



REBLEEDING RATE AND THE NEED OF BLOOD TRANSFUSION ARE HIGHER IN PATIENTS WITH UPPER GASTROINTESTINAL TUMOR BLEEDING THAN IN PATIENTS WITH PEPTIC ULCER BLEEDING

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SUMMARY – The aim of our 5-year study (from January 2008 to December 2012) was to compare the incidence of peptic ulcer bleeding (PUB) to bleeding from tumors of the upper gastrointestinal tract. The percentage of re-bleeding within the first 30 days of hospital admission, as well as the need of blood transfusions, are also reported. Statistical data were collected on 2198 patients who were treated in our emergency department due to upper gastrointestinal bleeding (UGIB) in the form of melena or hematemesis. Upper endoscopy performed within 24 hours of arrival revealed that 796 (36.2%) patients had a peptic ulcer, while the diagnosis of upper gastrointestinal tumor bleeding (UGITB) was verified in 61 (2.8%) patients. During the five-year study, it was shown that men had a higher prevalence of bleeding compared to women (PUB 62.3% vs. UGITB 52.5%). The cumulative incidence of UGIB was 126/100,000. It was found that the largest number of bleeding tumors were located in the stomach (n=58, 95%), with most of them being malignant tumors (n=55, 90%), specifically adenocarcinomas (n=48, 87.3%). The percentage of re-bleeding was lower (9.7% vs. 19.7%, $p < 0.01$) and blood transfusions were less often required (49.5% vs. 75.4%, $p < 0.01$) in PUB. Due to uncontrolled bleeding (5.9% vs. 3.3%, $p < 0.01$), surgical treatment was more often required in cases of PUB, as well as larger volumes of blood transfusion. Patients with PUB had a lower rate of re-bleeding, required surgical intervention more often, and required red blood cell transfusions less frequently.

Key words: *Upper gastrointestinal bleeding; Peptic ulcer bleeding; Upper gastrointestinal tumor bleeding*

Introduction

Upper gastrointestinal bleeding (UGIB) is a common medical emergency that accounts for 5% of emergency department manifestations *per year* and 2% to

3% of hospital admissions in developed countries¹. The most common cause of acute UGIB is non-variceal, where peptic ulcer bleeding (PUB) accounts for 28% to 59% of cases and upper gastrointestinal tumor bleeding (UGITB) for approximately 5% of all non-variceal bleeding²⁻⁵. GI bleeding was the initial presenting symptom of GI tumors in about 20% of patients⁶. The risk of death was considerably greater in patients with neoplasia of upper gastrointestinal tract (9.8%) compared to benign conditions (3.9% in

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patients with ulcer bleeding and 4.1% in those with non-ulcer bleeding). Among patients with upper GI malignant neoplasia, the mortality rate was significantly higher in patients with esophageal compared to cardiac or gastric neoplasia. The risk of death is greater in patients with progressed neoplasia and in those with the American Society of Anesthesiologists (ASA) score 3 or 4. In-hospital bleeding has been correlated with a considerably higher risk of mortality⁷.

Endoscopy has become the standard of care in the diagnosis and treatment of UGIB. Most national and international guidelines propose performing upper endoscopy within 24 hours of presentation in patients with UGIB^{8,9}. Despite major advances in diagnostic and therapeutic methods, PUB remains a significant problem and a serious factor of morbidity and mortality. Re-bleeding after initial hemostasis occurs in 10% to 30% of patients with PUB and in 5.2% of patients with UGITB^{7,8}.

The aim of this prospective study was to compare the epidemiological, clinical and endoscopic aspects of patients with PUB and patients with UGITB, and focus on the treatment and prognosis of PUB and UGITB in a tertiary care center.

Patients and Methods

Data were collected on consecutive patients over a 5-year period, from January 2008 to December 2012, that were referred to the Internal Medicine Emergency Room (ER) at the Sestre milosrdnice University Hospital Center in Zagreb, Croatia, due to UGIB. This was a prospective study that included all medical records of adult patients following endoscopic findings of UGIB.

On admission, history, clinical and laboratory data, endoscopic findings, treatment and clinical follow-up were documented. In all patients, upper gastrointestinal endoscopy was performed within 24 hours of admission. Inclusion criterion was peptic ulcer bleeding or UGITB found during emergency endoscopy, without any other possible causes of bleeding. All patients were treated with high-dose acid suppression therapy (pantoprazole or esomeprazole 80 mg as intravenous bolus, followed by 40 mg intravenously 2 times daily or 200 mg daily in the form of continuous infusion for at least 48 hours, followed by 40 mg daily by mouth).

The institution's Ethics Committee approved the study. Data were entered prospectively into a database, with patient details stored in a depersonalized manner to protect patient confidentiality.

Data collection

The following data were collected for each patient: demographic data, signs and characteristics of the bleeding episode, symptoms and history of liver disease, coexisting illness, drug use, laboratory results, endoscopic intervention, diagnosis including cause of bleeding, fresh blood/clots or stigmata of recent hemorrhage, medical treatment, rebleeding incidence, length of hospital stay, and cause of death.

Grading of overall health and comorbidity was performed according to the ASA classification (grade 1, normal healthy patients; grade 2, mild systemic illness; grade 3, severe, but incapacitating systemic illness, and grade 4, life-threatening illness).

Shock was specified as syncope or signs of shock on physical examination, with systolic blood pressure <100 mm Hg and pulse rate >100 beats/min.

Rebleeding was defined as one or more signs of ongoing bleeding, including fresh hematemesis or melena, hematochezia, aspiration of fresh blood *via* nasogastric tube, instability of vital signs, and reduction of hemoglobin levels by 2 g/dL or more over a 24-hour period after primary bleeding was stopped. Commonly used hemostatic procedures were epinephrine injections (1:10000 solution of epinephrine) and/or mechanical hemostasis with stainless steel hemoclips (Olympus, Japan) and/or thermocoagulation with a heater probe (Olympus, 7F, 20-30 joules).

Two biopsy samples were collected from the gastric antrum and body in all patients and the presence of *Helicobacter pylori* (*H. pylori*) infection was evaluated by histopathologic examination of the specimens using hematoxylin-eosin stain. In all patients with PUB and UGITB in whom recurrent bleeding was not observed, control endoscopy was conducted four to five days after initial hemostasis and biopsy specimens were obtained from the margins and base of gastric ulcers to exclude malignancy. In patients with UGITB, tumor biopsy was performed. Control endoscopy with histology was scheduled in all patients with gastric ulcers.

Documented clinical outcomes were 30-day rebleeding, 30-day mortality, surgical referral, and blood transfusion requirement.

Statistical analysis

Normality of data distribution was assessed with Kolmogorov-Smirnov test and appropriate non-parametric tests were utilized in following analyses. Cat-

egorical data were shown as absolute frequencies and corresponding percentages, and quantitative data as medians and corresponding interquartile ranges. Differences in categorical variables were analyzed by using χ^2 -test or Fisher exact test for counts below 5. Mann-Whitney U test was used to analyze differences in quantitative variables. All p values below 0.05 were considered significant. Data analysis software system IBM SPSS Statistics, version 21.0 (www.spss.com) was used in all statistical procedures.

Results

From January 2008 to December 2012, 2198 patients with UGIB were evaluated. There were 796 (36.2%) patients with PUB and 61 (2.8%) patients with UGITB. Of a total of 344 patients diagnosed with upper GI malignancy within 5 years, 17.7% had UGITB.

There was a statistically significant difference in median age of patients with UGITB and those with PUB (76 *vs.* 67 years, $p < 0.01$) (Table 1). Both PUB and UGITB occurred more often in men than in women, and difference in the incidence of UGIB was higher between men and women in PUB than in

UGITB (62.3/37.7% *vs.* 52.5/47.5%, $p = 0.12$). Posthemorrhagic anemia was more pronounced in patients with UGITB than in those with PUB (median hemoglobin level 93 *vs.* 81 g/L, $p < 0.01$). As compared with PUB patients, those with UGITB had *H. pylori* infection more often (75.4% *vs.* 41.4%, $p < 0.01$) and significantly greater comorbidity (ASA III-IV 95.1% *vs.* 57.9%, $p < 0.01$). Acetylsalicylic acid and non-steroidal anti-inflammatory drugs (NSAIDs) were more commonly used by patients with PUB, while those with UGITB more commonly used oral anticoagulant therapy (Table 1). Initial hemostasis was successful in over 50% of patients with either PUB or UGITB. Epinephrine injection was the most commonly used hemostatic procedure in UGITB, whereas in PUB mechanical hemostasis with stainless steel hemoclips or a combination of mechanical hemostasis and epinephrine injection was used in about 50% of the patients. Thermocoagulation was used in less than 6% of patients with either PUB or UGITB (Table 2).

Rebleeding occurred more often in patients with UGITB compared to those with PUB (19.7% *vs.* 9.7%, $p < 0.01$). There was no significant difference in 30-day mortality between the two groups (PUB 5.2% *vs.* UGITB 7.2%). Blood transfusion was more fre-

Table 1. Clinical characteristics of the patients at study entry, n (%)

	Peptic ulcer bleeding 796	Upper gastrointestinal tumor bleeding 61	p
Age			
Median (yrs), (range)	67 (20-100)	76 (58-93)	<0.01
Gender			
Male (n%)/female (n%)	496 (62.3)/300 (37.7)	32 (52.5)/29 (47.5)	0.12
Hb level median (range) (g/L)	93 (26-166)	81 (44-147)	<0.01
Shock	67 (8.4)	4 (6.7)	0.61
<i>Helicobacter pylori</i>	220/531(41.4)	46/61 (75.4)	<0.01
Comorbidity (ASA class)			
ASA I	110 (13.8)	0 (0.0)	
ASA II	225 (28.3)	3 (4.9)	<0.01
ASA III-IV	461 (57.9)	58 (95.1)	
Drugs			
NSAIDs	225 (28.3)	9 (14.8)	0.02
Aspirin	162 (20.4)	3 (4.9)	<0.01
Antiplatelet drugs	21 (2.6)	0 (0.0)	0.19
Anticoagulants	46 (5.8)	8 (13.1)	0.02

ASA = American Society of Anesthesiology; NSAIDs = non-steroidal anti-inflammatory drugs

Table 2. Endoscopic therapy and clinical outcomes, n (%)

	Peptic ulcer bleeding 796	Upper gastrointestinal tumor bleeding 61	p
Treatment			
Initial hemostasis	426 (53.5)	35 (57.4)	0.56
Types of initial hemostasis			
Epinephrine	177 (39.9)	22 (62.9)	0.02
Hemoclips	81 (19.7)	6 (17.1)	0.78
Epinephrine + hemoclips	144 (34.6)	5 (14.3)	0.01
Heat probe	17 (2.1)	2 (5.7)	0.62
Outcome			
Rebleeding	77 (9.7)	12 (19.7)	0.01
30-day mortality	41 (5.2)	5 (7.2)	0.30
Blood transfusion	94 (49.5)	46 (75.4)	<0.01
Number of units	3 (1-16)	2 (2-23)	<0.01
Red blood cells			
Emergency surgery	47 (5.9)	2 (3.3)	<0.01
Hospital stay (days) (median, range)	6 (0-45)	10 (1-28)	<0.01

quently required in patients with UGITB compared to those with PUB (75.4% *vs.* 49.5%, $p < 0.01$), but those with PUB required larger quantities of red blood cell units (3 *vs.* 2, $p < 0.01$). Patients with PUB more often required surgical intervention as compared to those with UGITB (5.9% *vs.* 3.3%, $p < 0.01$). Median length of hospital stay was longer in patients with UGITB (10 days *vs.* 6 days, $p < 0.01$) (Table 2).

Discussion

Patients with UGIB represent a significant public health issue. The mortality rate in patients with non-variceal UGIB was 5%-8% in the past decade. In recently published guidelines, an optimal management algorithm for patients with non-variceal UGIB has been proposed (early endoscopy, aggressive endoscopic and pharmacological treatment, assessment of patient overall health status). PUB accounts for about 40% of all UGIB cases, while 2%-4% of patients have UGITB^{7,10,11}. In our study, about 18% of patients with upper GI tract tumors were bleeding. The results are similar to those reported by Marmo *et al.*⁷ (about 20% of patients had UGITB) and Pittayanon *et al.*¹². Tumors of the upper GI tract bleed from erosions on the

tumor surface or due to tumor mass necrosis while acidic gastric environment facilitates clot degradation and damages mucous and epithelial barrier¹². UGIB occurs often in men, and median age is significantly higher in patients with UGITB as compared to those with PUB. Moreover, *H. pylori* infection is more common in patients with UGITB than in those with PUB. A study by Moss found that *H. pylori* infection was associated with 90% non-cardiac gastric adenocarcinoma arising from chronic atrophic gastritis and metaplasia¹³. In one Dutch prospective study, *H. pylori* infection was verified in 43% of patients with PUB, out of 65% of patients tested for *H. pylori*². Therefore, it is important to eradicate *H. pylori* regardless of the possible drug related adverse effects¹⁴. Patients with PUB were more often treated with acetylsalicylic acid and NSAIDs, while those with UGITB were more often on oral anticoagulant therapy. Based on literature data, patients with UGIB were taking NSAIDs in 29%-60% of all cases^{15,16}. Initial hemostasis was achieved in over 50% of patients with UGITB, most commonly using epinephrine injection, while in patients with PUB either hemoclip alone or in combination with epinephrine injection was used. Chen *et al.* and Arena *et al.* published case series of upper gastrointestinal bleeding

from different types of tumors which was successfully controlled by Hemospray. Based on experience in a very limited number of patients, the authors believe that Hemospray may be beneficial for both immediate hemostasis and as a bridging treatment for adjuvant therapy^{17,18}. Asakura *et al.* conclude that radiotherapy with 30 Gy in 10 fractions is an appropriate treatment for bleeding from advanced gastric cancer, especially in patients with poor prognosis¹⁹. Lee *et al.* demonstrated that in patients with bleeding from unresectable gastric cancer, transcatheter arterial embolization was safe and effective to achieve immediate hemostasis for active bleeding. Recurrent bleeding within 1 month occurred in 8% of patients²⁰.

Rebleeding rates and need of surgical referral were more common in patients with UGITB. In a study by Marmo *et al.*, there was no statistically significant difference in rebleeding rates between patients with UGITB and PUB, but the need of surgical intervention was more common in patients with UGITB⁷. Blood transfusion was needed more often in patients with UGITB, but those with PUB received larger red blood cell volumes. Median red blood cell units in patients with UGITB were 2 (2-23). In a study by Pittayanon *et al.*, a much larger mean red blood cell unit quantity was used (4.9-10.5±3.8-16) in patients with UGITB¹².

In our study, there was no significant distinction in 30-day mortality rates between the two groups, but Marmo *et al.* found the 30-day mortality to be significantly higher in patients with UGITB compared to those with benign conditions, especially in patients with advanced malignant disease and ASA score 3 or 4^{7,11}. Ljubicic *et al.* demonstrated that the Mallory-Weiss syndrome as the cause of upper GI bleeding carried the same risk of unwanted outcome and death as peptic ulcer bleeding particularly among elderly patients with moderate to severe overall comorbidities²¹. The length of hospital stay was longer in patients with UGITB than in those with PUB.

To our knowledge, this is the first study to compare rebleeding rates, need of blood transfusion and need of surgical intervention in patients with UGITB and PUB. Patients with UGITB are older and they have higher rebleeding rates, require surgical intervention less often, and are more often treated with blood transfusion than patients with PUB.

When considering possible limitations of our study, there is always a certain level of variation in endoscopic treatment approach by various medical teams, 30-

day period for patient follow-up, and the fact that the research took place in a tertiary care center.

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Sažetak

STOPA PONOVRNOG KRVARENJA I POTREBA ZA TRANSFUZIJOM KRVI VIŠE SU KOD BOLESNIKA S KRVARENJEM IZ GORNJEG DIJELA PROBAVNOG TRAKTA NEGO KOD BOLESNIKA S KRVARENJEM IZ PEPTIČNOG ČIRA

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Cilj ovog našeg petogodišnjeg istraživanja (od siječnja 2008. do prosinca 2012.) bio je usporediti incidenciju krvarenja kod peptičnog čira (*peptic ulcer bleeding*, PUB) i krvarećih tumora gornjeg probavnog trakta (*upper gastrointestinal bleeding*, UGIB). Prikazujemo koliki je bio postotak ponovnog krvarenja unutar 30 dana od prijma u bolnicu te kolika je bila potreba za transfuzijskom nadoknadom krvnih pripravaka. Kako bismo prikupili (statističke) podatke istraživanjem smo obuhvatili 2198 bolesnika koji su obrađeni putem naše Hitne službe kao UGIB u vidu melene ili hematemeze. Provedenom gornjom endoskopijom unutar 24 sata od dolaska utvrđeno je da se u 796 (36,2%) bolesnika radilo o peptičnom ulkusu, dok je dijagnoza krvarećeg tumora gornjeg probavnog trakta (UGITB) verificirana u 61 (2,8%) bolesnika. U istraživanju se pokazalo da su muškarci imali veću učestalost krvarenja (PUB 62,3% prema UGITB 52,5%). Kumulativna incidencija UGIB-a bila je 126/100.000. Ustanovljeno je da najveći broj krvarećih tumora anatomski obuhvaća želudac (n=58, 95%), u većini slučajeva se radilo o malignim tumorima (n=55, 90%), odnosno adenokarcinomima (n=48, 87,3%). Postotak ponovnog krvarenja bio je manji kod PUB-a (9,7% prema 19,7%, p<0,01) i rjeđe su zahtijevali transfuziju krvnih pripravaka (49,5% prema 75,4%, p<0,01). Usljed nekontroliranog krvarenja češće (5,9% prema 3,3%, p<0,01) je bilo potrebno kirurško liječenje kod PUB-a, kao i veći volumen krvnih pripravaka. Bolesnici s PUB-om imaju manju stopu ponovnog krvarenja, češće zahtijevaju kiruršku intervenciju te su rjeđe zahtijevali transfuzije koncentrata eritrocita.

Ključne riječi: *Gornje gastrointestinalno krvarenje; Krvarenje iz peptičnog čira; Krvarenje iz tumora gornjeg gastrointestinalnog trakta*