Original Article

Impact of Anti-Aggregant, Anti-Coagulant and Non-Steroidal Anti-Inflammatory Drugs on Hospital Outcomes in Patients with Peptic Ulcer Bleeding

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ABSTRACT

Background/Aims: There are a limited number of studies including the impact of antiplatelet drugs use on hospital outcomes for nonvariceal upper gastrointestinal bleeding. The aim of this study was to determine the effect of anti-aggregant, anti-coagulant and non-steroidal anti-inflammatory drugs upon hospital outcomes in patients with peptic ulcer bleeding. **Materials and Methods:** The patients under treatment with antiaggregant, anticoagulant or non-steroidal anti-inflammatory drugs were categorized as exposed group (n = 118) and the patients who were not taking any of these drugs were categorized as non-exposed group (n = 81). We analyzed the data of drug intake, comorbid disease, blood transfusion, duration of hospital stay, Blatchford/total Rockall score and diagnosis of patients. **Results:** In total, 199 patients were included. Of these 59.3% (exposed group) were taking drugs. The patients in exposed group were significantly older than those in non-exposed group (62.9 ± 17.3 years; 55.5 ± 19.3 years, P = 0.005, respectively). Mean number of red blood cell units transfused (2.21 ± 1.51; 2.05 ± 1.87, P = 0.5), duration of hospital stay (3.46 ± 2.80 days; 3.20 ± 2.30 days, P = 0.532) and gastric ulcer rate (33% vs 23.4%, P = 0.172) were higher in exposed group than in non-exposed group but the differences were not statistically significant. Total Rockall and Blatchford scores of the patients were significantly higher in exposed group than in non-exposed group (3.46 ± 1.72 vs 2.94 ± 1.87, P = 0.045; 10.29 ± 3.15 vs 9.31 ± 3.40, P = 0.038). **Conclusion:** Our study has shown that anticoagulants, antiaggregants and nonsteroidal anti-inflammatory drugs do not effect duration of hospital stay, red blood cell transfusion requirement and rebleeding for peptic ulcer bleeding.

Key Words: Anti-aggregant, anti-coagulant, non-steroidal anti-inflammatory drugs, nonvariceal upper gastrointestinal bleeding, peptic ulcer

Received: 29.07.2013, Accepted: 20.10.2013

How to cite this article: Solakoglu T, Koseoglu H, Atalay R, Sari SO, Yurekli OT, Akin E, *et al*. Impact of anti-aggregant, anti-coagulant and non-steroidal anti-inflammatory drugs on hospital outcomes in patients with peptic ulcer bleeding. Saudi J Gastroenterol 2014;20:113-9.

Acute upper gastrointestinal bleeding (AUGIB) is one of the most common gastrointestinal (GI) indications for hospitalization in gastroenterology clinics.[1] Most gastrointestinal bleeding (GIB) stops without treatment. Sometimes, however, it does not. Despite advances in therapeutic endoscopy, the mortality and morbidity of patients with AUGIB has remained relatively constant.[2] Anticoagulant drugs, corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are risk factors for AUGIB.[3,4] Peptic ulcer bleeding is the most common cause of nonvariceal upper gastrointestinal bleeding (NVUGIB). The factors-NSAIDs, Helicobacter pylori, psychological stress and gastric acid hypersecretion – have been identified as major risk factors for peptic ulcer.[5,6] NSAIDs increase the risk of peptic ulcer complications by 3-4-fold.[7] Moreover, low doses of acetylsalicylic acid (ASA) increase the risk for AUGIB; risk increases with accompanying use of clopidogrel and anticoagulant therapies.[8] It is known that warfarin, which is more commonly used in cardiovascular diseases, raises the bleeding risk.[9]

The primary aim of this study was to determine the effect of anti-aggregant, anti-coagulant and NSAIDs upon hospital

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Website: www.saudijgastro.com

DOI: 10.4103/1319-3767.129476

outcomes in patients with acute NVUGIB caused by peptic ulcer.

MATERIALS AND METHODS

Patient selection

Between January 2010 and December 2011, 277 patients with AUGIB who had undergone an inpatient upper endoscopy within 24 hours were analyzed retrospectively. We excluded 15 patients with esophageal and gastric variceal bleeding. Two hundred and sixty two hospitalized patients with NVUGIB were determined. We also excluded Sixty two patients were excluded due to GI malignancy, dieulofoy lesion and history of gastrectomy.

A total of 199 cases of gastroduodenal lesion (gastric ulcer, duodenal ulcer or erosion) over the age of 18 presenting with NVUGIB manifestations as hematemesis/coffee ground vomiting, melena were included in the study.

Of all, 118 patients under treatment with antiaggregant, anticoagulant or NSAIDs were categorized as exposed group and 81 patients who were not taking any of these drugs were categorized as non-exposed group. Patient selection scheme is summarized in Figure 1.

Management and therapy

In order to determine the risk factors of the patients, Rockhall and Blatchford scoring systems were used.[10,11] Initial endoscopic evaluations were performed within 24 hours of admission to all patients with AUGIB.[12] All promoting drugs which caused peptic ulcer bleeding were stopped and all patients received intravenous proton pump inhibitor (PPI) with 80 mg bolus followed by 8 mg/h continuous infusion for 48 or 72 hours. Patients were discharged with a prescription for a single daily-dose oral PPI for a duration as dictated by the underlying etiology. Clips, thermocoagulation or polidocanol sclerosant injection were used in patients with high risk lesions. Red Blood Cell (RBC) transfusions were performed according to the clinical guideline.[13,14] Indications for the RBC transfusion were as follows:

- Hemoglobin (Hb) <10 g/dL for those who have coronary artery disease
- Ischemia finding on electrocardiogram
- Symptoms of shock
- Hb <7 g/dL.

After the bleeding had been controlled, patients who were hemodynamically stable and without serious comorbidities were discharged from the hospital.

Statistical analysis

Clinical characteristics, scoring systems and endoscopical findings were analyzed by descriptive statistics (mean, percentage, standard deviation (SD), minimum and maximum values). The results are expressed as means ± SD. Bivariate analysis of all the variables pertaining to age, sex, total Rockall/Blatchford score, duration of hospital stay, number of RBC units transfused. Endoscopic findings were performed by the Chi-square test and by Student's t-test for either equal or unequal variances, as appropriate. All tests of significance were two-tailed, and a P value < 0.05 was considered to indicate statistical significance.

RESULTS

In total, 199 patients who were admitted to hospital for NVUGIB were included, with a mean age of 59.9 ± 18.5 years, of whom 19.1% were older than 80 years, and 67.3% were men. Characteristics of the patients are shown in Table 1. Most of the patients were over 60 years in exposed group (58.5%). Conversely most of the patients were under 60 years in non-exposed group (58%). The mean age of the patients in exposed group was 62.9 ± 17.3 years and in non-exposed group it was 55.5 ± 19.3 years ($P = 0.005$). The majority of patients were male in both groups. The percentage of patients taking at least one form of antiaggregant, anticoagulant agents or NSAIDs was 59.3 (118 patients). The distribution of patients according to age groups is shown in Figure 2.

For patients taking warfarin, mean international normalized ratio (INR) value (3.82 ± 3.03) was higher than the dose range that is suggested by the guides.[15] Comorbid diseases were reported in 58.8% (117 patients) of the patients; the most common were cardiovascular disease (39.32%) and hypertension (35.04%). Most of the patients were taking ASA and NSAIDs. The percentage of patients taking these drugs in exposed group were 77.2%. The other patients were taking warfarin (13.56%), clopidogrel (3.54%), dipyridamole (0.85%), and ASA with warfarin (5.93%). The total Rockall and Blatchford score of the patients in exposed group (3.46 ± 1.72; 10.29 ± 3.15) were higher than the patients in non-exposed group (2.94 ± 1.87; 9.31 ± 3.40) and this difference was statistically significant (p = 0.045 and $P = 0.038$ respectively).

The endoscopic findings of all patients were as follows: 127 (63.9%) of them had duodenal ulcer, 58 (29.1%) of them had gastric ulcer, and 14 (7%) of them had gastric erosion. Duodenal ulcer was the most common endoscopic finding in both groups. Gastric ulcers were observed in 33% of patients (39/118) in exposed group and 23.4% of patients (19/81) in non-exposed group ($P = 0.172$). A total of 155 patients (77.9%) had received RBC transfusions (2.15 ± 1.66 units of blood). Of these 63.9% ($n = 99$) were in exposed group. The mean number of RBC units transfused was higher in exposed group than in non-exposed group (2.21 ± 1.51 vs 2.05 ± 1.87), but the difference was not statistically significant ($P = 0.500$).

We performed endoscopic therapy for 16.1% of patients (32/199) who had active bleeding or lesion with a high risk of rebleeding. All patients with Forrest Ia, Ib and IIa ulcers had received endoscopic therapy. For 20 (16.9%) patients in exposed group and for 12 (14.8) %) patients in non-exposed group, endoscopic therapy was performed ($P = 0.051$). The rate of rebleeding was 5% (10/199). Three patients (2.5%) in exposed group and 7 patients (8.6%) in non-exposed group rebled ($P < 0.001$).

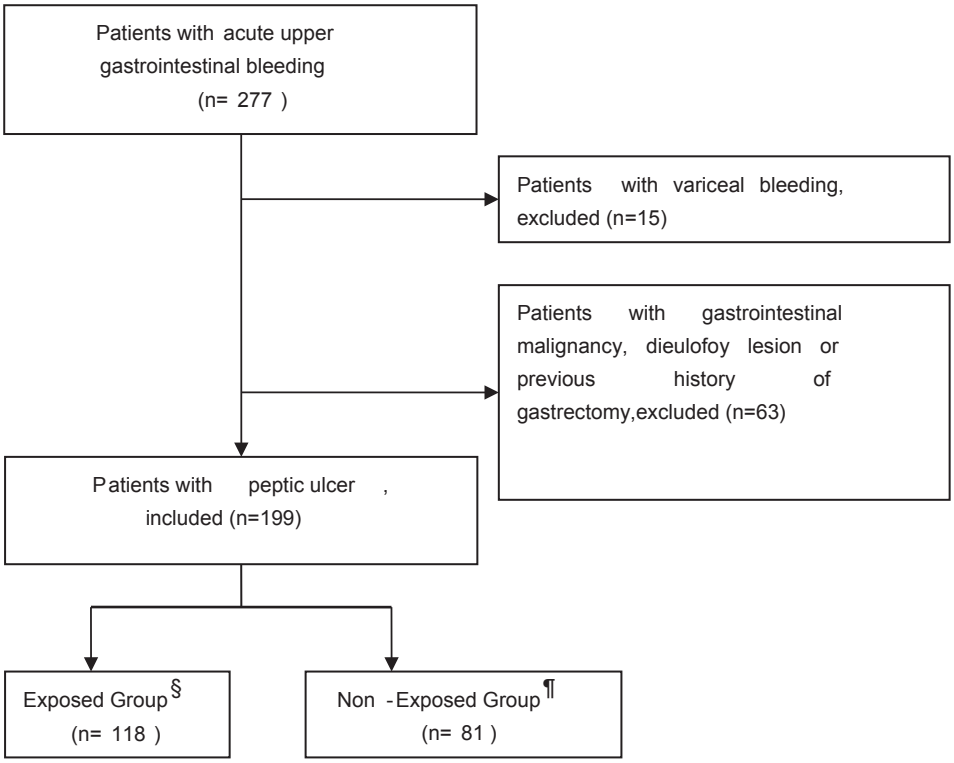

Figure 1: Patient selection. §Patients taking at least one form of antiaggregant, anticoagulant, and nonsteroidal anti-inflammatory drugs. ¶Patients taking none of these drugs

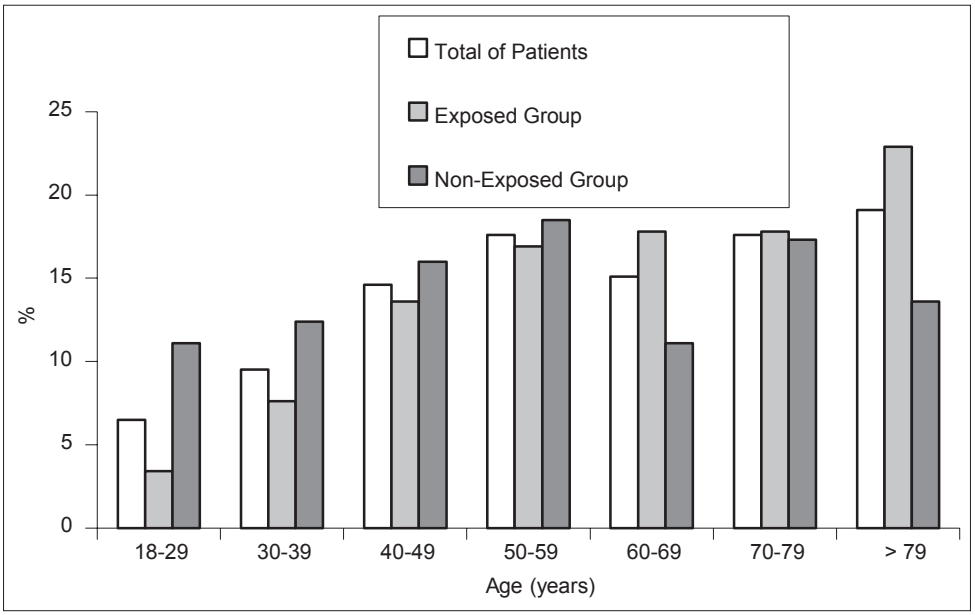

Figure 2: Distribution of patients according to age groups

The mean duration of hospital stay was 3.46 ± 2.80 days in exposed group, 3.20 ± 2.30 days in non-exposed group, and there was no statistical difference between the two groups (P = 0.532). Table 2 shows characteristics of the patients groups.

Table 1: Characteristics of patients (*n*=199)

Characteristics	Total number of patients *n*=199 (%)	Exposed Group (EG) *n*=118 (%)	Nonexposed Group (NEG) *n*=81 (%)	EG/NEG *P* value
Age (years)	59.9±18.5	62.9±17.3	55.5±19.3	0.005
Gender				
Male	134 (67.3)	76 (64.4)	58 (71.6)	>0.5
Female	65 (32.7)	42 (35.6)	23 (28.4)	>0.5
INR	1.41±1.23	1.58±1.54	1.13±0.46	0.016
Comorbidity	117 (58.8)	95 (80.5)	22 (27.2)	
Cardiovascular disease	46 (39.32)	46 (48.4)	-	
Hypertension	41 (35.04)	32 (33.7)	9 (40.9)	
Diabetes mellitus	11 (9.40)	5 (5.3)	6 (27.3)	
Chronic renal failure	8 (6.84)	5 (5.3)	3 (13.6)	
Chronic obstructive Pulmonary disease	4 (3.44)	1 (1.0)	3 (13.6)	
Pulmonary Thromboembolism	1 (0.86)	1 (1.0)	-	
Cerebrovascular event	4 (3.42)	3 (3.2)	1 (4.6)	
Cancer (breast/lung)	2 (1.71)	2 (2.1)	-	
Drug intake	118 (59.3)	118	-	
ASA	47 (39.8)	47 (39.8)	-	
NSAIDs	44 (37.3)	44 (37.3)	-	
Warfarin	16 (13.6)	16 (13.6)	-	
(ASA+Warfarin)	7 (5.9)	7 (5.9)	-	
Other (Clopidogrel, dipyridamole)	4 (3.4)	4 (3.4)	-	
Total rockall score	3.25±1.80	3.46±1.72	2.94±1.87	0.045
Blatchford score	9.89±3.28	10,29±3.15	9.31±3.40	0.038
Endoscopc findings	199	118	81	
Duodenal ulcer	127 (63.8)	67 (56.8)	60 (74.1)	0.275
Gastric ulcer	58 (29.1)	39 (33.0)	19 (23.4)	0.172
Gastric erosion	14 (7.0)	12 (10.2)	2 (2.5)	0.710
Number of RBC units transfused	2.15±1.66	2.21±1.51	2.05±1.87	0.500
Endoscopic treatment	32 (16.1)	20 (16.9)	12 (14.8)	0.051
Rebleeding	10 (5.0)	3 (2.5)	7 (8.6)	<0.001
Duration of hospital stay (days)	3.36±2.60	3.46±2.80	3.2±2.3	0.532
Mortality	1 (0.5)	1 (0.8)	-	
Surgery	-	-	-	
Forrest Ia, Ib, and IIa/others[a]	31/185	20/106	11/79	0.100

[a]Fourteen patients were not classified according to Forrest classification because of gastric erosion. RBC, red blood cell. ASA, acetylsalicylic acid. INR, international normalized ratio. NSAIDs, nonsteroidal anti-inflammatory drugs

DISCUSSION

NVUGIB is a common medical emergency that requires early treatment and its incidence is in 80 to 90% of all AUGIB.[16] Almost all people who develop AUGIB are treated in hospital and the guideline therefore focus on hospital care. The most common cause is peptic ulcer for NVUGIB.[3] In our study, peptic ulcer disease accounts for 76% of cases of acute NVUGIB, similar to other studies.[1,2,3]. Despite recent advances in endoscopic therapy, mortality rates have remained essentially unchanged at 5-10%.[16] This could be explained by the fact that patients are older. Branicki *et al*,[17] reported that the incidence of clinically significant AUGIB increased with age, particularly in those over 60 years, and was more common in men. The incidence rose from 23 in patients aged under 30 years to 485 in patients aged over 75 years, and it was present in 27% of patients aged over 80 years (18). The frequency was 2 times higher in male patients in comparison with female patients.[18] In our study, a total of 199 patients who were admitted to hospital for NVUGIB were included, with a mean age of 59.9 ± 18.5 years, of whom 19.1% were older than 80 years, 67.3% were men and comorbid diseases were observed in 58.8% of total patients, similar to other studies.[17-19]

For patients with and without complications of NVUGIB in the United States, the mean lengths of stay were 4.4 and 2.7 days respectively.[20] In another study, 175 and 83 cases of acute NVUGIB were identified at the American and Canadian centres, respectively. Cases at the American centre had a lower

Table 2: Characteristics of the patient groups (*n*=199)

Characteristics	Group (%)		*P* value
	Exposed *n*=118	Nonexposed *n*=81	
Age (year)	62.9±17.3	55.5±19.3	*P*=0.005
Gender			
Male	76 (64.4)	58 (71.6)	>0.5
Female	42 (35.6)	23 (28.4)	>0.5
INR	1.58±1.54	1.13±0.46	0.016
Total rockall score	3.46±1.72	2.94±1.87	0.045
Blatchford score	10,29±3.15	9.31±3.40	0.038
Endoscopc findings	118	81	
Duodenal ulcer	67 (56.8)	60 (74.1)	0.275
Gastric ulcer	39 (33.0)	19 (23.4)	0.172
Gastric erosion	12 (10.2)	2 (2.5)	0.710
Number of RBC units transfused	2.21±1.51	2.05±1.87	0.500
Endoscopic treatment	20 (16.9)	12 (14.8)	0.051
Rebleeding	3 (2.5)	7 (8.6)	<0.001
Duration of hospital stay (days)	3.46±2.80	3.2±2.3	0.532

RBC: Red blood cell, INR: International normalized ratio

mean duration of hospital stay (2.6 versus 3.9 days).[21] In a study from Turkey, mean duration of hospital stay for the patients with NVUGIB was 7.0 ± 5.7 days.[19] In our study, patients receiving drugs promoting peptic ulcer bleeding were older than the others. It is interesting that mean duration of hospital stay was not significantly different between these two groups. Although anti-aggregant, anti-coagulant and non-steroidal anti-inflammatory drugs increase the risk of peptic ulcer bleeding they may not effect the duration of hospital stay, and age may not be an important factor for the duration of hospital stay in patients with NVUGIB.

NSAIDs independently and significantly increase the risk of gastroduodenal ulcer and ulcer bleeding moreover they play an important role in ulcer development.[22] NSAIDs interfere with mucosal defense via direct toxic effects in addition to cyclooxygenase inhibition and subsequent depletion of endogenous prostoglandins.[22] In the meta-analysis of Derry and Loke,[23] it was seen that long term therapy with aspirin is associated with a significant increase in the incidence of GI bleeding. Recently, in another meta-analysis, it was reported that low doses of ASA increased the risk for GI bleeding; risk increased with accompanying use of clopidogrel and anticoagulant therapies.[8] In our study, most patients took at least one form of antiaggregant, anticoagulant or NSAIDs (59.3%). ASA and NSAIDs were the most common drugs used by the patients (39.8%, 37.3% respectively). Very few patients were taking clopidogrel and dipyridamole moreover they were not taking combined therapy. Endoscopic hemostatic therapy has been shown to reduce rebleeding, surgery and death among patients with high-risk endoscopic stigmata (Forrest Ia, Ib or IIa).[14,24,25] In our study, the need for therapeutic endoscopy was higher in patients receiving drugs but it was not statistically significant. Drugs do not impact on the RBC transfusion requirements and rebleeding. It is interesting that patients in non-exposed group had higher rate of rebleeding than those in exposed group. It may be explained by using PPI infusions in exposed group for longer duration than the others. Patients in exposed group might be receiving more intensive antisecretory and Helicobacter pylori eradication therapy than others. We know that PPI and Helicobacter Pylori eradication therapy reduce the risk of rebleeding in those with peptic ulcer.[26,27] Appropriate duration of PPI therapy is of critical importance to allow mucosal healing and to prevent rebleeding in high-risk patients.[28] Similar to the results of our study, Ahsberg *et al*,[29] showed that increased use of drugs that promote bleeding had no impact on incidence and mortality of nonvariceal GI bleeds, but the severity of bleeding had increased by using these drugs. Perhaps in our study the number of patients who rebled may have been too small to obtain accurate results.

Although it is well established that antiaggregant, anticoagulant and NSAIDs increase the risk of AUGIB, there are a limited number of studies indicating the impact of these drugs use on hospital outcomes for NVUGIB. Recently, Ortiz *et al*,[30] reported that neither anticoagulation nor antiplatelet treatment exerted an influence upon mortality, the need for urgent surgery or rebleeding in patients with NVUGIB. Also in this study it was found that anticoagulation is associated with a longer hospital stay (9.9 ± 9.4 days). Similarly, in our study the duration of hospital stay in the anticoagulated patients was 4.0 ± 2.6 days longer than in the untreated patients and patients treated with antiplatelet medication. But there was no difference between patients taking antiaggregant, anticoagulant or NSAIDs and patients taking none of these drugs. The other study from United States, demonstrated that antiplatelet agents' use did not significantly alter the course or outcome in GI bleeders admitted to hospital during their hospital stay. There was no difference between patients using antiplatelet agents and those not using antiplatelet with regard to total number of units transfused and overall duration of hospital stay.[31] Our study supported these findings but in the United States study the number of patients using antiplatet agents (n = 35) was lower than those (n = 118) in our study. Also these findings forced us to think again about withholding antithrombotic (anticoagulant and antiplatelet) therapy in patients with NVUGIB. The management of patients on antithrombotic drugs complicated by AUGIB is a clinical dilemma. These patients have increased tendency of thromboembolism because of their underlying cardiovascular occlusive diseases. Witt and *et al*,[32] reported that the decision to not resume warfarin therapy in AUGIB event was associated with increased risk for thrombosis and death. However, temporary discontinuation of antithrombotic therapy is often necessary to control bleeding or prevent early recurrent bleeding. Sung and *et al*,[33] suggested that in low-dose aspirin recipients who had peptic ulcer bleeding, continuous aspirin therapy may increase the risk for recurrent bleeding but potentially reduces mortality rates. Recently, Almadi *et al*,[34] performed a systematic review to identify dilemma of antiplatelet and anticoagulant therapy in patients with gastrointestinal bleeding and recommended that antiplatelet therapy in event of AUGIB be restarted as soon as possible and rate of overt AUGIB was reduced with PPI without an associate increase in cardiovascular events. The decision to withhold or restart anticoagulants should be individualised, balancing thromboembolic risk against risk of rebleeding. More studies a clinical outcome future studies with an adequate sample size including continuation of antithrombotic therapy in patients with NVUGIB are required.

Our study has several limitations. First, the results connot be generalized to all patients with AUGIB. This was a single center and a retrospective study. The number of patients was small and patients with rebleeding were much lower. low. Second, biopsy-based Helicobacter Pylori testing is

recommended by guidelines in patients presenting with a bleeding ulcer but in our study the presence or absence of Helicobacter Pylori infection was not specified.

In conclusion, patients who were taking drugs were older than the patients who were not taking any of these drugs. The need for therapeutic endoscopy was significantly higher in patients receiving drugs. Moreover, total Rockall, Blatchford scores and gastric ulcer rate were higher in patients taking drugs than the others. Probably, clopidogrel and dipyridamole does not effect peptic ulcer bleeding like ASA, warfarin and NSAIDs. It is known that antiaggregant, anticoagulant and NSAIDs cause AUGIB. But our study has shown that drugs do not effect duration of hospital stay, RBC transfusion requirements and rebleeding for AUGIB caused by peptic ulcer.

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Source of Support: Nil, **Conflict of Interest:** None declared.