Original Article

The Plausible Predictive Outcome of Intravenous Thrombolysis by High Levels of CRP on Admission in Patients with Myocardial Infarction

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Background: Although primary percutaneous transluminal coronary angioplasty is the method of choice for reperfusion in ST-elevation myocardial infarction, the intravenous thrombolysis is a more frequently used method. Thus it is important to identify the risks of reperfusion failure. In this regard, CRP as an inflammatory marker has shown promising value. The aim of this study is to investigate whether CRP level on admission is indicative of intravenous thrombolysis failure.

Methods: This study comprised 84 patients with STEMI. Samples were taken for CRP before initiation of thrombolysis. The correlation of CRP levels with thrombolysis results was investigated at the end of the study.

Results: The study population was divided according to their plasma CRP level on admission. The first group had CRP levels<0.5 mg/L (22 patients) and the second group had CRP levels≥0.5 mg/L (62 patients). There was a statistically significant difference (P=0.01) between the respondents to thrombolysis in the first (59.1%) and second groups (29.0%).

Conclusion: It was demonstrated that patients with low CRP levels on admission showed better response to intravenous thrombolysis while those with high levels of CRP showed unfavorable response.

Keywords: CRP, Intravenous Thrombolysis, Acute Myocardial Infarction

Introduction

Acute myocardial infarction (AMI) is one of the most common diseases in developed countries and its rate of mortality in the first 30 days after diagnosis is about 30%-50%.[1] Rapid and adequate reperfusion of the infracted myocardium is the only effective treatment in patients with ST-elevation AMI (STEMI) with resultant preservation of left ventricular systolic performance and more favorable prognosis.[2] Although primary percutaneous transluminal coronary angioplasty (PTCA) is the method of choice for reperfusion in patients with STEMI, intravenous thrombolysis is the more frequently used therapy in many centers with subsequent rescue PTCA in case intravenous thrombolysis fails to reperfuse the infarct-related artery.[3] So, in this setting the identification of the predictors of intravenous thrombolysis failure is very important as it may warrant careful attention paid to such patients. Many clinical and electrocardiographic criteria as well as biochemical markers have been suggested to help address thrombolysis failure and one of the most promising entities is the plasma C-reactive protein (CRP) level. The previously held idea that atherosclerosis is a progressive process which happens simply because of lipid precipitation around arterial wall is recently shadowed by an abundant load of evidence which supports the primary role of inflammation in the pathogenesis of atherosclerosis and in plaque rupture which is demonstrated by several markers including CRP, interleukin-6 and fibrino-

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gen.[4,5] Increased levels of different inflammation markers especially CRP have been associated with an augmented risk of developing coronary artery disease (CAD) in apparently healthy individuals or with poor prognosis in patients with known CAD.[6] CRP is a sensitive and non-specific marker of low grade systemic inflammation and is released by the liver.[7] Elevated plasma CRP levels in the first days of myocardial infarction may be related to myocardial necrosis and related to infarct size tissue, and predictive of complications such as left ventricular dysfunction and cardiac wall rupture. However, elevated CRP level on admission is an important short and long-term prognostic factor in acute coronary syndrome.[4,6,7] Therefore it seems that CRP measured on admission may have prognostic value in prediction of clinical outcome of patients with AMI and can serve as a guide to select initial treatment strategy.

The aim of this study is to determine the relationship between plasma CRP levels on admission and the outcome of intravenous fibrinolysis in patients with STEMI.

Patients and Methods

This cross-sectional study comprised 84 patients with STEMI and was conducted from June 2004 to January 2006. The patients were referred to the emergency wards of Faghihi and Nemazi hospitals affiliated with Shiraz University of Medical Sciences Shiraz-Iran. Patients included in the study were those with ECG changes as shown by ST segment elevation of ≥ 2 mm in ≥ 2 contiguous precordial leads or ≥ 1mm in ≥ 2 contiguous limb leads and no contraindication for intravenous thrombolysis. Intravenous thrombolysis was initiated in the first 6 hours after index pain and the door to needle time was less than 30 minutes for all patients.

Exclusion criteria were as follows:

1-ECG changes that interfered with correct diagnosis of ST elevation such as left bundle branch block.

2-Previous coronary artery bypass surgery (CABG), percutaneous coronary intervention (PCI) or AMI.

3- History of any conditions known to alter plasma CRP levels such as recent infection, cancer, rheumatologic disease, renal and hepatic failure.

4- Premature discontinuation of intravenous thrombolysis due to complications.

The use of previous medications was not taken into account when including the patients.

The university ethics committee approved the study and informed consent was obtained from all participants.

Before initiation of any drug therapy, a venous blood sample was taken and the coded samples were stored at -20 Celsius for analysis of high sensitivity CRP (hs-CRP) at the end of the study. Upon conclusion of the study, plasma hs-CRP levels were measured by a highly sensitive immunonephelometric method (miniphen® human C-reactive protein kit) by a technician blinded to the study goals with a lower limit of detection at 0.1 mg/L. The higher normal limit of plasma CRP was 0.5 mg/L and was considered as cut off point.

All the patients received 325 mg of chewable aspirin on admission which was continued daily with a dosage between 80 to 325 mg. Other drugs such as β-blockers, angiotensin-converting enzyme inhibitors, intravenous nitroglycerin, statins and anticoagulants were given according to published guidelines.[1] Streptokinase (heberkinase, Heber Biotec S.A., Havana, Cuba) 1,500,000 units diluted in 200 ml of normal saline was given via a peripheral venous line in 60 minutes. Ninety minutes after infusion of streptokinase, another 12 lead ECG was taken from the patients and compared with the baseline ECG by a cardiologist who was unaware of the study. A reduction of 50% or more in the sum of ST segment elevation in all affected ECG leads was considered as resolution of ST segment elevation and thus indicative of response to intravenous thrombolysis (group 1) and less than 50% reduction was considered as failure to therapy (group 2). The sum of ST segment elevation was measured 20 msec after the end of QRS with PR segment as the baseline.

Values are expressed as mean ± SD for normally distributed variables and as percentage for discrete variables. Pearson Chi-Square, Fisher's exact test and t-test were used as appropriate. P values of 0.05 or less were considered significant. The data were gathered using a questionnaire and then statistical analysis was performed using a commercially available computer program (SPSS® version 11 for Windows®, SPSS Inc., Chicago, Illinois, US).

Results:

The mean age of the patients under study was 57±11 years. There were 28 (33.3%) females and 56 (66.6%) males. Of 84 patients, 23 (27.3%) had diabetes, and 23 (27.3%) hypercholesterolemia. Thirty-six (42.8%) patients were smokers and 8

Table 1. Demographic and clinical features of study population

Variable	Responsive to thrombolysis (Group 1)	Not responsive to thrombolysis (Group 2)	P value
Number of patients	31 (36.9%)	53 (63.1%)	
Male	21 (67.7%)	35 (66%)	0.53
Age	54.9 ± 1.7	58.9 ± 1.6	0.52
Smoker	12 (38.7%)	24 (45.2%)	0.36
DM	6 (18.7%)	15 (28.3%)	0.26
BMI over 25	17 (54.8%)	22 (41.5%)	0.68
HTN	7 (22.5%)	28 (52.8%)	0.006
Hypercholesterolemia	8 (25.8%)	14 (26.4%)	0.58
Family history of CAD	2 (6.4%)	6 (11.3%)	0.37
Mean CRP level (mg/L)	2.5 ± 0.45	2.9 ± 0.47	0.11

(9.5%) had a significant history of familial ischemic heart disease, while some patients had more than one risk factor for coronary heart disease.

Totally 31 patients (37.0%) responded to intravenous thrombolysis and the remaining 53 (63.0%) non-responding cases subsequently underwent PCI. The mean CRP level in subjects who responded to intravenous thrombolysis was lower than that of the non-responsive patients, although the difference was not statistically significant (2.5±0.45 vs. 2.9±0.47, P=0.11). The basic demographic data of the population study is shown in Table 1.

The study population was also divided according to their plasma CRP level on admission. The first group had CRP levels<0.5 mg/L (22 patients) and the second group had CRP levels≥0.5 mg/L (62 patients). These two groups were compared considering their response to intravenous thrombolysis (Table 2). There was a statistically significant difference between the respondents to intravenous thrombolysis (59.1% of the patients in the first group) and non-respondents (29.0% of cases in the second group, P=0.01)

Discussion

As shown in the present study, about 37% of patients with STEMI responded to intravenous fibrinolytic therapy. All 84 patients were divided according to their plasma CRP levels on admission into two groups; one with high CRP levels (CRP≥0.5 mg/L) and the other with normal CRP levels (CRP<0.5 mg/L). They were then compared regarding their response to intravenous thrombolysis. It was demonstrated that patients with low CRP levels on admission exhibited better response to intravenous thrombolysis while those with high CRP levels showed unfavorable response and had to undergo subsequent rescue PCI. On the other, hand the mean CRP level in patients who were responsive to thrombolysis were lower than those who were not, although the difference was not statistically significant but may suggest that CRP level on admission may have important prognostic value.

Table 2. percentage of response to thrombolysis according to CRP levels on admission

CRP level	Response to therapy		Total
	Yes	No	
CRP < 0.5 mg/L	13 (59.09%)	9 (21.95%)	22
CRP ≥ 0.5 mg/L	18 (29.03%)	44 (70.96%)	62
	31 (36.90%)	53 (63.09%)	84

This study adds further evidence to the already expanding data that CRP as an inflammation marker plays an important part in the pathogenesis and prognosis of AMI.

Foussas et al have demonstrated that an elevated plasma CRP level provides additional prognostic value to TIMI risk scores in patients with either ST elevation or non-ST elevation.[11] This finding was also confirmed by Montaner at al but on the contrary Bennermo et al. have shown that markers of inflammation including CRP do not contribute to prognostic information beyond the previously described risk factors.[5,9]

A heightened inflammatory state has been associated with resistance to thrombolytic therapy as well as increased thrombus burden and impaired microvascular perfusion in patients treated for AMI. As a result, CRP can contribute both to thrombus formation and its stability and thus decreased efficiency of reperfusion therapy.[6,10] On the other hand, it is shown that successful reperfusion therapy at-

tenuates the inflammatory response by minimizing the release of inflammatory mediators from jeopardized myocardium as evidenced by negative correlation of CRP with TIMI flow grade in the culprit artery which may be an important benefit of thrombolytic therapy in AMI.[5,7] Considering these data, attention has been focused on the value of CRP level on admission to determine the best possible treatment strategies for patients. Although increased CRP levels in patients during admission is multifactorial and may reflect the extent of preexisting atherosclerosis or vulnerability of plaques. Also the presence of risk factors such as smoking and obesity, the extent of necrosis, early complicating infections or a combination of these entities as well as the influence of genetic factors and the use of medications such as statins, warrants much consideration to be given to CRP level on admission.[6,12] Gheno et al have reported that a high plasma CRP on admission was independently and positively related to mortality of hospitalized patients.[13] Tomoda et al, have found that elevated CRP levels in the first 6 hours of AMI were positively associated with more adverse outcome in admitted patients, including cardiac death after PTCA.[14] Nikfardjam et al have retrospectively shown that there was a positive association between plasma CRP levels on admission and 3-year cardiac mortality.[15] Tommasi et al, have shown that patients with increased levels of CRP early in the first 8 hours of uncomplicated AMI constituted a high-risk group for cardiac death and new acute coronary events during the first year.[16] Pietilä et al have demonstrated a gradual inverse relationship between peak plasma levels of CRP, estimated during the first days of ST elevation AMI, and the probability of 24 months survival.[17] However, in Pietilä's study, CRP measurements were made late in the course of AMI, and subsequently, CRP values were significantly influenced by the extent of intercurrent myocardial necrosis.[2] Zairis et al have shown that a high CRP level value before the start of intravenous thrombolysis is strongly associated with reperfusion failure which was also shown by Hoffmann et al and Foussas et al.[2,3,8] Interestingly Mueller at al. have also demonstrated that early revascularization does not ameliorate the negative prognostic impact of elevated CRP.[18] Dibra et al found that predictive value of CRP was confined to patients treated with intravenous thrombolysis and was not predictive of myocardial salvage in patients treated with stenting.[6] In a study by Amasyali et al, it was shown that ninety minutes after initiation of streptokinase, patients with normal CRP level (CRP<0.5 mg/L) achieve TIMI 3 flow more than those patients with high CRP level (CRP>0.5 mg/L) who generally reach TIMI 2 flow after reperfusion.[4]

The importance of plasma CRP level on admission was also highlighted in our study which was of cross-sectional nature, and reflected an actual clinical practice in many centers where primary PCI was not routinely performed and intravenous thrombolysis was the method of choice for reperfusion. CRP level determined on admission may be of specific value for early therapeutic decision making and patient treatment in the heterogeneous population of patients referred to heart centers. Patients with elevated CRP levels on admission may need special attention for identifying thrombolysis failure and possibly the appropriate adjustment of treatment.

As with previous reports, our study had some limitations. First of all it may be claimed that larger myocardial necrosis or longer pre-admission delay may be associated with both elevated CRP levels and less successful reperfusion and unfavorable outcome.[2] This cannot be excluded unless larger trials are done. The patients under study had not undergone catheterization immediately after administration of intravenous thrombolysis. Therefore, the estimated TIMI grades do not represent the flow in the infarction-related artery early after thrombolysis. However, complete ST-segment resolution is a reliable predictor of myocardial reperfusion and is well related to TIMI 3 flow in the infarct-related artery after thrombolysis.[2,19]

Another limitation of our study was the lack of totally matched patients in our study group which was due to a rather small sample size. Despite this limitation our patients were matched in all demographic data except the history of hypertension which was not known to affect CRP level but still other better designed studies with larger samples and improved matching are needed.

Another point worth mentioning is the success rate of reperfusion after intravenous thrombolysis with streptokinase in our study which was estimated to be about 37%. This was close to values reported by several studies with success rate within the range of 40%-75% and depending on several factors including patient's comorbidities, demographic data, admission time to emergency room, door to needle time, interpretation of ECG and even manufacturer of streptokinase.[20-24]

Finally it can be concluded that CRP level on admission may be used to predict the outcome of thrombolysis in patients with AMI and may in the

future be integrated into the protocol management of patients with AMI to avoid more invasive procedures.

Acknowledgement

This work was financially supported by Vice Chancellor for Research of Shiraz University of Medical Science. The authors declare that they have no conflicts of interest.

References

1 Van de Werf F, Ardissino D, Betriu A, Cokkinos DV, Falk E, Fox KA, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2003;**24**:28-66. [12559937]

2 Zairis MN, Manousakis SJ, Stefanidis AS, Papadaki OA, Andrikopoulos GK, Olympios CD, et al. C-reactive protein levels on admission are associated with response to thrombolysis and prognosis after ST-segment elevation acute myocardial infarction. *Am Heart J* 2002;**144**:782-9. [12422145]

3 Foussas SG, Zairis MN, Makrygiannis SS, Manousakis SJ, Anastassiadis FA, Apostolatos CS, et al. The significance of circulating levels of both cardiac troponin I and high sensitivity C reactive protein for the prediction of intravenous thrombolysis outcome in patients with ST segment elevation myocardial infarction. *Heart* 2007;**93**:952-6. [17344331]

4 Amasyali B, Kose S, Kilic A, Iyisoy A, Barcin C, Kursaklioglu H, et al. C-Reactive protein on admission and the success of thrombolytic therapy with streptokinase: is there any relation? *Int J Cardiol* 2003;**92**:27-33. [14602213]

5 Bennermo M, Held C, Hamsten A, Strandberg LE, Ericsson CG, Hansson LO, et al. Prognostic value of plasma C-reactive protein and fibrinogen determinations in patients with acute myocardial infarction treated with thrombolysis. *J Intern Med* 2003;**254**:244-50. [12930233]

6 Dibra A, Mehilli J, Schwaiger M, Schuhlen H, Bollwein H, Braun S, et al. Predictive value of basal C-reactive protein levels for myocardial salvage in patients with acute myocardial infarction is dependent on the type of reperfusion treatment. *Eur Heart J* 2003;**24**:1128-33. [12804927]

7 Tsakiris AK, Marnelos PG, Nearchou NS, Papadakis JE, Karatzis EN, Skoufas PD. The influence of thrombolytic therapy on C-reactive protein in ST-segment elevation acute myocardial infarction. *Hellenic J Cardiol* 2006;**47**:218-22. [16897925]

8 Hoffmann R, Suliman H, Haager P, Christott P, Lepper W, Radke PW, et al. Association of C-reactive protein and myocardial perfusion in patients with ST-elevation acute myocardial infarction. *Atherosclerosis* 2006;**186**:177-83. [16140308]

9 Montaner J, Fernandez-Cadenas I, Molina CA, Ribo M, Huertas R, Rosell A, et al. Post stroke C reactive protein is a powerful diagnostic tool among candidates for thrombolysis. *Stroke* 2006;**37**:1205-10. [16601211]

10 Akbulut M, Kutlu M, Ozbay Y, Polat V, Bilen MN, Baydas A et al. Efficacy of clopidogrel on reperfusion and high-sensitivity C-reactive protein in patients with acute myocardial infarction. *Mediators Inflamm* 2009;**2009**:932515. [19365587]

11 Foussas SG, Zairis MN, Lyras AG, Patsourakos NG, Tsirimpis VG, Katsaros K , et al. Early prognostic usefulness of C-reactive protein added to the Thrombolysis In Myocardial Infarction risk score in acute coronary syndromes. *Am J Cardiol* 2005 ;**96**:533-7. [16098307]

12 Topakian R, Strasak AM, Nussbaumer K, Haring HP, Aichner FT. Prognostic value of admission C reactive protein in stroke patients undergoing IV thrombolysis. *J Neurol* 2008;**255**:1190-6. [18484234]

13 Gheno G, Libardoni M, Zeppellini R, Cucchini F. C-reactive protein as a predictor of in-hospital death in the elderly with acute myocardial infarction. *Cardiologia* 1999;**44**:1023-8. [10687251]

14 Tomoda H, Aoki N. Prognostic value of C-reactive protein levels within six hours after the onset of acute myocardial infarction. *Am Heart J* 2000;**140**:324-8. [10925350]

15 Nikfardjam M, Müllner M, Schreiber W, Oschatz E, Exner M, Domanovits H, et al. The association between C-reactive protein on admission and mortality in patients with acute myocardial infarction. *J Intern Med* 2000;**247**:341-5. [10762450]

16 Tommasi S, Carluccio E, Bentivoglio M, Buccolieri M, Mariotti M, Politano M, et al. C-reactive protein as a marker for cardiac ischemic events in the year after a first, uncomplicated myocardial infarction. *Am J Cardiol* 1999;**83**:1595-9. [10392860]

17 Pietilä KO, Harmoinen AP, Jokiniitty J, Pasternack AI. C-reactive protein concentration in acute myocardial infarction and its relationship to mortality during 24 months of follow-up in patients under thrombolytic treatment. *Eur Heart J* 1996;**17**:1345-9. [8880019]

18 Mueller C, Buettner HJ, Hodgson JM, Marsch S, Perruchoud AP, Roskamm H, et al. Inflammation and long term mortality after non ST elevation acute coronary syndrome treated with a very early invasive strategy in 1042 consecutive patients. *Circulation* 2002;**105**:1412-5. [11914246]

19 de Lemos JA, Antman EM, Giugliano RP, McCabe CH, Murphy SA, Van de Werf F. St segment resolution and infarct related artery patency and flow after thrombolytic therapy. Thrombolysis in myocardial infarction (TIMI) 14 investigators. *Am J Cardiol* 2000;**85**:299-304. [11078296]

20 Bhatia L, Clesham GJ, Turner DR. Clinical implications of ST-segment non-resolution after thrombolysis for myocardial infarction. *J R Soc Med* 2004;**97**:566-70. [15574852]

21 Lee YY, Tee MH, Zurkurnai Y, Than W, Sapawi M, Suhairi I. Thrombolytic failure with streptokinase in acute myocardial infarction using electrocardiogram criteria. *Singapore Med J* 2008;**49**:304-10. [18418522]

22 Olson HG, Butman SM, Piters KM, Gardin JM, Lyons KP, Jones L ,et al. A randomized controlled trial of intravenous streptokinase in evolving acute myocardial infarction. *Am Heart J* 1986;**111**:1021-9. [3521245]

23 Clemmensen P, Grande P, Pedersen F, Granborg J, Svendsen JH, Madsen JK, et al. ECG and enzymatic indicators of therapeutic success after intravenous streptokinase for acute myocardial infarction. *Am Heart J* 1990;**120**:503-9. [2389686]

24 Hermentin P, Cuesta-Linker T, Weisse J, Schmidt KH, Knorst M, Scheld M, et al. Comparative analysis of the activity and content of different streptokinase preparations. *Eur Heart J* 2005;**26**:933-40. [15637085]