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COMPARISION OF OCULAR HYPOTENSIVE EFFECT OF BIMATOPROST VERSUS TIMOLOL BRIMONIDINE FIXED COMBINATION IN OPEN ANGLE GLAUCOMA PATIENTS

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A B S T R A C T

Purpose: To compare the ocular hypotensive efficacy and safety of topical Bimatoprost and fixed combination Brimonidine and Timolol maleate in. **Method:** Fifty patients of primary open angle glaucoma and Ocular hypertnsion patients were divided into 2 groups of 25 each. Group A received Bimatoprost 0.03% once daily and Group B received fixed combination Brimonidine tartarate 0.2% and Timolol maleate 0.5% twice daily (FCBT). Intraocular pressure was measured at 9am, 1pm and 4pm at first visit, 1 week, 1month, 3month and 6 month. Mean diurnal IOP and mean IOP at 9am, 1pm and 4 pm were the outcomes measured. **Result:** Mean diurnal IOP reduction for Bimatoprost and FCBT were 32.5% and 29.7% respectively. Bimatoprost group had lower mean IOP at 1pm and 4 pm ($p<.001$). 76% of eyes on Bimatoprost achieved IOP of < 18mmHg while 28% had IOP <18 mmHg with FCBT. No serious adverse effect was observed with either drug. **Conclusion:** Bimatoprost has higher IOP lowering efficacy and better diurnal control than FCBT. Both drugs are well tolerated.

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INTRODUCTION

Glaucoma is an optic neuropathy having intraocular pressure as the only modifiable risk factor. An additional 1 mm Hg lowering of intraocular pressure causes 10% lowering of glaucoma progression and a consistent intraocular pressure of less than 18mmHg at all follow up visits prevents the further deterioration of visual field [1,2].

Topical antiglaucoma medications form the mainstay of therapy in open angle glaucoma. Traditionally the beta blockers and more recently the prostaglandins form the first line therapy. When monotherapy fails a second drug is added. Brimonidine tartarate 0.2%, an alpha adrenergic agonist, commonly used as a first line and an additive therapy in glaucoma and ocular hypertension patients is a safe and effective drug[3,4]. The fixed combination of Timolol maleate 0.5% and Brimonidine tartarate 0.2% (FCBT) provides a better IOP lowering efficacy and lesser adverse effects as compared to the separate use of the two drugs [5].

Bimatoprost, a synthetic prostamide analogue, is one of the most potent IOP lowering agent being used for glaucoma management till date. Mean IOP reduction of Bimatoprost has been reported to be 34-36% [6].

Several studies comparing the efficacy of Bimatoprost 0.03% with fixed combination Dorzolamide 2% and Timolol 0.5% have found that both the drugs were effective ocular hypotensive agents but Bimatoprost was more consistent in its effect[7,8,9]. There are however no studies comparing the efficacy of Bimatoprost with FCBT in literature to the best of our knowledge. The purpose of our study was to evaluate the efficacy and safety of Bimatoprost and FCBT and to compare the hypotensive effect of Bimatoprost with FCBT in primary open angle glaucoma and ocular hypertensive patients.

MATERIAL AND METHODS

A prospective, randomized open label clinical study was done on 50 patients having bilateral primary open angle glaucoma (POAG) and ocular hypertension (OH) attending the out patient department of the Department of Ophthalmology, Hindu Rao Hospital, Delhi.

The study was approved by the ethical committee of Hindu Rao Hospital, Delhi and all the tenants of Helsinki declaration were followed. A written consent was taken from the patients prior to enrolment in the study. The authors do not have any financial interest in any of the products used in the study.

POAG was defined as IOP more than 21 mm Hg in both eyes without antiglaucoma medications, with typical glaucomatous visual field changes and/or optic nerve damage with no secondary cause identifiable. Ocular hypertension was defined as IOP more than 21 mm Hg with no visual field changes and/or optic nerve damage.

Patients having angle closure glaucoma, severe ocular trauma, intraocular surgery or argon laser trabeculoplasty, contact lens use, severe dry eye, concomitant systemic or ophthalmic medication known to affect IOP or interact with any topical drugs use. Active or chronic systemic diseases involving the cardiovascular, pulmonary or metabolic system, pregnancy

and suspected intolerance or hypersensitivity to any drug used in the study were excluded from the study.

Fifty patients were randomised into two groups. Twenty five patients were started on Bimatoprost 0.03% once daily (between 7pm- 8 pm) and another 25 patients were started on the fixed combination Brimonidine tartarate 0.2% and Timolol maleate 0.5% (FCBT) twice daily (between 7am-8am and 7pm-8 pm).

The patients who were on treatment with topical anti glaucoma medication prior to the onset of the study were required to follow the washout period protocol after which they were started on the study medication. The washout period followed was 4 days for parasympathomimetics and carbonic anhydrase inhibitors,2 weeks for sympathomimetics and α agonists,4 weeks for β blockers and 8 weeks for prostaglandins and prostamides. After the appropriate washout period the baseline IOP measurements were recorded prior to starting the study medications.

The initial examination included best corrected visual acuity, slit lamp examination, gonioscopy, intraocular pressure measurement, automated field charting and fundoscopy with 90D lens. The field charting, gonioscopy were repeated at the end of study at 6 months.

The intraocular pressure, visual acuity, slit lamp examination and fundoscopy were done at all visits. The tonometry was done three times a day at 9 AM, 1PM and 4 PM in every visit. IOP measurement was done by taking three measurements in each eye alternating between the two eyes, and average of the three was noted as final reading. IOP for each patient was calculated as the mean of the IOP values from both eyes.

The patients were followed up at 1 week, 1 month, 3 month and 6 month.

The primary outcome of this study was change in mean diurnal IOP from baseline. The other outcome measured were the change in mean IOP at different times of day (9AM, 1PM, 4PM) from baseline and IOP reduction in mm of Hg at 6 months. The adverse effects were noted as and when they appeared.

Change from baseline IOP for each patient was determined by first calculating the change for each eye and then taking the mean of these values.

The mean diurnal iop was defined as the mean of the readings taken at 9am, 1pm and 4pm for each eye and then taking the mean of these values.

Statistical Analysis

Statistical testing was conducted with the statistical package for the social science system version SPSS 17.0. Results are expressed as mean ± SD, numbers and percentages. The comparison of normally distributed continuous variables between two treatment groups was performed using Student's t test. Nominal categorical data between the groups were compared using Chi-squared test or Fisher's exact test as appropriate. P<0.05 was considered statistically significant.

RESULT

The demographic details of the patients are shown in table 1. All the 50 patients completed the study .Most of the patients were in the age group of 50-70 years, oldest being 67 years, and the number of females was greater than males in both the groups. However the gender difference between the groups was statistically insignificant (P<0.77).Washout was required in 19 patients in the Bimatoprost group and 20 patients in the FCBT group.

Table 1 Demography of the Patient Cohort

Parameters	Group A	Group B
Age(years)	53.32 ± 8.60	55.56 ± 9.63
Sex	M 11(44%) F 14(56%)	M 12(46%) F 13(52%)
Type of Glaucoma	POAG 16(64%) OHT 9(36%)	POAG 15(60%) OHT 10(40%)
Mean IOP at baseline	25.55 ± 3.88	26.60 ± 2.80

The mean diurnal IOP at base line of the 2 groups were not significantly different (p= 0.278).

The mean diurnal IOP values measured during the various visits are shown in table2. There was 32% and 29% reduction in the mean diurnal IOP from baseline by Bimatoprost and FCBT respectively from first month onwards. There was no statistical difference in the mean IOP at 9am in the two groups at all visits. One month onwards the mean IOP of Bimatoprost group was significantly lower than that of FCBT group at 1pm and 4pm (p<0.001). Bimatoprost provided a better diurnal control of IOP than FCBT at 1month, 3month and 6 month.

Table 2 Mean diurnal IOP recordings at the follow up visits

Mean IOP	Bimatoprost Group		FCBT Group		p value
	Mean ± SD	Change from baseline (%)	Mean ± SD	Change from baseline (%)	
Baseline	25.55 ± 3.88	0	26.60 ± 2.80	0	0.278
1st week	21.95 ± 3.08	14.1	22.98 ± 2.31	13.6	0.189
1st month	17.32 ± 1.24	32.2	18.75 ± 1.31	29.5	<0.001
3rd month	17.30 ± 1.79	32.2	18.71 ± 1.31	29.6	<0.001
6th month	17.23 ± 1.25	32.5	18.68 ± 1.30	29.7	<0.001

In the FCBT group 64% eyes had IOP between 18mm - 20 mm Hg and 28% eyes had IOP below 18mmhg.In the Bimatoprost group 76% eyes had IOP less than 18mmhg while 6% eyes had IOP less than 15mm Hg.

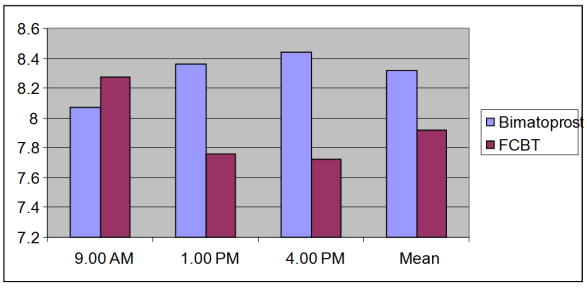

Fig1 Bar chart showing comparison of mean IOP reduction at different time of the day at 6 months.

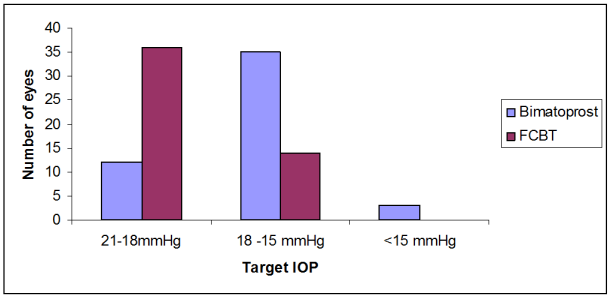

Fig 2 Target intraocular pressure achieved by the drugs.

Both the drugs were well tolerated. The common adverse effects encountered were conjunctival hyperemia, itching and burning of eyes and dry eye.

Table 3 Mean intraocular pressure recording at different times of day in the follow up period.

Time	Bimatoprost Group	FCBT group	p-value
1week			
9am	22.28 ± 3.10	23.33 ± 2.33	0.183
1pm	21.95±3.08	22.95±2.30	0.198
4pm	21.63 ± 3.06	22.65 ± 2.30	0.187
1month			
9am	17.82 ± 1.87	18.71 ± 1.83	0.097
1pm	17.17±1.30	18.88±1.15	<0.001
4pm	16.96 ± 1.05	18.67 ± 1.08	<0.001
3month			
9am	17.80 ± 1.87	18.69 ± 1.84	0.095
1pm	17.13±1.30	18.85±1.17	<0.001
4pm	16.96 ± 0.91	18.62 ± 1.06	<0.001
6month			
9am	17.78± 1.87	18.68±1.84	0.093
1pm	17.09± 1.30	18.81±1.18	<0.001
4pm	16.83 ± 1.04	18.56±1.03	<0.001

FCBT also caused fatigue and dry mouth in one patient each while periocular pigmentation was seen in one patient on Bimatoprost. Table 2 shows the side effects encountered during the study. The events encountered were mild and did not require the stoppage of the study medication.

Table 4

IOP (in mm of Hg)	Bimatoprost	FCBT
>18	12	36
18 -15	35	14
<15	3	0

Table 5 Adverse effects of Bimatoprost and FCBT.

Complaints	Bimatoprost	FCBT
Conjunctival hyperemia	3	3
Ocular pruritis	1	2
Burning sensation	1	1
Dry eye	2	1
Drymouth/throat	0	1
Periocular pigmentation	1	0
Fatigue	0	1

DISCUSSION

In the present study both Bimatoprost and FCBT decreased the baseline intraocular pressure significantly in patients of primary open angle glaucoma and ocular hypertension. In the Bimatoprost group the mean IOP reduction was 8.32mmhg and in the FCBT group reduction was 7.9mm Hg at the end of 6 months. The difference was statistically not significant. (p=.574).The mean diurnal intraocular pressure was 17.23±1.25mm Hg for Bimatoprost and 18.68 ±1.30mm Hg for FCBT at the end of the study period.

Intraocular pressure fluctuation follows a circadian rhythm and it is believed that glaucomatous damage progression is most likely in individuals with large diurnal fluctuations. The damage is known to occur during the intraocular pressure peaks. Thus maintaining a constant pressure throughout the day and night is the aim of glaucoma therapy.

Various studies have reported that prostaglandins analogs are the most effective topical agents presently available for lowering IOP [10,6]. Bimatoprost is a prostamides structurally and pharmacologically similar to $PGF_{2\infty}$ .The ocular hypotensive action is due to increase in both pressure dependant trabecular flow and pressure independent uveoscleral outflow facility. It is highly effective ocular hypotensive agent in controlling IOP over 24 hour period [11]. Bimatoprost 0.03%produces significantly greater reduction in intraocular pressure than Timolol maleate 0.5% in twice daily dose [11,12] . The clinical efficacy of Bimatoprost 0.03% has also been compared with dorzolamide Timolol fixed combination. Treatment with Bimatoprost provided greater reduction in mean IOP at 8am than dorzolamide timolol fixed combination. Also twice as many patients had IOP <16mmHg after 3months treatment with Bimatoprost than with dorzolamide timolol fixed combination [7].

Some studies comparing the efficacy and safety of Bimatoprost –.03% and dorzolamide timolol fixed combination found no difference between the two in the follow up period [13,14] .

In our study FCBT and Bimatoprost had comparable reduction in mean IOP at 9am (8.27mmHgvs8.07mmHg) (p=.763).This was probably because the morning dose of the drugs were between 7 and 8 am with FCBT reaching a peak effect within 2 hours. The 1pm and 4pm mean IOP after the first week visit showed significant difference between the two groups at all subsequent visits with Bimatoprost providing lower IOP than FCBT.

Kontas *et al* [15] reported that FCBT provides a significant diurnal IOP reduction from baseline IOP. Sherwood *et al* in their study comparing FCBT with monotherapy of the constituent parts found that the mean daytime IOP, decrease from baseline IOP and mean daytime IOP < 18 mm Hg were significantly greater with FCBT [5]. When compared with fixed combination dorzolamide - Timolol some studies have found it to be superior in terms of efficacy and adverse effects [5,16] while several studies have found them to be of comparable efficacy [17,18] .

In the advanced glaucoma intervention study it was found that IOP of <18mmhg at each visit was associated with minimal deterioration of visual field over 96 months [19] while Mao *et al* reported that eyes with IOP over 21mmhg has progressive optic disc cupping or visual field loss or both [20].

In our study 76% of eyes on Bimatoprost and 28% of eye on FCBT had IOP less than 18mmof Hg. In a large multicentre study with FCBT 39.5% achieved mean daytime IOP of <18 mm Hg while a similar study by Goni *et al* found 33% of the of subjects on FCBT achieved a target iop <18 mm of Hg. Bimatoprost was more successful in achieving a lower target pressure than FCBT.

No major adverse effects were encountered in our study. The most common side effect was mild conjunctival hyperemia with Bimatoprost followed by dry eye. All patients had dark iris colour hence no change in iris color was reported by the patients. The main adverse effect of Bimatoprost reported in literature are conjunctival hyperemia, pigmentation of periocular skin and iris and eyelash darkening [11,12].

It is generally believed that FCBT is better tolerated as compared to concomitant use of the component drugs. Goni *et al* reported ocular pain, pruritus, and headache as the most common side effects of the drug [21]. The most common side effect with FCBT in our study was ocular burning and

stinging followed by ocular pruritis. Dry mouth and fatigue was seen in one patient each.

CONCLUSION

Both Bimatoprost and FCBT are effective ocular hypotensive agent for treatment of primary open angle glaucoma. The IOP lowering efficacy of Bimatoprost is more than that of FCBT and it also provides a more consistent IOP throughout the day. Both the drugs are well tolerated.

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