A COMPARATIVE STUDY ON THE SAFETY AND EFFICACY OF TOPICAL BIMATOPROST WITH TIMOLOL MALEATE IN GLAUCOMA PATIENTS

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ABSTRACT

BACKGROUND

Glaucoma is a group of disorders characterized by increase in Intraocular Pressure (IOP), which can damage the optic nerve and if untreated can lead to gradual peripheral vision loss and irreversible blindness. Glaucoma classified into primary and secondary glaucoma. Primary glaucoma has two types Primary Open Angle Glaucoma (POAG) and Primary Angle Closure Glaucoma (PACG). Glaucoma is the second leading cause of blindness. Worldwide, it is estimated that about 66.8 million people have visual impairment from glaucoma with 6.8 million suffering from blindness.

AIMS AND OBJECTIVE

- To assess the level of IOP reduction of bimatoprost with timolol maleate and its statistical analysis.
- To compare the IOP lowering efficacy of bimatoprost with timolol maleate.
- To study the adverse drug reaction profiles of both the drugs.

MATERIALS AND METHODS

This study was designed to compare the efficacy and safety of topical anti-glaucoma drugs, Bimatoprost (0.03%) and Timolol maleate (0.5%) in patients with POAG attending at Regional Eye Hospital, Warangal.

RESULTS

In this study mean reduction of IOP at 2 wks., 6 wks., 12 wks., 24 wks. were 6.60 mmHg (23.21%), 9.6 mmHg (33.76%), 10.00 mmHg (38.68%), 11.20 mmHg (39.39%) for Bimatoprost and 4.20 mmHg (15.07%), 6.24% mmHg (23.39%), 7.36 mmHg (25.91%) and 7.64 mmHg (26.56%) for Timolol group respectively.

STATISTICAL METHOD

Student's 't' test was used for analysis of results.

CONCLUSION

Bimatoprost 0.03% ophthalmic solution was highly efficacious, well tolerated, systemically safe and minimal ocular side effects and less drug withdraw. It can be used as first line therapy to treat cases of POAG to reduce IOP. The only limitation for its use is regarding its cost. The topical bimatoprost preparations are expensive when compared to the topical Timolol maleate. But considering the reduction in IOP, the modifiable factor for preventing the progression of optic nerve head damage and preservation of visual function hence increase the quality of vision and life.

KEYWORDS

IOP, PACG, POAG, Bimatoprost, Timolol Maleate.

HOW TO CITE THIS ARTICLE: Polagani P, Maddikunta SV, Balakrishna N, et al. A comparative study on the safety and efficacy of topical bimatoprost with timolol maleate in glaucoma patients. J. Evolution Med. Dent. Sci. 2016;5(46):2874-2879, DOI: 10.14260/jemds/2016/670

INTRODUCTION

Glaucoma is a group of disorders characterized by increase in intraocular pressure (IOP), which can damage the optic nerve and can cause progressive degeneration of the retinal ganglion cells leading to deterioration of the visual fields. Glaucoma is classified into: 1) Primary glaucoma – which consists of two separate conditions, Open angle and angle closure glaucoma, 2) Secondary glaucoma – due to a specific anomaly or disease of the eye. In medical management, the topical anti-glaucoma drugs are the mainstay of the therapy for Primary Open Angle Glaucoma (POAG); this study was conducted in patients with POAG. It is the most common type of glaucoma, slowly progressive, painless and usually bilateral. Typically, the peripheral vision is affected first, so that the patient may be asymptomatic until late in the disease or non-specific symptoms like headache and frequent changes of presbyopic correction, reduced visual acuity.[1,2]

The most common risk factor known is raised Intraocular Pressure (IOP) and also it is the only modifiable one.[2,3] Other risk factors include race, increased age, decreased central corneal thickness with family history and low diastolic perfusion pressure. Diagnosis is made by Tonometry,

Financial or Other, Competing Interest: None.
Submission 07-04-2016, Peer Review 18-05-2016,
Acceptance 25-05-2016, Published 08-06-2016.
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DOI: 10.14260/jemds/2016/670

Gonioscopy, Ophthalmoscopy, Perimetry or Visual field tests are useful in disease progression and severity.

The prevention or control of raised Intraocular Pressure (IOP) is the primary goal in the management of glaucoma. Several studies concluded that low IOP is associated with reduced progression of visual field deterioration and Ocular Nerve Head (ONH) damage.[4,5]

Normal Tension Glaucoma Study (NTGS) established that aggressive IOP reduction (30%) reduced VF worsening from 30% to 10% over 5 yrs.[5] In the Advanced Glaucoma Intervention Study (AGIS), there was a clear IOP 'dose response' relationship with visual field progression, which showed a striking lack of visual field progression in patients who had a mean IOP of 12.3 mmHg. The OHTS (Ocular Hypertension Treatment Study) concluded that IOP reduction reduced the risk of optic nerve head damage by 10% to 5% over 5 yrs.

The topical anti-glaucoma medications, despite their overall safety, they have the potential to cause significant systemic side effects and to have serious interactions with oral medications. Pharmacokinetics makes ocular drug delivery more akin to intravenous than to oral administration. Topically administered medications gain access to the highly vascular nasal mucosa and are variably absorbed, avoiding first-pass hepatic metabolism. One drop of timolol 0.5% solution in each eye approximates a 10 mg oral dose for treating systemic hypertension or angina. All topical agents are considered equipotent when given systemically. The factors affecting the systemic absorption of the topical anti-glaucoma drugs are: the drop size, concentration of the drug and the amount of the absorption into the naso-lacrimal system.

Timolol maleate is a β1 and β2 (Non-selective) adrenoceptor antagonist. It does not have significant intrinsic sympathomimetic, direct myocardial depressing or local anaesthetic activity. It lowers IOP in both normotensive and in chronic open angle glaucoma patients.[6,7,8] It reduces IOP by 20-33%, on an average. Early trials demonstrated that it is more effective in lowering IOP as compared to epinephrine and pilocarpine. Timolol is the US-FDA's gold standard drug for glaucoma therapy, against which all new medications must be compared prior to approval.[8]

Bimatoprost, is a synthetic prostamide analog that was approved for use in US in 2001.[8,9] It lowers IOP by a dual mechanism: primarily by increasing pressure dependent (presumed trabecular meshwork) outflow, but also by increasing pressure-independent (Presumed uveoscleral) outflow. IOP lowering efficacy found to be 30.4-35.2%. The present study is to compare the efficacy and adverse effects of topical bimatoprost with timolol. Bimatoprost is more efficacious to timolol to control IOP, but timolol is more economical than bimatoprost. Long term control of IOP with bimatoprost is more effective than timolol and increases quality of vision.

The topical anti-glaucoma drugs are the main mode of therapy for POAG and as most of the patients may continue the therapy for the whole life with topical anti-glaucoma drugs like beta blockers, PG analogues, etc. They are more prone for both systemic and local adverse events of topical anti-glaucoma drugs. So there is a need for proper selection of a topical anti-glaucoma agents in patients with POAG.

Mechanism of Action	Drug Class	Preparations
Reduction of Aqueous Inflow	Adrenergic agonists	Brimonidine
		Apraclonidine
	β-blockers	Non-selective
		Timolol
		Levobunolol
		Carteolol
		Selective β – blockers
		Betaxolol
	Carbonic anhydrase inhibitors	Systemic
		Acetazolamide
		Methazolamide
		Dichlorphenamide
		Topical
		Dorzolamide
		Brinzolamide
Increase in Aqueous Outflow	Cholinergics Increase trabecular outflow	Pilocarpine
		Carbachol
	Prostaglandins and other lipid receptor agonists Increase uveoscleral outflow	Latanoprost (xalatan)
		Travoprost (travatan)
		Bimatoprost (lumigan)
		Unoprostone

Table 1: Mechanism of Action of Different Anti-Glaucoma Drugs.[2,4,6]

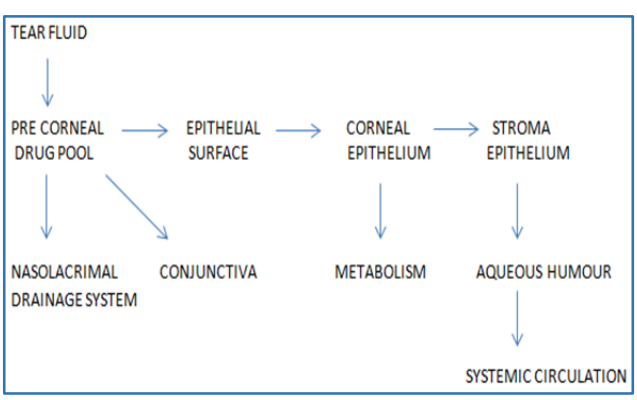


Fig. 1: Schematic Diagram of Ocular Pharmacokinetics for Topically Applied Drugs.[2]

MATERIALS AND METHODS

Objective

To compare the IOP lowering efficacy and to study the adverse drug reactions of Bimatoprost and Timolol maleate in POAG.

Study Design

The present study is a randomised, prospective, open labelled, balanced study in patients with POAG.

The study period is of 18 months' duration. The patients were selected from Outpatient Department of Regional Eye Hospital, Warangal.

Patient Selection

Patients were selected on the examination criteria of IOP recording with applanation tonometer, visual field recording

with Humphrey's analyser and angle estimation with four mirror goniolens from these patients diagnosed cases of POAG were taken into study.

Number of patients - a total 50 patients with POAG, divided into two groups, 25 in bimatoprost and 25 in timolol groups respectively. Patient selection done by simple randomisation.

Inclusion Criteria

1. Patient's age above 30 yrs.
2. Mean IOP >21 mmHg.
3. Patients with personal medical history, ophthalmic examination.
4. Patients with wide open angles on gonioscopy.
5. Patients with primary case of POAG.
6. In patients with bilateral raised IOP, the eye with higher IOP was selected.
7. Patients willing to follow-up for a period of 6 months. Scheduled follow-up visits at – 2 wks., 6 wks., 12 wks., 24 wks.
8. Patients willing to give written informed consent.

Exclusion Criteria

1. Age less than 30 years old.
2. H/O chronic or recurrent severe ocular inflammatory disease or ocular infection or inflammation.
3. H/O intraocular surgery within 6 months.
4. Gonioscopically closed angle.
5. Presence of any systemic disease or using any medication that can affect IOP.
6. Any abnormality preventing reliable tonometry of either eye.
7. Corneal abnormalities, dry eyes.
8. History of trauma.
9. History of severe or serious hypersensitivity to topical or systemic beta blockers or prostaglandins.
10. History of severe, unstable or uncontrolled cardiovascular, hepatic or renal disease, bronchial asthma or chronic obstructive pulmonary disease.
11. Pregnant and lactating women.

After the selection of patients, an informed consent was taken. And they have been prescribed topical preparations of either bimatoprost 0.03% (Administered once daily in the evening) or timolol maleate 0.5% (twice daily). After taking relevant history, systemic examination and screening of glaucoma includes visual acuity, refraction, ophthalmoscopy examination, applanation tonometry, gonioscopy, visual field analysis will be carried. Baseline IOP recording was first done at the time of selection at 9 am ± 1 hr, 1 pm ± 1 hr, 5 pm ± 1 hr. Mean of all these values has been taken as baseline. Then the patients were instructed about the medicine and advised to report if any adverse effect occurs. Methods of instillation and the methods of occluding the lacrimal duct by "double dot procedure" for reducing systemic absorption of the drug was explained. The patient asked to visit for follow-up at 2 wks., 6 wks., 12 wks., 24 wks.

At all visits, patients were asked about any complaints and systemic examination was done at every visit. Local examination of the eyes was done for lids, eye lashes, conjunctiva, cornea, iris and lens for identification of any adverse drug events, IOP recorded by Applanation tonometer at 10 am ± 1 hrs. gonioscopy examination and optic disc evaluation, perimetry is carried out and observations are recorded. Pulse rate and blood pressure were measured and recorded.

Characteristics of Glaucomatous Visual Field Defects

Asymmetrical across horizontal midline, located in the mid periphery, reproducible, not attributable to other pathology, clustered in neighbouring test points; defects should correlate with the appearance of the optic disc.

RESULTS

This study was conducted for a period of 18 months. The observation and analysis of the data is as follows.

Patient Demographic Data

There is no significant difference in demographic variables between the two groups.

	Bimatoprost	Timolol Maleate
No. of Patients	25	25
Mean Age	55.62 yrs.	54.92 yrs.
Males	13 (52%)	14 (56%)
Females	12 (48%)	11(44%)
Right Eye	11	12
Left Eye	14	13

Table 2: The Demographic Data of the Patients of POAG Selected for the Study

IOP Lowering Efficacy

Bimatoprost once daily showed significantly lower mean IOP at all follow-up visits.

- In the present study, mean reduction of IOP at 2 wks. (Initial fall) was 6.60 mmHg (23.21%) for Bimatoprost and 4.20 mmHg (15.07%) for Timolol group.
- Mean reduction of IOP at 6 wks. from baseline is 9.6 mmHg (33.76%) for Bimatoprost group and 6.24% mmHg (23.39%) for Timolol group.
- At 12 wks. is 10.00 mmHg (38.68%) for Bimatoprost group, 7.36 mmHg (25.91%) for Timolol group.
- Mean reduction of IOP from baseline at 24 wks. was 11.20 mmHg (39.39%) and Timolol was 7.64 mmHg (26.56%).

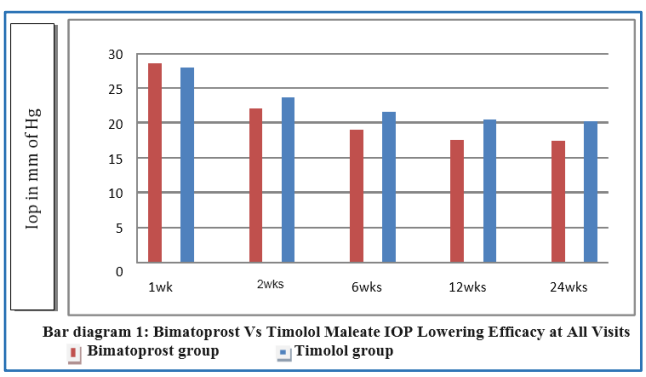
The reduction of Intraocular Pressure (IOP) from baseline to 24 wks. in Bimatoprost and Timolol treated patients is shown by graphical presentation in Graph I and Graph II and mean IOP reduction in both the groups from baseline to 24 wks. From 28.44 mmHg 17.24 mmHg in Bimatoprost group and from 27.88 mmHg to 20.24 mmHg in Timolol group is depicted in graph III. IOP reduction was approximately 3.56 mmHg higher than Timolol maleate for bimatoprost.

The percentage of patients reaching target pressure with Bimatoprost is 44%, whereas with Timolol it is only 4% shown in Table No. 5.

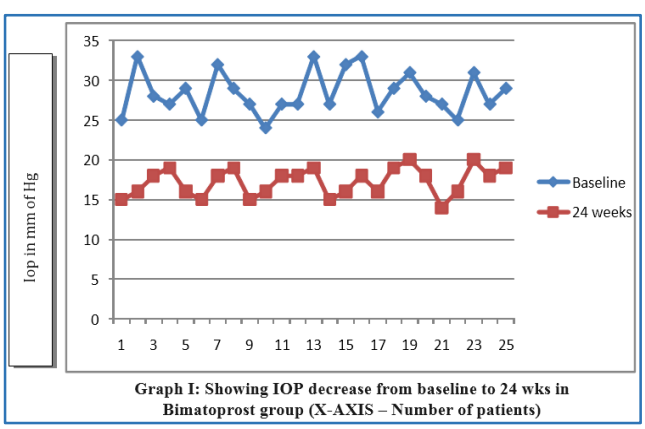
After conducting the study for 18 months on topical Bimatoprost (0.03%) once daily and Timolol (0.5%) twice daily in patients of POAG, the results are tabulated and statistical analysis done by 'T' test, as shown in the following data.

	Bimatoprost Group (mmHg)	Timolol Maleate Group (mmHg)	P-Value
Mean IOP at baseline	28.44±2.7	27.88±3.17	>0.68
Mean IOP at 2 wks.	21.84±2.96	23.68±2.8	<0.001
Mean IOP at 6 wks.	18.84±1.92	21.64±1.94	<0.001
Mean IOP at 12 wks.	17.44±1.55	20.52±2.29	<0.001
Mean IOP at 24 wks.	17.24±1.76	20.24±2.27	<0.001
Mean IOP difference at baseline & 24 wks.	11.20	7.64	<0.001

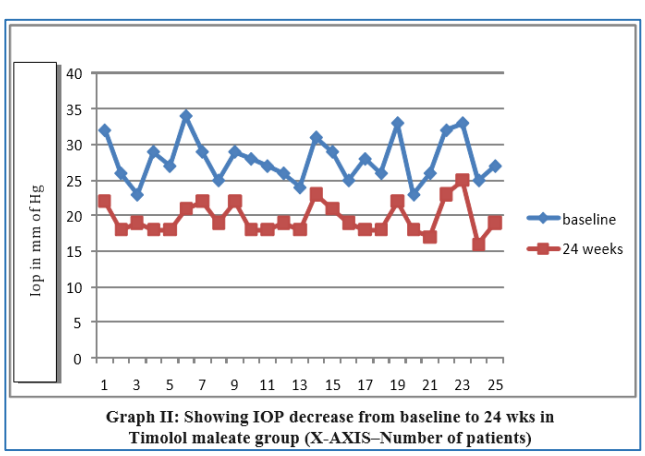
Table 3: Shows the Mean IOP that was Recorded at Baseline, 2 wks., 6 wks., 12 wks. and 24 wks. in Both Groups



Bar diagram 1: Bimatoprost Vs Timolol Maleate IOP Lowering Efficacy at All Visits



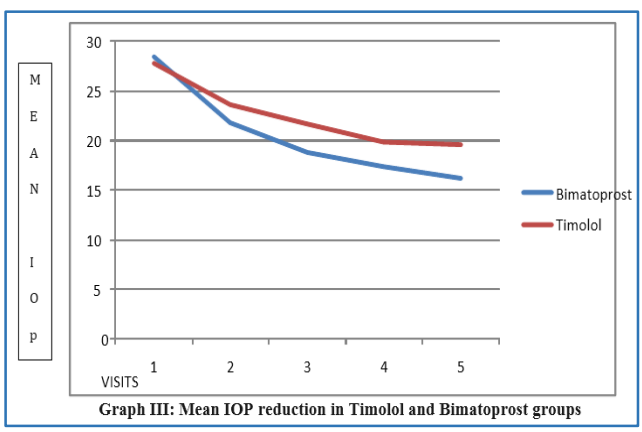
Graph I: Showing IOP decrease from baseline to 24 wks in Bimatoprost group (X-AXIS – Number of patients)



Graph II: Showing IOP decrease from baseline to 24 wks in Timolol maleate group (X-AXIS–Number of patients)

	Bimatoprost	Timolol
Mean IOP at baseline	28.44±2.7	27.88±3.17
After 2 wks. mean decrease in IOP	6.60 mmHg	4.20 mmHg
After 6 wks. mean IOP decrease	9.60 mmHg	6.24 mmHg
After 12 wks. mean IOP decrease	10.00 mmHg	7.36 mmHg
After 24 wks. mean IOP decrease	11.20 mmHg	7.64 mmHg

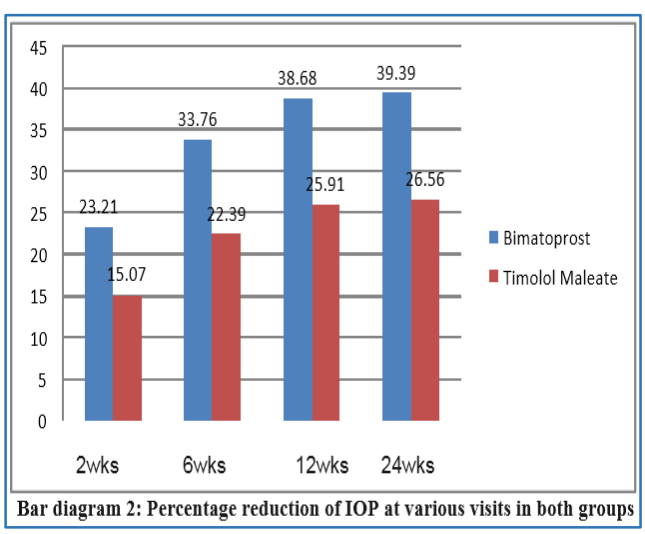
Table 4: Shows the Mean IOP Decrease at all Visits



Graph III: Mean IOP reduction in Timolol and Bimatoprost groups

	Bimatoprost	Timolol Maleate
At 2 wks. (Initial fall)	23.21%	15.07%
6 wks.	33.76%	23.39%
12 wks.	38.68%	25.91%
24 wks.	39.39%	26.56%

Table 5: Percentage Reduction of IOP at Various Visits



Bar diagram 2: Percentage reduction of IOP at various visits in both groups

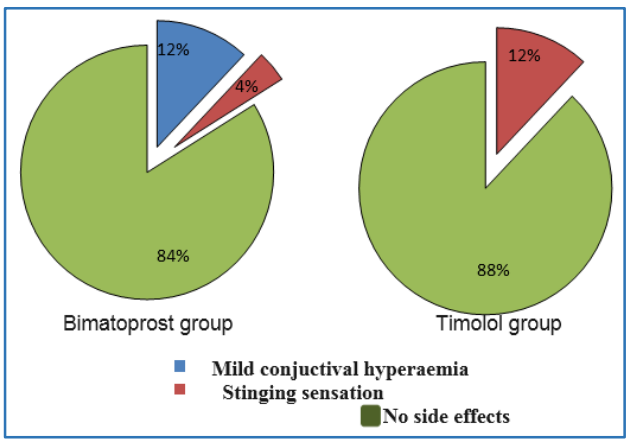
	Bimatoprost	Timolol Maleate
No. of patients	25	25
No. of patients with IOP		
< 17 mmHg	11 (44 %)	1 (4%)
17-20 mmHg	12 (48%)	15 (60%)
=/>20 mmHg	2 (8%)	9 (36%)

Table 6: Percentage of Patients Reaching Target Pressure

Safety and Tolerability

Most Common Adverse Effects Seen	Bimatoprost	Timolol Maleate
Conjunctival hyperaemia	3 (12%)	Nil
Stinging sensation	1 (4%)	3 (12%)
No. side effects	21(88%)	22(88%)

Table 7: Ocular Side Effects



Pie Diagram 1

Pie Diagram 1: Safety and Tolerability

Regarding adverse effects, no significant systemic side effects is noted. Depicted in Table 7. Ocular side effects observed are mild conjunctival hyperaemia in 12% of cases with Bimatoprost and nil with Timolol. Stinging sensation observed in 4% of cases with Bimatoprost and 12% with Timolol, which are depicted in pie diagram. No other local side effects observed.

Statistical Analysis

Student's t-test - Compare the differences between IOP between Bimatoprost and Timolol at week 24.

t=3.65.

SD=2.68.

DF=48.

P value <0.001 (Statistically significant).

Reduction in IOP by Bimatoprost 0.03% OD is statistically significant compared to Timolol 0.5% twice daily.

DISCUSSION

Glaucoma, is the second leading cause of blindness; worldwide about 66.8 million people were suffering from visual impairment from glaucoma and 6.8 million suffering from blindness.[1] The effective treatment for prevention of disease progression by lowering of Intraocular Pressure (IOP).[5,10]

Pharmacotherapy is the mainstay of treatment for glaucoma. Various topical anti-glaucoma drugs are being used now a days for control of IOP. Each of the drug has its own benefits and drawbacks. So the most effective drug with least toxic effects used are prostaglandin analogues and beta blockers.[6,7] So this study has taken to observe the efficacy, safety and adverse drug reactions with these two groups of drugs.

In this study, the IOP lowering efficacy of Bimatoprost was found to be superior to Timolol maleate. The mean IOP decrease with Bimatoprost was 11.20 mmHg and Timolol was 7.64 mmHg. The decrease in IOP was consistently approximately 3.56 mmHg greater than Timolol maleate and is statistically significant (Table 5).

Bimatoprost the latest prostamide analog and Timolol, which is very commonly used topical anti-glaucoma drug are taken in our study for comparison of their clinical efficacy and safety.

Previous Studies on Efficacy of Bimatoprost are as follows:

1. A 6-month comparative study by Sheerwood et al showed mean IOP reduction of 8.1 mmHg (33%) for Bimatoprost OD and 5.6 mmHg (22.8%) for Timolol group.[11]
2. One year randomised comparative study by Higgibotham et al 2002, showed mean reduction of 7.9 mmHg (30.6%) with bimatoprost OD and 5.3% (21%) with Timolol maleate BID.[12]
3. A 3-month comparative clinical trial by Whitcup et al 2003, showed 8.0 mmHg (32.4%) with bimatoprost OD and 5.5 mmHg (22.7%) with Timolol.[13]
4. A two-year comparative study by Cohen et al 2004 showed mean reduction of 7.8 mmHg with Bimatoprost and 4.6 mmHg with Timolol.[14]
5. Other comparative studies, Sheerwood et al, Higginbotham et al, Whitcup et al, Cohen et al concluded that significantly higher percentage of patients achieved low levels of IOP with Bimatoprost than with Timolol maleate.

In our study of 18 months also significant decrease in IOP with Bimatoprost, which is consistent with above studies.

The pharmacokinetics of Bimatoprost also contributes to the quick onset of action obtaining maximum reduction of IOP of 23.21% within 2 weeks. And this may be due to minimal enzymatic hydrolysis of Bimatoprost in the ocular tissues acting directly as an intact molecule.[9,15,16]

The most commonly reported side effects of Bimatoprost is conjunctival hyperaemia (i.e. ocular surface redness), which is observed in 12% cases.[16,17] which is only a cosmetic phenomenon.

Rate of conjunctival hyperaemia observed in topical Bimatoprost group was 23% (Cohen et al), 25.1% (Higginbotham et al), 30% (Whitcup et al). Lumigan Indian experience (L.E.E.D study group) showed very few adverse effects (2.7% conjunctival hyperaemia).[13,18,19]

This study is a prospective randomised study done in patients with POAG comparing IOP lowering efficacy, safety and adverse drug reaction of two topical anti-glaucoma drugs, Bimatoprost 0.03% once daily, a member of new class of agents called prostamide that acts by increasing both uveoscleral outflow and trabecular outflow.[20] Timolol Maleate, one of the oldest and commonest anti-glaucoma drug, is a non-selective beta blocker that acts by decreasing aqueous production.

Bimatoprost OD enabled a greater percentage of patients to achieve lower target pressures; 44% patients achieved IOP <17 mmHg. Once daily dosing also increases patient's compliance by bimatoprost was safe and well tolerated with negligible side effects.

CONCLUSION

In this study bimatoprost 0.03% ophthalmic solution was highly efficacious, well tolerated and systemically safe and

ocular side effects are also minimal and not severe enough to withdraw the drug and can be used as first line therapy to treat cases of POAG to reduce IOP.[16] The only limitation for its use is regarding its cost. The topical bimatoprost preparations are more expensive when compared to the topical Timolol maleate. But when considering the IOP reduction rate, which is the only modifiable factor for preventing the progression of Ocular Nerve Head (ONH).[5] damage and preservation of visual function also increase the quality of vision and life. Bimatoprost is the most recommended first line drug of choice for the cases of POAG, because each 1 mmHg IOP reduction decreases the risk of glaucoma progression by 10% and bimatoprost is more effective than other medications in reducing IOP.[6,10,16]

Wider use of this drug will establish the place of Bimatoprost in treatment of primary open angle glaucoma and ocular hypertension.

ACKNOWLEDGEMENT

I am much honoured to thank my Institution, Regional Eye Hospital and Kakatiya Medical College, Warangal, for granting this work. I want to thank Dr. B. Anandam M.D., Dr. V. L. M. Raman M.D., Dept. of Pharmacology; Dr. P. Vijaya Kumar M.S., D.O., Professor and Head of the Department of Ophthalmology; Dr. Ravindar M.S., D.O. and participants for their willingness to participate in this study.

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