiple doses of latanoprost<sup>9, 10, 11, 13</sup> or bimatoprost<sup>13, 14</sup> are administered.

When the medications were administered together, latanoprost was used in the evening and bimatoprost in the morning. Different results might be seen if the two medications were administered a few minutes apart in the evening. Lindén and Alm<sup>11</sup> observed that the administration of three drops of latanoprost with a 5 minute interval did not alter significantly the IOP lowering effect of this medication. Conversely, twice daily (12 hour interval) doses decreased the effect of the latanoprost in that study.<sup>11</sup>

In the control eyes, the change of the drugs used in phase 2 could lead to an IOP increase, as the washout period for latanoprost can extend up to 8 weeks.<sup>18</sup> However, this increase in IOP was not observed. Probably, the residual effect of the latanoprost was not sufficient to interfere with the mechanism of bimatoprost action.

In conclusion, the combination of bimatoprost and latanoprost should not be considered as a therapeutic option in POAG because of the paradoxical increase in IOP.

## Authors' affiliations

L M Doi, L A S Melo Jr, J A Prata Jr, Department of Ophthalmology, Federal University of São Paulo, São Paulo, Brazil  
J A Prata Jr, Faculdade de Medicina do Triângulo Mineiro, Uberaba, Brazil

Competing interests: The authors have no financial interests in any drug mentioned in this study.

Ethics approval: The protocol was approved by the ethics committee of the Federal University of São Paulo.

Correspondence to: Luiz Alberto S Melo Jr, R Leandro Dupret 488/161, São Paulo, Brazil 04025-012; [luizalberto@oftalmo.epm.br](mailto:luizalberto@oftalmo.epm.br)

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