Safety profile of atorvastatin in post myocardial infarction and post stroke patients

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Abstract
Background: The side effects of high dose atorvastatin treatment in post myocardial infarction and post stroke patients have not been studied in detail. The present work aim to study whether the toxicity profile of atorvastatin in Indian population is same as that of western countries. There are reports that atorvastatin decreases C-reactive protein levels in blood. This study further target to find whether the reduction in C-protein levels are dose dependent about which no conclusive data is available. **Methodology:** This observational prospective study was conducted in the subjects admitted with acute myocardial infarction or cerebrovascular accident in the form of infarct and started on atorvastatin as a part of treatment. 100 subjects in the age group 35-75 years were chosen and they were categorized into two different groups. The 1st group had subjects who were taking 10 mg and the 2nd, 40 mg of atorvastatin. The comparison of serum creatinine, serum uric acid, serum glutamate pyruvate transaminase (SGPT) and creatinine phosphokinase (CPK) were measured. They were followed up twice (at 6 weeks and 12 weeks) during the study period of 3 months and adverse effects were carefully monitored by clinical parameters and laboratory investigations. **Results:** After the 12 weeks study period, it was found that atorvastatin is well tolerated in low and high doses with minimal side effects and no dose response relationship was found in overall incidence of adverse effects. Besides, the reduction in C-reactive protein values with atorvastatin therapy following coronary and cerebrovascular events was not dose dependent. **Conclusion:** There is no significant difference in adverse outcome as far as low dose or high dose of atorvastatin usage is concerned in post coronary or cerebrovascular event therapy. And in addition the drug appeared to be safe and did not produce any major side effects in the study population during this trial.
Key Words: Atorvastatin, myocardial infarction, stroke, creatinine, SGPT and CPK.

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INTRODUCTION

Human beings are doggedly confronting life-threatening morbidities such as cardiovascular and cerebrovascular disorders. Cardiovascular diseases annually account for ~17 million deaths globally[1]. Whereas, stroke is the third leading cause of death worldwide after Ischemic Heart Disease (IHD) and Cancer[2]. The risk of cardiovascular mortality and morbidity are further increases among patients those who survived a stroke. India has a disproportionately higher burden of coronary artery disease than most developing countries. Atherosclerosis is the main factor for the pathogenesis of myocardial and cerebral infarctions. Nevertheless, high levels of plasma low density lipoproteins (LDL) and triglycerides (TG) along with decreased levels of high-density lipoproteins (HDL) are often the major root cause of atherosclerosis and ultimately myocardial and cerebral infarctions[1,3]. Since hyperlipidaemia is the most important risk factor for coronary artery disease, statins have become the first line therapy for reducing the risk of cardiovascular disease mortality. For instance, hyperlipidaemia is also important as a risk factor for cerebrovascular diseases, the

reduction in blood lipid level is an essential part of the treatment of cerebrovascular incidents. Atorvastatin is a widely prescribed drug to treat dyslipidaemia. The effectiveness of atorvastatin in lowering the cholesterol level is dose related and has been used in various doses ranging from 5 mg to 80 mg[4]. Statins are structural analogues of HMG CoA and competitively inhibit HMG CoA reductase, which catalyses the rate limiting step in cholesterol biosynthesis. Thus by reducing intracellular levels of cholesterol, atorvastatin up-regulate the expression of LDL receptors in liver cells and it leads to increased clearance of LDL from the blood stream[5]. In addition to improving lipid profile, statin have several beneficial biological, pleiotropic effects that contribute to their overall clinical benefit. These include reducing platelet aggregation and thrombus formation, improving fibrinolytic profile and lowering the inflammation and C-reactive protein. In patients with coronary artery disease and hyperlipidaemia, statins improve endothelial function, decrease plasma concentration of tumour necrosis factor alpha (TNF-α) and thereby reduces the morbidity and mortality[6-8]. There is increasing concern about the reports of increased risk of toxicities associated with statin therapy. The concern regarding the safety of HMG-CoA reductase inhibitors peaked after the voluntary worldwide withdrawal of Cerivastatin in August 2001, due to increased incidence of fatal rhabdomyolysis associated with its intake. The other serious adverse reactions reported include myositis, myopathy, polyneuropathy, cancer, liver and kidney toxicities, diabetes mellitus and haemorrhagic stroke. The minor adverse effects of statin therapy include abdominal cramps, diarrhoea or constipation, flatulence, dyspepsia, muscle pain, dizziness, headache, pharyngitis, flu syndrome, nausea and vomiting, sleep disturbances, fatigue, change in body temperature and blood sugar and dry skin[9]. The side effects of high dose atorvastatin treatment in post myocardial infarction and post stroke patients have not been studied in detail. The present work also aim to study whether the toxicity profile of atorvastatin in Indian population is same as that of western countries. There are reports that atorvastatin decreases C-reactive protein levels in blood. This study further target to find whether the reduction in C-protein levels are dose dependent about which no conclusive data is available.

MATERIALS AND METHODS

This observational prospective study was conducted in the casualty department and inpatient wards of general medicine department, Government medical college, Kozhikode. Subjects admitted with acute myocardial infarction or cerebrovascular accident in the form of infarct and started on atorvastatin as a part of current treatment were looked for. 100 subjects in the age group 35-75 years who fit the inclusion criteria were chosen. An informed written consent was obtained from all participants. Depending on their intake dosage of atorvastatin, they were categorized into two different groups. The first group had subjects who were taking 10 mg and the second, 40 mg of atorvastatin. The clinical parameters were assessed (serum creatinine, serum uric acid, serum glutamate pyruvate transaminase [SGPT] and creatinine phosphokinase [CPK]) and baseline investigations carried out in both groups. They were followed up twice (at 6 weeks and 12 weeks) during the study period of 3 months and adverse effects were carefully monitored by clinical parameters and laboratory investigations.

Sample size: Sample population consisted of 100 subjects were divided into two equal limbs on the basis of their drug dosage.

Inclusion Criteria: Subjects between 35-70 years admitted with acute myocardial infarction or cerebrovascular accident (infarct) and started on atorvastatin 10 mg or 40 mg as part of current treatment.

Exclusion Criteria: The following patients were excluded from the study – uncontrolled diabetes mellitus, uncontrolled hypertension, hypothyroidism, chronic alcoholic history, gastrointestinal diseases affecting absorption, any type of malignancy, past history of coronary revascularization procedures, significant valvular heart disease, serum creatinine > 2mg/dL, cardiac failure with EF (ejection fraction) <30%, abnormal liver enzyme values (>two times the upper limit for normal), unexplained creatinine kinase levels >6 times the normal, concomitant use of azoles, erythromycin, clarithromycin, cyclosporine, fibrates and niacin.

Statistical Analysis: Data regarding comparison of safety profile of atorvastatin in low and high dosage in post myocardial infarction and post stroke patients were collected, coded and entered in Microsoft Excel sheet which was rechecked and analysed using SPSS 16 statistical software. Description of the study subjects was done using Frequencies for qualitative variables and Mean and Standard Deviation for quantitative variables. Statistical testing of association of side effects in both groups was done using Pearson Chi square test and independent sample 't' tests. Statistical comparison was done using appropriate statistical tests and level of significance was taken as *p* value of 0.05.

RESULTS

A total of 100 patients who met the inclusion criteria were categorized into two groups based on their dosage intake of Atorvastatin. Those who took 10 mg dosage

were added to the first group and those on 40 mg dosage added to the second group. They were monitored for a period of 3 months. By the end of trial period, there were 5 dropouts from 10 mg group and 4 (including a death) in 40 mg group. Dropout rate was 9%, whereas response rate was 91%. The age, sex and other baseline parameters were similar in both groups. Majority of participants in both groups were in 60-70 years age. In group I, 24 (53.3%) of the participants were male and 21 (46.7%) were females. Whereas in group II, 27 (58.7%) were males and 19 (41.3%) were females. Thus, both the study groups were comparable in age (p - value = 0.77) and sex (p-value = 0.81) distribution (Figure 1 and 2).
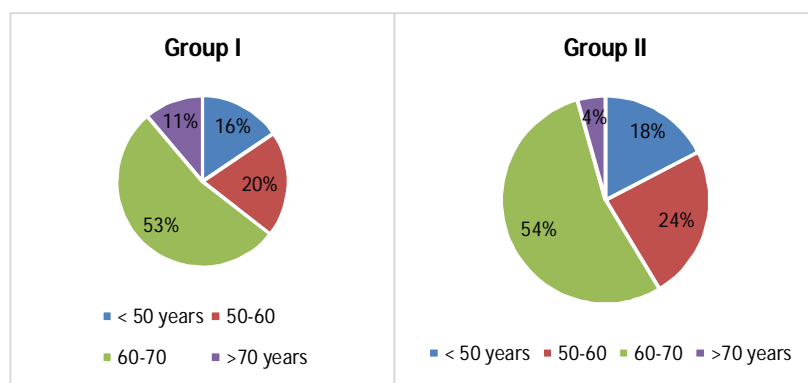

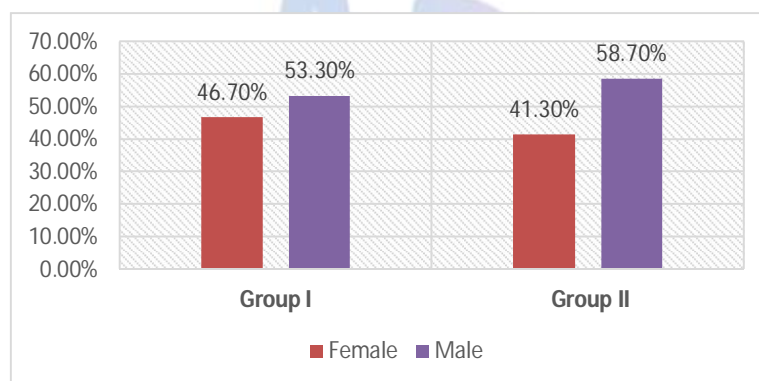**Figure 1:** Age distribution of subjects in group I and II

Figure 2: Gender wise distribution of subjects

In group I, there were 30 subjects having myocardial infarction (MI) and 15 having stroke, whereas in group II, these numbers were 30 and 16 respectively (p-value = 0.35) (table 1).

Table 1: Distribution of MI and Stroke in Group I and II

Disease	Group I (n=45)	Group II (n=46)
MI	30 (66.7%)	30 (65.2%)
Stroke	15 (33.3%)	16 (34.8%)

The C - reactive protein (CRP) values of both the study groups at base line, 6 weeks and 12 weeks are shown in table 2. The decrease in CRP at 6 weeks and 12 weeks are comparable (p value – 0.28) in both groups.

Table 2: Comparison of CRP values

Variable	Group I (Mean ± SD)	Group II (Mean ± SD)	p- Value
CRP at base	5.3 ± 10.2	4.3 ± 9.6	0.63
CRP at 6 weeks	3.6 ± 5.1	2.5 ± 3.1	0.21
CRP at 12 weeks	1.8 ± 1.9	2.9 ± 6.8	0.28

The comparison of serum creatinine, serum uric acid, serum glutamate pyruvate transaminase (SGPT) and creatinine phosphokinase (CPK) are shown in table 3, 4, 5 and 6 respectively.

Table 3: Comparison of serum creatinine (values are expressed in mg/dL)

Variable	Group I (Mean ± SD)	Group II (Mean ± SD)	p- Value
Creatinine at base	1.04 ± 0.18	1.03 ± 0.22	0.9
Creatinine at 6 weeks	1.04 ± 0.22	1.03 ± 0.19	0.9
Creatinine at 12 weeks	1.08 ± 0.21	1.04 ± 0.21	0.09

Table 4: Comparison of serum uric acid (values are expressed in mg/dL)

Variable	Group I (Mean ± SD)	Group II (Mean ± SD)	p- Value
Uric acid at base	4.8 ± 1.5	4.7 ± 1.5	0.5
Uric acid at 6 weeks	4.7 ± 1.3	4.6 ± 1.4	0.6
Uric acid at 12 weeks	4.8 ± 1.3	4.7 ± 1.4	0.7

Table 5: Comparison of SGPT level (values are expressed in U/L)

Variable	Group I (Mean ± SD)	Group II (Mean ± SD)	p- Value
SGPT at base	34.1± 14.2	38.2± 12.2	0.9
SGPT at 6 weeks	37.6 ± 10.5	42.0± 9.4	0.7
SGPT at 12 weeks	39.1 ± 11.0	43.5 ± 9.2	0.7

Table 6: Comparison of CPK level (values are expressed in U/L)

Variable	Group I (Mean ± SD)	Group II (Mean ± SD)	p- Value
CPK at base	150.0 ± 78.5	130.9 ± 55.2	0.18
CPK at 6 weeks	145.3 ± 52.9	142.5 ± 53.3	0.8
CPK at 12 weeks	152.2±53.3	143.0 ± 58.2	0.4

One subject in each group has myalgia (without CPK elevation). One subject in group I complained of mild polyarthralgia and one subject in group II had insomnia. The percentage of subjects reporting adverse effects were 4.44% in 10 mg group and 4.34% in 40 mg group. There is no significant difference in adverse effects in both 10 mg and 40 mg atorvastatin groups (*p*– value - 0.57) (table 7).

Table 7: Adverse effects in Group I and II

Adverse effect	Group I	Group II
Myalgia	1 (2%)	1 (2.1%)
Polyarthralgia	1 (2%)	0 (0%)
Insomnia	0 (0%)	1 (2.1%)

DISCUSSION

The present study was a hospital based one carried out to compare the safety profile of atorvastatin in low (10 mg) and high (40 mg) doses in post myocardial infarction and post stroke patients. The baseline characteristics were similar in both groups. The drug was well tolerated in both the doses. It is well known that atorvastatin decrease the C- reactive protein values in myocardial infarction and other thromboembolic events due to its anti-inflammatory effect. In the current study, the decrease in CRP from the baseline measured at 6 and 12 weeks were comparable in both the study groups. Changes in serum creatine and uric acid from the baseline showed no statistical significance in both the study groups. Hepatic function is also known to be affected by statin use[10]. This is measured by asymptomatic elevation of liver marker enzymes. In the present study, no subjects had elevated alanine amino transferase (ALT) or SGPT >3 times upper limit for normal. Moderate asymptomatic hepatic transaminase elevations (<3 times upper limit of normal) are common among patients taking statins, but serious liver damage is extremely rare[11]. Whereas nearly 50% of dyslipidaemia patients have coexisting non-alcoholic fatty liver diseases (NAFLD), a condition well known for fluctuating transaminase levels[12,13]. But, related to hepatic function, there were no adverse effects reported in this study by the use of both the doses of atorvastatin. One of the most common complaints related to satin use is its effect on muscular function, ranging from myalgia to myositis. Myopathy is the general term for all potential muscle problems such as muscle pain or weakness and can occur with or without elevated CPK. Statin related myopathy is usually symmetrical, involves large proximal muscle groups and resolves within two months of discontinuation of the medication. It occurs in 5% of the statin treated patients in clinical trials and 10% patients in clinical practice. But severe muscle toxicity from statin therapy is rare. The risk of myopathy is not related to the low density lipoprotein (LDL) lowering efficacy, but the dose or blood concentration of statin[14]. In general elevation of creatinine phosphokinase (CPK) of >10 times upper limit for normal is regarded as significant elevations justifying the discontinuation of statin treatment. However, there were no such cases observed in our study. Furthermore, the elevation of CPK from the baseline were comparable in both the groups at 6 and 12 weeks. The result of present investigation also supports the findings of Baigent *et al.,*[15], reporting that atorvastatin has low rates of myalgia at all doses (10-80 mg/day). The patient characteristics that increase the risk of myopathy include low body mass index, female gender, hypothyroidism, hepatic or renal dysfunction, age >80 years, polypharmacy and the use of medications that interact with statins[16]. No cases of new onset of diabetes mellitus was detected during the 12 weeks study period. Analysing the miscellaneous adverse effects spontaneously reported by the subjects, one subject in each group had myalgia (without CK elevation). There was a single case of mild polyarthralgia in 10 mg group and one case of insomnia in 40 mg group. Our results are consistent with DALI study[17] which showed that the number of adverse effects were same in low and high doses of atorvastatin. Another study by Barakat *et al*.,[18] concludes that different dosages of statins did not significantly affect the serum creatinine and glomerular filtration rate after 2 years. Results of the present investigation also correlate with the previous study of Ye *et al*.,[19] reporting that the overall incidence of treatment-associated adverse events observed with atorvastatin did not increase in the10 - 80 mg dose range. Therefore according to this observational study, there is no significant difference in adverse outcome as far as low dose or high dose of atorvastatin usage is concerned in post coronary or cerebrovascular event therapy. And in addition the drug appeared to be safe and did not produce any major side effects in the study population during this trial.

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