



A COMPARATIVE EVALUATION OF THE SAFETY AND EFFICACY OF FIXED DOSE COMBINATION OF BIMATOPROST/TIMOLOL WITH DORZOLAMIDE/TIMOLOL IN PATIENTS WITH PRIMARY OPEN-ANGLE GLAUCOMA.

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ABSTRACT

Fixed-combination ocular hypotensives have well tried advantages over monotherapy. This study compares the safety and efficacy of fixed-combination bimatoprost/timolol (BTFC) and Dorzolamide/timolol (DTFC) in patients with primary open-angle glaucoma or ocular hypertension. In this parallel study, sixty patients with raised intraocular pressure (IOP) received once-daily BTFC or twice-daily DTFC medication for twelve weeks. IOP was evaluated at 9 am and 12 pm at weeks 2, 4 and 6. Primary endpoint was mean IOP change at the end of the therapy. At week 12, statistically significant IOP reductions from baseline were observed in both BTFC and DTFC ($P < 0.001$) groups, regardless of assessment time. BTFC group showed greater significant decrease in mean IOP than DTFC at 12 weeks ($P < 0.001$). Both drug combinations were safe and well tolerated. Once-daily BTFC demonstrated to have greater IOP-lowering efficacy clinically.

KEYWORDS: Ocular hypertension, Bimatoprost.

INTRODUCTION

Glaucoma, a heterogeneous group of ocular disorders is the second leading cause of irreversible blindness globally, after cataract. It is characterised by optic neuropathy, which derives from various risk factors one of which is increased Intraocular pressure (IOP), the only modifiable risk factor.^[1] Glaucoma poses a significant health and economic consequences with nearly sixty million people being affected globally and 8-14 million being bilaterally blind.^[2]

Patients are often prescribed single drugs from different classes of available hypotensives to lower IOP which include carbonic anhydrase inhibitor and α -agonist, in addition to prostaglandin analogs and β -blockers. Monotherapy with these drugs often fails to achieve adequate control of IOP in 40% of patients treated for glaucoma in which case additional drug is added.^[3]

Topical beta adrenergic receptor antagonists (timolol, levobunolol, metipranolol, carteolol) decrease Aqueous Humour production by the ciliary body. Beta blockers mainly act through beta 1 and beta 2 receptors. Timolol a non selective beta antagonist, still is considered as first line in pharmacotherapy of glaucoma because of low cost, but pressure responsiveness to Timolol decreases

because of short term escape and long term drift .CAIs (2% Dorzolamide and 1% Brinzolamide, locally) lower IOP by reducing aqueous production as well as increase the ocular perfusion. Both drugs are given two to three times daily and are additive to Timolol. Topical CAIs also appear to increase ocular blood flow.

Prostaglandins are potent class of anti Glaucoma drugs with Latanoprost and latest introduced being, Travoprost and Bimatoprost. They offer a novel mechanism of intra ocular pressure reduction through enhanced uveo-scleral outflow. Common systemic side effects are absent and high potency as well as clinical superiority to others in IOP reduction has made this class of medications attractive as first line therapy. However, cost still remains an area of concern for country like ours. Achieving targeted IOP in POAG patients with single though potent topical hypotensive agent is difficult. The European Glaucoma Society recommends to add a second medication with different mechanism of action in these patients when the original agent shows some effectiveness. In fact use of more than one ocular hypotensive therapy to reduce IOPs in such patients may be expected to slow or stop disease progression.^[4] Combinations offer better compliance, decreased frequency of drops per day, fewer bottles to be handled

by the patients and reduced exposure to preservatives. In addition, the effective cost of medication may be reduced since the FDC is less expensive than the individual therapies.

Complementary mechanism of action and fixed combinations of prostaglandins and CAI with beta blockers is expected to produce better compliance resulting leading to improved patient outcome. Dorzolamide/timolol fixed combination (DTFC) is a popular combination into use by clinicians which has an established effectiveness as an IOP lowering agent in patients with POAG with high IOP.^[5] The lack of adherence to the treatment is the basic fault of patients to this painless and symptomless disease entity leading to failure in achieving the target IOP, deteriorating vision and irreversible blindness in the end for negligent patients. Taking into consideration the aforesaid modifiable reasons on the part of the patient, we used combined IOP lowering drugs in “fixed dose combinations”, FC.

Therefore, we planned to combine Bimatoprost /Timolol (BTFC) as fixed combination and compared its safety and efficacy to Dorzolamide/timolol (DTFC) fixed combination as hypotensive agents in POAG patients presenting with high IOP.

AIM AND OBJECTIVES

The aim of the study was to compare the safety and IOP lowering efficacy of the fixed combination Bimatoprost 0.03%/timolol 0.5% (BTFC) versus fixed combination Dorzolamide 2%/timolol 0.5% (DTFC) in patients with primary open-angle glaucoma presenting with high IOP.

MATERIAL AND METHODS

The present study was a randomized, prospective, parallel group and open labelled of twelve weeks duration which compared the safety and IOP-lowering efficacy of the fixed combination of Bimatoprost 0.03%/timolol 0.5% (BTFC) with the fixed combination Dorzolamide 2%/timolol 0.5% (DTFC) in patients with POAG with high IOP.

The study was approved by the Institutional Ethics Committee (IEC) of Rama Medical College Mandhana Kanpur Uttar Pradesh. Patients presenting in the out-patient department of Ophthalmology department with high IOP (>22 mmHg) underwent a preclinical workup. After obtaining written informed consent the eligible patients were enrolled in the study. They were randomized according to a computer software generated randomization schedule. The drop-outs were not taken into consideration as it was an intention-to-treat trial.

Patients of both sexes aged 30-80 years, newly diagnosed POAG with IOP > 22 mmHg and < 36 mm Hg in one or both eyes were included. Glaucoma is defined as either visual field defect or glaucomatous changes of the optic nerve head (neural rim loss, disc asymmetry, blood

vessel changes, peri papillary atrophy) in association with an elevated IOP (IOP above 22 mmHg). Sixty patients were screened for our study who presented in the out-patient department. Patients with IOP >36 mm Hg, history of glaucoma surgery or intraocular surgery in the past 6 months, ocular trauma or inflammation, pregnant, lactating or not employing adequate measures to prevent conception were excluded. Patients with cardiovascular or respiratory disease, hepatic or renal dysfunction, any history of systemic or topical hypersensitivity to prostaglandins, β -blockers, carbonic anhydrase inhibitors; were also excluded from our study design. Patients who fulfilled both the criteria were clinically assessed. A detailed ocular and medical history was obtained. Careful general physical examination along with systemic examination of respiratory and cardiovascular systems was done. Safety / tolerability evaluation was based upon self reported adverse effects. Ocular examination included BCVA (Best corrected visual acuity) using Snellen's chart, examination of lids, adnexa and lacrimal apparatus in diffuse light, Bio-microscopy of anterior segment using Carl Zeiss slit lamp to note any abnormality especially regarding conjunctival hyperemia. Direct ophthalmoscopy and slit lamp bio-microscopy with 78D lens was done to assess cup disc ratio (CD ratio) and Goldman appplanation tonometer was used to measure intraocular pressure on all visits.

Patients who required bilateral IOP-reducing therapy were treated in both eyes because it was an intention to treat trial, but the eye(s) that fulfilled all the inclusion criteria were enrolled as study eye(s). If both eyes fulfilled all inclusion criteria, then the right eye was selected for the analysis.

Sixty eligible patients were randomly allocated in to Group I or Group II to receive fixed combination of Bimatoprost/Timolol once daily in the evening or fixed combination Dorzolamide/Timolol twice daily respectively.

Patients were demonstrated the technique to instil the medication after enrolment in the trial. Patients in Group I instilled one drop into each eye, once daily, in the evening and patients in Group II instilled one drop into each eye, twice daily. The follow-up was done at two weeks, four weeks and at 12 weeks after the first visit. IOP measurements and visual acuity were taken at each follow-up examination at two, four and twelve weeks at 9 a.m. and 12 p.m. for all patients in both the groups. The primary end-point was reduction in IOP from baseline to week 12.

Any ocular and systemic side effects of conjunctival hyperemia, foreign body sensation, blurred vision, dry eye sensation, stinging, pruritus, iris pigmentation, eyelash changes, pulse rate changes, breathing difficulties, headaches, depression and gastrointestinal problems were assessed and documented at each visit.

Safety and tolerability of the study drugs was based on self reporting of any of the side effects. Data were collected and the analysis of each variable was performed on the change from baseline values using two tailed student 't' test. A 'p' value less than or equal to 0.05 was considered statistically significant.

RESULTS

Sixty eligible patients (35 males, 25 females) of POAG were enrolled for the study. Four patients from the Group

II (dorzolamide /timolol) group were considered dropouts due to no treatment visit data and were excluded.

The mean age of patients in group I was 54.30 ± 7.29 years & in Group II was 56.17 ± 10.99 years. There was no statistically significant difference between the ages of the patients of the two groups ($p=0.442$).

TABLE 1:- COMPARISON OF AGE FOR GROUP I AND GROUP II.

Age (in Years)	Group I		Group II	
	No.	% age	No.	% age
< 50	12	40.00	9	30.00
51-59	11	36.67	9	30.00
60-69	5	16.67	8	26.67
70-79	2	6.66	4	13.33
TOTAL	30	100	30	100
Mean \pm SD	54.30 ± 7.29		56.17 ± 10.99	
't' value	-0.775			
'p' value	0.442			
Significance	NS			

There was no statistical difference between the treatment groups for sex, diagnosis, visual acuity, gonioscopy values, horizontal and vertical cup-disc ratio. IOP levels in both treatment groups were similar at baseline: 27.72 ± 2.308 mmHg for Group I (Bimatoprost/timolol fixed combination) and 27.45 ± 2.483 mmHg for the Group II (dorzolamide/timolol fixed combination).

In Group I at 9.00 am the mean IOP decreased from 27.80 ± 2.34 mmHg to 17.62 ± 0.725 mmHg at 12th week, resulting in a decrease of 10.18 mmHg (36.61%). Group II at 9 am showed that the mean IOP decreased from 27.34 ± 2.54 mmHg to 18.90 ± 0.735 mmHg resulting in a fall of 8.44 mmHg (30.87%) (Table No. 2). In the same line at 12 pm, in Group I the mean IOP decreased from 27.61 ± 2.32 mmHg to 17.54 ± 0.752

mmHg at 12th week which accounts a fall of 10.07 mmHg (36.47%) and in Group II from 27.50 ± 2.49 mmHg to 18.84 ± 0.74 mmHg at 12th week thus resulting in a fall of 8.66 mmHg (31.49%) (Table No. 3). The reduction of IOP from the baseline in both the study groups was statistically significant at all time intervals and on all visits.

The greatest treatment difference occurred at 12th week in favor of bimatoprost/timolol fixed combination group ($p<0.001$). Significant IOP reduction from baseline was achieved with both groups ($p<0.001$). The mean reduction in IOP was 10.23 ± 2.302 mmHg for the bimatoprost/timolol fixed combination group and 8.55 ± 2.645 mmHg for the dorzolamide/timolol fixed combination group (Table No. 4).

TABLE 2: COMPARISON OF MEAN IOP AT 9.00 A.M. FOR GROUP I AND GROUP II.

Interval	Group I	Group II	't' Value	'p' Value	Sig.
	Mean \pm SD	Mean \pm SD			
Baseline	27.80 ± 2.34	27.34 ± 2.54	0.740	0.462	NS
2 Weeks	19.60 ± 0.830	19.91 ± 1.08	- 1.260	0.213	NS
4 Weeks	18.99 ± 0.816	19.44 ± 0.941	-1.991	0.051	NS
12 Weeks	17.62 ± 0.725	18.90 ± 0.735	- 6.759	0.001	S

TABLE 3:- COMPARISON OF MEAN IOP AT 12.00 P.M. FOR GROUP I AND GROUP II.

Interval	Group I	Group II	't' Value	'p' Value	Sig.
	Mean \pm SD	Mean \pm SD			
Baseline	27.61 \pm 2.32	27.50 \pm 2.49	0.172	0.864	NS
2 Weeks	19.36 \pm 0.930	19.68 \pm 1.13	- 1.184	0.241	NS
4 Weeks	19.04 \pm 1.075	19.46 \pm 0.87	-1.670	0.100	NS
12 Weeks	17.54 \pm 0.752	18.84 \pm 0.74	- 6.750	0.001	S

TABLE 4: COMPARISON OF MEAN DIURNAL IOP FOR GROUP I AND GROUP II.

Interval	Group 1	Group II	't' Value	'p' Value	Sig.
	Mean \pm SD	Mean \pm SD			
Baseline	27.72 \pm 2.308	27.45 \pm 2.483	0.619	0.537	NS
12 Weeks	17.58 \pm 0.734	18.86 \pm 0.723	- 9.588	0.001	S
Reduction	10.23 \pm 2.302	8.55 \pm 2.645	3.718	0.001	S

TABLE 5: OCULAR ADVERSE EFFECTS OF STUDY DRUGS.

Ocular adverse effects	Group I	Group II
Conjunctival hyperaemia	3	1
Burning / Stinging sensation	1	2
Foreign Body sensation	1	1
Photophobia	-	1
Eye Pain	-	4

Safety / tolerability evaluation was based upon self reported adverse effects. Dorzolamide / Timolol was associated with more frequent eye pain while Bimatoprost/Timolol was associated with more frequent conjunctival hyperaemia (Table No. 5). This data reflects that both the study combinations of hypotensive drugs were safe and well tolerated. There were no reported drop outs due to these side effects associated with the study.

DISCUSSION

Glaucoma is among the leading cause of painless irreversible blindness throughout the world. Primary open angle glaucoma is the second most important cause of permanent blindness in the Asia Pacific Region. Glaucoma poses significant health and economic consequences with millions being affected and majority being bilaterally blind worldwide. Glaucoma is a clinical manifestation which is characterized by constant or intermittent elevation of IOP with temporary or permanent damage to the structure and function of the eye. IOP is the only modifiable risk factor for this clinical entity and in achieving an optimal IOP in all patients may be difficult with monotherapy. For such patient's concurrent use of other IOP lowering agents as adjunct may be required. These combinations may improve compliance and convenience to the patient which has a better impact in the overall outcome of the therapy instituted.

We conducted an open labelled, prospective, randomized and parallel group clinical study on sixty patients for duration of twelve weeks. It aimed to evaluate the safety and efficacy of Fixed Combination of Bimatoprost 0.03% and Timolol 0.5% (BTFC) given once daily (Group I) versus Fixed Combination of Dorzolamide 2% and Timolol 0.5% (DTFC) given twice daily (Group II) in patients of primary open angle glaucoma or ocular hypertension. The patients who presented in the Ophthalmology OPD of Rama Medical College Kanpur with high IOP of >22 mmHg but <36 mmHg were selected and were randomly and equally (30 each) allocated into Group I and Group II. Ocular and medical history including any recent surgery was obtained and recorded in details for every enrolled patient. General physical examination was performed to rule out any co morbid conditions along with any respiratory or cardiac complications. Baseline IOP was measured on day 0 at 9 am and 12 pm and the therapy was initiated. Subsequently IOP was measured at week 2, week 4 and week 12 at 9.00 am and 12pm.

The observations were recorded and results of individual patients were compiled and statistically analysed for both the study groups. The mean age \pm SD of 30 patients enrolled in Group I and II were 54.30 ± 7.29 and 56.17 ± 10.99 years respectively. No statistical significant difference was observed in the mean ages in patients of two groups. Similarly difference with respect to the sex

and the eye involved (right or left) of both the study groups was also not statistically significant. Our analysis showed a statistical significant reduction in the IOP at all times and at each visit from the baseline in both the treatment groups. The deviation in the IOP achieved in the treatment groups was not statistically so significant at two and four week period but at week 12th Bimatoprost/timolol combination showed more efficacy. The decrement in IOP from baseline to 12 weeks in Group I was 10.18 and 10.07 at 9 Am and 12 pm respectively. Similar decrease was seen as 8.5 and 8.66 at 9am and 12 pm in Group II. The clinical implications of such a slim difference may be questioned but the reductions of IOP may have a great impact on clinical outcome of such patients. The difference in IOP reduction between two study groups was statistically significant at 12 weeks for both time readings ($p < 0.001$ both group).

A similar study design of twelve week duration was carried out by Alfonso Garcia Lopez et al.^[6] and they concluded that IOP reductions from baseline observed in the bimatoprost/timolol FC (BTFC) ($P < 0.01$) were statistically significant as compared to dorzolamide /brimonidine /timolol ($P < 0.0001$) DBTFC. Further follow up in the study at month 6, patients of BTFC exhibited no significant IOP increase but patients of DBTFC exhibited a statistically significant IOP increase ($P < 0.001$). These observations are in synchrony with our results for BTFC Group. Unlike our study, the researchers used a triple combination of DBTFC and compared it to the BTFC which yielded a slight better statistical significance. How much of this thin difference transforms to a better outcome in iop reduction clinically has to be followed up and evaluated. We did not follow up the patients for another three months so any rebound in IOP in either group cannot be commented.

A research study conducted by Coleman et al.^[7] compared Bimatoprost once daily with the Dorzolamide/timolol FC twice daily and concluded that Bimatoprost provided significantly greater IOP lowering compared with combined timolol and dorzolamide. Bimatoprost lowered mean IOP 6.8 mmHg to 7.6 mmHg from baseline, whereas combined timolol and dorzolamide lowered mean IOP 4.4 to 5.0 mmHg from baseline ($P < 0.001$). Study by Sharpe et al.^[8] suggested that IOP lowering efficacy of Bimatoprost can be comparable to DTFC but overall diurnal control in IOP is statistically better with bimatoprost. Our study results parallel with these studies which show the superiority of Bimatoprost as hypotensive. Sun X et al.^[9] observed a better mean IOP control, tolerability and ease of administration along with greater patient satisfaction with the use of BTFC when compared to the previously treated patients with other class of medications. Mean satisfaction scores were significantly higher for BTFC than for previous treatments among all patients (7.8 versus 6.0; $P < 0.0001$).

On the contrary Day et al.^[10] suggests that the intraocular pressures are lowered to a statistically similar extent with DTFC compared to bimatoprost in open-angle glaucoma. The mean diurnal intraocular pressures reported was 17.4 +/- 2.9 for Bimatoprost and 18.1 +/- 2.8 mmHg for DTFC ($p = 0.35$). This difference of results between DTFC and BTFC can be due to demographic, ethnic and racial diversity. One of the other reasons can be due to use of bimatoprost used singly where in our study we used a combination which had a greater benefit to the patient in iop lowering.

Martinez et al.^[11] also completed the study stating that the evening-dosed BTFC provides better IOP control than that of LTFC (Latanoprost/timolol) over 12 h.

Paralleling results of nearly equal efficacy and safety were also shown by Suzan et al.^[12] while comparing the fixed doses of bimatoprost/timolol maleate, latanoprost/timolol maleate and travoprost/timolol maleate on 24-h IOP. These studies have divulged observations from our results. It may be attributed to patients' demographic and racial difference as well as to the difference in the preparation of the study drugs and their clinical response. Extending this, we combined timolol with Bimatoprost as an additive to the therapy which is more likely to produce better effect as IOP lowering property. Majority of studies support our research work and show the superiority of Bimatoprost alone or in combination (BTFC) as IOP lowering therapy.

Both FC therapies were well tolerated. In all, 5 of 30 (16.67%) subjects in the BTFC group and 9 of 30 (30%) in the DTFC group reported adverse events. The most frequently occurring adverse effects reported in our study due to therapy were eye pain, eye irritation and conjunctival hyperaemia which were not long lasting. We documented that patients on BTFC reported conjunctival hyperaemia^[3] and foreign body sensation^[1] as commonest adverse effect of the BTFC group. Blurred vision and stinging^[2], foreign body sensation^[1] and eye pain^[4] was reported mainly with the DTFC therapy patients. These adverse effects of our study medications correspond to the adverse effect profile in an analogous study by Alfonso et al.^[6] Overall both the therapies were well tolerated by the patients. Sharpe et al.^[8] and Day et al.^[10] reported greater incidence of burning and stinging in the eye in Dorzolamide /timolol treated patients which corroborates to our observed adverse effect pattern. Self reporting of any adverse effect was the basis to evaluate the tolerability and safety in the record forms. The adverse effects were drug related and were mild ocular or peri-ocular in nature which did not warrant discontinuation of therapy. No significant difference was found between the number or severity of adverse effect profile. There were no dropouts due to documented adverse effects relating to the study medications. Both the drugs were well tolerated and safe throughout the study. Both the study combinations under study i.e.

Bimatoprost/timolol and dorzolamide/timolol fixed combinations are efficacious, safe and well tolerated as effective IOP lowering agents in patients of POAG.

We concluded that Bimatoprost/ timolol fixed combination dosed once daily is superior and better with consistent results as compared to Dorzolamide/timolol fixed combination dosed twice daily for POAG patients in lowering their IOPs. Bimatoprost/timolol FC has a 1.68 mmHg greater reduction in IOP with tolerable and self-limiting adverse effect profile as compared to Dorzolamide/timolol fixed combination.

Besides all carefulness in designing the study and carrying it out our study had limitations. The patients were not blinded to the study drugs. It was undertaken on limited number of patients in a single centre. It would be prudent to plan it with a longer study duration involving multi-centric patients who are followed up for long term clinical benefits.

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