Original Article

PREDICTIVE VALUE OF C-REACTIVE PROTEIN FOR THROMBOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION

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Abstract

The serum levels of C-reactive protein on admission may predict the efficacy of reperfusion in patients with acute myocardial infarction.

Objectives: This study was conducted to know the predictive value of CRP for success of thrombolysis and to know the prognostic value of C-reactive protein in patients having acute myocardial infarction.

Study Design: It was single center, open labeled cross sectional study.

Materials and Methods: Sixty patients of acute myocardial infarction diagnosed on clinical and ECG criteria, who received thrombolytic therapy with streptokinase, were included in the study. The diagnosis of acute myocardial infarction was made on clinical parameters and ECG criteria. The ECG changes were noted before starting thrombolysis. The baseline sample for C-reactive protein (CRP_1) was taken before starting thrombolysis. The time duration between onset of symptoms and start of thrombolysis was also noted. The thrombolysis was done with streptokinase infusion, 1.5 million units diluted in 100ml normal saline, intravenously over one hour. The ECG was repeated after six hours of completion of thrombolysis and, changes were noted and compared with ECG changes before thrombolysis. Now second sample for C-reactive protein (CRP_2) was taken after six hours of completion of thrombolysis. CRP was measured by a high sensitivity assay which can accurately measure basal levels of CRP throughout the currently accepted cardiovascular risk assessment range (0.20 – 10.0 mg/L). According to ECG findings after thrombolysis, all patients were divided into two groups. Group A was considered as successful group to thrombolysis, in whom ECG changes were settled. Group B was considered as unsuccessful group to thrombolysis, in whom ECG changes remained same as before thrombolysis.Both values of C-reactive protein, CRP_1 and CRP_2 were compared in both groups group A and group B.

Results: Plasma CRP values before and after thrombolysis had strong predictive value for success of thrombolysis, 63.3% (P value 0.002) and 93.3% (P value <0.001) respectively.

Conclusion: In addition to ECG, C-reactive protein is a strong predictor of response of thrombolytic therapy in patients with acute myocardial infarction.

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Key words: Acute coronary syndrome, high – sensitivity – reactive protein, Myocardial infarction.

Abbreviations and Acronyms: hs-CRP (high – sensitivity C-reactive protein), CRP (C-reactive protein), ACS (acute coronary syndrome), AMI (acute myocardial infarction).

Introduction

Ischemic heart disease is the leading cause of death worldwide. It is associated with high patient morbidity and mortality.

The inflammation plays a key role in the pathogenesis of atherosclerosis and plaque formation. The chronic inflammatory process can lead to an acute clinical event by the induction of plaque rupture and thus leading to acute coronary syndrome.[1,2]

Approximately half of all individuals who present with an acute coronary event do not have any of the conventional risk factors, such as smoking, diabetes and hypertension.[3] In recent years, new insights have revolutionized our understanding of potential inflammatory markers as risk factors for underlying cardiovascular disease.[4] The serum inflammatory markers are elevated in patients with acute coronary syndrome.[5] In particular, C-reactive protein has received great attention as one of these novel atherogenic markers.[6,7] Serum C-reactive protein is one of these inflammatory markers and is very sensitive marker for acute inflammatory reactions.[8]

Thrombolytic therapy and acute coronary intervention has reduced mortality significantly after acute myocardial infarction. Thrombolytic therapy reduces mortality by improving myocardial perfusion and reducing the incidence of life threatening arrythmias.[9] Many non-invasive markers, like resolution of chest pain, St-segment elevation and biochemical assays are used to assess the success of thrombolytic therapy.[10] Serum C-reactive protein is one of these biochemical markers that help to predict the efficacy of thrombolytic therapy in patients with acute myocardial infarction. The hs-CRP assays were used to assess outcomes in patients with unstable angina. and showed that hs-CRP values in the upper tertile (>3.0 mg/L) were associated with increased risk of developing myocardial infarction.[11] The adjusted relative risks of developing cardiovascular disease or ischemic events ranging from 2.3 to 4.8 in the highest quartile or quintile of data versus the lowest quartile or quintile and is defined as low risk < 1.0 mg/L, average risk 1.0 – 3.0 mg/L, high risk: > 3.0 mg/L and acute inflammation: > 10.0 mg/L respectively.[12]

Myocardial infarction (MI) is the major contributor to cardiovascular mortality. Once MI takes place, the immediate goal is to achieve reperfusion. C-reactive protein (CRP) is very useful biochemical marker that can predict thrombolytic response and prognosis in patients with acute myocardial infarction (AMI).[13]

In Pakistan few studies are conducted to see the relationship of CRP and cardiovascular disease. Elevated CRP is a predictor of adverse outcome in patients with acute coronary syndromes and helps in identifying patients who may be at risk of cardiovascular complications a study done at bolan medical college quetta.[14] High serum CRP levels rather than high LDL: HDL are associated with myocardial infarction in the patients presenting at NICVD with first myocardial infarction.[15]

This study was conducted to know the predictive value of CRP for success of thrombolysis in our population and to know the prognostic value of C-reactive protein in patients having acute myocardial infarction.

Patients and Methods

It was single center, open labeled, cross sectional study conducted at coronary care unit of services hospital Lahore from January 2013 to March 2013. Sixty patients of acute myocardial infarction diagnosed on clinical and ECG criteria, who received thrombolytic therapy with streptokinase, were included in the study. Those patients with acute myocardial infarction who did not receive thrombolytic therapy were excluded from the study.

Those patients of myocardial infarction who received thromboytic therapy but had some concomitant evidence of acute or chronic infection or inflammatory disease were also excluded from the study. The diagnosis of acute myocardial infarction was made on clinical parameters and ECG criteria, ECG changes with ST-segment elevation 2 mm or more in consecutive two chest leads and 1mm or more in consecutive two limb leads. The ECG changes were noted before starting thrombolysis. The baseline sample for C-reactive protein (CRP_1) was taken before starting thrombolysis. The time duration between onset of symptoms and start of thrombolysis was also noted. The thrombolysis was done with streptokinase infusion, 1.5 million units diluted in 100 ml normal saline, intravenously over

one hour. The ECG was repeated after six hours of completion of thrombolysis and, changes were noted and compared with ECG changes before thrombolysis. Now second sample for C-reactive protein (CRP_2) was taken after six hours of completion of thrombolysis. Venous blood samples were collected on admission for each patient and were immediately analyzed. CRP was measured by a high sensitivity assay which can accurately measure basal levels of CRP throughout the currently accepted cardiovascular risk assessment range (0.20 – 10.0 mg/L). About 5 ml blood was taken in non-anticoagulated vial for each sample. Both samples were sent to laboratory for analysis. The results of both samples, CRP_1 and CRP_2 were noted. A CRP value of 6 mg/l (the threshold for the upper tertile) was used to divide the patients into two groups: The values above this were high and below were defined as low. According to ECG findings after thrombolysis, all patients were divided into two groups. Group A, was considered as successful group to thrombolysis, in whom ECG changes were settled. Group B was considered as unsuccessful group to thrombolysis, in whom ECG changes remained same as before thrombolysis.Now the both values of C-reactive protein, CRP_1 and CRP_2 were compared in both groups group A and group B.

Data Analysis

The nominal variables were recorded as frequencies / percentages. The numerical data was recorded as Mean ± SD. Independent sample t test and paired sample t test, were used for analysis of numerical data. Pearson Chi-square test was used for correlation (cross tabulation) among different nominal variables.

Discriminant analysis was used to detect the predictive value of C-reactive protein for thrombolytic response. The SPSS version 10 was used for data analysis. The P value of less than 0.05 was considered as significant.

Results

In this study total 60 patients of acute myocardial infarction, receiving thrombolytic therapy with streptokinase were included. Out of these 60 patients 4 (7%) patients were having age 40 years (2 patients of 37 years and 2 of 40 years). Majority of them were among 41 – 60 years of age groups. Twenty patients (33%) were having age from 41 – 50 years and 26 patients (43%) were having their ages between 51 – 60 years. Only 10 patients (17%) were having ages between 61 – 70 years.

Chest pain, sweating, dyspnea and vomiting were the main clinical symptoms on presentation. Among them chest pain and sweating were the most common group of symptoms, in 30 (50%) of patients out of the total. Chest pain, sweating and dyspnea were one of the least common group of symptoms in this study, only 2 (3%) patients. Other groups of symptoms were chest pain and dyspnea in 4 (7%) patients, chest pain, sweating and vomiting in 7 (12%) patients and vomiting and vertigo were present in 6 (10%) patients. Eleven (18%) patients were having all the main symptoms i.e. chest pain, sweating, dyspnea and vomiting, out of the total. Out of total 60 patients, 20 patients (33%) were females and 40 (67%) were males.

Among these symptom groups, chest pain and sweating were the most common symptoms in males, 17 patients (57%) out of 30 patients in this symptom group. While vomiting and vertigo were the most common symptoms in females 4 (67%) patients out of 6 patients in this symptom group. Correlation study between males and females for symptom groups showed no significant correlation between sex and symptoms. The P value is 0.06.

In this study, there were seven types of myocardial infarctions. Among them, acute inferior wall MI was the most common, 25 (42%) patients out of total 60 patients. Next most common types were acute anterior wall MI and acute anterolateral wall MI, 10 (17%) and 13 (21%) respectively. Lateral wall MI and inferior wall with right ventricular infarcts were the least common types of infarcts in this study, only 2 (3%) pati-

Table 1: Types of Myocardial Infarction (frequency distribution).

Types	No. of Patients	Percentage
Inferior wall MI	25	42
Anterior wall MI	10	17
Anteroseptal MI	4	7
Anterolateral MI	13	21
Lateral wall MI	2	3
Inferoposterior wall MI	4	7
Inferior wall + right ventricular MI	2	3
Total	60	100

ents in each type. Acute anteroseptal MI and acute inferoposterior wall MI, were 4 (7%) patients in each type (Table 1).

Only 11 (18%) patients were having physical signs of heart failure e.g tachycardia, raised JVP, third heart sound, gallop rhythm and bilateral basal fine crepitations in chest, out of total 60 patients and 49 (82%) were without heart failure.

Successful thrombolysis based on ECG changes was observed in 39 (65%) patients out of the total. In 21 (35%) patients unsuccessful thrombolysis was considered whose ECG changes remained same as before thrombolysis (Table 2). There was significant correlation between time duration.

Table 2: Response of Thrombolytic Therapy (Percentage).

Groups	No. of Patients	Percentage
Group A	39	65
Group B	21	35
Total	60	100

Group A = Successful thrombolysis (based on ECG changes) Group B = Unsuccessful thrombolysis (based on ECG canges) (time between onset of symptoms and start of thrombolysis) and baseline C-reactive protein, CRP_1 (C-reactive protein before thrombolysis). The P value is < 0.001. The baseline C-reactive protein was high in 39 (65%) patients and low in 21 (35%) patients out of total 60. Majority of patients having high baseline C-reactive protein came between 3 – 4 and 5 – 6 hours after starting symptoms, 15 (25%) and 9 (7%) respectively, out of 39 patients. Fifteen (25%) patients came after 6 hours of starting symptoms, all of them were having high baseline C-reactive protein. Only in 5 (8%) patients, baseline C-reactive protein was high who came within two hours of starting symptoms. Majority of patients having baseline C-reactive protein low came within 2 hours after starting symptoms, 17 (28%) out of 21 (35%) patients. Only 4 (7%) patients were having baseline C-reactive protein low who came between 3 – 4 hours of starting symptoms (Table 3).

There was also significant correlation between C-reactive protein after thrombolysis (CRP_2) and time duration (time between onset of symptoms and start of thrombolysis). The P value is < 0.001. C-reactive protein after thrombolysis (CRP_2) was high only in 19 (32%) patients and was low in 41 (68%) patients. Majority of patients having high CRP values after thrombolysis came after 6 hours of starting symptoms, 13 (22%) out of 19 (32%) patients.

Table 3: Correlation between CRP_1 and Time Duration.

Time Duration/Hour	CRP_1		Total
	High	Low	
Upto 2 hours	5 (8%)	17 (28%)	22 (36%)
3-4 hours	15 (25%)	4 (7%)	19 (32%)
5-6 hours	4 (7%)	-	4 (7%)
Above 6 hours	15 (25%)	-	15 (25%)
Total	39 (65%)	21 (35%)	60 (100%)

P value < 0.001
Pearson Chi-square test
CRP_1 = C-reactive protein before thrombolysis

Only 6 patients had low CRP_2 who came between 5 – 6 hours and after 6 hours after starting symptoms, 4 (7%) and 2 (3%) respectively (Table 4).

Table 4: Correlation between CRP_2 and Time Duration.

Time Duration/Hour	CRP_2		Total
	High	Low	
Upto 2 hours	-	22 (36%)	22 (36%)
3 – 4 hours	6 (10%)	13 (22%)	19 (32%)
5 – 6 hours	-	4 (7%)	4 (7%)
Above 6 hours	13 (22%)	2 (3%)	15 (25%)
Total	19 (32%)	41 (68%)	60 (100%)

P value < 0.001
Pearson Chi-square test
CRP_2 = C-reactive protein after thrombolysis

The mean values of C-reactive protein before and after thrombolysis remained significant with significant P value: P value for CRP_1, 0.001 and < 0.001 for CRP_2. The mean value of C-reactive protein before thrombolysis (CRP_1) was 15.95 ± 19.87 in successful group to thrombolysis and 37.81 ± 27.00 in patients having unsuccessful thrombolysis (Table 5).

The mean value of C-reactive protein after thrombolysis (CRP_2) was 1.23 ± 7.69 and 37.05 ± 30.04 in

patients having successful and unsuccessful thrombolysis respectively (Table 5).

Table 5: Mean ± SD Values of C-Reactive Protein before and after Thrombolysis. CRP_1 = C-reactive protein before thrombolysis. CRP_2 = C-reactive protein after thrombolysis.

Group	No. of Patients	Mean ± SD
CRP_1 A	39	15.95 ± 19.87
B	21	37.81 ± 27.00
CRP_2 A	39	1.23 ± 7.69
B	21	37.05 ± 30.04

P value $CRP_1 < 0.001$
P value $CRP_2 < 0.001$
Independent student "t" test

There was significant difference in mean values of C-reactive protein before and after thrombolysis in patients having successful thrombolysis with significant P value of < 0.001. The paired difference between mean values of C-reactive protein before and after thrombolysis was 14.72 ± 19.31 (Table 6).

Table 6: Response of C - reactive protein (CRP 1 & 2) to Group A. CRP_1 = C-reactive protein before thrombolysis. CRP_2 = C-reactive protein after thrombolysis. Group A = Successful to thrombolysis

CRP	No. of Patients	Mean ± SD
CRP_1	39	15.95 ± 19.87
CRP_2	39	1.23 ± 7.69
Paired difference		14.72 ± 19.31

P value = 0.001
Paired sample "t" test

There was no significant difference in mean values of C-reactive protein before and after thrombolysis in patients having unsuccessful thrombolysis. The P-value is 0.086. The paired difference between mean values of C-reactive protein before and after thrombolysis was 0.76 ± 19.50 (Table 7).

There was significant correlation between basal C-reactive protein (CRP_1) and response of thrombolytic therapy with significant P value of 0.002. Out of 39 patients having successful thrombolysis, 20 (51%) patients had baseline C-reactive protein high and low in 19 (49%) patients. Out of 21 patients having unsuccessful thrombolysis, 19 (90%) patients had high baseline C-reactive protein and only 2 (10%) patients had low basal C-reactive Protein. The predictive value of baseline C-reactive protein for thrombolytic response was 63.3% (Table 8).

Table 7: Response of C - reactive protein (CRP 1 & 2) to Group B. CRP_1 = C-reactive protein before thrombolysis. CRP_2 = C-reactive protein after thrombolysis. Group B = Unsuccessful to thrombolysis.

CRP	No. of Patients	Mean ± SD
CRP_1	21	37.81 ± 27.00
CRP_2	21	37.05 ± 30.04
Paired difference		0.76 ± 19.50

P value = 0.086
Paired sample "t" test

Table 8: Correlation between C - reactive protein and Thrombolytic Response (Relationship of CRP_1 to Group A & B).

Groups	Total No. of Patients	C - reactive protein	
		Positive	Negative
Group A	39	20 (51%)	19 (49%)
Group B	21	19 (90%)	2 (10%)
Total	60	39 (65%)	21 (35%)

Predictive value of CRP_1 = 63.3%
P value = 0.002
Discriminant analysis
CRP_1 = C-reactive protein before thrombolysis

There was also very significant correlation between C-reactive protein after thrombolysis (CRP_2) and response of thrombolytic therapy with significant P-value of < 0.001. Out of 39 patients having successful thrombolysis, only 1 (3%) patient had high C-reactive protein after thrombolysis and 38 patients (97%) had low C-reactive protein after thrombolysis. While out of 21 patients having unsuccessful thrombolysis, 18 (86%) patients had high C-reactive protein after thro-

mbolysis and only 3 (14%) patients became low. The predictive value of C-reactive protein for response of thrombolytic therapy was 93.3% (Table 9).

In this study there was significant correlation between, C-reactive protein before and after thrombolysis and heart failure with significant P value. P value is 0.01 for baseline C-reactive protein and 0.03 for C-reactive protein after thrombolysis.

Table 9: Correlation Between C-Reactive Protein and Thrombolytic Response (Relationship of CRP_2 to Group A & B)

Groups	Total No. of Patients	C-Reactive Protein	
		High	Low
Group A	39	1 (3%)	38 (97%)
Group B	21	18 (86%)	3 (14%)
Total	60	19 (32 %)	41 (68 %)

Predictive value of CRP_2 = 93.3%
P value = <0.001
Discriminant analysis
CRP_2 = C-reactive protein after thrombolysis

Discussion

This study was conducted to know the predictive value of C-reactive protein for thrombolytic response, comparing CRP values to ECG changes before and after thrombolysis.

Sixty patients of acute myocardial infarction, receiving thrombolytic therapy with intravenous streptokinase were enrolled in the study.

Few studies was found in Pakistan in literature review.[14,15] The study was comparable to Auer[1] which included 25 patients of AMI, having age range 40 – 86 years, 18 (72%) males, 7 (28%) females, While in this study 60 patients of AMI were enrolled, having age range 37 – 70 years, 40 (67%) were males and 20 (33%) were females, which is quite comparable. In our study the baseline CRP values were significantly higher in patients with AMI than stable CAD (P-value 0.001), shortly after the onset of symptoms (12 hours after). While in our study 39 (65%) patients out of 60, were having high titres of C-reactive protein after 4 – 6 hours of onset of symptoms (P value< 0.001). In Auer's study the CRP values were compared in patients with AMI and stable CAD, while in this study CRP values were compared to ECG changes before and after thrombolysis in patients of acute myocardial infarction only. A study done at NICVD showed that high serum CRP levels rather than high LDL: HDL is associated with myocardial infarction in the patients presenting with first myocardial infarction.[15]

Zaires[16] study was also comparable to my study in view of association between plasma CRP levels and response of thrombolytic therapy. Three hundred nineteen patients of acute ST – segment elevation MI, who were given intravenous thrombolysis, their ECG changes (resolution of St-segment) after thrombolysis, were compared to plasma CRP values. Those patients having low plasma CRP values, were having higher incidence of resolution of ST-segment elevation (P value < 0.05), while there was low incidence of resolution of ST-segment elevation in patients having higher plasma CRP values (P values 0.06). While in our study those patients having complete resolution of ST – segment elevation (successful group to thrombolysis) were having significant difference in mean values of CRP before and after thrombolysis (Mean difference value 14.72 ± 19.31, P value < 0.001), and there was no significant difference in mean values of CRP in those patients whose ST – segment elevation did not resolve completely (unsuccessful to thrombolysis) after thrombolysis (Mean difference value 0.76 ± 19.50, P value 0.086).

This study is also comparable to Pietela[17] in view of assessing the response of thrombolytic therapy by measuring plasma CRP values. However the comparative parameters in this study were serial cardiac enzymes (CK – MB) and thalium scan, while in our study ECG was the comparative parameter. The number of patients was only 9, who were given intravenous streptokinase, while in my study 60 patients were enrolled.

According to Dibra[18] CRP levels on admission may predict the efficacy of reperfusion response in patients with AMI; this stands true for my study too. As 38 (97%) patients out of 39 (having successful thrombolysis) with elevated baseline CRP values, got reduction in CRP values, after thrombolysis and 18 (86%) patients out of 21 (those having unsuccessful thrombolysis) failed to have any change in plasma CRP values after thrombolysis). However in this study different combination of reperfusion strategies e.g stenting plus abciximab, thrombolysis with streptokinase alone and streptokinase plus abciximab were used, while in this study reperfusion was done only with streptokinase.

The current study is also comparable to Berton[19]

study in view of knowing the predictive values of C-reactive protein for association of heart failure with acute myocardial infarction. In Berton's study, baseline and subsequent CRP values were higher in patients having associated heart failure with AMI than those patients without heart failure (P value < 0.001). This also stands true in the present study which is recorded as in addition to the major objectives of study finding. As 11 (18%) patients who were having associated heart failure with AMI, all of them (100%) were having significant positive values of plasma CRP levels (P value < 0.05).

Conclusion

1. In addition to ECG, C-reactive protein is a strong predictor of response of thrombolytic therapy in patients with acute myocardial infarction.
2. C-reactive protein has prognostic value for outcome of the disease in patients with acute myocardial infarction.
3. Plasma C-reactive protein begins to rise 4-6 hours after onset of symptoms in acute myocardial infarction.

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