Original Research Article

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A study of effect of low dose atorvastatin therapy on high sensitivity C-reactive protein in patients with modifiable and non-modifiable cardiovascular risk factors in central India

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ABSTRACT

Background: Anti-inflammatory effects of statins have generated maximum interest, as has been demonstrated in a number of studies showing rapid decrease in CRP levels in patients of acute coronary syndromes. This CRP lowering property of statins has also translated into clinical benefits as suggested by reduction in rate of recurrent angina, recurrent myocardial infarction, and mortality.

Methods: This prospective, open, and controlled study was conducted on 160 indoor and outdoor patients, for total duration of two years (2005-2006), in GMC Bhopal, MP, India.

Results: In all the four groups, baseline serum hs-CRP was statistically significant (p value <0.01) higher than normal hs-CRP level. Mean reduction (%) in hs-CRP after 3 months of statin therapy was 83.6% in group A and 62.4% in group C which is highly significant (p value <0.001). In group B also, 26% hs-CRP reduction was noticed which is statistically significant (p value <0.01). Baseline hs-CRP was statistically significant high (p value <0.01) in hypertensive patients. Percentages reduction in group A (87%) and group C (66%) was statistically significant (p value <0.01). Baseline hs-CRP was statistically significant higher (p value <0.01) than normal population. After 3 months of statin therapy percentage reduction in group A and group C was statistically significant (p value <0.01).

Conclusions: Low dose atorvastatin can significantly reduce CRP level in patients with risk factors for cardiovascular disease. Early initiation of low dose atorvastatin can reduce this inflammatory marker in both ACS and high risk for ACS patients and can prevent major adverse cardiac events.

Keywords: Atorvastatin, High sensitivity C-reactive protein, Inflammatory marker

INTRODUCTION

Coronary Artery Disease (CAD) is amongst the leading causes of morbidity and mortality throughout the world. The underlying pathology in majority of the cases is atherosclerosis. Inflammation plays an important role in the onset and development of atherosclerosis but more importantly, inflammation is pivotal in evolution of a silent atherosclerotic plaque to an unstable "vulnerable plaque" leading to acute coronary syndrome.^{1,2}

Angiographic and histopathological studies of coronary arteries of patients who died after an acute Coronary event typically suggest that an intense inflammatory process characterized by presence of monocyte derived macrophages, foam cells and activated T-cells, occurs simultaneously at multiple sites and is maximum at the culprit lesion.^{3,4}

Markers of inflammation are also being investigated as predictors of coronary ischemic events, suggesting the key role of inflammation in progression atherosclerosis. C-Reactive Protein (CRP), an acute phase reactant, is most consistently associated in identifying subjects with greater risk of both first and recurrent cardiovascular events.⁵

Several large scale prospective epidemiological studies have shown that plasma levels of highly sensitive C-reactive protein (hs-CRP) correlate strongly with increased vascular event rates in healthy individuals, in patients with CAD and in patients with Acute Coronary Syndrome (ACS).⁶

Recent studies suggest that raised level of CRP is not merely a marker of inflammation but also an amplifier of it, so CRP is being regarded as an independent cardiovascular risk factor. This observation implies that bringing down the levels of CRP can help in primary as well as secondary prevention of cardiovascular events.⁷ Approximately two-third of total cholesterol in blood is produced endogenously and the rate regulating enzyme is 3-Hydroxy-3-Methyl Glutaryl Co-enzyme A (HMG-CoA) reductase. A wide spectrum of statin mediated actions, like attenuation of inflammation, plaque stabilization, and improvement of endothelial function favorably may contribute to potential benefits of statin therapy in acute coronary syndromes. Such multiple actions of statins, which are independent of cholesterol lowering, have been collectively termed as pleiotropic effects.8

Anti-inflammatory effects of statins have generated maximum interest, as has been demonstrated in a number of studies showing rapid decrease in CRP levels in patients of acute coronary syndromes. This CRP lowering property of statins has also translated into clinical benefits as suggested by reduction in rate of recurrent angina, recurrent myocardial infarction, and mortality. Statins inhibit the mevalonate pathway and thus downregulate prenylation process.⁹

All major statins like Lovastatin, Simvastatin, Pravastatin and Atorvastatin have shown almost similar and significant efficacy in reducing CRP levels, both on short term and long-term basis. However, Atorvastatin in high dose (80mg) is the most widely tried drug for reducing hs-CRP in ACS. The potential of low/moderate dose Atorvastatin in reducing CRP in patients with ACS is largely unknown. Hence this study was designed to evaluate the effect of low dose (20 mg) Atorvastatin on hs-CRP in patients with ACS and high-risk non-ACS patients and to correlate level of hs-CRP and its change with statin therapy with various risk factors and different clinical outcomes.

METHODS

Study design was this prospective, open, and controlled study was conducted on 160 indoor and outdoor patients,

for total duration of two years (2005-2006), in GMC Bhopal, MP, India.

Inclusion criteria

- Patients diagnosed to be suffering from ACS.
- Patients not having acute coronary syndrome but having risk factors like diabetes mellitus, hypertension, positive family history, smoking, obesity, dyslipidemia and postmenopausal state.
- Both males and females between the ages of 28-90 yrs.

Exclusion criteria

- Patients already taking statin and/ or other hypolipidemic drugs.
- Left bundle branch block, paced ventricular rhythm.
- Congestive heart failure, pulmonary edema / left ventricular ejection fraction (EF) < 30%.
- Severe anemia (Hb <5 gm%).
- Hepatic and renal dysfunction.
- Pregnancy or lactation.
- Planned or anticipated coronary revascularization at the time of screening.
- Any history of hypersensitivity or allergy to statin.
- Person suffering from acute systemic infection, rheumatoid arthritis, vasculitis (which is known to give rise to elevated CRP).
- Hypothyroidism.

Patients who fulfilled inclusion and exclusion criteria were enrolled after they signed an informed written consent. After enrollment, a thorough history, clinical examination, and laboratory investigations were done. Study groups patients were divided into following groups:

Group A (n=65): ACS patients who received statin therapy (Atorvastatin 20 mg/day).

Group B (n=30): ACS patients without statin therapy. Patients with ACS, who had not taken Atorvastatin due to any of the following reasons, were included in this group.

- Financial reasons,
- Poor compliance,
- Side effects of statins,
- Contraindications to statins.

Both group A and B also received Aspirin 150 mg, Clopidogrel 75mg, Metoprolol 25-50 mg BD, Ramipril 1.25-5 mg OD.

Group C (n=35): Non-ACS patients who received statin therapy. Patients not having ACS but with risk factors for it were included in this group. They were given Atorvastatin 20 mg/day for 3 months.

Group D (n=30): Non ACS patients who did not receive statin therapy. Inclusion and exclusion criteria were same as group, but these patients had not taken Atorvastatin because of same reason as in group B. The subjects (cases) were followed up for 3 months.

Estimation of serum hs-CRP was done at baseline and end of treatment, using quantitative immunoturbidimetric ultrasensitive kit from Tulip diagnostics, on semi-auto analyzer. CRP ultra is a latex immunoassay developed to accurately and reproducibly measure blood CRP levels in sera. When an antigen - antibody reaction occurs between CRP in a sample and anti CRP antibody which has been absorbed to latex particles, agglutination occurs. This agglutination is detected as an absorbance change. The measuring range of the kit as 0.005-16 mg/dl, the samples showing values higher than the upper limit were prediluted with normal saline and then evaluated.

Statistical analysis

The values included in the results were tabulated and percentage changes were calculated. Data was analyzed

using student's t-test and analysis of variance (ANOVA). Demographic and risk factor profile was analyzed by non-parametric tests. A p value of <0.05 was considered to be statistically significant.

RESULTS

Subjects fulfilling the inclusion exclusion criteria were prescribed Atorvastatin 20 mg 1 daily and followed up for next 3 months after baseline serum hs-CRP estimation. After 3 months, clinical evaluation and serum hs-CRP was repeated. Cardiac events were recorded and analysed for correlation with statin therapy and hs-CRP. On this basis following observations were recorded.

HTN was most common risk factors in both ACS and non-ACS groups (52.6% and 60% respectively) followed by smoking, DM, Family history of CAD, obesity, and dyslipidemia. Post-menopausal status was more common (16.8%) in ACS group as compare to non-ACS group (7.7%) (Table1).

Table 1: Cardiovascular risk factors profile of patients at baseline.

Risk factor	Group A	Group B	Total ACS patients	Group C	Group D	Total non- ACS patients	Total patients
HTN	32(49.2%)	18(60%)	50(52.6%)	21(60%)	18(60%)	39(60%)	89(55.6%)
DM	21(32.3%)	14(46.6%)	35(36.8%)	16(45.7%)	12(40%)	28(43%)	63(39.3%)
Smoking	34(52.3%)	15(50%)	49(51.5%)	15(42.8%)	16(53.3%)	31(47.6%)	80(50%)
Obesity	17(26.1%)	9(30%)	26(27.3%)	11(31.4%)	7(23.3%)	18(27.6%)	44(27.5%)
Dyslipidemia	20(30.7%)	7(23.3%)	27(28.4%)	11(31.4%)	8(26.6%)	19(29.2%)	46(28.7%)
Family H/o CAD	20(30.7%)	11(36.6%)	31(32.6%)	9(25.7%)	7(23.3%)	16(24.6%)	47(29.3%)
Postmenopausal status	11(17%)	5(16.6%)	16(16.8%)	1(2.8%)	4(13.3%)	5(7.7%)	21(13.1%)
Total	65	30	95	35	30	65	160

HTN- Hypertension, DM- Diabetes mellitus, CAD- Coronary artery disease, H/o- History of

Table 2: Serum level of hs-CRP at baseline and end of 3 months treatment.

Groups	Baseline hs- CRP (mg/dl)	After 3 months hs-CRP (mg/dl)	Mean (%) Change
Group A	4.84	0.79	4.05(83.6% reduction)
Group B	4.79	3.54	1.25(26% reduction)
Group C	2.05	0.77	1.28(62.4% reduction)
Group D	1.96	2.09	-0.13(12.7 % increase)

In all the four groups, baseline serum hs-CRP was statistically significant (p value <0.01) higher than normal hs-CRP level. Mean reduction (%) in hs-CRP after 3 months of statin therapy was 83.6% in group A

and 62.4% in group C which is highly significant (p value<0.001). In group B also, 26% hs-CRP reduction was noticed which is statistically significant (p value<0.01) (Table 2).

In all the groups, baseline hs-CRP was statistically significant higher (p value <0.01) in hypertensives. Percentages reduction in group A (87%) and group C (66%) was statistically significant (p value <0.01). Baseline hs-CRP was statistically significant higher (p value <0.01) than normal population. After 3 months of statin therapy percentage reduction in group A and group C was statistically significant (p value <0.01) (Table 3).

There was significant (p value <0.01) rise in baseline hs-CRP in smokers in all the four groups. After 3 months of statin therapy, a statistically significant (p value <0.01) reduction of 80.62% and 61.9% was noted in groups A and C respectively.

Table 3: Serum level of hs-CRP (in mg/dl) at baseline and end of treatment (3 months) in hypertensive patients of all groups.

Hypertensive Patients			Diabetic Patients hs-CRP			
Groups	Baseline	After 3 months	Mean change	Baseline	After 3 months	Mean change
Group A	6.18	0.78	5.4(87% reduction)	6.17	0.93	5.24(84.9% reduction)
Group B	5.28	3.96	1.32(25% reduction)	4.16	3.02	1.14(27.4% reduction)
Group C	1.98	0.67	1.31(66.16% reduction)	2.2	0.79	1.41(64% reduction)
Group D	2.16	2.31	-0.15(7% increased)	1.98	2.2	-0.22(11.1% Increase)

Table 4: Level of hs-CRP at baseline and end of treatment (3 months) in smokers and dyslipidemic patients of all groups.

	Patients wi	th smoking		Patients with dyslipidemia		
Cround	hs-CRP			hs-CRP		
Groups	Baseline After 3 months		Mean change	Baseline	After 3 months	Mean change
Group A	4.49	0.87	3.6(80.6% reduction)	6.83	0.95	5.88(86% reduction)
Group B	4.65	3.33	1.32(28.4% reduction)	4.06	2.96	1.1(27% reduction)
Group C	2.1	0.8	1.3(61.9% reduction)	1.56	0.59	0.97(62.1% reduction)
Group D	2.2	2.41	-0.21(9.54% increased)	2.06	2.46	-0.4(19.4% Increase)

Table 5: Level of hs-CRP (in mg/dl) baseline and end of treatment at 3 months in obese patients and patients with family h/o CAD in all groups.

	Obese Pat	tients		Patients with family h/o CAD		
Groups	hs-CRP			hs-CRP		
Groups	Baseline	After 3 months	Mean change	Baseline	After 3 months	Mean change
Group A	5.45	0.92	4.53(83% reduction)	4.74	0.71	4(85% reduction)
Group B	6.11	4.26	1.85(30.2% reduction)	4.27	3.21	1.06(24.82% reduction)
Group C	1.56	0.59	0.97(62.17% reduction)	1.49	0.57	1.92(61.7% reduction)
Group D	2.28	2.6	-0.32(14% increased)	1.84	2.1	-0.26(14.1% Increase)

Baseline hs-CRP was statistically significant higher (p value <0.01) in dyslipidemic patients of all groups. Hs-CRP reduction after 3 months was statistically significant in group A and group C (p value <0.01) (Table 4).

In obese patients of all groups, baseline hs-CRP was statistically significant (p value <0.01) higher. After statin therapy, percentage reduction of hs-CRP by 83.11% in group A and 62.17% in group C was statistically significant (p value <0.01). Baseline hs-CRP was statistically significant high in patients with family history of CAD. A statistically significant reduction of hs-CRP by 85% in group A and 61.7% in group C was noticed at the end of statin therapy (Table 5).

Baseline hs-CRP of post-menopausal females was significantly higher (p value <0.01) in all the groups. After 3 months of statin therapy, its percentage reduction was also statistically significant (p value <0.01) in group A and group C (Table 6).

Table 6: Level of hs-CRP (in mg/dl) at baseline and end of treatment (3 months) in post-menopausal females of all groups.

	Post-menopausal females					
Groups	hs-CRP					
	Raseline		Mean change			
	20,5011110	months				
Group A	0.70	0.4	0.3(42.8% reduction)			
Group B	5.63	3.86	1.77(32% reduction)			
Group C	3.2	1.2	2.0(62.5% reduction)			
Group D	1.22	1.37	-0.15(12.3% increase)			

DISCUSSION

The present study was undertaken to assess the effect of low dose Atorvastatin on hs-CRP in acute coronary syndromes and in patients having risk factors for acute coronary syndromes and correlation of hs-CRP levels with risk factors and clinical outcomes of ACS.

The demographic characteristics of patients in all four groups (group A- ACS with statin therapy, group B ACS without statin therapy, group C - non-ACS with statin therapy, group D-non-ACS without statin therapy) were comparable at baseline. There were more males in both the groups. The demographic profile in this study is consistent with previous studies in which acute coronary syndrome is reported to mainly affect middle aged men.¹⁰

The primary outcome parameter for efficacy comparison was change in hs-CRP levels. In the present study hs-CRP levels decreased significantly (83.6%) in group A which was treated with 20 mg of Atorvastatin for 3 months. The level of CRP also decreased (26%) in group B (control) (patients with ACS who had taken statin). The fall in hs-CRP was more in group A as compared to group B his greater reduction of hs-CRP in group A is likely to be caused by additional effect of Atorvastatin.

In group C which consisted of non-ACS patients who were having risk factors for ACS, Atorvastatin 20 mg per day for 3 months resulted in 62.4% hs- CRP reduction. While in the group of non-ACS patients, who had not taken statins (group D), increase at 12.7/% hs-CRP was found. This finding is suggestive of beneficial effect of statins in reducing hs-CRP in patients having risk factors for ACS.

The results of present study are in agreement with previous studies which have used different statins (Pravastatin, Simvastatin, Lovastatin and Atorvastatin) in different doses to show the effect of statin therapy on hs-CRP.¹¹

Two large scale observational studies reported a decrease of hs-CRP in range of 12-15% with the use of 20 mg Lovastatin or 40 mg Pravastatin or 80 mg Atorvastatin over a period of one year of follow up. 12 A community based prospective randomized trial in patients with established CAD showed that 40 mg Pravastatin resulted in 14% reduction in hs-CRP at 12 weeks. 13

Deshpande et al, showed a decrease of 24% n CRP alter 4 weeks of 13.8 mg/day of simvastatin and 17 mg/day of atorvastatin. In a Turkish study there was 47% reduction in CRP with 20 mg Atorvastatin after 4 weeks of t in patients with coronary artery disease. Is

Elevated hs-CRP has been linked with risk for CVD, including first and recurrent coronary events and poor outcome in acute coronary syndromes. Studies have shown that statin therapy reduces the risk of first acute coronary event and stroke associated with elevated CRP and recent evidence suggests that patients who have low CRP levels after statin therapy have better clinical outcome.¹⁶

In the present study, there was a highly significant reduction (83.6%) in hs- CRP level with 20 mg of Atorvastatin given for 3 months in patients with acute coronary syndromes and 62.4% in high risk non-ACS patients. The difference between degree of fall in hs-CRP in this study and other studies could be attributed to choose of patients (mainly ACS patients and at risk patients tor ACS). Another reason may be that different statins have variable anti-inflammatory effects.

In this study there was a decline of 20% n hs-CRP level in group B (control) also, who had not taken statin. This can be explained as aspirin, beta blockers and ACE inhibitors have also been proposed to have anti-inflammatory properties. Secondly, it could be due to stabilization of plaque leading to regression of inflammatory state.

In present study, an increase in hs-CRP by 12.79% was noticed effects of patients who had not taken statins as patients were devoid of beneficial effect of statin.

Very few studies have assessed the effect of low dose statins in patients with established coronary artery disease or ACS or at-risk patients for ACS. Results of this study show a significant reduction in hs CRP in patients of ACS with just 20mg Atorvastatin given for 3 months. The effect of low dose atorvastatin on hs-CRP may be of particular interest in view of new data emerging on early intervention with statins in ACS and high-risk group for ACS.

CONCLUSION

CRP is important risk factor for inflammation in both ACS and non-ACS patients. Low dose atorvastatin can significantly reduce CRP level in patients with risk factors for cardiovascular disease. Early initiation Low dose atorvastatin can reduce this inflammatory marker in both ACS and high risk for ACS patients and can prevent major adverse cardiac events.

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