Gastrointestinal bleeding in patients undergoing primary angioplasty for acute myocardial infarction: incidence, risk factors and prognosis

Akut miyokart enfarktüsü nedeniyle primer anjiyoplasti uygulanan hastalarda gastrointestinal kanama sıklığı, risk faktörleri ve prognoz

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Objectives: We investigated the incidence, predictors, and prognosis of gastrointestinal bleeding (GIB) in patients undergoing primary percutaneous coronary intervention (PCI) for ST-elevation myocardial infarction (STEMI).

Study design: We reviewed 2,541 consecutive patients (2,111 males, 430 females; mean age 56.5±11.8 years) who underwent primary PCI for STEMI. Data on clinical, angiographic findings, and in-hospital outcomes were collected. Gastrointestinal bleeding was defined as apparent upper or lower GIB or melena requiring cessation of antiplatelet or anticoagulant therapy and administration or erythrocyte infusion.

Results: Gastrointestinal bleeding was observed in 27 patients (1.1%). Compared to 2,514 patients without GIB, patients with GIB were older (65.9±13.5 years vs. 56.4±11.8 years; p<0.001), exhibited higher frequencies of female gender (p=0.016), renal failure (p<0.001), and admission anemia (p<0.001), and had a lower procedural success rate (77.9% vs. 91.5%; p=0.02). The development of GIB was associated with significantly higher in-hospital mortality (18.5% vs. 2.9%; p<0.001), longer hospital stay (13.1±6.8 days vs. 7.0±3.7 days, p=0.02), and increased inotropic requirement (37% vs. 6.7%; p<0.001). In multivariate analysis, inotropic requirement (OR 4.17, 95% CI 1.7-10.4; p=0.002), age above 70 years (OR 3.33, 95% CI 1.4-8.0; p=0.007), and glomerular filtration rate lower than 60 ml/min/1.73 m2 (OR 2.96, 95% CI 1.2-7.4; p= 0.02) were independent predictors of in-hospital GIB.

Conclusion: The development of GIB is not an uncommon complication after primary PCI for STEMI. These patients have a prolonged hospital stay and increased in-hospital mortality. Increased intropic requirement, age above 70 years, and impaired renal function are independent predictors of this complication.

Key words: Angioplasty, transluminal, percutaneous coronary/adverse effects; gastrointestinal hemorrhage/etiology; myocardial infarction/therapy.

Amaç: Bu çalışmada, ST yükselmeli miyokart enfarktüsü (STYME) nedeniyle primer perkütan koroner girişim (PKG) uygulanan hastalarda gastrointestinal kanama (GİK) sıklığı, risk faktörleri ve prognozu araştırıldı.

Çalışma planı: Çalışmaya STYME nedeniyle primer PKG uygulanan ardışık 2541 hasta (2111 erkek, 430 kadın; ort. yaş 56.5±11.8) alındı. Klinik, anjiyografik veriler ve hastane içi sonuçlar geriye dönük olarak toplandı. Gastrointestinal kanama, antitrombotik ya da antikoagülan tedaviyi kesecek ve eritrosit infüzyonu gerektirebilecek kadar belirgin olan alt ya da üst GİK veya kara dışkı varlığı olarak tanımlandı.

Bulgular: Primer PKG sonrası 27 hastada (%1.1) GİK gelişti. Gastrointestinal kanama görülmeyenlerle (n=2514) kıyaslandığında, GİK gelişenler hastalar daha yaşlıydı (65.9±13.5 ve 6.4±11.8; p<0.001); bu grupta kadın hasta oranı (p=0.016), böbrek fonksiyon bozukluğu (p<0.001) ve başvuru sırasında anemi (p<0.001) oranları daha yüksek; başarılı işlem oranı daha düşüktü (%77.9 ve %91.5; p=0.02). Gastrointestinal kanama gelişen hastalarda hastane içi mortalite yaklaşık altı kat daha yüksek (%18.5 ve %2.9; p=0.001), yatış süresi daha uzun (13.1±6.8 gün ve 7.0±3.7 gün, p=0.02), inotropik ajan ihtiyacı daha fazla (%37 ve %6.7; p<0.001) bulundu. Çokdeğişkenli analizde inotropik ajan kullanımı (OO 4.17, %95 GA 1.7-10.4; p=0.002), >70 yaş (OO 3.33, %95 GA 1.4-8.0; p=0.007) ve glomerüler filtrasyon hızının <60 ml/dk/1.73 m2 olması (OO 2.96, %95 GA 1.2-7.4; p=0.02) primer PKG sonrası GİK gelişimi için bağımsız belirleyiciler olarak bulundu.

Sonuç: Primer PKG ile tedavi edilen STYME'li hastalarda GİK gelişimi nadir bir komplikasyon değildir. Bu hastalarda hastane içi mortalite daha yüksek, hastanede kalış süresi daha uzundur. İleri yaş, böbrek fonksiyonlarında azalma ve inotropik ajan kullanımı bu komplikasyonun bağımsız belirleyicileri olarak bulunmuştur.

Anahtar sözcükler: Anjiyoplasti, translüminal, perkütan, koroner/yan etki; gastrointestinal kanama/etyoloji; miyokart enfarktüsü/tedavi.

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Primary percutaneous coronary intervention (PCI) is an effective treatment modality with increasing use in patients with ST-elevation myocardial infarction (STEMI). In addition to reduce the incidence of ischemic complications, effective concomitant antiplatelet and anticoagulant drugs with primary PCI also increase the frequency of bleeding complications particularly in high risk patients.[1] Reports from randomized trials demonstrated that post-PCI bleeding observed in patients with acute coronary syndrome prolonged hospital stay and increased in-hospital mortality of these patients.[2-5] In the HORIZONS-AMI study, prevention of post-primary PCI bleeding complications in patients with STEMI early and late stage survival rates.[6] Gastrointestinal bleeding (GIB) is one of the most important complication observed following treatment of STEMI patients with primary PCI.[7] As s result, it is important to identify high risk patients for GIB and closely monitor them with preventive treatment. In this study, incidence, risk factors and prognosis of GIB in patients with STEMI who undergo primary PCI were investigated.

PATIENTS AND METHOD

Patient group. A total of 2,825 consecutive patients who were diagnosed with STEMI in our emergency unit between October 2003 and March 2008 and who underwent coronary angiography 12 hours after the onset of symptoms (18 hours for patients with hemodynamic disorders and those with persistent chest pain) were retrospectively evaluated. The following criteria were used for the diagnosis of ST-elevation myocardial infarction: (*i*) ST-elevation in ≥2 consecutive leads (≥2 mm in the , ≥1 mm in the extremity leads), or newly developed bundle branch block, (*ii*) hemic type chest pain of 30 minutes duration, (*iii*) 2-fold increase in the serum creatine kinase of myocardial band (CK-MB) level. Patients who presented with cardiogenic shock (n=103), those who did not undergo primary PCI after emergency coronary angiography (n=96), and those who were referred for emergency coronary artery bypass graft surgery (n=85) were excluded from the study. The study group finally consisted of 2,541 patients (2,111 males, 430 females; mean age 56.5±11.8 years). The study protocol was approved by the Local Ethics Committee.

Data collection. Demographic characteristics, cardiovascular history and risk factors (cigarette smoking, hypercholesterolemia, diabetes mellitus, hypertension) of the patients, the pain-balloon and door-balloon times were obtained from hospital records. Daily blood sample results of all the patients on admission and thereafter were obtained from the medical records. Information about the type of STEMI was obtained from records of the electrocardiogram performed on admission.

The global left ventricular systolic ejection fraction was measured by the modified Simpson's method, using the Vingmed System V (General Electric, Norway) echocardiography device and 2.5 MHz transducer.[8]

Coronary angiography, primary angioplasty and stenting. Angiographic data were obtained from the catheter laboratory and evaluated. A loading dose of aspirin 300 mg and clopidogrel 300 mg were administered to all patients before the procedure. Emergency angiography and angioplasty were performed through the femoral artery. A bolus of heparin 10000 U was administered intravenously to all patients after femoral artery puncture. Flow in the infarct-related artery was evaluated according to the TIMI (Thrombolysis In Myocardial Infarction) classification.[9] Primary PCI (balloon angioplasty and/or stenting) was performed only in the infarct-related artery according the type of lesion. The acute phase procedural success was defined as a decrease in obstruction of more than 50% in the infarct-related artery at the end of every procedure and the provision of TIMI II-III flow. Patients who were admitted to the Coronary Intesive Care Unit were administered subcutaneous enoxaparin (1 mg/kg) twice daily with a daily aspirin 100 mg and clopidogrel 75 mg. Treatment with glycoprotein IIb/IIIa inhibitor depended on the physicians decision, whereas treatment with beta-blockers, ACE inhibitors and statin was made in accordance with the ACC/AHA guidelines. On the other hand, all patients were given famotidine 40 mg daily for preventive treatment.

Definitions. GIB was defined lower or upper GIB or the presence of dark stool which was significant enough to render discontinuation of antiplatelet or anticoagulant therapy, and administration of erythrocyte infusion. The pain-to-balloon time was defined as the time lapse between the start of symptoms and post-balloon angioplasty coronary reperfusion, whereas the door-to-balloon time was the time lapse between hospital visit and post-balloon angioplasty coronary reperfusion. Recurrent infarction was defined as the repeated increase in the CK-MB level with a repeated increase in the ST segment. Multivessel disease was defined as the presence of more than 50% obstruction in at least two main epicardial coronary arteries or the left main coronary artery. Renal function abnormality was defined as a glomerular filtration rate (GFR) <60 ml/min/1.73 m2 calculated from the Modification of Diet in Renal disease (MDRD) for-

Table 1. Demographic and clinical characteristics, angiographic and interventional data and in-hospital results of patient groups

	Gastrointestinal bleeding						
	Present (n=27)			Present (n=27)			
	Number	%	mean±SD	Number	%	mean±SD	*p*
Demographic and clinical data							
Age >70 years	14	51.9		360	14.3		**<0.001**
Female gender	10	37.0		420	16.7		**0.016**
Diabetes mellitus	6	22.2		616	24.5		0.77
Hypertension	14	51.9		1028	40.9		0.22
Hypercholesterolemia	4	14.8		925	36.8		**0.04**
Cigarette smoking	14	51.9		1363	54.2		0.29
History of percutaneous coronary intervention	3	11.1		193	7.7		0.46
History of coronary bypass surgery	-			73	2.9		0.82
History of myocardial infarction	3	11.1		271	10.8		0.96
Family history	3	11.1		437	17.4		0.60
Anterior myocardial infarction	14	51.9		1218	48.5		0.72
Glomerular filtration rate <60 ml/min/1.73m2	12	44.4		261	10.4		**<0.001**
Anemia on admission	13	48.2		618	24.6		**<0.001**
Left ventricular ejection fraction (%)			40±9			47±11	**0.02**
Angiographic and interventional data							
Multivessel disease	17	63.0		1443	57.4		0.56
Proximal lesion	17	63.0		1330	52.9		0.29
Tirofiban use	14	51.9		1232	49.0		0.76
Stenting	22	81.5		2136	85.0		0.57
Procedural success	21	77.9		2299	91.5		**0.02**
Contrast nephropathy	12	44.4		613	24.3		**0.01**
Pain-to-balloon time (hours)			3.3±2.5			3.2±2.8	0.77
Door-to-balloon time (minutes)			33±20			29±21	0.69
In-hospital results							
Mortality	5	18.5		73	2.9		**0.001**
Recurrence of infarction	1	3.7		49	2.0		0.56
Inotropic drug use	10	37.0		169	6.7		**<0.001**

mula.[10] Contrast nephropathy was defined as a 25% or a more than 0.5 mg/dl increase in the serum creatinine level within 72 hours of application of contrast substance to the baseline level. The use of oral hypoglycemic or insulin therapy at the time of presentation was considered as a diagnosis of diabetes mellitus, whereas the use of antilipidemic drugs or a total cholesterol level of ≥200 mg/dl was considered a diagnosis of hypercholesterolemia. A baseline hemoglobin level of <13 mg/dl in men and <12 mg/dl in women was considered as anemia.

Statistical analysis. Statistical evaluation of data was performed using the SPSS 15.0 program. Numerical data were expressed as mean±standard deviation whereas categorical data were expressed as percentages. Comparison of numerical values between two group was made using the Mann-Whitney U-test, whereas the difference between categorical variables was evaluated using the Chi-square test. Clinical and angiographic variables were analyzed using retrospective multivariate stepwise logistic regression analysis in order to investigate independent predictors of the development of GIB. A p value of <0.05 was considered as statistically significant.

RESULTS

Demographic and clinical characteristics, angiographic and interventional data and the in-hospital results of all the patients are shown in Table 1. GIB developed in 27 patients (1.1%) after primary PCI. This condition was observed in 66.7% of the patients (n=18) in the form of dark stool or hematochezia, and in 33.3% of the patients (n=9) as hematemesis. Comparison with patients who did not experience GIB demonstrated that patients with GIB were at a more advanced age (with a mean age of 65±13.5 vs. 56.4±11.8, p<0.001). The proportion of women, renal function abnormalities and the rate of anemia on ad-

mission were also found to be higher in this patient group. The incidence of diabetes mellitus, hypertension, and history of cigarette smoking was similar in both groups.

Angiographic and interventional characteristics. No significant difference was found between the groups with regards to distribution of the infarct-related arteries and the pain-to-balloon and door-to-balloon times. However, the success rate of the procedure was found to be lower in patients developed GIB (77.9% vs. 91.5%, p=0.02). There was no significant difference between patients with and those without GIB with respect to tirofiban use.

In-hospital results. The development of GIB was associated with nearly six-fold higher in-hospital mortality (18.5% vs. 2.9%, p=0.001), and a longer hospital stay (13.1±6.8 days vs. 7.0±3.7 days, p=0.02). No significant difference was observed between the groups regarding recurrence of the infarction. Increased inotropic requirement was also reported to be higher in patients who developed GIB (37% vs. 6.7%; p<0.001).

Variables with a significant effect on the development of GIB are shown in Table 2. In multivariate analysis, inotropic drug use (OR 4.17, 95% CI 1.7-10.4; p=0.002), age >70 years (OR 3.33, 95% CI 1.4-8.0; p=0.007), and GFR <60 ml/min/1.73 m2 (OR 2.96, 95% CI 1.2-7.4; p= 0.02) were found to be independent predictors of GIB development.

Table 2. Conditions affecting gastrointestinal bleeding during univariate and multivariate analyses

	Odds ratio	95% confidence interval	*p*
Univariate analysis			
Inotropic drug use	8.16	3.7 – 18.1	**<0.001**
Renal failure	6.48	2.9 – 14.4	**<0.001**
Age >70 years	6.44	3.0 – 13.8	**<0.001**
Unsuccessful procedure	3.05	1.2 – 7.6	**0.01**
Anemia on admission	3.05	1.4 – 6.6	**0.005**
Female gender	2.93	1.3 – 6.5	**0.007**
Contrast nephropathy	2.65	1.2 – 5.6	**0.01**
Multivariate analysis			
Inotropic drug use	4.17	1.7 – 10.4	**0.002**
Age >70 years	3.33	1.4 – 8.0	**0.007**
Renal failure	2.96	1.2 – 7.4	**0.02**

DISCUSSION

Varying incidence rate of GIB development following percutaneous coronary intervention have been reported. In the REPLACE-2 study where PCI was performed only under elective conditions, the incidence of GIB was found to be 0.6%.[11] Abbas et al.[4] reported this rate to be 2.3% in patients who underwent primary PCI for acute myocardial infarction. In our study the incidence of post-PCI development of GIB was 1.1%. Although these studies were similar, the low incidence of GIB in our study compared to the study by Abbas et al.[4] may be attributed to the relatively more advanced age of the patients in the latter. This is due to the fact that advanced age (>70 years) was a powerful risk factor for the development of GIB in both studies and the incidence of patients >70 years of age was twice that of our study (25% vs. 14%).

Various studies have reported a higher mortality rate in patients who developed GIB following acute myocardial infarction.[4,5] Similarly, the in-hospital mortality in patients who developed GIB following primary PCI in our study was found to be six-fold higher than in those without GIB (18.5% vs. 2.9%, p=0.001). It is not yet understood how GIB increases mortality in these patients. There have been many hypotheses of this subject. In a study conducted by Lewis et al.[12] on patients who developed GIB during their study in the intensive care unit, 75% of mortality was attributed to factors such as sepsis and multiple organ failure, and not directly to the effect of GIB. On the other hand, coronary ischemia, hypotension, anemia due to severe bleeding, activation of platelet and clotting factors associated with anemia and adverse effects of repeated blood transfusion were also reported to be possible factors associated with increased rates in these patients.[13]

Chin et al.[14] demonstrated that proton pump inhibitors reduced the post-PCI risk of GIB. As a result, identification of high risk patients for the development of GIB is important in order to provide preventive treatment. Abbas et al.[4] found advanced age as the only independent risk factors for the development of GIB following primary PCI. On the other hand, results of our study show that advanced age, renal failure, and inotro.pic drug use were very powerful independent risk factors for post-primary PCI development of GIB (OR 4.17, p=0.002). This powerful relationship between inotropic drug use and GIB in these patients may be due to gastritis and gastrointestinal mucosal ischemia due to physiological stress which is associated with left ventricular systolic dysfunction and hypotension.[14,15]

A decrease in renal function together with platelet dysfunction may adversely affect the clotting cascade. Use of unfractionated low molecular weight heparin may also lead to a decrease in clearance.[16-18] As a result, patients with renal failure are suggested to be more susceptible to bleeding complications. This results are consistent with the results of our study which de-

monstrate that a GFR <60 ml/min/1.73 m^2 was an independent predictor for the development of GIB (OR 2.96, p=0.02).

Another important result of our study was the high rate of anemia on admission observed in patients who developed GIB (48.2% and 24.6%, p<0.001). Similarly, Dauerman et al.[19] also reported a higher rate of bleeding complications in acute myocardial infarction patients with anemia. Despite the presence of a relationship between anemia on admission and the development of GIB during the univariate analysis of our study, this relationship was found to disappear in the multivariate analysis. These results suggest that anemia per se is not responsible for increases in the development of GIB; however, conditions such as advanced age, renal failure and left ventricular dysfunction which are commonly seen in patients with anemia may be responsible for the increase in GIB. On the other hand, presence of anemia on admission may be an indicator for an invisible gastrointestinal pathology and a finding of bleeding. Therefore, anemia in these patients may be a strong candidate for significant GIB.

The RESTORE study demonstrated that tirofiban, a glycoprotein IIb/IIIa inhibitor may safely be used in patients with acute coronary artery syndrome who underwent PCI, without increasing bleeding complications.[20] Similar to our study, Abbas et al.[4] did not also demonstrated that a relationship between glycoprotein IIb/IIIa inhibitor and the development of GIB.

Discontinuation of antibiotic and anticoagulant therapy before the scheduled time in patients with acute coronary syndrome who undergo PCI (particularly those with stents) may lead to severe problems. Aspirin, heparin and glycoprotein IIb/IIIa inhibitor (14 patients who used tirofiban) were discontinued in all patients who developed GIB in our study; however, treatment with clopidogrel was continued in 12 patients with a better clinical course of the condition. Interestingly no significant difference was found between patients with GIB who discontinued aspirin, heparin and tirofiban treatment and patients without GIB who continued this treatment, regarding the recurrence of myocardial infarction. Moreover, development of stent thrombosis during the in-hospital period was not reported in any of the 15 patients who had to discontinue clopidogrel treatment. The small number of patients who had to discontinue antibiotic and anticoagulant therapy due to GIB may have been the cause of these unexpected results.

In conclusion, development of GIB in STEMI patients who undergo primary PCI treatment is not an uncommon complication. The in-hospital mortality is high and the hospital stay is reported to be longer in these patients. On the other hand, advanced age, decreased renal function, and inotropic drug use are independent indicators of this complication.

Limitations of the study. There were some limitations while conducting the study. Primarily, this was a single-centered retrospective study which had some disadvantages of a retrospective study. Another limitation was the inability to randomize glycoprotein IIb/IIIa inhibitor and leaving its use to the discretion of the physician. This could have affected the relationship of glycoprotein IIb/IIIa inhibitor use with the development of GIB. It was not also possible to exclude patients who were susceptible to bleeding from the study since we had no data about their conditions. This could also have affected the results of the study. Finally, there was not enough data concerning the administration of non-cardiac treatment and its effect on patients with GIB. As a result, randomized studies are required to investigate the effect of proton pump inhibitors and mucosal preventive drugs in STEMI patients who are at a high risk of developing GIB.

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