Prognostic role of hs-CRP before and after Percutaneous Coronary Intervention in Patients with Stable Angina Pectoris

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Abstract:

Background and Objectives: Myocardial injury after percutaneous coronary intervention (PCI) occurs frequently and it is associated with an adverse clinical outcome. Mechanical factors have been implicated in this complication and the role of inflammation has not yet been clearly determined. We evaluated the effect of an inflammatory response during PCI on periprocedural myocardial injury.

Subjects and Methods: This prospective observational study was conducted in the Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh over a period between July'2012 to June'2013. A total of 200 patients studied who underwent elective coronary stenting. For the exclusion of mechanical injury to the myocardium, we excluded those patients who developed complications during PCI. The inflammatory response to PCI was calculated as the difference between the peak postprocedural hs-CRP level and the preprocedural hs-CRP level . We divided the patients according to the median value of hs- CRP: Group I <3 mg/L and Group II >3 mg/L.

Results: Postprocedural TnI elevation was were observed in 72 (36%) patients. The baseline clinical and angiographic characteristics were not difference between the two groups. The incidence of any TnI elevations was higher in the Group II than that in Group I (19.8% vs 42.6%, respectively, p<0.001). The incidences of TnI levels over 3 times the upper normal limit and 5 times the upper normal limit were also higher in Group II than in Group I (11.2% vs 21.7%, respectively, p=0.031, for a TnI level 3 times the upper normal limit, and 6.0% vs 13.9%, respectively, for a TnI level 5 times the upper normal limit. Multivariate analysis revealed that postprocedural hs-CRP elevation in high risk group were the significant independent predictors of postprocedural TnI elevation.

Conclusion: Elevated hs-CRP levels were associated with a higher risk of postprocedural troponin elevation in patients undergoing uncomplicated PCI. These results emphasized the role of inflammation in the pathogenesis of periprocedural myocardial injury. Measuring of hs-CRP either preprocedural or postprocedural in high risk patients is useful for predicting early cardiovascular events.

Key words: high-sensitive C-reactive protein; Percutaneous Coronary Intervention; Stable Angina Pectoris

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Introduction:

C-reactive protein (CRP) is an acute phase reactant made mainly in the liver. CRP is commonly measured to screen for inflammation or infection. CRP is produced by cells of liver, vascular wall such as endothelial cells, smooth muscle cells, and also by adipose tissue.[1] Chronic inflammation is pivotal in heart disease, studies have shown that high levels of CRP, measured by high-sensitivity CRP (hs-CRP), can be a marker of atherosclerosis. hs-CRP is an important predictor for cardiovascular events including myocardial infarction, cerebrovascular events, peripheral vascular disease, and sudden cardiac death in individuals without a history of heart disease. In patients with acute coronary syndrome, CRP level predicts mortality and cardiac complications. High CRP levels augur a worse prognosis in patients with acute coronary syndromes.[2] Percutaneous Coronary Intervention (PCI) with stent implantation is a mainstay in the management of severe coronary artery atherosclerotic disease.[3] The prognostic role of CRP in the risk of in-stent restenosis, and the consequent occurrence of coronary target-lesion revascularization, is

less well established than the relation of CRP to overall prognosis.[4]

The inflammatory process leading to, plaque growth, rupture, or activation is different from the healing inflammatory process after angioplasty and stent implantation, and the latter may also induce a strong inflammatory response by itself with confounding effects on the role of preprocedural inflammatory markers such as CRP.[5]

This analysis highlights the association between baseline CRP and postprocedural ischemic events, in particular, events that occur in the first few days after PCI. This relationship suggests that CRP may predict the risk of distal embolization or may play a direct role in augmenting microvascular inflammatory response after ischemic insult. Although its precise role in ischemic injury requires further elucidation, a focus on baseline CRP may prove useful for identification of patients who may benefit from adjunctive pharmacological or mechanical therapies around the time of PCI.

Materials and methods:
This Prospective observational study was carried out in the Department of Cardiology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, over a period between July 2012 to June 2013 . The study was performed among the patient who were diagnosed as Chronic stable angina and scheduled for Percutaneous Coronary Intervention (PCI). The eligibility criteria were as follows:

Inclusion Crietria:
Patients with stable angina pectoris and age between 25 - 75 years, were undergone coronary angiography followed by Percutaneous Coronary Intervention(PCI) with Bare Metal Stent.

Exclusion Criteria:
Any evidence of pericardial or endocardial disease, Valvular heart disease, Poorly controlled hypertension (SBP >160 mmHg and/or DBP>105mmHg), Left ventricular ejectioin fraction less than 40%, Patients with class III or IV heart failure, Previous Percutaneous Coronary Intervention (PCI) or Coronary artery bypass grafting (CABG), Patients refusal to undergo Percutaneous Coronary Intervension (PCI), Patients with Infective conditions, connective tissue diseases, neoplastic diseases, untreated thyroid disorder, abnormal renal and hepatic function, Life threating arrhythmias, Oestrogen replacement therapy, Thrombotic disorder, Contra-indication to aspirin or clopidogrel etc.

Grouping of patients : Done by randomization into –

Group-I: These are the patients scheduled for Percutaneous Coronary Intervention (PCI) with Stable Angina Pectris with normal hs-CRP level before coronary angiogram.

Group-II: These are the patients scheduled for Percutaneous Coronary Intervention (PCI) with Stable Angina Pectoris with high level of hs-CRP before coronary angiogram.

Ethical clearance was obtained from the Institutional Review Board (IRB) of BSMMU. According to Helsinki declaration for Medical Research involving Human Subjects 1964, all the patients be informed about the study design, the underlying hypothesis and the right for the participants to withdraw themselves from the projects at any time, for any reason, what so ever which will not hamper the standard duty of care anyway. Written informed consent will be obtained from each subject who will voluntarily provide consent to participate in the study. The ethical issues will be addressed accordingly.

Results:
This study was intended to compare the in hospital short-term outcome (in terms of arrhythmia,recurrent angina, non-fatal MI, urgent target vessel revascularization and death) in stable angina patients scheduled for elective percutaneous coronary intervention with hs-CRP < 3mg/l (Group-I) and that of with hs-CRP > 3mg/l (Group-II). Of 200 (two hundred) patients ,one hundred patients with hs-CRP < 3mg/l were assigned to Group-I and another one hundred patients with hs-CRP > 3mg/l to Group-II.

All patients were followed up to 72 hours after percutaneous coronary intervention to see the in-hospital short term outcome in the form of arrhythmia, non-fatal MI, recurrent angina, in-stent thrombosis, urgent target vessel revascularization or death.

Table-I: Showed that in Group 1-highest (31%) in the age of (45-54) years, then 30% in the age of (55-64) years, then 28% in the age of ≥65 years and lowest (11%) in the age <45 years. In Group 2-highest (38%) in the age of (55-64) years, then in the age of (45-54) years, 24% in the age of ≥65 years and lowest (12%) in the age of <45 years. Mean age of in group I- were 56.20±12.63 and in group 2- were 56.50±11.68. So the mean age was almost identical among the study population. There was no statistically (p>0.05) significant difference among the study population.

Table-II: Showed that in Group 1-the number of male patients were 86 (86%) and female patients were 14 (14%),

in Group 2- the number of male patients were 85 (85%) and female patients were 15 (15%). In this study out of two hundred patients 171 (85.5%) were male and 29 (14.5%) were female (Table-II). There was no statistically (p> 0.05%) significant difference regarding gender distribution among the studied groups.

Table-III: Showed that smoking was the most common risk factor among two groups. There were 73 smokers in group-I and in group-2. Hypertension was the second risk factors both groups. There were 21 hypertensive patients in group-1 and 25 in group-2. Diabetes Mellitis was the third risk factor among two groups, 15 were in group-1 and 19 in group-2. Dyslipidemia was present 07 in group-1 and 10 in group-2. There was no statistically (p>0.05%) significant difference regarding risk factors among the study groups.

Table-IV: Showed that in group-1, patients mean ejection fraction was (47.37±6.07), in group-2 patients mean ejection fraction was (43.44±7.79). So it was significantly(<0.001) lower in group-2 and than group-1. There was no significant difference in blood pressure measurement of the studied population. Regarding pulse,in in group-2,mean value was (90.99±23.06) and in group-

1,it was(8490.±20.03) So it was significantly (p<0.05) in group- 2 than in group-1.

Table V demonstrate the baseline laboratory investigation findings between the study groups revealed that Troponin I were almost homogeneously distributed between group-I and group-II but mean serum hs-CRP were significantly higher in group-II than in group-I (2.8±2.6 vs. 3.4±2.5 mg/l, p=0.010).

Table- VI showed Arrhythmias [11 (11.0%) vs 29 (29.0%); χ^2=10.125; p=0.001] and recurrent angina was [6 (6.0%) vs 19 (19.0%); χ^2=7.726; p=0.005] were significantly more in high h-CRP group than that of normal h-CRP group; while urgent revascularization [2 (2.0%) vs 8 (8.0%); χ^2=3.789; p=0.052]; Non-fatal myocardial infarction (MI) [5 (5.0%) vs 7 (7.0%); χ^2=0.355; p=0.552]; and mortality [3 (3.0%) vs 0 (0.0%); p=0.246]; did not differ significantly between high h-CRP group and normal h-CRP group. But the no complication [78 (78.0%) vs 51 (51.0%); χ^2=15.191; p=0.052] was significantly fewer in normal hs-CRP group than that of high hs-CRP group. Distribution of patients by inhospital short-term outcome was shown in table-VI

Total number exceed 100 in both group due to multiple complications in some of the patients.

Table-II
Distribution of study patients by gender (n=200).

Age groups (yrs)	Group I (N=100)		Group II (N=100)		Total (N=200)		P Value
	No	%	No	%	No	%	
Male	86	86	85	85	171	85.5	0.841[ns]
Female	14	14	15	15	29	14.5	
Total	100	100	100	100	200	100	

Group I : Patients with hs-CRP <3 mg/l ; Group II : Patients with hs-CRP >3mg/l; P value reached from Chi-square test; a : P value reaches from Stdent's t test; NS = Not Significant; N = Sample Size

Table-I
Distribution of study population by age groups (n=200).

Age groups (yrs)	Group I (N=100)		Group II (N=100)		Total (N=200)		P Value
	No	%	No	%	No	%	
<45	11	11	12	12	23	11.5	0.824[ns]
45-54	31	31	26	26	57	28.5	0.433[ns]
55-64	30	30	38	38	68	34.0	0.232[ns]
e"65	28	28	24	24	52	26.0	0.519[ns]
Total	100	100	100	100	200	100	
Mean±SD	56.20±12.6356.50±11.68				0.862[ns]		

Group I : Patients with hs-CRP <3 mg/l; Group II : Patients with hs-CRP >3mg/l; P value reached from Chi-square test; a : P value reaches from Stdent's t test; NS = Not Significant; N = Sample Size

Table-III

Risk factors distribution of study population (n=200).

Risk factors	Group I (N=100)		Group II (N=100)		Total (N=200)		P Value
	No	%	No	%	No	%	
Smoking	73	73	73	73	146	73.0	0.533[NS]
HTN	21	21	25	25	46	23.0	0.502[NS]
Dyslipidemia	07	07	10	10	17	8.5	0.502[NS]
DM	15	15	19	19	34	17.0	0.516[NS]

Group I : Patients with hs-CRP <3 mg/l; Group II : Patients with hs-CRP >3mg/l; P value reached from Chi-square test; NS = Not Significant; N = Sample Size

Table-IV

Hemodynamic and Echocardiographic parameters of study patients (n=200).

Outocme	Group I (N=100)		Group II (N=100)		Total (N=200)		P Value
	Mean	±SD	Mean	±SD	Mean	±SD	
Systolic BP(mmHg)	104.35	±25.87	105.40	±29.33	104.88	±27.59	0.789(NS)
Diastolic BP(mmHg)	68.10	±16.17	68.65	±18.20	68.37	±17.17	0.822(NS)
Pulse/min	84.90	±20.03	90.99	±23.06	87.95	±21.76	0.048(S)
Ejection Fraction	47.37	±6.07	43.44	±7.79	45.40	±7.24	0.0001(S)

Group I : Patients with hs-CRP <3 mg/l; Group II : Patients with hs-CRP >3mg/l; P value reached from Chi-square test; NS = Not Significant; N = Sample Size

Table-V

Comparison of laboratory investigations before and 24hs after PCI between groups (n=200).

Baseline laboratory investigations	Group		p-value
	Group-I(n=100)	Group-II(n=100)	
Serum hs-CRP (mg/l)[#]	2.8±2.6	3.4±2.5	0.010(S)
Serum Troponin I(ng/ml)[#]	0.01±0.05	0.5±0.03	0.56 (NS)
Outcomes 24hrs after procedures:			
Serum hs-CRP (mg/l)[#]	3.35±5.1	10.69±8.8	0.034(S)
Serum Troponin I (ng/ml)[#]	1.07±0.14	4.13±0.39	0.010 (S)

Data were analysed and presented as mean±SD using Students's t-test.
*Chi-square Test was employed to analyse the data; figure in the parentheses denote percentage

Table-VI

In-hospital short-term outcome after PCI of study patients

Outcome	Study group		p-value
	Group I (n=100)	Group-II (n=100)	
Arrhythmias	11 (11.0)	29 (29.0)	*p=0.001
Recurrent angina	6 (6.0)	19 (19.0)	*p=0.005
Urgent revascularization	2 (2.0)	8 (2.0)	*p=0.052
Non-fatal MI	5 (5.0)	7 (7.0)	*p=0.552
Death	0 (0.0)	3 (3.0)	*p=0.246
No complication	78 (78.0)	51 (51.0)	[†]p<0.001

Figures in the parenthesis denote corresponding percentage.
*Chi-Square (χ^2) Test and [†]Fisher's Exact test were employed to analyse the data.

Discussion:

In this study, we showed that elevated hs-CRP levels were associated with a higher risk of postprocedural troponin elevation in patients undergoing uncomplicated PCI. This finding is important because a higher degree of postprocedural myonecrosis is associated with an increased risk of adverse events during follow-up.

Vascular injury during PCI is associated with a systemic inflammatory response, and the degree of inflammation has been shown to correlate with the cardiovascular risk.[2] Preprocedural elevation of the CRP levels has recently emerged as a clinical predictor for periproce-dural myocardial injury. The increase in the serum CRP concentration follows the increase in the serum IL-6 concentration by 12-36 hours, and the serum CRP concentration reaches its peak value by 24 hours after the procedure.[2] Bonz et al (2003) found the increase in the serum concentrations of both IL-6 and CRP to be more obvious in patients with concomitant post-procedural troponin I elevation.[6] Saadeddin et al. 2002, reported prep-rocedural CRP elevation in 41% of 85 patients with stable angina and who undergoing PCI,[7] and this was associated with a 2.27-fold higher risk of developing periprocedural myocardial injury, and the latter was defined by a postprocedural troponin I elevation of >2 ng/mL. Ellis et al(2002) confirmed a nearly 4-fold higher preprocedural CRP level among die patients who developed postprocedural CK-MB elevation. Additionally,[8] Hong et al(2005) demonstrated that elevated preprocedural CRP levels are associated with neointimal hyperplasia and restenosis after PCI.[9]

Yet contradictory results have reported. Gaspardone et al(1998) excluded the patients with any postprocedural cardiac marker elevation and they still found CRP elevation (>0.5 mg/dL) within 48 hours after PCI in 99% of these patients.[10]

In our study, the baseline CRP level was similar between the two groups, yet the inflammatory response (CRP) during intervention was more associated with periprocedural myocardial injury. Although the subsets of patients or their medications in our study were different from those of other studies, our results consolidated the association between CRP and the troponin changes during PCI.

Different strategies such as platelet GP Ilb/IIIa inhibitors and high dose clopidogrel and statin have been proposed and tested to prevent peri-procedural myocardial infarction (Buffon et al.1999.[11] Many studies such as Morrow et al. 1998 have demonstrated that early statin therapy among

PCI patients is associated with significant advantages for decreased mortality and morbidity in different patient subsets.[12] Although the mechanism is not entirely clear, the anti-inflammatory effects of statins might contribute to the reduced myocardial injury during PCI. In the present study, prior statin therapy had no significant effect on postprocedural troponin elevation. However, only 12% of all the study patients were receiving prior statin therapy, and this lowered the power to detect differences between the patients with and without statin therapy.

The results of the present study suggest that systemic factors may affect the susceptibility to postprocedural troponin elevations. Ishikawa et. al. 2003 described that with excluding mechanical causes, structural and functional microvascular obstruction have been implicated in most cases of postprocedural myonecrosis.[13] Thus, CRP may be related to such pathological conditions as friability and hypercoagulability of the atheromatous lesion, which predispose to a patient to microembolization or clot formation at the site of the PCI-induced arterial injury. Kim et al. 2001 repored that systemic inflammation also provides a link between PCI-associated infarction and long-term events, the same as was reported by previous studies.[14] So, other therapeutic strategies that can inhibit the inflammatory response are needed to prevent peri-procedural myocardial injury.

Despite favourable outcome,the study has several limitations.The following limitations deserve mention.

1. This was a single centre study.

2. The study included a small number of patients than required, so conclusions may not be consistent with similar large- scale studies.

3. We did not follow up patients beyond 72 hours after the procedure, and as such,outcome beyond that period is not known.

Conclusion:

An elevated hs-CRP levels were associated with a higher risk of postprocedural troponin elevation in those patients who are undergoing uncomplicated PCI. These results emphasized the role of inflammation in the pathogenesis of periprocedural myocardial injury. Measuring of hs-CRP either preprocedural or postprocedural in high risk patient's is useful for predicting early cardiovascular events.

Recommendation:

Aggressive anti-inflammatory Medication can reduce myocardial injury after successful percutaneous coronary

intervention (PCI). Further multicenter study with larger samples is needed to validate the findings of the present study.

Conflict of Interest:

Acknowledgement:

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