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"AN ANALYTICAL STUDY OF EFFICACY AND ADVERSE REACTIONS OF FIXED DOSE COMBINATION OF BRINZOLAMIDE (1%) + BRIMONIDINE (0.2%) VERSUS MONOTHERAPYWITH BRINZOLAMIDE (1%) OR BRIMONIDINE (0.2%) IN PATIENTS WITH OPEN ANGLE GLAUCOMA"

Ophthalmology

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ABSTRACT

BACKGROUND: Glaucoma accounts for approximately 12% of the total blindness and is the third leading cause of blindness in India. The most common risk factor known is a raised intraocular pressure.[1] The current study is aimed at comparing the efficacy and adverse reactions of fixed dose combination of brinzolamide (1%) with brimonidine(0.2%) versus montherapy with brinzolamide (1%) or brimonidine (0.2%) in patients with POAG.

METHOD: Observational analytical study carried out in tertiary care teaching hospital on newly diagnosed patients of open angle glaucoma having open anterior chamber angle, glaucomatous optic nerve head changes, visual field damage and intraocular pressure of more than 21 mmhg recorded on atleast a few occasions [2] and started on treatment with brimonidine (0.2%) or brinzolamide (1%) or fixed dose combination of brimonidine(0.2%) and brinzolamide(1%). They were followed up for 2weeks, 1 month and 3 month.

RESULT: Mean IOP was significantly lower in BBFC group as compared to BRIM group. (19.48±1.61 vs 21.78±2.16 respectively). Similarly, mean IOP was significantly lower in BBFC group as compared to BRINZ group (19.48±1.61 vs 21.94±2.14 respectively). There was no change in fundus and visual field defects with any of the drugs. The difference of side effects among three groups was not significant (for local ADRs, p value= 0.953 and for systemic ADRs, p value= 0.885)

CONCLUSION: BBFC has significantly greater antihypertensive (IOP lowering effect) activity as compared to brinzolamide 1% monotherapy or brimonidine 0.2% monotherapy in patients with primary open angle glaucoma. BBFC has safety profile which is consistent with that of its individual components i.e. brimonidine and brinzolamide.

KEYWORDS

BBFC- Brimonidine+brinzolamide fixed dose combination, BRIM- Brimonidine eyedrop, BRINZ- Brinzolamide eyedrop, POAG- Primary open angle glaucoma

INTRODUCTION:

Glaucoma accounts for approximately 12% of the total blindness and is the third leading cause of blindness in India. Population based studies show a prevalence between 2% to 13% with about 11.2 million people aged 40 years and older with glaucoma in India.[2,3] Glaucoma is a chronic, progressive optic neuropathy, which is caused by a group of ocular conditions, which lead to damage of the optic nerve with loss of visual function. The most common risk factor known is a raised intraocular pressure.[1]

The goal of glaucoma treatment is to preserve good visual function for the patient's lifetime. This is accomplished by lowering the IOP to a level that will stop, or at least slow, the progression of optic nerve damage and its consequent visual loss.[4]

Medical management is frequently the first choice in most cases and has been the most effective means to delay the onset of glaucomatous optic nerve damage or to slow its progression. Brinzolamide is a highly specific, reversible and non-competitive inhibitor of carbonic anhydrase-II (CA-II). Inhibition of CA-II enzyme in the ciliary epithelium leads to decrease in bicarbonate ion formation and secretion into the posterior chamber and its subsequent decrease in sodium and fluid transport across the ciliary epithelium.[5] This results in a decrease in aqueous humour production and reduced IOP.

Brimonidine is a highly selective alpha-2 adrenergic receptor agonist that lowers IOP by a dual mechanism of action, involving reduction of aqueous humour production and stimulation of aqueous humour outflow through the uveoscleral pathway.[6] Fixed combination topical therapy is vigorously used to treat ocular hypertension (OHT) and glaucoma.

The current study is aimed at comparing the efficacy and adverse reactions of fixed dose combination of brinzolamide (1%) with brimonidine(0.2%) versus montherapy with brinzolamide (1%) or brimonidine (0.2%) in patients with POAG i.e.

1. To study the intraocular pressure lowering effect of brinzolamide and brimonidine fixed dose combination versus monotherapy in patients with open angle glaucoma.
2. To study visual assessment (in terms of visual fields) with brimonidine fixed dose combination versus monotherapy in patients with primary ope angle glaucoma.
3. To study suspected adverse reactions of brimonidine and brinzolamide monotherapy and fixed dose combination.

METHODS:

Study design: Observational analytical study
Place of study: Tertiary Care Teaching Hospital
Duration of study: One and Half year
Sampling method: Total consecutive sampling
Sampling size: All patients satisfying the inclusion criteria and exclusion criteria are included in the study

INCLUSION CRITERIA:

1. Adults (>18 years) of both sexes will be included.
2. Newly diagnosed patients of open angle glaucoma having open anterior chamber angle, glaucomatous optic nerve head changes, visual field damage and intraocular pressure of more than 21 mmhg recorded on atleast a few occasions[2] and started on treatment with brimonidine (0.2%) or brinzolamide (1%) or fixed dose combination of brimonidine(0.2%) and brinzolamide(1%) by the consultant.

EXCLUSION CRITERIA :

1. Pregnant women, lactating mothers and critically ill patients.
2. History of allergic hypersensitivity or poor tolerance to any of the components of the preparations used in this study.
3. History of ocular trauma.
4. History of any ocular surgeries.
5. Patients with other ocular disorders.

The study was undertaken in patients with open angle glaucoma attended the outpatient department of Ophthalmology or referred from other departments in the hospital. An approval was obtained from Institutional Ethics Committee for conducting the study. An informed, written and signed consent was obtained from all the patients before study enrolment after fully explaining the procedure and purpose of study. A detailed proforma was devised containing all essential details for each individual. The patients were asked about their name, age, sex and address.

A complete ophthalmic history was taken. A comprehensive clinical examination was done including Snellen Visual Acuity measurement, External Examination under torch light, Examination of anterior segment by slit lamp biomicroscopy , examination of anterior chamber angle with gonioscopy, Intra ocular pressure measurement by applanation tonometer and pachymetry, Perimetry, Examination of

the posterior segment by ophthalmoscopy (direct and indirect) and +90D biomicroscopy,fundus photography and routine systemic investigation.

A total of 123 patients fulfilled the inclusion criteria and were selected for the study.

The patients were divided into three groups:

Group I(39patients):

These patients were instructed to instill one drop of Brinzolamide (1%)+Brimonidine(0.2%) Fixed Dose combination twice daily.

Group II (38patients):

These patients were instructed to instill one drop of Brimonidine (0.2%) eye drop thrice daily.

Group III (46patients):

These patients were instructed to instill one drop of Brinzolamide(1%) eye drop thrice daily.

At screening visit, all the patients enrolled in the study underwent a complete physical examination including medical and ocular history, a complete ophthalmic examination as mentioned above.

During the study there were four visits by the patients, at baseline, at 2 weeks, at 1 month and at 3 months. At each visit patients' IOP measurements were performed with Goldman applanation tonometer twice for each eye, at least one hour apart. At each time three separate measurements were taken for each eye and the mean of the three readings was used in the statistical analysis. The IOP measurements were performed at approximately the same time of the day at each visit to reduce the effect of diurnal variation[7]. Also at each visit direct and indirect ophthalmoscopy and +90D biomicroscopy was done for fundus changes and perimetry for visual field changes was done.

The safety was monitored in terms of adverse effects which were defined as any changes from baseline in patient's ophthalmic and/or medical health that occurred during the course of the study and were recorded as solicited complaints of the patients or clinician's observations at each visit. The adverse reactions were graded as mild, moderate or severe. A serious effect was defined as potentially fatal, life threatening, sight threatening, permanently disabling, requiring hospitalization or requiring intervention to prevent impairment or damage.

Out of the total 123 patients, 5 patients were lost to follow up and 3 patients were discontinued the drug due to non serious treatment related adverse effects. Hence, 115 patients (133 eyes) were studies and followed up until the end of the study.

OBSERVATIONS AND RESULTS:

Table no. 1: Comparison of IOP (Intra-ocular pressure) between Brimonidine and brinzolamide fixed dose combination (BBFC) and Brimonidine (BRIM)eye drop at baseline, at 2 weeks, after 1 month and after 3 months

IOP	Category	Mean	Std. Deviation	P value
Baseline	BBFC (n=44)	26.82	1.69	<0.05
	BRIM (n=41)	25.29	1.91	
After 2 Weeks	BBFC (n=44)	19.48	1.61	<0.05
	BRIM (n=41)	21.78	2.16	
After 1 Month	BBFC (n=44)	18.43	1.45	<0.05
	BRIM (n=41)	20.34	1.87	
After 3 Months	BBFC (n=44)	17.68	1.44	<0.05
	BRIM (n=41)	19.68	1.56	

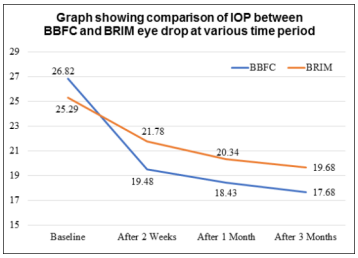

Table no.2: Comparison of IOP (Intra-ocular pressure) between Brimonidine and brinzolamide fixed dose combination (BBFC) and Brinzolamide (BRINZ) eye drop at baseline, at 2 weeks, after 1 month and after 3 months.

IOP	Category	Mean	Std. Deviation	P value
Baseline	BBFC (n=44)	26.82	1.69	<0.05
	BRINZ (n=48)	25.27	1.72	
After 2 Weeks	BBFC (n=44)	19.48	1.61	<0.05
	BRINZ (n=48)	21.94	2.14	
After 1 Month	BBFC (n=44)	18.43	1.45	<0.05
	BRINZ (n=48)	20.73	1.84	
After 3 Months	BBFC (n=44)	17.68	1.44	<0.05
	BRINZ (n=48)	20.23	1.59	

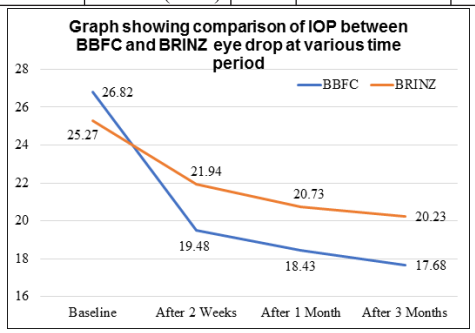

Table no.3: Mean reduction of IOP with respect to baseline over a period after 2 weeks, after 1 month and after 3 months.

Drugs given	Timings	Mean IOP	Mean reduction in IOP	p value
BBFC (n=44)	**Baseline**	26.82±1.69	7.44±1.93	<0.05
	After 2 weeks	19.48±1.61		
	Baseline	26.82±1.69	6.73±1.22	<0.05
	After 1 Month	18.43±1.45		
	Baseline	26.82±1.69	5.49±1.09	<0.05
	After 3 Month	17.68±1.44		
BRIM (n=41)	**Baseline**	25.29±1.91	3.51±1.34	<0.05
	After 2 weeks	21.78±2.16		
	Baseline	25.29±1.91	4.96±1.05	<0.05
	After 1 Month	20.34±1.87		
	Baseline	25.29±1.91	5.61±1.14	<0.05
	After 3 Month	19.68±1.56		
BRINZ (n=48)	**Baseline**	25.27±1.72	3.33±1.39	<0.05
	After 2 weeks	21.94±2.14		
	Baseline	25.27±1.72	4.54±1.25	<0.05
	After 1 Month	20.73±1.84		
	Baseline	25.27±1.72	5.04±1.34	<0.05
	After 1 Month	20.23±1.59		

Table no. 4: Cup-Disc ratio as per the Drugs given:

Cup-Disc Ratio	Drugs given			Total	Follow up after 2 weeks, 1 month and 3 months
	BBFC	BRIM	BRINZ		
0.4	0	10	4	14	No change
0.5	1	9	18	28	No change
0.6	1	12	14	27	No change
0.7	1	4	2	7	No change
0.8	9	6	6	21	No change
0.9	7	0	2	9	No change
1.0	25	0	2	27	No change
Total	44	41	48	133	--

Table no.5: Visual Field Changes as per the Drugs given:

Visual Field Changes	Drugs given			Total	Follow up after 2 weeks, 1 month and 3 months
	BBFC	BRIM	BRINZ		
Severe contraction of visual field	27	3	7	37	No change
Paracentral scotoma	0	7	18	25	No change
Ring scotoma	1	14	7	22	No change
Severe visual field loss	14	1	2	17	No change
Ring scotoma with nasal step	0	6	7	13	No change

Superior arcuate defect	0	4	2	6	No change
Severe constriction of central island	1	2	2	5	No change
Inferior arcuate scotoma	1	3	0	4	No change
Ring scotoma with paracentral scotoma	0	1	2	3	No change
Nasal step in superior nasal quadrant	0	0	1	1	No change
Total	44	41	48	133	--

Table no.5: Visual Field Changes as per the Drugs given:

Visual Field Changes	Drugs given			Total	Follow up after 2 weeks, 1 month and 3 months
	BBFC	BRIM	BRINZ		
Severe contraction of visual field	27	3	7	37	No change
Paracentral scotoma	0	7	18	25	No change
Ring scotoma	1	14	7	22	No change
Severe visual field loss	14	1	2	17	No change
Ring scotoma with nasal step	0	6	7	13	No change
Superior arcuate defect	0	4	2	6	No change
Severe constriction of central island	1	2	2	5	No change
Inferior arcuate scotoma	1	3	0	4	No change
Ring scotoma with paracentral scotoma	0	1	2	3	No change
Nasal step in superior nasal quadrant	0	0	1	1	No change
Total	44	41	48	133	--

Table no. 6: Local Adverse Effects based on Drugs given:

Local Adverse Effects	Drugs given			Total
	BBFC	BRIM	BRINZ	
Ocular Hyperaemia	1	1	3	05
Blurred Vision	2	1	1	04
Foreign body sensation	1	1	1	03
Conjunctivitis	0	1	1	02
Eye pain	0	1	1	02
No Local Adverse Effects	40	36	41	117
Total	44	41	48	**133 eyes**

Chi Square 3.87, P value 0.953

Table 7: Systemic Adverse Effects based on Drugs given:

Systemic Adverse Effects	Drugs given			Total
	BBFC	BRIM	BRINZ	
Decreased alertness	1	1	1	3
Altered taste sensation	0	1	1	2
Fatigue	1	0	1	2
Somnolence	1	1	0	2
Dry mouth	1	0	0	1
No Systemic Adverse Effects	40	38	45	123
Total	44	41	48	**133 eyes**

Chi Square 5.09, P value 0.885

DISCUSSION:

Mean IOP reduction:

In the present study, after the treatment of the patients with BBFC, BRIM and BRINZ it was found that BBFC significantly reduces IOP as compared to BRIM and BRIN alone($p<0.05$). The mean reduction in IOP from the baseline at the end of 3 months was found to be 7.44± 1.93 mmhg(21% to 34%) with BBFC, 5.61± 1.14 mmhg (18% to 27%) with BRIM and 5.04± 1.34 mmhg (15 % to 25%) with BRINZ.

Tin Aung et al performed a randomized, multicenter, double-masked trial evaluating the efficacy and safety of BBFC dosed twice daily versus each individual active component (ie, brinzolamide 1% and brimonidine 0.2%) for IOP reduction in patients with POAG or OHT.At 3 months, the mean change in diurnal IOP was statistically significantly greater with BBFC versus brinzolamide and brimonidine.Mean IOP reduction at 3 months was 26.7% to 36% with BBFC, 20.6% to 31.3% with BRIM and 22.4% to 27.9% with BRINZ.[8]

Realini et al reported a pooled analysis of the two preceding studies that included 1,350 subjects. Pair-wise comparison of pooled mean IOP (BBFC vs brinzolamide and BBFC vs brimonidine) showed reductions in IOP from baseline across visits and time points of 5.5–8.9 mmHg in the BBFC group, 4.2–5.9 mmHg in the brinzolamide group, and 3.3–6.9 mmHg in the brimonidine group.[9]

Nguyen et al conducted a multicenter, double-masked, parallel-group study in which 679 patients were randomized 1:1:1 to treatment with BBFC, brinzolamide, or brimonidine thrice daily. At the 3-month end point, mean IOP of the BBFC group was statistically significantly lower than that of either the brinzolamide group or the brimonidine group ($P<0.005$) across all time points.[10]

Whitson et al conducted a similar study(it is a 3-month extension of study by Nguyen et al) which was a randomized, multicenter, double-masked, three-month, three-arm contribution-of-elements study with a three-month safety extension. Patients were randomly assigned 1:1:1 to treatment with BBFC, brinzolamide 1%, or brimonidine 0.2% after a washout period. It was found that six-month mean IOP values were similar to those at three months, when the mean IOP in patients treated with BBFC was significantly lower than that of either monotherapy group.[11]

Katz et al also conducted a similar study which showed that at the end of 3 months, BBFC lowered IOP by 24.1%–34.9% from untreated baseline, while the brinzolamide- and brimonidine-group IOP reductions ranged from 16.9% to 22.6% and 14.3% to 25.8%, respectively.[12]

Table no.1: Change in IOP from baseline in various studies:

	Change in IOP (in mmhg) from baseline		
Studies	BBFC	BRIM	BRINZ
Our study	5.5 – 9.4	4.5 – 6.7	3.7 – 6.4
Tin aung et al	7.2 – 9.3	5.2 – 8.1	5.5 – 7.2
Realini et al	5.5 – 8.9	3.3 – 6.9	4.2 – 5.9
Nguyen et al	5.4 – 8.4	3.1 – 6.5	4.2 – 5.7
Whitson et al	5.4 – 8.4	3.1 – 6.5	4.2 – 5.7
Katz et al	7.1 – 8.8	4.3 -6.2	3.5 – 5.8

There was a study conducted by Gandolfi et al which was a double-masked noninferiority trial of BBFC versus concomitant therapy of brinzolamide 1% plus brimonidine 0.2% (in two separate bottles), both dosed twice daily. They observed that after 3 months, the mean diurnal IOP reduction from baseline with BBFC (8.5±0.16 mmHg) was no inferior to that with the concomitant treatment (8.3±0.16 mmHg).[13]

Visual field and Fundus changes after starting treatment:

In the present study, visual field and fundoscopy assessment was done at all the 3 visits i.e. 2 weeks, 1 month and 3 months in all three treatment groups, and it was found to have no changes in visual fields in any treatment group at any point of time.. Similarly, no changes were found in the fundus of the patients with treatment in any of the treatment groups. There is significant correlation between glaucomatous damage seen in posterior segment with the visual field defects. Focal and diffuse signs of glaucoma damage seen on stereo photographs often match damage shown on visual fields. In addition, damage shown on visual fields is often missed during clinical evaluation.[14]

The findings of the present study were similar to the studies below:

- Prata et al conducted a prospective, randomized clinical trial involving 54 glaucoma patients (54 eyes) who randomly received timolol maleate 0.5%, brimonidine tartrate 0.2%, or travoprost 0.004% in one randomly selected eye. No significant correlations between IOP reduction and changes in visual function were found ($P>0.30$).[15]
- Keiji Yoshikawa et al conducted a study to quantitatively evaluate

the association of intraocular pressure (IOP) reduction with visual field defect (VFD) progression in normal tension glaucoma (NTG) under medical therapy. During follow-up, visual field stage using the Markov model was constant in ~60%, with transitions in ~40%..[16]

- In the study conducted by Whitson et al, all three groups with BBFC, brimonidine and brinzolamide showed changes in ≤3% of patients for all fundus parameters. No clinically meaningful differences were noted for changes from baseline to the exit visit in cup/disc ratio..[11]

Safety and tolerability of the antiglaucoma drugs:

- A total of 29 patients experienced at least one treatment related adverse effects including the patients who were discontinued (BBFC, n=47, 17%; BRIM, n=44, 18.2% and BRINZ, n=50, 20%). In BBFC group, 8.5% of patients experienced local ADRs and 8.5% of patients experienced systemic ADRs. In BRIM group, 11.3% of patients experienced local ADRs and 6.8% experienced systemic ADRs. In BRINZ group 14% of patients experienced local ADRs and 6% experienced systemic ADRs. (As shown in table no.6 and 7). From BBFC group, 2 patients were discontinued treatment due to allergic conjunctivitis and conjunctivitis. From BRIM group 1 patient was discontinued treatment due to allergic conjunctivitis. These patients were given treatment accordingly and were recovered. No serious systemic adverse effects were noted. When comparison was done for all the three groups for local and systemic ADRs(As shown in table no.6 and 7, p value was not significant for both local and systemic ADRs(p=0.953 and p=0.885 respectively)
- In the studies mentioned above (in section Mean IOP reduction) i.e. Tin Aung et al, Realini et al, Nguyen et al, Whitson et al, Katz et al and Gandolfi et al, similar adverse effects like ocular hyperaemia, visual disturbances, conjunctivitis, ocular allergic-type reactions, and ocular discomfort were noted with the use of BBFC. Common systemic adverse effects reported in the trials included altered taste sensation, oral dryness, fatigue, somnolence, and decreased alertness[8,9,10,11,12,13]. The nonocular serious adverse events associated with either component were uncommon, and there were no clinically meaningful alterations found during systemic assessments.

CONCLUSIONS:

The study concludes that:

1. BBFC has significantly greater antihypertensive (IOP lowering effect) activity as compared to brinzolamide 1% monotherapy or brimonidine 0.2% monotherapy in patients with primary open angle glaucoma.
2. Visual fields were found unchanged in all the three groups i.e. BBFC, BRIM and BRINZ after treatment.
3. BBFC has safety profile which is consistent with that of its individual components i.e. brimonidine and brinzolamide.

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