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### **Research Article**

# Study on the safety profile of Latanoprost and Timolol in primary open angle glaucoma

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#### **ABSTRACT**

**Background:** Topical beta blockers, Timolol and the prostaglandin  $F2\alpha$  analogue Latanoprost are the most common prescribed medications as first line therapy. Their safety profiles have to be compared to justify the same. The objectives of this study were to compare the safety profile of Latanoprost with that of Timolol in the treatment of primary open angle glaucoma.

**Methods:** In this randomized open label 12-week study, 60 patients were randomized to receive either 0.005% of Latanoprost once daily in the evening or 0.5% of Timolol twice daily. Their safety was concluded by monitoring their adverse effects during follow-up visits at 2, 4, 6, and 12 weeks.

**Results:** Bradycardia was seen only in Timolol group whereas ocular adverse effects such as periocular pigmentation, the growth of eyelashes, and conjunctival hyperemia were seen only in Latanoprost group. Ocular discomfort was present equally in both the groups. Foreign body sensation was seen in both the groups, but it was more frequent in Latanoprost group. The blurring of vision was predominantly seen in Timolol group. Corneal anesthesia was seen in one of the patients on Timolol.

**Conclusions:** The incidence of adverse effects was not significantly different between Latanoprost and Timolol therapy. Both had favorable safety profiles. However, Latanoprost has safer systemic side effects profile when compared to Timolol.

Keywords: Beta blocker, Intraocular pressure, Prostaglandin analogue

#### INTRODUCTION

Glaucoma is defined as a disturbance of the structural or functional integrity of the optic nerve that can usually be arrested or diminished by adequate lowering of intraocular pressure (IOP). Glaucoma can be classified into open angle glaucoma, angle closure glaucoma, and juvenile glaucoma. Among these, Primary open angle glaucoma (POAG) is the most common type, constituting approximately 90-95% of all reported cases of glaucoma. Raised IOP is a significant risk factor for glaucoma. Beta adrenergic blockers are the most widely used ocular hypotensive agents. Among them Timolol is most commonly used as the first line therapy. They effectively lower IOP and have acceptable local tolerability. Prostaglandin analogues constitute a novel class of ocular hypotensive agents. Latanoprost, a prostaglandin analogue has come up with powerful ocular hypotensive effects. The

objective of present study was to compare the safety profile of Latanoprost with Timolol in patients with POAG.

#### **METHODS**

This study was a randomized, open label comparative parallel clinical trial conducted in Government Medical College Calicut. Patients aged 40 years or older with a diagnosis of POAG, baseline IOP (after washout) being more than 21 mmHg in each eye were enrolled in the study. The enrolled patients were randomly divided into two groups by computer generated table of 15 blocks. The sample size was determined to be 30 in each group, the study being conducted over a period of 1 year.

Written informed consent was obtained from the patient before starting the study. The patients fulfilling the inclusion criteria were undergone a washout of other IOP lowering medications before the baseline visit. The patients were randomly assigned to one of the two treatment groups, i.e., 0.005% Latanoprost ophthalmic solution once daily in the evening or 0.5% timolol maleate twice daily. The patients were given their medications after all evaluations at the baseline visit. Follow-up study was scheduled at 2 weeks, 4 weeks, 6 weeks, and 3 months after the baseline visit. The safety evaluation was performed by assessing of adverse effects, heart rate and blood pressure. Adverse effects if any were recorded and assessed at each visit.

Statistical analysis was done using Statistical Package for Social Service software. The patients who completed the entire 12 weeks of treatment period were included in the statistical analysis. Adverse effects in both the groups were compared using Chi-square test. p<0.05 was considered statistically significant.

#### RESULTS

A randomized, open label clinical trial comparing the safety of once daily Latanoprost with that of twice daily Timolol in patients with POAG was conducted. A total of 60 patients were enrolled in the study, out of which 28 patients in Timolol group and 27 patients in Latanoprost group completed the study. In the Timolol Group 1 patient did not come for follow-up after the second visit, another patient was lost to follow-up after the third visit. In the Latanoprost group 2 patients were lost to follow-up and 1 patient was changed over to a combination of Latanoprost and Timolol due to insufficient IOP control (Table 1).

The family history of glaucoma was seen in 10.7% of the patients in timolol group and 11.1% of the patients in Latanoprost group. History of diabetes mellitus was seen in 25% of patients in Timolol group and 44% of patients in Latanoprost group. History of hypertension was seen in 21.4% of Timolol group and 37% of Latanoprost group. History of a migraine was seen in 2% of patients in Timolol group. The major refractive error seen in both the groups was hypermetropia (Table 2).

Presence or absence of any adverse effect was analyzed by Chi-square test. In the Timolol group, 54% patients and in the Latanoprost group 70% patients experienced adverse effects and there was no statistically significant difference between the two groups (p>0.05) (Table 3 and Figure 1).

Bradycardia was seen only in Timolol group whereas ocular adverse effects such as periocular pigmentation, the growth of eyelashes and conjunctival hyperemia were seen only in Latanoprost group. Ocular discomfort was present equally in both the groups. Foreign body sensation was seen in both the groups, but it was more frequent in Latanoprost group. The blurring of vision was predominantly seen in Timolol group. Corneal anesthesia was seen in one of the patients on Timolol.

Table 1: Comparison of risk factors.

Risk factors	n (%)	
	Timolol	Latanoprost
Family h/o glaucoma	3 (10.71)	3 (11.11)
Diabetes mellitus	7 (25)	12 (44.44)
Hypertension	6 (21.43)	10 (37.04)
Migraine	2 (7.14)	0
Myopia	3 (10.71)	5 (18.52)
Hypermetropia	17 (60.71)	18 (66.67)
Emmetropia	8 (28.57)	4 (14.81)

Table 2: Distribution of patients based on adverse effects reported.

Adverse	n (%)		
effects	Timolol	Latanoprost	
Present	15 (53.57)	19 (70.37)	
Absent	13 (46.43)	8 (29.63)	

Table 3: Adverse effect profile.

Adverse effects	n (%)	
	Timolol	Latanoprost
Ocular discomfort	2 (7.14)	2 (7.14)
Corneal anesthesia	1 (3.57)	0
Foreign body sensation	3 (10.71)	5 (18.52)
Blurred vision	5 (17.86)	1 (3.7)
Bradycardia	4 (14.29)	0
Periocular pigmentation	0	4 (14.81)
Growth of eyelashes	0	7 (25.93)
Conjunctival hyperemia	0	6 (22.22)
Others	1 (3.57)	1 (3.7)

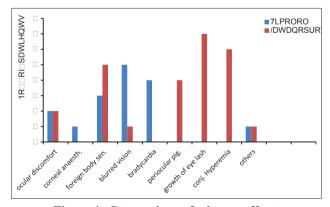


Figure 1: Comparison of adverse effects

#### DISCUSSION

Timolol reduces IOP by decreasing the aqueous humor production, whereas Latanoprost increases the uveoscleral

outflow, thereby reducing the IOP. Timolol by reducing aqueous flow could diminish the nutrient supply of lens and cornea and increase the concentration of waste products in the anterior chamber. However, drugs like Latanoprost which increase the uveoscleral outflow without affecting aqueous flow do not have this disadvantage.<sup>9</sup>

The present study was undertaken to compare the safety of twice daily 0.5% Timolol and once daily 0.005% Latanoprost in patients with POAG. Studies such as Barbados eye study<sup>10</sup> and Baltimore eye study<sup>11</sup> revealed a strong association between family history and POAG. In our study, around 11% of patients in each group had a family history of glaucoma.

Myopia is considered as one of the known risk factors for POAG, as proved by studies such as The Blue mountain study<sup>10</sup> and The Casteldaccia eye study.<sup>12</sup> However, the contrast to this in our study only 8 subjects had myopia and 35 subjects had hypermetropia. Subjects with other known risk factors for POAG such as diabetes<sup>10</sup> and hypertension<sup>13</sup> were also included and distributed in both the groups in our study. Around 19 glaucoma patients were diabetics and around 16 patients were suffering from hypertension.

In our study, we did not find a significant statistical difference in terms of adverse effects between the two groups. We found that ocular adverse effects such as conjunctival hyperemia, foreign body sensation, periocular pigmentation, and growth of eyelashes were mainly found in Latanoprost group, and blurring of vision was mainly found in Timolol group. Systemic side effect like bradycardia was found only in Timolol group. Corneal anesthesia was found in one patient belonging to Timolol group. Ocular discomfort was found equally in both the groups. This was in accordance with other studies. 14-16

Among the patients who dropped out, one patient among Latanoprost group was switched over to a combination of Latanoprost and Timolol due to lack of adequate IOP control and the rest were lost to follow-up. On comparing the adverse effects, ocular adverse effects such as conjunctival hyperemia, foreign body sensation, periocular pigmentation, and the growth of eyelashes were more with Latanoprost than Timolol though not statistically significant. However, in no instance were these complaints sufficiently severe to cause non-compliance to the use of drugs.

#### **CONCLUSION**

The incidence of adverse effects was not significantly different between Latanoprost and Timolol therapy. The adverse effects were mild and tolerable for both medications. Both had favorable safety profiles over the duration of this 3 months trial. Latanoprost has safer

systemic side effects profile when compared to Timolol. Unlike timolol, it does not compromise the nutrient supply to lens and cornea offering it an additional theoretical advantage. Hence, Latanoprost can be concluded as a better drug than Timolol. As the present study included a small number of patients within a limited period of time, further studies with a large number of patients have to be carried out to establish the data.

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