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A comparative study of topical fixed dose combination of brimonidine (0.2%) plus brinzolamide (1%) versus brimonidine (0.2%) plus timolol (0.5%) in patients of primary open angle glaucoma

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ABSTRACT

Background: Primary open-angle glaucoma (POAG), fundamentally results from impaired or suboptimal drainage of aqueous humor from the eye through the trabecular meshwork and/or uveoscleral pathways.
Aim and Objectives: the purpose of our study was to compare the efficacy and safety of Brimonidine 0.2% plus Brinzolamide 1% versus Brimonidine 0.2% plus Timolol 0.5% in patients with Primary Open Angle Glaucoma.
Materials and Methods: A total of 81 subjects including 84 eyes in group I (brimonidine plus timolol) and 78 eyes in group II (brimonidine plus brinzolamide) with open angle glaucoma were enrolled. The detailed glaucoma examination was done. IOP measurements at 9 am, 12 pm and 3 pm, during week 2, 4, 8 and 12 were used to assess efficacy. Adverse events were recorded. The statistical test used were Chi-square test, Unpaired t-test and Paired t-test.
Results: Majority of patients in group I obtained an IOP reduction of >30% at 9.00 am 92.3%), 12.00 pm (91.3%) and 3.00 pm (86.2%) after 12 weeks of therapy. Majority of patients in group II obtained an IOP reduction of >30% at 9.00 am (86.8%), 12.00 pm (87.7%) and 3.00 pm (71.9%) after 12 weeks of therapy.
Conclusion: Both drugs can thus be useful as second line therapy in the management of patients with POAG uncontrolled on monotherapy. Moreover, each drug has provided significant mean IOP reduction after three month of therapy at all visits and at all times.

1. Introduction

Glaucoma is a chronic progressive multi factorial optic neuropathy brought about by group of visual conditions which harm the optic nerve with resultant loss of visual function.[1] In India, it is the main source of treatable non-reversible visual deficiency.[2] It is estimated that 11.2 million persons aged 40 years and older suffer with glaucoma in India.[3,4]

Elevated intraocular pressure (IOP) is a key and the only factor that has been modified therapeutically to date, for the development and progression of glaucomatous optic neuropathy.[5,6]

Primary open-angle glaucoma (POAG), which records for most of ophthalmic OPD cases, fundamentally results from impaired or suboptimal drainage of aqueous humour from the eye through the trabecular meshwork and/or uveoscleral pathways.[7]

One of the major risk factors for POAG is found to be raised IOP, hence drugs that lower the IOP have the ability to avoid or postpone optic nerve damage and prolong vision.[8] IOP-lowering drugs are the basis of glaucoma care.[9] Patients with glaucoma having increased intraocular pressure (IOP) are initially managed with topical hypotensive agents as the treatment of choice.[10,11]

Currently, five classes of anti-glaucoma agents are used to lower IOP: prostaglandin analogues, β-blockers, carbonic anhydrase inhibitors, α-2 adrenergic agonists,

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and parasympathomimetics. Glaucoma pharmacotherapy is commenced with a single topical ocular hypotensive agent.[12] However, in many patients response to monotherapy may be inadequate to reach target intraocular pressure (IOP) and/or avoid worsening of glaucoma. In others, due to tachyphylaxis single agent may lose its potency over time.[13]

Thus, more than one drug is frequently required for satisfactory and tolerable medium to long-term control of IOP.[14] Multiple potential benefits are provided by fixed-combination therapies compared to concomitant treatment,[15] including increased compliance to treatment, minimized exposure to preservatives, and lower risk of sequential instillation of medicines.[16]

Present day adjunctive treatment includes a β-blocker with another class of medication, for example, a topical carbonic anhydrase inhibitor, prostaglandin analogue, or α-agonist.[17] For instance, timolol 0.5% is combined as an invariant with dorzolamide 2%, latanoprost 0.005% brimonidine 0.2%, travoprost 0.004% or bimatoprost 0.03%.[18]

Two main components of Brinzolamide 1% and Brimonidine 0.2% fixed combination (BBFC) are: a carbonic anhydrase inhibitor (Brinzolamide) and a α2-agonist (Brimonidine). Carbonic anhydrase (CA-II) enzyme found in the ciliary epithelium is inhibited by brinzolamide in a non-competitive and reversible manner, thereby reducing bicarbonate ion formation, resulting in subsequent reduction of the transport of sodium and fluids across the ciliary epithelium and reduced the formation of aqueous humour.[19]

Brimonidine, is a selective α_2 agonist, ocular hypotensive agent, which acts by decreasing aqueous humour formation and augmenting uveoscleral drainage.[20,21] Fixed combination of 0.2% brimonidine tartrate and 0.5% timolol maleate contains two active ingredients, alpha 2 agonist (brimonidine) and beta receptor antagonist. Timolol, β receptor antagonist, by its property of limiting blood flow to the iris root–ciliary body reduces aqueous formation.[22]

A fixed combination of brinzolamide 1% and brimonidine 0.2% (BBFC) was approved in the United States. In patients with primary open-angle glaucoma or ocular hypertension, BBFC acts via two synergistic mechanisms to decrease raised IOP: both brimonidine and brinzolamide reduces aqueous formation and increased aqueous drainage is brought about by brimonidine.[23] BBFC was found to be more efficacious in lowering IOP than its individual components brinzolamide or brimonidine as single drug therapy. In various drug trials, BBFC instilled three times daily (TID; a dosing regimen consistent with the approved dosing regimens of brinzolamide and brimonidine in the United States) is tolerated well and equally safe when compared to its single drug elements.[24–27]

Specific combinations of a carbonic anhydrase inhibitor (CAI) and beta-blocker 0.5% timolol maleate are widely used as second-line therapies, and further IOP reductions are required following inadequate efficacy of PGAs to achieve target. Currently, 1% brinzolamide and 0.5% timolol maleate fixed combination and dorzolamide and 0.5% timolol combination are available in the global market.[28] Brinzolamide and 0.5% timolol maleate (BTFC) fixed combination and DTFC ophthalmic solutions containing 2% dorzolamide (2% DTFC) were compared in other countries in terms of IOP-reducing efficacy and demonstrated superior eye comfort with BTFC.[28–30]

Both the drugs, Timolol and Brinzolamide have different mechanism of action and also their additive effect with Brimonidine has not been studied in detail in controlling IOP. Thus, the purpose of our study was to compare the efficacy and safety of Brimonidine 0.2% plus Brinzolamide 1% versus Brimonidine 0.2% plus Timolol 0.5% in patients with Primary Open Angle Glaucoma.

2. Materials and Methods

This study was conducted in department of ophthalmology, Teerthanker Mahaveer medical college and research centre, Moradabad, Uttar Pradesh. Informed consent was obtained from the subjects after explanation of the nature and possible consequences of the study. A total of 81 subjects including 84 eyes in group I and 78 eyes in group II with open angle glaucoma were enrolled.

2.1. Inclusion criteria

1. Male or female 18 years and above
2. Patients of POAG with IOP not controlled (> 21mmHg on topical monotherapy

2.2. Exclusion criteria

1. Cup/Disc > 0 8.
2. Patients having ocular surface disorders, ocular infection and inflammation or significant ocular trauma.
3. Known contraindication or hypersensitivity to any study medication
4. Patients using contact lenses.
5. Patients taking other systemic or ocular medications that could have substantial effect on intraocular pressure.
6. Patients with history of ocular surgery in last 3 months.
7. Pregnant and lactating women.
8. Patients not giving informed consent.

2.3. Study method

The demographic profile of the patients was taken (age and gender, address and occupation). The detailed history

was taken about the age at onset of symptoms, time since diagnosis of glaucoma, any precipitating factor, previous treatment and the current medications.

All enrolled patients were given a washout period of 2 weeks before the baseline examination.

The tools of investigation used were Snellen's visual acuity chart, refraction trial set, slit lamp, +78 diopter condensing lens, direct ophthalmoscope, Goldmann's applanation tonometer, Volk's G4 mirror goniolens, Humphery's automated perimeter (HFA, Carl Zeiss-Meditec. Model 740i) and CIRRUS HD-OCT, Carl Zeiss Meditec AG model 500.

After the initial approach and group assignment, we applied a protocol for the objective assessment of mean IOP. Mean IOP was compared within the group and inter-group at different intervals for each fixed dose combination. Also, any progression in visual field defect from baseline was recorded at 3 months. A checklist of adverse drug reactions was compared for each fixed dose combination.

3. Results

No statistically significant difference was observed among the two age groups. The range of age of the patients in group I was between 38 - 89 years with a mean of 56.82 years and in group II the patients were between 39 - 80 years with a mean of 57.03 years. (p = 0.81) (Figure 1)

At 2 week follow up visit, with initiation of treatment with brimonidine plus timolol there was a statistically significant reduction in the mean IOP of the study population from baseline. Initial decrease in IOP was drastic, but in further follow up the IOP was stabilized. Further, a statistically significant reduction in the mean IOP of the brimonidine plus timolol group was also obtained at 9.00 am, 12.00 pm and 3.00 pm at each follow up visits up to 12 weeks. Overall the Combination drug therapy has statistically significant reduction in IOP (P value-<0.001) at the end of 12 weeks. (Table 1)

Patients who were put on Simbrinza (group II), after commencing the treatment there was a statistically significant reduction in mean IOP from baseline to all subsequent visits at 2, 4, 8, and 12 weeks and at all times 9.00 am, 12.00 pm, and 3.00 pm (p<0.001). (Table 1)

Majority of patients in both the groups obtained an IOP reduction of >30% at 9.00 am, 12.00 pm and 3.00 pm after 12 weeks of therapy. (Table 2)

In both the study groups there was a reduction in mean IOP at 9.00 am and the difference between the two was statistically significant at 4 weeks (p=0.004) and 12 weeks (p=0.009). Also there was a reduction in the mean IOP at 12.00 pm in both groups and the difference between the two was not statistically significant at subsequent visits. At 3.00 pm there was a reduction in mean IOP in our study groups and the difference between the two was statistically significant at 2 weeks. (p=0.001) (Table 1)

There was no significant (p>0.05) difference in the mean change in IOP among the groups during all visits and at all times.

There was no significant (p>0.05) difference in the adverse effects between the groups. (Figure 1)

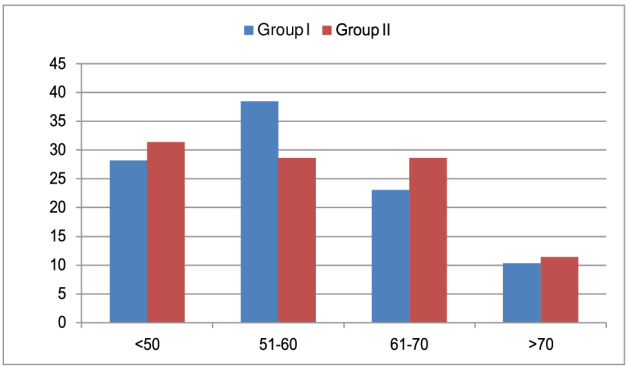

Fig. 1: Age distribution of the study population

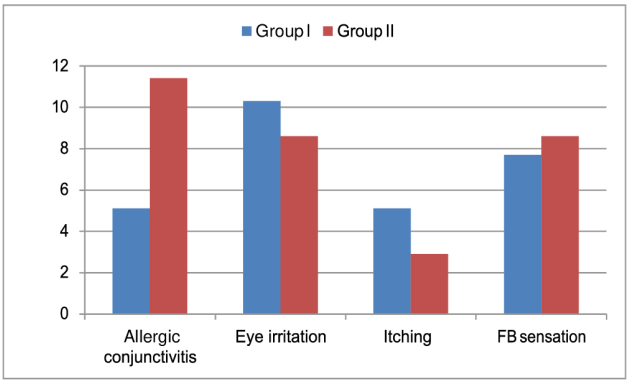

Fig. 2: Adverse effects in the study groups

4. Discussion

In pathophysiology of POAG raised IOP has been identified as one of the modifiable risk factor and therefore medications that control IOP have the potential to prevent and delay optic nerve damage and prolong vision.[11] IOP-lowering medications are the standard of care for glaucoma.[12]

Fixed dose combination therapies being used in this study were: brimonidinetartarate 0.2% - timolol maleate 0.5%- and brimonidine 0.2%-brinzolamide 1%.

In our study, we had taken 81 subjects in which group I had 42 subjects and group II had 39 subjects. The range of age of the patients in group I was between 38 - 89 years with a mean of 56.82 years and in group II the patients were between 39 - 80 years with a mean of 57.03 years. Male and female in group I, were 51.3% and 48.7% whereas in group II, it was 51.4% and 48.6% respectively.

Table 1: Intraocular pressure in group i and ii at 9.00 am, 12.00 pm and 3.00 pm and inter-group comparisons

Study Visits		Group I			**Group II**			**Group I vs Group II**
		IOP (mmHg)		p value[a]	IOP (mmHg)		p-value[a]	p-value[b]
		Range	Mean±S.D.		Range	Mean±S.D.		
	Baseline	22-32	24.90±2.03		22-26	24.14±1.57		0.060
	2 Weeks	18-28	4.71±1.73	<0.001	16-24	4.35±2.54	<0.001	0.240
9.00 AM	4 Weeks	10-22	10.89±2.91	<0.001	10-22	9.02±2.32	<0.001	0.004*
	8 Weeks	10-20	9.94±2.77	<0.001	10-24	8.80±2.44	<0.001	0.290
	12 Weeks	10-18	10.66±2.40	<0.001	10-22	9.08±2.11	<0.001	0.009*
	Baseline	18-30	24.36±3.05		22-30	23.94±2.01		0.330
	2 Weeks	16-28	4.10±2.93	<0.001	16-26	3.91±2.46	<0.001	0.560
12.00 PM	4 Weeks	10-22	9.05±3.68	<0.001	10-24	9.20±3.11	<0.001	0.160
	8 Weeks	10-20	9.87±3.73	<0.001	10-22	9.20±2.91	<0.001	0.470
	12 Weeks	10-18	9.79±3.61	<0.001	10-22	9.31±2.92	<0.001	0.850
	Baseline	18-32	23.54±3.24		16-26	22.46±2.43		0.070
	2 Weeks	14-28	5.15±3.24	<0.001	16-26	2.74±2.84	<0.001	0.001*
3.00 PM	4 Weeks	10-20	8.71±3.81	<0.001	10-26	7.77±2.70	<0.001	0.720
	8 Weeks	10-20	8.79±3.99	<0.001	10-24	7.21±3.69	<0.001	0.210
	12 Weeks	10-22	9.30±4.31	<0.001	10-24	7.42±3.62	<0.001	0.060

[a]Repeated measures ANOVA test, [b] Unpaired t-test, * Significant difference

Table 2: PercentageIOP reduction at 9.00 am, 12.00 pm and 3.00 pm after 12 weeks inGroupI and II

	IOP reduction	**Group I**		**Group II**		**p-value**
		N	%	N	%	
	>20-25%	0	0	0	0	
9.00 am	>25.01-30%	6	7.7	9	13.2	0.271[#]
	>30%	72	92.3	59	86.8	
	>20-25%	3	4.3	2	3.1	
12.00 pm	>25.01-30%	3	4.3	6	9.2	0.501[#]
	>30%	63	91.3	57	87.7	
	>20-25%	1	1.5	1	1.8	
3.00 pm	>25.01-30%	8	12.3	15	26.3	0.139[#]
	>30%	56	86.2	41	71.9	

Chi-squaretest [#]Non-significant difference

2 patients were lost to follow up in both the groups. 1 patient was excluded from each group as the IOP was not controlled. In group II, 1 patient could not tolerate the adverse effects of drug brimonidine plus brinzolamide.

Chan K et al., conducted a study in which they compared ocular comfort of brimonidine 0.2%/timolol 0.5% and dorzolamide 2%/timolol 0.5%. The study enrolled 30 subjects with an average age of 42.9 years (Standard deviation [SD], 18.6 years), and ranged in age from 20 to 79. Two thirds of subjects (20) were female.[31]

Among all the patients who were put on brimonidine plus timolol, 53.8% had diabetes whereas in the simbrinza group, diabetes was present in 48.6%. The difference again was not statistically significant. No other potential systemic or ocular association was present in any patient in both the groups.

In our study, the mean IOP at baseline in group I at 9:00 am, 12:00 and 3:00 pm was 24.90±2.03, 24.36±3.05 and 23.54±2.95, respectively. It was observed that after initiation of treatment with brimonidine plus timolol at 2 week follow up visit there was a statistically significant reduction in the mean IOP of the study population from a baseline of 24.90±2.03 mmHg to 4.71±1.73 mmHg at 9.00 hours. At 12.00 pm and 3.00 pm from 24.36±3.05 mmHg and 23.54±3.24 mmHg at baseline came down to 9.79±3.61 mmHg and 9.30±4.31 mmHg by the end of 12 weeks respectively. Overall the combination drug therapy has statistically significant reduction in IOP (P value-<0.001).

Craven ER et al.,[32] compared the safety and IOP lowering capacity drug combination of brimonidine-timolol versus each drug as monotherapy. A significant shift towards the lower target pressure range in the fixed brimonidine/timolol group compared with each of the monotherapy groups was present (P<0.001).

Majority of patients in group I in our study obtained an IOP reduction of >30% at 9.00 am (92.3%), 12.00 pm (91.3%) and 3.00 pm (86.2%) after 12 weeks of therapy.

Crichton AC[4] observed that) brimonidine plus timolol showed IOP decrease of 16.1% from base reading. In regards to overall IOP distribution achieved with brimonidine plus timolol, over double the percentage of eyes achieved target at endpoint as compared to baseline, increasing from the baseline of 31% to 70% by Visit 3. On this measure, over two-thirds of the treated eyes (68%) achieved ≥15% reduction in IOP from baseline.

The mean IOP at baseline in group II at 9:00 am, 12:00 pm and 3:00 pm was 24.14±1.57, 23.94±2.01 and 22.46±2.43, respectively in our study. At all subsequent visits, there was a statistically significant reduction in mean IOP from baseline ($p<0.001$). 9.08 ± 2.11 mmHg was the mean change in IOP from baseline to 12 weeks.

The baseline mean IOP in group II at 12.00 pm was 23.94±2.01 mmHg. At all follow up visits, there was a statistically significant reduction in mean IOP from baseline ($p<0.001$). The mean change in IOP from baseline to 12 weeks was 9.31±2.92 mmHg.

The baseline mean IOP in group II at 3.00 pm was 22.46±2.43 mmHg. At further follow ups there was a statistically significant reduction in mean IOP from baseline ($p<0.001$). The mean change in IOP from baseline to 12 weeks was 7.42±3.62 mmHg. Majority of patients in group II obtained an IOP reduction of >30% at 9.00 am (86.8%), 12.00 pm (87.7%) and 3.00 pm (71.9%) after 12 weeks of therapy.

A randomized, Phase III, drug trial of BBFC versus brinzolamide or brimonidine was carried out in patients with open-angle glaucoma or ocular hypertension. It concluded that the LS mean IOP after 3 months of treatment was significantly lower with BBFC as compared to brinzolamide or brimonidine. Also mean IOP reductions from baseline and percentage change in IOP from baseline were greater with BBFC.[25]

Further our study demonstrated that there was a reduction in the mean IOP at 9.00 am in the study groups and the difference between the two was statistically significant at 4 weeks ($p=0.004$) and 12 weeks ($p=0.009$). There was no significant difference in the mean change in IOP between the groups at all the visits and at all times ($p>0.05$).

Not much change in visual acuity was found in either group at each study visits including the last visit at 12 weeks with Snellen's visual acuity ranging from 6/6-6/18 in 85.9% and 82.9% group I and group II respectively, and 6/24 – 6/60 was present in 14.1% of group I and 17.1% of group II.

In our study, no difference in the CD ratio was observed in both the groups at each study visit including the last visit at 12 weeks. Additionally, no significant change in visual field assessment was observed in either group. Also, at 12 weeks follow up visit we found no statistically significant difference in mean OCT RNFL thickness from baseline.

In our study, majority of patients (10.3%) had complaint of eye irritation followed by foreign body sensation (7.7%). Allergic conjunctivitis and itching was complained by equal number of patients (5.1%). No significant ($p>0.05$) difference in the adverse effects between the groups was observed.

Realini T et al. in there study, observed that the brinzolamide-containing groups demonstrated a higher incidence of blurred vision and dysgeusia as compared with the brimonidine group and the brimonidine-containing groups showed a higher incidence of ocular hyperemia.[27]

5. Conclusion

This study demonstrated that fixed dose combination, brimonidine plus timolol and brimonidine plus brinzolamide provide effective lowering of IOP in patients with POAG, besides being safe and well tolerated. Moreover, each drug has provided significant mean IOP reduction after three month of therapy at all visits and at all times. Considering that both the drugs have a similar safety profile, both can be used as a hypotensive agent for POAG.

6. Source of Funding

None.

7. Conflict of Interest

None.

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