A Study on Prevalence of Elevated HSCRP in Acute Vascular Events

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ABSTRACT

Introduction: Acute vascular events like coronary and cerebrovascular accidents continue to be a major public health problem in the industrialised and developing countries in diagnosis and management over last three decades. The role of inflammation pathogenesis of atherosclerosis has been firmly established in past two decades. Numerous studies have shown association of pro-inflammatory biomarkers with incident hypertension, metabolic syndrome, coronary artery disease, ACS, stroke, peripheral artery disease, recurrent coronary and cerebrovascular events. High sensitive CRP is a sensitive marker of inflammation and tissue injury in arterial wall. CRP is a glycoprotein, produced by liver and plays a vital role in development of atherosclerotic disease in cardiac and cerebral circulation, the serum level of which has long been known to increase the risk of acute vascular events. In clinical studies, circulating HsCRP has been bound to correlate with prognosis of acute vascular events. Thus, HsCRP is an indicator of underlying inflammation. Study aims and objectives were to determine the prevalence of elevated HsCRP in 50 patients with acute vascular events. To compare with 50 controls of non vascular acute event. To determine role of hsCRP in determining the morbidity and mortality. To analyze the levels of hsCRP in patient without any other specific CVS risk factors.

Material and Methods: A 50 cases were enrolled for the study, who attended the inpatient clinics and who were admitted in the Department of Internal Medicine and Department of Cardiology, Government General Hospital, Guntur, Andhra Pradesh. Patients selected for the study, satisfied all the inclusion and exclusion criteria. Written consent was obtained from all patients participating in the study. Age and sex matched controls (50) were also studied for comparison and meaningful interpretation of data. The controls were recruited from other acute cases that were recruited from the wards.

Results: The prevalence of elevated Hs CRP in selected cases >0.3mg/L - 46/50(92%).Prevalence of elevated Hs CRP in control >0.3mg/L - 35/50(70%). Most of the cases were between age 40 and 60year, we had found that mean age of cases is 51.4years.There is male predominance and, Sex wise distribution male 34(68%), female 16(32%).

Conclusion: In our study it is clearly shown that most of patient selected had very high prevalence (92%) of elevated hsCRP among patients with acute vascular events. Level of elevated hsCRP more in vascular events than compared to non vascular events Elevated hsCRP is no role in mortality and morbidity vascular events A high prevalence (93.3) of elevated HsCRP patients with acute vascular events without risk factors.

Keywords: CVD, Atherosclerosis, HsCRP

INTRODUCTION

Acute vascular events like coronary and cerebrovascular accidents continue to be a major public health problem in the industrialized and developing countries in diagnosis and management over last three decades. During the past decades major improvement has been achieved in management of these patients. For example, coronary care unit in 1960s, pharmacological reperfusion therapy in 1980s, catheter based interventions for MI in 1990's etc., despite these developments, vascular events remains a major cause for hospital morbidity and mortality. Not only this, they are also important from clinical, psychological and social point of view. First a large number of asymptomatic individuals are at serious risk of developing these vascular events because of their genetic predisposition, smoking, unhealthy dietary habits or physical inactivity. Second, evidence is emerging that medical practice doesn't adequately implement preventive actions in asymptomatic high risk individuals. Thus these vascular events remain an important health problem and merits continued attention from clinical researchers, epidemiologists and practising physicians. The role of inflammation pathogenesis of atherosclerosis has been firmly established in past two decades. Numerous studies have shown association of pro-inflammatory biomarkers with incident Hypertension, Metabolic syndrome, Coronary artery disease, ACS, Stroke, peripheral artery disease, recurrent coronary and cerebrovascular events. High sensitive CRP is a sensitive marker of inflammation and tissue injury in arterial wall. CRP is a glycoprotein, produced by liver and plays a vital role in development of atherosclerotic disease in cardiac and cerebral circulation, the serum level of which has long been known to increase the risk of acute vascular events. In clinical studies, circulating hsCRP has been bound to correlate with prognosis of acute vascular events. Thus, hsCRP is an indicator of underlying inflammation. We aimed to study serum concentration of hsCRP in patients with vascular events and nonvascular events and their subsequent outcome. The World Health Organization currently recognizes cardio- vascular disease (CVD) as the top cause of morbidity and mortality in the adult population worldwide, responsible for approximately 17 million deaths in 2008, representing 48% of global mortality from non-communicable diseases, and with an estimated projection of 23.6 million yearly decreases by 2030[1]. Given

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the epidemic status CVD has reached worldwide and the it generates a profound impact on public health systems at all levels2 Prevention strategies have become a first line topic of scientific interest, particularly concerning risk factors and their involvement in the onset and development of disease. The Third Report of the Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (ATP III) categorizes cardiovascular risk factors as (a)non modifiable, such as age, gender, and ethnicity; (b) modifiable, including Diabetes mellitus, Hypertension, Dyslipidemia, and Smoking; and (c) emerging risk factors, encompassing triacylglyceride, homocysteine, and various inflammatory markers. CRP an acute phase reactant, remains the most studied molecule from the latter category, exhibiting many properties which may intervene in atherogenesis3. Nonetheless, ongoing intense debate remains regarding its relative importance among other risk factors and its true impact on this process. Study aims and objectives were to determine the prevalence of elevated hsCRP in 50 patients with acute vascular events, to compare with 50 controls of non vascular acute event, to determine role of hsCRP in determining the morbidity and mortality and to analyze the levels of hsCRP in patient without any other specific CVS risk factors.

MATERIAL AND METHODS

A single centre matched case- control study was conducted in the Department of Internal Medicine and Department of Cardiology, Government General Hospital, Guntur, Andhra Pradesh.

50 cases were enrolled for the study, who attended the inpatient clinics and who was admitted in the Department of Internal Medicine and Department of Cardiology, Government General Hospital, Guntur, Andhra Pradesh. Patients selected for the study, satisfied all the inclusion and exclusion criteria. Written consent was obtained from all patients participating in the study. Age and sex matched controls (50) were also studied for comparison and meaningful interpretation of data. The controls were recruited from other acute cases that were recruited from the wards.

Study duration: This study was conducted for a period of eighteen months from January 2015 to September 2016.

Methods: Detailed clinical history was taken from each patients and a complete review of their case notes performed. A complete clinical examination of the nervous system and cardiovascular system was done for each patient.

Laboratory methods

To all selected patients, following investigations were done. ECG, ECHO, CPK MB, CT BRAIN, FBS, FLP, HsCRP Other relevant investigations were done, hsCRP was measured after admission in hospital within 1st 24hrs hsCRP were estimated by VITROS 5.1 chemistry system and VITROS 5600 integrated system to quantitatively measure CRP in human serum or plasma. As per the normative data from VITROS 5600 system, manual and current literature, the cardiovascular risk was determined as Low risk with

hsCRP levels < 1.0 mg/L, Medium risk if 1.0-3.0 mg/L, High risk when > 3.0 mg/L. For our study we considered hsCRP level of ≥ 3 mg/L as high risk

Inclusion criteria
For case
1. Age more than 15 years and less than 60
2. Acute myocardial infarction Evidenced by ECG, elevated CK MB, or ECHO
3. Ischemic stroke Evidenced by Two CT BRAIN taken at least 3 days gap showing signs of ischemia
4. Unstable angina Evidenced by ECG or elevated CK MB
5. Those who are willing for study

For controls
1. Age more than 15 less than 60 years.
2. Event should be acute
3. Presence of any illness
4. No cardiovascular risk factors

Exclusion criteria
1. Age less than 15 and more than 60 years
2. Smoking
3. Alcoholism
4. Patient with previous attacks
5. Other inflammatory conditions SLE, Scleroderma, Rheumatoid arthritis, Other Connective Tissue Disorders
6. Immunosuppresant therapy **7.** Patient lost follow up.

STATISTICAL ANALYSIS

The significance of difference between two proportions was indicated by the chi-square (x^2) statistic, fisher's exact test. p value calculated by Two-tailed. Difference were considered to be significant if ($P<0.01$).

RESULTS

In our study of 50 patients were selected as cases and 50 patients selected as controls to analyze the following
1. To determine the prevalence of elevated hsCRP patients with acute vascular events
2. To compare with 50 controls of non vascular acute event.
3. To determine role of hsCRP in determining the morbidity and mortality
4. To analyze the levels in patient without any other specific CVS risk factors

When we divide and analyze as follows
i) With risk factors and elevated hsCRP
ii) Without risk factors only elevated hsCRP
iii) Controls.

Prevalence of elevated HsCRP: The prevalence of elevated Hs CRP in selected cases >0.3mg/L - 46/50(92%) Prevalence of elevated Hs CRP in control >0.3mg/L - 35/50(70%).In considering for the statistical analysis, we had used Chi-square test and the result was obtained as follows: P value = 0.0095. According to the above results, the P value is <0.05. So, this signifies that HsCRP has a definitive role in the cardiovascular pathology. P value = 1.0.There is no statistical difference between prevalence of elevated hsCRP

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in cases with and without risk factors. There is no statistical difference in proportion of patient with elevated hsCRP among dead and alive cases. Therefore elevated hsCRP is not a indicator of mortality and morbidity. Most of the cases were between age 40 and 60 years, we had found that mean age of cases is 51.4years.There is male predominance and, Sex wise distribution male 34(68%), female 16(32%). (Table-1)

Risk factors distribution: 35(70%) cases have underlying risk factors.15(30%) patients have no risk factors. 18(36%) cases have family history of vascular events, 29(58%) cases have Hypertension, 26(52%) cases have Diabetes, 25(50%) cases have LDL>100, 20(40%) cases HDL<50 in females<40 in males, 20(40%) cases have TGL>150, by above statistics in our study. Hypertension, followed by Diabetes is major risk factor associated with elevated HsCRP.(Table-2)

Average elevated HsCRP: There is an elevated level of hsCRP seen in 46(92%) cases normal levels in 4 cases. In controls elevated hsCRP found in 43(89%) and 7 cases normal value. The average elevated level of CRP in cases with risk factors and without risk factors are significantly above level of controls we have selected. The average elevated hsCRP in total cases is 2.217mg/l, in cases with risk factors 2.37mg/l, in cases without risk factors 1.84mg/l, and for controls 1.46mg/l. The average elevated hsCRP is more for cases with risk factors than without risk factors, elevation of hsCRP parallel to conventional risk factors.(Table-3)

Class wise distribution for all cases: 50 cases are taken for study, among them MI cases are 17(34%) and unstable angina 18(36%) and ischemic stroke 15(30%). Overall more number of cardiovascular cases are studied. In 17(34%) MI cases, 14 cases have intermediate risk levels of hsCRP i.e., 1 to 3mg/dl, 2 cases have high risk levels, 1 case have low risk levels of hsCRP. In 18(36%) unstable angina cases, 13 cases have intermediate risk levels of hsCRP, 5 cases have low risk levels. In 15(30%) of stroke cases, 9 cases have low risk level of hsCRP, 5 cases intermediate risk level and 1 low risk level. It is observed that intermediate risk levels of hsCRP more associated with cases in MI and Unstable angina. HsCRP levels in ischemic stroke more on low risk level side and elevation of hsCRP more in cardiovascular cases than stroke cases. This shows that hsCRP has a definite role in the cardiovascular morbidity and mortality. Regarding the distribution of cases without risk factors, 2 MI cases, 10 unstable angina, 3 ischemic stroke, and total 15 cases. All MI have intermediate risk levels of hsCRP, in unstable angina 6 cases intermediate risk and 4 cases low risk levels of hsCRP. In ischemic stroke 2 with low risk hsCRP levels, 1 with intermediate risk level. In total, among cases without risk factors, 9 with intermediate risk value i.e., CRP between 1 and 3mg/l. 6 cases are with low risk value. The distribution of cases over all, 32(64%) cases are in intermediate risk group, 15(30%) cases are with low risk group and 3 patients are in high risk group. Most of cases fall in intermediate risk value group and clearly show the hsCRP association with the vascular events. (Table-4)

Sl. No	Baseline features	Cases	Control
1	Male	34	25
2	Female	16	25
3	CKMB	35	0
4	2D ECHO	35	0
5	Hypertension	29	0
6	Diabetes mellitus	26	0
7	FBS	26	0
8	LDL>100	25	0
9	HDL<50 for Female <40 for Male	20	0
10	TGL	20	0
11	Family History	18	0
12	CT Brain	15	0
13	Death	5	1

Table-1: Baseline characters

Risk factor	No. of patients (out of 50)
Hypertension	29(58%)
Diabetes mellitus	26(52%)
LDL>100	25 (50%)
HDL <50 for female	20(40%)
TGL >150	20(40%)
Without Risk factor	15(30%)

Table-2: Risk factors distribution

Normal	Total Cases	Cases without risk factors	Cases with risk factors	Control
<0.3	2.217	1.84	2.37	1.46

Table-3: Average elevated CRP

Type of diseases	Low	Intermediate	High	Total
Myocardial infarction	1	14	2	17
Unstable angina	5	13	0	18
Stroke	9	5	1	15

Table-4: Class wise distribution f0r all cases

Mortality and associated risk factors: Total deaths in our study are five. Three deaths due to MI, one death each due to unstable angina and ischaemic stroke. Coming to deaths relation with levels of hsCRP, most of the patients who were died i.e. 3(9.3%) in number belong to intermediate (32 cases) risk group, 1 (6.6%) with low risk (15 cases) and 1(33%) with high risk (3 cases).Most of deaths in cases occurred in intermediate risk. On comparing the mortality in patients with various risk factors, hyperlipidemia plays a major role i.e. nearly 4 of the 5 deaths. Hypertension and diabetes are second most leading co morbid condition.

DISCUSSION

C-reactive protein is an acute phase reactant indicating the presence of infections or non-infective inflammation, as well as the risk of vascular events[4]. It has been suggested that the relationship between increased serum CRP levels and vascular risk is because of the inflammation seen in atherosclerosis.CRP, one of the acute phase reactants, is

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an indicator of a novel plasma marker of atherothrombotic disease[5]. Furthermore, elevated plasma levels of CRP are not disease-specific, but are sensitive markers produced in response to tissue injury, infectious agents, immunological stimuli, and inflammation.

CRP is a nonspecific protein produced in the liver, and its serum levels increase in cases of infection, tissue damage, and inflammation. The CRP level is lower than 2 mg/L in healthy population. Standard assays can measure only levels of CRP higher than 3 mg/L. High sensitive CRP is a new method which determines lower levels. We used the hsCRP method in our study and showed significant differences in the CRP level between patients and controls. We determined the mean serum levels of hsCRP to be significantly higher in patients. Recent available data suggest that ischemic stroke triggers an acute phase response, resulting in an increased level of circulating CRP, as well as other inflammatory molecules, such as IL-6 and fibrinogen. However, the degree of inflammatory response to ischemic stroke is variable. A number of prospective epidemiologic studies have shown the relationship between CRP and stroke. Many other studies suggest that the risk of stroke is 2–4 times higher in patients with an increased level of CRP, and conclude that the CRP level is more important than LDL-cholesterol in predicting the risk of cardiovascular accidents. C-reactive protein has been accepted as a sensitive indicator of atherothrombosis in stroke patients, and CRP levels have been found to be higher in stroke patients compared to the healthy population. Although the proximate cause of most brain infarcts is thrombus formation, atherosclerosis is the chief underlying cause[5]. Previous studies found the CRP levels to be higher, but not useful predictors of prognosis in brain stroke cases. Arenillas et al. concluded that C-reactive protein predicted further ischemic events. Another study showed increased one-year risk in ischemic stroke and CRP levels at the time of hospital discharge. In our study, in most of the cases were between age 40 and 60 years, we had found that mean age of cases is 51.4years. In our study there is male predominance and, Sex wise distribution male 34(68%), female 16(32%). In our study 35(70%) cases have underlying risk factors.15 (30%) patients have no risk factors. 18(36%) cases have family history of vascular events, 29(58%) cases have Hypertension, 26(52%) cases have Diabetes, 25(50%) cases have LDL>100, 20(40%) cases HDL<50 in females<40 in males, 20(40%) cases have TGL>150, by above statistics in our study. Hypertension, followed by Diabetes is major risk factor associated with elevated hsCRP. In our study there is an elevated level of hsCRP seen in 46(92%) cases normal levels in 4 cases. In our study in controls elevated hsCRP found in 43(89%) and 7 cases normal value. The average elevated level of CRP in cases with risk factors and without risk factors are significantly above level of controls we have selected. The average elevated hsCRP in total cases is 2.217mg/l, in cases with risk factors 2.37mg/l, in cases without risk factors 1.84mg/l, and for controls 1.46mg/l. In our study, the average elevated hsCRP is more for cases with risk factors than without risk factors, elevation of hsCRP

parallel to conventional risk factors. In our study, 50 cases are taken, among them MI cases are 17(34%) and unstable angina 18(36%) and ischemic stroke 15(30%). Overall more number of cardiovascular cases are studied. In 17(34%) MI cases, 14 cases have intermediate risk levels of hsCRP i.e., 1 to 3mg/dl, 2 cases have high risk levels, 1 case have low risk levels of hsCRP. In 18(36%) unstable angina cases, 13 cases have intermediate risk levels of hsCRP, 5 cases have low risk levels. In 15(30%) of stroke cases, 9 cases have low risk level of hsCRP, 5 cases intermediate risk level and 1 low risk level. From the above analysis it is observed that intermediate risk levels of hsCRP more associated with cases in MI and Unstable angina. hsCRP levels in ischemic stroke more on low risk level side and elevation of hsCRP more in cardiovascular cases than stroke cases. This shows that hsCRP has a definite role in the cardiovascular morbidity and mortality. Regarding the distribution of cases without risk factors, 2 MI cases, 10 unstable angina, 3 ischemic stroke, and total 15 cases. All MI have intermediate risk levels of hsCRP, in unstable angina 6 cases intermediate risk and 4 cases low risk levels of hsCRP. In ischaemic stroke 2 with low risk hsCRP levels, 1 with intermediate risk level. In total, among cases without risk factors, 9 with intermediate risk value i.e., CRP between 1 and 3mg/l. 6 cases are with low risk value. From the above analysis it is clearly shows that the cases without risk factors also have elevated hsCRP and elevated hsCRP is associated with MI and stroke. And hsCRP have association with cardiovascular events than stroke. Regarding the distribution of cases over all, 32(64%) cases are in intermediate risk group, 15(30%) cases are with low risk group and 3 patients are in high risk group. Most of cases fall in intermediate risk value group and clearly show the hsCRP association with the vascular events. Regarding the mortality, total death in our study five, three deaths in MI, one death each in unstable angina and ischaemic stroke. Coming to deaths relation with levels of hsCRP, most of the patients who were died i.e. 3(9.3%) in number belong to intermediate (32 cases) risk group, 1 (6.6%) with low risk (15 cases) and 1(33%) with high risk (3 cases). In our study most of deaths in cases occurred in intermediate risk. On comparing the mortality in patients with various risk factors, hyperlipidemia plays a major role i.e. nearly 4 of the 5 deaths. Hypertension and diabetes are second most leading co morbid condition.

In 2016 Li J, et al. published a paper on sub analysis clinical Trial Clopidogrel in High-Risk Patients with Acute Non disabling Cerebrovascular Events (CHANCE) Trial[6]. In This sub study of chance trial suggested that HsCRP levels played a role in predicting recurrent stroke and functional outcome in acute patients with minor ischemic stroke or high-risk TIA. In this study cases were followed for 90days and observed for further recurrent stroke and functional out come. By above table there is close relation between our study and CHANCE Trial in some parameters i.e., % females, some risk factors distribution, and % low risk value of hsCRP and intermediate risk. In both studies hypertension is most common risk factor, followed by diabetes. Our study

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and CHANCE Trial comparable except for some variables. This may due to our study conducted in small group and hospital based study, and single centric.

In 2014 Elkind MS, et al. published paper, C-reactive Protein as a Prognostic Marker after Lacunar Stroke, The Levels of Inflammatory Markers in the Treatment of Stroke (LIMITS) Study[7] LIMIT STUDY was an international, multicenter, prospective ancillary biomarker study nested within Secondary Prevention of Small Sub cortical Strokes (SPS3), in that patient hsCRP collected after 60 days after lacunar stroke, and predict risk of recurrent strokes and other vascular events. Among 1244 lacunar stroke patients (mean 63.3 ± 10.8 years), median hsCRP was 2.16 mg/L (our study 2.217mg/l). There were 83 recurrent ischemic strokes (including 45 lacunes), 16 hemorrhagic strokes, and 115 major vascular events (stroke, MI, vascular death) among LIMITS participants, over a median follow-up of 3.0 years. Compared to the bottom quartile of hsCRP (<0.93 mg/L), those in the top quartile ($\geq$4.86mg/L) were at increased risk of recurrent ischemic stroke. Some parameters of LIMIT Study are comparable with our study and there is increased risk of recurrent vascular events (MI, ischeamic stroke) with increased hsCRP levels after admission during follow up.

Rajeshwar K et al; in 2012 published article, C-Reactive Protein and Nitric Oxide Levels in Ischemic Stroke and Its Subtypes: Correlation with Clinical Outcome[8]. High levels of CRP may also be associated with poor outcome. The study was taken up to investigate the prognostic value of CRP within 24 h of onset of ischemic stroke. 581 patients with first stroke and 575 age and sex matched healthy controls were involved in the study. High-sensitivity C-reactive protein (hsCRP) levels were estimated, and follow-up interviews were conducted with patients at 3, 6, and 12 months post-event to determine stroke outcome. In addition to this, plasma NO (nitrate and nitrite) was measured to detect the serum NO (an important biomarker of inflammation and oxidative stress) levels in ischemic stroke patients and controls. The relationship between CRP value and poor outcome was studied. There was a significant association between elevated levels of CRP and NO with the disease. In conclusion, hsCRP and NO levels predict the incidence of ischemic stroke and hsCRP is an independent prognostic factor of poor outcome at 3 months.

 Chaudhuri JR, et al; in 2015 published a paper in Iranian journal, High HsCRP level is strongly associated with, an independent predictor of acute ischemic stroke[9]. The association was found in all ischemic stroke subtype they recruited 210 consecutive acute stroke patients and 150 age and sex matched controls. Stroke patients were admitted within 72 hours of onset, at Yashoda Hospital, Hyderabad, India. The study period was from Jan 2011 to Dec 2012. Serum hsCRP level was assessed in all stroke patients and controls on the day of admission. The mean hsCRP was significantly higher in stroke patients (3.8 ± 2.5) than controls (1.8 ± 1.5) (P < 0.001). High hsCRP had higher frequency in stroke patients 130 (61.9%) compared to controls 10 (6.6%), P < 0.001. High hsCRP was more prevalent in the. Stroke

subtypes of cardio embolic stroke (83.3%) and large artery atherosclerosis (72%). High hsCRP level was significantly associated with hypercholesterolemia (P = 0.001), age (P = 0.01), and mortality (0.04). After adjustment of regression analysis it was observed that high level hsCRP is independently associated with acute ischemic stroke (Odds 4.5; 95% CI: 2.5-12.2); especially the stroke subtypes of cardio embolic stroke, (odds ratio 3.4, 95% CI: 1.9-10.5) and large artery atherosclerosis (odds ratio 2.1, 95% CI: 1.5 3.8). Dewan KR, et al; in 2011 published an article High CRP level is associated with stroke severity at admission and is an independent predictor of early seven day mortality after ischemic stroke[10]. Cross sectional study was done including 100 consecutive cases of acute ischemic stroke admitted; Thirteen percent patients expired by 7th day. In the expired group, CRP was positive in 15.3 percent, 15.3 percent and 61.5 percent in patients with lacunar, cardio embolic and large artery atherosclerotic infarction respectively (p 0.19). CRP was positive in all 7 patients (53.8%) who had expired with severe NIHS scale (p 0.004).

CONCLUSIONS

In our study it is clearly shown that most of patient selected had very high prevalence (92%) of elevated hsCRP among patients with acute vascular events. Level of elevated hsCRP More in vascular events than compared to non vascular events. Elevated hsCRP has no Role in mortality and morbidity vascular events. A high prevalence (93.3) of elevated HsCRP among patients with acute vascular events without risk factors.

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