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Brinzolamide (1%) Plus Timolol Maleate (0.5%) Versus Dorzolamide (2%) Plus Timolol Maleate (0.5%): A Randomized, Open-Label, Multicentric, Active-Controlled, Prospective Study

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A B S T R A C T

Background: To evaluate the safety and efficacy of brinzolamide plus timolol maleate (BT) versus dorzolamide plus timolol maleate (DT) fixed-dose combination in primary open-angle glaucoma. Since limited comparative clinical studies have been conducted between BT and DT in the small number of Iraqi population, we have conducted this study in a larger Iraqi patient population. **Methods:** Patients with primary open-angle glaucoma received BT or DT, and the parameters were measured at five time points. The objective was to evaluate the change in the intraocular pressure(IOP, mmHg), tolerability, and adverse events. **Results:** Baseline IOP was 27.660±6.3297 for BT and 29.446±6.3148for DT in the left eye, and 27.910±7.3483for BT and 28.986±5.7688 for DT in the right eye. The reduction from baseline IOP was similar in both treatment groups, i.e., Brinzolamide (1%) plus timolol maleate (0.5%) (BT) and dorzolamide (2%) plus timolol maleate (0.5%) (DT) [P=0.227 (left eye) and P=0.144 (right eye)]. However, patient tolerability was better for BT with lesser ocular discomfort, pain, and blurring at the 3-month follow-up. The VAS scores for ocular discomfort, ocular pain, and ocular blurring showed a better effect in the BT treatment group as compared to the DT treatment group. [VAS scores at final follow-up (visit 5, three months follow-up): Ocular discomfort = 0 in 28 patients (BT group) and 21 patients (DT group), ocular pain = 0 in 37 (BT group) and 34 patients (DT group), ocular blurring was 0 in 38 patients (BT group) and 32 patients (DT group)]. **Conclusions:** Both BT and DT effectively controlled the IOP. However, patients with BT were less likely to have ocular discomfort, pain, and blurring than patients on DT.

Keywords: Brinzolamide/timolol, dorzolamide/timolol, fixed combinations, glaucoma; intraocular pressure

A R T I C L E I N F O

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CONTENTS

1. Introduction

Glaucoma is a chronic neurodegenerative ocular condition and the second most common cause of irreversible blindness. The global burden of this disease in 2020 was79.6 million, and the prevalence was 3.54% (Michelessi et al., 2018; Ahmad et al., 2020). Glaucoma causes damage to the optic nerve head and retinal nerve fiber layer leading to visual field defects. It is classified as open-angle or angle-closure glaucoma. Both subtypes are further classified as primary or secondary forms. Primary open-angle glaucoma is the most common, responsible for about 70% of the glaucoma cases (Michelessi et al., 2018).High intraocular pressure(IOP), older age, family history of glaucoma, myopia, low perfusion pressure, and thinner central cornea are the risk factors for primary open-angle glaucoma (Michelessi et al., 2018).Primary open-angle glaucoma is an open angle of the anterior chamber, typical optic nerve head changes, and raised IOP. Patients can progressively lose peripheral vision, followed by blindness (Padala et al., 2020).IOP is not considered a diagnostic criterion for glaucoma; however, it is a significant risk factor for glaucoma progression (Holló Get al., 2009).

As per the latest guidelines of the European Glaucoma Society, monotherapy should be the first-choice treatment. If target IOP is not achieved, then switching to another monotherapy is preferred. The guidelines recommend switching to a combination therapy only when the monotherapy is ineffective. Combination therapy can include prostaglandin analogs with a beta-blocker or Rho kinase inhibitor, or carbonic anhydrase inhibitor with an alpha-2 agonist. Combination therapy is not recommended as a first-choice treatment unless patients have a very high IOP or advanced glaucoma. For primary open-angle glaucoma, medications or laser trabeculoplasty is the preferred treatment. If combination therapy is required, not more than three-drug combinations is advised (Bagnasco et al., 2021). The guidelines laid down by the American Academy of Ophthalmology (AAO) also recommended similar treatment for primary open-angle glaucoma. The AAO guidelines recommend medications, laser trabeculoplasty, or incisional surgery. Prostaglandin analog is the most preferred medication. Switching to another monotherapy or combination therapy is recommended when target IOP is not achieved (Gedde et al., 2020).

A monotherapy of an IOP-lowering agent for several patients does not reduce IOP or sufficiently maintain the target IOP for an extended period. Hence, combination therapy is preferred (Holló et al., 2014; Liu et al., 2019). The Ocular Hypertension Treatment Study had shown that nearly 50% of patients required additional IOP-lowering agents after 1st year of treatment (Fechtner et al., 2016). Using combination therapy can help reduce the IOP and prevent glaucoma progression (Michelessi et al., 2018; Petrov et al., 2018).

Patients prescribed combination therapy are recommended to instill two or more eye drops more than once a day. However, this approach can increase side effects because of preservatives and decreased patient compliance. Further, simultaneous administration of two or more drops can reduce the effect of the drug administered first. For these reasons, fixed-dose combination (FDC) therapy is preferred in which a single formulation has two drugs and can be instilled as a single eye drop (Michelessi et al., 2018; Petrov et al., 2018).FDCs help improve patient compliance as the tolerability is higher, and patients need to use the eye drops only twice daily (Galose et al., 2016; Petrov et al., 2018). In comparison to monotherapy, FDC therapy also helps to reduce the long-term treatment costs (Galose et al., 2016; Petrov et al., 2018).Nowadays, many FDC eye drops in the market contain a combination of timolol and beta-blockers, carbonic anhydrase inhibitors, α- 2 agonists, or prostaglandin analogs (Januleviciene et al., 2010; Michelessi et al., 2018; Petrov et al., 2018; Liu et al., 2019; Padala et al., 2020).

Combining carbonic anhydrase inhibitors and beta-blockers has better IOP-reducing efficacy than mono therapy. Also, these medications are usually well-tolerated by the patients (Altafini et al., 2015). FDCs of carbonic anhydrase inhibitors, and beta-blockers currently available include brinzolamide (1%) plus timolol maleate (0.5%) (BT) and dorzolamide (2%) plus timolol maleate (0.5%) (DT) (Sanseau et al., 2013). This clinical study aimed to compare the IOP-lowering effect and assess the tolerability and safety profile of BT versus DT FDCs in patients with primary open-angle glaucoma. Since limited comparative clinical studies have been conducted between BT and DT in

the small number of Iraqi population, we have conducted this study in a larger Iraqi patient population.

2. Materials and methods

Study design

This was a randomized, open-label, multicentric, active-controlled prospective phase-IV study conducted across eight cities in Iraq. This study evaluated the safety and efficacy of BT and DTFDCs in patients with primary open-angle glaucoma. Brinzolamide-Timolol has been marketed and prescribed by doctors in Iraq for the past five years. The primary objective was to evaluate the mean change in the IOP. The secondary objectives of our clinical study were to compare the two FDCs' tolerability and adverse events profile and assess the safety in terms of ocular pain, discomfort and blurring.

Patients

A total of 200patients per group were chosen for this study. As this is a post-marketing surveillance study without any intervention, no ethics committee approval was obtained. However, the study was conducted as per the ethical principles described in the Declaration of Helsinki, and patient consent was obtained verbally.

Inclusion criteria

Inclusion criteria were male and female (age≥18 to ≤65 years), with bilateral primary open-angle glaucoma, IOP≥15 mmHg at 9:00hr during baseline visits, and newly diagnosed/treatment-naive. In addition, the patients were required to be willing to comply with the study protocol.

Exclusion criteria

Exclusion criteria was patients with a history of hypersensitivity to any of the study medications or excipients in the study medications; a history of ocular trauma or intraocular surgery in either eye within 6 months or experience of ocular laser surgery in either eye within three months of the screening examination; ocular infection, ocular inflammation, a history of or current clinically significant or progressive retinal disease, such as retinal degeneration, diabetic retinopathy, or retinal detachment in either eye; best corrected visual acuity score of <0.2 (decimal visual acuity) in either eye; any abnormality preventing reliable applanation tonometry of either eye; angle grade 2 or less in either eye (Shaffer classification); severe visual field loss in either eye (judged by the investigator); use of any additional topical or systemic ocular hypotensive medication indicated for glaucoma or intraocular hypertension during the study; use of corticosteroid medications via ocular or systemic routes during the study; sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third-degree atrioventricular block, overt cardiac failure, or cardiogenic shock; severe allergic rhinitis and bronchial hyper-reactivity; hyperchloremic acidosis; severe renal impairment; hypersensitivity to sulfonamides; pregnant or lactating, or intending to become pregnant during the study period; previous or current therapy with another investigational agent within 30 days prior to the screening examination; previous or current evidence of a severe illness or any other condition that could make the patient unsuitable for the study (judged by the investigator); patients with a history of drug abuse or alcohol use.

Treatment and evaluation

Patients were randomized by using computer-generated randomization into two groups. One group received BT, and the other group received DT. In both groups, the eye drops were administered via a topical route. All the patients received one drop, twice a day, for three months. The patients were instructed to instill eye drops between 8:00–9:00 and 20:00-21:00 hours daily. All the patients were evaluated at baseline (visit 1), at two weeks (visit 2), and 1-, 2-, and 3-months (visit 3, 4, and 5, respectively) follow-up. During the study period, IOP was measured at 10:00 hours every day. IOP was measured using Goldman applanation tonometry. The mean IOP value of the two measurements was recorded for each eye and was compared between the two groups. In all the study patients, one eye was chosen as the target eye to evaluate the efficacy of the treatment. The target eye was the one that satisfied all the inclusion/exclusion criteria or with a higher IOP at the baseline. If the IOPs were equal for both eyes, the right eye was chosen as the target eye. The patients were also evaluated for their medical and ophthalmic history during the baseline and follow-up visits.

Study endpoints

Efficacy assessment

During the study follow-up, patients were asked about adverse events and compliance. The patient's response was recorded using the Visual analogue scale (VAS) with a score of 0 to ten (score 0=absence of adverse events and 10=severe adverse events). The parameters assessed by using VAS were ocular discomfort, ocular pain, and ocular blurring. The investigator completed a clinical success evaluation on the final patient visit (three months- follow-up). The patients were considered clinically successful after checking the IOP-lowering efficacy, tolerability, and adverse events.

Tolerability and safety assessment

At the discretion of the investigator, patients were excluded from the study if they experienced any serious or intolerable adverse events during any visit; if the investigator believed that continued participation was not in the best interest of the patient; if the patient did not adhere to the study protocol; or if there was a deviation in the study protocol. Patients were also discontinued from the study if they withdrew their consent. The investigator documented the reasons for patient withdrawal in the Study Conclusion section of the Case report form (CRF)/eCRF.

Clinical success

The study patient was considered a clinical success if the investigator successfully continued the treatment on the patient for three months. In addition, we also considered parameters like the IOP-lowering effect, tolerability, and adverse events while finding clinical success in a patient.

Statistical analysis: Statistical analysis was performed using PS Power and Sample Size Calculations (SAS) Software, version 2.1.30 for MS Windows. The two groups were compared using Student's t-test for independent samples. Comparison within the treatment group was conducted using repeated measure Analysis of variance

(ANOVA) followed by paired t-test as a post hoc two-group comparison. We used the Chi-square test to compare the categorical data (age and sex). The data were expressed as mean ± standard deviation (Mean±SD), frequencies (number of cases), and percentages. No interim analysis was conducted during the study. A p-value less than 0.05 was considered statistically significant.

Power analysis

Power analysis was done for the change in IOP over the study period as the primary outcome of this study. Student's t-test for independent samples was chosen to perform the analysis; the α error level was fixed at 0.05, and the sample size was 50 participants for each group.

3. Results and Discussion

Characteristics of the participants

This study estimated 200 patients per group; however, data for only 100 patients (50 patients per group) was available by the end of the study. Patient demographics for the two treatment groups did not show any statistical difference. Both the treatment groups had more female participants (48% in BT and 52% in DT), and the mean ages were BT = 56.760±8.6839 and 57.040±13.3676 (*P=0.901*) (See table 1). Baseline characteristics (visit 1): Mean IOP for both the eyes between the groups did not show any significant difference [BT = 27.660±6.3297 mmHg and DT = 29.446±6.3148 mmHg (*P=0.161*) for the left eye and BT = 27.910±7.3483 and DT = 28.986±5.7688 (*P=0.417*) for the right eye]. The parameters assessed by VAS also did not show any significant differences. The VAS score at baseline were BT = 3.540±2.3142 and DT = 3.540±2.1401, for ocular discomfort (*P=1.000*); BT = 2.600±2.3561 and DT = 2.540±2.6589, for ocular pain (*P=0.905*); BT = 2.280±2.0508 and DT = 2.160±1.9832, for ocular blurring (*P=0.767*).

Mean IOP reduction

The repeated measure ANOVA for the mean IOP values within each group showed a reduction in IOP at two weeks follow-up (visit 2) compared to the baseline. However, there was no significant reduction in the mean IOP values within groups at other follow-up visits (visits 3, 4, and 5; see table 2, figure 1A and figure 1B). The mean IOP value was not significantly different between BT and DT groups at baseline and follow-ups.

Tolerability

The VAS score for ocular discomfort during the final follow-up (visit 5) was 0 in 28 patients from the BT treatment group and 21from the DT treatment group. The VAS scores for ocular pain were also 0 in 37 patients from the BT treatment group and 34 patients from the DT treatment group during the final follow-up (visit 5).Similarly, the VAS score for ocular blurring was 0 in 38 patients from the BT treatment group and 32 from the DT treatment group during the final follow-up (visit 5) (Figure 2). These results show that the patients tolerated both BT and DT FDCs; however, BT showed better tolerability than DT.

Ocular discomfort

The repeated measure ANOVA and student's t-test for the mean values for ocular discomfort showed a significant reduction between and within groups [BT = 1.740±2.0385 and DT = 2.520±2.0277, at two weeks follow-up (visit 2), *P=0.082*; BT = 1.180±1.4525 and DT = 1.880±1.6615, at one month follow-up (visit 3), *P=0.027*; BT = 0.920±1.4263 and D = 1.680±1.7431, at two months follow-up (visit 4), *P=0.019*; and BT = 0.900±1.5419 and D = 1.700±1.7871, at three months follow-up (visit 5), *P=0.018* (see table 3 and figure 3A)]. There was a marked reduction in the percentage of ocular discomfort in participants of the BT group at all follow-ups (see figure 3B) compared to patients of the DT group.

Ocular pain

The repeated measure ANOVA for the mean values for ocular pain showed a significant reduction between groups [BT = 1.000±1.4846 and DT = 1.960±2.7476, at two weeks follow-up (visit 2), *P=0.032*; BT = 0.840±1.2513 and DT = 0.960±1.4978, at one month follow-up (visit 3), *P=0.665*; BT = 0.620±1.2103 and D = 0.720±1.1959, at two months follow-up (visit 4), *P=0.679*; and BT = 0.500±1.1473 and D = 0.720±1.4434, at three months follow-up (visit 5), *P=0.401* (see table 4 and figure 4A)]. There was a significantly lower percentage of ocular pain seen in the patients of the BT group at all follow-ups (see figure 4B) compared to patients in the DT group.

Ocular blurring

The repeated measure ANOVA for the mean values for ocular blurring showed a reduction in the values between groups. Compared to DT, the BT treatment group showed a better reduction in the ocular blurring; however, the changes were not statistically significant. [BT = 1.060±1.3463 and DT = 1.200±1.7496, at 2 weeks follow-up (visit 2), *P=0.655*; BT = 0.660±1.0806 and DT = 0.900±1.3590, at one month follow-up (visit 3), *P=0.331*; BT = 0.500±1.1112 and D = 0.840±1.3607, at two months follow-up (visit 4), *P=0.174*; and BT = 0.460±1.1287 and D = 0.800±1.5518, at three months follow-up (visit 5),*P=0.213* (see figure 5)].

Clinical success

The rate of clinical success was different between each treatment group. Though the change in mean IOP was similar in BT and DT groups, the VAS scores for ocular discomfort, ocular pain, and ocular blurring showed a better effect in the BT group.

Discussion

Combination therapy usually requires the instillation of two or more eyedrops more than once a day. This approach decreases patient compliance and increases side effects because of preservatives (Michelessi et al., 2018; Petrov et al., 2018).Also, if problems like ocular pain, discomfort, or blurring occur after taking eyedrops, the patient is non-compliant to the treatment regimen (Inoue et al., 2014; Rajurkar et al., 2018; Boyd et al., 2022).Moreover, simultaneous administration of two or more eye drops can reduce the effect of the drug administered first. Therefore, FDC therapy is preferred (Michelessi et al., 2018; Petrov et al., 2018). In addition to reducing side effects, FDC eye drops also offer other advantages over multiple eye drops, such as reduced treatment costs and simple dosing. Also, comfortable instillation of FDC eye drops improves patient

compliance and is integral to the overall tolerability (Sanseau et al., 2013; Galose et al., 2016).

A combination of carbonic anhydrase inhibitors and beta-blockers has better IOP-reducing efficacy than monotherapy. Itis well-tolerated by the patients (Altafini et al., 2015). FDCs of carbonic anhydrase inhibitors and beta-blockers currently available include brinzolamide (1%) plus timolol maleate (0.5%) and dorzolamide (2%) plus timolol maleate (0.5%) (Sanseau et al., 2013). Clinical studies conducted earlier compare the effect of BT and DT. Since limited comparative clinical studies have been conducted between BT and DT in the small number of Iraqi population, we have conducted this study in a larger Iraqi patient population.

In a study, Galose et al. compared the IOP-lowering effect and tolerability of BT and DT in 73 patients; they found DT to be more effective than BT (Galose et al., 2016).A prospective clinical therapeutic studyby Adnan et al. also compared the efficacy and side effects of BT and DT in 50 patients in Iraq. According to the results obtained from this study, both the FDCs were similarly effective in reducing the IOP; however, BT was more tolerated than DT (Adnan et al., 2015). Our study found that BT and DT were similarly effective in reducing the mean IOP at the 2-weeks follow-up. Also, the IOP was maintained for over three months by BT and DT.

A prospective, double-masked, randomized, active-controlled, crossover, multicenter study conducted by Mundorf et al. compared ocular discomfort and patient compliance for BT and DT. This study showed an increased patient preference for BT over DT. Ocular discomfort scores and ocular pain were greater with DT compared to BT (Mundorf et al., 2008). In a multicenter, prospective, patient-masked, randomized, crossover study conducted by Sansaeu et al., to check the ocular discomfort and patient preference between BT and DT, the FDC containing BT was more tolerable. A significantly higher number of patients preferred BT over DT. The adverse events reported in this study were mild and resolved without additional treatment (Sanseau et al., 2013).A prospective, single-masked crossover study by Altafini et al. studied the patient preference for BT versus DT. Similar to the previous studies, BT was preferred by the patients as the ocular discomfort was lower with BT (Altafini et al., 2015). BT and DT have a common beta-blocker, i.e., timololmaleate but different carbonic anhydrase inhibitors, namely brinzolamide and dorzolamide. In our randomized, open-label, multicentric, active-controlled prospective phase-IV study conducted on 100 patients, the mean score for ocular discomfort was higher in DT and statistically significant compared with BT.

We used the VAS scoring system to measure ocular discomfort, ocular pain, and ocular blurring. We found a significant difference in the mean scores for ocular discomfort and pain. BT treatment was more effective in reducing ocular discomfort, pain, and blurring with a mean score of 0.900±1.5419, 0.500±1.1473, and 0.460±1.1287, respectively, respectively, at 3-month follow-up (visit 5). However, a statistically significant difference was only observed between ocular discomfort and pain (P=0.018). During the second visit (week 2), there was a significant difference between the mean score for ocular pain for both the groups, with BT being more effective than DT (P=0.032). However, the data obtained were not statistically different in the subsequent follow-ups.

The baseline mean IOP values were slightly higher in the DT group; however, the mean IOP values remained nearly the same over the subsequent visits for the next three months. Thus, a BT and DT might have a similar IOP-lowering effect despite different tolerability. A limitation of our study was the small sample size. Larger scale studies might give a clearer picture of the applicability of these findings to the population. Also, we compared the effects of both the FDCs for a relatively shorter duration(three months). Longer studies lasting a year might reveal more insights. Both BT and DT effectively controlled the IOP. As discussed before, ocular side effects can lower patient compliance. Compared with the DT group, patients taking BT were less likely to have ocular discomfort, pain, and blurring than patients on DT.

Table 1. Patient demographics

Treatment	Male	Female	Age (years) (Mean ± SD)	p-value
BT	24 (44%)	26 (48%)	56.760 ± 8.6839	0.901
DT	22 (48%)	28 (52%)	57.040 ± 13.3676	

P-value in comparison to BT and DT.

BT, Brinzolamide + Timolol; DT, Dorzolamide + Timolol; S.D., Standard deviation; SEM, Standard error of mean.

Table 2. Mean change in intraocular pressure

Timepoints		Treatment	Mean ± SD (n=100)	t-value	p-value
Baseline (visit 1)	**IOP_L**	**BT**	27.660 ± 6.3297	-1.412	0.161
		DT	29.446 ± 6.3148		
	IOP_R	**BT**	27.910 ± 7.3483	-0.814	0.417
		DT	28.986 ± 5.7688		
2 weeks (visit 2)	**IOP_L**	**BT**	18.760 ± 3.0476	0.416	0.678

		DT	18.506 ± 3.0609		
	IOP_R	**BT**	18.666 ± 3.5672	0.093	0.926
		DT	18.604 ± 3.0822		
1 month (visit 3)	**IOP_L**	**BT**	17.220 ± 2.3412	-1.204	0.232
		DT	17.800 ± 2.4744		
	IOP_R	**BT**	17.040 ± 2.2584	-0.996	0.322
		DT	17.480± 2.1594		
2 months (visit 4)	**IOP_L**	**BT**	16.720 ± 2.2410	-1.338	0.184
		DT	17.320 ± 2.2446		
	IOP_R	**BT**	16.460 ± 2.2058	-1.737	0.086
		DT	17.220 ± 2.1693		
3 months (visit 5)	**IOP_L**	**BT**	16.430 ± 2.4578	-1.215	0.227
		DT	17.080 ± 2.8774		
	IOP_R	**BT**	16.120 ± 2.3443	-1.472	0.144
		DT	16.840± 2.5424		

P-value = From baseline to next visit and between each visit. IOP-L, Intraocular pressure in the left eye; IOP-R, Intraocular pressure in the right eye; BT, Brinzolamide + Timolol; DT, Dorzolamide + Timolol; S.D., Standard deviation.

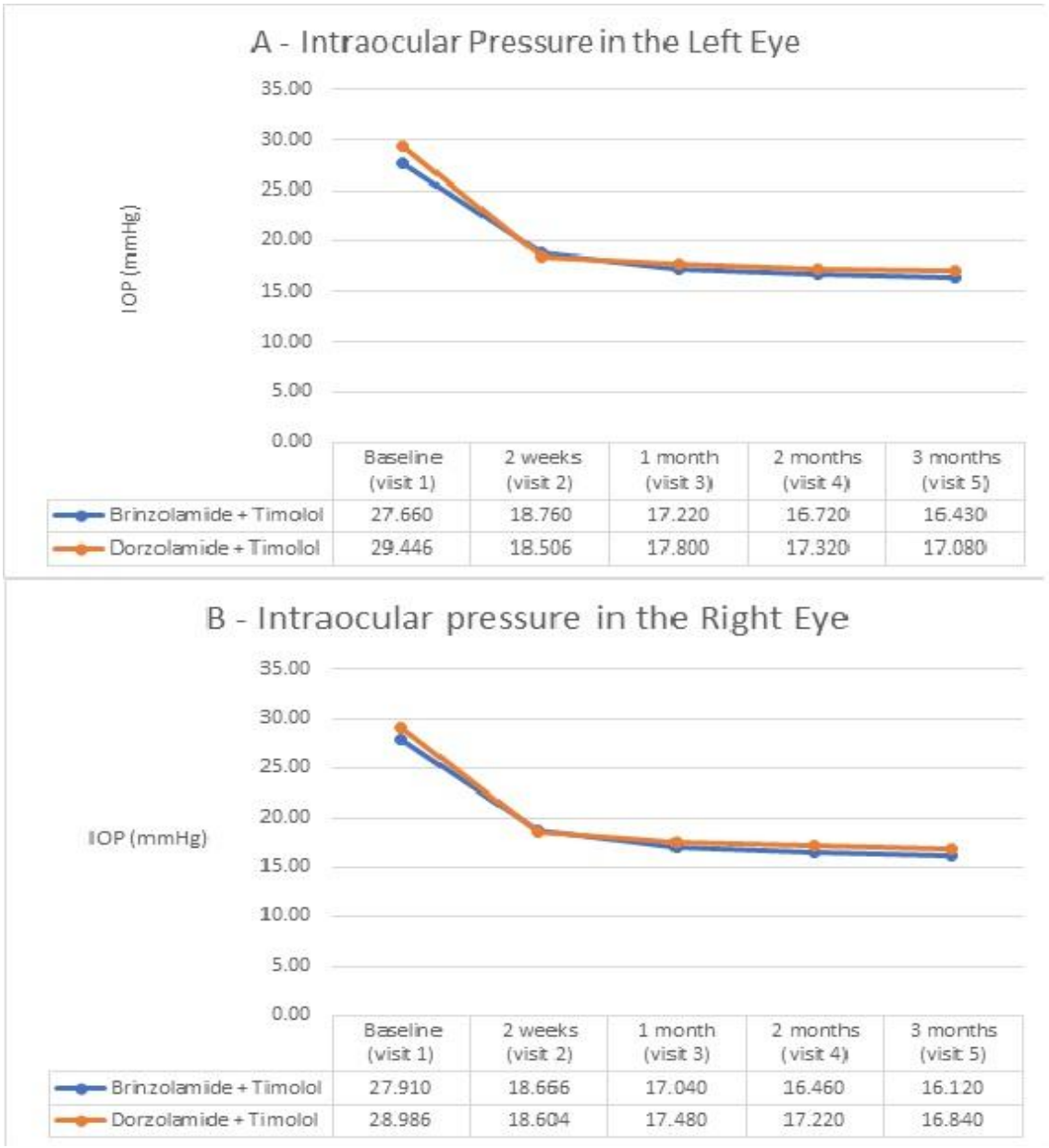

Figure 1. Mean change in intraocular pressure IOP, Intraocular pressure

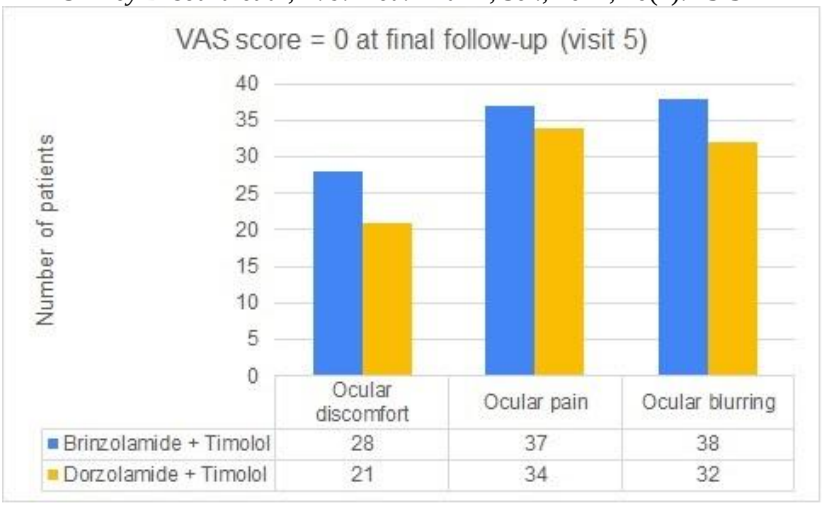

Figure 2. VAS Score for ocular discomfort during final follow-up

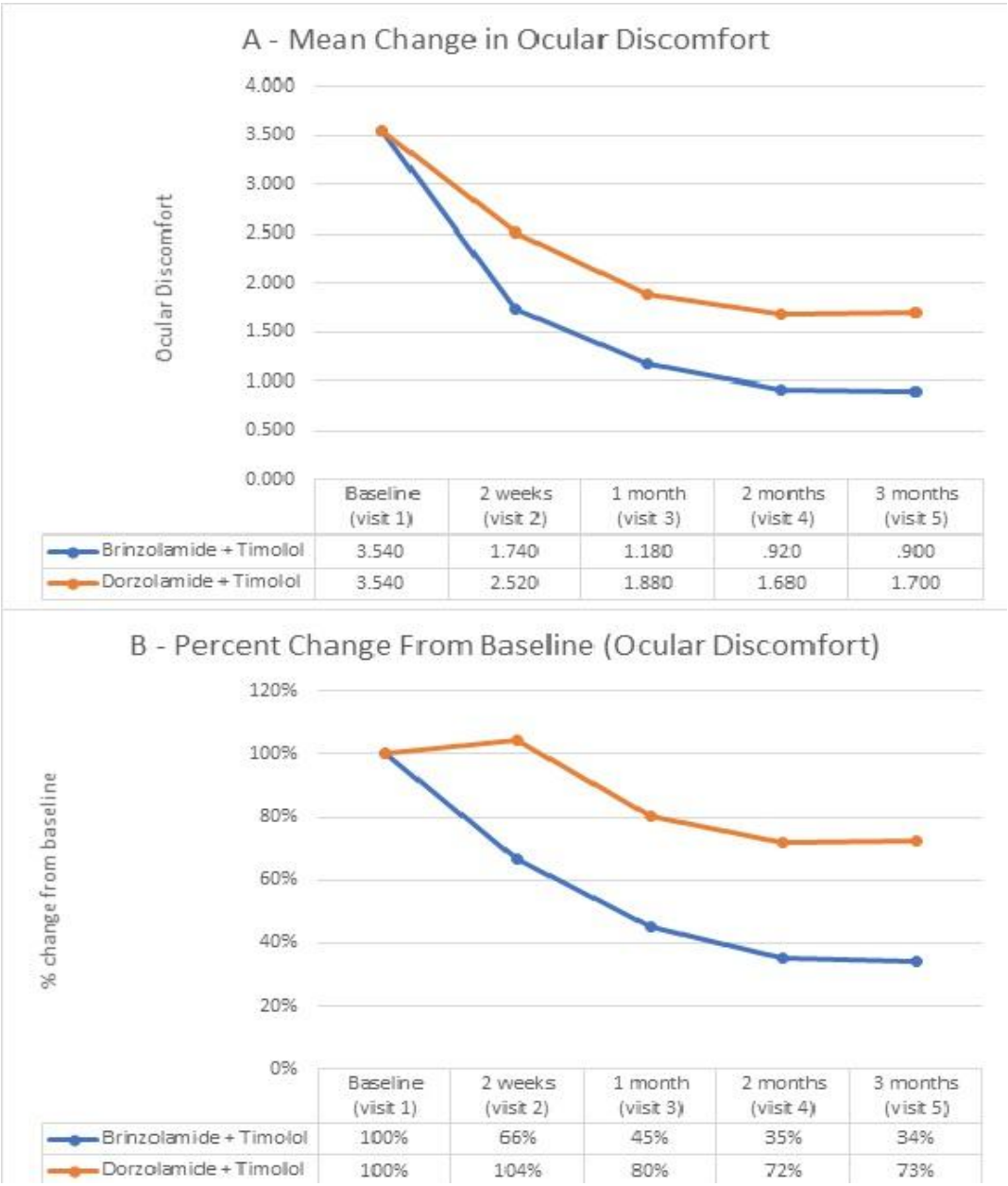

Figure 3. Mean change and per cent change in ocular discomfort

Table 3. Mean change in ocular discomfort

Timepoints	Treatment	Ocular discomfort [Mean ± SD (n=100)]	t-value	p-value
Baseline	BT	3.540 ± 2.3142	0	1.000
	DT	3.540 ± 2.1401		
2 weeks (visit 2)	BT	1.740 ± 2.0385	-1.921	0.058
	DT	2.520 ± 2.0227		
1 month (visit 3)	BT	1.180 ± 1.4525	-2.243	0.027
	DT	1.880 ± 1.6615		
2 months (visit 4)	BT	0.920 ± 1.4263	-2.386	0.019
	DT	1.680 ± 1.7431		
3 months (visit 5)	BT	0.900 ± 1.5419	-2.397	0.018
	DT	1.700 ± 1.7871		

P-value = From baseline to next visit and between each visit. BT, Brinzolamide + Timolol; DT, Dorzolamide + Timolol; S.D., Standard deviation.

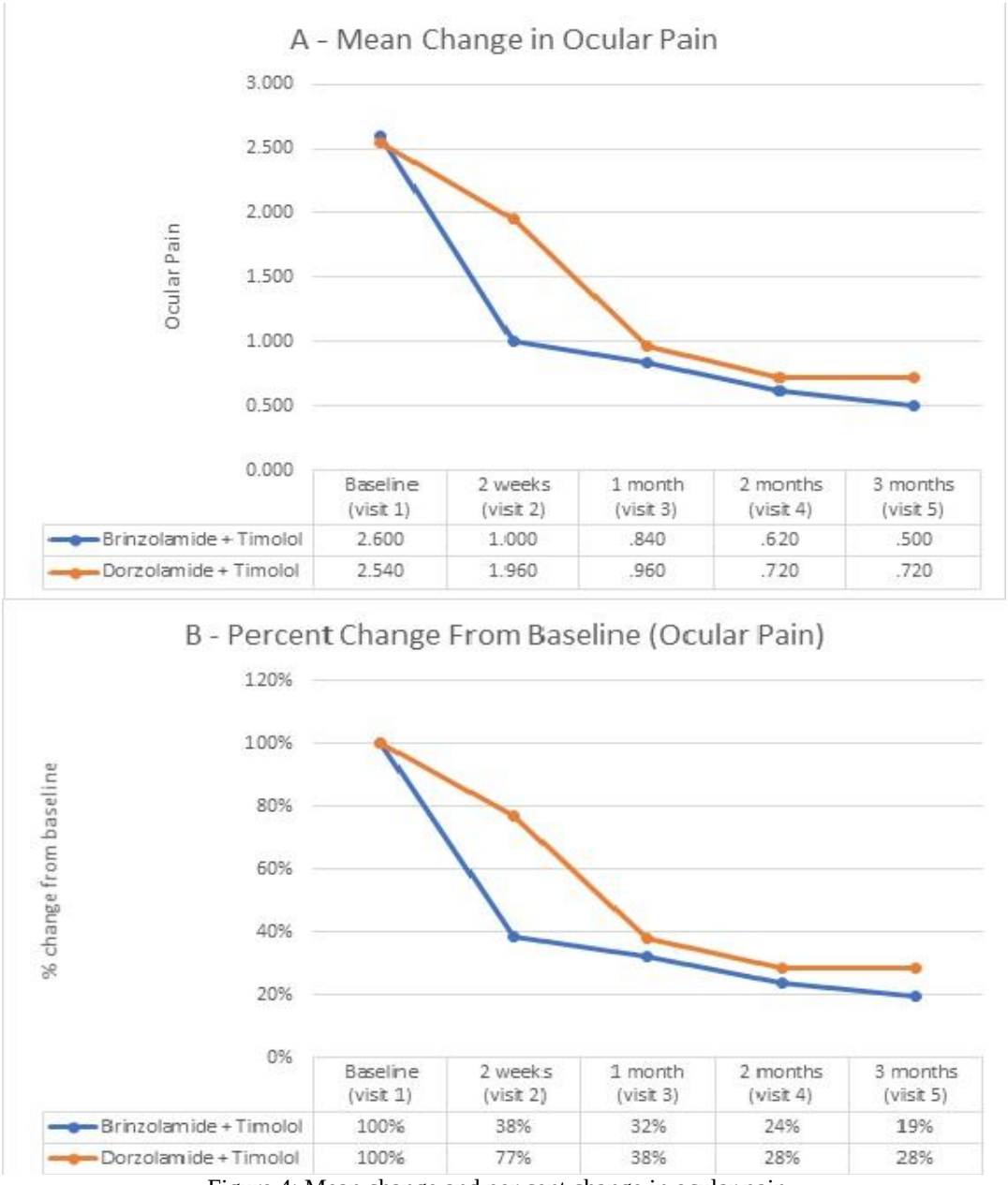

Figure 4: Mean change and per cent change in ocular pain

Table 4. Mean change in ocular pain

Timepoints	Treatment	Ocular pain (Mean ± SD) [Mean ± SD (n=100)]	t-value	p-value
Baseline (visit 1)	BT	2.600 ± 2.3561	0.119	0.905
	DT	2.540 ± 2.6589		
2 weeks (visit 2)	BT	1.000 ± 1.4846	-0.2714	0.032
	DT	1.960 ± 2.7476		
1 month (visit 3)	BT	0.840 ± 1.2513	-0.435	0.665
	DT	0.960 ± 1.4978		
2 months (visit 4)	BT	0.620 ± 1.2103	-0.416	0.679
	DT	0.720 ± 1.1959		
3 months (visit 5)	BT	0.500 ± 1.1473	-0.844	0.401
	DT	0.720 ± 1.4434		

P-value = From baseline to next visit and between each visit.
BT, Brinzolamide + Timolol; DT, Dorzolamide + Timolol; S.D., Standard deviation.

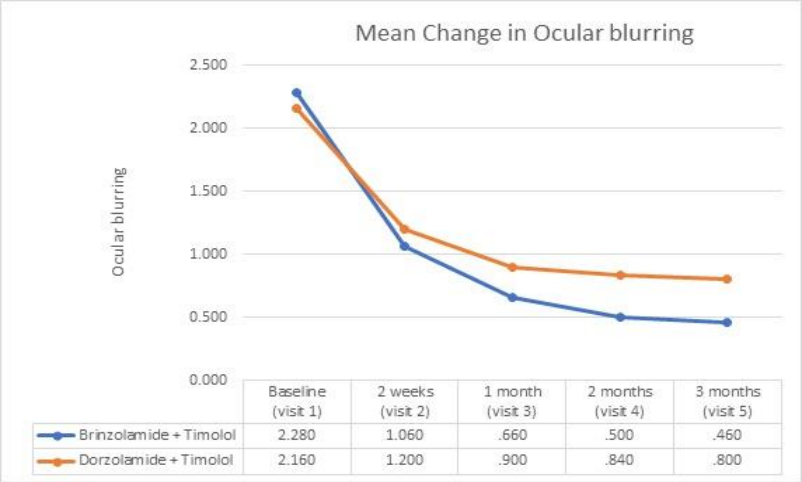

Figure 5. Mean change in the ocular blurring

4. Conclusion

Our findings suggest that BT might be a more appropriate choice as anFDC in patients requiring more than one drug for their treatment. However, further studies will be necessary to confirm the superiority ofBTin a larger patient group. Further studies should also aim to determine the effects of long-term exposure to both BT and DT in terms of patient compliance.

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Declarations

Ethics Committee Approval and Patient Consent

The experiment has been performed in accordance with the principles of Declaration of Helsinki.

Consent to Publish

Not applicable

Authors' Contributions

All authors contributed equally to this work.

Competing Interests

The authors declare that they have no competing interests.

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