To study the comparison of efficacy and side effect profile of bimatoprost 0.03% versus fixed combination timolol 0.5% and dorzolamide 2% in patients with primary open angle glaucoma or ocular hypertension

Ramandeep Kaur[1,*], Sachin Walia[2], Harsimran Singh[3], Navreet Kaur[4]

1Junior Resident, 2Professor & HOD, 3Assistant Professor, Dept. of Ophthalmology, Rajindra Hospital, Patiala, Punjab

***Corresponding Author:**
Email: dr.ramanbhangu27@gmail.com

Abstract

Aims: To study IOP lowering efficacy and side effect profile of bimatoprost 0.03% versus fixed combination timolol 0.5% and dorzolamide 2%.

Settings and Design: Prospective, open, randomized, parallel group, comparative study, 100 patients of POAG/ocular hypertension with moderate glaucomatous damage attending the outpatient department of ophthalmology, at our institute were included.

Materials and Methods: The patients were randomly assigned to one of the two treatment groups, each having a sample size of 50 patients. Group 1 instilled 1 drop of Bimatoprost 0.03%at 8 p.m. (once daily) for 12 weeks and Group 2 instilled 1 drop of fixed drug combination of timolol 0.5% and dorzolamide 2% at 8a.m. and 1 drop at 8p.m. for 12 weeks. All the patients were subjected to the detailed ocular examination following examination and tests at baseline, 4 weeks, 8 weeks and 12 weeks after starting the study treatment.

Results: Both the groups showed comparable IOP reductions in the patients. There was no statistically significant difference in the mean IOP reduction among the two groups' at all follow-up visits. The most frequently reported adverse effect was conjunctival hyperaemia in bimatoprost group and burning, stinging sensation in eyes and taste perversion in the DTFC group.

Conclusion: Bimatoprost can be used as a long term monotherapy agent in the treatment of POAG and ocular hypertension providing good efficacy with an easy dosing regimen and without much side effects.

Keywords: Bimatoprost, Timolol dorzolamide, Primary open angle glaucoma, Ocular hypertension

Access this article online

Website:
www.innovativepublication.com

DOI:
10.5958/2395-1451.2016.00038.X

Introduction

The term glaucoma refers to a group of diseases that have in common a characteristic optic neuropathy with associated visual function loss.[1] The gradual loss of visual field can lead to total irreversible blindness if the disorder is not diagnosed and treated properly.

There are three mainstays to the treatment of glaucoma: pharmacologic, laser, or surgical treatment. The first line of therapy is topical medication. Many medications now exist to help control IOP in a variety of classes. Beta-adrenergic antagonists have been a mainstay of therapy for many years. They remain the most commonly prescribed drug, but more recent classes of glaucoma medications have come into favour. These include prostaglandin F2-alpha agonists, alpha-2 agonists, and carbonic anhydrase inhibitors. The prostaglandin analogues have gained favour as primary therapy, but in many instances, beta-blockers remain the first-line therapy in treatment of glaucoma.[2] Sometimes single agents do not achieve the desired therapeutic effects, thus combinations of medications from various classes can be used to attempt to achieve the desired results. The use of combination therapy frequently is necessary at any stage of the disease,[3,4] as it has been reported in the Ocular Hypertension Treatment Study(OHTS)(2002),[4] and in the Collaborative Initial Glaucoma Treatment Study(CIGTS) (2001),[5] where up to 50% and 75% of patients, respectively, required 2 or more drugs to reach their target pressure. Previous studies showed that both the PGA's and dorzolamide timolol fixed combination have a good pressure lowering effect with less dosing regimen. So this study was conducted to investigate the efficacy and safety of bimatoprost 0.03%, administered once a day in the evening compared with a fixed combination of timolol 0.5% and dorzolamide 2% administered in the morning and in the evening in an attempt to compare the IOP reduction, compliance to therapy and side effect profile of the drugs amongst the two groups of patients already on monotherapy with timolol.

Materials and Methods

In this prospective, open, randomized, parallel group, comparative study, 100 patients of POAG/Ocular Hypertension attending the Outpatient Department of Ophthalmology, at our institute were included. In both the groups, the eye that was affected more was considered as the study eye. If the eyes had

nearly similar damage then by convention right eye was studied.

The patients were randomly assigned to one of the two treatment groups, each having a sample size of 50 patients.

Group 1): consisted of 50 patients of primary open angle glaucoma/ocular hypertension. This group instilled 1 drop of Bimatoprost 0.03%at 8 p.m. (once daily) for 12 weeks.

Group 2): consisted of 50 patients of primary open angle glaucoma/ocular hypertension. This group instilled 1 drop of fixed drug combination of timolol 0.5% and dorzolamide 2% at 8a.m. and 1 drop at 8p.m. for 12 weeks.

All the patients were subjected to the following examination and tests at baseline, 4 weeks, 8 weeks and 12 weeks after starting the study treatment.

Best corrected visual acuity using Snellen's chart.

Detailed ocular examination including Eye lashes, lid and adnexa was done using diffuse light.

Biomicroscopy of anterior segment was done using Topcon slit lamp to note any abnormality especially regarding conjuctival hyperaemia using CCLRU grading scale.[6]

- Tear film break up time for dry eye
- *Goldmann applanation tonometry* was used to measure intraocular pressure (measured at baseline, 4 weeks, 8 weeks and 12 weeks at 8 a.m., 12 noon, 4 p.m. and 8 p.m.)

Angle of anterior chamber was assessed by doing gonioscopy with Goldmann goniolens to exclude the cases of angle closure glaucoma.

- Cornea, iris, lens and pupil were examined.
- Anterior chamber with cells and flare was graded based on SUN classification.[7]
- Dilated fundus examination - Direct ophthalmoscopy and slit lamp indirect ophthalmoscopy with 90 D lens was done to assess cup disc ratio (CD ratio), neuroretinal rim health and retinal nerve fibre layer on all visits.
- Visual field testing was done with Humphrey Field Analyser

Whole data was recorded and analyzed using following statistical tests:

Mean values, Standard error of mean, Student's 't' test (paired 't' test) and Chi Square Test (χ^2)

A difference between the treated and control group which would have arisen by chance is 'p' value. If it is less than 0.05, it is considered significant (S), 'p' value less than 0.01 is considered highly significant (HS).If it is more than 0.05, it is considered non-significant (NS).

Results

The 2 groups were comparable for baseline characteristics for age, gender, IOP, vertical CDR and visual fields (mean deviation) with $p > 0.05$.

IOP reductions of the two groups bimatoprost 0.03% and DTFC were clinically significant at 4 weeks, 8 weeks and 12 weeks.

Both the groups showed comparable IOP reductions in the patients. The difference in the mean IOP between the two groups at various follow-up visits was tested using unpaired two-tailed t-test. The mean decrease in IOP at 12 weeks by bimatoprost in our study was 6.26±1.56 mm Hg, whereas with the DTFC it was by 6.66±1.69 mm Hg. There was no statistically significant difference in the mean IOP reduction among the two groups at all follow-up visits.

The most frequently reported adverse effect at 4 weeks was conjunctival hyperaemia in bimatoprost group and burning, stinging sensation and taste perversion in DTFC group. Conjunctival hyperaemia was present in 13 cases (26%) in bimatoprost group and in 5 cases (10%) in the DTFC group. The difference was statistically significant. Burning/Stinging was present in 5 cases(10%) in the DTFC group and in 1 case (2%) in the bimatoprost group. Again the difference in the two groups was significant. Taste perversion was also more in DTFC group though the difference was not statistically significant. But these side effects were mild and none of the patients discontinued the drug because of any side effects. Other ocular side effects were absent at in both the groups.

Certain ocular side effects like eyelash lengthening /skin pigmentation/CME were not seen because of short duration of study (12 weeks). As for systemic side effects (bradycardia, malaise, headache) no group showed any systemic side effect.

Table 1: Comparison of mean IOP of the groups at baseline

Time	**Group A** Bimatoprost	**Group B** DTFC	**p value (Unpaired *t* test)**	**Significance**
	Mean±SD	**Mean±SD**		
8 am	24.62±1.59	24.80±1.96	0.615 (0.505)	NS
12 noon	24.48±1.50	24.70±1.89	0.520 (0.645)	NS
4 pm	24.32±1.58	24.60±1.83	0.415 (0.818)	NS
8 pm	24.24±1.65	24.48±1.81	0.490 (0.693)	NS

Table 2: Comparison of mean IOP of the two groups at 8 am

Interval	Group A Bimatoprost	Group B DTFC	p value (Unpaired *t* test)	Significance
	Mean±SD	Mean±SD		
Baseline	24.62±1.59	24.80±1.96	0.615 (0.505)	NS
4 weeks	17.68±1.09	18.04±1.05	0.097 (1.678)	NS
8 weeks	17.90±1.03	18.26±0.83	0.058 (1.920)	NS
12 weeks	18.38±0.67	18.30±0.58	0.524 (0.640)	NS

Table 3: Comparison of mean IOP of the groups at 12 noon

Interval	Group A Bimatoprost	Group B DTFC	p value (Unpaired *t* test)	Significance
	Mean±SD	Mean±SD		
Baseline	24.48±1.50	24.70±1.89	0.520 (0.645)	NS
4 weeks	17.62±1.07	17.86±0.97	0.242 (1.177)	NS
8 weeks	17.66±1.12	17.92±0.89	0.203 (1.281)	NS
12 weeks	18.26±0.72	18.08±0.80	0.242 (1.177)	NS

Table 4: Comparison of mean IOP of the groups at 4 pm

Interval	Group A Bimatoprost	Group B DTFC	p value (Unpaired *t* test)	Significance
	Mean±SD	Mean±SD		
Baseline	24.32±1.58	24.60±1.83	0.415 (0.818)	NS
4 weeks	17.30±1.16	17.68±1.22	0.114 (1.593)	NS
8 weeks	17.38±1.12	17.66±1.12	0.214 (1.250)	NS
12 weeks	18.10±0.84	18.06±0.87	0.815 (0.234)	NS

Table 5: Comparison of mean IOP of the groups at 8 pm

Interval	Group A Bimatopros t	Group B DTFC	p value (Unpaired *t* tes t)	Significanc e
	Mean±SD	Mean±SD		
Baselin e	24.24±1.65	24.48±1.8 1	0.490 (0.693)	NS
4 weeks	17.18±1.10	17.18±1.2 1	1.000 (0.000)	NS
8 weeks	16.94±1.13	17.28±1.2 5	0.156(1.428)	NS
12 weeks	18.10±0.79	17.84±0.8 2	0.109 (1.619)	NS

Table 6: Incidence of side effects among patients in the two treatment groups at 12 Weeks

Side effect	Group A Bimatoprost (%age)	Group B DTFC (%age)	p value (McNemar Chi Squre Test)
Conjuntival Hyperemia	13 (26%)	5 (10%)	0.033
Burning/Stinging	1 (2%)	5 (10%)	0.102
Taste Perversion	0	3 (6%)	1.00
Dry Eye	0	0	-
Hypertrichosis	0	0	-
Skin Pigmentation	0	0	-
CME	0	0	-
SPK	0	0	-
Breathlessness	0	0	-

Discussion

Despite the presence of so many risk factors associated with glaucoma the current therapy for glaucoma focuses on lowering IOP to a level at which the progression of glaucomatous damage is halted and recent studies have illustrated the importance of lowering IOP to prevent optic nerve damage. As both the groups had significant decrease in IOP during each of the follow up. the reduction was compared within the groups and the results showed that the decrease in IOP was comparable in both the groups The difference was not statistically significant between the groups There was no significant difference in the mean IOPs' between the two groups measured at 8 am, 12 noon, 4 pm and 8 pm at 4 weeks, 8 weeks and 12 weeks follow up visits ($p>0.05$).

These results were similar as studies conducted by Ozturk et al,[8] and Day et al,[9]. These studies compared ocular hypotensive effects of bimatoprost and timolol-dorzolamide combination in patients with elevated intraocular pressure.

In contrary to our study Coleman et al,[10] conducted a 3-month randomized controlled trial of bimatoprost versus combined timolol and dorzolamide in patients with glaucoma or ocular hypertension. In individuals with glaucoma or ocular hypertension,

uncontrolled on a topical β-blocker alone, bimatoprost lowered IOP more consistently than combined timolol and dorzolamide. At the 8:00 am measurements, bimatoprost lowered mean IOP 6.8 mmHg to 7.6 mmHg from baseline, whereas combined timolol and dorzolamide lowered mean IOP 4.4 mmHg to 5.0 mmHg from baseline and the difference was statistically significant.

Side effect profile was also assessed during the study. Overall, both the study regimens were well tolerated during the followup. A few ocular side-effects reported were transient and mild in both the groups except for two cases. The most common ocular side-effects were mild conjunctival hyperaemia in bimatoprost and burning / stinging in DTFC group. No change in iris colour was observed or reported by patients. This was to be expected in view of the short time duration of the study and also because of dark colour of the iris of our indian study population. No serious systemic side effects were present at any of the follow up requiring discontinuation of the study These results were comparable with the studies conducted by Coleman et al,[10] and Ozturk et al,[8] which concluded that though conjunctival hyperemia was the main side effect of the bimatoprost it was mild and transient not requiring discontinuation of the treatment.

- So our study concluded that Bimatoprost can be used as a long term monotherapy agent in the treatment of POAG and ocular hypertension providing good efficacy with an easy dosing regimen and without much side effects.

References

1. American Academy of Ophthalmology. Glaucoma. Basic and Clinical Science Course. 2011–2012; San Francisco, CA, USA.
2. Bateman DN, Clark R, Azuara-Blanco A, Bain M, Forrest J. The effects of new topical treatments on management of glaucoma in Scotland: an examination of ophthalmological health care. Br J Ophthalmol. 2002;86:551–4.
3. Hoyng PF and van Beek LM. Pharmacological therapy for glaucoma: a review. Drugs 2000;59:411–34.
4. Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP et al. The Ocular Hypertension Treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open angle glaucoma. Arch Ophthalmol 2002;120:701–13.
5. Lichter PR, Musch DC, Gillespie BW, Guire KE, Janz NK, Wren PA et al. Interim clinical outcomes in the Collaborative Initial Glaucoma Treatment Study comparing initial treatment randomized to medication or surgery. Ophthalmology 2001;108:1943–1953.
6. Pult H, Murphy PJ, Purslow C, Nyman J, Woods RL. Limbal and Bulbar Hyperaemia in Normal Eyes. Ophthalmic Physio Opt 2008;28:13–20.
7. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol. 2005;140:509-16.
8. Ozturk F, Ermis SS, Inan UU. Comparison of the ocular hypotensive effects of bimatoprost and timolol-dorzolamide combination in patients with elevated intraocular pressure: a 6-month study. Acta Ophthalmologica Scandinavica, 2007;85:80–83.
9. Day DG, Sharpe ED, Beischel CJ, Jenkins JN, Stewart JA, Stewart WC. Safety and efficacy of bimatoprost 0.03% versus timolol maleate 0.5%/ dorzolamide 2% fixed combination. Eur J Ophthalmol. 2005;15:336-42.
10. Coleman AL, Lerner F, Bernstein P, Whitcup SM. A 3-month randomized controlled trial of bimatoprost (LUMIGAN) versus combined timolol and dorzolamide (Cosopt) in patients with glaucoma or ocular hypertension. 2003;110:2362-68.