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# A comparative study on the efficacy of brinzolamide/timolol versus brinzolamide/brimonidine fixed drug combinations in primary open-angle glaucoma

Sudeepthi Padala<sup>1</sup>, Ramam Sripada<sup>1\*</sup>, Srivalli Bhaskari Padmavathi Gundabattula<sup>1</sup>, Krishna Jyothi Tadi<sup>2</sup>, Prabhakar Rao Nallamothe<sup>2</sup>, Farzaneh Raveshi<sup>1</sup> and Dasaratha Dhanaraju Magharla<sup>1</sup>

## Abstract

**Background:** To compare the efficacy of brinzolamide 1%/timolol 0.5% fixed drug combination (BTFC) with brinzolamide 1%/brimonidine 0.2% fixed drug combination (BBFC) among the patients with primary open-angle glaucoma (POAG).

**Results:** The treatment with BTFC in the Group A subjects showed a significant decrease in the intraocular pressure ( $p = 0.0355^*$ ) and a significant increase in the central corneal thickness ( $p = 0.0087^*$ ). Similarly, in the Group B subjects, the treatment with BBFC showed a significant decrease in the intraocular pressure ( $p = 0.0327^*$ ) and a significant increase in the central corneal thickness ( $p = 0.0227^*$ ). In the process of comparing both the fixed drug combinations, there was no significant difference observed in the aspect of efficacy between both the groups in the decrease of intraocular pressure ( $p = 0.7100$ ) and in the increase of central corneal thickness ( $p = 0.4077$ ).

**Conclusion:** Both the fixed drug combinations almost showed a similar efficacy in treating the respective groups, and there is no significant difference observed in the aspect of efficacy between both the fixed drug combinations in decreasing the intraocular pressure and in increasing the central corneal thickness.

**Keywords:** Brimonidine, Brinzolamide, Glaucoma, Pachymeter, Timolol

## Background

Glaucoma refers to a collection of diseases where increased intraocular pressure (IOP) adversely impacts the optic nerve and subsequently the visual field. It was observed as the second leading cause of global blindness (12.3%) after cataract [1]. According to the National Eye Institute, approximately more than 3 million people in the USA are suffering from glaucoma and this number may reach up to 4.2 million by the year 2030. World Health Organization (WHO) estimates that around 4.5 million people in the world became blind due to glaucoma [2–4]. Approximately,

60 million people were affected globally by glaucoma, and India was the second most affected country as per the statistics of WHO with a share of 12 million cases. Advanced age, diabetes, hypertension, and thyroid disorders were some of the major risk factors of glaucoma. Andhra Pradesh Eye Diseases Survey estimated that glaucoma was more prevalent (3%) in Andhra Pradesh when compared to Tamil Nadu (2%). The prevalence of glaucoma is expected to reach 79.6 million by 2020 impacting all countries, while the highest increase is expected to be in China and India which together may comprise around 40% of the cases globally [5].

Primary open-angle glaucoma (POAG) is a chronic, progressive, and irreversible multifactorial optic neuropathy that is characterized by an open angle of the

\* Correspondence: [ramampharmd7@gmail.com](mailto:ramampharmd7@gmail.com)

<sup>1</sup>Department of Pharmacy Practice, GIET School of Pharmacy, Rajahmundry, Andhra Pradesh, India

Full list of author information is available at the end of the article

anterior chamber, typical optic nerve head changes, and progressive loss of peripheral vision (typical visual field changes) followed by central visual loss (blindness) for which intraocular pressure (IOP) is an important risk factor. The anti-glaucoma medications used in the treatment of POAG are prostaglandin analogues,  $\beta$ -adrenoceptor antagonists,  $\alpha$ -agonists, carbonic anhydrase inhibitors, and rho kinase inhibitors. Many patients require multiple medications for adequate intraocular pressure maintenance which can be achieved by using the fixed drug combinations. Fixed drug combinations provide several benefits which include simplified treatment regimens, enhanced treatment adherence, elimination of the potential washout of the first drug by the second, and minimizing the exposure of eyes to the preservatives [6–8].  $\beta$ -adrenoceptor antagonists are the most commonly used agents in combination with other drug classes, and these are contraindicated in many patients owing to local allergy (or) systemic side effects. Therefore, a fixed drug combination without a  $\beta$ -adrenoceptor antagonist should be warranted for POAG patients who were contraindicated to  $\beta$ -adrenoceptor antagonists [9–12]. In this study, we made an attempt to compare the efficacy of brinzolamide 1%/timolol 0.5% fixed drug combination (BTFC) with brinzolamide 1%/brimonidine 0.2% fixed drug combination (BBFC) among the non-contraindicated and contraindicated subjects to  $\beta$ -adrenoceptor antagonists, respectively, in the treatment of POAG.

## Methods

This was a prospective study conducted after getting the ethical clearance from the Institutional Ethics Committee (IEC), and the data were collected by strictly adhering to the inclusion and exclusion criteria. Patients of both the genders, who were diagnosed with primary open-angle glaucoma with an age of above 18 years, were included in this study. Exclusion criteria involves pregnant women, nursing women, women who were planning to conceive and who were using adequate birth control measures, subjects with chronic/recurrent inflammatory eye diseases, and patients with drug-induced glaucoma [13].

The diagnosis of POAG is based on the IOP measured by using the Goldmann applanation tonometer and also by analyzing the visual field defects. The other criteria in the diagnosis includes glaucomatous disc with the presence of focal or diffuse optic disc rim with or without any defects in the layers of retinal nerve fibers. The central corneal thickness in these patients was measured by using a pachymeter.

### Measurement of the intraocular pressure by the Goldmann applanation tonometer

The thicker cornea shows a higher IOP than it actually exists which indicates the risk of developing glaucoma.

The diagnosis of glaucoma is made after conducting a comprehensive eye examination. Initially, the optic nerve examination is done by using the stereo biomicroscopic slit lamp. It measures the cup-to-disc ratio and disc rim integrity as the glaucoma patients usually have higher cup–disc ratio [14–18]. Further, the intraocular pressure is measured using Goldmann applanation tonometry which is considered as the golden standard for the measurement of IOP. However, Goldmann applanation tonometry is dependent on corneal rigidity, curvature, thickness, and other biochemical properties. So, there is a high probability for error in patients with atypical corneas (or) other ocular conditions [19].

Initially, the prism was disinfected with isopropyl alcohol 70% and was cleaned by using sterile water. Further, it was wiped with a clean dry swab (as the residue of disinfectant may cause a caustic burn on the cornea). The graduation is marked at “0” on the prism which is present in white color on the tonometer head, and the calibrated dial was set to 10 mmHg on the tonometer. The patient was asked to sit comfortably at an appropriate height by properly resting their chin on the chin rest, and the forehead should be placed against the head band of the slit lamp. The magnification of the slit lamp was set to 10 $\times$ .

### Procedure

The IOP was measured after the administration of the local anesthetic drops in order to block the transmission of pain signals, and the fluorescein strips were used to stain the eyes. The beam of the slit on tonometer was adjusted towards the right side of the patient during the IOP measurement of the right eye, while it can be adjusted to the left-hand side of the patient during the IOP measurement of the left eye. Blue and green filters are moved to produce the coloured beam. The beam produced was bright making the fluorescein rings more visible. After fixing the gaze, the patient was asked to look straight with eyes opened widely. By using the thumb, the patient’s eyelid must be held gently without applying much pressure on the eye. The blue light from the slit lamp was directed towards the prism ensuring that the head is perpendicular to the eye. The tonometer was slowly moved forward until the prism rests at the centre of the cornea. Using the other hand, the calibrated dial on the tonometer was turned clockwise until the two fluorescein circles in the prism were observed to meet forming a horizontal “S” shape. The readings on the dial were recorded after withdrawing the prism from the corneal surface. The same procedure was repeated for the other eye after wiping the prism with a disinfectant swab [20].

### Measurement of the central corneal thickness by using the pachymeter

Few studies suggested that applanation pressures vary significantly depending on the corneal thickness as some

of the patients diagnosed with ocular hypertension actually maybe normotensive but corrected for increased corneal thickness. Thus, along with the intraocular pressure measurement, the corneal thickness was also measured in order to make accurate interpretations in the process of diagnosis [19]. Corneal thickness serves the need to measure the pressure in the eyes as it masks the accurate readings of the eye pressure, leading to misinterpretation. A pachymeter is a simple, painless test to measure the central corneal thickness. The normal range of corneal thickness is 540–560  $\mu\text{m}$ . Patients with a thin cornea usually show low IOP readings. It becomes a threat if the IOP reading obtained is higher than the actual reading, which states the risk of developing glaucoma leading to loss of vision if left untreated. Patients with thicker cornea show higher IOP than the suspected readings thus lowering the risk of developing glaucoma [21].

#### Procedure

After administering a drop of 0.5% proparacaine anesthetic into the affected eye, the patient was asked to look straight without blinking. An ultrasound probe tip was gently placed at the center of the cornea perpendicular to the posterior surface of the eye. The ultrasound rays were passed through the cornea via a probe that receives the echoes from the cornea and displays the readings of central corneal thickness [22–24].

#### Fixed drug combinations prescribed to the study subjects

The patients who were diagnosed with POAG were categorized into two groups. Patients who were not contraindicated with  $\beta$ -adrenoceptor antagonist were categorized into Group A, while the patients who were contraindicated with  $\beta$ -adrenoceptor antagonist were categorized into Group B.

Group A subjects were prescribed with brinzolamide 1%/timolol maleate 0.5% ophthalmic suspension which is a combination of carbonic anhydrase inhibitor and  $\beta$ -adrenoceptor antagonist. This combination (BTFC) was used to reduce the elevated intraocular pressure primarily by reducing aqueous humor secretion by different mechanisms of action. Brinzolamide acts by decreasing the production of the clear fluid inside the eye and timolol works by reducing the production of aqueous humor in the ciliary epithelium. The combined effect of these two substances is highly effective than either substance used alone [25]. This ophthalmic suspension was administered by the patients as one drop twice daily into the affected eye(s). Group B subjects were prescribed with brinzolamide 1%/brimonidine tartarate 0.2% ophthalmic suspension which is a combination of carbonic anhydrase inhibitor and  $\alpha$ 2-adrenergic agonist. This combination (BBFC) is of two proven drugs into a single dosage form. Brimonidine also decreases the fluid production

along with the benefit that increases the fluid outflow [26]. This ophthalmic suspension was administered by the patients as one drop three times a day into the affected eye(s). To compare the efficacy of these two fixed drug combinations, the IOP and the corneal thickness were measured at baseline followed by 4th week, 8th week, and 12th-week follow-ups.

#### Statistical analysis

The data were analyzed by using the statistical software Statistical Package for Social Sciences (SPSS version 21.0). Mean and standard deviations were calculated, and *t* test was performed in order to obtain the *p* values at 95% confidence interval ( $p \leq 0.05$ ). The statistically significant values were denoted with an asterisk (\*).

#### Results

In this study, a total of 80 subjects were recruited and were divided into two groups, having 40 subjects in each group. Group A subjects were prescribed with the brinzolamide/timolol fixed drug combination (BTFC) and Group B subjects were prescribed with brinzolamide/brimonidine fixed drug combination (BBFC). Among the Group A subjects, 23 (57.5%) were males, and 17 (42.5%) were females, while in the case of the Group B subjects, 26 (65.0%) were males, and 14 (35.0%) were females. Table 1 represents the age-wise categorization of subjects recruited in the study. Majority of the glaucoma patients were observed in the age group of 51–60 years (32.5%) followed by the age group 61–70 years (28.8%). Very few cases were observed in the age group 31–40 years (2.5%). This result indicates that glaucoma is more prevalent among the elderly population when compared to the younger population.

Table 2 represents the mean IOP readings of the subjects in Group A and Group B. Among the Group A subjects, the mean IOP in the right eye was observed to be 22.40 ( $\pm 4.8$ ) mmHg at baseline which was reduced to 14.10 ( $\pm 2.6$ ) mmHg with a difference of 8.3 mmHg, while in the case of the left eye, the mean IOP at baseline was observed to be 21.98 ( $\pm 5.1$ ) mmHg which was reduced to 12.70 ( $\pm 2.1$ ) mmHg with a difference of 9.28 mmHg after 12 weeks of treatment with BTFC (*p* value =

**Table 1** Age-wise categorization of subjects recruited in the study

Age	Male	Female	Total
31–40	1 (2.0)	1 (3.2)	2 (2.5)
41–50	9 (18.4)	7 (22.6)	16 (20.0)
51–60	13 (26.5)	13 (41.9)	26 (32.5)
61–70	17 (34.7)	6 (19.4)	23 (28.8)
71–80	9 (18.4)	4 (12.9)	13 (16.2)
<b>Total</b>	<b>49 (100)</b>	<b>31 (100)</b>	<b>80 (100)</b>

**Table 2** Mean intraocular pressure before and after the treatment in Group A (BTFC) and Group B (BBFC) subjects

IOP of the eyes	BTFC		BBFC	
	Before	After	Before	After
Right eye	22.40 (± 4.8)	14.10 (± 2.6)	22.33 (± 4.3)	14.30 (± 2.3)
Left eye	21.98 (± 5.1)	12.70 (± 2.1)	22.15 (± 3.8)	13.25 (± 2.2)

0.0355\*). Among the Group B subjects, the mean IOP in the right eye was observed to be 22.33 (± 4.3) mmHg at baseline which was reduced to 14.30 (± 2.3) mmHg with a difference of 8.03 mmHg, while the mean IOP in the left eye was observed to be 22.15 (± 3.8) mmHg at baseline which was reduced to 13.25 (± 2.2) mmHg with a difference of 8.9 mmHg after 12 weeks of treatment with BBFC (*p* value = 0.0327\*). In the subjects who were treated with BTFC, the intraocular pressure was reduced to 14.10 (± 2.6) mmHg in the right eye and 12.70 (± 2.1) mmHg in the left eye after the treatment, while in the case of the subjects who were treated with BBFC, the intraocular pressure was reduced to 14.30 (± 2.3) mmHg in the right eye and 13.25 (± 2.2) mmHg in the left eye after the treatment for 12 weeks (*p* value = 0.7100).

Table 3 states the IOP readings of the right and left eyes of Group A subjects based on the age-wise categorization. In this group, the highest reduction of the mean IOP in the right and left eyes were observed in the age group 71–80 years with a difference of 10.5 mmHg and 11.5 mmHg, respectively.

Table 4 states the IOP readings of the right and left eyes of Group B subjects based on the age-wise categorization. In this group, the highest reduction of the mean IOP in the right eye was observed in the age group 31–40 years with a difference of 10.00 mmHg, and in the case of the left eye, the highest mean IOP reduction was observed in the age group 41–50 years with a difference of 10.25 mmHg.

Table 5 represents the mean central corneal thickness readings of the right and left eyes of Group A and Group B. In the case of Group A (BTFC), the mean central corneal thickness of the right eye was increased from 462.3 (± 38.3) to 509.4 (± 11.5) µm, and the difference increased was observed to be 47.1 µm, while in the case of

**Table 3** Mean intra ocular pressure before and after the treatment in Group A (BTFC) subjects based on age

Age	Right eye		Left eye	
	Before	After	Before	After
41–50	21.92 (± 2.7)	14.75 (± 2.9)	21.67 (± 3.2)	13.42 (± 2.1)
51–60	22.46 (± 6.3)	14.15 (± 2.7)	21.85 (± 6.5)	12.69 (± 2.3)
61–70	22.36 (± 5.4)	13.64 (± 2.4)	21.82 (± 5.6)	12.09 (± 1.7)
71–80	23.75 (± 4.3)	13.25 (± 2.2)	23.75 (± 4.3)	12.25 (± 2.6)
Overall	22.40 (± 4.8)	14.10 (± 2.6)	21.98 (± 5.1)	12.70 (± 2.1)

**Table 4** Mean intra ocular pressure before and after the treatment in Group B (BBFC) subjects based on age

Age	Right eye		Left eye	
	Before	After	Before	After
31–40	23.0 (± 1.4)	13.0 (± 2.8)	23.0 (± 1.4)	12.5 (± 2.1)
41–50	22.0 (± 4.3)	12.2 (± 0.9)	22.0 (± 4.3)	11.75 (± 1.7)
51–60	21.62 (± 5.0)	14.31 (± 2.6)	21.46 (± 3.2)	13.15 (± 2.5)
61–70	24.67 (± 4.7)	15.0 (± 2.8)	24.42 (± 4.7)	14.17 (± 2.5)
71–80	20.22 (± 1.5)	14.56 (± 1.1)	20.0 (± 1.8)	13.0 (± 1.2)
Overall	22.33 (± 4.3)	14.3 (± 2.3)	22.1 (± 3.8)	13.25 (± 2.2)

the left eye, the mean corneal thickness was increased from 462.9 (± 38.1) to 511.3 (± 12.4) µm and the difference increased was observed to be 48.3 µm (*p* value = 0.0087\*). In the case of Group B (BBFC), the mean central corneal thickness of the right eye was increased from 469.1 (± 36.1) to 511.2 (± 9.0) µm, and the difference increased was observed to be 42.1 µm, while in the case of the left eye, the mean corneal thickness was increased from 472.3 (± 43.3) to 511.5 (± 9.1) µm, and the difference increased was observed to be 39.2 µm (*p* value = 0.0227\*). In the subjects who were treated with BTFC, the mean central corneal thickness was increased to 509.4 (± 11.5) µm in the right eye and 511.3 (± 12.4) µm in the left eye after the treatment, while in the case of the subjects who were treated with BBFC, the mean central corneal thickness was increased to 511.2 (± 9.0) µm in the right eye and 511.5 (± 9.1) µm in the left eye after the treatment for 12 weeks (*p* value = 0.4077).

Table 6 represents the mean central corneal thickness readings of the right and left eyes of Group A subjects based on the age-wise categorization. In this group, the maximum increase of the mean corneal thickness in the right eye was observed in the age group 51–60 years with a difference of 54.8 µm, and in the case of the left eye, the maximum increase of the mean corneal thickness was observed in the age group 71–80 years with a difference of 56.5 µm.

Table 7 represents the mean central corneal thickness readings of the right and left eyes of the Group B subjects based on age-wise categorization. In this group, the

**Table 5** Mean corneal thickness before and after the treatment in Group A (BTFC) and Group B (BBFC) subjects

Corneal thickness of the affected eye	BTFC		BBFC	
	Before	After	Before	After
Right eye	462.3 (± 38.3)	509.4 (± 11.5)	469.1 (± 36.1)	511.2 (± 9.0)
Left eye	462.9 (± 38.1)	511.3 (± 12.4)	472.3 (± 43.3)	511.5 (± 9.1)

**Table 6** Mean corneal thickness before and after the treatment in Group A (BTFC) subjects based on age

Age	Right eye		Left eye	
	Before	After	Before	After
41–50	464.8 (± 40.5)	509.3 (± 11.6)	460.8 (± 33.9)	512.8 (± 12.2)
51–60	453.7 (± 32.7)	508.5 (± 13.8)	457.2 (± 31.7)	509.8 (± 13.9)
61–70	469.0 (± 37.7)	508.0 (± 9.4)	472.5 (± 41.0)	509.3 (± 11.6)
71–80	464.0 (± 59.6)	516.5 (± 10.3)	460.8 (± 67.4)	517.3 (± 12.7)
Overall	462.3 (± 38.3)	509.4 (± 11.5)	462.9 (± 38.1)	511.3 (± 12.4)

maximum increase of the mean corneal thickness in the right and left eyes was observed in the age group 41–50 years with differences of 66.0  $\mu\text{m}$  and 55.3  $\mu\text{m}$ , respectively.

## Discussion

In glaucoma, treatment with fixed drug combinations may improve the adherence that serves the need in the management of disease progression and prevention of vision loss by reducing the intraocular pressure and increasing the central corneal thickness. In this study, the patients who were diagnosed with POAG were categorized into Group A and Group B and were prescribed with BTFC and BBFC fixed drug combinations, respectively. The elevated intraocular pressure is a major risk factor for the development and progression of glaucoma. In the present study, a significant reduction of the intraocular pressure in both eyes was observed on treatment with both BTFC ( $p$  value = 0.0355\*) and BBFC ( $p$  value = 0.0327\*). Hence, there is no significant difference in the aspect of efficacy between the two groups in reducing the intraocular pressure ( $p$  value = 0.7100). A significant reduction in the IOP was observed in all the age groups of the study participants after the treatment with BTFC (right eyes  $p$  value = 0.0011\* and left eyes  $p$  value = 0.0008\*) and similarly with BBFC (right eyes  $p$  value = 0.0006\* and left eyes  $p$  value = 0.0002\*).

As a part of the study, the corneal thickness of the subjects was recorded using the pachymeter to assess the risk. This approach is mainly due to the impact of

**Table 7** Mean corneal thickness before and after the treatment in Group B (BBFC) subjects based on age

Age	Right eye		Left eye	
	Before	After	Before	After
31–40	492.0 (± 28.2)	519.0 (± 15.5)	487.0 (± 21.2)	519.0 (± 12.7)
41–50	443.5 (± 26.4)	509.5 (± 7.5)	450.0 (± 29.7)	505.3 (± 7.0)
51–60	459.3 (± 39.2)	509.1 (± 6.8)	465.0 (± 42.9)	508.7 (± 7.3)
61–70	470.1 (± 30.1)	510.8 (± 9.3)	469.2 (± 43.6)	512.8 (± 8.2)
71–80	488.2 (± 37.8)	513.9 (± 11.0)	493.4 (± 49.7)	514.9 (± 11.3)
Overall	469.1 (± 36.1)	511.2 (± 9.0)	472.3 (± 43.3)	511.5 (± 9.1)

central corneal thickness on intraocular pressure as it masks the accurate readings of the eye pressure. The normal value of central corneal thickness is 555  $\mu\text{m}$ . Sometimes, the actual IOP may be underestimated in patients with thinner cornea and overestimated in patients with thicker cornea. Hence, the correction factor of  $\pm 3$  mmHg IOP for every 50  $\mu\text{m}$  was used to obtain the accurate readings. A significant increase in the central corneal thickness in both the eyes was observed on treatment with both BTFC ( $p$  value = 0.0087\*) and BBFC ( $p$  value = 0.0227\*). There is no significant difference in the aspect of efficacy in increasing the central corneal thickness between the two groups ( $p$  value = 0.4077). A significant increase in the central corneal thickness was observed in all the age groups of the study participants after the treatment with BTFC (right eyes  $p$  value = 0.0010\* and left eyes  $p$  value = 0.0014\*) and similarly with BBFC (right eyes  $p$  value = 0.0051\* and left eyes  $p$  value = 0.0024\*). The IOP when measured alone may not provide enough data in determining the effect of anti-glaucoma medications in lowering the IOP. This is due to the differences between the actual IOP readings and the readings obtained from applanation tonometry which is related to the central corneal thickness. Hence, in our study, the central corneal thickness was also measured to provide the accurate readings of the IOP.

The present study differs from the other studies done by Michaud and Friren [27], Sherwood et al. [28], Kaback et al. [29], Stefano et al. [13], and Nguyen et al. [30] as they have included the measurement of IOP or CCT alone. But in our study, we implicated both the methods for distinguishing the patients from ocular hypertension to normotension glaucoma which is usually misinterpreted in diagnosing glaucoma patients.

In a recent study, Nguyen et al. [30] compared the efficacy of BBFC with brinzolamide alone and brimonidine alone. According to their study, mean diurnal IOP in patients of the group using BBFC was statistically significant compared with the other two drugs prescribed alone, and they have stated that a combination medication is frequently required for adequate control of IOP which can be achieved by the concurrent use of two drugs from different classes providing multiple potential benefits. Kaback et al. [29] compared the efficacy of brinzolamide/timolol fixed combination with brinzolamide alone and timolol alone stating that the IOP-lowering efficacy of fixed drug combination (brinzolamide/timolol) in glaucoma patients is superior when compared to the patients who were prescribed with brinzolamide monotherapy and timolol monotherapy [29].

As most of these studies demonstrated the comparison between combination therapy versus monotherapy in lowering the intraocular pressure and these studies limit the assessment of a fixed drug combination versus

concomitant administration of the same individual drugs, they restrict the direct comparison with other classes of IOP-lowering agents. But our study lays a special emphasis on overcoming these barriers by comparing the two fixed drug combination therapies having three different classes of IOP-lowering agents in treating the primary open-angle glaucoma. Diurnal variations of the intraocular pressure and follow-up of the patients for a longer period of time were the limitations of this study.

## Conclusion

This was the foremost study that compared the efficacy of two recently marketed fixed drug combinations. The treatment with BTFC in non-contraindicated  $\beta$ -adrenoceptor antagonist (Group A) subjects and the treatment with BBFC in contraindicated  $\beta$ -adrenoceptor antagonist (Group B) subjects showed a significant decrease in the intraocular pressure and a significant increase in the central corneal thickness that showed a positive impact in managing primary open-angle glaucoma. In comparison, both the fixed drug combinations almost showed a similar efficacy in treating the subjects of the respective groups and there is no significant difference observed in the aspect of efficacy between both the fixed drug combinations in decreasing the intraocular pressure and in increasing the central corneal thickness.

## Abbreviations

WHO: World Health Organization; POAG: Primary open-angle glaucoma; IOP: Intraocular pressure; BTFC: Brinzolamide/timolol fixed combination; BBFC: Brinzolamide/brimonidine fixed combination; IEC: Institutional Ethics Committee; SPSS: Statistical Software Package for Social Sciences

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## Authors' contributions

This study was designed by SP, RS, and KJT. Diagnosis of glaucoma and treatment allocation were done by KJT and PRN. Data collection and follow-up were done by SP, SBPG, FR, and DDM. Statistical analysis and manuscript drafting were done by RS and SP. The authors have read and approved the final manuscript.

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## Ethics approval and consent to participate

This study was conducted after obtaining the ethical clearance from the institutional ethics committee of GIET School of Pharmacy, Rajahmundry, Andhra Pradesh, India (GSPRJY-IEC/Pharm.D/2018/03). Written informed consent was taken from all the study participants to participate in this study.

## Consent for publication

Consent for publication was obtained from all participants in the study.

## Competing interests

The authors declare that they have no competing interests.

## Author details

<sup>1</sup>Department of Pharmacy Practice, GIET School of Pharmacy, Rajahmundry, Andhra Pradesh, India. <sup>2</sup>Akira Eye Hospitals, Rajahmundry, Andhra Pradesh, India.

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