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The association of serum uric acid levels on coronary flow in patients with STEMI undergoing primary PCI

Mahmut Akpek[a], Mehmet G. Kaya[a,*], Huseyin Uyarel[b], Mikail Yarlioglues[a], Nihat Kalay[a], Ozgur Gunebakmaz[a], Orhan Dogdu[a], Idris Ardic[a], Deniz Elcik[a], Omer Sahin[a], Abdurrahman Oguzhan[a], Ali Ergin[a], Charles M. Gibson[c]

[a] Department of Cardiology, Erciyes University School of Medicine, Kayseri, Turkey
[b] Department of Cardiology, Balikesir University School of Medicine, Balikesir, Turkey
[c] Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA

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ABSTRACT

Objective: Uric acid has been shown as a predictor and an independent risk factor for coronary heart disease, but little is known regarding the association of uric acid levels with coronary blood flow in STEMI. We hypothesized that elevated uric acid levels would be associated with impaired flow and perfusion in the setting of STEMI treated with primary PCI.
Methods: Two hundred and eighty nine patients with STEMI who treated primary PCI were enrolled to study. Patients were divided into two groups based upon the TIMI flow grade. No-reflow was defined as TIMI Grade 0, 1 and 2 flows (group 1). Angiographic success was defined as TIMI 3 flow (group 2). Uric acid, MPV and high sensitive CRP were measured. Major adverse cardiac events (MACE) were defined as in stent thrombosis, non-fatal myocardial infarction and in-hospital mortality.
Results: There were 126 patients (mean age 63 ± 11 and 71% male) in group 1 and 163 patients (mean age 58 ± 12 and 80% male) in group 2. Uric acid, MPV, and hs-CRP levels on admission were higher in group 1 ($p = 0.0001$ for each). A uric acid level ≥5.4 mg/dl measured on admission had a 77% sensitivity and 70% specificity in predicting no-reflow at ROC curve analysis. In-hospital MACE was significantly higher in group 1 (29% vs. 7%, $p = 0.0001$). At multivariate analyses, high plasma uric acid (odds ratio (OR) 2.05, <95% confidence interval(CI) 1.49–2.81; $p < 0.0001$), hs-CRP (OR 1.02, <95% CI 1.01–1.03; $p = 0.0007$) and MPV (OR 3.09, <95% CI 1.95–4.89; $p < 0.0001$) levels were independent predictors of no-reflow post primary PCI and uric acid (OR 2.75, <95% CI 1.93–3.94; $p < 0.0001$), hs-CRP (OR 1.01, <95% CI 1–1.02; $p = 0.006$) levels, but not MPV, were independent predictors of in-hospital MACE.
Conclusion: Plasma uric acid level on admission is a strong and independent predictor of poor coronary blood flow following primary PCI and in hospital MACE among patients with STEMI. Except for predictive value, uric acid levels may be a useful biomarker for stratification of risk in patients with STEMI and may also lead to carry further therapeutic implications.

1. Introduction

Rapid restoration of infarct related arterial (IRA) flow is associated with improved ventricular performance and lower mortality among patients with myocardial infarction [1,2]. However, poor arterial flow and no-reflow phenomena may limit the benefits of recanalization of the IRA [3].

Several biomarkers are associated with poorer outcomes in ST-elevation myocardial infarction (STEMI). Mean platelet volume (MPV) is an easily measured platelet indices, which increase during platelet activation [4]. Furthermore, increased MPV levels have been associated with poor clinical outcome in survivors of myocardial infarction [5] and higher MPV correlates with thrombolysis failure in patients presenting with STEMI treated with thrombolytic therapy [6]. C-reactive protein (CRP) is an acute phase protein and several studies have shown that CRP may have prognostic value in patients with acute coronary syndromes and undergoing percutaneous coronary intervention (PCI) [7–10].

Uric acid, the end product of purine metabolism in circulation, is an independent risk factor for cardiovascular disease but the underlying pathophysiology is not clear. The relationship between circulatory uric acid levels and endothelial dysfunction has been demonstrated previously [11–13]. It has been shown that coronary flow reserve, a marker of coronary microvascular function,

* Corresponding author. Tel.: +90 505 3784696; fax: +90 352 4377634.
E-mail address: drmgkaya@yahoo.com (M.G. Kaya).

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is significantly greater in participants with lower serum uric acid concentrations [14]. It has been also demonstrated that high serum uric acid level is associated with slow coronary flow in patients underwent elective angiography [15].

Uric acid has been shown as a predictor and an independent risk factor for cardiovascular events and is also an independent risk factor for coronary heart disease [16,17], but little is known regarding the association of uric acid levels with coronary blood flow in the setting of STEMI. Given that elevated uric acid is associated with poorer flow during elective angiography, we hypothesized that elevated uric acid levels would be associated with impaired flow and perfusion in the setting of STEMI treated with primary PCI.

2. Materials and methods

2.1. Study population

Two hundred and eighty nine consecutive patients (male 76% and mean age 60 ± 12) who were admitted with STEMI within 6 h from symptom onset were enrolled the study. All of the patients were treated with primary PCI at our institution from 2006 to 2010. STEMI was defined as: typical chest pain >30 min duration with ST elevation >1 mm in at least two consecutive leads on the electrocardiogram or new onset left bundle brunch block. Patients were divided into two groups based upon the Thrombolysis In Myocardial Infarction (TIMI) flow grade score [18]. No-reflow was defined as TIMI grade 0, 1 and 2 flows (group 1) [5,8,19–21] post PCI. Angiographic success was defined as TIMI 3 flow (group 2). Exclusion criteria included treatment of STEMI in the previous 24 h with thrombolytic drugs, a history of gout, active infections, systemic inflammatory disease, known malignancy, end stage liver and renal failure. Informed consent was obtained from all patients and the protocol was approved by the Ethics Committee and the institutional review board of Erciyes University Medical School.

2.2. Coronary angiography and PCI procedure

All of primary PCI procedures were performed with standard femoral approach with a 7-French guiding catheter. After administration of 5000 IU of heparin and 300 mg clopidogrel loading dose conventional wire crossing, direct stenting was implanted whenever possible; in the remaining cases, balloon pre-dilatation was carried out. The type of stents (bare metal or drug-eluting stent) were left to the operator's discretion. In each patient who treated with tirofiban, tirofiban was administrated after primary PCI procedure in coronary care unit. Use of systemic bolus of tirofiban, followed by a 12-h continuous infusion, was left to the operator discretion. To achieve maximal dilatation each coronary angiogram was preceded by intracoronary injection of 100 μg nitroglycerine. The Thrombolysis in Myocardial Infarction (TIMI) grade was assessed by three independent interventional cardiologists. Intra and inter-observer variabilities were obtained from random samples of 100 patients. The intra- and inter-observer variabilities for TIMI 0–1 were 6 and 8%, respectively; for TIMI 2 the corresponding values were 1 and 3%, respectively; and for TIMI 3 both intra- and inter-observer variability were 0%.

2.3. Laboratory analysis and echocardiography

In all patients, antecubital venous blood samples for the laboratory analysis were drawn on admission in the emergency room. Uric acid, glucose and lipid profile were determined by standard methods. High sensitive CRP was measured by using a BN2 model nephlometer (Dade-Behring). Citrate based anticoagulated blood samples stored at +4 °C and MPV levels were measured by *Sysmex* K-1000 auto analyzer within 30 min of sampling. Transthoracic echocardiography was performed for each patient immediately after primary PCI in intensive cardiac care unit. All measurements were performed using a commercially available machine (Vivid 7® GE Medical System, Horten, Norway) with a 3.5-MHz transducer.

2.4. Follow-up and major adverse cardiac events

Major adverse cardiac events (MACE) were defined as in stent thrombosis, non-fatal myocardial infarction and in-hospital mortality during in-hospital follow up period. In-stent thrombosis was defined as angiographically documented total occlusion. Non-fatal myocardial infarction was defined as recurrent chest pain and/or development of new ECG changes accompanied by a new rise ≥20% of cardiac biomarkers measured after the recurrent event. In-hospital mortality had to be verified death due to myocardial infarction, cardiac arrest or other cardiac causes.

2.5. Statistical analysis

Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. We report continuous data as mean and standard deviation or median. We compared continuous variables using Student *t*-test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. Pearson correlation coefficients examined the degree of association between examined variables. p value <0.05 was considered as significant. The Receiver Operating Characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of Uric acid, MPV, hs-CRP and their respective, optimal cut-off value for predicting poor coronary flow after primary PCI in patients with STEMI. The effects of different variables on No-reflow and in hospital MACE were calculated in univariate analysis for each. The variables for which the unadjusted p value was <0.10 in logistic regression analysis were identified as potential risk markers and included in the full model. We reduced the model by using backward elimination multivariate logistic regression analyses and we eliminated potential risk markers by using likelihood ratio tests. p value <0.05 was considered as significant and confidence interval (CI) was 95%. All statistical analyses were performed with the SPSS version 15 (SPSS, Inc., Chicago, Illinois).

3. Results

There were 126 patients (mean age 63 ± 11 and 71% male) in group 1 and 163 patients (mean age 58 ± 12 and 80% male) in group 2. Baseline characteristics are shown in Table 1. Mean age was significantly higher in group1 ($p = 0.0001$). With respect to coronary risk factors; there was significant difference in the presence of diabetes mellitus (DM) ($p = 0.0001$) and prior coronary artery disease ($p = 0.0001$) but there was no significant difference in hypertension and active smoking ($p = 0.169$ and $p = 0.254$, respectively).

With respect to baseline laboratory status, the serum glucose level on admission was significantly higher in group 1 ($p = 0.0001$), while there was no significant difference in serum lipid profile, glomerular filtration rate (GFR), hemoglobin (Hg), platelet and white blood cell count (WBC) between groups. Also, left ventricular ejection fraction (LVEF) and pain to balloon time were not significantly different between groups ($p = 0.112$ and $p = 0.429$, respectively).

A greater proportion of patients with multi-vessel disease (more than 50% occlusion for each coronary artery) were in group 1 ($p = 0.0001$). Left anterior descending artery is the more common infarct related artery (IRA) in both groups, but there is no significant difference in involvement of circumflex, right coronary artery, left anterior descending artery and saphenous graft or left internal mammarian artery as IRA between groups ($p = 0.381$,