

# Serum Lipid Profiles of Primary Open Angle Glaucoma Patients Treated with Topical Timolol

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## Introduction:

Among the blood lipids, low-density lipoprotein (LDL) is atherogenic & high-density lipoprotein (HDL) is protective against coronary heart disease (CHD).<sup>1-5</sup> A correlation between the severity of CHD and the blood levels of both HDL and LDL cholesterol has been consistently observed. A high level of HDL cholesterol is associated with a less severe and reduced risk of CHD; the inverse is true for a low level of HDL cholesterol.<sup>6-8</sup> It has been seen that as low as a 1% fall in cholesterol results in a 2-3% fall in the rate of CHD.<sup>9-11</sup> Glaucoma affects up to 2% of the world population over the age of 40 years and up to 10% over the age of 80 years.<sup>12-13</sup> Primary open-angle glaucoma (POAG) is the most

## Abstract:

### Background:

Primary open-angle glaucoma (POAG) and atherosclerosis both are fairly common diseases among elderly persons, any adverse changes in serum lipids as a result of glaucoma therapy can increase the risk of coronary heart disease many folds. As topical beta blockers are also widely used and often the first line therapy in many patients requiring treatment for glaucoma for a long time, there is also a possible risk that  $\beta$ -blockers such as timolol adversely affect serum lipid profiles.

### Objective:

The study aimed to evaluate the effect of topical timolol on serum lipid profiles.

### Methods:

This cross-sectional observational study was performed in the department of ophthalmology, Bangabandhu Sheikh Mujib Medical University With convenience type of sampling technique 40 patients with newly diagnosed cases of primary open-angle glaucoma were selected. Baseline fasting lipid profiles were estimated and then timolol maleate 0.5%, 1 drop 12 hourly in both eyes were prescribed. At follow-up after 4 and 12 weeks, again fasting lipid profiles were estimated of the same patients.

### Results:

In this study the baseline mean TC, HDL, LDL & TG were  $175.4 \pm 19.28$ ,  $46.63 \pm 5.33$ ,  $104.98 \pm 18.49$ ,  $120.48 \pm 28.30$  (mg/dl  $\pm$  SD) respectively. Baseline TC/HDL was  $3.81 \pm 0.06$ . At follow up after 4 weeks there were increased level of TC, LDL, TG, TC/HDL by 0.45% ( $P=0.822$ ), 0.8% ( $P=0.807$ ), 1.82% ( $P=0.375$ ), and 3.14% ( $P=0.307$ ) respectively and HDL level decreased by 2.68% ( $P=0.232$ ). At follow-up, after 12 weeks in comparison to baseline lipid levels, there was an increased level of TC, LDL, TG, and TC/HDL by 0.98% ( $P=0.959$ ), 3% ( $P=0.996$ ), 2.8% ( $P=0.104$ ), and 17.0% ( $P=0.001$ ) respectively and HDL level decreased by 13.61% ( $P=0.001$ ).

### Conclusion:

Topical timolol significantly lowers the plasma HDL level. Since the low level of HDL is strongly associated with an increased risk of myocardial infarction, our study cautions against the use of timolol in patients with a previous history of coronary heart disease.

**Keywords:** Topical beta blocker, Timolol, Plasma lipids.

prevalent type of glaucoma which affect male and female equally.<sup>12</sup> Main classes of glaucoma medication are  $\beta$ -blockers,  $\alpha$ -agonist, carbonic anhydrase inhibitors, prostaglandin analogs, miotics and osmotic agents. Among beta blockers timolol maleate is commonly used. It is a non-selective  $\beta$ -blocker and lowers IOP satisfactorily by inhibiting aqueous humor production.<sup>14-17</sup> A large proportion of patients with glaucoma are being satisfactorily treated with timolol maleate 0.5% as a sole therapy since 1978.<sup>18-19</sup> Approximately 80% of the volume of topically administered eye drops is absorbed systemically through nasopharyngeal mucosa within 15 to 30 seconds of instillation.<sup>20</sup>

Moreover its plasma level thus achieved may be equivalent to that obtained after intravenous administration as 50-70% of the drug escapes first-pass metabolism.<sup>18</sup> As primary open-angle glaucoma and atherosclerosis both are fairly common diseases among elderly persons, any adverse changes in serum lipids as a result of glaucoma therapy can increase the risk of coronary heart disease many folds. Orally taken beta blockers for the treatment of systemic hypertension have been shown in numerous studies to have a significant effect on plasma lipid profiles as well as airway and cardiovascular diseases.<sup>20-21</sup> As topical beta blockers are also widely used and often the first-line therapy in many patients requiring treatment for glaucoma or ocular hypertension for a long time, there is also a possible risk of HDL level abnormality.<sup>12</sup> We decided to carry out a study using timolol to ascertain that a side effect on serum lipoproteins levels was not going undetected in so many patients on treatment for glaucoma. Coleman et al<sup>10</sup> found that HDL decreased by 9% and TC/HDL ratio increased by 8%, triglycerides increased by 12% with timolol use within 76 days. Freedman et al<sup>9</sup> found that timolol causes an 8% decrease in HDL and a 10% raised in TC/HDL ratio within 8 weeks. So we think it would be a baseline study for Bangladesh and will help to take decisions during the use of topical timolol for a long time in some glaucoma patients with risk of coronary heart disease.

#### Methods:

This cross-sectional observational study was conducted at the Department of Ophthalmology, Bangabandhu Sheikh Mujib Medical University (BSMMU) from July 2013 to September 2014. Patients attending the Department of Ophthalmology, BSMMU who was diagnosed with a case of POAG, was the source of the sample. Convenience type sampling technique was applied to collect the sample from the study population as per inclusion and exclusion criteria. Primarily a total number of 45 patients presenting with POAG were enrolled in this study. 2 patients were excluded due to unsatisfactory IOP in 1st follow-up visit and 3 patients were excluded due to discontinued follow-up. Finally, 40 patients were included in our study. Complete clinical evaluation including history, general examination, and relevant ocular and systemic examinations was performed in the ophthalmology department. Ocular examinations included-BCVA, Pupilary light reaction, RAPD, Ocular motility, Slit lamp examination of the anterior segment and fundus

examination with the help of +78D condensing lens Direct and indirect ophthalmoscopy, IOP measurement by Goldmann applanation tonometer, Gonioscopy by Goldmann 3 mirror contact lens & Perimetry done by Humphrey automated visual field analyzer. In our study according to Shaffer's system, grade 4 and 5 are considered open-angle. Grade 2, 1, 0, and slit angle are considered narrow-angle and were excluded from the study. Baseline fasting lipid profiles were measured in the department of Biochemistry, BSMMU by quantitative colorimetric method. After getting the baseline lipid profile levels timolol maleate 0.5% eye drops 1 drop 12 hourly in both eyes was prescribed. Patients were advised not to change their dietary habits and physical activities and to follow up at the end of the 4th & 12th weeks. In follow-up at the end of the 4th and 12th weeks fasting lipid profiles were measured again in the same laboratory with the same procedure. Then baseline fasting lipid profiles were compared with the follow-up fasting lipid profiles. There would be some confounding factors in this study such as bad patient compliance with regular use of topical timolol, change in dietary habits, and change of habit of exercise. These factors have been minimized as much as possible. The demographic information, relevant history, examination findings, and investigation reports of all the study subjects were recorded in the data collection sheet. After compilation, all the data were presented in the form of tables, figures, and graphs, as necessary. Statistical analysis of the results was done by using computer-based software, IBM SPSS 22.0. A probability 'P' value of 0.05 or less was considered as significant

#### Results:

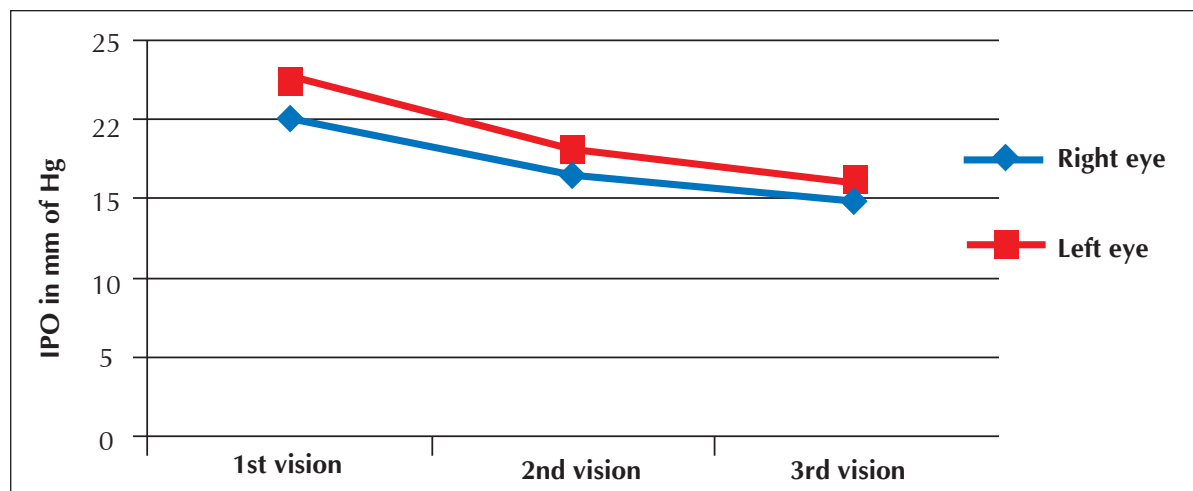
Among the 40 patient 12(30%) were in 40-45 age group, 6(15%) were in 46-50 age group, 13(32.5%) were in 51-55 age group and 9(22.5%) were in 56-60 age group. The mean age was found  $50.08 \pm 6.3$  years with a range from 40 to 60 years. Out of 40 study patients, 29(72.5%) were male and 11(27.5%) were female. So male-female ratio was 2.6:1.

Table-I and figure-1 showed the trend of mean IOP changes in both eyes in different visits. Timolol reduced mean IOP by 17.04% ( $P=0.001$ ) in the right eye and by 18.91% ( $P=0.001$ ) in the left eye between the 1st and 2nd visit and between the 2nd and 3rd visit the mean IOP reduction of the right eye was 9.34% ( $P=0.044$ ) and the left eye was 11.08% ( $P=0.001$ ). The mean IOP reduction between the 1st and 3rd visit was 27.36% ( $P=0.001$ ) in the right eye and 28.12% ( $P=0.001$ ) in the left eye.

**Table-I: Comparison of IOP (in mm of Hg) at different visits (n=40)**

Comparison of lipid profile of 1st and 2nd visit (n=40)				
IOP (mm of Hg)	1st visit Mean±SD	2nd visit Mean±SD	Decreased (%)	p-value
Right eye	19.95 ± 5.11	16.45±3.57	17.04	0.001s
Left eye	22.4 ±2.77	18.15±2.48	18.91	0.001s
Comparison of IOP (in mm of Hg) at 2nd and 3rd visit (n=40)				
IOP (mm of Hg)	2nd visit Mean±SD	3rd visit Mean±SD	Decreased (%)	p-value
Right eye	16.45 ± 3.57	14.75 ± 3.34	9.34	0.044s
Left eye	18.15 ± 2.48	16.1 ± 2.75	11.08	0.001s
Comparison of IOP (in mm of Hg) at 1st and 3rd visit (n=40)				
IOP (mm of Hg)	1st visit Mean±SD=	3rd visit Mean±SD	Decreased (%)	p-value
Right eye	19.95 ± 5.11	14.75±3.34	27.36	0.001s
Left eye	22.4 ±2.77	16.1±2.75	28.12	0.001s

s = Significanat



**Figure-1: Trend of mean IOP changes in both eyes in different visits**

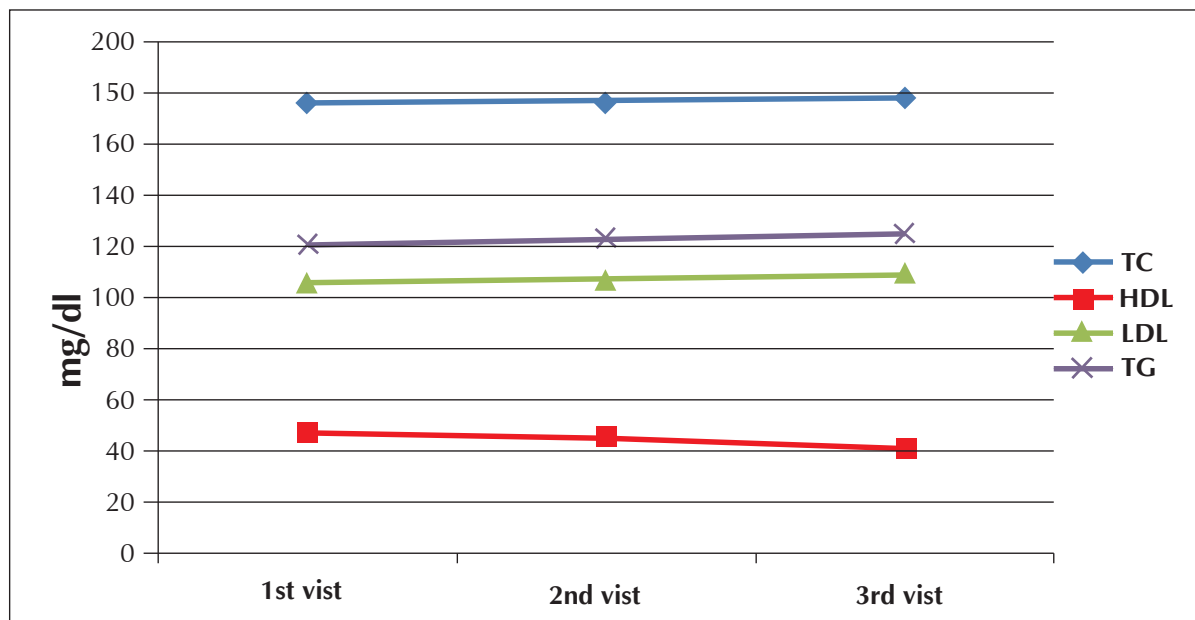
In this study the baseline (at first visit) mean TC, HDL, LDL & TG were 175.4±19.28, 46.63±5.33, 104.98±18.49, 120.48±28.30 (mg/dl±SD) respectively. Baseline TC/HDL was 3.81±0.06. At follow up after 4 weeks there were increased level of TC, LDL, TG, TC/HDL by 0.45% (P=0.822), 0.8% (P=0.807), 1.82% (P=0.375), and 3.14% (P=0.307) respectively and HDL level decreased by 2.68%

(P=0.232). At follow-up, after 12 weeks in comparison to baseline lipid levels, there was an increased level of TC, LDL, TG, and TC/HDL by 0.98% (P=0.959), 3% (P=0.996), 2.8% (P=0.104), and 17.0% (P=0.001) respectively and HDL level decreased by 13.61% (P=0.001). (Table-I and figure-2 & 3)

**Table-II: Comparison of lipid profile at different visits (n=40)**

Comparison of lipid profile of 1st and 2nd visit (n=40)				
Lipid profile	1st visit Mean±SD	2nd visit Mean±SD	Increased/Decreased (%)	p-value
TC (mg/dl)	175.4±19.28	176.20±19.36	0.45	0.822ns
HDL (mg/dl)	46.63±5.33	45.38±5.19	2.68	0.232ns
TC/HDL ratio	3.81±0.61	3.93±0.62	3.14	0.307ns
LDL (mg/dl)	104.98±18.49	105.83±18.04	0.80	0.807ns
TG (mg/dl)	120.48±28.30	122.68±29.18	1.82	0.375ns
Comparison of lipid profile of 2nd and 3rd visit (n=40)				
Lipid profile	2nd visit Mean±SD	3rd visit Mean±SD	Increased/Decreased (%)	p-value
TC (mg/dl)	176.20±19.36	177.13±19.70	0.52	0.868ns
HDL (mg/dl)	45.38±5.19	40.28±5.32	11.23	0.001s
TC/HDL ratio	3.93±0.62	4.46±0.70	13.48	0.001s
LDL (mg/dl)	105.83±18.04	108.15±19.37	2.19	0.824ns
TG (mg/dl)	122.68±29.18	123.85±27.89	0.95	0.493ns
Comparison of lipid profile at 1st and 3rd visit (n=40)				
Lipid profile	1st visit Mean±SD=	3rd visit Mean±SD	Increased/Decreased (%)	p-value
TC (mg/dl)	175.4±19.28	177.13±19.70	0.98	0.959ns
HDL (mg/dl)	46.63±5.33	40.28±5.32	13.61	0.001s
TC/HDL ratio	3.81±0.61	4.46±0.70	17.0	0.001s
LDL (mg/dl)	104.98±18.49	108.15±19.37	3.0	0.996ns
TG (mg/dl)	120.48±28.30	123.85±27.89	2.8	0.104ns

ns = Not significant, s= significant



**Figure-2: Trend of mean lipid profile changes in different visits**

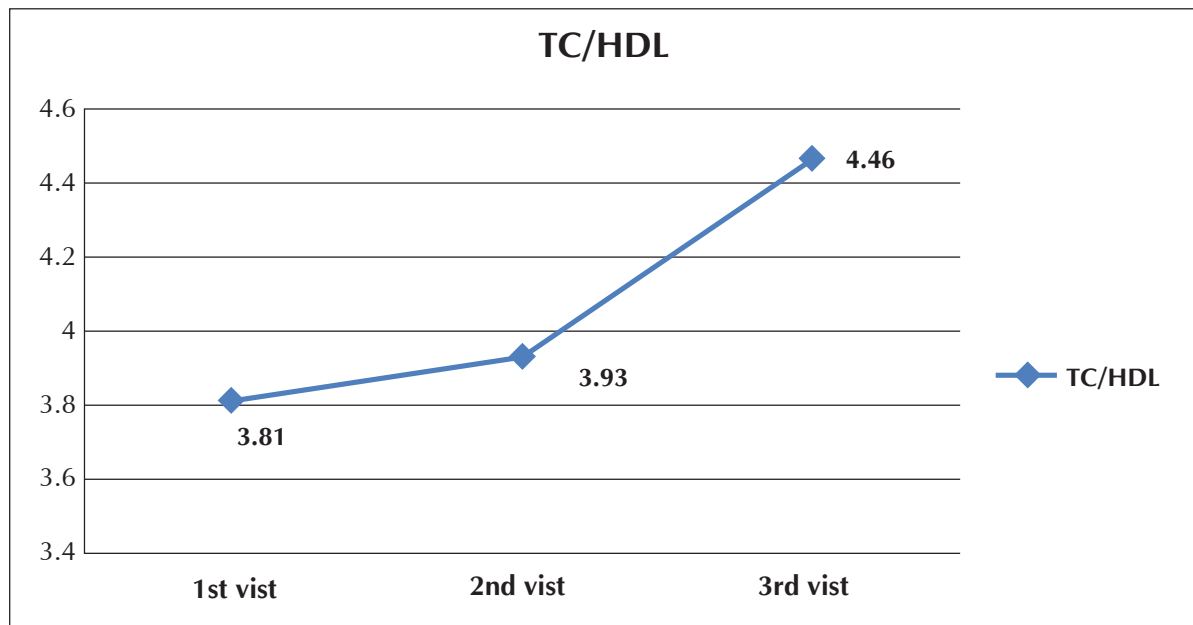


Figure-3: Trend of change of mean TC/HDL in different visits

#### Discussion:

In this study, a total number of 45 patients who were newly diagnosed with primary open-angle glaucoma were enrolled. Finally, 40 patients completed 3 months follow-up. The remaining 5 patients withdrew from the study due to inadequate IOP control or discontinued follow-up. So our dropout rate was 11%. In a previous study<sup>10</sup> their primary enrollment was 40 healthy volunteers, 28 subjects completed the 2-month follow-up, so the dropout was 30%. In our study, the comparatively low dropout rate may be due to the study on POAG patients not on healthy subjects. Last follow-up after the start of timolol drop was at the end of 12 weeks. In another study, the last follow-up was after 8 weeks.<sup>23</sup> In this study among the 40 patients, ages ranged from 40 to 60 years with a mean age of 50.08 6.3 years compared to the previous study by West & Simson<sup>24</sup> with an age range of 46 to 80 years and a mean age of 67.5 years. POAG affects males and females equally<sup>12</sup> But in this study, the majority (72.5%) of the patients were male. This may be due to less or little access of our females to the hospital. Our study showed that within one month, timolol reduced mean IOP by 17.04% ( $P=0.001$ ) in the right eye and by 18.91% ( $P=0.001$ ) in the left eye. These changes were statistically signifi-

cant. The mean IOP reduction of the right eye between the 2nd and 3rd visit was 9.34% ( $P=0.044$ ) and the Mean IOP reduction of the left eye between the 2nd and 3rd visit was 11.08% ( $P=0.001$ ). All these changes were statistically significant and were consistent with the previous report of up to 26% reduction of IOP by timolol<sup>18</sup> and it was noticed that the rate of reduction of IOP was more in the first month and less in the next two months. The mean lipid profiles difference were not statistically significant between 1st visit and 2nd visit of our study population. Regarding the 2nd and 3rd visits the mean TC, LDL, TG differences were not statistically significant but mean HDL, TC/DHL differences were statistically significant. Regarding 1st and 3rd visits, the also mean TC, LDL, and TG differences were not statistically significant but the mean HDL, and TC/DHL differences were statistically significant. So it was shown that up to one month there was no significant effect of topical timolol on serum lipid profiles but within 3 months there was a significant effect. Previously several studies have evaluated the influence of topical beta-blockers on serum lipids levels. Coleman et al.<sup>10</sup> applied topical timolol maleate 0.5%, to 28 healthy volunteers for an average of 76 days and found that HDL decreased by 9% and TC/HDL ratio increased by

8%, triglycerides increased by 12 %. Our present study report is also consistent with these reports. Freedman et al.<sup>9</sup> compared the effect of topical carteolol 1% and timolol maleate 0.5% on lipid levels in 58 healthy normolipidemic adult men using a masked, randomized, crossed-over design. Treatment with each drug resulted in a decrease in HDL. Here timolol causes an 8% decrease in HDL and a 10% raised in TC/HDL ratio. Murli et al.<sup>23</sup> monitored the effect of topical timolol on lipid profiles in 25 patients and found a significant decrease (12%) in HDL levels after 12 weeks. Thus findings of the present study are more or less consistent with the findings of previous studies. It was observed in our study that topical use of timolol maleate 0.5% though causes change in a different component of lipid profile, effect on HDL was more marked. Mean HDL at 1st visit was 46.63±5.33 mg/dl and at 3rd visit 40.28±5.30 mg/dl. It was a 6.35 mg/dl (13.61%) reduction of HDL within three months of timolol use. We stratified the 40 patients into 40-45; 46-50; 51-55 and 56-60 years age groups. Regarding changes in mean HDL in all 4 age groups within 1st and 3rd visit, we found a reduction of HDL by 14.87%(0.001), 12.80%(0.001), 12.56%(0.001), and 13.2%(0.001) respectively. It was shown that the reduction of HDL levels in all four different age groups was statistically significant. Though dyslipidemia should be more marked in the older age group, in this study inter age group changes were not significant. This may be due to the similar effect of topical timolol on serum lipids in different age groups. There were 29 male and 11 female patients in the present study. Regarding 1st and 3rd visits, in male patients mean HDL decreased by 21.27% (P=0.001), and in female patients mean HDL decreased by 15.56% (P=0.001) The mean HDL difference between 1st visit and 3rd visit in both male and female groups were statistically significant. But between the male and female groups, the differences were not significant. This may be due to the that the effect of timolol on lipid profile was similar in the case of males and females.

#### Conclusion:

The topical use of timolol (Beta- blocker) decreases serum HDL and increases TC/HDL ratio. So while treating POAG patients with timolol serum level of lipid profile should be carefully monitored. In the patients associated with the risk of coronary

heart disease, such drugs should be avoided with an alternative treatment option. However, further studies with longer duration are required to rationally establish the effect of topical timolol on lipid profiles.

#### Limitations:

The period of study was insufficient to conduct a qualitative study. The study failed to conclude that the effect of timolol on serum lipid profiles was either dose-dependent or not.

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