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World J Gastroenterol 2005;11(9):1365-1368
World Journal of Gastroenterology ISSN 1007-9327

• *BRIEF REPORTS* •

Acute upper gastrointestinal bleeding in patients on long-term oral anticoagulation therapy: Endoscopic findings, clinical management and outcome

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Received: 2004-05-25 Accepted: 2004-06-29

Abstract

AIM: Acute gastrointestinal bleeding is a severe complication in patients receiving long-term oral anticoagulant therapy. The purpose of this study was to describe the causes and clinical outcome of these patients.

METHODS: From January 1999 to October 2003, 111 patients with acute upper gastrointestinal bleeding (AUGIB) were hospitalized while on oral anticoagulants. The causes and clinical outcome of these patients were compared with those of 604 patients hospitalized during 2000-2001 with AUGIB who were not taking warfarin.

RESULTS: The most common cause of bleeding was peptic ulcer in 51 patients (45%) receiving anticoagulants compared to 359/604 (59.4%) patients not receiving warfarin ($P<0.05$). No identifiable source of bleeding could be found in 33 patients (29.7%) compared to 31/604 (5.1%) patients not receiving anticoagulants ($P= 0.0001$). The majority of patients with concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs) (26/35, 74.3%) had a peptic ulcer as a cause of bleeding while 32/76 (40.8%) patients not taking a great dose of NSAIDs had a negative upper and lower gastrointestinal endoscopy. Endoscopic hemostasis was applied and no complication was reported. Six patients (5.4%) were operated due to continuing or recurrent hemorrhage, compared to 23/604 (3.8%) patients not receiving anticoagulants. Four patients died, the overall mortality was 3.6% in patients with AUGIB due to anticoagulants, which was not different from that in patients not receiving anticoagulant therapy.

CONCLUSION: Patients with AUGIB while on long-term anticoagulant therapy had a clinical outcome, which is not different from that of patients not taking anticoagulants. Early endoscopy is important for the management of these patients and endoscopic hemostasis can be safely applied.

Key words: AUGIB; Anticoagulant therapy; Endoscopy

Thomopoulos KC, Mimidis KP, Theocharis GJ, Gatopoulou AG, Kartalis GN, Nikolopoulou VN. Acute upper gastrointestinal bleeding in patients on long-term oral anticoagulation therapy: Endoscopic findings, clinical management and outcome. *World J Gastroenterol* 2005; 11(9): 1365-1368
http://www.wjgnet.com/1007-9327/11/1365.asp

INTRODUCTION

Acute upper gastrointestinal bleeding (AUGIB) is a severe complication in patients receiving long-term oral anticoagulant therapy. The number of people presenting with AUGIB while on warfarin therapy is increasing because of the expanding indications for long-term anticoagulant therapy[1]. Patients with prosthetic heart valves, chronic or paroxysmal atrial fibrillation, recurrent deep venous thrombosis, hypercoagulable diseases, and vascular diseases are currently maintained on long-term anticoagulants. Despite advances in monitoring the gastrointestinal bleeding in these patients, frequent and major bleeding occurs in up to 20% patients[1-5]. The risk of bleeding is influenced by the intensity of anticoagulant therapy, age (over 65 years), history of gastrointestinal bleeding, presence of serious comorbid conditions (acute myocardial infraction, renal insufficiency, severe anemia) and concurrent use of aspirin[1,6-8]. These patients are usually old in age and the majority has coexisting diseases, which are known to increase the morbidity and mortality of AUGIB[9,10].

We reviewed all cases of AUGIB, occurring in patients on oral anticoagulant therapy. The purpose of this study was to describe the causes and clinical outcome of these patients as well as the efficacy of diagnostic and therapeutic endoscopy. Moreover, endoscopic findings, emergency surgical hemostasis and mortality were compared with those of patients with AUGIB not taking anticoagulants.

MATERIALS AND METHODS

Study design

From January 1999 to October 2003, patients admitted to

two university hospitals due to AUGIB and those with gastrointestinal bleeding on anticoagulant therapy were retrospectively included. AUGIB presented as hematemesis and/or melena, or other clinical or laboratory evidence of acute blood loss from the upper gastrointestinal tract. All patients were included irrespectively of the international normalized ratio (INR) and no patient was excluded because of age or comorbid diseases.

The causes and clinical outcome (blood transfusions, hospitalization days, emergency surgery and in-hospital death) of these patients were compared with those of 604 patients hospitalized during 2000-2001 due to AUGIB who were not taking warfarin.

Oral coagulant therapy was stopped and fresh frozen plasma was given to patients with prolonged INR. An emergency endoscopy, according to our current practice, was performed during the first 24 h after partial correction of the INR with fresh frozen plasma. In patients with peptic ulcer, a detailed visual assessment of the ulcer crater was made to document the presence of acute bleeding (spurting or oozing) or stigmata of recent hemorrhage (non-bleeding visible vessels, adherent clot or spots). In all patients with peptic ulcer bleeding, having active spurting or oozing bleeding or a non-bleeding visible vessel during emergency endoscopy, an endoscopic injection hemostasis with adrenaline 1:10 000 diluted in 0.9% saline was performed. About 10 mL was routinely injected and up to 20 mL in difficult cases. Blood pressure and pulse rate were checked before endoscopy and after injection therapy. In patients with negative upper gastrointestinal endoscopy, a subsequent colonoscopy was performed to exclude lower gastrointestinal bleeding lesions.

Patients at low risk of thromboembolism (atrial fibrillation, remote history of deep venous thrombosis) were taken off anti-coagulants for a short period, and then in accordance to the endoscopic findings, warfarin was started again after a few days. In other patients heparin was started when risk of rebleeding was low according to the endoscopic findings and heparin therapy was switched to oral anticoagulant therapy after a few days.

All patients were routinely observed by the same team of physicians, gastroenterologists and surgeons. The age, sex, previous consumption of non-steroidal anti-inflammatory drugs (NSAIDs), Hb at admission, cause of bleeding, presence of bleeding stigmata, re-bleeding rate, emergency surgical hemostasis, blood transfusions, hospitalization days and mortality of the patients were registered in standardized database categories.

All patients with peptic ulcer, erosive lesions and esophagitis were treated with proton pump inhibitors intravenously. The criteria for emergency surgical hemostasis in non-variceal AUGIB were continuing bleeding despite adequate transfusion of more than 5 units in 24 h or 12 units in 48 h and rebleeding in hospital with hemodynamic evidence of shock (systolic pressure <100 mmHg, pulse rate >100/min).

Statistical analysis

Continuous variables were presented as mean±SD. Differences between groups were tested for significance by using the Student's t test or χ^2 test with the Yates continuity correction when appropriate. A P value less than 0.05 was considered statistically significant. All analyses were conducted by using statistical software (SPSS, version 10.0).

RESULTS

Characteristics of the patients

Between January 1999 to October 2003, 111 patients with AUGIB on warfarin therapy were hospitalized (69 men, 42 women) with a mean age of 67.7±11.3 years. All patients but two underwent endoscopy within 24 h of admission. Thirty-five patients (31.5%) received NSAIDs in the week preceding the onset of bleeding (Table 1).

Presenting features were: melena in 87 patients (78.4%), hematemesis and melena in 17 (15.3%), hematemesis in 1 (0.9%), hemochesia in 3 (2.7%) and coffee ground vomiting in 3 (2.7%). A mechanical heart valve in 43 (38.7%), atrial fibrillation in 38 (34.2%), cerebrovascular accidents in 15 (13.5%) and venous thrombosis in 6 (5.4%) were the most common indications for warfarin therapy.

Table 1 Clinical characteristics and outcome in patients with AUGIB while on oral anticoagulant therapy

	Patients taking anticoagulants (n = 111)		Patients not taking anticoagulant (n = 604)	
	n	(%)	n	(%)
Age, in year (±SD)[1]	67.7 (11.3)		62.9 (17.5)	
Male/female	69/42		490/146	
NSAIDs use	35	31.5	404	63.5
Coexisting illnesses (overall)	111	100	368	57.8
Blood transfusions	2.1	2.3	1.6	1.6
Hospitalization days	7.7	3.3	5.9	4.1
Emergency surgery (overall)	6/111	5.4	23/604	3.8
Total mortality (overall)	4/111	3.6	20/604	3.3

[1]P = 0.001, [2]P = 0.006.

Causes of bleeding

The most common cause of AUGIB in patients receiving anti-coagulants was peptic ulcer in 50 patients (45%) compared to 359/604 (59%) patients not receiving warfarin (P<0.0001). Erosive lesions of stomach or duodenum in 14 patients (12.6%) and benign or malignant tumors in 8 patients (7.2 %) were the next most common causes. No identifiable source of bleeding could be found in 33 patients (29.7%) compared to 31/604 (5.1%) patients not receiving anti-coagulants (Table 2). Concurrent use of NSAIDs was related to endoscopic lesions. The majority of patients with concurrent use of NSAIDs (26/35, 74.3%) had a peptic ulcer as a cause of bleeding, while 31/76 (40.8%) patients not taking NSAIDs had a negative upper gastrointestinal endoscopy and subsequent colonoscopy (Table 3).

Clinical outcome

Twenty-three patients with active bleeding or non-bleeding visible vessels underwent injection hemostasis. The initial endoscopic hemostasis succeeded in all patients with active

Table 2 Causes of AUGIB

	Patients taking anticoagulants (n = 111)		Patients not taking anticoagulants (n = 604)	
	n	(%)	n	(%)
Peptic ulcer	51	45	359	59.4
Gastric/duodenal erosions	12	10.8	43	7.1
Varices			84	13.9
Benign and malignant tumors	8	7.2	17	2.8
Mallory-Weiss tears	1	0.9	30	5.0
Vascular lesions, Dieulafoy's lesions	4	3.6	6	0.9
Other diagnoses	1	0.9	17	2.8
Uncooperative patient	2	0.9	17	2.8
No cause of bleeding (No identifiable source)	33	29.7	31	5.1

Table 3 Causes of bleeding in relation to the concurrent use of NSAIDs

	Previous NSAID use (n = 35)		No NSAID use (n = 76)	
	n	%	n	%
Peptic ulcer	26	74.3	25	32.9
Gastric/duodenal erosions	3	8.6	9	11.8
Benign and malignant tumors	2	5.7	6	7.9
Vascular lesions, Dieulafoy's lesion	2	5.7	2	2.6
Mallory-Weiss tears, esophagitis	1	2.9		
Uncooperative patient			2	1.3
No cause of bleeding (no identifiable source)	1	5.7	32	40.8

bleeding except one who had massive bleeding. A second hemostasis after rebleeding was performed in 7 patients with adrenaline injection either in 3 patients alone or in combination with mechanical clips in 4 patients. Permanent hemostasis succeeded in three patients. There was no remarkable change in blood pressure or pulse rate in patients who underwent injection hemostasis and no patient had cardiac arrhythmias or complications of uncontrollable bleeding due to hemostasis.

Four patients with peptic ulcer and 2 with tumor (5.4%) were operated for continuing or recurrent hemorrhage compared to 23/604 (3.8%) patients not receiving anticoagulants. Four patients died, the overall mortality was 3.6% in patients with AUGIB due to anti-coagulants. This was not different from that in 20/604 (3.3%) patients not receiving anticoagulant therapy (Table 1).

The patients with no identifiable cause of bleeding or minimal lesions (gastroduodenitis) had a more favorable outcome compared to the patients at high risk of rebleeding lesions (Table 4). These patients needed a less amount of blood transfusion 1.3±1.8 and 3.0±2.5 (P = 0.003). Rebleeding rates and need for emergency surgery were rare (1/45 and 0/45, and 11/65 and 6/65, respectively, P<0.05) in comparison to the patients with high risk of rebleeding lesions (Table 4).

Table 4 Clinical outcome of patients in relation to the endoscopic findings

	Negative endoscopy or gastroduodenitis (n = 45) n (%)	Other endoscopic lesions (n = 65) n (%)	P
Transfusions (SD)	1.3 (1.8)	3.0 (2.5)	0.004
Hospitalization days (SD)	7.5 (2.1)	8.2 (2.6)	NS
Rebleeding	1	10	0.038
Emergency surgical hemostasis	0	6	0.049
Mortality	1	3	NS

DISCUSSION

The gastrointestinal tract is the most common site of significant bleeding in patients receiving long-term oral anticoagulant therapy[11]. Bleeding can be caused by many different lesions. The most common cause is peptic ulcer (duodenal or gastric) although less frequent in patients not taking anti-coagulant drugs (45% *vs* 59.4%, P<0.0001). Of those patients with concurrent use of NSAIDs, the majority had peptic ulcer bleeding (74.3%). NSAIDs have ulcerogenic activity and also inhibit platelet cyclooxygenase resulting in suppression of thromboxane A2-dependent platelet aggregation. Although many drugs are known to interact with warfarin, there have been no conclusive data to indicate an increased risk of bleeding except for NSAIDs especially aspirin during warfarin therapy[1,7].

Early endoscopy in patients on warfarin therapy is mandatory, as it can reveal lesions requiring endoscopic hemostasis. In up to two-thirds of patients, endoscopy could lead to the diagnosis of previously unrecognized lesions such us peptic ulcer, polyps, arteriovenous malformation or tumors. On the other hand, a great number of patients had no lesion on upper and complementary lower gastrointestinal endoscopy (29.7%). However, this increased to 40.8% in patients not taking NSAIDs higher than that in the unselected patients with AUGIB (5.1%). In our subgroup of patients with negative endoscopy or lesions at trivial risk of rebleeding (e.g., gastroduodenitis), only one had re-bleeding and none required emergency surgical hemostasis. In these patients, due to the favorable outcome, we could avoid the introduction of heparin therapy, and continue oral anti-coagulant therapy after correcting INR in therapeutic range with fresh frozen plasma. This could reduce the hospitalization time. The achievement of a therapeutic INR needed approximately 4 d, resulting in several hospital days waiting a targeted coagulation status[12-15].

No patient in our group had any procedure-related complications or uncontrollable bleeding due to diagnostic and/or therapeutic endoscopy, although in the majority of patients anti-coagulation was not completely reversed. Emergency surgical hemostasis was required in 5.4% of patients, which was not different from that in patients not taking anti-coagulants (3.8%). Endoscopic hemostasis injection with adrenaline solution could be safely performed in anti-coagulated patients after their resuscitation. The efficacy of hemostasis was good, even if anti-coagulation was incompletely reversed. Although bleeding was greater in anti-coagulated patients from the injection sites, no patient suffered from uncontrollable bleeding after endoscopic injection therapy. Successful endoscopic diagnosis and therapy at rates comparable with those achieved in non-

anti-coagulated patients were also reported by Choudari *et al*[16] in a group of bleeding anti-coagulated patients, by applying injection therapy or a heater probe. Among the patients suffering from peptic ulcer bleeding who received endoscopic hemostasis after partial correction of the INR to 1.5 to 2.5, the incidence of uncontrollable bleeding and emergency surgery were similar to those of patients not taking warfarin.

The overall mortality rate was low and was not different from that of patients not receiving anti-coagulant therapy. It is known that the majority of deaths in patients with acute gastrointestinal bleeding were due to untreatable diseases, especially, end stage malignancies, cirrhosis and irreversible cardiac diseases. Although the majority of anti-coagulated patients had concurrent diseases, the presence of end stage malignancies, cirrhosis or other irreversible diseases would discourage doctors to prescribe oral anti-coagulant drugs. Moreover, symptomatic thromboembolism after transient withdrawal of long-term anti-coagulant therapy was uncommon and death was rare. The risk of a major thromboembolic event in the absence of antithrombotic therapy in patients with mechanical heart valves was 4/100 patient-years[17]. The risk of thromboembolic events during the interruption of warfarin treatment was even lower in patients at low risk of embolic events (deep venous thrombosis, atrial fibrillation not associated with valvular disease, bioprosthetic valves and mechanical valves in the aortic position) and was estimated to be 1-2 per 1 000 patients[18].

In conclusion, patients with AUGIB while on long-term anti-coagulant therapy had a clinical outcome, which was not different from that of patients not taking anti-coagulants. Early endoscopy is important because endoscopic findings have a prognostic value regarding the final outcome and may direct the management of these patients. Endoscopic hemostasis is the treatment of choice and can be safely applied.

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Assistant Editor Guo SY **Edited by** Wang XL and Gabbe M