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Diagnostic Value of MPO in Patients Admitted for Suspected Acute Coronary Syndrome – A Study of Adult in Mostar, Bosnia and Herzegovina

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A B S T R A C T

We assessed the diagnostic efficacy of plasma Myeloperoxidasis (MPO) alone or in combination with cardiac troponin I (cTnI) for detecting ACS in patients presenting with chest pain initiating within 24 h before the hospital admission. In this prospective cohort study were included all respondents who have visited outpatient clinic of internal diseases, University Hospital Mostar because of chest pain and suspected acute coronary syndrome within 24 h of the onset of the period of 6 months and the total sample consisted of 114 patients. Troponin and myeloperoxidase were significantly positively correlated at the beginning of treatment, myeloperoxidase was significantly positively associated with adverse cardiovascular events during hospitalization and myocardial infarction ($p<0.05$), with the regression analysis did not show a significant predictor in the development of myocardial infarction ($p>0.05$). Sensitivity of myeloperoxidase as a valid test detection of myocardial infarction at baseline was 0.15 and specificity was 0.85, suggesting good diagnostic value usable in the clinical practice.

Key words: *myeloperoxidasis, aterosclerosis, coronary artery disease, chest pain, diagnosis*

Introduction

Acute myocardial ischemia is one of the main causes of chest pain and accurate identification is of utmost importance to avoid unnecessary hospital admissions and inadequate hospital releases[1–4]. Early diagnosis of acute coronary syndrome (ACS) is frequently a challenging task, while immediate risk stratification remains crucial for the prompt implementation of appropriate therapy in this setting[5–10]. The correct final diagnosis is supported by the type of pain, electrocardiogram (ECG) and release pattern of myocardial necrosis markers[11,12]. Many patients with chest pain have normal levels of creatine kinase isoenzymes or troponins at presentation but subsequently have a myocardial infarction, require revascularization, or die within six months[13–15]. However, the prolonged release pattern of troponins, well-established biomarkers of myocardial necrosis, and limited sensitivity of the routine troponin assay make it difficult to diagnose acute coronary syndrome (ACS) at an early stage[5–10]. Additional biochemical measures, ideally based on the pathophysiology of plaque vulnerability, are needed[13–15]. Employing markers that increase rapidly after the symptom onset may enhance triage and therapeutic decision-making in patients suspected for ACS[5–10]. Inflammation has been linked to all stages of the development of vulnerable plaque, from initial lipid deposition to plaque rupture and its thrombotic complications[13–15], and extensive monocyte and neutrophil infiltration is seen in fissured, thrombosed plaques in patients with acute coronary syndromes[16,17].

Accumulating evidence suggests that Activation of leukocytes, and in particular polymorphonuclear neutrophils with concomitant release of the heme-enzyme myeloperoxidase (MPO), is closely linked to coronary plaque injury, and thus an early event in acute coronary disease[15,18–20]. Myeloperoxidase has been linked to the development of lipid-laden soft plaque[14,15], the activation of protease cascades affecting the stability and thrombo-

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genicity of plaque[16,17]. In fact, MPO demonstrated to promote endothelial dysfunction by oxidizing endothelial nitric oxide[21–26], leading to vasoconstriction[27,28] and oxidatively converting low-density and high-density lipoproteins to proatherogenic derivatives[14,29]. Also, MPO has been shown to activate matrix metalloproteinases, enzymes involved in plaque rupture, and myocardial fibrosis[30]. Moreover, MPO adversely affected myocardial remodeling, thereby adding to its potential mechanistic involvement in heart failure[31]. It has been established as a valuable marker of cardiovascular disease that independently predicts the risk of patients presenting with chest pain[6,5]. The fact that MPO release from leukocytes is connected to plaque rupture stimulated investigations assessing the clinical value of MPO plasma levels as early markers of ACS[20]. These retrospective analyses using a single time point determination of MPO suggested, that MPO is a prognostic indicator within the first hours after symptom onset, in which markers of myocardial necrosis like troponin and creatinine kinase isoenzymes are still non-elevated and lack diagnostic or prognostic information, respectively[20,32]. Indeed, recent studies indicated that the increase of MPO plasma levels precedes myocardial tissue injury[20] and suggested a potential for MPO as a diagnostic marker with high negative predictive value complementing troponins by facilitating to rule out ACS in patients presenting early after chest pain onset[33]. However, other studies failed to show a diagnostic utility of MPO plasma levels in ACS patients[10,34]. Moreover, it has been shown that MPO is an independent predictor of long-term major cardiovascular events in patients presenting with chest pain, acute myocardial infarction and a variety of other cardiovascular disorders[1,2,5–7]. Whether MPO has the potential to evolve as an additive diagnostic tool in patients admitted with suspected myocardial infarction should be evaluated[5,6,9,20,32,35,36].

Materials and Methods

According to its structure this is a cross-sectional study. The study included subjects who arrived at the admission department of the Clinic for Internal Medicine, University Clinical Hospital Mostar because of chest pain and suspected acute coronary syndrome within 24 hours of onset of pain, in the period of six months, from December 1, 2011 to June 31, 2012. This study obtained the approval of the ethical acceptability from the Ethics Committee of the University Clinical Hospital Mostar, and the consent and permission to conduct the testing from the head of the Department of Internal Medicine SKB Mostar. Each patient was asked to sign a consent form before being included in the study.

At admission department, after taking the anamnesis, physical examination and ECG insight patients were divided into three groups: 1) Patients with myocardial infarction with ST segment elevation. 2) Patients with acute coronary syndromes without ST segment elevation, some of which had a number of changes in the ECG (ST segment depression, T wave changes), while others had no changes in the ECG. Subsequently, based on the concentration of trponin the diagnosis of myocardial infarction without ST elevation or unstable angina pectoris was set. 3) In a certain number of respondents problems were not a result of acute coronary syndrome but of stable angina pectoris or were not a consequence of coronary heart disease. The study included a total of 114 patients. 77 (67.5%) cases involved men and 37 (32.5%) cases involved women (χ^2=14.035, df=1, p< 0.001). The average age of the patients was 64.8±13.6 years. The youngest participant was 20 and the oldest 90 years. At the age of up to 50 years were 12 (10.5%) patients, aged between 50–64 years 46 (40.4), while at the age of 65 years or more were 56 (49.1%) patients (χ^2=27.310, df=2, p<0.001). Blood samples were taken within 24 hours of the onset of pain on arrival at the admission department from all patients who were due to chest pain and suspected ACS, then on the seventh day and a month after the onset of chest pain. The catalytic activity of myeloperoxidase (MPO) was measured in the plasma of patients using chemiluminescent microparticle immunoassay (CMIA) on an Abbott Architect i2000 Analyzer. It is an immunoassay of two steps to determine the catalytic activity of NGAL. In the first step, the MPO present in the sample binds to the paramagnetic microparticle-labeled anti-MPO antibodies. After washing, in the second step, the binding of anti-MPO antibody labeled acridine results after washing in chemiluminescent signal the intensity of which is proportional to the catalyst concentration of MPO in the sample.

Statistics

Statistical tests were used to study the sensitivity, specificity, positive and negative predictive value. For the analysis of categorical variables χ^2-test was used. Parametric tests were used to test differences of symmetrically distributed variables between the investigated groups, while the asymmetrically distributed variables were tested with nonparametric tests (Mann-Whitney U, Kruskal Wallis).

Results

The most common diagnosis at admission was myocardial infarction (STEMI+NSTEMI), while the fewest number of cases was unstable angina pectoris (χ^2= 16.947, df=3, p<0.001). In 7% of respondents have experienced fatal outcome (χ^2=84.246, df =1, p<0.001) (Table 1).

After a complete analysis of correlation between the predictive value of myeloperoxidase in blood and the final outcome of the disease, we analyzed the sensitivity, specificity, and positive and negative value of myeloperoxidase in all observed time points of measurement. In the beginning of treatment for myeloperoxidase, the assay sensitivity was 0.15. The specificity of myeloperoxidase as a valid test in the overall recognition of myocardial infarction was 0.85, while the positive predictive value was 0.52, and negative predictive value was 0.49 (Table 2).

On the seventh day treatment sensitivity of myeloperoxidase as a valid test in the overall recognition of myocardial infarction was 0.07, specificity was 0.92. The positive predictive value was 0.50, while the negative predictive value was 0.51 (Table 3).

On the 30th day treatment sensitivity of myeloperoxidase as a valid test in the overall recognition of myocardial infarction was 0, the specificity was 0.98. The positive predictive value was 0, while the negative predictive value was 0.50 (Table 4).

Discussion

As already mentioned, in the analysis of correlation between myeloperoxidase and AMI and adverse cardiovascular events during hospitalization, in addition to correlation and this predictive value in the development of myocardial infarction we also evaluated the value of MPO as a valid test of detection of myocardial infarction through its sensitivity, specificity and positive and negative predictive value. Sensitivity of myeloperoxidase in this recognition in the beginning of treatment was 0.15. Its specificity was 0.85. while the positive predictive value was 0.52, and negative predictive value was 0.49. With a longer period of hospitalization MPO sensitivity in identifying myocardial infarction was falling, while the specificity was increasing. In accordance with these results, the findings of previous studies such as multi-center studies of Volker and his colleagues[37] show that MPO gives no diagnostic information for patients with symptoms of acute chest pain, when added to the sensitive troponin I, as both sensitivity and specificity of MPO in relation to troponin was lower. Because of the high negative predictive value achieved in his research, Volker hypothesized that the MPO could become a useful marker for the exclusion of AMI at an early stage and as D-dimer in patients with suspected pulmonary embolism, it can help for faster triage of patients with acute pain chest. However, results of previous studies differ significantly among themselves and similar hypotheses are relatively unreliable. Thus, for instance Sawicki and colleagues[38] found in their study that the MPO showed

TABLE 1
DISTRIBUTION OF RESPONDENTS TO DIAGNOSIS AND TREATMENT OUTCOME

Variables	N	%	χ^2	p
Dijagnose			16.947	<0.001
Stable angina pectoris	43	37.7		
Unstable angina pectoris	13	11.4		
NSTEMI	25	21.9		
STEMI	33	28.9		
Outcome			84.246	<0.001
Survivors	106	93.0		
Died	8	7.0		

NSTEMI – non-ST segment elevation myocardial infarction
STEMI – ST segment elevation myocardial infarction

TABLE 2
DISTRIBUTION OF ELEVATED MPO IN THE BEGINNING OF TREATMENT IN RELATION TO THE FINAL OUTCOME OF THE DISEASE

Myeloperoxidas levels in the beginning of treatment	Diagnosed miocardial infarct		Not diagnosed miocardial infarct		Total	
	N	(%)	N	(%)	N	(%)
Elevated	9	15.5	8	14.3	17	14.9
Not elevated	49	84.5	48	85.7	97	85.1

TABLE 3
DISTRIBUTION OF ELEVATED MPO ON THE SEVENTH DAY OF TREATMENT COMPARED TO THE FINAL OUTCOME DISEASE

The level of myeloperoxidase on the seventh day of treatment	Diagnosed myocardial infarction		Not diagnosed with myocardial infarction		Total	
	N	(%)	N	(%)	N	(%)
Elevated	4	7.5	4	7.1	8	7.3
Not elevated	49	92.5	52	92.9	101	92.7

TABLE 4
DISTRIBUTION OF ELEVATED MYELOPEROXIDASE ON THE 30TH DAY OF TREATMENT COMPARED TO THE FINAL OUTCOME DISEASE

The level of myeloperoxidase on the 30th day of treatment	Diagnosed myocardial infarction		Not diagnosed with myocardial infarction		Total	
	N	(%)	N	(%)	N	(%)
Elevated	0	7.5	1	1.8	1	0.9
Not elevated	53	100.0	54	98.2	107	99.1

excellent specificity and very good sensitivity in patients with ACS, and a much better diagnostic efficacy in patients with unstable angina and non – ACS patients compared with troponin. On the other hand, in relation to all above studies MPO sensitivity in this study was extremely low, and the specificity was significantly higher and relatively close to troponin specificity. Despite the studies in which the MPO proved to be a promising biomarker, Peacocck and his colleagues[39] proved that the MPO has limited clinical use in the intensive care units. They showed that the MPO is a poor diagnostic tool in patients with suspected ACS.

The results of this study and the results of previously conducted studies worldwide show marked variations in each of the studied objectives of this study, starting from the correlation between the predictor values of myeloperoxidase and myocardial infarction and adverse cardiovascular events to the quality of myeloperoxidase as a diagnostic tool in the early identification of myocardial infarction and the difference in the level of myeloperoxidase depending on the diagnostic entity. The reason for these differences in results can be different methodological principles of research, different creation of the test sample as well as different size of the study population. The reasons can be not only methodological frameworks but also a variety of demographic characteristics of the studied populations. Variations on this scale require additional studies the methodological structure of which will to be directed not to broad spectrum of issues related to myeloperoxidase and its role, but specifically directed, increasing the size of the test sample in order to reduce discrepancies in the results, and the results could be more reliable.

Conclusion

Patients with normal troponin and myeloperoxidase have a reduced likelihood of developing myocardial infarction and subsequent cardiovascular events during hospitalization. The level of myeloperoxidase in the regression analysis did not show a significant predictor in the development of myocardial infarction during hospitalization, but is a significant predictor for the development of adverse cardiovascular events.

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DIJAGNOSTIČKA VRIJEDNOST MIJELOPEROKSIDAZE U BOLESNIKA SA SUMNJOM NA AKUTNI KORONARNI SINDROM

S A Ž E T A K

Ispitivali smo dijagnostičku učinkovitost plazmatske MPO pojedinačno ili u kombinaciji sa srčanim troponinom I (cTnI) za otkrivanje ACS kod bolesnika s bolovima u prsima koji počinju unutar 24 sati prije prijema u bolnicu. U ovo prospektivno kohortno istraživanje su uključeni svi ispitanici koji su se javili u prijemnu ambulantu Klinike za unutarnje bolesti SKB Mostar zbog bolova u prsima i sumnje na akutni koronarni sindrom unutar 24 sata od nastupa bolova u razdoblju od 6 mjeseci, s ukupnim uzorkom od 114 pacijenata. Troponin i mijeloperoksidaza su značajno pozitivno povezene na početku liječenja, mijeloperoksidaza je značajno pozitivno povezana s neželjenim kardiovaskularnim događajima tijekom hospitalizacije i infarktom miokarda ($p<0,05$), pri čemu se u regresijskoj analizi nije pokazala kao značajan prediktor u razvoju infarkta miokarda ($p>0,05$). Osjetljivost mijeloperoksidaze u prepoznavanju infarkta miokarda na početku je bila 0,15, a specifičnost 0,85, što upućuje na dobru dijagnostičku vrijednost upotrebljivu u kliničkoj praksi.