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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%, phi: 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 antagonists (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 washout 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 ± 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 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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