ALANINE AMINOTRANSFERASE LEVELS AND MONOCYTE COUNT INDEPENDENTLY PREDICT 30-DAY OUTCOMES IN ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS WITH SUCCESSFULLY RESTORED CORONARY TIMI-3 FLOW BY PRIMARY PERCUTANEOUS CORONARY INTERVENTION

Alanin Aminotransferaz Düzeyleri ve Monosit Sayısı Primer Perkutan Koroner Girişim ile Başarılı TIMI-3 Koroner Akım Sağlanan ST Yükselmeli Miyokard İnfarktüsünde 30 Günlük Sonuçları Bağımsız Olarak Öngörür

ABSTRACT

Aim: To investigate the relationship of various hematological and biochemical parameters besides the cardiac enzymes with 30-day outcomes in patients with successfully restored coronary TIMI-3 flow by primary percutaneous coronary intervention (p-PCI).

Materials and methods: Two hundred patients with ST elevation myocardial infarction (STEMI), with no history of prior myocardial infarction (MI), who underwent p-PCI and had TIMI-3 flow, were enrolled, consecutively. The primary endpoint of the study was defined as the composite of death, fatal and non-fatal MI, target vessel revascularization and cerebrovascular event.

Results: Only ALT concentration (OR: 1.010, 95% CI: 1.003-1.018, P = 0.008), monocyte count (OR: 1.002, 95% CI: 1.001 - 1.004, P = 0.005), hypertension (OR: 3.010, 95% CI: 1.081 - 8.384, p = 0.035) and lower LVEF (OR: 0.926, 95% CI: 0.875 - 0.981, P = 0.008) were independent predictors of primary endpoint in multivariate logistic regression analysis.

Conclusion: We found that elevated liver enzymes as determined by serum Alanine aminotransferase levels and monocyte count as well as hypertension and lower LVEF independently predicted 30-day outcomes in patients with successfully restored coronary flow by p-PCI. These parameters may provide new aspects, to identify the pathophysiology and prognosis of acute vascular events, which in turn may facilitate discovery of new treatment modalities.

Key words: STEMI; Liver enzymes; Alanine aminotransferase; Monocyte count; Primary PCI; Major adverse cardiac events.
Introduction

ST segment elevation myocardial infarction (STEMI) is a major public health problem and the leading cause of death in developed countries. Primary percutaneous coronary intervention (p-PCI) is the best reperfusion therapy due to improved survival and reduction of combined clinical endpoints in treatment of STEMI [1-3].

The main purpose of p-PCI is to open occluded coronary artery urgently in order to slow progression of myocardial infarction, by providing sufficient blood flow to threatened myocardium. However, despite a patent infarct-related artery with restored blood circulation, some patients still suffer poor short and long-term outcomes. Therefore, prediction of short and long-term outcomes in patients with successfully restored coronary flow by p-PCI and clarification of related factors may be important in improving the prognosis of high risk individuals in STEMI.

During STEMI, there are many routinely evaluated hematological and biochemical parameters besides the cardiac enzymes. The prognostic role of these parameters in patients with restored blood flow has not adequately been determined.

In this study, we investigated relationship of several hematological and biochemical parameters besides the cardiac enzymes with 30-day outcomes in patients with TIMI-3 flow following successful p-PCI.

Methods

Study Population

This study, having prospective observational cohort study design, was conducted in the cardiology clinics at Rize Education and Research Hospital and Dr. Siyami Ersek Cardiovascular and Thoracic Surgery Center. Two hundred patients with STEMI and no history of prior MI, who underwent p-PCI and have been restored TIMI-3 flow, were enrolled between 1 January and 31 December 2011 consecutively. All patients were examined by an experienced cardiologist immediately after hospitalization. The study was performed in accordance with the principles stated in the Declaration of Helsinki and approved by the local Ethics Committees of Rize University, Faculty of Medicine and Dr. Siyami Ersek Cardiovascular and Thoracic Surgery Center.

Clinical characteristics, which consisted of multiple descriptors from each patient’s history and physical examination, were collected by physicians from cardiology clinics of each patient and were stored in the database of coronary angiography laboratory at each institute. We recorded the baseline characteristics, which include hypertension, diabetes mellitus, smoking status, family history for coronary artery disease and lipid parameters. Killip score and TIMI risk score was also calculated and used for risk stratification [4, 5].

Coronary angiography and primary PCI

All of the patients received 300 mg aspirin and 600 mg clopidogrel prior to the procedure. At the start of the procedure, 5000-10,000 IU (adjusted according to weight) intravenous heparin was administered. Coronary stenting directly, or followed by balloon angioplasty, was performed where eligible. Glycoprotein IIb–IIIa inhibitor (tirofiban) was administered at the preference of the operator. After the procedure, patients were followed in the intensive coronary unit (ICU) until stabilization. All of the patients were treated according to the recommendations of ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction [6].

Selective coronary angiography was performed urgently at the angiography laboratory using Standard Judkins technique through the femoral artery. Multiple views were obtained in all patients, with visualization of the left anterior descending and left circumflex coronary in at least 4 views, and the right coronary artery in at least 2 views. The TIMI (Thrombolysis In Myocardial Infarction) Flow Grade was used to scale coronary flow [7]. TIMI grade 3 flow at the intervened coronary artery with a residual stenosis of <20% was considered successful PCI. Two invasive cardiologists who were blinded to the patients’ identities, electrocardiogram (ECG) and echocardiography findings and outcomes analyzed every case.

Laboratory measurements

Cardiac biomarkers levels including creatine kinase (CK), creatine kinase-MB fraction (CK-MB) and Troponin-I and inflammatory markers including leukocytes were measured at our emergency department and used in the analyses as admission values. The lipid samples were drawn by venipuncture to perform routine blood chemistry after fasting for at least 8 hours. Glucose, creatinine, and lipid profile were determined by standard methods. White blood cell (WBC, leukocyte) counts were obtained from an automated cell counter (Coulter Gen-S, COULTER Corp, Miami, USA). Admission blood samples were centrifuged immediately and serum specimens for high-sensitivity CRP (hsCRP) were frozen and stored at −20°C before analysis. Serum levels of hsCRP were determined by the immunoturbidimetric method performed on the Abbott auto-analyzer (Architect C1600, Abbott,

Table 1: Baseline and follow-up parameters of study population.
Statistical significance was defined as $P < 0.05$. The SPSS statistical software (SPSS 15.0 for windows, Inc., Chicago, IL, USA) was used for all statistical calculations. Regression analysis was used for multivariate analysis of independent variables. All tests of significance were two-tailed.

Categorical variables were defined as percentages. Continuous variables were given as mean ± standard deviation; variables were compared by Student t test and the $\chi^2$ test was used.

Results

The baseline clinical characteristics are presented in Table 1. The study population consisted of 200 patients with STEMI who underwent p-PCI. The patients who experienced any MACE component during follow-up demonstrated higher rate of hypertension ($P = 0.032$), increased liver enzymes (GGT activity: $P = 0.001$ and ALT levels: $P = 0.004$), hematological markers (leukocyte and monocyte counts: $P = 0.037$ and $P = 0.002$, respectively, and MPV value: $P = 0.033$), increased hsCRP levels ($P < 0.001$), lower LVEF% ($P = 0.008$) and a higher TIMI risk score ($P = 0.025$) in comparison to patients without MACE.

Increased levels of ALT, hsCRP, GGT activity, monocyte count, MPV, higher TIMI risk score, depressed left ventricular ejection fraction, and low ACE/ARB and statin usage were predictors for MACE (Table 2). In our study, ALT levels correlated to NLR ratio ($r = 0.263, P < 0.001$), admission CK-MB ($r = 0.524, P < 0.001$), peak CK-MB ($r = 0.313, P < 0.001$), hsCRP ($r = 0.148, P = 0.044$), pain to balloon time ($r = 0.222, P = 0.002$) and TIMI risk score ($r = 0.162, P = 0.022$).

Only ALT level (OR: 1.010, 95% CI: 1.003 - 1.018, $P = 0.008$), monocyte count (OR: 1.002, 95% CI: 1.001 - 1.004, $P = 0.005$), hypertension (OR: 3.010, 95% CI: 1.081 - 8.384, $P = 0.035$) and lower LVEF% (OR: 0.926, 95% CI: 0.875 - 0.981, $P = 0.008$) were the independent predictors of MACE in multivariate logistic regression analysis.

When we investigated specific determinants of MACE components, death and TVR were mainly related to increased ALT and monocytes, but re-MI was related only ALT level (Table 3).

Discussion

In this study, we demonstrated that increased concentrations of ALT, monocyte at admission, hypertension and low EF independently predict of 1-month MACE in patients with STEMI followed successful p-PCI with well-restored coronary flow. Despite being statistically dependent, admission values of GGT, hsCRP, MPV and female gender were also higher in patients with MACE. Additionally, patients whom did not receive ACE/ARB and statin treatments were more prone to MACE. One important aspect of our study is that we included only patients with good coronary flow; therefore, our results may have a value in classifying patients even though they seem at lower risk and guiding clinical treatment.

We revealed a strong relationship between monocyte count, death and TVR in subgroup analyses of MACE. In addition, there was a trend for increased re-infarction in patients with higher monocyte counts, although not reaching significance. Monocytes have a very important role in mediating inflammation during myocardial infarction. The different subtypes of monocytes might have different actions. Monocytes differentiate into macrophages, becoming as a source of cytokines and growth factors that regulate extracellular matrix metabolism, after
recruitment to the infarction tissue [14, 15]. During healing process, ventricular geometry and function alters considerably [16, 17]. Optimum healing after MI requires a coordinated process, balancing debris removal and repair of the myocardial extracellular matrix. Excessive inflammation and eventually adverse remodeling can both cause heart failure [18-20]. Moreover, recent studies revealed detrimental effects of monocytes and macrophages in microvascular damage after reperfusion in patients with STEMI and stent restenosis [21, 22]. Monocytes, in addition to fundamental effects in inflammation, may influence platelets causing reactivation [23, 24]. We think that, monocytes increase MACE due to both increased inflammation, remodeling and platelet reactivation. Although a statistically insignificant tendency, observation of higher MPV values in patients with MACE may support this hypothesis.

ALT is mainly located in hepatocytes and renal tubular epithelium, however some activity is present in skeletal and cardiac muscle [25]. Surprisingly, admission ALT values independently predicted all endpoints and combined MACE. The mechanism of this relationship is not totally clarified. Lazzeri et al. identified admission ALT concentration as a predictor of in-hospital mortality in non-diabetic patients, in a group of 1000 STEMI patients following mechanical reperfusion [26]. A recent study demonstrated an association between increased liver enzymes and mortality, congestive heart failure, shock, or stroke 30 days after STEMI [27]. Similar to our study, ALT displayed a strong correlation with infarct size assessed by enzyme levels in both of these previous studies. In addition, ALT also correlated to hsCRP, admission and peak CK-MB, paint to balloon time and TIMI risk score in our study. Nevertheless, the association of ALT with re-MI and TVR may suggest possible different mechanisms except infarct related pathways.

Another source of ALT might be liver due to acute hepatic congestion or relative hypotension associated with larger infarction. Accordingly, unlike chronic heart failure, which mainly shows cholestatic pattern of liver enzyme elevation, acute heart failure and ischemic hepatitis most often result in elevated transaminases [28-31]. The pathophysiological procedure regarding elevated ALT levels, increased TVR, re-infarction and mortality is still hypothetic. We think that further studies are needed to clarify this relationship. Another potential explanation is that elevated liver enzymes including ALT and GGT are associated with the metabolic syndrome via non-alcoholic fatty liver disease. This hypothesis may be supported by that although AST is known as a more related parameter to myocardial necrosis than ALT, it was not an independent parameter for MACE inpatient with well-perfused myocardium.

The relationship between CRP and cardiac mortality in patients with acute myocardial infarction, have been demonstrated by previous many studies[32-34]. Despite, being high in MACE group, hsCRP was not an independent variable for the study outcomes in our study. Possible explanations for this may be that CRP is a nonspecific marker or lack of an adequately numbered study population to demonstrate possible independent relation. In both situations, our study supports that monocyte and ALT are more important than CRP in this patient population.

Gamma-glutamyl transferase (GGT), the enzyme responsible for the extracellular catabolism of glutathione, has a role in oxidation of LDL cholesterol within the atherosclerotic plaque and progression of atherosclerosis[35-37]. GGT activity has been demonstrated to be an independent risk factor for myocardial infarction (MI) and cardiac death in patients with documented coronary artery disease (CAD)[38-41]. Recent studies have revealed the prognostic importance of GGT in patients undergoing mechanical revascularization for STEMI [42, 43]. However, in our study group, although GGT was significantly increased in MACE group, it was not a statistically significant predictor of MACE independent of other parameters.

Mean platelet volume (MPV), a marker for platelet reactivity, has been shown to be predictive of unfavorable outcomes among survivors of STEMI [44]. In our study, MPV was also higher in patients with MACE, but with only a tendency to predict to MACE. In our opinion, platelet reactivity is also important for this patient population, but relatively small sample size of our study may have prevented to represent its possible independent relation. As a result, even though successfully re-perfused by primary PCI, the patients with high admission levels of ALT and monocyte may be prone to an increased cardiovascular morbidity and mortality; therefore may be targeted to gain more benefit with intensive therapy such as antiplatelet, anticoagulant, ACEi/ARB and statins.

**Study limitations:** Our study population, involving 200 patients, is rather small. Although we excluded known chronic hepatic or cholestatic disease, we may not exactly state that elevated ALT is due to MI, not a previous disorder like nonalcoholic fatty liver disease. Moreover, we only included patients with successful reperfusion and TIMI-3 flow, thus our results do not apply to all patients with STEMI.

**Conclusion:** We found that elevated liver enzymes as determined by serum Alanine aminotransferase level and monocyte count as well as hypetension and lower LVEF independently predicted 30-day outcomes in patients with successfully restored coronary flow following primary PCI. These parameters may provide new aspects, to identify the pathophysiology and prognosis of acute vascular events, which in turn may facilitate discovery of new treatment modalities.


