ORIGINAL ARTICLE

Comparative Effect of Timolol, Levobunolol and Betaxolol on IOP in Patients of Chronic Simple Glaucoma

Rashmi Sharma, Kamlesh Kohli, Bhuvneshwar Kapoor, R. K. Mengi*, P. Sadotra*, Ujala Verma

Abstract

In this prospective randomized parallel study we compared the effects of topical timolol maleate, levobunolol hydrochloride and betaxolol hydrochloride on intraocular pressure (IOP) in the patients of primary open angle glaucoma after 16 weeks of instillation as 1 drop 12 hourly in 0.5% concentration. 23 eyes of 16, 19 eyes of 12 and 20 eyes of 12 patients were included in timolol, levobunolol and betaxolol groups respectively. Timolol, levobunolol and betaxolol lowered IOP by 13.05 ± 1.53, 14.05 ±1.47 and 7.58 ± 0.90 mm of Hg respectively after 6weeks and by16.12±1.67,16.28 ±1.85 and 8.535 ± 0.983 mm of Hg respectively after 16 weeks (P<0.001). Both levobunolol and timolol produced greater reduction in IOP than betaxolol (P<0.001). The results of our study indicated that betaxolol is less efficacious in lowering IOP in Indian patients and could only be preferred over timolol in glaucoma patients with associated chronic obstructed pulmonary disease (COPD) or bronchial asthma. However, Levobunolol could be a better alternative to timolol , as being a longer acting agent with IOP control for 24 hrs after single instillation and can be used as once a day instillation with better safety profile.

Key Words

IOP, Glaucoma, Levobunolol, Betaxolol, Non-contact tonometer, Timolol

Introduction

The glaucomas are a family of "silent diseases" at least until the later stages and if not treated, invariably result in irreversible blindness. The early detection and adequate treatment minimizes the visual morbidity from these conditions. The current management of glaucoma is directed to lower IOP (intraocular pressure) and the medical therapy is always the first line treatment for the management of primary open angle glaucoma. The most frequently used medical treatment in lowering IOP is a topical ß-blocker. The introduction of timolol in 1978, was a milestone in ocular pharmacology as it has several advantages over cholinergic and adrenergic agonists (1). However, continued clinical experience with it has disclosed various potentially serious systemic effects with its topical use. These potential cardiovascular, pulmonary and metabolic systemic effects limited its usefulness in some patients (2). Moreover, the patients of glaucoma may have to continue ocular ß–blockers during several decades of adult life and are thereby exposed to the systemic and metabolic effects of the therapy for many years. The wide range of these adverse reactions may result from the nonselective inhibition of both $ß_1$&$ß_2$ adrenergic receptors (3). Till date, timolol maleate remains the most widely prescribed drug for elevated IOP (4). The continued search for relatively safer compounds led to the introduction of many new compounds like betaxolol and levobunolol. Betaxolol is a

From The Postgraduate Department of Pharmacology & Therapeutics and *Ophthalmology, Govt. Medical College, Jammu (J&K).
Correspondece to: Dr. Rashmi Sharma, Sr. Demonstrator, P.G Deptt. of Pharmacology & Therapeutics, Govt. Medical College, Jammu.

cardioslective $ß_1$–blocker and levobunolol is a nonselective ß–blocker with long duration of action (5,6). These were introduced recently in our country for the management of raised IOP .As not much work has been reported on these drugs in Indian patients so we compared the efficacy of two new therapeutic options betaxolol and levobunolol with conventional timolol in lowering IOP in patients of primary open angle glaucoma.

Materials and Methods

The study was conducted in the Postgraduate Department of Pharmacology and Therapeutics in collaboration with Postgraduate Department of Ophthalmology, Government Medical College Jammu in a prospective randomized parallel design after taking permission from institutional ethics committee. Forty newly diagnosed patients of primary open angle glaucoma of both the sexes in the age group of 40 to 80 years with IOP of 26 mm of Hg and more were included in the study after complete screening for exclusion criteria like hypersensitivity to either oral or topical use of timolol, betaxolol and levobunolol, ophthalmic surgical procedures within three months of the study, bronchial asthma or chronic obstructive pulmonary disease, sick sinus syndrome, sinus bradycardia, 2nd or 3rd degree heart block, congestive heart failure, myocardial infarction, diabetes mellitus, myasthenia gravis, any systemic malignancy ,liver or renal diseases, psychiatric problems and use of more than one intraocular pressure lowering drugs. Written informed consent was obtained from all the patients. The patients were randomized to receive timolol maleate 0.5% or levobunolol hydrochloride 0.5% or betaxolol hydrochloride 0.5% as 1drop 12 hourly instillation. Twenty-three eyes of 16, 19 eyes of 12 and 20 eyes of 12 patients were assigned to timolol, levobunolol and betaxolol group respectively. Each patient was kept under treatment for 16 weeks and had to undergo three post–registration visits at 0, 6 and 16 weeks. During each visit, visual acuity and IOP were recorded. Visual acuity (distant) was measured with Snellen's test types. For near vision, visual acuity at the ordinary reading distance was accessed by using reading test types of varying sizes, the notation being based on the printers "point" systems. The IOP was recorded during each visit with the help of a non-contact tonometer (the air-puff tonometer). This tonometer was introduced by Grolman in 1972 (7). It uses the Goldmann applantation principle, but instead of using a prism the central part of the cornea is flattened by a jet of air .The time required to sufficiently flatten the cornea relates directly to the level of IOP. This tonometer is based on Imbert-Fick's law which states that pressure (P) within a sphere is roughly equal to the external force (F) needed to flatten a portion of the sphere divided by the area (A) of the sphere flattened (P=F/A). It has an advantage, as no topical anesthesia is required. The effects of the three drugs on IOP were statistically analysed using paired t-test and analysis of variance was used to compare the effects of three drugs. Inter group comparison was done by using unpaired t-test. P-value< 0.05 was considered statistically significant.

Observations

Timolol, levobunolol and betaxolol produced significant reduction in IOP both after 6 weeks and 16 weeks of topical use (P<0.001) (Table 2, Fig. 1). After applying ANOVA a statistically significant difference was found among these three groups both after 6 weeks and 16 weeks (Table 3, Fig. 2). Both levobunolol and timolol produced more reduction in IOP than betaxolol both after 6 weeks and 16 weeks (P value<0.001). No change in visual acuity was observed during the study in any of the groups.

Table. 1 Patients Characteristic

S. No.			
Mean age ± S.D (years)			
Mean			

PR=Pulse Rate, SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure, IOP=Intraocular Pressure.

Table. 2 Effects of Timolol (n=23), Levobunolol (n=19) and Betaxolol (n=20) on IOP

Visits	Timolol group: Mean IOP (mm of Hg) (mean± S.E.M)	Levobunolol group: Mean IOP (mm of Hg) (mean± S.E.M)	Betaxolol group: Mean IOP (mm of Hg) (mean± S.E.M)
0 wk	33.82±1.59	33.45±1.99	33.48±1.06
6wks	20.90±0.97*	19.39±1.21*	25.895±1.14*
16wks	18.40±0.77*	17.16±0.93*	24.945±1.33*

*P value<0.001.

Table. 3 Comparative effects of Timolol (n=23), Levobunolol (n=19) and Betaxolol (n=20) on IOP

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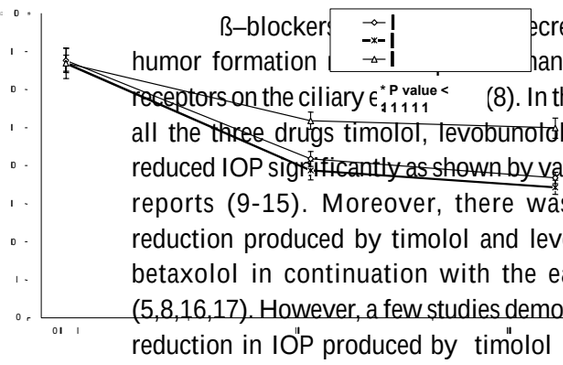
*Computed F.ratio >3.15 (Table F.ratio)
After applying ANOVA a statistically significant difference was found among the three groups .
Timolol Vs betaxolol=Pvalue<0.001.
Timolol Vs levobunolol=Pvalue>0.05.

Fig. 1. Effects of 0.5% Timolol (n = 23), 0.5% Levobunolol (n = 19) and 0.5% Betaxolol (n=20) on IOP.



Discussion

ß–blockers decreasing aqueous humor formation mainly through $ß_2$-receptors on the ciliary epithelium (8). In the present study all the three drugs timolol, levobunolol and betaxolol reduced IOP significantly as shown by various published reports (9-15). Moreover, there was greater IOP reduction produced by timolol and levobunolol than betaxolol in continuation with the earlier reports (5,8,16,17). However, a few studies demonstrated similar reduction in IOP produced by timolol and betaxolol which could be attributed to the fact that these studies were of longer duration that might have resulted in the

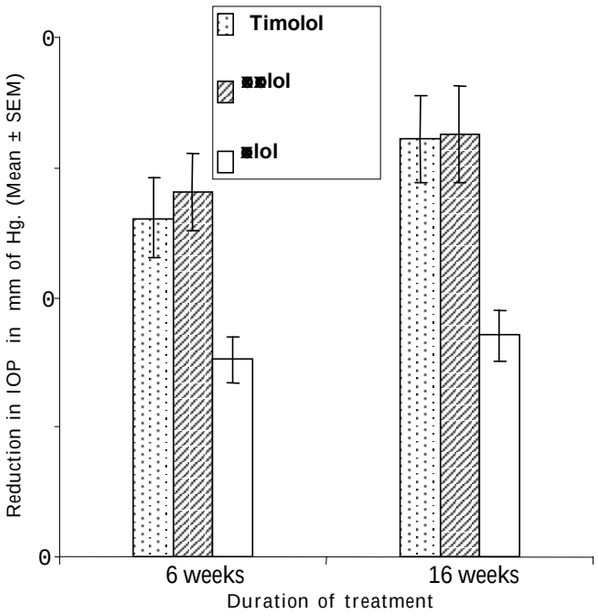


Fig. 2 Comparative effects of 0.5% Timolol (n = 23), 0.5% Levobunolol (n = 19) and 0.5% Betaxolol (n = 20) on IOP

decreased efficacy of timolol; as the phenomenon of "long term drift" is well known with timolol (3,18,1). Moreover, in the study conducted by Berry P. David.et al. (1984) (3) both the drugs were used in adjunctive therapy with pilocarpine, which might have blunted the actual effect of both timolol and betaxolol .A few studies demonstrated greater reduction in IOP with 0.5% levobunolol than 0.5% timolol in contrary to the present study (12,8). Wandel, Thaddeus and co-workers(1986) (12) used 0.5 % levobunolol and 0.5% timolol as once daily instillation (in the morning) and the IOP was measured before the instillation of drug during each follow- up visit (during the study), which might have resulted in reported greater reduction in IOP with levobunolol than timolol as levobunolol is a longer acting drug with efficient ocular hypotensive control for 24 hours after instillation. However, West R. David et al compared the effects of levobunolol and timolol on IOP in post-operative patients with eyes in hyper-metabolic state. As levobunolol has major metabolite "Dihydro-levobunolol", which is equipotent to levobunolol, so it produced greater reduction in IOP than timolol in the above study (8,19).

Conclusion

Betaxolol is less efficacious than timolol in lowering IOP and should only be preferred over timolol in glaucoma patients with associated COPD or bronchial asthma because of its beta-1 selectivity. However, levobunolol could be a better alternative to timolol, as being a longer acting agent with IOP control for 24 hrs after single instillation, it can be used as once a day instillation with better safety profile; as once a day instillation will further decrease its plasma concentration achieved after topical use. Although, further studies are required to confirm its safety and efficacy after once a day instillation.

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