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Research Article

Efficacy and Cost Analysis of Brinzolamide 1%/Brimonidine 0.2% Fixed Combination (BBFC) Therapy Vs Separate Concomitant Brinzolamide 1% and Brimonidine 0.2% Therapy: A Comparative Study

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Abstract

Purpose: The aim of the study was to compare the intraocular pressure (IOP) lowering efficacy and cost analysis of Brinzolamide 1%/Brimonidine 0.2% fixed combination (BBFC) therapy versus separate concomitant Brinzolamide 1% and Brimonidine 0.2% (Brinz + Brim) therapy.

Methods: A prospective, randomized, comparative, cross over, 12-week study was conducted on forty patients of primary open angle glaucoma or ocular hypertension. Enrolled patients were randomized into two groups (Group A and B) of twenty patients each. For the first 6 weeks of the 12-week study period, Group A patients received Brinzolamide 1%/Brimonidine 0.2% fixed combination (BBFC) therapy and Group B patients received concomitant Brinzolamide 1% and brimonidine 0.2% (Brinz + Brim) therapy, each given twice daily. After the 6-week follow-up visit, Group A patients were crossed over to concomitant Brinzolamide 1% and Brimonidine 0.2% (Brinz + Brim) therapy while the Group B patients were crossed over to Brinzolamide 1%/brimonidine 0.2% fixed combination (BBFC) therapy. IOP was assessed at baseline and at 6-week and 12-week visits at 9 am (before instillation of drug) and 11 am (post dose, peak effect). The daily cost of both the therapies was calculated by maximum retail price and average drop count per bottle. The cost-effectiveness of both therapies was then calculated as cost of therapy/mm Hg fall in IOP.

Results: There was no statistically significant difference between the patient characteristics of the two groups. The mean age for Group A was 64.15 years and for Group B was 63.45 years. In Group A, 10 (50%) were females and in Group B, 11 (55%) were females. There was no statistical difference between the baseline IOP of both the groups. At both time points, IOP lowering from baseline after 6 weeks of therapy with either BBFC or Brinz + Brim was statistically significant ($p < 0.00001$). After 6 weeks, the mean IOP reduction from baseline in Group A (BBFC) was calculated to be 7.98 ± 1.31 mmHg (31.11%) and for Group B (Brinz + Brim) was calculated to be 7.87 ± 0.98 mmHg (30.56%). The difference in mean IOP reduction between both the groups at 6 weeks was statistically insignificant ($p = 0.39$). After 6 weeks visit when the therapies were switched among both groups, the mean IOP at the 12-week visit was statistically similar to the mean IOP of the same group at 6 weeks visit. The side effect profile of both the therapies was similar, none of the patients having any serious side effect warranting discontinuation of the treatment. For 6-week study period, cost per mm Hg IOP reduction for BBFC therapy and Brinz + Brim therapy was respectively found to be Rs 45.7 ± 0.4 per mmHg and Rs 67.54 ± 0.29/mmHg per mmHg. The total 6-weekly cost of BBFC therapy was found to be Rs 364.72 ± 3.15 ($ 4.2) while that of Brinz + Brim therapy was Rs 531.55 ± 2.33 ($ 7.43). Using cost minimization analysis, it was found that Brinz + Brim therapy costs Rs 166.83 ± 3.27 ($ 2.63) more than BBFC therapy to attain similar IOP reduction for a period of 6 weeks.

Conclusion: Brinzolamide 1%/Brimonidine 0.2% fixed combination (BBFC) is an effective and safe IOP lowering therapy with an auxiliary advantage of being more economical than concomitant separate Brinzolamide 1% and Brimonidine 0.2% therapy.

Keywords: Brinzolamide; Brimonidine; Brim Therapy; BBFC Therapy

Introduction

Glaucoma is a group of disorders characterized by progressive degeneration of the retinal ganglion cells and the optic nerve axons which can lead to irreversible blindness if left undiagnosed and untreated [1]. Glaucoma is the second largest cause of blindness overall and is the most common cause of irreversible blindness in the world [2]. The goal of glaucoma management primarily is to prevent the risk factors, especially elevated Intraocular pressure (IOP), using topical medications, laser therapy or surgery [1].

Presently, IOP reduction is the only evidence-based therapy available for glaucoma management.[3] The first-line of topical anti-glaucoma therapy includes prostaglandin analogs and β-blockers. Other options available are carbonic anhydrase inhibitors (e.g. brinzolamide) and sympathomimetics (e.g. brimonidine) [4]. In many cases, monotherapy is often inadequate in achieving target IOP and preventing disease progression. Effectiveness of a single medication may be lost with time due to tachyphylaxis [5]. Thus frequently a combination of medications is required to achieve target IOP in long term which can either be done by concomitant administration of two separate medications or a fixed combination product of two drugs of different classes [6].

Use of fixed-combination therapy is preferred due to various factors including decreased exposure to preservatives, increased patient convenience, and avoidance of washout of first medication by administration of second. These factors could increase the likelihood of adherence to therapy by the patient and at a potentially lower cost [7].

In April 2013, the US Food and Drug Administration (FDA) approved brinzolamide 1%/brimonidine 0.2% fixed combination, a new fixed-combination ocular antihypertensive that did not include a β-blocker [8]. Since most of the drug combinations included Timolol, patients with any contraindication to the use of beta-blockers like bronchial asthma, obstructive airway diseases, second or third-degree heart block and severe congestive heart failure could not use these combination drugs [9]. With this beta-blocker free combination, more such patients have option to use anti-glaucoma medication and thereby delaying laser or surgical therapy.

Glaucoma needs long term treatment which can be a financial burden to the patient and may result in low adherence to the treatment. This makes cost a major hurdle in the success of glaucoma treatment. The financial burden to the patient increases as the severity of disease increases. Therefore, medications required to treat chronic illnesses like glaucoma should justify their cost [10]. Pharmaco-economic evaluation of glaucoma therapy needs to be targeted at assessment of its efficiency i.e. health effects weighed against the costs incurred for attaining them. The decision of choosing a therapy should, therefore, be based on both efficacy and cost of therapy [11].

The decision of glaucoma therapy should be made keeping in mind cost of the drug along with its efficacy. As topical anti-glaucoma treatment is a long term intervention, it needs to be cost effective if the best use of finite resources is to be made. This study took into account the Maximum Retail Price (MRP), overfilling of vials, underfilling of vials, number of drops per bottle and drop size in calculating the actual costs rather than relying merely on the market price of the vials. These costs when weighed against the IOP lowering efficacy of the therapies lead to cost effectiveness analysis of the concerned therapy.

Methods

This 6-week, prospective, randomized, open label cross over study was conducted on forty patients of POAG or Ocular Hypertension attending the Outpatient Department of Ophthalmology, Government Medical College, Patiala. All patients included in the study were > 18 years of age, having unilateral or bilateral primary open angle glaucoma or ocular hypertension with baseline IOP < 30 mmHg in one or both eyes.

Exclusion criteria for this study included any contraindication or hypersensitivity to any of the study drug, having acute angle closure glaucoma or with closed anterior chamber, diagnosis of secondary glaucoma, history of any intraocular surgery within 6 months of commencement of study, active infection or inflammation of eye, pregnant and lactating females.

Forty patients fulfilling these criteria were enrolled in the study and written informed consent was obtained. The consent was taken in accordance with Declaration of Helsinki and all were given an option to prematurely exit the study without having to assign any reason for doing so. Patients were then randomized, using random numbers, into two groups (Group A and B) with twenty patients in each group and their baseline IOP was recorded on day 0 at 9

am and 11 am. Patients in group A were asked to instil one drop of Brinzolamide 1%/Brimonidine 0.2% fixed combination (BBFC), 2 times a day at 9 am and 9 pm for 6 weeks. Group B patients were asked to instil one drop of Brinzolamide 1% (2 times a day at 8 AM and 8PM), and one drop of brimonidine 0.2% concomitantly (Brinz + Brim), (2 times a day at 9 am and 9 pm) for 6 weeks. After 6 weeks of therapy the patients were crossed over to other therapy i.e. Group A patients instilled one drop of Brinzolamide 1% (2 times a day at 8 AM & 8PM) and one drop of brimonidine 0.2% concomitantly (Brinz + Brim), (2 times a day at 9 am and 9 pm) for 6 weeks and Group B instilled one drop of Brinzolamide 1%/ Brimonidine 0.2% fixed combination (BBFC), 2 times a day at 9 am and 9 pm for 6 weeks. The formulations used in the study were Simbrinza (BBFC) (Novartis India, Mumbai), Azopt (Brinzolamide 1%) (Alcon Laboratories, Bengaluru, India) and Alphagan (Brimonidine 0.2%) (Allergan India, Bengaluru). IOP was again recorded in OPD at 6-week and 12-week visit at 9 am (before instillation of study drug) and 11 am (post dose, peak effect) using Goldmann Applanation Tonometer. Effectiveness of the drugs was calculated in terms of mmHg fall in mean IOP. All the observations were compiled and subjected to appropriate tests for statistical analysis using SPSS software version 22.0 Chicago, Illinois, USA.

To determine the cost, five commercially available sized bottles each of BBFC, Brinzolamide 1% and Brimonidine 0.2% were taken and drops per bottle was calculated by collecting in a graduated measuring cylinder with bottles held at 135° (angle at which drops are instilled in the eyes) to it. The actual, not labeled volume was determined for each bottle. Daily cost of particular anti-glaucoma medication was calculated by dividing the cost of one bottle by total number of drops in a bottle and multiplying by number of drops required daily. Thereafter 6-weekly cost of both the therapies was calculated. In pharmaco-economic study of two similarly efficacious therapies, cost minimization analysis was done directly by comparing the cost of both therapies.

$$\text{Cost per day per eye} = \text{Cost per bottle} \times \frac{\text{No. of drops required per day per eye}}{\text{No. of drops per bottle}}$$

$$\text{Cost for 6 weeks of therapy per eye} = \text{Cost per day per eye} \times 42$$

Cost-effectiveness of each drug was calculated by:

$$\frac{\text{Cost of drug for 6 weeks}}{\text{IOP lowering at 6 weeks}}$$

Being a cross-over study design all forty patients included in the study received both forms of therapy for 6 weeks each. This reduced the impact of confounding variables in our study by allowing each subject to be his/her own internal comparison. Theoretically, this study design can achieve the same degree of precision as a parallel study design, but with half the sample size (Figure 1).

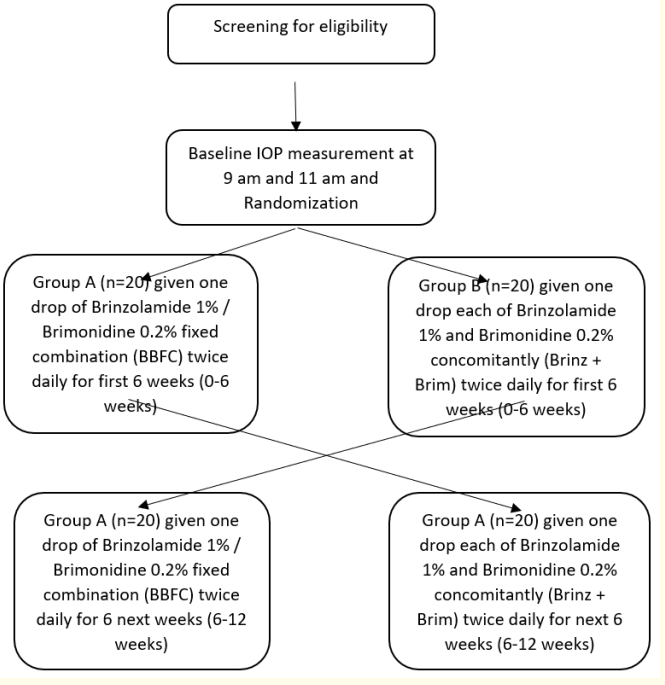

Figure 1: Study design.

Results

Patient characteristics

Forty patients were enrolled in the study with 20 patients in each group (Group A and Group B). The mean age in Group A was 64.15 years and for Group B was 63.45 years (Table 1). There was no statistical difference between the age of patients in the two groups (p = 0.74). In Group A 10 (50%) patients were females and 10 (50%) were males and in Group B 11 (55%) patients were females and 9 (45%) were males (Table 2). There was no statistical difference in gender distribution between the two groups (p = 0.75).

Age (years)	Group A		Group B	
	No. of Pts	Percentage	No. of Pts	Percentage
≤50	1	5.00%	1	5%
51-60	5	25%	7	35%
61-70	11	55.00%	9	45.00%
71-80	3	15.00%	3	15.00%
Total	20		20	
Mean	64.15 ± 6.79		63.45 ± 6.66	
Median	64.5		65	
Range	49 - 78		48 - 75	

Table 1: Age distribution in both groups.

Gender	Group A		Group B	
	No. of Patients	Percentage	No. of Patients	Percentage
Female	10	50%	11	55.00%
Male	10	50%	9	45.00%
Total	20	100%	20	100%

Table 2: Gender distribution in both groups.

IOP lowering efficacy

There was no statistically significant difference in baseline mean IOP at 9 am and 11 am measurements between both the groups ($p > 0.05$). At 6-week visit, there was no statistically significant difference in mean IOP between both groups (Table 3).

	Group	Baseline Mean ± SD (mmHg)	p value	Week-6 Mean ± SD (mmHg)	p value (group A vs B)
9:00 AM	Group A (BBFC)	26.3 ± 1.78	0.31	18.1 ± 0.97	0.63
	Group B (Brinz + Brim)	26.55 ± 1.39		18.25 ± 1.02	
11:00 AM	Group A (BBFC)	25 ± 1.83	0.46	17.25 ± 1.06	0.7
	Group B (Brinz + Brim)	24.95 ± 1.57		17.5 ± 0.94	

Table 3: Comparison of mean IOP of both groups at baseline and 6-week visit.

Mean IOP reduction from baseline for Group A, at the end of 6 weeks of BBFC therapy was found to be 8.2 ± 1.32 mmHg (9 am recording) and 7.75 ± 1.45 mmHg (11 am recording). Mean IOP reduction at both time points was statistically significant at both time points ($p < 0.00001$). Similarly, mean IOP reduction from baseline for Group B, at the end of 6 weeks of Brinz + Brim therapy was found to be 8.3 ± 0.98 mmHg (9 am recording) and 7.45 ± 1.1.4 mmHg (11 am recording).Mean IOP reduction at both time points was statistically significant at both time points ($p<0.00001$) (Figure 2).

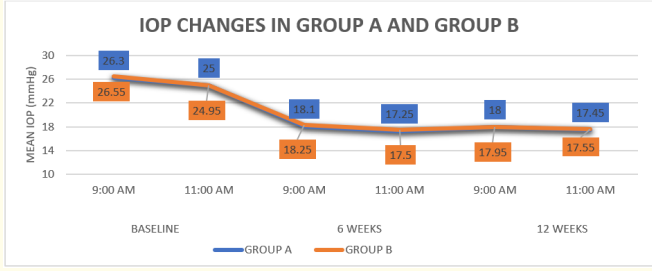

Figure 2

At the end of 6 weeks, mean reduction of IOP from baseline for Group A (BBFC) was calculated to be 7.98 ± 1.31 mmHg (31.11%) and for Group B (Brinz + Brim) was calculated to be 7.87 ± 0.98 mmHg (30.56%) (Table 4).

Group	Average of 9 am and 11 am		p value	Mean IOP reduction (mmHg vs baseline)	Percentage reduction
	Baseline	6 weeks			
Group A (BBFC)	25.65 ± 1.79	17.67 ± 0.95	< 0.00001	7.98 ± 1.31	31.11%
Group B (Brinz + Brim)	25.75 ± 1.43	17.87 ± 0.96	< 0.00001	7.87 ± 0.98	30.56%

Table 4: Mean and percentage IOP reduction in both groups.

After 6 weeks visit when the therapies were switched among both the groups, the mean IOP at the 12-week visit was statistically similar to the mean IOP of the same group at 6-week visit at both time points ($p > 0.05$) (Table 5).

Groups		Mean IOP		p value (group A vs B)
		6-week visit	12-week visit	
Group A	9:00 AM	18.1 ± 0.97	18 ± 1.07	0.42
	11:00 AM	17.25 ± 1.06	17.45 ± 0.94	0.26
Group B	9:00 AM	18.25 ± 1.01	17.95 ± 0.89	0.7
	11:00 AM	17.5 ± 0.95	17.55 ± 1.05	0.71

Table 5: Comparison of mean IOP in both groups after cross-over of therapies at 6-week visit.

Side effect profile

At 6 weeks visit, in Group A, most common side effect was ocular hyperemia (15%) followed by increased lacrimation (5%) and stinging sensation (5%). In Group B, most common side effect was ocular hyperemia (15%) followed by increased lacrimation (10%), stinging sensation (5%) and altered taste sensation (5%). At 12 weeks visit, in Group A, most common side effect was ocular hyperemia (15%) followed by increased lacrimation (10%) and stinging sensation (5%). In Group B, most common side effect was ocular hyperemia (10%) followed by stinging sensation (5%) and altered taste sensation (5%).

In Group A, incidence of ocular hyperemia and stinging sensation remained same at 6 weeks and 12 weeks visit while incidence of increased lacrimation increased by 5 percent. In Group B, incidence of ocular hyperemia decreased by 5 percent and incidence of increased lacrimation decreased by 10 percent at 12 weeks visit in comparison to 6 weeks visit (Table 6).

Visits	Side effects	Group A		Group B	
		n	Percentage	n	Percentage
0 - 6 weeks	Ocular Hyperemia	3	15%	3	15%
	Increased Lacrimation	1	5%	2	10%
	Stinging Sensation	1	5%	1	5%
	Altered Taste	0	0	1	5%
6 - 12 weeks	Ocular Hyperemia	3	15%	2	10%
	Increased Lacrimation	2	10%	0	0
	Stinging Sensation	1	5%	1	5%
	Altered Taste	0	0	1	5%

Table 6: Side effect profile of both groups.

It is worth mentioning that the present study could not perform appropriate comparative statistical analysis on the incidence of side effects in the two groups as it was not adequately powered to do the same.

Cost analysis

In this study we did the volumetric analysis of both the therapies by comparing the actual volume per bottle, under filling and overfilling of bottles, drops per bottle and drops per ml of drug in the bottles. The actual volume of BBFC bottle was found to be 4.96 ± 0.08 ml while that of separate Brinzolamide and Brimonidine bottles was 5.04 ± 0.05 ml and 4.98 ± 0.08 ml respectively. It was found that BBFC bottle had 133.6 ± 1.14 drops/bottle while that of brinzolamide and brimonidine bottles had 142.6 ± 0.54 and 127.2 ± 1.3 drops/bottle respectively. Number of drops per ml in BBFC bottle was 26.93 ± 0.23 while that in Brinzolamide and Brimonidine vials were 28.29 ± 0.1 and 25.54 ± 0.26 respectively. The drop size in BBFC was then calculated to be 0.037 ± 0.0005 ml while in separate Brinzolamide and Brimonidine bottles was 0.035 ± 0.0004 ml and 0.039 ± 0.001 ml respectively.

Drug	Volume (ml)	Drops/bottle	Drops/ (ml)	Drop Size (ml)
BBFC	4.96 ± 0.08	133.6 ± 1.1.4	26.93 ± 0.23	0.037 ± 0.0005
Brinzolamide	5.04 ± 0.05	142.6 ± 0.54	28.29 ± 0.1	0.035 ± 0.0004
Brimonidine	4.98 ± 0.08	127.2 ± 1.3	25.54 ± 0.26	0.039 ± 0.001

Table 7: Volumetric analysis of drugs under study

From the above parameters and maximum retail price of the bottles in the market we calculated the cost per day, 6-weekly cost and extrapolated that to yearly cost of both therapies per eye. The INR exchange rate for USD (Dollars) was taken at 1USD = Rs.72.61, hence, cost in USD was also calculated. It was found that concomitant Brinz + Brim therapy was costlier than BBFC therapy with per eye per day costs of Rs12.65 ± 0.055 ($ 0.177) and Rs 8.68 ± 0.075 ($ 0.11) respectively. The 6-weekly cost of BBFC therapy was found to be Rs 364.72 ± 3.15 ($ 4.2) while that of concomitant Brinz + Brim therapy was Rs 531.55 ± 2.33 ($ 7.43). The yearly cost of BBFC therapy was extrapolated to be Rs 3169.66 ± 27.39 ($ 36.5) and that of concomitant Brinz + Brim therapy was Rs 4505.536 ± 19.75 ($ 64.60) respectively.

Cost-effectiveness i.e. cost per mm reduction of IOP was then calculated. The costs and effectiveness included in the calcula-

tion were 6-weekly costs (42 days) and average (9 am and 11am) IOP lowering at 6 weeks. Cost- effectiveness for BBFC therapy and separate concomitant Brinz + Brim therapy were Rs 45.7 ± 0.4/mmHg and Rs 67.54 ± 0.29/mmHg respectively. The cost per percent IOP reduced for 6 week BBFC therapy and concomitant Brinz + Brim therapy was observed to be Rs 11.72 ± 0.1 and Rs 17.2 ± 0.45 respectively. The IOP lowering efficacy of both the therapies was found to be statistically similar in our study. Thus, applying the cost-minimization analysis by directly comparing the cost incurred with both the therapies for the study period of 6 weeks, we observed that separate concomitant Brinz + Brim therapy costs Rs 166.83 ± 3.27 ($ 2.63) more than the Brinzolamide and Brimonidine Fixed Combination (BBFC) therapy to attain similar IOP lowering ($p > 0.05$) for a period of 6weeks.

Drug	MRP (Rs)	Cost per day per eye (Rs)	Cost per 6 weeks per eye (Rs)	Cost per year per eye (Rs) (extrapolated)
BBFC	580	8.68 ± 0.075	364.72 ± 3.15	3169.66 ± 27.39
Brinz + Brim	859	12.65 ± 0.055	531.55 ± 2.33	4505.53 ± 19.75

Table 8: Daily, 6-weekly and yearly cost of therapy per eye.

Discussion

Glaucoma is the leading cause of irreversible blindness in the world [2]. The most common form of open-angle glaucoma is primary open-angle glaucoma (POAG). Patients of POAG often have substantial limitations in visual function and quality of life (QOL) [12].

More than 50% of glaucoma patients need more than one drug to reach their target intraocular pressure. Use of fixed drug combinations provides the convenience of two or more medications in a single formulation, reduction of dosing frequency and reduced exposure to preservatives. Because glaucoma is a chronic disease, the long-term tolerability of the eye drops determines patient's persistence and willingness to take the prescribed medication. Fixed drug combinations potentially improve patient comfort and adherence to treatment. Patients are able to administer multiple ocular hypotensive agents with less medication bottles. Hence the complexity of treatment regimen is simplified [13].

In the present study, mean reduction in IOP after 6 weeks of BBFC therapy from mean baseline IOP of 25.65 ± 1.79 mmHg was 7.98 ± 1.31 mmHg (31.11% reduction) and that with concomitant Brinz + Brim therapy was 7.87 ± 0.98 mmHg from mean baseline IOP of 25.75 ± 1.43 mmHg (30.56% reduction). At both time points i.e. 9 am and 11 am, significant reduction ($p < 0.00001$) in mean IOP was observed after 6 weeks of both therapies when compared to the mean IOP of the respective time points at baseline.

Nguyen., *et al*. in 2013 evaluated the efficacy of BBFC in POAG and OHT patients and observed the mean IOP decrease of 7 mmHg (29%) from the baseline [14]. Aung., *et al*. in 2014 evaluated the efficacy of BBFC in POAG and OHT patients and calculated the mean IOP decrease from baseline to be 6.9 - 9.3 mmHg (26.7% - 36.0%) [15]. In our study we observed the mean IOP decrease of 7.98 mmHg (31.11%) from the baseline in patients using BBFC therapy.

Gandolfi., *et al*. in 2014 compared the IOP lowering efficacy of BBFC vs concomitant Brinzolamide 1% and Brimonidine 0.2% therapy in POAG and OHT patients and observed that the IOP lowering in BBFC group from baseline was 8.5 mmHg (32.19%) which was non inferior to concomitant Brinzolamide 1% and Brimonidine 0.2% therapy that was 8.3 mmHg (31.30%) [16]. Similarly, Wang., *et al*. in 2020 compared the IOP lowering efficacy of BBFC vs concomitant Brinzolamide 1% and Brimonidine 0.2% therapy in POAG and OHT patients and calculated the IOP decrease from baseline in BBFC group to be 7.2 mmHg (29.26%) which was statistically similar to the IOP decrease in concomitant Brinzolamide 1% and Brimonidine 0.2% therapy group which was 7.3 mmHg (29.67%) [17]. In the present study, mean IOP reduction at the end of 6 weeks was statistically similar between the Brinzolamide 1% plus Brimonidine 0.2% Fixed Combination (BBFC) therapy and separate concomitant Brinzolamide 1% and Brimonidine 0.2% therapy in patients of POAG and OHT. After 6 weeks visit when the therapies were switched among both groups, the mean IOP at the 12 weeks visit was statistically similar to the mean IOP of the same group at 6 weeks visit. These observations are consistent with the observations of the above mentioned studies. Majority of our patients included in the study found the use of BBFC therapy (single fixed combination vial) to be more convenient than separate concomitant therapy.

In the present study, we compared the actual volume, drops per bottle, overfill/underfill of bottles and number of drops per ml of the vials of BBFC, Brinzolamide 1% and Brimonidine 0.2%. We observed a slight difference between the labelled volume of the drug

and actual volume of the drug in all 3 preparations. The labelled volume for BBFC, Brinzolamide 1% and Brimonidine 0.2% was 5 ml each, while actual volume observed was 4.96 ± 0.08 ml, 5.04 ± 0.05 ml and 4.98 ± 0.08 ml respectively. BBFC and Brimonidine 0.2% bottles were found to be under filled by 0.8% and 0.4% respectively while Brinzolamide 1% bottle was found to be overfilled by 0.8%.In a study conducted by Rylander and Vold in 2008, the actual volume of Brimonidine 0.2% was observed to be 5.15 ± 0.07 ml with overfill by 3 ± 1.4%; while that of Brinzolamide 1% was 4.99 ± 0.10 ml with underfill by 0.2 ± 2.0% [18]. Overfill describes the volume of drug in a bottle in excess of the volume labelled on the bottle and underfill describes the volume of drug in the bottle less than the labelled volume of the bottle. Both the parameters were considered while evaluating cost of the therapy. If the bottle is overfilled, the cost incurred per day would be low and vice versa.

The number of drops per ml is an important determinant of daily cost of anti-glaucoma medication. As the number of drops per ml increases, the cost per day decreases and vice versa. In the present study, number of drops per ml for BBFC bottle was 26.93 ± 0.23; for Brinzolamide 1% it was 28.29 ± 0.1 and for Brimonidine 0.2% it was 25.54 ± 0.26 per ml.In a study conducted by Rylander and Vold in 2008 the average drops per ml for different anti glaucoma drugs were calculated. For Brinzolamide 1% it was observed to be 29.64 ± 1.11 and for Brimonidine 0.2% it was 24.83 ± 1.57 per ml [18]. These observations were similar to that of this present study.

In the present study, we evaluated the drop size in ml of all three preparations under study. The drop size of BBFC, Brinzolamide 1% and Brimonidine 0.2% was observed to be 0.037 ± 0.0005 ml, 0.035 ± 0.0004 ml and 0.039 ± 0.001 ml respectively. In a study conducted by Kumar., *et al*. in 2011, they concluded that the alteration in the eye drop delivery system, reduced drop size and alteration of the physical properties of the medication can greatly diminish the cost of treatment and also improve the therapeutic index [19]. Other important factors in determining drop size are the dispensing angle, dispensing rate and the residual volume of liquid in the dropper bottle. A dispensing angle of 45 degrees from horizontal leads to a decrease in drop volume [20]. Glass or plastic dropper bottles deliver the ophthalmic solution in drops with a volume that ranges from 25 µL to 70 µL. The optimal volume of drop should be 20 µL considering the fact that the capacity of pre-corneal space is low, there is risk of adverse systemic effects due to absorption of the drug via the nasal mucosa as well as accounts for wastage. This makes the drop size important for both economic and therapeutic point of view [19].

In the present study, we compared per day, 6-weekly and extrapolated yearly cost of therapy with BBFC and separate concomitant Brinz + Brim. It was observed that the per day cost of therapy with BBFC was Rs 8.68 ± 0.075 ($ 0.11) per eye while that with separate concomitant Brinz + Brim therapy was Rs 12.65 ± 0.055 ($ 0.177) per eye. The 6 weekly cost of therapy in rupees with BBFC was Rs 364.72 ± 3.15 ($ 4.2) per eye while that with concomitant Brinz + Brim therapy was 531.55 ± 2.33 ($ 7.43) per eye. The extrapolated yearly cost of therapy in rupees with BBFC was Rs 3169.66 ± 27.39 ($ 36.5) per eye while that with concomitant Brinz + Brim therapy was Rs 4505.536 ± 19.75 ($ 64.60) per eye.

But, cost analysis alone is not a complete economic analysis as a treatment with higher cost may be more efficacious than a relatively cheaper treatment with lower efficacy and higher adverse effect incidence. The cost-effectiveness ratio for both the therapies in terms of cost per mmHg lowering of IOP from baseline was evaluated in the present study for the study period of 6 weeks. Cost-effectiveness for BBFC therapy was Rs 45.7 ± 0.4 per mmHg and for concomitant Brinz + Brim therapy was Rs 67.54 ± 0.29per mmHg. We observed that the concomitant Brinzolamide 1% and Brimonidine 0.2% therapy costs Rs 166.83 ± 3.27 ($ 2.63) more than the Brinzolamide 1%/Brimonidine Fixed Combination (BBFC) therapy to attain similar IOP lowering for a period of 6 weeks. As the adverse effects with the therapies were mild, none requiring additional treatment or withdrawal of the therapy, no additional cost for treating any adverse effect was incurred during the course of present study. Patients were instructed properly on how to instil their eye drops, to reduce any wastage, keeping in mind that if any patient misses his or her eye while instilling the drops or accidentally administers more than the prescribed dose, it will lead to increase in cost of therapy. This study is based on the best case scenario, assuming no wastage of the medication.

As the glaucoma management requires long term therapy with anti- glaucoma topical medications and there are numerous options available in the market, the choice of therapy should also be based on the economic evaluation i.e. health benefits obtained versus cost incurred in attaining them. Thus the deciding criterion should be cost-effectiveness rather than efficacy or cost alone.

To best of our knowledge, this is the first study comparing cost effectiveness of Brinzolamide 1%/Brimonidine Fixed Combination (BBFC) with concomitant Brinzolamide 1% and Brimonidine 0.2% therapy. However, there are a few limitations to our study. It was an

open labelled study with a limited number of patients and a short time frame of 6 weeks. Also, IOP measurements were done on two specific time points instead of a 24-hour diurnal monitoring as the patients denied hospital admission in absence of any non-ocular disease. However, the preliminary results of our study show that BBFC has safe and efficacious IOP lowering besides also being a cheaper alternative to separate concomitant Brinzolamide 1% and Brimonidine 0.2% therapy. Future studies need to further explore the cost effectiveness and potential side effects over long time duration exceeding 1 year to get more robust conclusions on proper medical treatment of this chronic debilitating disease.

Conclusion

From our study, we concluded that there was no statistically significant difference in the IOP lowering efficacy between Brinzolamide 1%/Brimonidine 0.2% Fixed Combination (BBFC) and separate concomitant Brinzolamide 1% and Brimonidine 0.2% therapy. Thus, our study shows that BBFC is an effective and safe IOP lowering therapy with an auxiliary advantage of being more economical than separate concomitant Brinzolamide 1% and Brimonidine 0.2% therapy.

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Nil.

Conflicts of Interest

None of the authors have any financial interest in any of the pharmacotherapeutic brands used in the study.

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