RANDOMIZED DOUBLE BLIND CROSS OVER STUDY OF EFFICACY OF LATANOPROST 0.005% ONCE DAILY VERSUS TIMOLOL MALEATE GEL FORMING SOLUTION 0.5% ONCE DAILY IN EMMETROPIC VOLUNTEERS WITHOUT ANY KNOWN OCULAR DISEASE

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ABSTRACT

Purpose: To compare the effect on intra-ocular pressure of Latanoprost vs. Timolol Maleate Gel Forming Solution in emmetropic volunteers without any known ocular disease.

Methods: Thirty emmetropic volunteers without any known ocular disease were randomized in a double blinded cross-over study for Latanoprost once daily and Timolol Maleate Gel Forming Solution once daily. Intra-ocular pressure and ocular side effects were recorded at baseline, 30 minutes, 2 hours, 12 hours, and 24 hours of instillation.

Results: Action of Timolol Maleate gel forming solution 0.5% started within 30 minutes with mean reduction in IOP (Mean ± 2SD =0.0667±0.5074), and at 2 hours (0.8667±1.1426). Its effect sustains for 12 hours (1.0667±1.5698) and then wears off at 24 hours (0.1333±1.3628). The mean reductions of intra-ocular pressure by Latanoprost 0.005% (OD) at 30 minutes, 2 hours, 12 hours, and 24 hours were (0.0333±0.3652), (0.6000±1.4480), (1.6333±1.5298), and (0.6667±1.6046) respectively. These differences were statistically significant over 24 hours ($p<0.05$).

Conclusion: Both Latanoprost 0.005% (OD) and Timolol Maleate Gel Forming Solution 0.5% (OD) cause reduction of intra-ocular pressure in emmetropic volunteers without any known ocular disease. Latanoprost shows more sustained reduction in intra-ocular pressure over 24 hours.

Key words: Latanoprost (LT) - Timolol Maleate Gel Forming Solution (Timolol GFS) - Intra-ocular pressure (IOP).

Glaucoma is a progressive optic neuropathy with characteristic optic nerve head changes and decrease in retinal sensitivity that lead to visual loss1. Once the disease is diagnosed, treatment is required to stop progressive damage and generally medical treatment is the first therapeutic approach. β Adrenergic antagonists like Timolol have been considered for many years as the drugs of choice in most cases, while other agents like adrenergic agonists and parasympatheticomimetic agents were used as second line drugs. However, new drugs have been introduced for glaucoma treatment, like selective α agonists, carbonic anhydrase inhibitors and prostaglandins broadening the therapeutic choices. Latanoprost (13, 14-dihyro- 17-phenyl- 18, 19, 20-trinor-prostaglandin F2α-isopropil-ester) is a prostaglandin analogue that produces an ocular hypotensive effect. It has been established that the major mechanism of action is an increase uveo-scleral outflow with little or no effect on aqueous humor flow. The action of Latanoprost starts within 3-4 hours and the peak is achieved at 8-12 hours. Timolol is a non-selective β1 and β2 blocker. It's onset of action is within 30 minutes, with a peak at 2 hours and a duration of up to 24 hours. Administration is twice daily. Timolol Maleate gel forming solution 0.5% is a gel forming solution with established results of showing efficacy of lowering intraocular pressure on once daily dosage equivalent to twice-daily instillation of Timolol Maleate 0.5%.

The purpose of this study is to compare the intraocular pressure (IOP) reducing effect of Latanoprost (OD) vs. Timolol GFS (OD) in emmetropic volunteers without any known ocular disease.

Methods

Study Design

A unicentric randomized, double blind, cross over comparative study design was employed. The study was started on May 1, 2001and completed on June 25, 2001.

Patients

Number of patients

A total of 30 patients were enrolled into the study from the Department of Ophthalmology, B.Y.L. Nair Ch. Hospital, Mumbai according to the following inclusion and exclusion criteria.

Inclusion criteria

Patients between 18 to 60 years of age with emmetropic vision visiting Department of Ophthalmology, B.Y.L. Nair Ch. Hospital, Mumbai, giving written, informed consent and agreeing to comply with protocol requirements.

Exclusion criteria

Age less than 18 years or more than 60 years.
Pregnant women / Breast-feeding mothers.
History of hypersensitivity to Latanoprost, Timolol Maleate GFS, preservatives used, and local anesthetic agent Xylocaine 4% eye drop.
Patients with any known ocular disease.
History of Respiratory illnesses (e.g. Asthma).
History of Cardio-vascular disease.
History of Hypertension.
History of Metabolic disorder.
History of Trauma.
Previous treatment with anti-glaucoma drugs.

Previous treatment with steroids (topical or systemic) in past six months.
Present use of any ocular therapy.
Presence of any major illness (e.g. Tuberculosis, Diabetes mellitus).
Participation in a new drug study in the past six months.
Study Procedures (as shown in Table 1)
Visit 1 (Day 1)
Patients consenting to participate in the study had their medical history and ophthalmic examination and baseline clinical assessments recorded. Patients' pre-procedure intra-ocular pressure was recorded with Applanation tonometer after instillation of one drop of 4% Xylocaine in the trial eye. Patients were randomized according to the randomization code and the drug was instilled accordingly in the trial eye of the subject. After a period of 30 minutes, intra-ocular pressure was measured again with the same instrument. After 2 and 12 hours of the instillation of the study medication intra-ocular pressure was measured.
Visit 2 (Day 2)
Patients were asked to return for same randomization as a follow up after 24 hours for intra-ocular pressure measurement. Patients were asked to return for second randomization on day 8th and reminded to provide attention, and visit Department of Ophthalmology, B.Y.L. Nair Ch. Hospital, Mumbai if any untoward or embarrassing effects were noticed.
Patients were requested to report Department of Ophthalmology, B.Y.L. Nair Ch. Hospital, Mumbai as soon as they suffer from any illness, or start any concomitant medication.
Visit 3(Day 8)
Any adverse experiences were elicited by asking the question "How have you been feeling since the last visit?" Medical history, ophthalmic examination and baseline clinical assessment were made. Intra-ocular pressure in the trial eye was recorded. After instilling the study medication in the trial eye, according to randomization code, intra-ocular pressure were measured after 30 minutes, 2 hours, and 12 hours.

Schedule of Examination (measurement of IOP,mm Hg)

Visit 1	Visit 2	Visit 3	Visit 4
Randomization I		Randomization II	
Baseline (0 hr)	24 hrs	Baseline (0 hr)	24 hrs
½ hr		½ hr	
2 hrs		2 hrs	
12 hrs		12 hrs	

Visit 4 (Day 9)
Patients were asked to return for second randomization as a follow up after 24 hours for intra-ocular pressure measurement, and asked for any untoward or embarrassing effects. Patients are reminded to watch any adverse effects of the study medication and report immediately to the doctor.
Randomization
Patients were entered into the study and assigned a unique patient number which identifies the individual patient. Both medication packs carried a patient number as an identification number, which was assigned according to the randomization list prepared by coordinator using Microsoft Excel version 97.
The patient received the treatment as per the patient number assigned to him. No patient was entered more than once in the study. Each patient was randomized after insuring that all patient recruitment criteria were met.
Study Therapy
Latanoprost (13, 14-dihyro- 17-phenyl- 18, 19, 20-trinor-prostaglandin F2α-isopropil-ester) 0.005% OD and
Timolol Maleate GFS (gel forming solution) 0.5% OD
Study Time Table
First patient to be entered : 1/ 5 / 2001
Last patient to be completed: 25/ 6 / 2001

Results
A total of thirty patients were included into randomized double blinded cross over study.
Action of Timolol Maleate gel forming solution 0.5% started within 30 minutes with mean IOP reduction of (Mean $\pm$ 2SD =0.0667$\pm$0.5074), and at 2 hours (0.8667$\pm$1.1426). Its effect sustains for 12 hours (1.0667$\pm$1.5698) and then wears off at 24 hours (0.1333$\pm$1.3628). The mean reductions of intra-ocular pressure by Latanoprost 0.005% (OD) at 30 minutes, 2 hours, 12 hours, and 24 hours were (0.0333$\pm$0.3652), (0.6000$\pm$1.4480), (1.6333$\pm$1.5298), and (0.6667$\pm$1.6046) respectively.
Comparing the efficacy of Latanoprost 0.005% (OD) and Timolol Maleate gel forming solution 0.5% (OD) at 30 minutes, there is no significant difference in reduction of intra-ocular pressure ($p=0.5725$). At 120 minutes, there is a significant difference in reduction of IOP in Latanoprost group ($p=0.1033$).
There is a very significant reduction of intra-ocular pressure at 12 hours with Latanoprost group, as compared to that of Timolol Maleate gel forming solution ($p=0.0045$). Also at 24 hours, Latanoprost very significantly maintains the reduction of

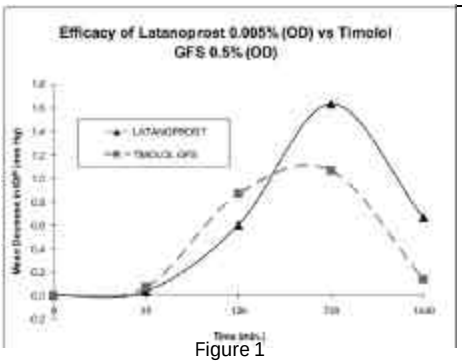

Figure 1

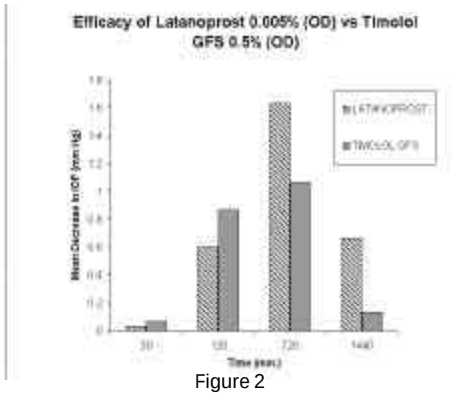

Figure 2

pressure (p=0.0071), as shown in Figure 1 and 2. The percentage reduction in intra-ocular pressures

Table 2: Measurement of intra-ocular pressure reduction from baseline (in mmHg, percentage)

	Latanoprost 0.005% (n=30)	Timolol Maleate gel forming solution 0.5% (n=30)
30 min	0.0333 (0.20%)	0.0667 (0.42%)
120 min	0.6000 (3.67%)	0.8667 (5.43%)
720 min	1.6333 (10.00%)	1.0667 (6.68%)
1440 min	0.6667 (4.08%)	0.1333 (0.84%)

from baseline at specified intervals in both study arms are shown in Table 2.

No adverse events were reported in the study. The ocular side effects of Latanoprost and Timolol Maleate gel forming solution are found as shown in Table 3.

This study showed that both drugs achieve sustained reduction in intra-ocular pressure over 24 hours. The effect of Latanoprost is more than Timolol Maleate gel forming solution at 24 hours (p=0.0071).

Table 3: Ocular Side effects

Ocular Side effects	Latanoprost 0.005% (n=30)	Timolol Maleate gel forming solution 0.5% (n=30)
Foreign body sensation	2 (6.67%)	0 (0%)
Itching	1 (3.33%)	0 (0%)
Burning	0 (0%	0 (0%)
Tearing	3 (10%)	1 (3.33%)
Conjunctival Hyperemia	3 (10%)	2 (6.67%
Pain	0 (0%)	0 (0%)
Photophobia	0 (0%)	1 (3.33%)
Iris pigmentation	0 (0%)	0 (0%)

Discussion

Latanoprost is a prostaglandin lipophilic ester analogue that remains inactive until enzymatic hydrolysis at corneal tissue, which activates the drug. Latanoprost incorporates substantial changes in its molecular structure that improve the selectivity and action of the drug at the prostanoid FP receptors and increases the therapeutic index of the drug for glaucoma treatment.

Since this drug was introduced, there had been several reports about the hypotensive effect of the drug compared to other anti-glaucomatous agents. In our study, the hypotensive effect of Latanoprost 0.005% (OD) has been compared to that of Timolol Maleate gel forming solution 0.5% (OD) in emetropic volunteers without any known ocular disease. The prostaglandin analogue achieved a higher reduction in average IOP at 12 hours (1.6333 vs. 1.0667, p<0.005) and the IOP reduction with respect to baseline being 10.00% and 6.68% respectively. Latanoprost showed to be more effective in achieving sustained reduction in intra-ocular pressure (IOP) over 24 hours than Timolol Maleate gel forming solution (p<0.005). This may be due to intrinsic mechanism of action of the substance. At the ciliary body, prostaglandins induce the secretion of enzymes called metalloproteases that reduce the resistance to uveo-scleral outflow. Possibly, the synthesis of enzymes increases over a period of time inducing a progressive IOP reduction. On the contrary, Timolol GFS obtains less reduction in IOP in emmetropic volunteers without any known ocular disease. The study shows that both drugs achieve IOP reductions without loosing effect over 24 hours.

In our study, the most frequent ocular side effects were conjunctival hyperemia, foreign body sensa-

tion, and tearing; especially in the Latanoprost treated group. Only one patient experienced photophobia in Timolol GFS arm of the study.

In conclusion the results of our study show that both drugs achieve sustained reduction in intra-ocular pressure over 24 hours. The effect of Latanoprost is more than Timolol Maleate gel forming solution over 24 hours ($p<0.005$).

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Jean-Martin Charcot, 1889

Let someone say of a doctor that he really knows his physiology or anatomy, that he is dynamic--these are real compliments; but if you say he is an observer, a man who knows how to see, this is perhaps the greatest compliment one can make.

William Osler, 1919

Learn to see, learn to hear, learn to feel, learn to smell, and know that by practice alone can you become expert. Medicine is learned by the bedside and not in the classroom. Let not your conceptions of the manifestations of disease come from words heard in the lecture room or read from the book. See, and then reason and compare and control. But see first.