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ORIGINAL PAPER

Comparison of fixed combinations of dorzolamide/timolol and brimonidine/timolol in patients with primary open-angle glaucoma

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Abstract To compare the short-term effectiveness and ocular side-effects of fixed combinations of dorzolamide/timolol (DTFC) and brimonidine/timolol (BTFC) in patients with primary open-angle glaucoma (POAG). Forty-two eyes of 42 patients newly diagnosed with primary open-angle glaucoma were assessed prospectively. One of the two eyes was chosen randomly and treated with DTFC (2 × 1) for 4 weeks. The treatment was then stopped to allow a 4-week wash-out period. Following the wash-out period, the same eye was treated with BTFC (2 × 1) for 4 weeks. Intraocular pressure (IOP) values were measured before and after each treatment at 0800, 1,200 and 1,600 h. Tear function test results and ocular side-effects were also recorded. The mean baseline IOP values for DTFC and BTFC were 24.1 ± 1.8 and 24.6 ± 2.4 mmHg, respectively. The mean IOP values after 4 weeks of treatment with DTFC or BTFC were 17.1 ± 2.9 and 16.9 ± 2.5 mmHg, respectively. Both medications reduced IOP values significantly ($P = 0.0000$). The effectiveness of both medications was similar ($P = 0.7363$). Both combinations significantly reduced the amount of tear secretion and tear break-up time ($P = 0.0000$). Eye burning was more common with DTFC than with BTFC ($P = 0.0182$). Other adverse effects were observed at similar rates for both combinations. This study demonstrated that the IOP-reducing effects of DTFC and BTFC in patients with POAG are similar. The side-effect profile of BTFC is similar to that of DTFC. Lower occurrence of a burning sensation may improve patient compliance in the BTFC group.

Keywords Fixed combination · Intraocular pressure · Open-angle glaucoma · Side-effects

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Introduction

Primary open-angle glaucoma (POAG) is a progressive optic neuropathy characterized by cupping of the optic disc and visual field changes. The most important risk factor for glaucoma-induced loss of vision is intraocular pressure (IOP). Reducing IOP prevents or retards the development of glaucoma in ocular hypertensive patients, and slows optic nerve damage and vision loss in patients with glaucoma [1–3]. The most widely used agents for reducing IOP are prostaglandin analogues, β-blockers, α-agonists and carbonic anhydrase inhibitors. In the Collaborative Initial Glaucoma Treatment Study, it was reported that >75% of subjects in the medical treatment group required more than one topical medication to reach an ocular hypotensive effect [4]. Therefore, if a pharmacological therapy with

a single agent is inadequate to lower IOP levels to a predefined target value, then the first monotherapy should be changed; if this is still not sufficient then additional agents can be added. However, addition of a second topical agent may lower compliance whereas use of fixed combination medications in such patients may increase patient compliance and thus the success of treatment [5].

In contemporary glaucoma treatment, a topical β-blocker is used together with a topical carbonic anhydrase inhibitor, or a selective α-agonist, or a prostaglandin analogue in patients who require combined drug therapy. Fixed combinations of dorzolamide 2%/timolol 0.5% (Cosopt; Merck & Co Inc., NJ, USA) and brimonidine 0.2%/timolol 0.5% (Combigan; Allergan Inc., CA, USA) are frequently used products in POAG treatment. In this study, we aimed to compare these two fixed combination products in terms of IOP-lowering efficacy and ocular side-effects.

Materials and methods

This prospective study included 42 eyes of 42 adult (age >18 years) patients newly diagnosed with POAG in our clinic. Only patients with POAG were evaluated; patients with chronic angle-closure glaucoma or pseudoexfoliative glaucoma were not included in the study. POAG is defined by an IOP level >21 mmHg, glaucomatous changes in the optic nerve head, and visual field loss related with these changes, and finally absence of secondary glaucoma findings. Inclusion criteria were age >18 years, IOP levels between 22 and 34 mmHg, and visual acuity at least 5/10. Exclusion criteria were ocular inflammation, previous laser trabeculoplasty, laser iridotomy, trauma or previous intraocular surgery, and advanced glaucomatous damage, ocular surface diseases such as conjunctivitis, dry eye and keratitis. Patients with known hypersensitivity to any of the study drugs or vulnerable to systemic side-effects were excluded. All patients were informed about the study details and possible outcomes of the study therapies. Approval from the hospital's ethics committee and written informed consent from all patients was obtained after complete explanation.

All patients underwent full ophthalmologic examination including visual acuity assessment, biomicroscopy, dilated fundus examination, and gonioscopy. Patients with closed or barely closed angles on gonioscopic examination were excluded from the study. Pretreatment IOP levels were measured by Goldmann applanation tonometry at time points 0800, 1200 and 1600 h and the arithmetical mean of these measurements was accepted as the IOP. All patients underwent a 24-2 full-threshold visual field test by using a Humphrey automatic perimeter device. A Schirmer's test was conducted and tear break-up time was measured before-treatment. After all these baseline evaluations, dorzolamide/timolol fixed combination (DTFC) 2 × 1 (0800 and 2000 h) was started in both eyes of all patients. No drugs other than the study drugs were used prior to the study. One of the eyes was randomly chosen as the study eye; the other eye was not included in the analysis. After 4 weeks of treatment, all patients were re-evaluated by a full ophthalmologic examination. IOP values were measured by Goldmann applanation tonometry at time points 0800, 1200, and 1600 h and the mean of these measurements was recorded as IOP. A Schirmer's test and tear break-up time measurement were performed again after the treatment. In addition, local side-effects related to drug use were assessed. Each patient was questioned for symptoms of burning, redness, foreign body sensation, itching, secretion, dryness and blurred vision. In addition, standardized photography was used to evaluate and compare the presence and changes in conjunctivitis, blepharitis, corneal epitheliopathy.

The DTFC treatment was then stopped for a 4-week wash-out period. At the end of the wash-out period, ophthalmologic examinations, IOP measurements, and tear function tests were performed again and a fixed combination of brimonidine/timolol (BTFC) 2 × 1 (0800 and 2000 h) treatment was started. After 4 weeks of BTFC treatment, all examinations and laboratory tests were performed again. Side-effects were also recorded.

Product efficacy was determined by comparison of pre- and post-treatment IOP values for each drug. Comparisons of the two fixed combinations were made by comparing pre- and post-treatment values. Tear function test results and treatment-related ocular side-effects were also compared. Statistical analyses were performed by SPSS 16.0 software. Parametric variates were compared by paired samples t test and Student's t test. Side-effect profiles were evaluated by χ^2 test. The statistical significance level was adjusted to $P < 0.05$.

Results

This study included 42 eyes of 42 patients (M/F 12/30; mean age 60.2 ± 12.0 years). IOP measurements showed that both DTFC and BTFC treatments for 4 weeks produced a significant reduction in IOP levels. Pre- and post-treatment mean IOP levels were 24.1 ± 1.8 and 17.1 ± 2.9 mmHg ($P = 0.0000$) for DTFC, and 24.6 ± 2.4 and 16.9 ± 2.5 mmHg ($P = 0.0000$) for BTFC. The IOP-lowering efficacy (29.0% for DTFC and 31.3% for BTFC) of both products was similar and there were no differences between the pretreatment IOPs ($P = 0.2836$) and between the post-treatment IOPs ($P = 0.7363$). Figure 1 depicts pre- and post-treatment IOP levels for both fixed combinations.

When we assessed the tear function tests of the patients, the Schirmer scores before and after DTFC treatment for 4 weeks were 13.3 ± 2.8 and 12.3 ± 3.8 mm, respectively ($P = 0.0000$). Similarly, the Schirmer scores before and after BTFC treatment were 14.1 ± 2.2 and 13.2 ± 3.0 mm, respectively ($P = 0.0000$). The mean Schirmer scores of the two study drugs before and after treatment were not statistically different. Comparisons between before-treatment scores and after treatment scores resulted in P values of 0.1485 and 0.2314, respectively. We also compared tear break-up times and found that DTFC treatment resulted in a significant decrease in tear break-up time. The mean tear break-up times before and after DTFC treatment were 10.1 ± 1.8 and 9.1 ± 1.6 s ($P = 0.0000$). Similarly, BTFC treatment reduced tear break-up time. The mean tear break-up times before and after BTFC treatment were 10.9 ± 1.9 and 9.9 ± 1.9 s ($P = 0.0000$). The before-treatment scores were similar with both study medications ($P = 0.0506$); on the other hand, the after treatment scores of DTFC were significantly lower than the after treatment scores of BTFC ($P = 0.0397$). Table 1 shows the changes in tear break-up time before and after treatment with both drugs.

Ocular side-effects and biomicroscopic findings are given in Table 2. Side-effect distributions for DTFC and BTFC were burning (43 and 19%), foreign body sensation (28 and 12%), itching (12 and 12%), and conjunctival hyperemia (12 and 14%). Burning was significantly more common with DTFC treatment ($P = 0.0182$). Other side-effects were observed at similar frequencies for the two study drugs.

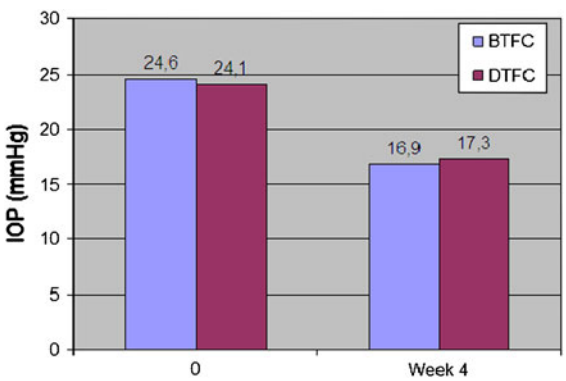

Fig. 1 Changes in intraocular pressure values before and after 4 weeks of treatment with DTFC and BTFC. *BTFC* brimonidine/timolol fixed combination, *DTFC* dorzolamide/timolol fixed combination, *IOP* intraocular pressure

Table 2 Ocular side-effects of medication

	Dorzolomide/timolol (%)	Brimonidine/timolol (%)	P value
Burning	18 (43)	8 (19)	0.0182
Foreign body sensation	12 (28)	5 (12)	0.0736
Conjunctival hyperemia	5 (12)	6 (14)	>0.9999
Blurred vision	3 (7)	2 (5)	0.6446
Itching	5 (12)	5 (12)	>0.9999
Secretion	3 (7)	3 (7)	>0.9999
Dryness	3 (7)	2 (5)	0.6446
Blepharitis	2 (5)	1 (2)	0.5565

Table 1 Changes of tear function test results before and after treatment

	Before Tx Schirmer (mm)	After Tx Schirmer (mm)	P value	Before Tx TBT (s)	After Tx TBT (s)	P value
DTFC	13.3 ± 2.8	12.3 ± 3.8	0.0000	10.1 ± 1.8	9.1 ± 1.6	0.0000
BTFC	14.1 ± 2.2	13.2 ± 3.0	0.0000	10.9 ± 1.9	9.9 ± 1.9	0.0000

DTFC dorzolamide/timolol fixed combination, *BTFC* brimonidine/timolol fixed combination, *TBT* tear break-up time, *Tx* treatment

Discussion

One of the most important factors that affects the success of treatment in glaucoma therapy is patient compliance. In a study, 80% of glaucoma patients showed non-compliance to instructions of treatment [7]. It is reported that in patients who require more than one drug, compliance to treatment is low. Because of inadequate waiting time between the doses of different drugs, a washing effect occurs and consequently the efficacy is reduced [8]. Therefore, fixed combinations are recommended to increase patient compliance, and thus the success of treatment [6]. Fixed combinations of dorzolamide/timolol and brimonidine/timolol are frequently preferred in glaucoma therapy. The present study was conducted to compare the efficacy and side-effects of these two fixed combinations in the short term.

Many previous studies compared the efficacy of DTFC with BTFC. Nixon et al. [9] reported that 3 months of BTFC treatment was more effective in reducing IOP than DTFC (7.7 and 6.7 mmHg, respectively). Centofanti et al. [10] reported that patients who were on 0.5% timolol treatment showed a significant IOP reduction when brimonidine was added to timolol treatment compared to the addition of dorzolamide. García-Feijoó et al. [11] reported that BTFC treatment resulted in 1.70 further reduction in IOP when compared to DTFC. On the other hand, Arcieri et al. [12] found that DTFC led to a 7.4 mmHg reduction in IOP level whereas the decrease was 7.8 mmHg with BTFC treatment. The difference was not statistically significant and they concluded that both drugs had similar efficacy. In our study, both combinations led to significant IOP reductions after a 4-week treatment period. The mean reduction in IOP with DTFC and BTFC was 7.0 and 7.7 mmHg, respectively, at the end of 4 weeks. Thus, BTFC produced a slightly greater (0.7 mmHg) reduction in IOP when compared to DTFC; however, this difference was not statistically significant. These results are in agreement with those of Arcieri et al. [12].

Ocular side-effect profiles of DTFC and BTFC have been compared in many previous studies and the most commonly observed side-effects were reported to be burning/foreign body sensation, conjunctival hyperemia, pain, itching and conjunctivitis [12–15]. The symptoms of burning and foreign body sensation after drug administration are more common with DTFC than with BTFC [12–14]. Chan et al. [13] evaluated burning duration after instilling the drug and reported that burning time was longer with DTFC when compared to BTFC. Sharpe et al. [15] reported that the side-effect profiles were similar in both drugs, but burning and pain sensations after dripping of the drug were significantly higher in patients on DTFC treatment. Side-effects observed in our study with respect to occurrence rate were burning, foreign body sensation, conjunctival hyperemia, and itching. Among these side-effects, only post-instillation burning was significantly higher in DTFC treatment. The pH value of the dorzolamide/timolol fixed combination is 5.65 compared to 6.5–7.3 for BTFC. The difference in pH value may be responsible for the degree of burning experienced by recipients of these drugs [6]. Although adverse events such as burning, foreign body sensation, dryness, and blepharitis are more common in DTFC when compared to BTFC, the difference was not statistically significant. However, these findings support previous results which state that the side-effect profile of BTFC is better than that of DTFC.

We are not aware of any previously published study that assessed the effects of DTFC and BTFC on tear function tests. To our knowledge, this is the first study to undertake such a comparison. We demonstrated that both DTFC and BTFC lowered the scores of the Schirmer test and significantly shortened the time of tear break-up. When we compared the two drugs, the before and after treatment values were not significantly different. In light of the above considerations, we concluded that both combinations may exacerbate the symptoms of patients with dry eye.

The present study has some limitations. The sample size was small and quite homogenous, and the follow-up period was short. Increasing the number of patients, adding other types of glaucomas to the study, and increasing the follow-up period may produce results closer to what is actually experienced in practice. This study was designed to detect the incidence of ocular adverse effects but not quantify them. Quantifying ocular adverse effects might provide a better representation of drug compliance.

In conclusion, in the short term both BTFC and DTFC effectively lower IOP. The side-effect profile of BTFC is similar to that of DTFC. Lesser occurrence of a burning sensation may improve patient compliance in the BTFC group. Both combinations significantly lower tear secretion and tear break-up time.

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Conflict of interest None.

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