A Study on Role of Circulating HsCRP As A Biomarker of Clinical Significance in Acute MI And Identification of Extent of Involvement, Risk Assessment And Post Mi Complications.

KEYWORDS

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ABSTRACT

Introduction: Myocardial infarction (MI) due to coronary artery disease (CAD) has become a leading cause of death worldwide surpassing malnutrition and infectious diseases especially in a developing country like India. However, recent technological advances in diagnostic tools have led to the utilization of various blood biomarkers of clinical significance in detecting heart disease like myocardial infarction at an early stage. Various lipid, protein and enzymatic biomarkers like lipoproteins, CK-MB, troponin and inflammatory acute phase proteins have been studied extensively for the early detection and management. There is a need for studies involving a single biomarker of detection as well as for identification of the extension of involvement to decide on effective management of patient. Hence we have focused on the study of variations in serum high sensitive C reactive protein (hsCRP) concentration and its correlation with the extent of lesion involvement in MI.

Some clinical studies have shown circulating levels of CRP correlating with total infarct size in acute MI, post MI complications and with prognosis. Thus CRP is beginning to emerge as a marker of underlying coronary inflammation indicating the extent of myocardial necrosis. Keeping in view the significance of this aspect of role of hsCRP estimation, we studied 50 cases presenting with acute coronary syndrome (ACS) to King George Hospital, Visakhapatnam, India from December 2012 to September 2014. We measured hsCRP level in each patient to determine the association between hsCRP and ACS and its significance in the prognosis.

Results: Acute coronary syndrome was observed to be highest among the age group of 41 to 50 years and chest pain was the most common presenting complaint with smoking as the most common risk factor. Out of 50 patients with acute coronary syndromes, 34(68%) patients had STEMI, 8 (16%) had UA and 8 (16%) had NSTEMI. Out of 34 patients who had STEMI, extensive anterior wall involvement was the most common type. Right ventricular failure was the most common complication seen in 15(30%) patients. Serum hsCRP levels were significantly increased in 34 (68%) out of 50 patients of acute coronary syndrome, and 30 (60%) patients with high hsCRP levels developed post MI complications with LVF being the most common. All the values showed statistical significance was (P<0.01).

Conclusion: Present study has shown a strong correlation not only in the various levels of serum hsCRP and ACS, but has also shown an association between the concentration of the hsCRP and the extent of myocardial involvement and post MI complications. The observed strong association establishes the role of inflammatory markers in atherosclerosis and progress to acute myocardial infarction and post MI complications. Hence hsCRP being an acute phase protein, a strong inflammatory marker with a longer half-life can be considered as a robust biomarker of clinical significance. The fact that more number of STEMI patients having increased levels of hs-CRP shows increased incidence of adverse cardiac outcomes, when compared with UA/NSTEMI, suggest that hs-CRP levels may be related to the severity of inflammatory processes associated with multiple plaque rupture or infarct expansion in the spectrum of acute coronary syndrome. Raised hs-CRP levels are independent markers of adverse outcomes. Hence hs-CRP levels obtained at admission in acute coronary syndromes can be used as a marker for identification of patients who are likely to develop significant complications in the immediate in-hospital course and to predict the prognosis.

However, the limitation of this study includes a small sample size and a single serum hsCRP measurement instead of serial estimations at intervals and this limitation can be overcome in our future studies.

Introduction

Coronary artery disease (CAD) is a leading cause of death worldwide even in a developing country like India. Despite progress in the prevention of cardiovascular diseases, a significant proportion of first cardiovascular event occurs among individuals without traditional risk factors. The advancements in understanding pathophysiologic mechanisms of atherosclerotic vascular diseases have brought new insight regarding potential indicators of underlying hidden atherosclerosis and cardiovascular risk. Coronary plaque disruption, with consequent platelet aggregation and thrombosis, is the most important mechanism by which atherosclerosis leads to the acute ischemic syndromes of unstable angina, acute myocardial infarction, and sudden death1.

With growing evidence that atherosclerosis is an inflammatory process, several plasma markers of inflammation have been evaluated as potential tools for the prediction of coronary events2. However, recent technological advances in diagnostic tools have led to the utilization of various blood biomarkers of clinical significance in detecting heart disease like myocardial infarction at an early stage. Various lipid, protein and enzymatic biomarkers like...
lipoproteins, CK-MB, troponin and inflammatory acute phase proteins have been studied extensively for the early detection and management. Inflammation releases inflammatory cytokines from the inflamed tissue, which stimulates liver to synthesize a number of acute phase proteins, including the prototypical acute phase reactant, CRP. There is a need for studies involving a single biomarker of detection as well as for identification of the extent of involvement to decide on effective management of patient. Hence we have focused on the study of variations in serum high sensitive C reactive protein (hs-CRP) concentration and its correlation with the extent of lesion involvement in MI. Some clinical studies have shown circulating levels of hs-CRP correlating with total infarct size in acute MI, post MI complications and with prognosis. Thus hs-CRP is beginning to emerge as a marker of underlying coronary inflammation indicating an extent of myocardial necrosis. The present study is an observational and prospective estimation of hsCRP level to determine the association between hsCRP and ACS and its significance in the prognosis.

2. Material and Methods

Study design: The present study was conducted selecting fifty patients in age group ranging between 30 to 80 years with a male to female ratio of 4:1 with acute coronary syndromes (ST elevation Acute myocardial Infarction (STEMI) or Unstable angina (UA) or Non ST elevation Myocardial Infarction (NSTEMI)) who were admitted in Intensive Cardiac Care Unit of King George Hospital, Visakhapatnam, Andhra Pradesh, India from December 2012 to September 2014. Written consent was taken from each patient or closest relative.

Inclusion Criteria: Patients admitted to ICCU of King George Hospital with the diagnosis of STEMI, UA or NSTEMI. Diagnosis of Acute coronary syndrome was made based on history, physical examination and electrocardiogram.


Detailed history, clinical examination and laboratory tests were the tools used to exclude these conditions.

Study patients underwent the following Investigations: Hb%, TC, DC, ESR, RBS, RFT, ECG, 2D ECHO, CK-MB, Troponin T, Fasting Lipid Profile & hsCRP levels measured within 6 hours of admission.

The present study was focussed on hsCRP levels and an association was studied with the extent of involvement and with post MI complications.

Laboratory method of measuring hs C-reactive protein::
hs-CRP was measured on TURBILYTE-CRP using turbidimetric immunoassay for the determination of C-reactive protein in serum of the patient and is based on the principle of agglutination reaction. The test sample was mixed with TURBILYTE-CRP latex reagent and allowed to react. Presence of CRP in the test specimen results in the formation of an insoluble complex producing a turbidity, which is measured by spectrophotometer at 546 nm wavelength. The increase in turbidity corresponds to the concentration of CRP in the test specimen. hs-CRP levels were measured on the day of admission within 6 hours. The hs-CRP detection limit of this test is 1 mg/L. Therefore, values of <1mg/L were taken as Low or no risk, 1-3mg/L as average risk, >3 mg/L as High risk as per AHA/CDC risk assessment guidelines.

All patients were followed up for 30 days and observed for the development of complications.

STATISTICAL ANALYSIS:
Statistical analysis was performed using Chi-square test. Results were considered significant if P <0.05.

3. Results

After analysing the data out of fifty patients in age group ranging between 30 to 80 years with a mean age of 58.21 years where the highest incidence seen between 41 and 50 years with male to female ratio of 4:1 with acute coronary syndromes. Chest pain was the most common symptom accounting for 43(86%) patients, followed by sweating in 34(68%), Breathlessness in 18(36%), Vomiting in 12(24%) and Giddiness in 4(8%) patients. In this study the most common risk factor was Smoking, accounting for 35 (70%) patients followed by Diabetes (32%) and Dyslipidaemias (50%). It is noted that out of 40 male patients who suffered acute coronary syndromes, 35 (87.5%) were smokers.

Out of 50 patients with acute coronary syndromes, 34 patients (68%) had STEMI and 16 patients had UA/NSTEMI, out of which 8 (16%) had UA and 8 (16%) had NSTEMI. Out of 34 patients who had STEMI, 15(44%) had Extensive anterior wall involvement (most common type) followed by Anteroseptal 10(29.4%), Inferior wall 7(20.5%) and Anterolateral walls 5(14.7%) in descending order of frequency.

In our hospital, pharmacological reperfusion performed to eligible patients was Streptokinase 1.5 million units infusion. Out of 34 patients with STEMI. Only 21 patients were eligible for Streptokinase therapy. Chest pain of more than 12 hrs duration and established Q waves (9 patients) was the most common cause to withhold thrombolyis followed by Hypotension (4 patients). LVF was the most common complication seen in 15(30%) patients, followed by Cardiogenic shock 6(12%), AV block 6(12%), and 2(4%) had LBBB. 5(10%) patients had VT/ VF and died. Thus 34 (68%) patients suffered from complications whereas 16 (32%) patients did not have any complications.

Distribution of Post MI complications with hs CRP levels among various types of Acute Coronary Syndromes:
Out of the 50 patients 15 had AMI, out of which 13 had hs-CRP>3mg/L and met with complications. Other complications in descending order of frequency.(Ref table 1)

| TABLE 1: DISTRIBUTION OF POST MI COMPLICATIONS WITH hs-CRP LEVELS AMONG VARIOUS TYPES OF ACS |
|-----------------------------------------------|-----------------|-----------------|
| DIAGNOSIS | No of Cases | hs CRP <3 mg/L | hs CRP >3 mg/L |
|-----------------------------------------------|-----------------|-----------------|
| AMI | 15 | 0 | 13 |
| NSTEMI | 16 | 1 | 5 |
| Total | 50 | 4 | 30 |
Post MI Complications in relation to hs-CRP Levels: 15 patients had Left ventricular failure, out of which 13 had hs-CRP levels >3mg/L and 2 had hs-CRP levels <3mg/L (Ref table 2).

TABLE 2: POST MI COMPLICATIONS IN RELATION TO hs-CRP LEVELS

<table>
<thead>
<tr>
<th>Post MI Complications</th>
<th>Quartiles of hs-CRP (mg%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>1-3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>AV Block</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>LBBB</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VT/VF &amp; DEATH</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Association between hs-CRP Level and Post MI Complications:
Out of 34 patients with complications, only 4 showed hsCRP levels <3mg/l and 30 showed hsCRP levels=3mg/L.
And out of 16 without complications, 12 showed hsCRP levels<3mg/L and only 4 showed hsCRP levels>3mg/L.

Chi Square value test value was 30.09 . At one degree of freedom, P value is statistically very significant (p<0.01). This indicates patients with hs-CRP levels, measured within 6hrs of admission are at high risk range according to AHA/ CDC risk assessment guidelines and are prone to develop complications.

Other Investigations:
Raised blood glucose (RBG) : RBG levels were found elevated in 16(32%) patients who were known diabetes mellitus patients. Diabetes mellitus is one of the risk factor for IHD and is considered as IHD equivalent. Troponin T was positive in 42 patients, out of which 34 patients had raised hs-CRP and 30 patients met with complications. CK MB was raised in 36 patients, out of that 34 patients had raised hs-CRP and 30 met with complications.

Discussion
Chest pain is the most common presenting symptom in 86% of cases. This is similar to PS Singh et al showing the commonest presenting symptom as chest pain (90%). Followed by sweating (75%) and breathlessness (60%). It is also comparable to Huggins et al study.

Smoking is the most common risk factor, found in 35 (70%) patients, in contrast to other studies, Mohmoud Suleiman et al study where smoking was observed in 40% of patients , In Salim Yusuf et al study, 65.19% of patients were smokers , In PS Singh et al study, smoking was major risk factor (65%). In Foussas et al study, smoking was observed in 57% of patients.

Abnormal lipid profile was seen in the Present study showing 25 (50%) patients with lipid abnormalities., This correlates with other studies .In Foussas et al study, 64.6% of patients had lipid abnormalities. And in Mohmoud Suleiman et al study, 41% of patients had dyslipidemias.

Diabetes Mellitus: In the present study 16 (32%) patients had diabetes as the risk factor, this correlates with other studies. In Foussas et al study, diabetes mellitus was seen in 31% of patients and in Mohmoud Suleiman et al study, diabetes was present in 30% of patients. In PS Singh et al study, Diabetes was seen in 32%.

Hypertension: In the present study 7 (14%) patients had hypertension, this differs from many other studies like Foussas et al study (51%) and Mohmoud Suleiman et al study (53%) and PS Singh et al study (33%). This correlates with Salim Yusuf et al study, (19.3%).

Type of ACS: Out of 50 ACS patients in the present study, 34 (68%) had STEMI, 8 (16%) had UA and 8 (16%) had NSTEMI. This correlates with Saeed et al study where 71% patients had STEMI, 12% had NSTEMI and 17% with unstable angina. It differs from Magdalena Krintus et al study where out of 220 patients with ACS, 96(43.6%) had UA, 57(25.9%) with NSTEMI and 67(30.4%), had STEMI.

Present study also differs with Sheikh et al study, where out of 963 patients, 187 are controls and Out of 776 patients with ACS, 232 had UA ie.,29.8 %, 258 had STEMI ie., 33.2% and 286 had NSTEMI ie.,36.8%., Almost similar number of patients had STEMI in Mohmoud Suleiman et al study.

Reperfusion Therapy in the present study only 14 (41%) patients with STEMI underwent reperfusion therapy in the form of pharmacological thrombolysis with streptokinase,

Serum hs-CRP In the present study was estimated on the day of admission within 6 hours. This correlates with most studies (refer table 4).

As per the risk Categorisation of patients based on hs-CRP levels according to CDC/AHA Guidelines 2003 we considered values of < 1mg/L as normal concentration of CRP and low risk, values between 1-3mg/L were taken as average risk, values of > 3mg/L were taken as high risk. This correlates with most studies, (Refer table 3).

TABLE 3: CATEGORISATION BASED ON hs-CRP LEVELS IN VARIOUS STUDIES

<table>
<thead>
<tr>
<th>Studies</th>
<th>Low Risk</th>
<th>Average Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present Study</td>
<td>&lt;1mg/L</td>
<td>1-3mg/L</td>
<td>&gt;3mg/L</td>
</tr>
<tr>
<td>David et al</td>
<td>&lt;1mg/L</td>
<td>1-3mg/L</td>
<td>&gt;3mg/L</td>
</tr>
<tr>
<td>Buckley Di et al</td>
<td>&lt;1mg/L</td>
<td>1-3mg/L</td>
<td>&gt;3mg/L</td>
</tr>
<tr>
<td>Morrow et al</td>
<td>&lt;1mg/L</td>
<td>1-3mg/L</td>
<td>&gt;3mg/L</td>
</tr>
</tbody>
</table>

Relation of Raised hs-CRP levels with Post MI complications in various studies: In this study of 50 patients with ACS, 34 (68%) had raised hs-CRP levels (>3mg/L), of which 30 (60%) patients met with complications , This is in correlation with most recent studies. Refer table 4.

TABLE 4: RELATION OF hs-CRP LEVELS WITH POST MI COMPLICATIONS IN VARIOUS STUDIES

<table>
<thead>
<tr>
<th>Studies</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present Study</td>
<td>34 (68%) patients had raised hs-CRP levels (&gt;3mg/L). And 30 (60%) patients who had hs-CRP levels&gt;3mg/L met with complications</td>
</tr>
<tr>
<td>Morrow et al</td>
<td>Patients with serum CRP levels 1–3mg/L had a greater mortality risk in comparison with those with levels &lt;1mg/L. The mortality risk for patients &gt;3mg/L was even higher.</td>
</tr>
</tbody>
</table>

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The current study assessed the role of hs-CRP across the spectrum of acute coronary syndrome (ACS) in patients with STEMI (68%), NSTEMI (36%), and UA (16%). The study showed a significant 3-fold increase in mortality risk among patients with STEMI compared to NSTEMI and UA. The results indicated that high hs-CRP levels were associated with increased risk of adverse events, including in-hospital mortality, post-MI angina, and cardiac death. The study also highlighted the importance of hs-CRP levels in risk stratification and planning of effective interventions in ACS management.

**Limitations of this study:**

- The study was limited by the sample size and may not be applicable to all populations.
- The use of hs-CRP levels in risk stratification requires further validation in larger, multicentre studies.
- The study was conducted in a single centre, which may limit the generalizability of the findings.

**Conclusion:**

The study showed that hs-CRP levels are a valuable prognostic marker for adverse events in ACS. Further research is needed to validate the findings in larger and more diverse populations.
estimation, which was not done in this study.

Conclusion
Plasma CRP levels on admission serves to identify high risk patients in the setting of acute coronary syndromes. Among patients presenting with acute coronary syndromes with elevated hs-CRP (>3mg/L) level is associated with significant post MI complications (60%) with significant statistical value (p<0.01). Our study has shown a strong correlation not only in the various levels of serum hsCRP and ACS, but has also shown an association between the concentration of the hsCRP and the extent of myocardial involvement and post MI complications. The observed strong association establishes the role of inflammatory markers in atherosclerosis and progress to acute myocardial infarction and post MI complications. Hence hsCRP being an acute phase protein, a strong inflammatory marker with a longer half-life can be considered as a robust biomarker of clinical significance.

The fact that more number of STEMI patients having increased levels of hs-CRP has increased incidence of adverse cardiac outcomes, when compared with UA/NSTEMI, suggest that hs-CRP levels may be related to the severity of inflammatory processes associated with multiple plaque rupture or infarct expansion in the spectrum of acute coronary syndrome. Raised hs-CRP levels are independent markers of adverse outcomes. Hence hs-CRP levels obtained at admission in acute coronary syndromes can be used as a marker for identification of patients who are likely to develop significant complications in the immediate in-hospital course and to predict the prognosis.

Conflict of Interests
The authors declare that they have no conflict of interests.

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