

# Comparison of timolol 0.5% + brimonidine 0.2% + dorzolamide 2% versus timolol 0.5% + brimonidine 0.2% in a Mexican population with primary open-angle glaucoma or ocular hypertension

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**Background:** The purpose of this study was to evaluate the efficacy and safety of two fixed combinations, ie, timolol 0.5% + brimonidine 0.2% + dorzolamide 2% (TBD) versus timolol 0.5% + brimonidine 0.2% (TB) in patients with primary open-angle glaucoma or ocular hypertension.

**Methods:** We performed a 3-month, randomized, double-blind study in patients with primary open-angle glaucoma or ocular hypertension and an intraocular pressure of 21–30 mmHg. Patients were randomly assigned to receive one drop of TBD or TB twice a day. The primary efficacy endpoint was change in intraocular pressure after 3 months of treatment. Safety measures were assessed by the presence of adverse events.

**Results:** Mean baseline intraocular pressure was similar at 8 am and 4 pm in the treatment groups (TBD  $22.3 \pm 0.9$  mmHg, TB  $22.4 \pm 1.8$  mmHg,  $P = 0.558$ ; TBD  $19.02 \pm 1.3$ , TB  $19.08 \pm 1.2$ ,  $P = 0.536$ , respectively). At the end of the study, the mean intraocular pressure was significantly lower in the TBD group at both 8 am ( $16.19 \pm 2.0$  mmHg versus  $18.35 \pm 1.4$  mmHg,  $P = 0.000$ ) and 4 pm ( $14.74 \pm 2.4$  mmHg versus  $16.77 \pm 1.4$  mmHg,  $P = 0.000$ ).

**Conclusion:** Fixed-combination TBD was more effective than fixed-combination TB for reducing IOP in patients with primary open-angle glaucoma.

**Keywords:** primary open-angle glaucoma, ocular hypertension, intraocular pressure, fixed combination

## Introduction

Glaucoma is a common and potentially blinding ocular disease of multifactorial etiology. It is characterized by progressive acquired loss of retinal ganglion cells and their axons, leading to optic nerve atrophy and appearance of characteristic cupping of the optic disc associated with corresponding visual deficit. It is frequently associated with elevated intraocular pressure (IOP). This damage can lead to permanent vision loss if it is not treated.<sup>1,2</sup>

Population studies indicate that one in 40 adults older than 40 years has glaucoma, with loss of visual function. The disease affects approximately 60 million people worldwide, with 8.4 million being bilaterally blind. Even in developed countries, half of glaucoma cases are undiagnosed. Glaucoma is mostly asymptomatic until late in the disease when visual problems arise.<sup>3</sup>

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Elevated IOP is an important and modifiable risk factor for the development and progression of glaucoma.<sup>1</sup> It has been demonstrated that lowering IOP effectively delays development of glaucoma in patients with ocular hypertension, as well as progression of established glaucoma.<sup>4</sup> Topical hypotensive medication is considered as first-line treatment in the initial management of increased IOP. Nevertheless, target IOP levels are not always achieved with a single medication, and patients frequently require multiple medications, which can lead to unsatisfactory adherence with treatment.<sup>3,5-7</sup> According to the Ocular Hypertension Treatment Study, after 5 years of IOP-lowering treatment, 40% of patients need at least two drugs.<sup>8</sup>

Fixed combinations for glaucoma and ocular hypertension treatment are increasing. These fixed combinations contain two medications in a single bottle, and offers several advantages, including enhanced convenience, improved adherence, and reduced exposure to preservatives.<sup>6</sup>

The efficacy and safety of fixed combinations has been evaluated previously in different studies.<sup>7</sup> The purpose of this study was to compare the efficacy and safety of fixed combinations of timolol 0.5% + brimonidine 0.2% + dorzolamide 2% (TBD) versus timolol 0.5% + brimonidine 0.2% (TB) for IOP reduction.

## Materials and methods

We conducted a prospective 3-month, randomized, double-blind, multicenter clinical trial to compare the efficacy and safety of TBD versus TB on IOP reduction. The protocol was reviewed and approved by our ethics committee, and was conducted in compliance with the Declaration of Helsinki and in accordance with Good Clinical Practice standards. All patients who participated in the study provided their written informed consent. The study is registered on the International Standard Randomized Controlled Trial Number Register (ISRCTN48477221).

Adult patients with primary open-angle glaucoma, ocular hypertension, pseudoexfoliative glaucoma, or pigmentary glaucoma, and a mean IOP of 21–30 mmHg were enrolled. Primary exclusion criteria included blindness in one eye, visual field loss indicative of end-stage glaucoma, normal-tension glaucoma, optic nerve cupping  $\geq 0.8$ , any active ocular disease other than glaucoma or ocular hypertension that would interfere with study interpretation, history of cataract surgery within 3 months prior to baseline, contraindication of any medication used in the protocol, and pregnancy, risk of pregnancy, or breastfeeding.

The primary efficacy endpoint was the IOP-lowering effect after 3 months of treatment. Patients were assessed for eligibility at a screening visit 6 weeks before baseline when a medical and ocular history was taken, IOP was measured in both eyes (using a calibrated Goldmann applanation tonometer), as well as Snellen visual acuity measurement and visual field test using automated perimetry (Humphrey's 24-2 Sita Standard). Abnormal findings on slit-lamp examination (biomicroscopy) and fluorescein dye were graded as mild, moderate, or severe. Safety outcome measures included adverse events and ocular signs.

All IOP-lowering medications were suspended in eligible patients, who underwent a 6-week washout period prior to baseline and, if their IOPs were considered detrimental, they were excluded from the study. Patients were evaluated at five study visits, ie, at baseline, and at 15, 30, 60, and 90 days after enrollment. At each study visit, IOP was measured in each eye at 8 am and 4 pm, slit-lamp examination using biomicroscopy and Snellen visual acuity measurement tests were performed, and use of concomitant medications were recorded.

Patients were randomly assigned 1:1 to receive TBD or TB. To maintain masking, bottles of the study drugs were overlabeled so that they had an identical appearance when provided to patients. Patients were instructed to instill one drop of either TBD (KrytanteK Ofteno<sup>®</sup>; Laboratorios Sophia, Guadalajara, Mexico) or TB (Combigan D<sup>®</sup>; Allergan Inc, Irvine, CA) in each eye twice a day, ie, in the morning at 8 am ( $\pm 15$  minutes) and in the evening at 8 pm ( $\pm 15$  minutes) for 3 months. The trial medication was discontinued if either the investigator or patient thought that it was not in the patient's best interests to continue, or if the patient became pregnant.

Ocular findings and adverse events regardless of relationship to treatment were monitored throughout. Investigators recorded observed adverse events, as well as those reported by patients or elicited by questioning. Adverse events were classified as mild, moderate, or severe. Only randomized patients who concluded the study without major protocol violation and provided IOP measurements at all visits were included in the per-protocol analysis.

## Statistical analysis

Baseline and final differences in IOP between the treatment groups were analyzed using the Mann–Whitney test. Before study initiation, it was determined that at least 42 patients were needed per group to detect a difference of at least

2 mmHg in mean IOP reduction between treatments using a significance level of 0.05, with a power of 0.80.

## Results

Fifty-six patients per group were recruited for this study from 11 centers in Mexico. A total of 106 patients were included in the per-protocol analysis. None of the patients presented with pseudoexfoliative or pigmentary glaucoma. The mean age was  $62.5 \pm 10.2$  years in the TBD group and  $60.6 \pm 12.7$  years in the TB group. Demographic characteristics are shown in Table 1.

The primary efficacy endpoint was the IOP-lowering effect at both 8 am and 4 pm after 3 months of treatment. The mean baseline IOP was similar between the groups at 8 am (TBD  $22.3 \pm 0.9$  mmHg, TB  $22.4 \pm 1.8$  mmHg,  $P = 0.558$ ) and at 4 pm (TBD  $19.02 \pm 1.3$  mmHg, TB  $19.08 \pm 1.2$  mmHg,  $P = 0.536$ , Table 2). After baseline, and at all study visits, the mean 8 am IOP at 15, 30, and 60 days after enrolment was significantly lower in the TBD group (Figure 1). The same pattern was observed when IOP was assessed at 4 pm (Figure 2). Furthermore, at the conclusion of the study, the mean IOP was significantly lower in the TBD group at 8 am ( $16.19 \pm 2.0$  mmHg versus  $18.35 \pm 1.4$  mmHg,  $P = 0.000$ ) and at 4 pm ( $14.74 \pm 2.4$  mmHg versus  $16.77 \pm 1.4$  mmHg,  $P = 0.000$ , Table 3).

Adverse events were documented in eight patients, of whom six were excluded from the study. These events included ocular burning (mild in one patient and moderate in another), itching (severe in one patient), foreign body sensation (mild in one patient), redness (severe in one patient), dizziness (severe in one patient), headache (mild in one patient), and bradycardia (mild in one patient), the latter not being related to the study drug. These data are summarized in Table 4.

## Discussion

The aim of treating glaucoma and ocular hypertension is to reduce IOP.<sup>5</sup> Elevated IOP is an important risk factor for progression of glaucoma, so achieving and maintaining a

**Table 1** Demographic features of study groups

n		Female n (%)	Male n (%)	Age*
TBD	56	42 (76)	14 (24)	$62.5 \pm 10.2$
TB	56	56 44 (80)	12 (20)	$60.6 \pm 12.7$

**Note:** \*Data is presented in mean  $\pm$  standard deviation.

**Abbreviations:** TBD, timolol-brimonidine-dorzolamide; TB, timololbrimonidine.

**Table 2** Difference in IOP between groups at 8 am

	TBD (n = 108)	TB (n = 104)	P
Baseline	$22.3 \pm 0.9$	$22.4 \pm 1.8$	0.558
Day 15	$18.0 \pm 2.0$	$19.5 \pm 3.4$	0.000
Day 30	$16.4 \pm 1.5$	$18.4 \pm 1.3$	0.000
Day 60	$16.3 \pm 2.5$	$18.3 \pm 2.0$	0.000
Day 90	$16.2 \pm 2.0$	$18.4 \pm 1.4$	0.000

**Note:** Data is presented in mean  $\pm$  standard deviation.

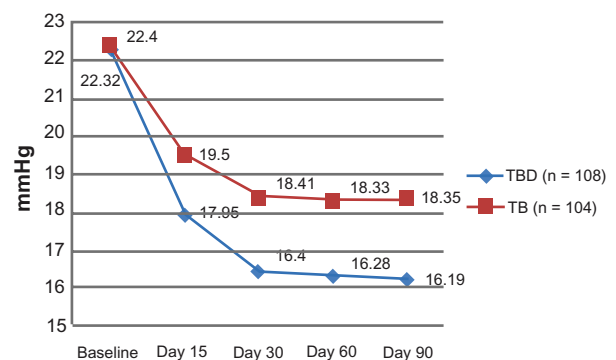
**Abbreviations:** IOP, Intra Ocular Pressure; TBD, timolol-brimonidine-dorzolamide; TB, timololbrimonidine.

low IOP minimizes the risk of glaucomatous progression and vision loss.<sup>9,10</sup>

Different classes of drugs are available for IOP reduction, the most commonly used being the prostaglandin analogs, beta-blockers, alpha agonists, and carbonic anhydrase inhibitors. Single medication is sometimes insufficient to reduce IOP, and patients may require different combinations to achieve their target IOP.<sup>6,10</sup>

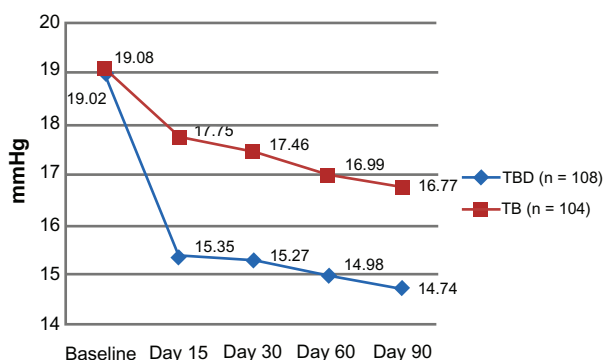
Fixed combinations, ie, two drugs contained in a single bottle, have emerged as a treatment option, offering several advantages and fewer adverse events.<sup>6</sup> A number of studies have evaluated the efficacy and safety of these combinations, and it has been demonstrated that combinations are superior to monotherapy with their constituent parts.<sup>1,4-7,10,11</sup>

García-Sánchez et al<sup>5</sup> compared administration of a fixed combination of latanoprost + timolol with an unfixed combination of brimonidine and timolol in patients with elevated IOP for 6 months. They observed that the fixed combination reduced IOP more effectively at all assessment times and was better tolerated than the unfixed combination. In our study, we compared a triple fixed combination of TBD and a double fixed combination of TB. Although our study is different because we used fixed combinations and did not



**Figure 1** Mean change from baseline IOP at each visit between groups at 8 am.

**Abbreviations:** IOP, Intra Ocular Pressure; TBD, timolol-brimonidine-dorzolamide; TB, timolol-brimonidine.



**Figure 2** Mean change from baseline IOP at each visit between treatment groups at 4 pm.

**Abbreviations:** IOP, Intra Ocular Pressure; TBD, timolol-brimonidine-dorzolamide; TB, timolol-brimonidine.

use a prostaglandin analog, we can compare our results for IOP reduction taking into account the use of fixed combinations, and we observed that the TBD combination was more effective than TB.

In a previous study, Baiza-Durán et al<sup>12</sup> compared two fixed combinations, ie, timolol + dorzolamide + brimonidine versus timolol + dorzolamide. The conclusion of their study was that the triple combination appeared to be safer and more effective for reducing IOP than the double fixed combination. Similarly, our investigation demonstrated that the TBD combination was more effective than TB in reducing IOP in the population studied.

Finally, a study by Fechtner et al<sup>7</sup> compared triple therapy (a fixed combination of brimonidine-timolol plus latanoprost) with double therapy (timolol plus latanoprost); in this study, patients were on latanoprost treatment and required additional IOP-lowering. Adjunctive therapy comprised a fixed combination of brimonidine + timolol or timolol only plus latanoprost; thus, a triple combination was used. This study concluded that triple therapy (fixed combination of brimonidine + timolol plus latanoprost) reduced IOP significantly more effectively than double therapy (timolol plus latanoprost). Our study results are similar in that we

**Table 3** Difference in IOP between groups at 4 pm

	TBD (n = 108)	TB (n = 104)	P
Baseline	19.0 ± 1.3	19.1 ± 1.2	0.536
Day 15	15.4 ± 1.2	17.8 ± 0.9	0.000
Day 30	15.3 ± 1.3	17.5 ± 1.7	0.000
Day 60	15.0 ± 2.3	17.0 ± 2.6	0.000
Day 90	14.7 ± 2.4	16.8 ± 1.4	0.000

**Note:** Data is presented in mean ± standard deviation.

**Abbreviations:** IOP, Intra Ocular Pressure; TBD, timolol-brimonidine-dorzolamide; TB, timololbrimonidine.

**Table 4** Adverse events presented in study groups

	TBD (n = 56)	TB (n = 56)
Ocular burning	1 <sup>b</sup>	1 <sup>a</sup>
Itching	1 <sup>c</sup>	
Foreign body sensation	1 <sup>a</sup>	
Redness		1 <sup>c</sup>
Dizziness		1 <sup>c</sup>
Cephalaea		1 <sup>a</sup>
Bradycardia		1 <sup>a</sup>

**Note:** Classified as: <sup>a</sup>Mild; <sup>b</sup>moderate; <sup>c</sup>severe.

**Abbreviations:** TBD, timolol-brimonidine-dorzolamide; TB, timolol-brimonidine.

also demonstrated that a triple combination is more effective than a double combination when reducing IOP. In the study by Fechtner et al<sup>7</sup>, triple therapy was used, but was not a fixed combination and involved two different bottles of medication.

The ultimate goal of treating glaucoma is to preserve the remaining visual field. Only treatment to reduce IOP has shown evidence of being effective in preserving the visual field. Monotherapy remains the preferred initial choice of treatment in glaucoma, using prostaglandin analogs and  $\beta$ -blockers as initial treatment for lowering IOP. Prostaglandin analog eye drops are preferred due to their strong IOP-reducing action and the convenience of requiring only once-daily administration, except in the event of side effects, intolerance, or patient refusal. Nevertheless, target IOP levels are not always achieved with a single medication, and patients frequently require multiple medications, which can lead to unsatisfactory adherence with treatment.<sup>3,5–7,13</sup> Adherence with treatment for glaucoma is better when regimens are simple rather than complex.<sup>14</sup> Use of two or more bottles of IOP-lowering medication may be associated with an increase in noncompliance, and the advantage of fixed combinations is that a single bottle can contain up to three medications, thus minimizing the number of bottles and drops that need to be used by the patients, and facilitating adherence to treatment. Fixed combinations are important adjuncts for the treatment of glaucoma but should generally be used only when monotherapy has not provided adequate IOP reduction. TBD is a good treatment option when a combination is required. One possible disadvantage is that TBD must be administered twice a day as opposed to prostaglandins, which only need to be administered once a day. Another possible disadvantage is that the incidence of treatment-related adverse events could be higher on TBD than on any other combination. Another drawback could be that it is not possible to change the drug concentration or dosing schedule for one component medication independently of the other when using a fixed

combination like TBD. Further studies will be needed to determine the long-term safety and efficacy of a fixed combination of TBD, as well as its effectiveness in providing additional IOP-lowering over 24 hours.

## Conclusion

New trends in glaucoma treatment suggest more aggressive strategies are needed for IOP reduction. This can be achieved using different drugs with different pharmacodynamics. Using this fixed combination, low doses of different drugs can be administered, and in this way, the onset of adverse effects could be delayed or diminished. The use of fixed combinations is preferred over separate use of their components to improve adherence and persistence with treatment. A fixed combination of TBD administered twice a day is more effective than a fixed combination of TB twice a day for reducing IOP.

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## Disclosure

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