

Research Article**Effect of Topical Betaxolol and Timolol on Plasma Cholesterol and Triglyceride Level in Primary Open-Angle Glaucoma of Indian Patients****Dr Rishendra Singh Sisodiya¹, Dr Abdulhamid S Mavli², Dr Chitrani Singh³**¹Assistant professor, Department of ophthalmology, Pacific institute of medical sciences, Udaipur, Rajasthan, India²Assistant professor, Department of PSM, Pacific institute of medical sciences, Udaipur, Rajasthan, India³Junior resident, Department of ophthalmology, Pacific institute of medical sciences, Udaipur, Rajasthan, India***Corresponding author**

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Abstract: Primary open angle glaucoma is the most common form of glaucoma. This type of glaucoma develops slowly and sometimes without noticeable sight loss for many years. It usually responds well to medication especially if caught early and treated. To evaluate the effect of topical timolol and betaxolol on plasma lipids particularly triglyceride and cholesterol level. Twenty patients (15 eyes) and ten patients (12 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 14 weeks. Lipid profile and IOP of each patient were recorded at 0, 6 and 14 weeks. Lipid profile was estimated in fasting condition by colorimetric method in semi automated biochemistry analyzer. In results the mean concentration of serum cholesterol(mg/dl), Triglyceride(mg/dl), HDL(mg/dl), VLDL(mg/dl) LDL(mg/dl) is 179 ± 8.8 , 166.32 ± 8.9 , 30.25 ± 6.6 , 33.26 ± 6.3 , 115.49 ± 6.8 respectively in timolol treated group at the end of 14 weeks as compared to 175.12 ± 7.2 , 146.32 ± 7.4 , 33.23 ± 5.4 , 33.26 ± 6.3 , 108.63 ± 6.8 in betaxolol treated group and the difference between them is found to be statistically significant (p-value is less than 0.05). Topical timolol and betaxolol lowered IOP by 13.05 ± 1.53 and 16.15 ± 1.43 , after 6 weeks and by 8.05 ± 1.63 and 9.12 ± 1.33 mmHg respectively, after 14 weeks (p > 0.05). In conclusion Topical application of betaxolol is superior and safe as compared to timolol.

Keywords: Plasma lipids, topical betaxolol, timolol, glaucoma

INTRODUCTION:

Primary open-angle glaucoma is described distinctly as a multifactorial optic neuropathy that is chronic and progressive, with a characteristic acquired loss of optic nerve fibers. Such loss develops in the presence of open anterior chamber angles, characteristic visual field abnormalities, and intraocular pressure that is too high for the continued health of the eye. It manifests by cupping and atrophy of the optic disc (see the image below), in the absence of other known causes of glaucomatous disease. Screening the general population for primary open-angle glaucoma is most effective if targeted toward those at high risk, such as African Americans and elderly individuals, especially if the screening consists of intraocular pressure measurements combined with assessment of optic nerve status. 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 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

The study was conducted at Shyam shah medical college and hospital, Rewa, MP, India from June 2007 to January 2008 in department of ophthalmology in collaboration with department of biochemistry.

Total of 38 newly diagnosed patients of both sexes with 55 eyes of primary open-angle glaucoma in the age group of 40–70 years, having painless diminution of vision, glaucomatous optic disc damage and IOP more than 26 mmHg, attending ophthalmology OPD (out patient department) after taking their informed consent. All the patients were subjected to detailed medical and ophthalmic history; complete medical and ocular examination; Blood investigation like CBC, LFT, RFT, blood sugar fasting, Lipid profile, urine for routine examination; and ECG. Only 30 patients (27 eyes) ([Table/Fig 1]) were included in the study after complete screening for all the exclusion criteria.

Exclusion criteria:

Patients 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, 20 (15 eyes) and 10 (12 eyes) patients were randomised to receive timolol maleate 0.5% and betaxolol hydrochloride 0.5%, respectively.

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 14 weeks ([Table/Fig 2]). Each patient had to undergo two more post-registration visits, first after 6 weeks and second after 14 weeks.

Blood Samples were collected in fasting state from all participants at the interval of 6 weeks and 14 weeks for estimation lipid profile Like Triglyceride, Cholesterol, HDL cholesterol, LDL cholesterol and VLDL cholesterol estimation.

Serum cholesterol was estimated by CHOD-PAP method, Triglyceride by GPO-PAP method and HDL by direct precipitation method by using transasia kit in semi automated biochemistry analyzer in ERBA CHEM 5 PLUS V2.

VLDL cholesterol is measured by calculation. (Friedwald Formula)

$VLDL = TG/5$

LDL is calculated from HDL and VLDL result. (Friedwald Formula)

$LDL = \text{Total cholesterol} - HDL - VLDL$

Statistical Analysis

Results obtained are analyzed statistically by calculating p-value by using online student t-test calculator.

Mean, SD (standard deviation) and SEM (standard error of mean) was calculated. p-value less than 0.05 was considered as a difference of significance.

RESULTS

In the present study, topical timolol and betaxolol produced significant change in plasma lipid levels after 6 weeks of the study. Topical timolol produced significant rise in TC ($p < 0.05$), LDL cholesterol ($p < 0.05$), TG ($p < 0.05$), VLDL cholesterol ($p < 0.05$) a reduction in HDL cholesterol ($p < 0.05$) after 14 weeks of therapy ([Table/Fig 1-3]). Whereas, topical betaxolol produced insignificant effect on plasma lipids even after 14 weeks of the therapy ([Table/Fig 1-3]).

Table 1: Age and sex wise distribution of participants along with lipid profile and IOP level at first visit

| Parameter | Timolol(n=20) | Betaxolol(n=10) |
|---------------------------------|---------------|-----------------|
| Age (year) | 56.12 ±3.5 | 61.12 ± 4.3 |
| Male: Female | 15:5 | 6:4 |
| IOP(Intraocular pressure)(mmhg) | 34.12 ±6.5 | 29.12 ±3.5 |
| Total cholesterol(mg/dl) | 173.12 ±8.9 | 178 ±10.9 |
| Triglyceride(mg/dl) | 143.32 ±8.9 | 146 ±9.2 |
| HDL cholesterol(mg/dl) | 36.23 ±5.6 | 31.21 ±5.9 |
| VLDL cholesterol(mg/dl) | 28.6 ±6.3 | 29.2 ±5.9 |
| LDL cholesterol(mg/dl) | 108.29±4.5 | 117 ±5.3 |

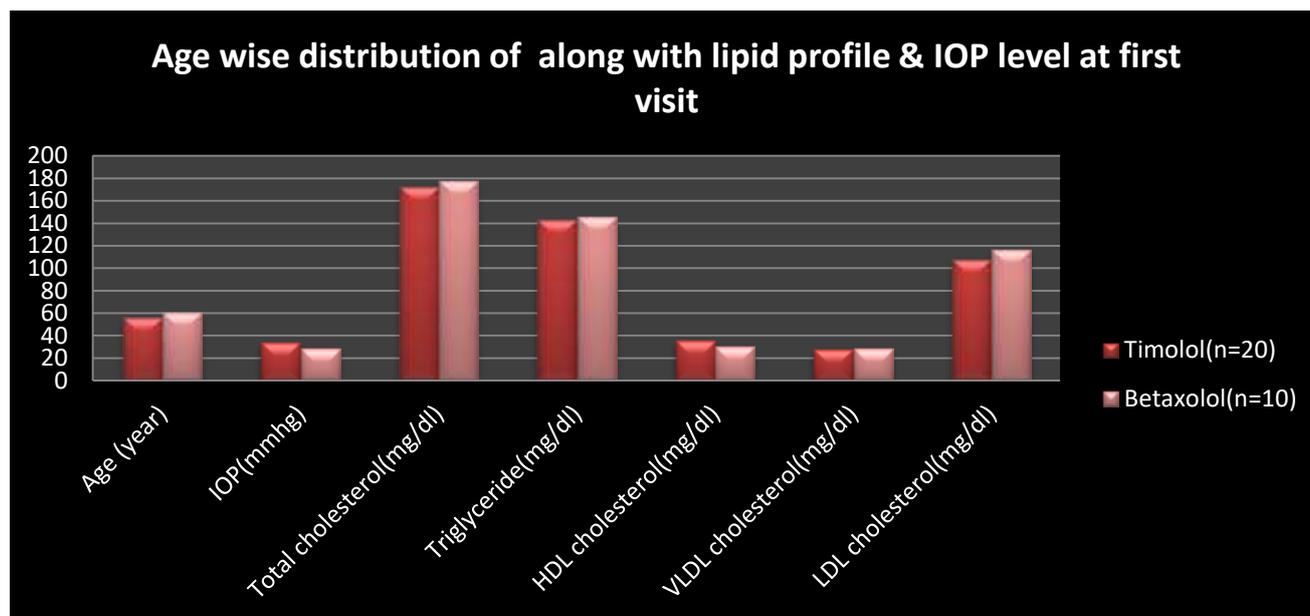


Fig- 1: Age wise distribution of participants along with lipid profile and IOP level at first visit

Topical timolol and betaxolol lowered IOP by 13.05 ± 1.53 and 16.15 ± 1.43, after 6 weeks and by 8.05 ± 1.63 and 9.12 ± 1.33mmHg respectively, after

14 weeks (p >0.05) ([Table- 4]). No adverse effect was reported in any of the group.

Table 2: Comparison of effect of tropical timolol on lipid profile at 0 weak,6 weak and 14 weak interval

| Parameter | 0 weak | 6 weak | 14 weak | p-value(between 0 weak and 6 weak) |
|--------------------------|-------------|-------------|-------------|------------------------------------|
| Total cholesterol(mg/dl) | 173.12 ±8.9 | 176.11 ±7.8 | 179 ±8.8 | <0.05(Significant) |
| Triglyceride(mg/dl) | 143.32 ±8.9 | 146 ±6.8 | 166.32 ±8.9 | <0.05(Significant) |
| HDL cholesterol(mg/dl) | 36.23 ±5.6 | 38.23 ±9.6 | 30.25 ±6.6 | <0.05(Significant) |
| VLDL cholesterol(mg/dl) | 28.6 ±6.3 | 29.2 ±4.3 | 33.26±6.3 | <0.05(Significant) |
| LDL cholesterol(mg/dl) | 108.29 ±4.5 | 108.68 ±5.5 | 115.49±6.8 | <0.05(Significant) |

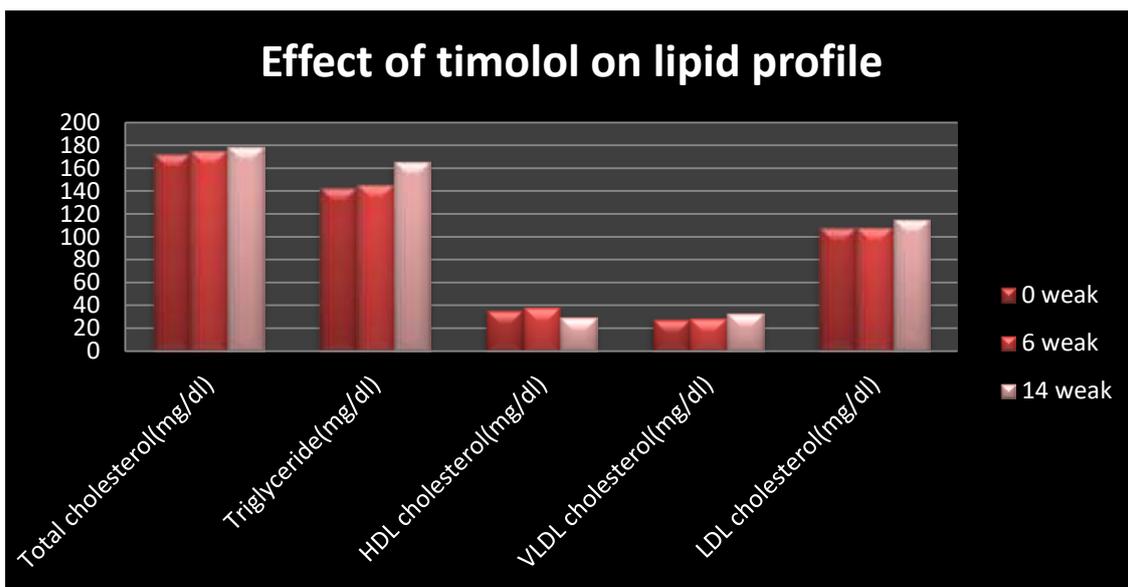


Fig- 2: Graphical presentation of effect of tropical timolol on lipid profile at 0 weak,6 weak and 14 weak interval

Table 3: Comparison of effect of tropical Betoxolol on lipid profile at 0 weak,6 weak and 14 weak interval

| Parameter | 0 weak | 6 weak | 14 weak | p-value(between 0 weak and 6 weak) |
|--------------------------|--------------|--------------|--------------|------------------------------------|
| Total cholesterol(mg/dl) | 173.12 ± 8.9 | 172.11 ± 7.8 | 175.12 ± 7.2 | >0.05(Non Significant) |
| Triglyceride(mg/dl) | 143.32 ± 8.9 | 144 ± 6.7 | 146.32 ± 7.4 | >0.05(Non Significant) |
| HDL cholesterol(mg/dl) | 36.23 ± 5.6 | 35.9 ± 9.6 | 33.23 ± 5.4 | >0.05(Non Significant) |
| VLDL cholesterol(mg/dl) | 28.6 ± 6.3 | 28.8 ± 4.3 | 33.26 ± 6.3 | >0.05(Non Significant) |
| LDL cholesterol(mg/dl) | 108.29 ± 4.5 | 107.41 ± 5.5 | 108.63 ± 6.8 | >0.05(Non Significant) |

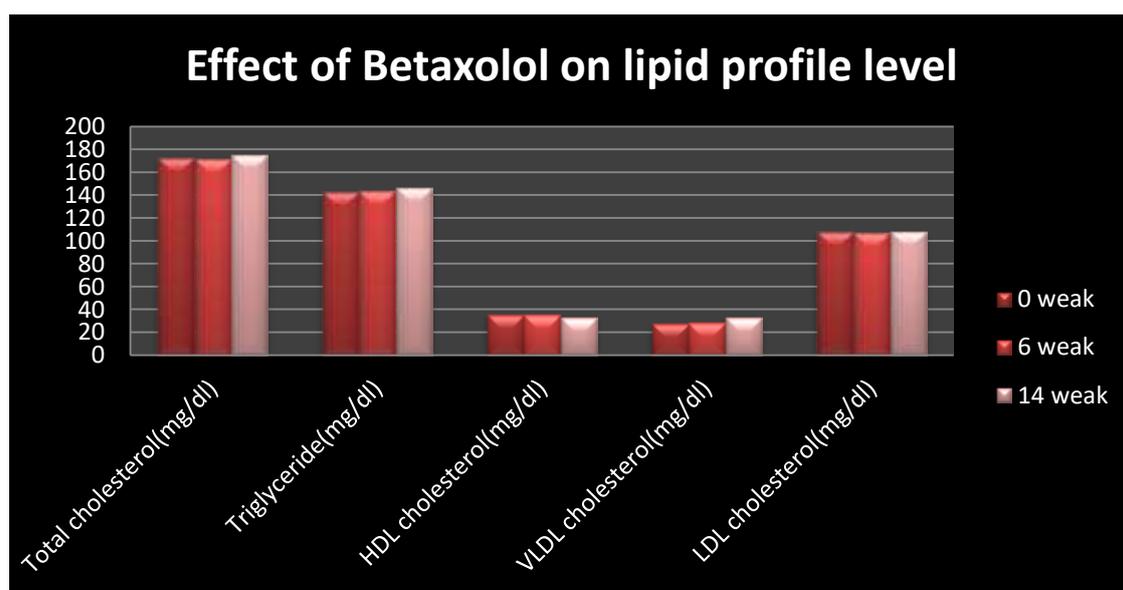


Fig-3: Graphical presentation of effect of tropical Betoxolol on lipid profile at 0 weak,6 weak and 14 weak interval

Table 4: Comparative effects of timolol (n = 20) and betaxolol (n = 10) on IOP

| Visit | Mean reduction in (IOP mmHg) in timolol group (mean \pm SEM) | Mean reduction in (IOP mmHg) in Betoxolol group (mean \pm SEM) | p-value |
|-------|--|--|---------|
| 6 wk | 13.05 \pm 1.53 | 8.05 \pm 1.63 | >0.05 |
| 14 wk | 16.15 \pm 1.43 | 9.12 \pm 1.33 | >0.05 |

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]. The present study also demonstrated a significant rise in LDL: HDL and TC: HDL cholesterol ratios in timolol group after 14 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 than 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]. 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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