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RESEARCH ARTICLE

AN OPEN LABEL PROSPECTIVE RANDOMIZED TRIAL TO COMPARE THE EFFICACY TOLERABILITY AND COST EFFECTIVENESS OF BRAND NAME VERSUS TWO DIFFERENT GENERIC DRUG OF FIXED COMBINATION DORZOLAMIDE 2% AND TIMOLOL 0.5% IN THE TREATMENT OF PRIMARY OPEN ANGLE GLAUCOMAPHY

Mustafa ELİAÇIK[1]

1 İstanbul Medipol University, Department of Ophtalmology Istanbul.

ABSTRACT

Introduction: To compare the efficacy tolerability and cost effectiveness of brand name versus two different generic drug of fixed combination dorzolamide 2% and timolol 0.5% in the treatment of primary open angle glaucoma.

Methods: Sixty-six eyes of 66 patients with newly diagnosed, open-angle glaucoma were included in this prospective, examiner masked, randomized study. All patients underwent routine ophthalmic examinations at baseline and 6 months of treatment. After initial examination, patients were randomly divided into three groups and prescribed to use fixed combination treatment of dorzolamide/timolol (D/T) brand name and two different generic name drops. Retrobulbar blood flow was assessed with color Doppler imaging (CDI). At end-of-treatment assessments, patients were requested to fill in a questionnaire based on "the Comparison of Ophthalmic Medications for Tolerability".

Results: Intraocular pressure (IOP) and CDI measurements were similar at baseline. Compared to baseline, the brand name drop had a better resistive index lowering effect than two other generic drugs, however the difference was not statistically significant (p=0.056). Brand name D/T fixed combination provided greater significant mean IOP reductions from baseline than two other generic name drops (p=0.001). There were no statistically significant differences in the IOP lowering effect between generic drops (p=0.562). Tolerability was similar between groups. Generic bottles failed to last a month for 80% patients.

Discussion: Brand name product of D/T fixed combination is exactly more effective in IOP reduction and seems to be having a better lowering effect on resistive index, even a statistically significant result was not found.

Keywords: Dorzolamide 2% and Timolol 0.5% Combination; Generic Drug; Retrobulbar Blood Flow; Collor Doppler Imaging; Cost Effectiveness

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INTRODUCTION

Glaucoma is a progressive disorder characterized by structural and functional abnormalities of the optic nerve. Even though intraocular pressure (IOP) is the most important modifiable factor in the progression of glaucoma, the disease has multiple risk factors, including retrobulbar hemodynamics[1]. Ganglion cell death and visual field loss can exist even among individuals for whom IOP measurements defined as normal range [2].

Therefore, current topical antiglaucoma drugs have been tested for their potential vasomotor activities [3-5]. In the mid-90s both topical sulfonamids, dorzolamide and followed shortly thereby after by brinzolamide were discovered and used clinically as an antiglaucoma drug [6]. No new members of this class have been clinically announced in the last decade. The major role of carbonic anhydrase inhibitors (CAIs) on IOP is reducing aqueous humor secretion by inhibition of carbonic anhydrase in the ciliary processes. In addition to

Correspondence Address: İstanbul Medipol University, Department of Ophtalmology, Koşuyolu Mahallesi Harem Yolu Üzeri E-5, 34718 Kadıköy, İstanbul **E-mail:** drmustafaeliacik@gmail.com

IOP lowering effect of this group drugs, dorzolamide and brinzolamide also increase the retrobulbar ocular blood flow by arterial vasodilation [7,8]. Because of this dual effect, CAIs are good choices for combining with other antiglaucoma agents.

Earlier detection of glaucoma, increasing number of elderly patients, using more aggressive therapies to reach target IOPs levels have increased cost for medical treatment of glaucoma [9]. We believe that, in the future, the management of glaucoma has considerable economic consequences. Some clinical commissioning groups make arrangements to prescribe generic drugs instead of brand-drug to reduce total cost of glaucoma prescribing [10,11].

A brand-name drug product is originally discovered and developed by a pharmaceutical company. After FDA approval was taken, the innovator company can market and sell this 'brand-name' product until to recoup money spent during development and to generate a profit the patent life expires. A generic drug is a drug which contains the same active ingredients as the original formulation. Generic manufacturers do not spend the cost of drug discovery, and also have little interest in proving the safety and efficacy of the drugs through clinical trials [12].

The patent for one of the most commonly prescribed fixed combination medication dorzolamide 2% with timolol 0.5% (Cosopt; Merck and Co, Inc., Whitehouse Station, NJ) expired in April 2011. Although an increase was observed in numbers of generic drugs during the years after 2011, no clinical assessment has done to investigate differences between brand-name drug and generic ones. The aim of this study to investigate the effects of dorzolamide/timolol brand-name drug and two different generic drugs on intraocular pressure and retrobulbar hemodynamics, and compare the subjective tolerability on newly diagnosed primary open angle glaucoma (POAG) patients during six months treatment period.

METHODS

A prospective, randomized clinical trial was conducted at Medipol University School of Medicine, Department of Ophthalmology between February 2015 and August 2015 after the study protocol was approved by the Ethics Committee of Medipol University. The tenets of the Declaration of Helsinki were followed and all patients provided informed consent prior to enrollment. Sixty six patients with primary open-angle glaucoma were included in this study. While unmasked staff were responsible for distribution of study medication, masked staff conducted routine ophthalmic examinations and retrobulbar blood flow measurement examinations with color doppler imaging (CDI).

POAG was defined as either by elevated IOP > 21 mmHg in at least 2 consecutive reliable examinations, typical glaucomatous optic nerve damage and retinal nerve fibber loss characteristic of glaucoma, presence of characteristic glaucomatous visual field (VF) demonstrated using Humphrey Standard Achromatic Perimetry (Humprey Inc., Dublin, CA), open angles detected by gonioscopy.

Exclusion criteria were described as having exfoliation or pigmentary glaucoma, history of acute angle closure, mean deviation of visual field testing (Humphrey30-2 program) of - 10 dB or worse, vertical and horizontal cup/disc ratio equal or greater than 0.9, ocular inflammation or infection within the last 3 months, orbital or ocular trauma, intraocular surgery within the last 6 months, history of renal or hepatic disease, asthma or respiratory disease, allergy to either of the drugs used in the study.

All patients underwent routine ophthalmic examinations at baseline and 6 months of treatment, including full ophthalmic examination, visual acuity, IOP measurement with a slit-lamp mounted Goldmann applanation tonometer. After initial examination, patients was randomly divided into three groups and prescribed to use fixed combination treatment of dorzolamide/ timolol brand name and two different generic name drops.

Retrobulbar blood flow in the ophthalmic artery (OA), the central retinal artery (CRA), and the posterior ciliary arteries (PCA) was assessed with CDI examinations. CDI examinations were performed by the same experienced observer (blinded to the treatment) in the supine position. Patients were instructed to avoid caffeine intake, smoking, and exercise for 2 h prior to study visit. A 7.5 MHz linear probe calculating peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistive index (RI) was applied to the closed eyelid using a coupling gel with the examiner's hand resting on the orbital margin to avoid any pressure on the eye. One eye of each patient was randomly selected for statistical analysis of IOP and retrobulbar hemodynamic changes.

To assess the local tolerance of topical glaucoma medication at 6 months, patients were requested to fill in a questionnaire based on "the Comparison of Ophthalmic Medications for Tolerability" (COMTOL) questionnaire supplemented with most frequently observed side effects listed in Pharmacotherapeutic Compass[13,14].

All statistical tests were performed using the IBM SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to check the normal distribution of quantitative data. For the numerical data, 1-way analysis of variance was performed for the comparison among 3 groups. The paired sample t test was used for comparing the IOP values between pretreatment and posttreatment. Independent sample t test was used to compare the difference of IOP values between the groups. P value <0.05 was considered statistically significant.

RESULTS

Brand name Cosopt (Merck & Co., Whitehouse Station, NJ, USA) was compared to two different groups of generic D/T fixed combination; Oftomix (Bilim Pharmaceuticals, Turkey) and Dorzotim (Sandoz, Turkey). Patients were divided into three groups and twenty two eyes of 22 individuals were included in each group. First group (Group A) received original dorzolamide/timolol fixed combination, second (Group B) and third group (Group C) received generic ones; Dorzotim and Oftomix, respectively. Patient characteristics in the different study groups are presented in Table 1. The mean age, sex, mean systolic and diastolic blood pressures and the amount of general medication were comparable in all three study groups. The following mean IOP measurements were recorded at baseline: 24.5 mmHg in the Group A, 24.6 mmHg in the Group B, and 24.9 mmHg in Group C. The mean IOP values did not differ significantly among the different groups at baseline. (p = 0.541) There was a statistically significant reduction in IOP from baseline in all groups. Compared with baseline, the IOP after 6 months of treatment was statistically significantly reduced by 8.8 ± 1.1 mmHg in Group A, 7.3 ± 1.1 mmHg in Group B and 6.7 ± 0.8 mmHg in Group C.

Table 1. Demographic characteristics of the study population

	Group A (N=22)	Group B (N=22)	Group C (N=22)	p value
Age (years;mean±SD)	58.4±9.3	59.7±9.1	58.7±8.7	0.461
Gender(Male[%]:Female[%])	11[50]:11[50]	10[45.4]:12[54.5]	12[54.5]:10[45.4]	0.830
IOP(mmHg;mean±SD)	24.5±2.8	24.6±2.9	24.9±2,6	0.541
Mean Clinic SPB(mmHg;mean±SD)	122.6±14.3	126.4±13.4	124.3±14.0	0.353
Mean Clinic DPB (mmHg;mean±SD)	85.4±8.4	88.6±7.3	87.3±6.8	0.542
Medications(mean±SD)	1.3±1.2	1±1.3	1.2±1.05	0.103

Table 2. Resistive index of retraobulbar bloodflow at sixth month

Resistive index	Group A (mean ± SD)	Group B (mean ± SD)	Group C (mean± SD)	p value
Ophthalmic artery	0.53 ± 0.09	0.55 ± 0.07	0.56 ± 0.07	0.652
Central retinal artery	0.59 ± 0.07	0.63 ± 0.07	0.65 ± 0.11	0.059
Short posterior ciliary artery(temporal)	0.61± 0.05	0.65 ± 0.07	0.64 ± 0.07	0.075
Short posterior ciliary artery (nasal)	0.59 ± 0.08	0.63 ± 0.07	0.63 ± 0.08	0.066

On comparing the IOP reduction achieved amongst the three groups, there was a statistically significant difference between Group A and Group B as well as between Group A and Group C while the difference between Group C and Group B was statistically insignificant.

The comparisons of the CDI measurements after the six months of treatment are summarized in Table 2. No statistically significant difference was detected between the groups in the pretreatment period with respect to all measured blood flow

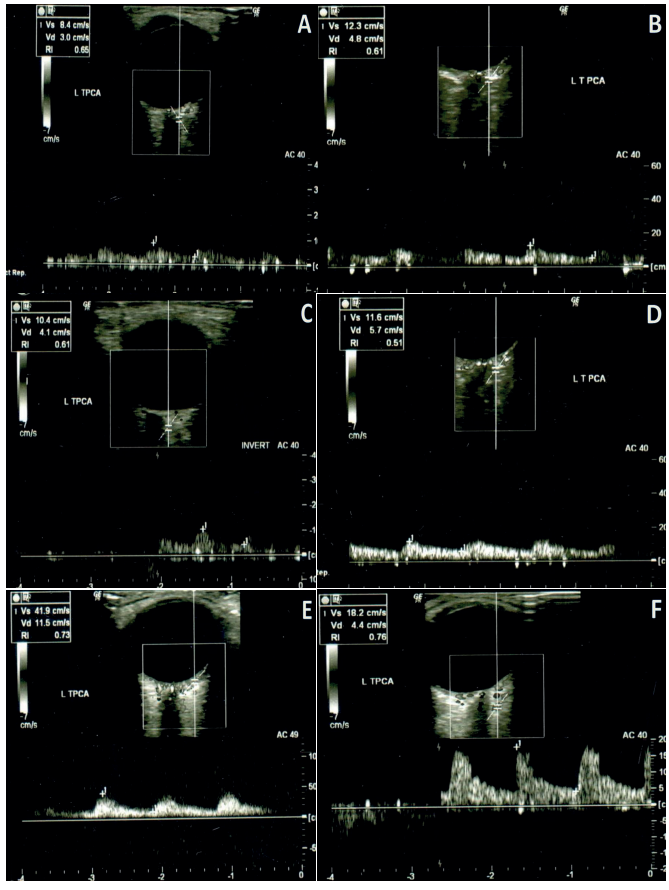

Figure1: Baseline and at the 6th month resistive of index of brand name and two generic drug

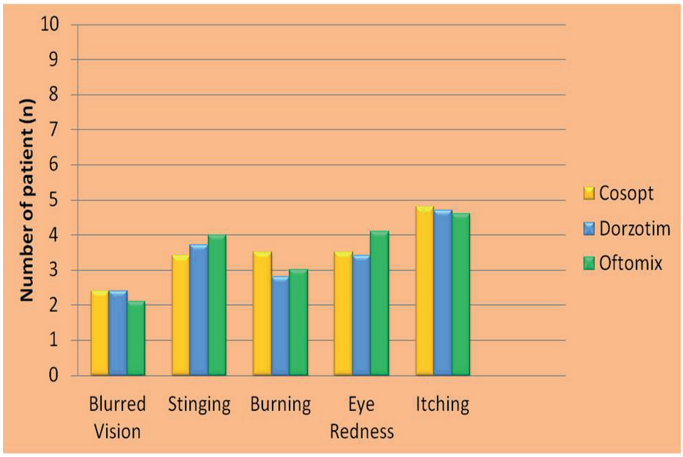

Figure 2: Responses to the Comparison of Ophthalmic Medications for Tolerability (COMTOL) questionnaire among groups.

parameters for all arteries. All retrobulbar velocities increased and resistive index reduced during treatment among all three drops. Even though no statistically difference was found between groups, brand name drug seemed to have a better resistive index lowering effect than two other generic drugs (Figure 1).

No serious adverse effects were detected in the study. Responses to the Comparison of Ophthalmic Medications for Tolerability (COMTOL) questionnaire showed no statistical significant difference in side-effect frequency among groups. Group A had a significantly lower bottle usage compared with Groups B and C ($p < 0.001$) (Figure 2).

DISCUSSION

Antiglaucoma ophthalmic drops are one of the most widely used topical treatments in all over the world [9,15]. The recent marketing approvals of various generic versions of ophthalmic drops have renewed questions in the ophthalmology field about whether a generic version of an ophthalmic drug product is the same as the innovator drug product [16,17]. Although the bioequivalence model is applicable for most systemic drugs, ophthalmic products pose a unique challenge, given the inability to measure drug concentrations in the eye [18]. Since 1992, generic ophthalmic solutions have essentially been required by policy to have all of the same active and inactive ingredients in the same concentrations as the innovator.18 Also generic versions of ophthalmic product must meet the same batch requirements for identity, strength, purity, quality, dosage form, and route of administration. Delivery devices, more specifically bottle designs and dimensions, are not closely regulated. Clinical trials on the safety and the effectivity of generic drugs similar to those med [18-20]. Bioavailability and efficacy studies are required only if there is a change in active ingredient(s), inactive ingredient(s), application with regard to application device (eg, inhalation chamber). We conducted a study of effectivity, safety and annual cost of three ophthalmic products for treating glaucoma including two of brands and generic dorzolamide/timolol fixed combination. Since Stewart et al reported timolol maleate 0.5% gel forming solution (TXE, Merck) demonstrates a lower intraocular pressure eight hours after dosing than does timolol maleate 0.5% gel forming solution in primary open-angle glaucoma and ocular hypertension patients, much more studies done about IOP lowering effect of brand name and generic name products [21]. These results are compatible with those reported by Narayanaswamy et al.and Eagan et al. They both reported result for efficiancy of original and generic products of Latanaprost. Narayanaswamy et al. point to differences between Xalatan and Latoprost, a generic latanaprost product, in their impact on intraocular pressure in primary open angle glaucoma (POAG) or ocular hypertension (OH) patients. In their a single-center, randomized, crossover, two period comparative study, subjects were divided in two groups randomly. Group A received Xalatan for weeks 1-12 followed by Latoprost for weeks 13-24 and Group B received Latoprost for weeks 1-12 followed by Xalatan for weeks 13-24. According to their findings IOP lowering effect of Xalatan was higher than that with Latoprost during the first part of the study and also after crossover the drops in Group A, the IOP rose from 14.29 +/- 1.61 mmHg to 15.36 +/- 1.71 mmHg at week 24 [22]. Eagan et al. also conducted a cross-over, single center masked three-month study with 35 POAG petients to detect differences of Xalatan and generic products (Latalux, manufactured by Sanitas, AB in Lithuania). As a result of their study they reported a significantly greater number of IOP reductions below 14 mmHg occurred for patients treated with Xalatan as compared to generic latanoprost [23]. This finding may be clinically significant, as achieving a target IOP < 14 mmHg can help prevent progression in moderate to advanced glaucoma. In this study we also found original D/T fixed combination more effective in lowering IOP than two different generic products. In contrast to our findings Kim et al reported that IOP-lowering effect of the generic drug Batidor was similar to that of the brand-name drug Cosopt in the monotherapy and combination therapy with PGs [24]. In our opinion efficiency of antiglaucoma drops could not be disclosed only with IOP-lowering effect. On the basis of recent observations, it must be emphasized that modern antiglaucoma therapies should aim to

affect not only intraocular pressure but also other factors such as ocular blood flow. In our study we also examined the effect of all three D/T fixed combination on retrobulbar blood flow in study group. Even though there was no statistically significant difference between those products; original product reduced resistive index much more than generic ones. To support our preliminary results much more studies must be conducted on these effect among large patient groups. Those some previous studies also targeted to assess the safety brand versus generic antiglaucoma products. No statistically significant difference was noted about the safety of those products by those four studies in accordance with the results obtained in our study [21-24]. Within antiglaucoma drops, one the most studied question is "Could generic drops provide a cheaper treatment costs in glaucoma treatment. In our study we also found that original product was used much longer than generic products. Both generic bottles failed to last a month. Consequently, it is possible to point delivery devices, more specifically bottle designs and dimensions, as a cause of this difference. The bottle design of original product is more convenient to drop a single drop than two other bottles design. None of the studies above could give an exactly answer to this question but according to their results all researchers express that to stop progression of glaucoma is more important factor than savings. No one could foresee the results of glaucoma treatment with generic products.

In conclusion, brand name product of D/T fixed combination is exactly more effective in IOP reduction and seems to be having a better lowering effect on resistive index, even a statistically significant result was not found. Further investigations with other types of antiglaucoma drugs are needed to confirm our results.

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