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Review Article

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A Comparative study on the effect of HMG-CoA reductase inhibitors on C-Reactive Protein in patients with Acute Coronary Syndrome

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Abstract

Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications. Statins have diverse effects on the cellular mediators of inflammation and immunity that may be partially responsible for their efficacy in preventing cardiovascular disease, and which have encouraged their use in treating immune/inflammatory diseases. C-reactive protein (CRP) has emerged as a very important marker of inflammation. Concentrations of highly sensitive (hs)-CRP correlate strongly with increased vascular event rates in patients with acute coronary syndrome (ACS).As there are only few comparative studies in Indian literature regarding the effect of HMG –CoAreductase inhibitors on C-reactive protein in patients with acute coronary syndrome**,** the present study is undertaken.

Keywords: Acute coronary syndrome, HMG-CoA reductase inhibitors, Atorvastatin, Rosuvastatin, C - reactive protein (CRP),High-Sensitivity C-Reactive Protein (hs-CRP).

Introduction

Acute Coronary Syndrome (ACS) is a syndrome due to decreased blood flow in the coronary arteries such that part of the heart muscle is unable to function properly or dies. The most common symptom is chest pain, often radiating to the left arm or angle of the jaw, pressure-like in character, and associated with nausea and sweating. The most dramatic presentation of coronary artery disease resulting in increased mortality is acute coronary syndrome which covers a group of clinical conditions including acute ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI) and unstable angina (UA).These types are named according to the appearance of the electrocardiogram.

ACS should be distinguished from stable angina, which develops during exertion and resolves at rest. In contrast with stable angina, unstable angina occurs suddenly, often at rest or with minimal exertion, or at lesser degrees of exertion than the individual's previous angina ("crescendo angina"). New onset angina is also considered unstable angina, since it suggests a new problem in a coronary artery. Though ACS is usually associated with coronary thrombosis, it can also be associated with cocaine use. Cardiac chest pain can also be precipitated by anemia, bradycardias or tachycardias.

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Inflammation plays an important role in the onset and development of atherosclerosis which is the underlying cause of ACS. Recently markers of inflammation are being investigated as predictors of coronary ischemic events suggesting the key role of inflammation in progression of atherosclerosis.

Statins, also known as HMG-CoA reductase inhibitors, are a class of lipid-lowering medications. Statins have been found to reduce cardiovascular disease (CVD) and mortality in those who are at high risk. The evidence is strong that statins are effective for treating CVD in the early stages of a disease (secondary prevention) and in those at elevated risk but without CVD (primary prevention). Side effects of statins include muscle pain, increased risk of diabetes mellitus,and abnormalities in liver enzyme tests. Additionally, they have rare but severe adverse effects, particularly muscle damage. Contraindications of Statins include Pregnancy and Breastfeeding, Active Liver Disease, Elevation of Liver Enzymes and Allergic Reactions. They inhibit the enzyme HMG-CoA reductase which plays a central role in the production of cholesterol. High cholesterol levels have been associated with cardiovascular disease.

C-reactive protein , an acute phase reactant, is one of the most widely known biomarkers of cardiovascular disease. Concentrations of hs-CRP correlate strongly with increased vascular event rates in patients with acute coronary syndrome (ACS) .Anti-inflammatory effects of statins characterized by CRP lowering have generated maximum interest in reducing coronary events . All major statins have shown almost similar efficacy in reducing CRP concentrations, using equipotent doses. Apart from having cholesterol lowering effect, a wide spectrum of statin mediated actions like attenuation of inflammation, plaque stabilization and improvement of endothelial dysfunction may contribute to potential benefits of statin therapy in ACS. Such multiple actions of statins which are independent of cholesterol lowering have been collectively termed as “pleiotropic effects”. This study was planned to compare the effect of HMG-CoA reductase inhibitors (atorvastatin and rosuvastatin) on CRP in patients with acute coronary syndrome.

Review of literature

1.Bijan Zamani [1]et al**;(2016)** conducted a prospective randomised clinical trial study on Effects of high versus low-dose atorvastatin on high sensitive C-reactive protein in acute coronary syndrome on on 180 patients who had developed coronary artery disease . The patients were divided randomly into two groups and then two therapeutic protocols were given to them. One group medicated by high-dose atorvastatin (40 mg) and the other group received low-dose atorvastatin (20 mg). There were 180 patients consisted of 34 females and 56 males in low-dose atorvastatin group (L-DA group), and 30 females and 60 males in high-dose atorvastatin group (H-DA group) (P = 0.533). In this study atorvastatin in high doses decreased hs-CRP levels about 40% and in low doses it only caused decrease of 13.3%, and significant correlation was observed between two groups (Paired Sample T-test) (P = 0.001). Also atorvastatin in high doses decreased LDL levels about 23% and in low doses it only decreased 10%, and significant correlation was observed between two groups (Paired Sample T-test) (P = 0.001). Atorvastatin in high doses decreased HDL levels about 9% and in low doses it only decreased 6%, and again significant correlation was observed between two groups (P = 0.009). The present study confirms the novel observation that atorvastatin therapy results in a significant reduction in hs-CRP levels.

2.**Karaca**[2] *et al* **; (2003)** Conducted a study on “ Atorvastatin affects C-reactive protein levels in patients with coronary artery disease”. After measuring the baseline levels of CRP and lipid fractions, the patients were divided into two groups. In Group A (n = 46), atorvastatin (20 mg/day) was administered in addition to classic antianginal treatment (beta-blocker, nitrate and aspirin). In Group B (n = 32), the usual antianginal treatment was continued. Following 4 weeks of treatment the same measurements were repeated. In Group A, CRP decreased from 20.3 mg/dl to 10.8 mg/dl (p < 0.001). In Group B, CRP decreased from 17 mg/dl to 12.8 mg/dl (p < 0.01). The decrease in group A was more than in group B (p = 0.003). In patients with CAD, atorvastatin exerted an anti-inflammatory effect represented by decreasing CRP levels. This effect was independent of the change in low density lipoprotein cholesterol (LDL-C) or high density lipoprotein cholesterol (HDL-C) levels.

3.Ankur Gupta[3]*et al*;**(2008)** conducted aprospective, open study on “Effect of atorvastatin on hs-CRP in acute coronary syndrome”. The study was conducted on 100 patients enrolled over a period of 15 months. The aim of the study is to evaluate the effect of a lower dose (20 mg) of atorvastatin on hs-CRP concentrations in patients with ACS. The patients were divided into two groups. Group A (n = 50) patients received atorvastatin 20 mg dayfor 4 weeks in addition to standard anti-anginal treatment. Group B (n = 50) patients received standard anti-anginal treatment without atorvastatin. The hs-CRP concentrations decreased in both groups, but the decrease was greater in group A. The decrease in hs-CRP was also significantly greater in the subgroups of smoking, hypertension and past history of cardiovascular disease with atorvastatin. The use of a lower dose (20 mg) of atorvastatin can offer an attractive approach for early treatment of patients with ACS.

4. Ridker PM[4]*et al* **;(2001)** conducted a randomized study on “Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events.” The level of C-reactive protein was measured at base line and after one year in 5742

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participants in a five-year randomized trial of lovastatin for the primary prevention of acute coronary events. The rates of coronary events increased significantly with increases in the base-line levels of C-reactive protein. Lovastatin therapy reduced the C-reactive protein level by 14.8 percent (P<0.001), an effect not explained by lovastatin-induced changes in the lipid profile. As expected, lovastatin was effective in preventing coronary events in participants whose base-line ratio of total cholesterol to high-density lipoprotein (HDL) cholesterol was higher than the median ratio, regardless of the level of C-reactive protein (number needed to treat for five years to prevent 1 event, 47; P=0.005). However, lovastatin was also effective among those with a ratio of total to HDL cholesterol that was lower than the median and a C-reactive protein level higher than the median (number needed to treat, 43; P=0.02). In contrast, lovastatin was ineffective among participants with a ratio of total to HDL cholesterol and a C-reactive protein level that were both lower than the median (number needed to treat, 983; P=0.80). Statin therapy may be effective in the primary prevention of coronary events among subjects with relatively low lipid levels but with elevated levels of C-reactive protein.

5.Balk EM[5] *et al* ;**(2003)** conducted a study on "Effects of statins on nonlipid serum markers associated with cardiovascular disease". Studies reporting original data in at least 10 participants on the effect of statins on outcomes of interest, excluding studies of cerivastatin, drug combinations, and patients with organ transplants. All statins are effective at lowering C-reactive protein levels, and the effect is not dose-dependent. Amongnonlipid serum markers examined, only C-reactive protein levels are statistically significantly affected by statins. These findings suggest that statin-mediated anti-inflammatory effects may contribute to the ability of statins to reduce risk for cardiovascular disease. Overall, however, available data are insufficient to support recommendations for using nonlipid serum markers in decisions regarding statin therapy for individual patients.

6.Macin SM[6] *et al*; **(2005)** conducted a randomized, double-blind, placebo-controlled study on "acute anti-inflammatory effect atorvastatin in patients with acute coronary syndrome".CRP levels are associated with cardiovascular risk. This study was conducted on 90 consecutive patients admitted within 48 hours of onset of ACS with CRP levels > or =1.4 mg/dL. Patients were assigned to atorvastatin 40 mg daily or placebo over 30 days. C-reactive protein levels, lipid profiles, serum fibrinogen, white cell count, and erythrocyte sedimentation rate were measured at entry, hospital discharge, and 1 month later. No correlation was found between changes in CRP and cholesterol levels. C-reactive protein levels in ACS were rapidly reduced with atorvastatin. These data provide evidence that statins have fast and early anti-inflammatory effects in addition to lipid-lowering effects in ACS.

7.Suyog Sindhu[7] *et al* ; **(2011)** conducted a study on Effects of atorvastatin and rosuvastatin on high-sensitivity C-reactive protein and lipid profile in obese type 2 diabetes mellitus patients. A total of 40 subjects with 20 in each group were randomly allocated to two groups. Group 1 patients received atorvastatin and that of Group 2 rosuvastatin treatment for 6 months. The patients were administered atorvastatin (40-80 mg) and rosuvastatin(10-40 mg) in accordance to their LDL-C status as per NCEP-ATP III guidelines. The parameters studied were, hs-CRP and lipid profile comprising LDL-C, HDL-C, TG and TC. Results obtained from the study, clearly indicate that atorvastatin (A) as well as rosuvastatin(R) have significant effect on lowering of hs-CRP levels (for A *P*=0.001; for R *P*=0.002), reducing LDL-C levels (for A *P*=0.008; for R *P*=0.001), elevating HDL-C levels (for A P=0.02; for R *P*=0.001) along with reducing TC (for A *P*=0.003; for R *P*=0.002) and TG (for A *P*=0.000; for R *P*=0.000) levels in obese T2DM patients. It is also seen that there is no significant (*P*>0.05) difference in effect of atorvastatin and rosuvastatin in lowering of hs-CRP levels, elevating HDL-C levels and reducing TG levels in obese T2DM patients. However, percentage lowering of LDL-C (P=0.000) and TC (*P*=0.001) by rosuvastatin is to a greater extent than that caused by atorvastatin in these patients. Thus this study throws light on the fact that rosuvastatin should be preferred over atorvastatin in obese T2DM patients in whom LDL-C and TC levels are deviated from normal reference values. In rest of obese T2DM either of atorvastatin or rosuvastatin can be employed to lower hs-CRP levels, to elevate HDL-C levels or to reduce TG levels.

8. Michael F. Bullano[8] *et al*; **(2007)** conducted a retrospective, longitudinal cohort study on "Effectiveness of rosuvastatin versus atorvastatin in reducing lipid levels and achieving low-density-lipoprotein cholesterol goals in a usual care setting". Approximately 8 million members were extracted and used in this retrospective, longitudinal cohort study. Patients age 18 years or older who were newly initiated on rosuvastatin or atorvastatin, were included. Changes in lipid levels and attainment rates of goal LDL cholesterol levels were estimated after accounting for baseline covariates using regression techniques. A total of 453 patients met the study criteria. The mean dose of rosuvastatin was 11 mg compared with 15 mg for atorvastatin. No significant differences were found in HDL cholesterol and triglyceride levels between groups. Patients treated in a usual care setting with rosuvastatin had significantly greater reductions in LDL cholesterol, non-HDL cholesterol, and total cholesterol levels compared with those receiving atorvastatin.

Conclusion

HMG-CoA reductase inhibitors (statins) are a class of lipid-lowering medications. Statins have been found to reduce cardiovascular disease .C-reactive protein, a

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marker of inflammation, is a potential predictor of cardiovascular disease risk, and statins reduce CRP levels. A high-sensitivity C-reactive protein (hs-CRP) test may be used to help evaluate an individual for risk of cardiovascular disease. A large number of studies have been conducted to examine the effects of HMG-CoA reductase inhibitors on C-reactive protein. This review concluded that both atorvastatin and rosuvastainhave significant effect on lowering CRP levels in patients with acute coronary syndrome.

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