Association between admission mean platelet volume and coronary patency after thrombolytic therapy for acute myocardial infarction

Akut miyokart enfarktüsünde başvurudaki ortalama trombosit hacmi ile trombolitik tedavi sonrası koroner açıklık arasındaki ilişki

Ayşe Saatcı Yaşar, M.D., Emine Bilen, M.D., İsa Öner Yüksel, M.D., Uğur Arslantaş, M.D., Fatih Karakaş, M.D., Özgür Kırbaş, M.D., Mehmet Bilge, M.D.

Department of Cardiology, Atatürk Education and Research Hospital, Ankara

Objectives: High levels of mean platelet volume (MPV) have been shown to be a predictor of poor clinical outcome among survivors of myocardial infarction. We evaluated the association between admission MPV and infarct-related artery (IRA) patency in patients treated with thrombolytic therapy for acute myocardial infarction (AMI).

Study design: We retrospectively evaluated 133 consecutive patients with ST-elevation AMI, who received thrombolytic therapy within 12 hours of chest pain. Sixty-five patients received streptokinase and 68 patients received recombinant tissue-type plasminogen activator, based on the discretion of the physician. Blood samples were taken before thrombolytic therapy and MPV was measured. Coronary angiography was performed within a mean of two days after thrombolytic therapy and the flow in the IRA was assessed with the TIMI flow grade and corrected TIMI frame count (CTFC).

Results: After thrombolytic therapy, TIMI 3 flow was achieved in 62 patients (46.6%), whereas 71 patients (53.4%) had insufficient TIMI flow. Patients with insufficient TIMI flow had a significantly higher mean admission MPV (9.8±1.5 fl *vs.* 8.6±1.4 fl; p<0.001) and were more likely to have been given streptokinase (p=0.02). The two groups were similar with respect to the type of IRA and the number of diseased vessels (p>0.05). There was a weak correlation between MPV and CTFC (p=0.01). Multivariate analysis showed MPV (OR 1.871, 95% CI 1.402-2.498; p<0.001) and the type of thrombolytic agent (OR 2.915; 95% CI 1.333-6.374; p=0.007) as independent predictors of insufficient TIMI flow. The receiver operating characteristic analysis yielded a cutoff value of 8.885 fl for MPV to predict insufficient TIMI flow, with sensitivity and specificity being 70.4% and 66.1%, respectively.

Conclusion: Our findings show that a higher admission MPV is associated with an increased risk for insufficient TIMI flow in the IRA after thrombolytic therapy for AMI.

Key words: Coronary angiography; coronary circulation; myocardial infarction/therapy; myocardial reperfusion; platelet count; thrombolytic therapy.

Amaç: Ortalama trombosit hacminde (OTH) yüksek düzeylerin miyokart enfarktüsü sonrası sağ kalanlarda kötü klinik gidişi öngördürücü olduğu gösterilmiştir. Çalışmamızda, akut miyokart enfarktüsü nedeniyle trombolitik tedavi uygulanan hastalarda, başvuru sırasındaki OTH ile enfarkt ile ilişkili arter (EİA) açıklığı arasındaki ilişki değerlendirildi.

Çalışma planı: Çalışmada, ST yükselmeli akut miyokart enfarktüsü ile başvuran ve göğüs ağrısının ilk 12 saati içinde trombolitik tedavi uygulanan ardışık 133 hasta geriye dönük olarak incelendi. Hekimin tercihiyle 65 hastaya streptokinaz, 68 hastaya rekombinan doku tipi plazminojen aktivatörü uygulandı. Trombolitik tedavi öncesinde alınan kan örneklerinde OTH ölçüldü. Tüm hastalara trombolitik tedaviden ortalama iki gün sonra koroner anjiyografi yapıldı ve EİA açıklığı TIMI akım derecesi ve düzeltilmiş TIMI kare sayısı ile değerlendirildi.

Bulgular: Trombolitik tedavi ile 62 hastada (%46.6) EİA'da TIMI 3 akım sağlanırken, 71 hastada (%53.4) yetersiz TIMI akım saptandı. Yetersiz akım görülen hastalarda başvuru anındaki OTH anlamlı derecede daha yüksek bulundu (9.8±1.5 fl ve 8.6±1.4 fl; p<0.001); ayrıca, bu grupta streptokinaz daha yüksek oranda uygulanmıştı (p=0.02). İki grup EİA tipi ve hastalıklı damar sayısı açısından benzer bulundu (p>0.05). Ortalama trombosit hacmi ile düzeltilmiş TIMI kare sayısı arasında zayıf ilişki görüldü (p=0.01). Çokdeğişkenli analizde OTH (OO 1.871, %95 GA 1.402-2.498; p<0.001) ve trombolitik ajan tipi (OO 2.915; %95 GA 1.333-6.374; p=0.007) yetersiz TIMI akımının bağımsız öngördürücüleri olarak bulundu. ROC analizinde, OTH'nin yetersiz TIMI akımını öngörmesinde kesim değeri 8.885 fl, duyarlık ve özgüllüğü sırasıyla %70.4 ve %66.1 bulundu.

Sonuç: Bulgularımız, akut miyokart enfarktüsünde, başvuru anındaki yüksek OTH'nin trombolitik tedavi sonrası EİA'da yetersiz TIMI akım riski ile ilişkili olduğunu göstermektedir.

Anahtar sözcükler: Koroner anjiyografi; koroner dolaşım; miyokart enfarktüsü/tedavi; miyokart reperfüzyonu; trombosit sayımı; trombolitik tedavi.

Received: August 11, 2009 *Accepted:* December 9, 2009

Correspondence: Dr. Ayşe Saatcı Yaşar. TSK Rehabilitasyon Merkezi Lojmanları, V1 Blok, No: 9, 06530 Bilkent, Ankara, Turkey. Tel: +90 312 - 291 25 25 / 4808 e-mail: drasaatciyasar@yahoo.com

Platelets play a crucial role in both the pathogenesis of acute myocardial infarction and the occurrence of coronary artery reocclusion.[1] The size of the platelets, represented by mean platelet volume (MPV), has been shown to be closely related to their reactivity.[2] Large platelets are metabolically and enzymatically more active than small ones, having a higher thrombotic potential.[3] Thus, increased MPV is associated with a poor prognosis following myocardial infarction.[4-6]

Reestablishment of coronary blood flow is the primary goal of thrombolytic therapy in acute myocardial infarction.[7-9] To our knowledge, there has been no report on the predictive value of MPV for the patency of infarct-related artery (IRA) following thrombolytic therapy. In this study, we aimed to evaluate the association between admission MPV and IRA patency in patients treated with thrombolytic therapy for acute myocardial infarction. Coronary flow was assessed with both TIMI (Thrombolysis in Myocardial Infarction) flow grade[10] and corrected TIMI frame count (CTFC).[11]

PATIENTS AND METHODS

This retrospective study included 133 consecutive patients who were admitted, from May 2005 to March 2009, with acute ST-elevation myocardial infarction and received thrombolytic therapy within 12 hours of chest pain. Patients with cardiogenic shock and those who did not undergo coronary angiography after thrombolytic therapy were excluded. Clinical, echocardiographic, and laboratory data were collected from hospital records. The local ethics committee approved the study.

Acute ST-elevation myocardial infarction was diagnosed based on a history of typical chest pain lasting >30 min and electrocardiographic ST-segment elevation of ≥1 mm in at least two contiguous leads.

Intravenous thrombolytic therapy consisted of streptokinase (1.5 million U over 60 min) in 65 patients, and recombinant tissue-type plasminogen activator (r-tPA) (15 mg bolus followed by an infusion of 0.75 mg/kg over 30 min -maximum 50 mg- and then an infusion of 0.50 mg/kg over 60 min -maximum 35 mg) in 68 patients. The choice of streptokinase or r-tPA was based on the decision of the physician who prescribed the treatment. As adjunctive therapy, all patients received daily aspirin of 300 mg and clopidogrel with a starting dose of 300 mg and a maintenance dose of 75 mg. Additionally, weight-based enoxaparin was administered until hospital discharge considering the patient's age and renal function.[12]

Mean platelet volume was measured as part of the complete blood count before initiation of thrombolytic therapy. Peripheral venous blood samples were taken into standard EDTA-containing tubes and measurements were made on a Beckmann Coulter LH 780 Hematology Analyzer. Plasma glucose, total cholesterol, LDL and HDL cholesterol, and triglyceride levels were measured within 24 hour of admission. Peak creatine kinase and creatine kinase-MB levels during hospital stay were also recorded.

Coronary angiography was performed within a mean of two days after thrombolytic therapy and included multiple orthogonal views of the IRA. All angiograms were reviewed by an interventional cardiologist who was blinded to the clinical characteristics of the patients, and one-, two-, or three-vessel disease were defined as the presence of greater than 50% diameter stenosis in one, two, or three coronary arteries, respectively. The TIMI flow grade in the IRA was analyzed at the TIMI Angiographic Core Laboratory as previously defined.[10] To evaluate coronary flow objectively as a continuous angiographic index, TIMI frame count was performed using a frame counter on a cineviewer to estimate the number of cineframes showing contrast medium to first reach standardized distal coronary landmarks in the IRA. Corrected TIMI frame count was obtained by dividing the TIMI frame count of the left anterior descending coronary artery by 1.7.[11]

Statistical analysis. Continuous data are presented as mean±standard deviation (SD) and categorical variables as percentages. Differences between groups in continuous variables with and without a normal distribution were determined by the Student's t-test or Mann-Whitney U-test, respectively. Categorical variables were compared with the chi-square test. Spearman's correlation coefficient was calculated to examine the association between two continuous variables. Univariate analysis was performed to identify potential predictors of TIMI 3 flow and variables with a p value of less than 0.1 were entered into a multivariate logistic regression analysis to identify independent predictors. Receiver operating characteristic (ROC) curve was constructed to determine the predictive value of MPV in TIMI 3 flow. A p value of less than 0.05 was considered statistically significant.

RESULTS

After thrombolytic therapy, TIMI 3 flow was achieved in the IRA in 62 patients (46.6%), whereas 71 patients (53.4%) had insufficient TIMI flow. There were no significant differences between the two groups with

Table 1. Demographic, clinical, laboratory, echocardiographic, and angiographic characteristics of the patients

	TIMI III flow (n=62)			<TIMI III flow (n=71)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (years)			57.4±11.3			59.5±12.0	0.3
Sex							0.43
Males	49	79.0		52	73.2		
Females	13	21.0		19	26.8		**<0.001**
Body mass index (kg/m^2)			26.8±3.7			27.8±4.5	0.32
Smoking	43	69.4		40	56.3		0.12
Diabetes mellitus	12	19.4		20	28.2		0.23
Hypertension	19	30.7		29	40.9		0.22
Systolic blood pressure (mmHg)			115.6±14.5			124.2±20.6	**0.008**
Diastolic blood pressure (mmHg)			69.5±9.7			72.4±11.2	0.13
Time to treatment (hours)			2.7±2.1			3.6±2.8	0.11
Location of infarction							0.39
Anterior	26	41.9		35	49.3		
Inferior/other	36	58.1		36	50.7		
Type of thrombolytic agent							**0.02**
Streptokinase	24	38.7		41	57.8		
r-tPA	38	61.3		30	42.3		
Laboratory data							
Hemoglobin (mg/dl)			14.3±1.7			14.2±1.6	0.84
White blood cell count (×10^9/l)			11.2±4.6			11.1±3.6	0.93
Platelet count (×10^9/l)			242.1±56.7			243.3±66.3	0.91
Mean platelet volume (fl)			8.6±1.4			9.8±1.5	**<0.001**
Total cholesterol (mg/dl)			196.7±48.4			193.8±48.4	0.74
LDL-cholesterol (mg/dl)			128.2±41.8			118.8±36.3	0.16
HDL-Cholesterol (mg/dl)			37.7±8.5			37.0±8.4	0.43
Triglyceride (mg/dl)			159.2±111.0			192.4±152.8	0.37
Fasting blood glucose (mg/dl)			140.1±51.2			165.0±76.5	0.14
Peak creatine kinase (U/l)			1,785.5±1,278.7			1,911.4±1,466.2	0.81
Peak creatine kinase-MB (U/l)			138.7±139.0			133.2±122.3	0.99
Echocardiographic data							
Left ventricular ejection fraction			41.7±8.6			39.0±10.3	0.10
Left ventricular wall motion score			11.2±6.7			13.4±7.6	0.08
Angiographic data							
Infarct related artery							0.38
Left anterior descending	26	41.9		38	53.5		
Left circumflex	10	16.1		8	11.3		
Right coronary	26	41.9		25	35.2		
Number of diseased vessels							0.7
One vessel	25	40.3		19	26.8		
Two vessels	15	24.2		30	42.3		
Three vessels	22	35.5		22	31.0		
Corrected TIMI frame count			27.1±7.6			73.7±29.9	**<0.001**

regard to age, gender, body mass index, smoking, hypertension, diabetes mellitus, time from symptom onset to treatment, or location of infarction (p>0.05, Table 1). Although diastolic blood pressures were similar, systolic blood pressure was significantly higher in patients with impaired epicardial flow (p=0.008). Patients with impaired epicardial flow were more likely to have been given streptokinase as thrombolytic agent compared to those with restored epicardial flow (p=0.02, Table 1). While platelet count, white blood cell count, and hemoglobin concentration did not differ between the two groups, patients with impaired epicardial flow had a significantly higher mean admission MPV (9.8±1.5 fl *vs*. 8.6±1.4 fl; p<0.001, Table 1). Fasting plasma glucose, total-cholesterol, LDL and HDL cholesterol, triglyceride, peak creatine kinase and creatine kinase-MB levels were similar in both groups (p>0.05).

Echocardiographic findings including left ventricular ejection fraction and wall motion score were similar in both groups (p>0.05, Table 1). On angiographic examination, the two groups did not differ with respect to the type of IRA and the number of diseased vessels (p>0.05, Table 1).

Correlation analysis showed a weak negative correlation between MPV and platelet count (r=-0.218, p=0.01) and positive correlation between MPV and CTFC (r=0.210, p=0.01).

Univariate analysis identified the type of thrombolytic agent (streptokinase *vs*. r-tPA) and MPV as potential predictors of insufficient TIMI flow. In multivariate analysis, MPV (odds ratio 1.871, 95% CI 1.402-2.498; p<0.001) and the type of thrombolytic agent (odds ratio 2.915; 95% CI 1.333-6.374; p=0.007) were independent predictors of insufficient TIMI flow.

The receiver operating characteristic analysis yielded a cutoff value of 8.885 fl for MPV to predict insufficient TIMI flow, with the area under the ROC curve being 0.735 (95% CI 0.65-0.82), and sensitivity and specificity being 70.4% and 66.1%, respectively.

DISCUSSION

The main finding of this study is that, compared to patients with TIMI 3 flow, patients with insufficient TIMI flow in the IRA after thrombolytic therapy for acute myocardial infarction have a significantly higher mean admission MPV. In addition to the type of thrombolytic agent, MPV was an independent predictor of insufficient TIMI flow after thrombolysis. Our findings suggest that patients with higher MPV values may have an impaired response to thrombolytic agents.

An elevated MPV has been reported as a risk factor for recurrent infarction and death among survivors of myocardial infarction.[5] The admission MPV has also been shown to be a strong and independent predictor of impaired angiographic reperfusion and six-month mortality in patients undergoing primary percutaneous intervention for acute ST-segment elevation myocardial infarction.[4] Reestablishment of IRA flow is associated with decreased mortality in patients with acute myocardial infarction. It may be speculated that failure to restore epicardial coronary blood flow after thrombolytic administration could contribute at least in part to higher morbidity and mortality rates in patients with an elevated MPV.

The present study confirms the observation that intravascular activation of platelets could contribute to failed reperfusion after thrombolysis. Gurbel et al.[13] reported that increased baseline levels of P-selectin and platelet endothelial cell adhesion molecule-1 were correlated with delayed and unsuccessful coronary thrombolysis in patients with acute myocardial infarction. It was observed that high levels of soluble P-selectin sustained in patients with failed reperfusion.[14] In the present study, we determined admission MPV, a marker of platelet reactivity, as an independent predictor of insufficient TIMI flow in the IRA. Moreover, MPV was correlated with CTFC, which further strengthens the findings of this study.

Mean platelet volume has been shown to be inversely correlated with total platelet count.[15] We also found a negative correlation between MPV and platelet count. In a previous study, higher platelet count on presentation was associated with an increased rate of TIMI 3 flow at 90 minutes after fibrinolytic therapy in patients with acute myocardial infarction.[16] The authors proposed that a lower peripheral platelet count could reflect a larger coronary artery thrombus or a thrombus with a higher platelet count. Considering the inverse relationship between MPV and platelet count, this hypothesis may also explain our finding of an association between higher MPV and insufficient TIMI flow after thrombolytic therapy, as it is known that platelet-rich thrombi are more resistant to fibrinolysis than are fibrin- and erythrocyte-rich thrombi.[1]

One important limitation of this study results from its retrospective design. Although patency of the IRA should be assessed at 90 minutes after the start of thrombolytic therapy, it was not possible to perform coronary angiography at 90 minutes and we analyzed TIMI flow grade at a mean of two days. Further prospective large trials are needed to confirm our results.

In conclusion, we showed that a higher MPV on presentation was associated with an increased risk of insufficient TIMI flow in the IRA after thrombolytic therapy in patients with acute myocardial infarction. The presence of larger, more reactive platelets may play a role in decreased likelihood of successful reperfusion with thrombolytic therapy. Our findings may be clinically important in view of the association between TIMI 3 flow and improved outcome after thrombolysis for myocardial infarction.

REFERENCES

1. Serebruany VL, Malinin AI, Callahan KP, Binbrek A, Van Dde Werf F, Alexander JH, et al. Effect of tenecteplase versus alteplase on platelets during the first 3 hours of treatment for acute myocardial infarction:

the Assessment of the Safety and Efficacy of a New Thrombolytic Agent (ASSENT-2) platelet substudy. Am Heart J 2003;145:636-42.
2. van der Loo B, Martin JF. A role for changes in platelet production in the cause of acute coronary syndromes. Arterioscler Thromb Vasc Biol 1999;19:672-9.
3. Corash L, Tan H, Gralnick HR. Heterogeneity of human whole blood platelet subpopulations. I. Relationship between buoyant density, cell volume, and ultrastructure. Blood 1977;49:71-87.
4. Huczek Z, Kochman J, Filipiak KJ, Horszczaruk GJ, Grabowski M, Piatkowski R, et al. Mean platelet volume on admission predicts impaired reperfusion and long-term mortality in acute myocardial infarction treated with primary percutaneous coronary intervention. J Am Coll Cardiol 2005;46:284-90.
5. Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. Lancet 1991; 338:1409-11.
6. Pabón Osuna P, Nieto Ballesteros F, Moríñigo Muñoz JL, Sánchez Fernández PL, Arribas Jiménez A, Diego Domínguez M, et al. The effect of the mean platelet volume on the short-term prognosis of acute myocardial infarct. Rev Esp Cardiol 1998;51:816-22. [Abstract]
7. Anderson JL, Karagounis LA, Becker LC, Sorensen SG, Menlove RL. TIMI perfusion grade 3 but not grade 2 results in improved outcome after thrombolysis for myocardial infarction. Ventriculographic, enzymatic, and electrocardiographic evidence from the TEAM-3 Study. Circulation 1993;87:1829-39.
8. Anderson JL. Overview of patency as an end point of thrombolytic therapy. Am J Cardiol 1991;68:11E-16E.
9. Califf RM, Topol EJ, Gersh BJ. From myocardial salvage to patient salvage in acute myocardial infarction: the role of reperfusion therapy. J Am Coll Cardiol 1989;14:1382-8.
10. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med 1985;312:932-6.
11. Gibson CM, Murphy SA, Rizzo MJ, Ryan KA, Marble SJ, McCabe CH, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. Circulation 1999;99:1945-50.
12. Antman EM, Morrow DA, McCabe CH, Jiang F, White HD, Fox KA, et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST-elevation myocardial infarction. Design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment-Thrombolysis In Myocardial Infarction study 25 (ExTRACT-TIMI 25). Am Heart J 2005;149:217-26.
13. Gurbel PA, Serebruany VL, Shustov AR, Dalesandro M, Gumbs CI, Grablutz LB, et al. Increased baseline levels of platelet P-selectin, and platelet-endothelial cell adhesion molecule-1 in patients with acute myocardial infarction as predictors of unsuccessful thrombolysis. Coron Artery Dis 1998;9:451-6.
14. Kayıkçıoğlu M, Can L, Mete-Erdem N, Kültürsay H, Payzin S, Kokuludağ A, et al. Soluble P-selectin and the success of thrombolysis in acute myocardial infarction. Int J Cardiol 2001;79:223-9.
15. Giles C. The platelet count and mean platelet volume. Br J Haematol 1981;48:31-7.
16. Wong CK, French JK, Gao W, White HD. Relation of initial platelet counts to Thrombolysis In Myocardial Infarction-3 flow rates at 90 minutes after commencing fibrinolytic therapy in patients with acute myocardial infarction. Am J Cardiol 2002;90:54-7.