



An Open Prospective, Randomized Controlled Study to Evaluate the Antianginal Effect of Atorvastatin in Patients of Coronary Artery Disease with Dyslipidemia

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Abstract

Background: Elevated baseline levels of total serum cholesterol strongly correlate with increased incidence of cardiovascular disease and mortality. Atorvastatin lower elevated LDL cholesterol levels, resulting in substantial reduction in coronary events and deaths from CAD.

Aim & Objectives: To study antianginal effect of atorvastatin in patients of Coronary Artery Disease with Dyslipidemia.

Methods: An open prospective randomized, controlled study was conducted for duration of 2 months in patients of CAD. 30 patients fulfilling the inclusion criteria and have none of the exclusion criteria were enrolled after taking written informed consent. Patients were randomly divided into two groups (A and B) of 15 each. Group A-was started on conventional treatment like nitrates, antiplatelet drugs (aspirin/clopidogrel), beta-blockers, CCBs, ACE inhibitors. Group B-was started on Atorvastatin 20 mg once a day at night in addition to conventional treatment. History of frequency of anginal attacks per month, attacks of dyspnoea per month was taken, compared and statistically analyzed. Lipid profile was repeated at every visit and changes were statistically analyzed.

Results & Conclusion: Frequency of attacks of angina in patients of CAD with dyslipidemia given Atorvastatin (Group B) in addition to conventional treatment was significantly decreased (from 2.13 ± 0.64 to 1.87 ± 0.51 , 95 % CI= 0.95-3.67, $p = 0.003$). but not in Group A. Difference in frequency of angina attacks between group A and group B was statistically not significant at baseline and 30 days but significant at 60 days (95 % CI= 0.19-1.40, $p = 0.01$). There was also a statistically significant reduction in frequency of attacks of dyspnoea in group B patients. We concluded that atorvastatin in dose of 20 mg has antianginal effects in addition to its known hypolipidemic effect.

Key words: Coronary artery disease, atorvastatin, frequency, anginal attacks, dyspnoea, lipid profile

INTRODUCTION

Coronary artery disease (CAD) is typically defined as a more than 50% stenosis of any epicardial coronary artery.

^[1] Coronary artery disease is the end result of accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium with oxygen and nutrients. Most individuals with coronary artery disease show no evidence of disease for decades as the disease progresses slowly before the first onset of symptoms, often a sudden heart attack finally arises. After decades of progression some of these atheromatous plaques may rupture and along with activation of blood clotting system start limiting blood flow to heart muscle leading to myocardial infarction. It is known that segments of thickened intimal structure are also present in everyone from birth, particularly at bifurcations of the vessels. This thickened intimal coat may also contain lipid deposits since childhood. In the first three decades of life, lesions grow because more lipids accumulate and intimal thickness increases, leading to occasional symptomatic vessel obstruction.^[2]

Elevated baseline levels of total serum cholesterol strongly correlate with increased incidence of cardiovascular disease and mortality. In Indian patients with CAD, high triglycerides levels are found more often than high cholesterol level. An increase of triglycerides from 90mg/dl to 180mg/dl is associated with doubling the incidence of CAD.^[3]

Statins, or 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (HMG-CoA inhibitors) form a class of hypolipidemic drugs used to lower cholesterol levels in

people with or at risk of cardiovascular disease. They lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Nowadays, statins seem to play a crucial role in modulating cardiovascular disorders such as acute coronary syndrome, not only by affecting lipids, but also by exerting a number of pleiotropic effects beyond lipid lowering, such as plaque stabilization.^[4]

Statins e.g. atorvastatin lower elevated LDL cholesterol levels, resulting in substantial reduction in coronary events and deaths from CAD. Therapeutic benefits of statins include plaque stabilization, improvement of coronary endothelial function, inhibition of platelet thrombus formation, and anti-inflammatory activity.^[5]

CAD is becoming more prevalent every day. We now know that controlling the risk factors for this pathology is of utmost importance to prevent the formation of atheromatous plaque. There is no longer any doubt that an increase in serum cholesterol is essential for the development and the progression of atherosclerosis. Therefore lowering cholesterol level is a key factor in controlling this disease. It is suggested that the association of statins and conventional treatment in patients with stable angina reduces effort-induced ischemia.^[6]

The most widely recommended approach to statin therapy is LDL- cholesterol based, "treat-to-target" strategy, in which lipid-modifying medications are titrated to achieve specific LDL cholesterol levels. This strategy is the basis of the NCEP (National Cholesterol Education Program) III guidelines.^[7]

Since coronary artery disease is a very common disease and known to cause a plethora of health problems, thus treatment strategy with high efficacy, lesser adverse effects and with better compliance is required.

Present study aims to evaluate the effects of addition of Atorvastatin 20 mg once a day at night to conventional treatment on frequency of attacks of angina per month, frequency of attacks of dyspnoea per month and lipid profile at different time intervals.

AIMS AND OBJECTIVES

The study is designed to evaluate the effects of addition of atorvastatin 20 mg once a day at night to conventional treatment in decreasing the frequency of attacks of angina per month in cases of CAD.

MATERIAL AND METHODS

The present study was conducted by Department of Pharmacology in association with Department of Medicine of Govt. Medical College and Rajindra Hospital, Patiala. 30 patients of CAD were enrolled from both indoor and outdoor department of Medicine. These cases were selected on the basis of following criteria:-

Inclusion criteria

- Age > 40 years.
- Dyslipidemic patients with frank stable angina (Stress induced angina).
- Dyslipidemic patient showing the ECG changes of old ischemia or precipitated by stress test.

Exclusion criteria

- Patients of hypertension leading to CHF.
- Patients with rheumatic valvular lesion on clinical examination.
- Patients having congenital heart disease based on clinical examination
- Patients with hepatic or renal failure.
- Patients allergic to any component of the study drugs
- Patients who refused to give informed written consent

Study design and randomization

An open prospective randomized, controlled study was conducted for duration of 2 months in patients of CAD. The patients fulfilling the inclusion criteria and have none of the exclusion criteria were included after taking written informed consent. This study was conducted with the permission of institutional ethical committee and all study procedures were performed according to the declaration of Helsinki. A detailed history of all patients was obtained and recorded. The complete clinical examination was done. Lipidogram and ECG of all patients were done at baseline. Then, these patients were randomly divided into two groups of 15 each by using block randomization (block size = 4).

- Patients of two groups were advised to follow lifestyle modification like regular exercise, quit smoking, low fat diet and avoid alcohol.
- Group A—was started on conventional treatment like nitrates, antiplatelet drugs (aspirin/clopidogrel), beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors.
- Group B—was started on Atorvastatin 20 mg once a day at night in addition to conventional treatment.

The duration of study was 2 months. The Frequency of attacks of angina and angina equivalents like dyspnoea were asked subjectively and noted.

Observations of lipid profile, frequency of anginal attacks per month, frequency of attacks of dyspnoea per month were compared and evaluated.

Statistical analysis

The results of observation of individual patients were pooled for each group. Data was expressed as mean \pm standard deviation (SD). Baseline characteristics between the two groups were compared by using Chi square test (χ^2) for categorical variables and independent 't'- test for numerical variables. Intra-group comparison was done by using paired 't' test. Inter-group comparison was done using student's 't' test and Chi square test (χ^2). 95 % confidence interval (CI) was also calculated for different parameters. P value of less than 0.05 was considered as statistically significant. The data was statistically analyzed by using SPSS version 20.

OBSERVATIONS AND RESULTS

Baseline comparison:

According to gender: In group A, 8 (53.33%) males and 7 (46.67%) females were included. In group B, 7 (46.67%) males and 8 (53.33%) females were included. This difference was statistically non- significant ($p > 0.05$).

Past history: In group A past history of CAD, Hypertension and diabetes were present in 7, 5 and 7 patients respectively, while absent in 8, 10 and 8 patients respectively. In group B past history of CAD, Hypertension and diabetes were present in 6, 6 and 5 patients respectively, while absent in 9, 9 and 10 patients respectively ($p > 0.05$).

Personal history: in group A, 4 patients were smokers and 5 patients were alcoholics, 4 patients had sedentary life style. While in group B, 4 patients were smokers and 6 were alcoholics, 5 patients had sedentary life style. The difference of personal history between group A and B was not significant, so both the groups were comparable ($p > 0.05$).

Baseline comparison for other parameters between the two groups has also shown no significant difference (Table 1). Therefore, both the groups were comparable at baseline

Table1. Baseline comparison of age, frequency of attacks of angina and dyspnoea and lipid parameters between two groups

| PARAMETERS | Group A | Group B | 'p' value |
|---|--------------------|--------------------|-----------|
| | Mean \pm SD | Mean \pm SD | |
| Age | 56.0 \pm 4.71 | 55.8 \pm 5.21 | > 0.05 |
| Frequency of attacks of angina per month | 2.93 \pm 0.704 | 2.60 \pm 0.632 | > 0.05 |
| Frequency of Episodes of dyspnoea per month | 4.13 \pm 0.640 | 4.00 \pm 0.655 | > 0.05 |
| TC (mg %) | 260.60 \pm 36.56 | 280.87 \pm 22.64 | > 0.05 |
| TG (mg %) | 199.73 \pm 31.54 | 196.93 \pm 19.04 | > 0.05 |
| LDL (mg %) | 184.40 \pm 14.09 | 195.80 \pm 17.42 | > 0.05 |
| HDL (mg %) | 37.40 \pm 3.11 | 38.33 \pm 2.05 | > 0.05 |

Comparison of frequency of attacks of angina per month in group A (conventional treatment group) at different time interval: The mean baseline frequency of attacks of angina per month \pm standard deviation was 2.93 ± 0.70 . All patients receiving conventional treatment alone showed decrease in frequency of attacks of angina per month from 2.93 ± 0.70 to 2.80 ± 0.77 after 60 days of treatment. This difference was statistically not significant

Comparison of frequency of attacks of angina per month in group B (conventional treatment group plus atorvastatin) at different time interval: as evident from table no. 2, all patients receiving atorvastatin in addition to conventional treatment showed decrease in frequency of attacks of angina per month from 2.60 ± 0.63 to 2.53 ± 0.74 and 2.00 ± 0.84 at 30 and 60 days, respectively. This table showed 2.69% and 23.07% decrease in frequency of attacks of angina per month at 30 and 60 days. Decrease in frequency of attacks of angina per month per months was

statistically not significant after 30 days but significant at 60 days (95 % CI= 0.95-3.67, $p= 0.003$).

As observed in Table. 3, group A (conventional treatment group) showed 4.43% decrease in frequency of attacks of angina per month from base line. While group B (Atorvastatin in addition to conventional treatment group) showed 2.69% and 23.07% decrease in frequency of attacks of angina per month from baseline. Difference between group A and group B was statistically not significant at baseline and 30 days but significant at 60 days (95 % CI= 0.19-1.40, $p = 0.01$).

Changes in other parameters

There was a statistically significant reduction in frequency of attacks of dyspnoea in group B from baseline to end of the study. Also, there was a significant improvement in all lipid parameters i.e. TC, TG, LDL-C and HDL-C in group B from baseline to end of the study but there was worsening of lipid parameters from baseline to end of the study in group A (table. 4)

Table 2. Comparison of frequency of attacks of angina in group B patients.

| Time interval | Mean \pm SD | %age change | 95 % Confidence Interval (CI) | 'p' Value |
|---------------|-----------------|-------------|-------------------------------|-----------|
| Baseline | 2.60 \pm 0.63 | - | - | - |
| After 30days | 2.53 \pm 0.74 | - 2.69% | 0.21-1.00 | 0.33 |
| After 60days | 2.00 \pm 0.84 | - 23.07% | 0.95-3.67 | 0.003 |

Table 3. Comparison of change of frequency of attacks of angina per month between group A (conventional treatment group) and group B at different time interval from baseline.

| Time interval | Group | Mean \pm SD | %age change | 95 % Confidence Interval (CI) | 'P' value |
|---------------|---------|-----------------|-------------|-------------------------------|-----------|
| Baseline | Group A | 2.93 \pm 0.70 | - | - 0.16- 0.83 | 0.18 |
| | Group B | 2.60 \pm 0.63 | - | | |
| After 30 days | Group A | 2.93 \pm 0.70 | - | -0.14 - 0.94 | 0.14 |
| | Group B | 2.53 \pm 0.74 | - 2.69% | | |
| After 60days | Group A | 2.80 \pm 0.77 | - 4.43% | 0.19-1.40 | 0.01 |
| | Group B | 2.00 \pm 0.84 | - 23.07% | | |

Table 4. Inter- group comparison of frequency of attacks of dyspnoea and lipid parameters

| PARAMETERS | Group A | | Group B | | 'p' value |
|-----------------------------------|--------------------|--------------------|--------------------|--------------------|-----------|
| | At baseline | At 60 days | At baseline | At 60 days | |
| Frequency of Episodes of dyspnoea | 4.13 \pm 0.640 | 4.07 \pm 0.59 | 4.00 \pm 0.655 | 3.47 \pm 0.52 | 0.01 |
| TC (mg %) | 260.60 \pm 36.56 | 279.29 \pm 28.56 | 280.87 \pm 22.64 | 212.47 \pm 23.22 | <0.001 |
| TG (mg %) | 199.73 \pm 31.54 | 223.33 \pm 36.33 | 196.93 \pm 19.04 | 156.87 \pm 19.76 | <0.001 |
| LDL (mg %) | 184.40 \pm 14.09 | 196.87 \pm 11.59 | 195.80 \pm 17.42 | 135.33 \pm 17.82 | <0.001 |
| HDL (mg %) | 37.40 \pm 3.11 | 36.60 \pm 3.29 | 38.33 \pm 2.05 | 40.80 \pm 1.82 | <0.001 |

DISCUSSION

During the past three decades there has been a substantial increase of CAD in developing countries particularly in India, while during the same period there has been a significant decline in CAD mortality in developed countries. The current estimate of 25 million CAD patients is projected to increase 40 million by the year 2020.^[8]

It has been found that the high cholesterol levels are associated with increased risk of CAD and further, increase in LDL-C and decrease in HDL-C favors the progression of an atheromatous plaque associated with CAD.

The group of drugs 'statins' have been used to lower serum cholesterol levels and thus aiming to lower the morbidity and mortality with CAD.

In the present 2 month study, we studied the antianginal effects of Atorvastatin 20 mg once a day at night in addition to conventional antianginal treatment.

For antianginal effects, parameters taken were frequency of attacks of angina per month, frequency of episodes of dyspnoea per month.

Our study has shown a significant decrease in ischemic events as is evident by decreased frequency of attacks of angina (by 23.07%, $p=0.003$) and angina equivalents like dyspnoea (by 13.25%, $p=0.01$) in patients on atorvastatin in addition to conventional drugs (Group B)

Sever et al (2003) observed that the reductions in major cardiovascular events with atorvastatin are large, given the short follow-up time atorvastatin significantly decreased the cardiovascular events.^[9]

Shavelle (2007) observed that treatment with statins reduced the frequency and severity of angina, thereby improving quality of life, reduced future cardiovascular events including MI and death by approximately 25–30% in patients with established CAD and improves survival. A review of multiple studies indicates that the benefits of statins are proportional to the level of low density lipoprotein (LDL) reduction—that is, lower concentrations of LDL are associated with fewer cardiovascular events.^[10]

Blumenthal et al (2000) demonstrated that treatment with atorvastatin was associated with significant reduction in ischemic events and a significant delay in time to first ischemic event.^[11]

In a study done by Maruyama et al (2011, CIRCLE study), it was found that there was significant decrease in lipid parameters and decrease in ischemic events with atorvastatin compared with no statin group. Atorvastatin significantly prevented major adverse cardiac events (MACE) compared with no statin group.^[12]

Thus our result is in conformity with the studies done by Sever et al (2003), Shavelle (2007), Blumenthal et al (2000) and Maruyama et al (2011), where atorvastatin has shown its potential to decrease the frequency of ischemic events.

In atorvastatin treatment group, 2 patients developed lower limb pain which was mild in nature and did not lead to any restriction of routine activities; the patients were reassured and monitored closely for any further complaint. No other severe adverse events were reported in both groups and none of the patient withdrew from the study drugs during this study.

Limitations of the study

There were some limitations of this study. These are:

- No blinding was done
- The study involved only 30 patients, so the sample size was small
- Sample size was not calculated before the start of the study
- Study was not powered to detect the difference between two groups
- Control group treatment was not fixed; patients in this group were given different antianginal drugs according to the decision of the treating physician.

SUMMARY AND CONCLUSION

From the results of our study following conclusions were drawn:

- Atorvastatin given in addition to conventional treatment caused significant reduction in frequency of attacks of angina per month as compared to patients on conventional treatment alone.
- Atorvastatin given in addition to conventional treatment caused significant reduction in frequency of attacks of dyspnoea as compared to patients on conventional treatment alone.
- Reduction in cholesterol levels was associated with the reduction in frequency of attacks of angina and improvement in symptoms of Angina.
- It was therefore concluded from the present study that Atorvastatin in dose of 20 mg had antianginal effects in addition to its known hypolipidemic effect.

- Further studies of longer duration involving large number of patients of CAD without dyslipidemia are required to find whether this antianginal effect was independent of lipid lowering effects.

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