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The value of routine blood test parameters obtained at admission to predict acute stent thrombosis in patients with st-segment elevation myocardial infarction

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Abstract

The purpose of this study was to investigate whether biochemical parameters on admission can predict the development of acute stent thrombosis within 24 hours of presentation in patients with ST-segment elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI). This retrospective study included patients who were hospitalized for acute STEMI and treated with primary PCI between September 2009 and May 2018. The patients were divided in to two groups according to the presence or absence of acute stent thrombosis following primary PCI. After comparison of biochemical parameters in the two groups, variables displaying difference between the two groups were further analyzed for their predictive role in stent thrombosis. Two hundred and twenty-two STEMI patients treated with primary PCI were enrolled in the study. Among these, 102 experienced acute stent thrombosis within 24 hours of presentation. There was no significant difference instant diameter, stent length and ejection fraction between the groups. Age ,gender, diabetes, hypertension and smoking status were comparable between the two groups. Serum bilirubin and uric acid levels were significantly higher in the stent thrombosis group than the non-stent thrombosis group. Logistic regression analysis revealed that uric acid (OR: 1.482, 95% CI: 1.23-2.342, p=0.034) and total bilirubin (OR: 1.733 95% CI: 1,12-2.046, p= 0.003) levels were significant predictors for stent thrombosis in subjects admitted with STEMI. Admission serum bilirubin and uric acid levels may predict acute stent thrombosis in STEMI patients undergoing primary PCI.

Keywords: Stent, thrombosis, bilirubin, uric acid, myocardial infarction

Introduction

Widespread use of primary percutaneous coronary intervention (PCI) for the treatment of stable coronary artery disease and acute coronary syndromes has led to a substantial improvement in the morbidity and mortality associated with ST-elevation myocardial infarction (STEMI). Despite the recent advances in stent technology, and utilization of ultra-thin polymer layers for drug delivery, stent thrombosis still remains a frequent complication of percutaneous coronary interventions [1]. Stent thrombosis is classified as acute (within the first 24 hours), subacute (>24 hours to 30 days), late (>30 days to 1 year) and very late (>1 year), based on the timing of the symptom associated with stent thrombosis [2]. Blood-stent interaction before endothelialization of the stent struts lead to the activation of the extrinsic pathway of the coagulation cascade and a systemic prothrombotic response [3].

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Given that the mortality form stent thrombosis is higher than the occlusion of a native coronary artery, determination of subjects prone to stent thrombosis may improve survival in STEMI. However, there are currently no simple blood tests which can be used to assess subjects' risk for stent thrombosis. Previous studies have shown that simple blood tests including mean platelet volume, neutrophil to lymphocyte ratio, reticulocyte distribution width, and gamma-glutamyl transferase, bilirubin and uric acid levels could be used for identifying subjects with higher risk for cardiovascular mortality in various clinical settings [4-8]. However, the role of various simple blood tests in the prediction of stent thrombosis remains unclear.

This study aimed to investigate whether simple blood tests performed on admission could be helpful in identifying patients at risk for stent thrombosis.

Material and Methods

Following ethics committee approval, the patient group was identified through retrospective review of the medical files of 222 patients presenting with STEMI to Gaziantep Ersin Arslan Research and Training Hospital between September 2009 and May 2018. Subjects with previous stent thrombosis, those had more than one stent, those with liver or renal dysfunction (except for very mild

cases), and patients with hemolytic disorders, chronic obstructive pulmonary disease, chronic inflammatory conditions or neo plastic diseases, history of gout were excluded from the study. Patients who received uric acid-lowering medications, and those receiving glycoprotein IIb/IIIa inhibitors as a consequence of slow-flow or no-reflow following PCI were also not included in the final analyses. Angiography records were reviewed by two interventional cardiologists blinded to study data. Demographic characteristics, coronary artery disease risk factors and laboratory results were retrieved from the institutional digital database.

A group consisting of aged matched patients admitted within the same time intervals who did not develop stent thrombosis subsequent to primary PCI was randomly selected as the control group. In the PCI group, patients with acute stent thrombosis were defined as follows: those with visible thrombus and patients with absence of blood flow in the operated vessel or distal to the vessel, or a filling defect consistent with thrombus as detected by repeat coronary angiography with in the first 24 hours. Age, gender, comorbidities (diabetes mellitus, smoking, hyperlipidemia, hypertension, positive family history of coronary artery disease), serum bilirubin, fasting blood glucose, lipid profile, uric acid and renal and hepatic enzyme levels were reviewed for all patients. The study was conducted in line with Helsinki Principles; and the Ethics Committee of Gaziantep University approved the study (number:2018/36).

Angioplasty Procedure

Angioplasty was performed under local anesthesia using Seldinger technique for femoral access. All patients were administered 100 IU/kg UF heparin, 300 mg of ASA and 600 mg of clopidogrel prior to percutaneous intervention. Activated clotting time (ACT) was not checked on a routine basis. In the case of a procedure taking longer than 45 minutes, ACT value was checked and an additional 2500 IU dose of UF heparin was administered as needed.

Laboratory Analyses

Blood samples for analysis were obtained during the initial evaluation of patients at the emergency department and taken into standard EDTA-containing tubes. All measurements were performed 15 minutes after blood collection using a Cell-Dyn 3700 System (Abbot, Abbott Park, Illinois, USA) for complete blood count. Total bilirubin and uric acid concentrations were measured using an automated analyzer (AU 2700, Beckman-Coulter, Japan). Conventional units of serum bilirubin were converted to SI units using the following formula: 1 mg/dL =0.05847953 μmol/L. Conversion factors of 0.0555, 0.0259 and 0.0113 were used to convert from mg/dL to mmol/L for glucose, high- and low-density lipoprotein cholesterol (HDL-C, LDL-C) and triglyceride measurements, respectively.

Primary outcome

The difference in admission laboratory measurement between patients developing or not developing stent thrombosis subsequent to primary PCI was the primary outcome measure of this study.

Statistical Analyses

Data analysis was performed using the SPSS software, version 20.0 (SPSS Inc, Chicago, IL, USA). Shapiro-Wilk test was used to check the normality of data distribution. Continuous variables were expressed as mean ± standard deviation and categorical variables were presented as percentages. Normally distributed variables were analyzed with the independent samples t test. Non-normally distributed variables were analyzed with the Mann Whitney U test. Chi-square test was used for comparison of categorical variables. Binary logistic regression analysis was performed to determine independent correlates of stent thrombosis. A stepwise model with backward selection method was used, and p values of <0.1 were selected for inclusion for the next step. Results were tabulated as odds ratio (OR) and 95% confidence intervals (CI). P value less than 0.05 was considered statistically significant.

Results

The study sample consisted of 222 patients with STEMI (mean age 59.12 ± 0.93 years, 70.7% male) of whom 102 developed stent thrombosis within 24 hours of the primary PCI. There were no significant differences between the two groups with respect to age, gender, diabetes, hypertension, hyperlipidemia, smoking status, left ventricular ejection fraction, stent diameter and length ,number of diseased vessels, culprit artery (Table 1). Table 2 demonstrates admission laboratory measurements of the two groups. Subjects developing stent thrombosis had significantly higher total bilirubin (0.71±0.03 mg/dl vs. 0.55±0.04 mg/dl, p=0.012) and uric acid concentrations (5.69±0.30 mg/dl vs. 4.96±0.16 mg/dl, p=0.023) compared to subjects who did not develop stent thrombosis(Figures 1 and 2).

Binary logistic regression revealed that uric acid levels (OR = 1.482, 95% CI:1.23–2.342, p = 0.034) and total bilirubin levels (OR =1.733, 95% CI:1.12–2.046, p = 0.003)were predictive for the presence of stent thrombosis (Table3).

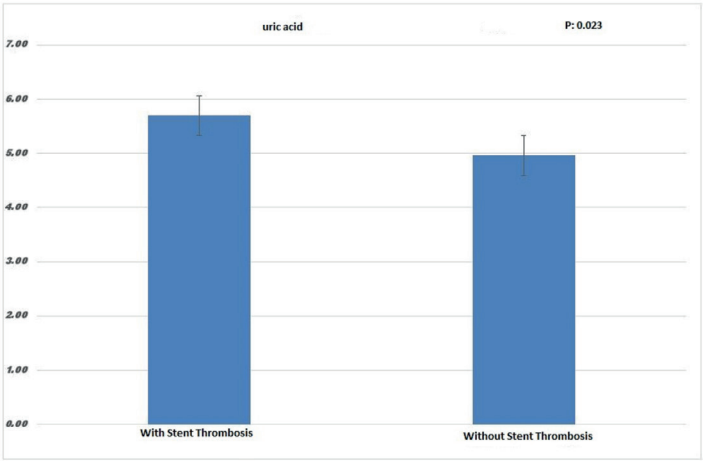

Figure 1. Comparison of the level of Uric acid between groups.

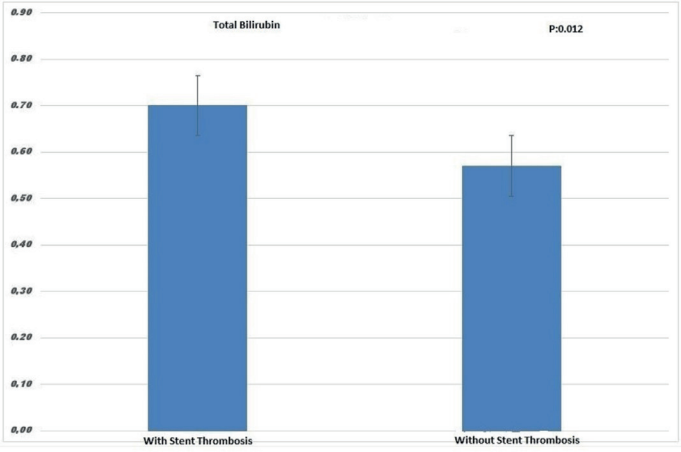

Figure 2. Comparison of the level of Bilirubin between groups.

Table 1. Clinical, demographic and angiographic characteristics of patients

Characteristics	With Stent Thrombosis (n=102)	Without Stent Thrombosis (n=120)	p
Age (years)	60.33±1.1	58.07±0.98	0.41
Gender (n, male)	76 (75.2)	81 (67.5)	0.24
DM, n (%)	32 (31.7)	50 (41.7)	0.12
HT, n (%)	61 (68.5)	68 (56.7)	0.23
HL, n (%)	52 (51.48)	75 (62.5)	0.08
Smoking, n (%)	62 (78.2)	79 (65.8)	0.41
LVEF (%)	47.77±0.80	50.54±0.91	0.51
Stent diameter, (mm)	3.02±0.29	3.03±0.33	0.83
Stent length (mm)	23.24±0.81	25.29±0.73	0.49
Number of diseased vessels			
SVD ,n (%)	38 (37.2%)	45(37.5%)	0.68
TVD, n (%)	35(34.3%)	41(34.1%)	0.72
ThVD, n (%)	29 (28.4%)	34 (28.3%)	0.82
Culprit artery			
LAD	50 (49%)	59 (49.1%)	0.83
CX	12(11.7%)	14 (11.6%)	0.84
RCA	40(39.2%)	47 (39.1%)	0.83

CX: Circumflex Coronary Artery; DM: Diabetes Mellitus; HT: Hypertension; HL: Hyperlipidemia; LAD: Left Anterior Descending Artery ; LVEF: Left Ventricular Ejection Fraction; RCA: Right Coronary Artery ;SVD: Single Vessel Disease; ThVD: three-Vessel Disease; TVD:Two Vessel Disease.

Table 2. Admission laboratory measurements of the two groups

Parameters	With Stent Thrombosis (n=102)	WithoutStent Thrombosis (n=120)	P
HGB (mg/dl)	14.6± 1.7	13.8 ± 1.7	0.082
WBC (103/mm^3)	11.84±3.42	11.92±2.92	0.680
Urea(mg/dl)	33.75±14.27	34.36±13.05	0.765
Creatinin(mg/dl)	0.93±0.23	1.24±0.34	0.393
Glucose (mg/dl)	197.84±100.41	169.56±82.94	0.096
GGT(U/L)	34.91±22,62	35.65±31.62	0.930
T. BIL. (mg/dl)	0.71±0.03	0.55±0.04	0.012
AST(IU/L)	79.34±12.06	83.68±13.7	0.828
ALT(IU/L)	36.56±2.75	30.65±2.25	0,104
Uric acid (mg/dl)	5.69±0.30	4.96±0.16	0.023
LDL-C (mg/dl)	122.09±2.53	126.69±3.62	0.320
HDL-C (mg/dl)	34.55±0.84	33.10±0.89	0.245
Triglycerides(mg/dl)	167.46±12.07	187±15.12	0.314
Albumin (g/L)	4.23±0.38	3.81±0.03	0.228
Total protein (g/L)	6.39±0.07	6.39±0.72	0.975

ALT: Alanine Aminotransferase; AST: Alanine Aminotransferase; HDL-C: High Density Lipoprotein Cholesterol; HGB: Hemoglobin; LDL-C: Low-Density Lipoprotein Cholesterol; T.BIL: Total Bilirubin; WBC: White Blood Cell Count.

Table 3. Predictors for the presence of stent thrombosis

	OR	95% CI	P-value
Hemoglobin	0.986	0.842-1.156	0.866
Glucose	1.02	0.985-1.042	0.932
Uric acid	1.454	1.186-2.243	0.039
Total bilirubin	1.733	1.118-2.049	0.004

OR: odds ratio; CI: confidence interval
Variables significant at p<0.1 in the univariate analyses were included in the multivariate logistic regression analysis

Discussion

This study shows admission total bilirubin and uric acid levels are significantly higher in subjects who developed subsequent stent thrombosis compared to those whose stent remained patent within the first 24 hours of primary PCI. Moreover, logistic regression results indicate that admission total bilirubin and uric acid levels may predict subsequent stent thrombosis in patients undergoing primary PCI for STEMI.

Previous data has shown that bilirubin might have a protective effect against coronary artery disease owing to its antioxidant action in stable coronary artery disease [9,10]. In patients with stable coronary artery disease, the increase in bilirubin levels has been shown to be associated with the severity of coronary artery disease and poor outcomes [11]. However, elevated bilirubin levels may also exist in acute coronary syndromes. Previous data has shown that serum bilirubin levels are independently associated with no-reflow and in-hospital MACE in subjects undergoing primary PCI for STEMI [12]. Additionally, elevated bilirubin levels were linked to higher total thrombus burden in STEMI patients [13]. Serum bilirubin level was also reported to positively correlate with distal thromboembolic events in patients undergoing percutaneous transluminal angioplasty (PTA) for peripheral artery disease. [14]Scientific evidence suggest that elevated bilirubin levels may occur secondary to an increase in heme oxygenase-1 (HO-1) activity in acute MI[15]. While high total bilirubin levels were found to be associated with in-hospital adverse outcomes in patients with STEMI undergoing primary PCI, no correlation was found with long-term mortality[16]. This finding suggests that bilirubin may act as an acute phase reactant in the acute phase of the coronary thrombotic event. Consistent with previous data, we found a significant association between acute stent thrombosis and serum total bilirubin levels in our study population. To the best of our knowledge, there is no study in the literature that examined the relationship between acute stent thrombosis and serum bilirubin levels.

Advances instent technology has led to reduced rates of acute stent thrombosis; however, it still remains as a critical complication following primary PCI due to multi factorial etiology. In addition to confounding factors, such as the extent of vascular disease and the length of the stent used, inflammation caused by the acute coronary event and the consequent pro thrombotic environment may also facilitate stent thrombosis [1]. Thus, it seems plausible that increased bilirubin levels may indicate a pro-inflammatory state caused by factors associated with stent thrombosis.

Elevated uric acid has been associated with cardiovascular mortality in subjects with atherosclerotic vascular disease[17]. It is not clear whether this association represents a cause-effect relationship or a condition that accompanies cardiovascular events. Uric acid is associated with endothelial dysfunction and inflammation[18]. Uric acid has also been linked with thrombosis in several clinical settings. Prior studies have demonstrated that high serum uric acid levels are correlated with left a trial thrombosis in patients with mitral stenosis and thrombosis in patients with Behcet's disease[19,20]. Our findings show that, elevated admission uric acid level is also associated with stent thrombosis following primary PCI. With this in mind, we suggest that elevated serum total bilirubin and uric acid levels measured at admission might be useful tools for predicting subsequent stent thrombosis in subjects presenting with STEMI.

There are several limitations concerning this study. The retrospective design and relatively small sample size (considering the wealth of discriminating characteristics in STEMI) are the major limitations. There are many factors that affect the success of primary PCI such as vascular structure, the extent of atherosclerosis, where the lesion is, length of the stent, at what time the patient's MI comes, lesion length, etc. The lack of examination some of these variables is a limitation of the study. Longitudinal sampling for serum total bilirubin and uric acid levels, which could have shown important time-bound effects / relationships, is also lacking. Nevertheless, given that there is no previous data showing the association between stent thrombosis and serum total bilirubin and uric acid levels, our findings might provide a basis of research for further studies.

Conclusion

In the present study, elevated serum total bilirubin and uric acid levels on admission were found to be independent risk factors associated with the development of acute stent thrombosis in STEMI patients. Moreover, serum total bilirubin and uric acid levels may predict subsequent stent thrombosis in STEMI. Our findings suggest that, utilization of simple and readily-available laboratory tests might provide critical clues for identification of those at high risk for stent thrombosis among patients presenting with STEMI. Patients with high uric acid and total bilirubin levels can be considered as risky patients in terms of stent thrombosis and treatment strategy can be determined by considering other risk factors for thrombosis (preferring more potent antiaggregant drugs and increasing the duration of dual antiaggregant drugs, etc.).

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
The financial support no have.

Ethical approval
The study was conducted in line with Helsinki Principles; and the Ethics Committee of Gaziantep University approved the study (number:2018/36).

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