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RESEARCH ARTICLE

A comparative study on the efficacy and cost-effectiveness of latanoprost and timolol in glaucoma

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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. Ocular hypotensive agents have the potential to lower the IOP and preserve vision. **Aims and Objectives:** The aims of the study were to compare topical latanoprost eye drop and topical timolol eye drop as appropriate and cost-effective management of primary open-angle glaucoma (POAG). **Materials and Methods:** A total of 70 newly diagnosed patients POAG who fulfilled the inclusion/exclusion criteria were enrolled and randomized into two groups. The first group L-Group was prescribed topical latanoprost 0.005% eye drop once daily, whereas the second group T-Group was prescribed topical timolol 0.5% eye drop twice a day. Final reduction in IOP was recorded after 3 months of treatment in both the groups. The cost-effectiveness was calculated as the cost of the drug per mmHg fall in IOP. **Results:** In our study, the IOP lowering efficacy of latanoprost was found to be superior to timolol. In the latanoprost group, the mean reduction in IOP from baseline to final visit was 10.13 mmHg, whereas only 5.84 mmHg in the timolol group. The average cost-effective ratio was found to be Rs. 32.4/ mmHg and Rs. 6.16/mmHg for latanoprost and timolol, respectively. Hence, timolol proved to be more cost effective as compare to latanoprost. **Conclusion:** Although latanoprost was found to be superior to timolol in reducing the IOP, yet because of its high cost the treatment should be started with timolol and latanoprost should only be used as an add-on therapy in cases not able to achieve target IOP by timolol monotherapy or in whom timolol is contraindicated.

KEY WORDS: Intraocular Pressure; Latanoprost; Timolol; Open Angle Glaucoma; Cost-effectiveness

INTRODUCTION

Glaucoma is a chronic, progressive optic neuropathy occurring due to a group of ocular conditions, which can lead to damage of optic nerve and visual function loss. Constant increase in intraocular pressure (IOP) occurs either due to increased formation of aqueous humor or due to its inadequate outflow or drainage. It may also be due to the raised pressure in the episcleral veins.[1]

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It is estimated that there are more than 66.8 million cases of glaucoma worldwide and it will increase to 80 million by 2020.[2] It is the second leading cause of preventable blindness with 11.2 million persons above 40 years.[3] In southern India, the prevalence of primary open-angle glaucoma (POAG) in persons 40 years and above is 1.7% in the rural area (The Aravind Comprehensive Eye Survey) and 3.5% in the urban area (Chennai glaucoma study).[4]

The cornerstone for the treatment of glaucoma lies in the reduction of increased IOP. Although a wide variety of antiglaucoma drugs are available, yet treatment is usually initiated either with a topical beta-adrenergic antagonist or a topical prostaglandin analog.[5]

Timolol is a beta-adrenergic blocking agent. It reduces IOP by decreasing aqueous humor production by acting on ciliary epithelium.[6] Maximum IOP reducing effect of timolol is seen at 2 h after initiation and lasts for 24 h. Approximately 80% of topically administered drug is reported to drain through nasolacrimal duct and absorbed systemically. This systemically absorbed timolol can cause adverse effects such as bradycardia, hypotension, bronchospasm, and respiratory failure.[7,8] Hence, it is contraindicated in patients who have a history of cardiac disease or asthma.[9]

Prostaglandin analogs are the latest therapeutic agents in glaucoma medication.[10] Latanoprost reduces IOP by stimulating aqueous humor drainage primarily through the uveoscleral outflow pathway but significant effects on trabecular outflow have also been reported.[11,12] Prostaglandin analogs have been shown to be more effective in lowering IOP than timolol.

As new antiglaucoma drugs are being continuously added to the pharmaceutical armamentarium, the ophthalmologists are in a dilemma for selecting the best antiglaucoma drug from the vast array of available options. Therapeutic decisions for glaucoma therapy should be taken with due consideration of the cost of the drug along with its efficacy and safety so that the patient can adhere to the treatment and maintain compliance.

Even though prostaglandins are proven to be highly efficient, but its main drawback is its high cost. With this view in mind, we conducted the present study to compare the efficacy and cost-effectiveness of latanoprost and timolol as antiglaucoma therapy.

MATERIALS AND METHODS

It was conducted as an open-labeled, prospective, interventional, simple randomized clinical study to compare efficacy, safety, and cost-effectiveness of latanoprost and timolol in patients of POAG in the Department of Pharmacology in collaboration with Department of Ophthalmology, Rohilkhand Medical College and Hospital Bareilly. Institutional Ethical Committee clearance was sought before initiation of the study. The period of the study was 12 months (November 2017–October 2018) duration.

Convenient sampling technique was adopted. Newly diagnosed cases of glaucoma of both genders and above 40 years of age were included in the study. A written informed consent was taken from every patient.

Pregnant and lactating women and patients having a history of any ocular infection or inflammation, known case of uncontrolled cardiovascular, hepatic or renal disease, bronchial asthma, and chronic obstructive pulmonary disease were excluded from the study.

A total of 70 patients constituted the sample size. They were randomly divided in two groups. The first group, i.e., L-Group was prescribed topical latanoprost 0.005% eye drop once daily whereas the second group, i.e. T-Group was prescribed topical timolol 0.5% eye drop twice a day. Applanation tonometer was used to measure IOP at each visit. The first reading was taken as a baseline reading. Patients under treatment were subsequently monitored and reassessed at 1st week (first follow-up) → next at 4th week (second follow-up) → next at 3rd month (third follow-up) for the evaluation of IOP, monitoring of other changes in the eyes and for assessment of any adverse effects.

Cost Analysis of Latanoprost and Timolol Medications

We performed a cost-effective analysis by determining the cost incurred by the patient per mmHg of IOP reduction by latanoprost and timolol, respectively. Daily cost of the drug was calculated by dividing the cost per ml of the bottle by number of drops per ml and multiplying by the number of drops required daily. Thereafter, 3 months cost of both drugs was calculated. Then, average cost-effective ratio (ACER) and incremental cost-effective ratio (ICER) were calculated.

Statistical analysis was performed on patients who had completed the 3 months of the treatment period. Drugs effect in term of change in IOP was compared using independent *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 80 patients were enrolled in the study, of which 70 patients completed the study. Finally, there were 36 patients in latanoprost and 34 in the timolol group [Table 1]. Most of the study participant were in the mean age of 50-55 years with the male prepondarance. Although the mean IOP in both the groups was comparable at baseline but Latanoprost therapy produced a greater reduction in mean IOP at each follow up as comare to Timolol therapy ($P < 0.001$) [Table 2].

Cost Analysis of Latanoprost and Timolol as Antiglaucoma Agents

In our study, we found treatment with latanoprost to be costlier than timolol. The daily cost and 3-month cost for latanoprost were Rs. 3.6 and Rs. 329, respectively, whereas it was Rs. 0.41/day and Rs. 36/month for timolol. Average cost-effectiveness ratio, i.e., cost/mmHg of IOP reduction was calculated as,

Average cost-effectiveness ratio = [Cost of drug for 3 months]/[IOP lowering at 3 months]

ACER of latanoprost and timolol was 32.4 and Rs. 6.16, respectively [Table 3]

Since latanoprost therapy was both more effective and more expensive than its comparator timolol, hence, an ICER was calculated which showed the extra cost per unit of the outcome obtained in comparing to choose the one treatment option to another [Table 4].

$$\text{ICER was calculated as} = \frac{\text{Cost of drug A (Latanoprost)} - \text{Cost of drug B (Timolol)}}{\text{IOP lowering Latanoprost} - \text{IOP lowering Timolol}}$$

Table 1: Demographic profile of the participants

Characteristics	Latanoprost	Timolol
Mean age	52.95±9.43	51.05±9.78
Males (%)	21 (61.1)	19 (55.9)
Females (%)	14 (38.9)	15 (44.1)
Mean baseline IOP	23.60±1.10	23.78±0.89

IOP: Intraocular pressure

Table 2: Comparison of mean IOP reduction by latanoprost and timolol group by student independent *t*-test

Visits	Latanoprost	Timolol	*t*-value	*P*-value
	Mean±S.D	Mean±S.D		
Baseline	23.60±1.10	23.78±0.89	0.780	0.438#
1st follow-up	19.31±0.83	21.38±1.07	9.588	<0.001*
2nd follow-up	16.30±0.70	19.38±1.14	14.009	<0.001*
3rd follow-up	13.47±0.97	17.94±0.92	19.75	<0.001*

P>0.05 – Not significant, *P*<0.05 – Significant, *P*<0.001 – Highly significant.
IOP: Intraocular pressure

The ICER was calculated to be Rs. 68.2, which means an extra Rs. 68.2, was required for each additional mm Hg IOP reduction by latanoprost for 3 months as compared with timolol. Therefore, on the basis of its cost/mm Hg reduction and ICER, timolol is considered more cost effective as compared to latanoprost.

DISCUSSION

Glaucoma is a potentially blinding ocular disease having multiple causes. Raised IOP is a significant and modifiable risk factor in the development and progression of glaucoma.[13] This disease is often insidious in onset and gradually progressive, resulting in permanent visual loss. Hence, it is also called as the "silent thief of sight.[14]" Many randomized clinical trials have shown that reducing IOP slows the onset and progression of glaucoma.[15,16]

Increasing age is a major risk factor for POAG. In our study, the majority of patients attending the ophthalmology outpatient department was in the age group of 40–60 years and had a higher number of males 41 (59%) than females 29 (41%).

The IOP lowering efficacy of latanoprost was found to be superior to timolol. In the latanoprost group, the mean reduction in IOP from baseline to 3rd month (final follow-up) was 10.13 mmHg and in the timolol group was 5.84 mmHg. The difference in IOP reduction by the two drugs from baseline to final FU visit was 4.29 mmHg. This difference in IOP was also statistically significant. This proves that latanoprost was more efficacious in reducing IOP as compared to timolol.

In the present study, local adverse effects were commonly found. There were no serious adverse effects observed in both groups and both study medications were well tolerated. Conjunctival hyperemia was seen in majority of patients who received latanoprost compared to patients who received timolol. Dry eye, blurred vision, and headache were mostly reported in the timolol group.

Table 3: Cost analysis of latanoprost and timolol eye drops

Drugs	Concentration	Ml	Cost/Bottle (Rs.)	Cost/ml (Rs.)	Dose/day affected eye (Drops)	Cost/day (Rs.)	Cost/Month (Rs.)	Cost of 3 Month (Rs.)
Latanoprost (Lacoma Eye Drop) Ajanta Pharma	0.005	2.5 ml	229	91.6	1	3.6	109	329
Timolol (OCUTIM Eye Drop) CIPLA	0.5	5 ml	26	5.2	2	0.41	12	36

Table 4: Incremental cost-effectiveness ratio

Parameters	Latanoprost	Timolol	Difference in cost	Difference in effectiveness	ICER
Cost/mm Hg IOP reduction	32.4	6.16	293	4.29	68.2
Average fall in IOP	10.13	5.84			

IOP: Intraocular pressure, ICER: Incremental cost-effective ratio

Our study results were in concordance with a number of other epidemiological studies which showed that prevalence of glaucoma increases dramatically with age, especially after the age of 40 years,[17-20] whereas a study done by Sharma *et al*.[21] showed that the highest number of patients belonged to >60 years of age group (34%). It may be due to a decline in retinal ganglion cell number and reduced neural capacity with advancing age.

Studies of gender influence on glaucoma prevalence have been conflicting. Our study results were similar with other observations documented by Agarwal *et al*.,[20] Das *et al*.,[22] Mehani *et al*.,[23] and Parrish *et al*.[24] and results were in contrast to a study done by Soumya *et al*.,[25] who had more females (32) as compared to males (28) in their study subjects.

In our study, the IOP lowering efficacy of latanoprost was found to be superior to timolol. Our study results were in agreement with other studies done by Soumya *et al*.[25] Rao and Narayanan,[26] Gulati *et al*.,[27] and Harasyamowycz *et al*.[28] A meta-analysis done by Zhang *et al*.[29] showed that latanoprost once-daily administration produces a consistent reduction in IOP and stabilizes the IOP diurnal curve as well, whereas timolol has no additional benefit of stabilization of IOP compared to latanoprost. This fact again reinforces the superior efficacy of latanoprost over timolol.

In India, there was a lack of pharmacoeconomic data on POAG. Unlike western countries, in India, therapy is relatively cheaper but still many cannot afford. In our study, the cost-effective analysis of antiglaucoma drugs (latanoprost and timolol) was done by evaluating the ACER and ICER.

Our study findings revealed that treatment with latanoprost was costlier than timolol with the daily cost of affected eye Rs. 3.6 and Rs. 0.41 for latanoprost and timolol, respectively, and the 3 months cost of drugs Rs. 329 for latanoprost and Rs. 36 for timolol. The ACER of both drugs in our study was calculated for the period of 3 months and cost/ mm Hg reduction was found to be Rs. 32.4/mmHg and Rs. 6.16/ mmHg for latanoprost and timolol, respectively.

Since treatment with latanoprost was both more expensive and more effective than its comparator timolol, so in this condition ICER was calculated which determined the additional cost paid for each unit of additional fall in IOP by latanoprost as compared to timolol.

The calculated ICER value was Rs. 68.2. This means that for each unit of additional fall in IOP obtained with latanoprost, the patient has to pay an additional amount of Rs. 68.2, but this was more than the patient's willingness to pay. Therefore, on the basis of ICER, timolol was considered more cost effective as compared to latanoprost. Our study results were consistent to study findings done by Holmstrom *et al*.,[30] Day *et al*.,[31] and Lachaine *et al*.[32]

CONCLUSION

Hence, we conclude that although latanoprost has higher IOP lowering efficacy as compared to timolol, still considering the economic conditions of the patients in a developing country like India, we recommend that the management of glaucoma should be initiated with timolol, as it is quite effective and affordable to the patients and latanoprost should be reserved as the add on drug in patients in whom target IOP is not achieved by timolol monotherapy or in case of any contraindication to the use of timolol.

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