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SHORT TERM EFFECTS OF ROSUVASTATIN ON PLASMA CONCENTRATION OF HIGH SENSITIVITY C-REACTIVE PROTEIN IN PATIENTS WITH CHRONIC STABLE ANGINA

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ABSTRACT

Objective: To determine the short term effects of rosuvastatin on elevated base line high-sensitivity C-reactive protein (hs-CRP) in patients with chronic stable angina.

Methodology: This Quasi-experimental comparative study was conducted in Cardiology department, Lady Reading Hospital Peshawar, between March 2010 and February, 2011. We selected 44 consecutive patients age 40 years or above, of any gender having hs-CRP levels $\geqslant$1.2mg/l with chronic stable angina. Base line levels of hs-CRP, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and creatine phosphokinase (CPK) were measured in fasting status. These patients were treated with rosuvastatin 20 mg once daily at night and followed up for one month. Using SPSS version 16 data was analyzed.

Results: Mean age was 53$\pm$7.2 and 50% were females. Following treatment with rosuvastatin 20mg for one month the mean hs-CRP levels reduced from 4.08$\pm$2.56 to 2.72$\pm$2.40 (95%CI, 0.41 to 2.29, p=0.006). Similarly mean total cholesterol levels decreased from 185.88$\pm$37.62 to 147.45$\pm$38.35, (p=0.0001). LDL cholesterol decreased from 118.34$\pm$31.31 to 86.63$\pm$35.72 (p= 0.0001). But mean HDL cholesterol had no significant increase from baseline levels i.e. from 32.18$\pm$9.93 to 33.95$\pm$7.65 (p=0.174). TGs levels reduced from 240.11$\pm$123.66 to 197.43$\pm$88.24 (p=0.008). Mean CPK levels did not differ significantly from base line at follow up, from 101.43$\pm$58.63 to 96.22$\pm$55.10 (p=0.646).

Conclusion: Short term treatment with rosuvastatin significantly decreases elevated hs-CRP levels in patients with chronic stable angina.

Key Words: hs-CRP, chronic stable angina, rosuvastatin, lipid profile

INTRODUCTION

Worldwide, symptomatic coronary artery disease in patients with chronic stable angina is frequently treated by percutaneous coronary intervention, but recent evidence has not shown significant improvement in reducing mortality with this approach vs. modern medical therapy.[1] It is increasingly clear that cardiovascular outcomes depend on an understanding of the biology of atherosclerotic disease, which may involve vascular inflammation, endothelial dysfunction, and plaque instability.[2] That is why current research is focusing more on finding newer therapeutic target to maximize modern medical therapy. One such target recently identified is high sensitivity C-reactive protein (hs-CRP), which is an inflammatory biomarker and a novel risk factor as well.[3] Patients with chronic stable coronary artery disease are having elevated base line hs-CRP levels[4] and is associated with rapidly progressive coronary artery disease in patients with stable angina.[5]

Statins therapies reduce vascular inflammation and improve endothelial function.[6] Various trials have confirmed that statin therapy reduces hs-CRP levels[7] and this has been observed among healthy persons,[8] patients with stable coronary artery disease,[9] and those with the acute coronary syndrome.[10] Other secondary prevention trials have reported that reduction in hs-CRP levels with statin therapy were associated with regression in atheroma burden[11] as well as reduced cardiovascular events rate like myocardial infarctions, revascularization and deaths.[12] The aim of this study was to determine the short term effects of rosuvastatin on elevated base line hs-CRP in patients with chronic stable angina.

METHODOLOGY

This quasi-experimental comparative study was carried out at the department of cardiology, Lady Reading Hospital, from March 2010 to February 2011. All patients age 40 years or above, of any gender that had chronic stable angina, visiting our cardiology out patients department who were willing to give consent were included in the study. Patients with following characteristics were excluded;

1. Previous or current use of rosuvastatin therapy.

2. Patients who had acute coronary syndrome or any sort of coronary intervention within one month from the time of induction to study were excluded, a period adequate for any residual effects of acute ischemia or stress on hs-CRP levels, to disappear.[13]

3. Patients with inflammatory conditions such as recent acute illness ($\leqslant$1 month duration), severe arthritis, lupus.[16]

4. Patients having history of taking immunosuppressant agents such as cyclosporine, antituberculous like Rifampin, antiepileptic like phenytoin, and antifungal like Ketoconazole.

Using WHO software for sample size calculation, the sample size was calculated as 44 cases with average 4.2mg/l $\pm$2.68 SD[8] of base line hs-CRP, 2.2mg/l $\pm$2.0SD[8] of achieved hs-CRP, 95% power of test, 5% significance level and 2.80 combined standard deviation of high-sensitivity C-reactive protein.[8]

After taking approval from hospital ethical committee, a total 44 consecutive patientsr having hs-CRP levels $\geqslant$ 1.2mg/l presented with chronic stable angina were selected. Patients with baseline levels more than 10mg/l were reevaluated after minimum of 3 weeks. The diagnosis of chronic stable angina was made in the presence of at least one of the following criteria; (1) a history of characteristic chest pain or discomfort (constricting in nature, radiating to jaw and or left arm for $\leqslant$ 30 min) provoked by exercise, relieved on rest and or nitrates (up to 1.5mg sublingual) administration, and or (2) evidence of reversible ischemia on exercise electrocardiography or other imaging studies. Canadian Cardiovascular Society functional class (CCS) was used for the assessment of severity of angina. Base line levels of hs-CRP, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides were measured on fasting serum in hospital laboratory. The Tina-quant CRPHS immunoturbidimetric assay for hs-CRP from Roche was used. Hitachi P-800 System Pack performed all analysis. These patients then were treated with rosuvastatin 20 mg in open label fashion once daily at night and followed up for one month. Short term effects were 5% decrease in hs-CRP levels (termed as achieved hs-CRP) from baseline with or without any change in the angina function class of patients' symptoms following administration of rosuvastatin 20 mg daily for one month.

Data was analyzed using SPSS version 16. Categorical variables were presented as frequencies and percentages. Numerical variables were presented as Median and Mean $\pm$SD. Mean differences of hs-CRP and lipid profiles were compared by paired Student's t test. Correlation between continuous variable and categorical variables were determined by Pearson's correlation and chi square test, respectively. P value $\leq$0.05 was considered significant.

RESULTS

A total of 61 chronic stable angina patients were evaluated to select 44 patients with hs-CRP levels 1.2mg/l or more. Base line characteristics of patients, their mean hs-CRP levels and lipid profile are shown in Table 1.

Base line hs-CRP levels had no significant correlations to age ($r = 0.024$, $p = 0.879$), total cholesterol ($r = -0.067$ $p = 0.664$), LDL cholesterol ($r = -0.046$, $p = 0.767$), HDL cholesterol ($r = -0.66$, $p = -0.672$) Triglycerides ($r = 0.117$, $p = 0.449$) or CPK levels ($r = 0.118$, $p = 0.444$s).

All 44 patients were available at their 30th day follow up. They all took rosuvastatin 20mg tablets once daily for 30

days. Mean follow up hs-CRP levels were reduced from 4.08±2.56 mg/l to 2.72±2.40 mg/l with their range from 0.4mg to 9.5mg/l. This was statistically significant reduction with 95% confidence interval from 0.41 to 2.29 and p=0.006. Thus Achieved hs-CRP levels were reduced by 33.33% of base line mean levels and 37.7 % of base line median hs-CRP levels at one month follow up. Similarly mean total cholesterol levels decreased significantly from 185.88 ±37.62 (112-275) to 147.45±38.35 (34-217) {95%CI, 25.29 to 51.39, p<0.0001} with 20.5% reduction of the baseline mean. LDL cholesterol also decreased from 118.34 ±31.31 (49-176) to 86.63 ±35.72 (13-166) {95%CI, 19.29 to 44.11, p<0.0001}, [27% reduction of the baseline mean]. Triglycerides levels reduced from 240.11 ±123.66 (73-628) to 197.43 ±88.24 (56-447) {95%CI, 11.52 to 73.83, p=0.008}, [17.9% reduction of the baseline mean]. But mean HDL cholesterol had no significant increase from baseline levels 32.18 ±9.93 (16-65) to 33.95 ±7.65 (21-51) {95%CI, –4.36 to 0.81, p=0.174}, [-3% increase of the baseline mean], as well as mean CPK levels did not differ significantly from base line at follow up, {from 101.43 ±58.63 (46-333) to 96.22 ±55.10}(10-292) {95%CI, -17.43 to 27.88, p=0.646}, [0.05% reduction of the baseline mean]. Follow up hs-CRP levels had no significant correlation to age or lipid profile as shown in Table 2.

There was nonsignificant trend (P=0.305) toward improved angina functional class symptoms after treatment as 45.5% of patients were having CCS-I symptoms as compared to 22.7% before treatment. Similarly none of the patients was having CCS-IV symptoms (Table 3).

Table 1: Base line Characteristics

Total no. of patients	**44**
Age-----yr	
Mean	53 ±7.2
Range	40-70
Female-------% (n)	50 (22)
Angina functional class	
*CCS-Class-I	22.7% (10)
CCS-Class-II	54.5% (24)
CCS-Class-III	18.2% (8)
CCS-Class-IV	4.5% (2)
Hs-CRP levels(mg/l)	
Mean	4.08±2.56 (1.2-9.90)
Median	3.05
Inter quartile range	2.1-5.6
Mean total Cholesterol (mg/dl)	185.88±37.62 (112- 275)
Mean LDL Cholesterol (mg/dl)	118.34 ±31.31 (49-176)
Mean HDL Cholesterol (mg/dl)	32.18 ±9.93 (16-65)
Mean Triglyceride (mg/dl)	240.11 ±123.66 (73-628)
Mean CPK (IU)	185.88±37.62 (112- 275)

* Canadian Cardiovascular Society functional class

Table 2: Pearson Correlation of Follow up hs-CRP Levels to Age and Follow up Lipid Profile

	Age	**Total Cholesterol**	**LDL Cholesterol**	**HDL Cholesterol**	**TG Cholesterol**	**CPK***
Pearson Correlation (r)	0.012	-0.148	-0.143	-0.221	-0.029	-0.141
P- value	0.936	0.339	0.355	0.149	0.852	0.362

*Creatine Phosphokinase

Table 3: Follow up Canadian Cardiovascular Society Angina Function Class and Achieved hs-CRP levels

Angina FC	Frequency	Percent	Chi-Square Tests
CCS-I	20	45.5	P=0.305
CCS-II	21	47.7	
CCS-III	3	6.8	
Total	44	100.0	

DISCUSSION

Mean age of our patients with chronic stable angina was much younger (53±7.2 yrs) as compared to the European population[14] this is in consistent with frequent premature CAD disease occurrence in south Asian population.[15] The present study illustrated that plasma hs-CRP levels were significantly reduced from base line mean following one month treatment with rosuvastatin in patients with chronic stable angina. We have achieved 33.3% reduction in mean hs-CRP levels (corresponds to 37.7% reduction of lower quartile of achieved median hs-CRP levels). This was far greater reduction than our target of 5%. Similarly, total cholesterol decreased by 20.5%, LDL cholesterol by 27% and triglycerides by 17.9% of their respective mean levels. But mean HDL cholesterol had no significant increase from baseline levels i.e. about 3% increase from base line mean levels. These results were in consistent with our study hypothesis generating JUPITER trial.[8] In that study Ridker et al demonstrated that treatment with rosuvastatin had led to 37% reduction of lower median hs-CRP levels, 50% reduction in the median LDL cholesterol and 17% in the median triglycerides levels, while HDL cholesterol increased by 4% at 12 month follow up. All these effects were statistically significant.[8] As their 12 month follow up median CRP levels were same as that of 36 month follow up (2mg/l), we can assume that rosuvastatin brings down hs-CRP levels significantly earlier in the course of treatment which is maintained for longer time with continued treatment.[8] Moreover, we demonstrated rosuvastatin effect on low base line hs-CRP levels (⩾1.2mg/l) as compared with JUPIETR (⩾2mg/l), which was previously not studied.[8] JUPITER had also shown that reduction in hs-CRP levels were associated with reduction in primary end point of the study including death from cardiovascular causes, non fatal MI, non fatal stoke or unstable angina.[8]

Jacques et al determined that effects of atorvastatin on changes in hs-CRP levels were dose dependent.[16] It has also been reported that rosuvastatin is more potent than atorvastatin in reducing the baseline hs-CRP and LDL cholesterol levels.[17] We used rosuvastatin in 20mg dosage which is higher than one routinely prescribed dose which could be account for more robust reduction in hs-CRP levels. None of our study patients has complained of any statin related side effects especially myositis or myopathy. Base line levels of serum CPK measured 101.43IU were paradoxically little reduced 96.22IU at follow up. Though this reduction is too little but can account for anti inflammatory properties of rosuvastatin.[18] A Meta analysis of 18 trials reported that Statin related myopathy (CPK >10 times the upper limit of normal) are infrequent.[19]

This study failed to determine statistically significant correlation between severity of anginal symptom and achieved CRP levels at follow up. But this is in contrast to the recent research that has demonstrated that in patients with stable angina, atorvastatin was found as effective as the well-established anti-anginal therapy, amlodipine.[20] This failure in the present study may be because of either our study follow up period was much shorter or we did not evaluate patients objectively by standard methods to illicit symptoms and ischemia.

We identified no relation of either base line or follow up hs-CRP levels to the age, gender or lipid profile. This was previously reported in JUPITER trial that the relative hazard reductions for the primary end points including levels of hs-CRP were independent of age, gender or lipid profile.[21]

In the current strategies of global risk assessment in patients with known CAD disease,[22] lipid testing is the only blood test routinely recommended. But hs-CRP levels are independent risk predictors for functional status of the patients, future vascular events and even arterial remodeling in patients with chronic coronary artery disease.[23-25] Thus hs-CRP levels evaluation may have the potential to improve cardiovascular risk prediction models in secondary prevention of CAD.

The present study has certain limitations. First, it was single centre non randomized trial. Second, objective methods for evaluation of anginal symptoms and ischemia were not followed in the present study.

CONCLUSION

Short term treatment with rosuvastatin significantly decreased elevated base line hs-CRP levels in patients with

chronic stable angina. However, further multi-centre randomized trial may be required to determine the benefit of such reduced hs-CRP levels in term of anginal symptoms and recurrent ischemic events in the local population.

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