National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Efficacy and safety of timolol and latanoprost in the treatment of primary open-angle glaucoma

Soumya R[1], Jayanthi C R[1], Sujatha B L[2]

[1]Department of Pharmacology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India, [2]Department of Ophthalmology, Bangalore Medical College and Research Institute, Bengaluru, Karnataka, India

Correspondence to: Soumya R, E-mail: soumya.rsn@gmail.com

Received: April 03, 2017; **Accepted:** April 18, 2017

ABSTRACT

Background: Glaucoma is a chronic, progressive optic neuropathy which leads to optic nerve damage and loss of visual function. Elevated intraocular pressure (IOP) is the most important and only modifiable risk factor. Hence, the goal of glaucoma therapy is to lower IOP, and ocular hypotensive agents have the potential to prevent optic nerve damage and preserve vision. **Aims and Objectives:** Aims and objectives of the study are to compare the efficacy and safety of timolol 0.5% versus latanoprost 0.005% in the treatment of primary open-angle glaucoma (POAG). **Materials and Methods:** A total of 60 newly diagnosed patients of POAG who fulfilled the inclusion/exclusion criteria were enrolled and randomized into two groups of 30 each to receive timolol 0.5% twice daily and latanoprost 0.005% once daily in the evening. IOP was recorded at baseline and each follow-up visit. The patients were followed every 4 weeks for 12 weeks. Adverse effects, if any, were also recorded at each visit. **Results:** At 12 weeks both timolol and latanoprost effectively reduced IOP, but the reduction was significantly greater ($P < 0.0001$) with latanoprost (7.97 ± 1.27 mmHg, 31.25%) compared with timolol (6.77 ± 1.48 mmHg, 25.9%). More number of eyes ($\chi^2 = 4.6$, df = 1, $P = 0.032$) treated with latanoprost (46, 76.6%) achieved a specific target IOP as compared to those treated with timolol (35, 58.3%). Both the study medications were well tolerated. **Conclusion:** Latanoprost was found to be more potent and efficacious in reducing IOP with good tolerability in patients with POAG.

KEY WORDS: Intraocular Pressure; Latanoprost; Primary Open Angle Glaucoma; Timolol

INTRODUCTION

Glaucoma is a chronic, progressive optic neuropathy which leads to optic nerve damage and loss of visual function.[1] It is one of the leading causes of irreversible blindness worldwide second only to cataract.[2] Globally, about 66.8 million are affected, 6.7 million of these being bilaterally blind.[3] India has an estimated 12.8 million cases, which is about one-fifth of the global burden of glaucoma.[4]

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2017.7.0412418042017	

The prevalence of primary open-angle glaucoma (POAG) in persons aged 40 years and above in southern India is 1.7% in the rural (The Aravind comprehensive eye survey) and 3.5% in the urban (Chennai glaucoma study) sectors.[5,6] While the national blindness survey 2001 showed that glaucoma is responsible for 5.9% of blindness in India, there has been a more than threefold increase in proportion of glaucoma blindness compared to that found in the previous national survey 1989.[2]

Elevated intraocular pressure (IOP) has been identified as a major risk factor for POAG. Drugs that reduce IOP has the potential to prevent or delay optic nerve damage and preserve vision.[7] The goal of glaucoma therapy is to lower IOP with the use of medications, laser or surgery, the latter two being generally reserved for those who fail medical

therapy.[1,4] The ocular hypotensives - topical β blockers, α adrenergic agonists, prostaglandin analogs, carbonic anhydrase inhibitors and miotics – constitute the therapeutic arsenal in the management of POAG. β blockers which reduce the aqueous formation and prostaglandin analogs that increase uveoscleral outflow are the most commonly used the first line drugs.

Traditionally, timolol, the prototype ocular β blocker has been considered as the first line agent and standard of reference in glaucoma therapy.[8] However, recent studies have questioned the 24 h efficacy of timolol, its effect on blood pressure, ocular perfusion pressure, its adverse effect profile and associated non-compliance, which could be potential limitations.[9,10] The prostaglandin analogs have been shown to be as or more effective in lowering IOP than timolol. The prototype drug latanoprost, being more potent and longer acting, has been shown to have higher documented efficacy in the form of additional 5% (an average of 1.6 mmHg) decrease in IOP when compared to timolol.[3] It also reduces nocturnal IOP, achieves target IOP in more number of patients, has lesser systemic side effects and lesser non-responder rate with a convenience of once daily dosing, as compared to timolol.[11-14] Studies have also shown that latanoprost produces persistent therapeutic effect with reduced need for additional medications or therapy changes as compared to patients on timolol.[9] Hence, prostaglandin analogs have now become the most popular ocular hypotensives relegating timolol to the second position.

Considering the high prevalence of glaucoma in India and the irreversible blindness caused by it, the proportion of which is ever increasing, research on glaucoma management is pertinent. The various advantages of latanoprost over timolol and the paucity of comparative studies between timolol and latanoprost as monotherapy in POAG with regard to efficacy and safety among Indians prompted us to undertake this study.

MATERIALS AND METHODS

This was an open-labeled, randomized prospective study conducted between October 2013 and May 2015 in the Regional Institute of Ophthalmology, Minto Hospital attached to Bangalore Medical College and Research Institute, Bengaluru.

After obtaining institutional ethics committee clearance and written informed consent, the out-patients at the glaucoma clinic aged above 18 years, newly diagnosed to be suffering from POAG and fulfilling the inclusion/exclusion criteria were enrolled in the study. Patients suffering from amblyopia, legal blindness (6/60 or less) in either eye, acute angle closure glaucoma, optic nerve disease, advanced cataract, dry eye, and ocular infection or inflammation within the previous 3 months were excluded from the study. Patients with previous intraocular surgery, severe trauma and hypersensitivity or any systemic contraindications to study medications were also excluded from the study.

A total of 60 patients were recruited and randomized in a 1:1 ratio into two groups of 30 each to receive either timolol 0.5% eye drops twice daily (Group 1) or latanoprost 0.005% eye drops once daily in the evening (Group 2). Randomization was done with a computer-generated table which was retained with the nurse in the glaucoma clinic for allocation concealment.

Demographic data, ocular history, medical history, concomitant medications and details of general, systemic and ophthalmological examination were recorded in the study proforma at baseline visit (visit 1). Follow-up was done at 4 weeks (visit 2), 8 weeks (visit 3) and 12 weeks (visit 4) after administering the study drugs. A deviation of ±2 days for first follow-up and ±1 week for subsequent follow-ups was accepted. At follow-up visits pulse rate, blood pressure, IOP, slit lamp examination findings, and visual acuity were recorded. When both eyes fulfilled the eligibility criteria, both were regarded as study eyes and IOP was measured in each eye at the subsequent follow-up visits. IOP was measured with Goldmann applanation tonometer at 9 am and mean of 2 readings was taken at each of the visits. Target IOP was calculated at baseline visit with the following formula: TP = IP (1 - IP/100) - Z ± 2, where TP = Target pressure, IP = Initial pressure and Z = Functional status (disc damage/field changes - Z = 0 in glaucoma suspect, Z = 1 in early glaucoma, Z = 3 in moderate glaucoma, Z = 5 in severe glaucoma and Z = 7 in end-stage glaucoma).

Adverse events were recorded and graded according to severity as mild (awareness of sign or symptom, but easily tolerated), moderate (enough discomfort to cause interference with usual activity), and severe (incapacitating with inability to work or do usual activity).

Sample Size Calculation

Sample size was estimated as 24 patients in each group using mean reduction in IOP of 6 mmHg and standard deviation (SD) 1.8 with timolol and mean reduction in IOP of 7.1 mmHg and SD 1.2 with latanoprost from the previous studies.[3] Alpha error was set at 5% and power of the study at 80%. A total of 60 patients (30 in each group) were recruited to allow for dropout/withdrawal rate of 15-20%.

Statistical Analysis

The data collected was tabulated and analyzed using mean and SD. Continuous variables were compared within the

group using repeated measures ANOVA and between the groups using unpaired *t*-test. Categorical data were expressed as percentages/proportions and Chi-square-test was done to compare the categorical variables.

RESULTS

Demographic Characteristics

Table 1 represents the epidemiologic profile of the patients included in the study. The mean age was 60 ± 11 years in the timolol group and 55.2 ± 12.8 years in the latanoprost group ($P = 0.167$). Most of the patients belonged to the age group of 41-65 years in both the treatment groups ($\chi^2 = 1.46$, df = 2, $P = 0.48$). There were 12 (40%) male and 18 (60%) female patients in the timolol group and 16 (53.33%) male and 14 (46.67%) female patients in the latanoprost group ($\chi^2 = 1.07$, df = 1, $P = 0.3$). Both the treatment groups were age and gender at baseline.

Mean Reduction in IOP

The baseline mean IOP was comparable between the two groups ($P = 0.354$). Both timolol and latanoprost effectively reduced IOP compared to baseline (ANOVA - $P < 0.0001$, Table 2 and Figure 1). The reduction in the latanoprost group (7.12 ± 1.2 mmHg) was significantly higher than the reduction in the timolol group (5.93 ± 1.33 mmHg) at week 4 ($P < 0.0001$). The reduction at week 12 was also significantly more with latanoprost (7.97 ± 1.27 mmHg, 31.25% vs. 6.77 ± 1.48 mmHg, 25.9%, $P < 0.0001$) compared to timolol (Figures 2 and 3).

A significantly more number of eyes ($\chi 2 = 4.6$, df = 1, $P = 0.032$, Figure 4) treated with latanoprost (46, 77%) achieved target IOP as compared to those treated with timolol (35, 58%).

Table 1: Demographic characteristics of the study population

Parameters	Group 1 (n=30)	Group 2 (n=30)	*P* value*
Age (years)			
18-40	2	5	
41-65	21	19	0.48
≥66	7	6	
Gender			
Male	12	16	0.3
Female	18	14	
Habits			
Smoking	7	8	0.878
Alcohol	14	14	1.0
Comorbidities			
Nil	16	15	
DM	6	7	0.94
HTN	5	6	
DM+HTN	3	2	

*Represents the *P* value on intergroup comparison, DM: Diabetes mellitus, HTN: Hypertension

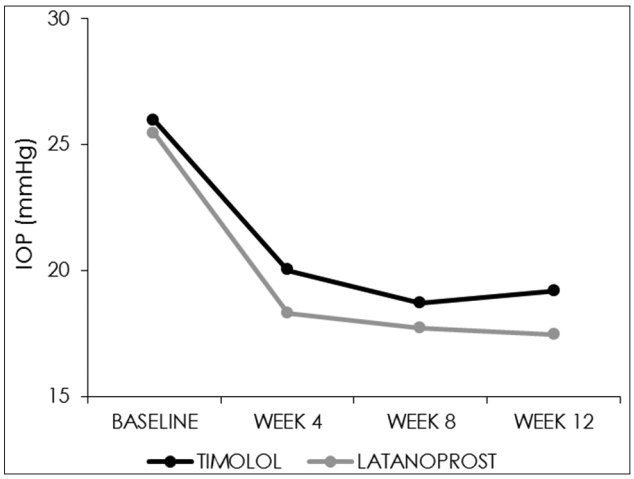

Figure 1: Temporal depiction of mean intraocular pressure in the study groups

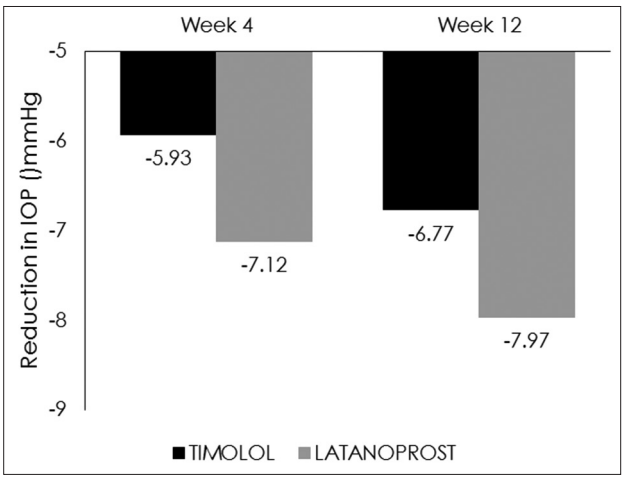

Figure 2: Reduction in intraocular pressure at weeks 4 and 12

Table 2: Mean IOP at each visit in the timolol and latanoprost groups

Group (n=60 eyes)	Baseline (mmHg)	Week 4 (mmHg)	Week 8 (mmHg)	Week 12 (mmHg)	*P* value
Timolol (mean±SD)	25.93±2.93	20±2.9	18.68±2.31	19.17±1.96	<0.0001#
Latanoprost (mean±SD)	25.42±3.14	18.3±2.33*	17.7±2.21	17.45±2.02*	<0.0001#

**P*<0.0001 on intergroup comparison with unpaired *t*-test, #*P* value obtained by intragroup comparison with ANOVA, IOP: Intraocular pressure, SD: Standard deviation

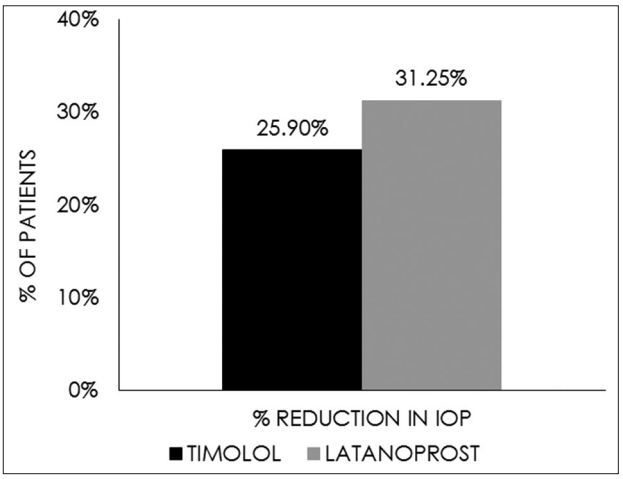

Figure 3: Percentage reduction in intraocular pressure at week 12

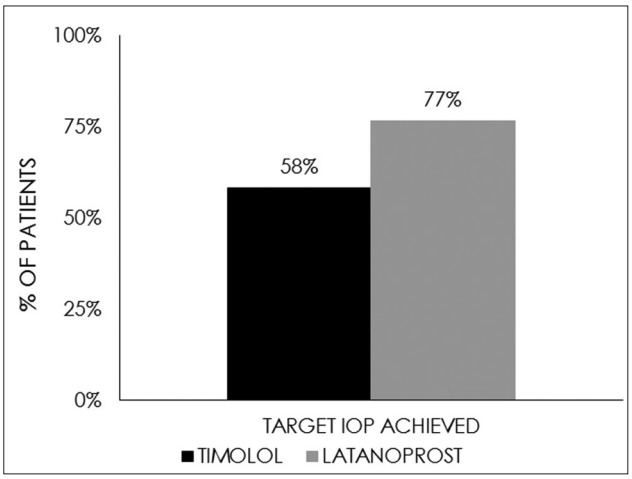

Figure 4: Percentage of eyes achieving target intraocular pressure

Table 3: Ocular adverse effects

Adverse effects	Timolol number of patients (%)	Latanoprost number of patients (%)
Blurred vision	2 (6.6)	1 (3.3)
Burning	3 (10)	3 (10)
Dry eye	3 (10)	2 (6.6)
Headache	4 (13.3)	2 (6.6)
Conjunctival hyperemia	3 (10)	8 (26.6)

Adverse Effects

Both the study medications were well tolerated. The adverse effects encountered were mild to moderate local ocular adverse effects, and there was no statistically significant difference between the groups ($P = 0.54$, Table 3).

DISCUSSION

Glaucoma with its increasing prevalence is the second leading cause of blindness globally and the third in India. It has a significant impact on patients' health-related quality of life and also adds to the societal economic burden.[15] In this study, most of the glaucoma patients enrolled belonged to the age group of 41-65 years with no gender predilection. Both timolol and latanoprost effectively reduced mean IOP from baseline at study termination, but the reduction with latanoprost was significantly higher compared to timolol. The study medications were well tolerated with few mild to moderate local ocular adverse effects.

Increasing age is a major risk factor for POAG. Most of the patients enrolled belonged to the age group of 41-65 years with no statistically significant difference between the two treatment groups ($P = 0.167$). The mean age was 60 ± 11 years in the timolol group and 55.2 ± 12.8 years in the latanoprost group. These results correlate with the visual impairment project and a number of other epidemiological studies which show that the prevalence of glaucoma increases dramatically with age especially after the age of 40 years.[16-18] This might be due to the decline in retinal ganglion cell number and reduced neural capacity. Thus, in older individuals, fewer ganglion cells need to be lost before there is detectable visual field loss. An alternate hypothesis is that ageing may increase the inherent vulnerability of ganglion cells to IOP insult.[19] As the risk of glaucoma increases substantially with age, the number of those at risk of glaucoma is expected to grow exponentially over time with increasing life expectancy in India. Studies of gender influence on glaucoma prevalence have been conflicting. In this study, there were a total of 28 males and 32 females among the study population with no statistically significant difference. This is consistent with the results obtained in both the studies conducted in urban and rural South Indian populations, where no significant statistical association between gender and glaucoma prevalence was found.[6,20] While a Bayesian meta-analysis conducted by Rudnicka et al. and the Aravind Comprehensive Eye Survey reported higher rates of POAG among males, The Blue Mountains Eye Study conducted by Mitchell et al. reported higher rates in females.[5,21,22]

Among the 60 patients suffering from POAG enrolled in this study, 13 of them were diabetic, 11 were hypertensives and 5 subjects had both diabetes and hypertension (HTN). Although high IOP, advancing age, positive family history and ethnicity are the best-established risk factors, a number of potential new risk factors have been identified more recently. People with diabetes are twice as likely to develop glaucoma as are non-diabetics. The evidence from experimental studies suggests that this may be attributed to enhanced susceptibility of the eye to stress and compromised autoregulation in diabetes. Widespread vascular damage in diabetes may also exacerbate the ischemic insult seen in glaucoma.[19] While the meta-analysis conducted by Bonovas et al. and the Blue Mountains Eye Study reported a significant and consistent association between diabetes mellitus and glaucoma, the Rotterdam study and the Baltimore Eye Survey have failed to find any positive association.[23-26] The evidence for the

effect of blood pressure on glaucoma remains controversial due to their complex relationship. Higher systolic and mean arterial blood pressures were associated with a higher prevalence of POAG in the Los Angeles eye study.[27] The Blue Mountains Eye Study, the Egna-Neumarkt glaucoma study and the Rotterdam Eye Study also found that systemic HTN increases the susceptibility to glaucoma, possibly due to a positive correlation between blood pressure and IOP.[28-30] Despite this positive correlation, the actual change in IOP with increasing blood pressure is small. It is also a counter-intuitive association given that a high blood pressure should produce a high ocular perfusion pressure and thus give a protective effect.[19] Indeed, other epidemiological studies like the Barbados Eye Study and the early manifest glaucoma trial have found a greater prevalence of glaucoma in people with low blood pressure and suggest that systemic HTN could actually be a protective factor, consistent with the possibility that low ocular perfusion pressure injuries ganglion cells[31,32] but to draw conclusions from this study would not be apt given the limited number of participants and the complex and controversial associations between diabetes, HTN and glaucoma.

The most important and the only proven modifiable risk factor for glaucoma is increased IOP.[33] The role of IOP reduction in preventing optic nerve damage and visual loss has been upheld in numerous randomized prospective trials. Medical therapy is the standard of care in POAG and also the mainstay of initial and long-term IOP reduction in other types of glaucoma.[34] Evaluation of efficacy of timolol versus latanoprost was the primary objective of this study. The baseline mean IOP was comparable between the two groups ($P = 0.354$). There was a significant reduction in mean IOP at 12 weeks in both timolol (6.77 ± 1.48 mmHg, 25.9%) and latanoprost (7.97 ± 1.27 mmHg, 31.25%) groups but it was significantly greater ($P < 0.0001$) with latanoprost 0.005% administered once daily in the evening compared to timolol 0.5% administered twice daily. Hence, latanoprost was found to be a more potent and effective ocular hypotensive than timolol. Similar outcomes were noted in a meta-analysis of randomized controlled trials comparing latanoprost with timolol conducted by Zhang et al. who found that both latanoprost 0.005% administered once daily and timolol 0.5% administered twice daily reduced IOP. However, latanoprost (30.2%) showed better IOP lowering effect compared to timolol (26.9%).[3] The study results were also consistent with a pooled-data analysis of three randomized double-masked studies done by Hedman and Alm in which a 1.2 mmHg more reduction ($P < 0.0001$) in diurnal IOP was seen with latanoprost compared to timolol.[14] Similar observations were also made in studies from India, Egypt and the Philippines[11,12,35] The Scandinavian, UK and the United States Latanoprost Study Groups have also upheld these findings. Another way to evaluate the clinical efficacy of different ocular hypotensive drugs is to analyze the number of patients reaching a specific target IOP. In this study, significantly more eyes ($\chi^2 = 4.6$, df = 1, $P = 0.032$) treated with latanoprost (46, 76.6%) achieved target IOP as compared to those treated with timolol (35, 58.3%). These results are in line with the study conducted in the Philippines.[12]

The adverse effects encountered were mild to moderate local ocular adverse effects, and there was no statistically significant difference between the groups ($P = 0.54$). There were no serious adverse effects observed in either group, and both study medications were well tolerated. Conjunctival hyperemia was seen in more number of patients receiving latanoprost compared to patients receiving timolol but was not statistically significant. Increased iris pigmentation, which is a known side effect of prostaglandin analogs was not seen in the latanoprost-treated patients in this study. While a similar adverse effect profile was also seen in studies conducted in Egypt and the Philippines, a significantly higher incidence of conjunctival hyperemia and iris pigmentation was noted in patients treated with latanoprost compared to timolol in the meta-analysis and few other studies mentioned earlier.[3,11,12] Failing to find increased iris pigmentation in this study could be due to the dark irides of the study subjects or a short study duration. There were no systemic side effects observed in both the treatment groups during the study, though according to previous studies latanoprost is said to be associated with lesser systemic side effects. Ophthalmic timolol has been reported to reduce blood pressure, cause bradycardia and bronchospasm in patients with cardiovascular or pulmonary disorders warranting caution in its use.[3]

Although topical β blockers are the first line drugs in the management of glaucoma, in recent times prostaglandin analogs have become the most popular ocular hypotensives. However, there is a paucity of comparative studies between timolol and latanoprost in the Indian population. In this context, this study would add valuable evidence to aid in decision making of glaucoma management. An active-controlled and randomized study design with allocation concealment adds to the strength of the study. However, short-time frame and open-labeled design are the major limitations of this study. Furthermore, since glaucoma is a chronic disease, it would be preferable to evaluate the cost-effectiveness of the IOP-lowering agents over a longer period as latanoprost though more effective than timolol, is also more expensive.

CONCLUSION

The prostaglandin analog latanoprost was shown to have a higher documented efficacy in the form of additional 1.2 mmHg decrease in IOP with more number of eyes reaching target IOP, similar patient tolerability as timolol and a convenience of once daily dosing. Hence, latanoprost is a preferable and effective option for the management of POAG.

ACKNOWLEDGMENTS

The authors would like to thank the faculty and postgraduate students from the Departments of Pharmacology and Ophthalmology, Bangalore Medical College & Research Institute, Bengaluru, for their support in conducting the project work.

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How to cite this article: Soumya R, Jayanthi CR, Sujatha BL. Efficacy and safety of timolol and latanoprost in the treatment of primary open-angle glaucoma. Natl J Physiol Pharm Pharmacol 2017;7(8):844-850.

Source of Support: Nil, **Conflict of Interest:** None declared.