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ORIGINAL ARTICLE / RESEARCH

Effect of Topical Timolol and Betaxolol on Plasma Lipids in Indian Patients of Primary Open-Angle Glaucoma

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ABSTRACT

Background: The β-blockers adversely affect plasma lipids.
Aim: To evaluate the effect of topical timolol and betaxolol on plasma lipids.
Setting and Design: The present prospective randomised single-blind parallel study was conducted in Postgraduate Department of Pharmacology and Therapeutics in collaboration with Postgraduate Department of Ophthalmology of a medical college.
Materials and Methods: Sixteen (23 eyes) and 12 (20 eyes) patients of primary open-angle glaucoma with intraocular pressure (IOP) more than 26 mmHg were randomised to receive timolol maleate 0.5% and betaxolol hydrochloride 0.5%, respectively, as one drop twice a day instillation for 12 weeks. Lipid profile and IOP of each patient were recorded at 0, 6 and 12 weeks. Plasma lipids were estimated by standard method using photoelectric colorimeter.
Statistical Analysis: Effects of the individual drug on study parameters were analysed by using student's paired t-test, and inter-group comparison was done by using unpaired t-test. P-value ≤0.05 was considered statistically significant; 95% confidence intervals (CI) were calculated according to the standard procedures laid down.
Results: In the present study, topical timolol raised total cholesterol by 17.50 ± 2.69 mg% ($p < 0.0001$), LDL cholesterol by 16.27 ± 2.48 mg% ($p < 0.0001$), TG cholesterol by 14.56 ± 2.58 mg% ($p = 0.0002$), VLDL cholesterol by 2.91 ± 0.51 mg% ($p = 0.0002$), TC:HDL by 0.56 ± 0.07 ($p < 0.0001$), LDL:HDL by 0.47 ± 0.11 ($p < 0.0001$) and reduced HDL cholesterol by 1.68 ± 0.07 mg% ($p = 0.035$) after 12 weeks, while topical betaxolol produced insignificant effect on plasma lipids. Topical timolol and betaxolol lowered IOP by 13.05 ± 1.53 and 7.58 ± 0.90 mmHg, respectively, after 6 weeks and by 16.12 ± 1.67 and 8.535 ± 0.983 mmHg, respectively, after 12 weeks ($p < 0.001$).
Conclusions: In the present study, topical instillation of betaxolol was found to be superior to topical timolol with better safety profile (plasma lipids).
Key words: Plasma lipids, topical ß-blockers, glaucoma therapy

Introduction

The introduction of topical timolol – a non-selective β-adrenergic antagonist – as a treatment in open-angle glaucoma in 1978 was a milestone in the ocular pharmacology, as it has several advantages over cholinergic and adrenergic agonists. However, continued clinical experience has disclosed various potentially serious systemic effects with its topical use because of its absorption into the systemic circulation through the naso-lacrimal duct. Moreover, its plasma levels thus achieved may be equivalent to that obtained after intra-venous administration, as 50–70% of the drug escapes

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first pass metabolism [1],[2]. These systemic effects after topical use of β-blockers may be of clinical significance in the elderly who commonly have undiagnosed reversible airway diseases, cardiovascular diseases and metabolic abnormalities, especially dyslipidaemia.

Advanced age, diabetes mellitus, hypertension, positive family history and obesity are known risk factors for both chronic heart disease (CHD) and increased intraocular pressure (IOP) [3],[4]. Serum lipids are additionally related to the risk of atherosclerosis. However, no association has been established so far between lipid levels and IOP. Still serum lipid fractions may be important in the chronic therapy of glaucoma, as the glaucoma patients may continue ocular β-blockers during several decades of adult life and are thereby exposed to the systemic and metabolic effects of such therapy for many years. Timolol and betaxolol are commonly used drugs for the management of glaucoma in our country. Betaxolol is a cardio-selective β_1-adrenergic antagonist with the theoretical advantage of better corneal penetration, fewer systemic effects and excellent lipid aqueous solubility with twice as high concentration in aqueous humor as that of timolol and much lower concentration in plasma [2],[5],[6]. However, only a few studies are available demonstrating significant effect of topical timolol on serum lipids [7],[8]. Moreover, no study so far has come to our notice comparing the effects of topical timolol and betaxolol on plasma lipids in the Indian patients of glaucoma, so we conducted the present study to evaluate the effect of topical timolol and betaxolol on plasma lipid in Indian patients of primary open-angle glaucoma.

Materials and Methods

This study has been described according to the CONSORT guidelines for the presentation of clinical trials. This prospective randomised single-blind parallel study was conducted in the Postgraduate Department of Pharmacology and Therapeutics in collaboration with Postgraduate Department of Ophthalmology, Government Medical College Jammu, after taking permission from the institution's ethics committee. Sample size for the study was not definitely set before study, as it was not certain how many patients of chronic simple glaucoma attending Ophthalmology Department during the study period would be fulfilling all the inclusion criteria for the study. Total of 34 newly diagnosed patients of both sexes with 52 eyes of primary open-angle glaucoma in the age group of 40–80 years, having painless diminution of vision, glaucomatous optic disc damage and IOP more than 26 mmHg, attending ophthalmology OPD (out patient department) during the period from 01.04.2003 to 31.10.03, were initially enrolled for the study after taking their informed consent. All the patients were subjected to detailed medical and ophthalmic history; complete medical and ocular examination; haematological tests like Hb, BT, CT, TLC, DLC, ESR; biochemical tests – LFT, RFT, blood sugar fasting, urine for routine examination; and ECG.

Only 28 patients (43 eyes) ([Table/Fig 1]) were included in the study after complete screening for all the exclusion criteria such as history of hypersensitivity to either oral or topical use of timolol and betaxolol; ophthalmic surgical procedures within 3 months of the study; history of bronchial asthma or chronic obstructive pulmonary disease or bronchospastic disorder; cardiac dysfunction including sick sinus syndrome, sinusbradycardia, second- or third-degree heart block, congestive heart failure and myocardial infarction within last 6 months; diabetes mellitus; dyslipidaemias; myasthenia gravis; any systemic malignancy; liver and renal diseases; psychiatric problems; and use of more than one IOP-lowering drugs or concomitant use of any other medication. During first post-registration visit at 0 week, baseline lipid profile and IOP of all the patients were recorded. Finally, 16 (23eyes) and 12 (20 eyes) patients were randomised to receive timolol maleate 0.5% and betaxolol hydrochloride 0.5%, respectively. Timolol maleate 0.5% (Iotim® – F.D.C. Ltd) and betaxolol hydrochloride 0.5% (Optipress® – Cipla) for the study were purchased from the market. Both the study drugs were available in white plastic containers of equal size. Before providing drugs to the patients, the cover labels on the bottles were removed and replaced by paper slips containing study code.

Each patient was advised to instil one drop of only the dispensed drug in the affected eye twice daily after occlusion of naso-lacrimal duct and was kept under treatment for 12 weeks ([Table/Fig 2]). Each patient had to undergo two more post-registration visits, first after 6 weeks

and second after 12 weeks. Patients were instructed not to change their dietary habits and life style during the study. Patient's compliance was assessed by asking the patients to maintain personal diary in which they were to note down time and date of each instillation.

Table/Fig 1: Patient characteristics

SN (mean ± SD)	Timolol (*n* = 16)	Betaxolol (*n* = 12)
Age (years)	57.88 ± 16.66	61.5 ± 10.83
Male:female	11:5	7:5
IOP (mmHg)	33.82 ± 9.17	30.48 ± 4.05
TC (mg%)	176.12 ± 22.08	187.66 ± 23.09
TG (mg%)	140.75 ± 55.10	146.75 ± 31.84
VLDL (mg%)	28.15 ± 11.02	29.35 ± 6.36
LDL (mg%)	100.97 ± 23.27	111.65 ±24.99
HDL (mg%)	47 ± 7.53	46.66 ± 8.67
LDL:HDL	2.21 ± 0.68	2.42 ± 0.77
TC:HDL	3.82 ± 0.73	4.14 ± 0.88

Both timolol and betaxolol groups are statistically comparable ($p > 0.05$).

IOP = intra-ocular pressure; TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; HDL = high-density lipoprotein; SD = standard deviation, *n* = number of patients.

IOP and lipid profile of each patient were recorded during each visit in the morning just before the instillation of the drug (morning dose). Plasma lipids were estimated by photoelectric colorimeter (electronic controlled 5 filter/8 filter model).

Method of calculation

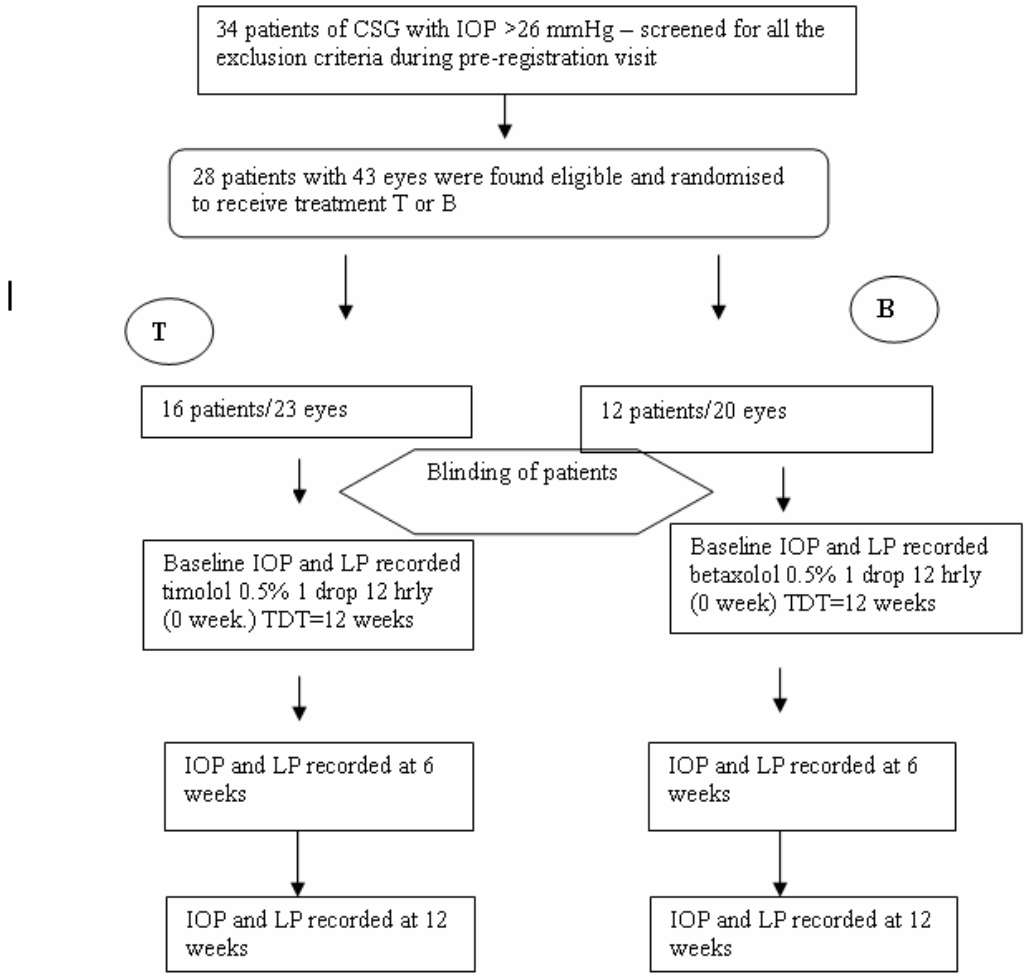
The reagents were prepared according to the manufacturer's instructions given in the kits. Three test tubes were labelled as blank (B), standard (S) and test (T). One millilitre (1000 µl) of reagent was taken in each of the tubes and pre-warmed at 37°C for at least 5 minutes; 0.01 ml (10 µl) of patient's serum was taken in tube labelled 'T' for total cholesterol (TC), triglyceride (TG), and low-density lipoprotein (LDL) estimation and 0.05 ml for high-density lipoprotein (HDL) estimation. Similar quantities of standard and blank solutions were put in the respective tubes. All the tubes were incubated for 5 minutes at 37°C. Reagent blank (B) was used to set the spectrophotometer at the respective wavelengths. Green filter was used. Absorbance of all the three tubes was recorded and calculations were done as

$$\text{Concentration of unknown solution} = \frac{\text{absorbance of unknown} \times \text{conc. of standard}}{\text{absorbance of standard}}$$

TC was estimated by cholesterol oxidase peroxide method (CHOD/POD method) using cholesterol reagent set provided by Pointe Scientific INC., TG by using Clinichem Triglycerides (fluid stable) kit procured from Cadila Health care Ltd., HDL by HDL cholesterol kit from Dr. Reddy's Lab., LDL by LDL cholesterol kit (Quali TEST) procured from Rashmi Diagnostic Pvt. Ltd., and very low-density lipoprotein (VLDL) by using the FRIEDWALD'S formula (VLDL = TG/5); LDL/HDL and TC/HDL ratios were estimated from the values obtained above. IOP was recorded during each visit with the help of the air-puff applanation tonometer on pulse air-200, non-contact tonometer (canon T_2). As effect on IOP was not the main outcome of the study, non-contact tonometer was used to record IOP in order to increase patient's compliance, as it is patient friendly and less time consuming.

Statistical Analysis

Effect of the individual drug on plasma lipids and IOP in comparison to the baseline values was analysed by using student's paired *t*-test, and inter-group comparison of the effect on IOP was done by using unpaired *t*-test. *P*-value ≤ 0.05 was considered statistically significant; 95% CIs were calculated according to the standard procedures laid down. Each parameter was expressed in mean ± SD (standard deviation) or mean ± SEM (standard error of mean). Each eye was considered as a separate unit for calculation in case of IOP and each patient was considered as a unit for calculation in case of lipids. Effects of both the topical drugs, used in the study, on the plasma lipids were measured as primary outcome variables. However, secondary variables like risk of coronary artery disease could not be calculated because of short duration of the study.



[Table/Fig 2] Flow chart showing study design. CSG = chronic simple glaucoma; IOP = intraocular pressure; LP = lipid profile; TDT = total duration of therapy; hrly = hourly; T = timolol group; B = betaxolol group.

Results

In the present study, topical timolol and betaxolol produced insignificant change in plasma lipid levels after 6 weeks of the study. Topical timolol produced significant rise in TC ($p < 0.0001$), LDL cholesterol ($p < 0.0001$), TG cholesterol ($p = 0.0002$), VLDL cholesterol ($p = 0.0002$), TC:HDL ($p < 0.0001$) and LDL:HDL ($p < 0.0001$) and a reduction in HDL cholesterol ($p = 0.035$) after 12 weeks of therapy ([Table/Fig 3]). Whereas, topical betaxolol produced insignificant effect on plasma lipids even after 12 weeks of the therapy ([Table/Fig 3]).

Topical timolol and betaxolol lowered IOP by 13.05 ± 1.53 (CI = 9.77–16.33) and 7.58 ± 0.90 mmHg (CI = 5.69–9.47), respectively, after 6 weeks and by 16.12 ± 1.67 (CI = 12.56–19.68) and 8.535 ± 0.983 mmHg (CI = 6.48–10.58), respectively, after 12 weeks ($p < 0.001$) ([Table/Fig 4]). No adverse effect was reported in any of the group.

Table/Fig 3: Effects of 0.5% timolol (*n* = 16) and 0.5% betaxolol (*n* = 12) on plasma lipids

Plasma lipid (mean ± SEM)	0 week	6 weeks	12 weeks	*P*-value using two-tail *t*-test between 0 and 12 weeks
Effect of timolol				
TC (mg%)	176.125 ± 5.521	176.18 ± 5.549	193.625 ± 6.183 (11.77–23.23)†	<0.0001*
TG (mg%)	140.75 ± 13.77	140.725 ± 13.774	155.31 ± 14.49 (9.052–20.07)†	0.0002*
LDL (mg%)	100.975 ± 5.819	100.96 ± 5.829	117.25 ± 6.467 (10.98–21.56)†	<0.0001*
VLDL (mg%)	28.15 ± 2.75	28.142 ± 2.755	31.062 ± 2.893 (1.81–4.01)†	0.0002*
HDL (mg%)	47 ± 1.884	46.956 ± 1.846	45.31 ± 2.02 (1.52–1.84)†	0.0351*
LDL:HDL	2.214 ± 0.171	2.213 ± 0.171	2.683 ± 0.212 (0.25–0.69) †	<0.0001*
TC:HDL	3.829 ± 0.183	3.831 ± 0.182	4.394 ± 0.233 (0.39–0.73)†	<0.0001*
Effect of betaxolol				
TC (mg%)	187.66 ± 6.66	187.708 ± 6.727	189.91 ± 6.47 (2.90–7.43)†	0.780
TG (mg%)	146.75 ± 9.191	145.75 ± 9.191	148 ± 8.83 (0.45–2.05)†	0.840
LDL (mg%)	111.65 ± 7.214	111.69 ± 7.212	109.85 ± 7.12 (0.75–2.85)†	0.839
VLDL (mg%)	29.35 ± 1.838	29.34 ± 1.834	29.40 ± 1.76 (–0.23–0.33)†	0.840
HDL (mg%)	46.66 ± 2.505	46.66 ± 2.505	47.76 ± 2.50 (0.93–1.27)†	1.000
LDL:HDL	2.423 ± 0.222	2.418 ± 0.222	2.49 ± 0.238 (–0.02–0.26)†	0.526
TC:HDL	4.140 ± 0.256	4.135 ± 0.252	4.138 ± 0.258 (–0.08–0.01)†	0.315

*****Statistically significant difference.

†CI (95% confidence interval of difference in levels between 0 and 12 weeks).

TC = total cholesterol; TG = triglycerides; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein; HDL = high-density lipoprotein; SEM = standard error of mean; 0 week = baseline values; 6 weeks = values after 6 weeks of therapy; 12 weeks = values after 12 weeks of therapy; *n* = number of patients.

Table/Fig 4: Comparative effects of timolol (*n* = 23) and betaxolol (*n* = 20) on IOP

Visit (weeks)	Mean reduction in IOP (mmHg) in timolol group (mean ± SEM)	Mean reduction in IOP (mmHg) in betaxolol group (mean ± SEM)	*P*-value (CI)
6	13.05 ± 1.53	7.58 ± 0.90	<0.001 (2.45–13.39)†
12	16.12 ± 1.67	8.53 ± 0.98	<0.001 (3.33–11.85)†

†CI (95% confidence interval of difference in reduction in IOP produced by timolol and betaxolol)

SEM = standard error of mean; 6 weeks = values after 6 weeks of therapy; 12 weeks = values after 12 weeks of therapy; *n* = number of patients; IOP = intraocular pressure.

Discussion

The β-blockers adversely affect plasma lipids by inhibiting enzyme lipoprotein lipase; moreover, β-blockade is also accompanied by increase in α-adrenergic tone, which further lowers lipoprotein lipase activity [4],[9–11]. However, certain β-blockers also tend to reduce insulin sensitivity, which in turn lowers lipoprotein lipase activity and increases lecithin-cholesterol activity (LCAT), thereby elevating HDL cholesterol by suppressing the HDL–LCAT cycle [11]. In our study, topical timolol produced a rise in TC of 10%, LDL cholesterol of 16%, TG cholesterol of 10%, and VLDL cholesterol of 10% and a reduction in HDL cholesterol of 4%, after 12 weeks of study. The present study also demonstrated a significant rise in LDL:HDL and TC:HDL cholesterol ratios in timolol group after 12 weeks of the study. These findings are in conformity with the results of previous reports. Coleman and associates were first to observe an increase of 12% in TG, a decrease of 9% in HDL cholesterol and an increase of 8% in TC:HDL cholesterol after topical administration of timolol [7]. Then, Freedman and associates demonstrated a reduction of 8% in HDL cholesterol and a rise of 10% in TC:HDL cholesterol with timolol after its topical use [8]. Yamamoto et al. and Stewart et al. demonstrated a statistically significant fall in HDL cholesterol and a rise in TC:HDL cholesterol after topical timolol therapy [4],[12]. In a study from India, topical instillation of 0.5% timolol maleate in 25 patients produced significant decrease in HDL levels after 2 months of therapy [13]. In this study, levels of LDL, VLDL and TG were also increased, but the changes were not statistically significant.

However, a previously reported study demonstrated no significant change in TC, HDL cholesterol and TG levels after instillation of timolol 0.5% twice daily for 15 weeks [14]. Similarly, in another population-based study from Sydney (1992–1994), no statistically significant differences were found in any blood lipid mean levels between 63 people who had used topical timolol for at least 1 year and 2597 nonusers [15]. However, male timolol users had a mean value of HDL cholesterol 0.13 mmol/L (11%) lower then the mean value of male nonusers [15].

Topical betaxolol produced statistically non-significant effect on lipid profile in the present study. The effect of oral betaxolol on plasma lipid levels is yet unclear. One study demonstrated no effect on lipid profile, whereas another demonstrated significant increase in levels of TC, LDL cholesterol and TG after betaxolol therapy [16],[17].

As primary-angle glaucoma and atherosclerosis both are fairly common diseases among elderly persons, any adverse change in serum lipids as a result of glaucoma therapy can increase the risk of CHD many folds. It has been seen that as low as 1% fall in cholesterol results into 2–3% fall in the rate of CHD [1],[18]. Again LDL is highly atherogenic as a result of its low binding affinity for the LDL receptors, prolonged $t_{1/2}$ and long resistance to oxidation [19],[20]. A 10% reduction in LDL can decrease the rate of CHD by 50% over 5 years, and a 10% increase in LDL can increase the risk of CHD by 20% [21],[22]. However, every 1 mg/dl increase in HDL can reduce the risk of CHD by 2–3% [1],[23]. Moreover, the ratio of LDL to HDL cholesterol provides a composite marker of risk, with the ratio below 3 indicating lower risk and above 5 indicating a higher risk of CHD [24]. It has been observed that LDL:HDL cholesterol ratio more than 5 is associated with a 19.2% chance of experiencing a CHD event in the next 8 years [25]. Even a reduction in TG has direct benefit on CHD risk and its desirable levels are less than 200 mg% in plasma [25],[26], [27]. By extending the above analysis to 10% rise in TC, 16% rise in LDL and 4% decrease in HDL levels after 12 weeks of timolol therapy, a theoretical risk of 20–30%, 32% and 8–12%, respectively, for CHD could be suspected. However, the concentration of the drug reaching systemic circulation has direct influence on the lipid profile, but the selection of 23 eyes in 16 patients and 20 eyes in 12 patients in timolol and betaxolol group, respectively, was due to ethical constrains, and hence study drugs were only instilled in the glaucomatous eyes and not in the healthy eyes of the patients. Moreover, the present study was carried out on patients of chronic simple glaucoma without any cardiac or metabolic abnormality or concomitant use of any medication known to affect plasma lipids; thus, many-fold increase in risk of CHD could be suspected in the actual scenario of clinical practice in presence of other risk factors like

hypertension, cigarette smoking, diabetes mellitus, dyslipidaemias, etc.

Nonetheless, reasonable concern remains that lipid changes induced by topical β-blockers may be detrimental and could reduce the therapeutic benefits of these drugs, as seen with the use of diuretics and β-blockers in hypertensive patients to reduce incidence of CHD [7]. Moreover, this potentially atherogenic effect of ocular β-blockers may influence the choice of the glaucoma therapy, especially in younger patients who may require treatment for longer period of time [8]. In the present study, topical betaxolol was found to be superior to topical timolol with better safety profile. However, further studies with large sample size are required to rationally establish quantitative superiority of topical betaxolol over timolol drops in relation to systemic absorption and changes in serum lipid fractions after long duration of therapy.

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