Evaluation of Plasma Levels of C - reactive protein as a Predictor of Restenosis after Percutaneous Coronary Intervention

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Abstract

Background- Restenosis after percutaneous revascularization is a troublesome endpoint, and the role of inflammation is well-accepted in the restenosis process. To predict this untoward result, an investigation of acute phase reactants has been applied. In this study, we tried to find the predictive role of pre- and post-intervention C-reactive protein (CRP) levels for clinical restenosis rates in a 6 month follow-up.

Methods- Having been selected in a non-randomized double-blind clinical trial, seventy-four patients underwent percutaneous coronary intervention (PCI) for a single non-occlusive coronary stenosis. The plasma CRP level was measured just before the procedure and 24 hours afterwards. Patients with acute MI, multi-vessel PCI, previous PCI or CABG and some other situations that could affect acute phase reactants were excluded.

Results- There was no significant relation between the pre-intervention CRP level and the restenosis rate or the clinical signs of restenosis (MI, angina pectoris and ECG changes). It was the same for 24 hours post-PCI CRP level; however, the restenosis rate was significantly related to the ratio of CRP levels at pre- and post-PCI (P: 0.004).

Conclusion- The ratio of pre- and post-PCI CRP levels could have a predictive role for restenosis after PCI ***(Iranian Heart Journal 2004; 5(1,2):81-85).***

Key words: C-reactive protein (CRP) coronary restenosis percutaneous coronary intervention (PCI)

Percutaneous transluminal coronary angioplasty (PTCA) is an established revascularization procedure.[1] Restenosis is a major long-term complication after any revascularization procedure, and for PTCA the restenosis rate is between 30-60% after 6 months.[1,2] Intramural balloon inflation of an atherosclerotic vessel leads to arterial wall damage[1] and activates platelet deposition and coagulation cascade.[1,3] It seems that these pathways play a key role in local inflammation of these vessels and also pre-neointimal proliferation, which has a role in restenosis development.[1,3]

In the inflammation process during PTCA, a significant increase of serum C-reactive protein (CRP) level has been reported previously.[1,4,5] CRP is an acute phase reactant and non-specific marker of inflammation which increases during cardiac events in patients with coronary artery disease.[6,7] Furthermore, it has been shown that a significant increase of CRP is closely related to the post-PTCA restenosis rate and has a prognostic value of late restenosis after PTCA. Although some documents confirm that CRP is related to late restenosis after PTCA,[1,5,8] there is evidence which refutes this hypothesis.[9] In the inflammatory process, pathologic burden, procedural events and risk factors have a main role in restenosis after PTCA.

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In this study, we tried to find whether the CRP level has a predictive role for the determination of late restenosis in six months' follow-up after PTCA.

Material and Methods

Patient Population

In this non-randomized double-blind clinical trial, we selected 74 consecutive patients who underwent PTCA on a single non-occlusive coronary stenosis. They were selected from over 411 patients who were undergoing percutaneous coronary intervention (PCI) and who were enrolled in the catheterization laboratory registry of our department. Patients with acute myocardial infarction and significant unstable angina three months before angioplasty, multi-vessel PTCA, total occlusion, previous PTCA or CABGS, left ventricular ejection fraction below 30%, left bundle branch block, significant valvular heart disease, myocarditis, cardiomyopathy, hepatic, renal or thyroid diseases, acute infection or inflammatory diseases in the last 6 months were excluded. The patients consisted of men and women in the age range of 25 to 70 years old. The patients gave written informed consent for all the study conditions regarding research definitions. Clinical researchers for the procedure, follow-up and lab tests were different, and only the last researcher had a code from any given case. The patients were also blinded to the CRP results.

Blood Sampling and laboratory assay

Blood samples for the measurement of CRP were taken immediately before PCI and 24 hours after the procedure. Coded serum samples were stored at -70° C and analyzed in a single batch at the end of the study; thus the management of the patients was independent of the results. CRP was assayed by sandwich Eliza kits 0 with 0 system.

Coronary angiography review

Expert cardiologists performed the interventions, and the cardiologists who were blinded to the study results reviewed all the pre- and post-PCI angiograms (single observer).

A successful procedure was considered as a final percent diameter stenosis of less than 50% with TIMI 3 flow in the absence of recurrent ischemia, MI, death or need for urgent CABG during the hospital period.

Follow-up

Creatine kinase was measured every 6 hours for 24 hours after the procedure, and ECG was recorded daily until hospital discharge. Clinical examination, ECG and lab tests were performed at first visit, month 1 and 3, and ECG, lab tests and exercise tolerance test (ETT) were performed at the end of the six months' follow-up after PCI.

End points

Early adverse events were abrupt closure (TIMI 0-1), luminal dissection or delayed run off (TIMI 2) and rest angina or MI before hospital discharge confirmed by ECG signs and lab tests.

Late events were clinical restenosis (typical angina, MI and death) or ischemia at ETT ($\geq 1^{mm}$ S-T segment depression). Only patients with these signs underwent repeated angiography and/or next revascularization procedures.

Statistical Analysis

Patients' data sheets and documents were checked by the head cardiologist, and after troubleshooting, the data were analyzed by an epidemiologist with commercial software (SPSS version 10.00) and Friedman test.

Results

60.9% of the patients were male. All the patients presented with stable angina, and no one had unstable angina. The risk factors and their prevalence in the selected patients were hypertension (34.1%), hyperlipidemia (52.2%), diabetes (17.4%), smoking (39.1%) and family history (30.4%). Target vessels and their characteristics are shown in Tables I and II.

Table I. Target vessels

Target Vessel	Prevalence (%)
LAD	39.1
LCX	4.3
LAD and RCA	8.7
RCA	4.3
OM	8.7
LAD and Diagonal	34.8
Total	100%

Table II. Characteristics of target lesions

Characteristics	Prevalence (%)
Luminal diameter < 2.5 mm	17.4
Luminal diameter 2.5 -3 mm	73.9
Luminal diameter > 3 mm	8.7
Discrete lesion (<10mm length)	43.5
Tubular lesion (10 - 20 mm length)	47.8
Diffuse lesion (> 20mm length)	8.7
Eccentric lesion	95.7
Moderate tortuousity of proximal segment	87
Irregular contour	100
Calcification	0
Ostial lesion	0
Thrombus presence	0

PCI was completely successful for all of the patients. Stent was deployed for 91.3% of the patients, it being primary stenting in 97.8% of them.

The clinical findings for post-PCI restenosis and their prevalence were ECG changes (73.9%), angina pectoris (65.2%) and dyspnea (69.6%). CRP levels, pre- and post-intervention, are demonstrated in Table III.

Table III. CRP levels (mg/dl)

Process	Follw-up condition	Min	Max	STD	Mean
Pre - intervention	Restenosis	0.115	1.340	0.400	0.505
	Non-restenosis	0.157	4.600	1.557	1.330
Post - intervention	Restenosis	0.775	3.720	1.023	2.588
	Non-restenosis	0.225	6.7	1.935	1.814

There was no significant relation between the pre-intervention CRP and the restenosis rate (P: 0.723) or the clinical signs of restenosis (MI, angina pectoris and ECG changes (P values 0.457, 0. 693 and 0.619, respectively). This result was similar for 24 hours post-PCI CRP level (P values: 0.603, 0.263, 0.086 and 0.637, respectively), but the restenosis rate was significantly related to the ratio of CRP level at pre- and post-PCI (P: 0.004). This result, based on ANOVA test, is illustrated in Table IV. As previously stated, CRP is an acute phase reactant protein made up of 5 identical 23kD subunits, arranged as a donut. It rises 100-fold after 24 to 48 hours during inflammatory processes, and the site of its synthesis and secretion is hepatocytes in response to cytokines such as interleukin6.[10]

Table IV. CRP ratio at pre- and post-PCI

Index	Late Restenosis	Non-restenosis
Mean	8.06	1.77
Minimum	2.35	0.89
Maximum	25.22	4.69
STD	7.54	0.97
ST-error	2.67	0.25
Number of analyzed data	25	46

It is found that this elevation may reflect the degree of the underlying inflammatory response and the extent of immune injury to tissues.[10]

It is confirmed that CRP is present in atherosclerotic plaques but not in the

normal vessel wall.[8] It has also been shown by many documents that CRP not only is a marker of inflammatory processes but also has a main role in atherogenesis.[3,11,12] In 1982, de Baur et al.[13] showed that individuals with myocardial infarction developed elevated CRP levels.

Berk, et al.[14] showed that there were significant differentiations for CRP roles between patients with stable and unstable angina. Ridker, et al. confirmed that risk of myocardial infarction and stroke might be predicted by CRP level.[15] In addition, it has been confirmed that baseline values of CRP before PCI can predict complications after PCI[16] and that not only may they reflect restenosis but they may also be a coronary instability inflammatory instigator.[10] Another study demonstrated that the high CRP levels that persisted for longer than 48 hours after stent deployment might be a marker for an increased risk of angiographic restenosis 6 months after the procedure.[17] Some studies[9] state that the pathologic burden rather than the CRP level may have a predictive role for clinical restenosis after PCI.

In our study, we tried to determine the predictive role of CRP before and after PCI for clinical restenosis. In addition, we tried to investigate the notion that PCI as an invasive procedure leads to cell wall injury and produces an inflammatory process that increases the CRP level and whether this increment has a predictive role for clinical restenosis.

In light of our results, there was no relation between the CRP levels - neither 24 hours before nor 24 hours after PCI - and the clinical restenosis rate, hence our inability to find a predictive role for it. These conflicting results between those of our study and that of some other studies may partly be due to normal range CRP levels before PCI in our patients.

Aside from the above-mentioned findings, our study yielded an impressive result: that the ratio of CRP levels before and after PCI had a good relation with clinical post-PCI restenosis (P: 0.004), as shown in Table IV. Finding a specific index for this correlation to predict the post-PCI restenosis rate or prognosis requires a more extensive study with a sufficient sample size, which we hope will take place in the future.

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