

Comparative Evaluation of the Efficacy of the Bimatoprost 0.03%, Brimonidine 0.2%, Brinzolamide 1%, Dorzolamide 2%, and Travoprost 0.004%/Timolol 0.5%-Fixed Combinations in Patients Affected by Open-Angle Glaucoma*

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ABSTRACT

Purpose: This is a retrospective, comparative, head-to-head, not commissioned study about the efficacy of bimatoprost 0.03%, brimonidine 0.2%, brinzolamide 1%, dorzolamide 2%, and travoprost 0.004%/timolol 0.5%-fixed combinations in patients affected by naïve open-angle glaucoma and IOP > 25 mmHg. **Patients and Methods:** Files from 70 patients (35 M, 35 F, mean age 69.52 y, S.D. 11.56, range: 37 - 87 y) in our Glaucoma Service were retrospectively analyzed as long as 12 months. Every subgroup, including 14 age- and sex-matched patients, was allocated to 1 of the 5 groups of the fixed combinations monotherapy. Data recorded after 3 months follow-up were statistically analyzed by descriptive and ANOVA statistics as percentage of IOP reduction from baseline. **Results:** All the fixed combinations were effective in lowering IOP. The mean percentage reduction was: brimonidine/timolol 43.57%, dorzolamide/timolol 37.67%, bimatoprost/timolol 35.60%, travoprost/timolol 33.25% and brinzolamide/timolol 23.0%. The brimonidine/timolol fixed combination showed to be statistically significant more effective only than brinzolamide/timolol fixed combination ($p = 0.001$). Setting the α error to 5%, the power of the study is 26%, ϕ : 0.842. **Discussion:** In all this cohort of patients the target IOP was successfully achieved. All the fixed combinations used in this study had a very good profile of efficacy. Brimonidine, dorzolamide, bimatoprost and travoprost/timolol fixed combinations statistically significantly reduced the percentage of IOP from baseline ($p = 0.001$) more than brinzolamide/timolol fixed combination.

Keywords: Bimatoprost 0.03%; Brimonidine 0.2%; Brinzolamide 1%; Dorzolamide 2%, Travoprost 0.004%/Timolol 0.5% Fixed Combinations; Efficacy; IOP

1. Introduction

Glaucoma is a progressive, and potentially blinding, optic neuropathy. The aetiology of glaucoma is multifactorial, but, to date, reduction of intraocular pressure (IOP) is the only evidence-based therapy for glaucoma. IOP reduction is achieved by the use of topical medications [1].

Fixed combinations of IOP-lowering medications have been developed by combining different pharmacologic classes of ocular hypotensive drugs commonly prescribed for the treatment of elevated IOP in patients affected by open-angle glaucoma or ocular hypertension. Modern fixed combinations pair beta-adrenoceptor an-

tagonists (beta-blocker) with either prostaglandin analogs or carbonic anhydrase inhibitors. Potential benefits of fixed combinations include better compliance, reduction in exposure to preservatives, and elimination of the wash-out effect.

The first fixed combination was produced by Merck Sharp & Dohme Inc. (White-House Station, NJ, USA): 2% dorzolamide-0.5% timolol (DTFC, Cosopt[®]). A new fixed combination of the carbonic anhydrase inhibitor brinzolamide 1% and timolol 0.5% (BRINTFC, Azarga[®]) has been developed after 0.004% travoprost-0.5% timolol (TRAVOTFC, Duotrav[®]) (Alcon Research, Ltd., Ft. Worth, Texas, USA). Other fixed combinations produced and commercialized by Allergan are 0.2% brimonidine-0.5% timolol (BRIMOTFC, Combigan[®]) and 0.03% bimatoprost-0.5% timolol (BIMATOFc, Ganfort[®]).

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Different studies stress the efficacy and safety of BRIMOTFC versus the unfixed components or another fixed combination [2-9]. Other papers underline the efficacy and safety of DTFC, even three times a day [10-18]. BRINTFC was recently compared to DTFC. Mostly 1% brinzolamide-0.5% timolol ophthalmic suspension is associated with a statistically significantly less ocular discomfort profile than 2% dorzolamide-0.5% timolol ophthalmic solution [19-22]. BIMATOFc was compared to 0.03% bimatoprost [23]. The fixed combination provided an additional statistically significant reduction in IOP [24,25]. TRAVOTFC and BIMATOFc were compared to 0.005% latanoprost-0.5% timolol [26-29]. TRAVOTFC offers the potential benefits of increased patient adherence, reduced exposure to preservatives (now BAK-free), and reduced cost [30-38]. The aim of this study is to compare the efficacy of these fixed combinations.

2. Patients and Methods

This is a retrospective, comparative, head-to-head, not commissioned study on Caucasian outpatients, affected by naïve open-angle glaucoma, who were assessed in our Glaucoma Service in the last 12 months from 01-01-2011 till 12-31-2011. Inclusion criteria were: diagnosis of open-angle glaucoma based on the European Glaucoma Society Guidelines criteria [39] with IOP > 25 mmHg, medical therapy by only one fixed combination previously cited in the worst eye. Exclusion criteria included: contraindications to β -blockers; closed or barely open anterior chamber angles; ocular surgery or argon laser trabeculoplasty; ocular inflammation or infection; neovascular patients; hypersensitivity to benzalkonium chloride (BAK) or to any other fixed combination or any other component of the solutions; any history of refractive surgery, pregnancy, breastfeeding, or childbearing potential without adequate contraception. All patients included in their files: uncorrected and corrected visual acuity, baseline IOP > 25 mmHg measured by Goldmann applanation tonometry, adjusted by pachymetry, diurnal tonometric curve, fundus oculi, 30-2 Sita standard Humphrey visual field analyzer including visual field index, HRT and OCT. Main outcome of this paper is to measure the percentage of IOP reduction at 10 am \pm 1 hour due to each fixed combination after three months from baseline. All data were analyzed by descriptive and ANOVA statistical analysis.

3. Results

A total of 70 files from patients in the Glaucoma Service (35 M, 35 F, mean age 69.52 years, S.D. 11.56, range: 37 - 87 years) (**Table 1**) matched the inclusion criteria and were analyzed. These glaucoma patients were originally

naïve with IOP > 25 mmHg. We enrolled 14 patients who were treated with one of the following fixed combinations: bimatoprost 0.03% plus timolol 0.5% (Group A), brimonidine 0.2% plus timolol 0.5% (Group B), brinzolamide 1% plus timolol 0.5% (Group C), dorzolamide 2% plus timolol 0.5% (Group D), and travoprost 0.004% plus timolol 0.5% (Group E) (**Table 2**). In all patients, after three months follow-up, IOP was lower than 18 mmHg and no patient discontinued the therapy or needed laser- or surgical therapy. **Table 3** shows the mean percentage of IOP reduction from baseline due to any fixed combination used: Group B (brimonidine 0.2% plus timolol 0.5%, BRIMOTFC) 43.57%, Group D (DTFC) 37.67%, Group A (bimatoprost 0.03% plus timolol 0.5%, BIMATOFc) 35.60%, Group E (travoprost 0.004% plus timolol 0.5% (TRAVOTFC) 33.25%, and Group C (brinzolamide 1% plus timolol 0.5%, BRINTFC) 23.0%. The ANOVA test was not statistically significant between Group B and D (BRIMOTFC and DTFC) ($p = 0.053$), Group B and A (BRIMOTFC and BIMATOFc) ($p = 0.221$), Group B and E (BRIMOTFC and TRAVOTFC) ($p = 0.167$) but statistically significant between Group B and C (BRIMOTFC and BRINTFC) ($p = 0.001$) (**Table 4**). Setting the α error to 5%, the power of this study is 26%, phi: 0.842.

4. Discussion

This is the first paper in the Literature to compare these fixed combinations all together. All the data were age- and sex-matched, so there is no gender difference in the efficacy of drug combination. The results of this retrospective study clearly show the great efficacy of the fixed combinations used, mostly brimonidine 0.2%-timolol

Table 1. Demographics.

PATIENTS	MALE	FEMALE	MEAN AGE	S.D.	RANGE
70	35	35	69.52 y	11.56	37 - 87 y

Table 2. Fixed combinations (Number of patients).

GROUP	COMBINATION	NUMBER OF PATIENTS
GROUP A	BIMATOPROST 0.03%-TFC	14
GROUP B	BRIMONIDINE 0.2%-TFC	14
GROUP C	BRINZOLAMIDE 1%-TFC	14
GROUP D	DTFC	14
GROUP E	TRAVOPROST 0.004%-TFC	14
TOTAL		70

Legenda: DTFC: dorzolamide 2% timolol 0.5% fixed combination; TFC: timolol 0.5% fixed combination.

Table 3. Results (% of IOP reduction).

BRIMONIDINE 0.2%-TFC (GROUP B)	43.57
DORZOLAMIDE 2%-TFC (GROUP D)	37.67
BIMATOPROST 0.03%-TFC (GROUP A)	35.60
TRAVOPROST 0.004%-TFC (GROUP E)	33.25
BRINZOLAMIDE 1%-TFC (GROUP C)	23.0

Legenda: TFC: timolol 0.5% fixed combination.

Table 4. Results.

BRIMONIDINE 0.2%-TFC vs DORZOLAMIDE 2%-TFC	P = 0.053
BRIMONIDINE 0.2%-TFC vs BIMATOPROST 0.003%-TFC	P = 0.221
BRIMONIDINE 0.2%-TFC vs TRAVOPROST 0.004%-TFC	P = 0.167
BRIMONIDINE 0.2%-TFC vs BRINZOLAMIDE 1%-TFC	P = 0.001

Legenda: TFC: timolol 0.5% fixed combination.

0.5% fixed combination (**Table 4**). All the mean percentage reduction after three months follow-up, due to these drugs, was not statistically significant, apart from brinzolamide 1%-timolol 0.5% fixed combination. This fixed combination was commercialized later and it has a good comfort profile in almost all the patients treated but, maybe, less IOP-lowering efficacy. In conclusion all these fixed combinations have a good profile of safety, efficacy and tolerability. According to our experience, it is mandatory to customize medical therapy to any glaucoma patient, as in refractive surgery.

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