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Original Article

Risk factors for upper gastrointestinal bleeding requiring hospitalization

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Abstract: Objective: To analyze the causes of upper gastrointestinal bleeding (UGIB) in northeast China. Methods: In-patients with hematemesis, melena, and/or hematochezia who underwent upper endoscopy with an identified source at The First Hospital of Jilin University were enrolled in this study. The cause of bleeding, patient age, clinical features and drugs were retrospectively evaluated. Results: A total of 1,740 patients were included in this study. Among these patients, mean age was 57 ± 13 years and 1340 (77%) were male. Bleeding from varices was more common than from ulcers among patients with hematemesis with/without melena (47% vs. 30%, P<0.01). Varices were the most common cause of gastrointestinal bleeding in 672 (39%) patients, followed by peptic ulcer disease in 600 (34%) patients. One hundred twenty (7%) patients had acute UGIB associated with drugs, in which non-steroidal anti-inflammatory drugs (NSAIDs) were identified as the main drugs associated with UGIB. Among these 120 patients, 60 (50%) patients used aspirin, 9 (8%) patients used aspirin combined with clopidogrel, 30 (25%) patients used Chinese herbal medicines, 18 (15%) used aminopyrine-phenacetin, and 12 (10%) patients used corticosteroids. Conclusion: Varices was the most common cause of UGIB, followed closely by ulcers. The proportion of patients who had cancer was higher in the elderly group. The incidence of varices was higher in the middle-aged group. In addition, 7% of patients who had UGIB took NSAIDs (aspirin), clopidogrel, or Chinese herbal medicines.

Keywords: Upper gastrointestinal bleeding, in-patients, varices, ulcers

Introduction

Overt upper gastrointestinal bleeding (UGIB) is defined as bleeding proximal to the ligament of Treitz with symptoms of hematemesis, melena, or occasionally hematochezia. UGIB is a common medical condition that requires frequent hospitalization and significant health care expenditure in the United States [1].

With the development of endoscopic techniques, determining the etiology, diagnosis, and instituting appropriate treatments for UGIB has made considerable progress. Commonly reported causes of UGIB include ulcer disease, varices, Mallory-Weiss tears, erosive esophagitis, and erosive gastropathy. The relative proportions of these etiologies vary among reports and likely depend on the type of health care setting in which the patients are maintained [2-4]. After the discovery of *Helicobacter pylori*, a major cause of peptic ulcers, *H. pylori* eradication strategies have decreased the association of the incidence of *H. pylori* in the pathogenesis of bleeding peptic ulcers [5]. However, due to the aging population of most industrialized countries, diseases that affect the elderly such as cardiovascular and cerebrovascular diseases have also increased. This is mostly due to the extensive use of non-steroidal anti-inflammatory drugs (NSAIDs) and other anticoagulants [6]. With the changing demographics, etiologies of UGIB may also change. The current study aims to determine current causes of UGIB in a typical Chinese population.

Patients and methods

Patients

Patients hospitalized for overt UGIB at The First Hospital of Jilin University from January to December 2014 were retrospectively included in this study. The institutional review board

Table 1. Study population characteristics with upper gastrointestinal bleeding hospital admission in First Hospital of Jilin University, 2014 (*N*=1,740)

Characteristics	*n* (%)
Mean age (SD)	56.5 ± 12.8
Male	1,332 (77)
Bad habits	
Smoking alone	186 (11)
Alcohol alone	186 (11)
Smoking and Alcohol	408 (23)
Primary presenting symptoms	
Hematemesis	1,128 (65)
Melena alone	534 (31)
Hematochezia alone	78 (4)

Note: SD, standard deviation.

Table 2. Sources of upper gastrointestinal bleeding hospital admission in First Hospital of Jilin University, 2014 *N*=1,740 (%)

Peptic ulcer disease	600 (34)
Gastric ulcer	264 (15)
Duodenal ulcer	282 (16)
Duodenal and gastric ulcer	54 (3)
Varices	672 (39)
Tumor	248 (14)
Erosive/hemorrhagic gastropathy	78 (4)
Mallory-Weiss tear	44 (3)
Other	98 (6)

approved the study and waived informed consent.

Methods

Inclusion criteria were as follows [7]: (1) patients aged 18 years and older; (2) patients who underwent upper endoscopy for symptoms of overt bleeding (hematemesis, melena, and/or hematochezia), in which the source of bleeding was identified in the esophagus, stomach, or duodenum; (3) patients with multiple sources of UGIB, in which the principal cause was determined based on the review of endoscopic findings and clinical presentations. For patients with multiple episodes of gastrointestinal bleeding, the first bleeding episode was considered the initial symptom.

Exclusion criteria were as follows: patient with a lower gastrointestinal source.

Patients were divided into three groups: the young group (18-39 years old), the middle-aged group (40-59 years old), and the elderly group (aged ≥60 years old). Differences in the source of UGIB among these three groups were determined, and statistical significance was determined among the common causes of UGIB.

Data collection

All data were extracted from medical records including patient demographics (age, gender and insurance status), medication history (concomitant medication use, timing, duration and dosage) and outcome (improvement, surgical operation, or death). Endoscopy reports were reviewed in detail. Bleeding features and sources of UGIB were identified.

Statistical analysis

Data were analyzed by SPSS version 21.0. Descriptive statistics were used to measure each variable. Descriptive statistics are reported as mean ± SD for continuous variables with normal distribution. X^2-test was used for numeration of data. *P*-values <0.05 were considered statistically significant.

Results

Patient demographics and clinical features

A total of 1,740 patients hospitalized with overt gastrointestinal bleeding were enrolled in this study. The source of bleeding was documented by upper endoscopy in all patients. Mean age of patients was 57 ± 13 years, and 77% of patients were male (**Table 1**). Among the 1,740 patients, 1,128 (65%) patients presented with hematemesis with or without melena, 534 (31%) patients presented with melena alone, and 78 (4%) patients presented with hematochezia alone.

The frequency of UGIB sources

The frequency of UGIB sources are presented in **Table 2**. Varices were the most common cause in 672 (39%) patients, followed by peptic ulcer disease in 600 (34%) patients and others causes (reflux esophagitis, gastritis, duodenitis, *etc.*) in 98 (6%) patients (**Table 2**). In the young group, the main etiology was peptic ulcer; while in the middle-aged group, varices were the main etiology. In the elderly group,

Table 3. Sources of upper gastrointestinal bleeding hospital admission by age group in First Hospital of Jilin University, 2014

	N (%)					
	Young group (18-39 years)	Middle-aged group (40-59 years)	Elderly group (≥60 years)	*Total*	X^2	*P*
Peptic ulcer disease	90 (44.6)	270 (31.9)	240 (34.7)	600 (34.5)	11.551	0.003
Gastric ulcer	12 (5.9)	126 (14.9)	126 (18.2)	264 (15.2)	18.382	<0.001
Duodenal ulcer	60 (29.7)	132 (15.6)	90 (13.0)	282 (16.2)	32.542	<0.001
Duodenal and gastric ulcer	18 (8.9)	12 (1.4)	24 (3.5)	54 (3.1)	30.949	<0.001
Varices	48 (23.8)	390 (46.1)	234 (33.8)	672 (38.6)	45.515	<0.001
Tumor	6 (3.0)	90 (10.6)	152 (22.0)	248 (14.3)	63.764	<0.001
Erosive/hemorrhagic gastropathy	28 (13.9)	42 (5.0)	8 (1.2)	78 (4.5)	59.84	<0.001
Mallory-Weiss tear	18 (8.9)	12 (1.4)	14 (2.0)	44 (2.5)	38.33	<0.001
Other	12 (5.9)	42 (5.0)	44 (6.4)	98 (5.6)	1.432	0.489
Total	202	846	692	1,740		

Table 4. Sources of upper gastrointestinal bleeding hospital admission by symptoms in First Hospital of Jilin University, 2014

	Hematemesis With/ Without Melena (N=1128)	Melena Alone (*N*=534)	Hematochezia Alone (*N*=78)	X^2	*P*
Peptic ulcer disease	336 (30)	240 (45)	24 (31)	37.351	<0.001
Varices	534 (47)	114 (21)	24 (31)	105.414	<0.001
Erosive/hemorrhagic gastropathy	24 (2)	42 (8)	12 (15)	50.53	<0.001
Tumor	138 (12)	72 (13)	6 (8)	2.194	0.337
Mallory-Weiss tear	12 (1)	12 (2)	6 (8)	20.162	<0.001
Others	84 (7)	54 (10)	6 (8)	3.429	0.188

Table 5. Outcomes of upper gastrointestinal bleeding during hospitalization in First Hospital of Jilin University, 2014 (*N*=1,740)

Median hospital days	
Non-variceal	7
Ulcers (*N*=600)	7
No ulcers or varices (*N*=468)	7
Varices (*N*=672)	7
Mortality (*n*, %)	
Young	4
Middle-aged	26
Elderly	80

peptic ulcer and varices were the most common causes. In addition, the proportion of cancer (22%) was higher in the elderly group than in the young and middle-aged groups (*P*<0.01, *P*<0.01, respectively) (**Table 3**).

Sources of UGIB were categorized by symptoms (**Table 4**). Varices were more common than ulcers as a cause among patients with hematemesis with/without melena (47% *vs.* 30%, P<0.01), whereas ulcers were more common than gastroesophageal varices as a source among patients with melena alone (45% *vs.* 21%, P<0.01).

Clinical outcomes

Average length of stay in the hospital was seven days (**Table 5**). In addition, 110 patients died including four patients in the young group, 26 patients in the middle-aged group, and 80 patients in the elderly group. Mortality in the elderly group was significantly higher than in the young and middle-aged groups (*P*<0.01, *P*<0.01, respectively).

Drug-related factors

In this study, 120 (7%) patients had UGIB associated with drugs. NSAIDs were found to be the main drugs causing UGIB. Among these 120

Table 6. Drug-related upper gastrointestinal bleeding with upper gastrointestinal bleeding hospital admission in First Hospital of Jilin University, 2014

Drugs	Youg	Middle-aged	Elderly	Total	X^2	*P*
Chinese herbal medicine	2	18	10	30	4.945	0.079
Corticosteroids	4	4	4	12	22.293	0.001
Aminopyrine-Phenacetin	2	6	10	18	0.691	0.429
Aspirin (clopidogrel)	0	18	42	60	13.095	0.001
Total	8	46	66	120		

patients, 60 (50%) patients used aspirin, 18 patients used aspirin combined with clopidogrel, 30 (25%) patients used Chinese herbal medicines, 18 (15%) patients used aminopyrine-phenacetin, and 12 (10%) patients used corticosteroids (**Table 6**). Drug-related gastrointestinal bleeding in the elderly group was significantly higher than in the middle-aged group ($P<0.05$).

Discussion

This study revealed that the incidence of varices in the middle-aged group was higher than in the young and elderly groups. This is consistent with the fact that esophageal variceal bleeding is mainly caused by post-hepatic cirrhosis in China, and the peak age of onset of cirrhosis is 35-48 years [8]. The influence of factors on alcohol, mental stress, smoking and the development of liver cirrhosis due to hepatitis B result in the earlier appearance of bleeding esophageal varices [9]. Gastric ulcers in elderly patients are associated with the degradation of function of the gastric mucosa, reduced secretion, and loss the nutritional factors of the gastric mucosa [8].

The elderly are often afflicted with a variety of underlying diseases, and many are on the long-term use of NSAIDs. The latter are associated with an increased incidence of gastric ulcer [10]. One study reported that the total fraction of peptic ulcers due to the long-term use of NSAID was approximately 25% [11].

Among NSAIDs, aspirin is commonly used in the therapy of various diseases [12]. NSAIDs are efficacious in the treatment of many diseases due to their potent anti-inflammatory, anti-thrombotic and analgesic actions; and are recommended prophylactically against cardiovascular disorders and prevention against stroke incidence [11, 12]. However, gastrointestinal complications result from the use of NSAIDs, and NSAIDs are among the most common drug side effects in China due to its widespread use. Side effects of these drugs are primarily localized in the stomach, which include bleeding, ulcers and perforations. Previous studies have exhibited that a commonly used NSAID, acetylsalicylic acid (ASA), directly damages the surface of the epithelium and impairs the mucosal defense in the gastric mucosa. This is mainly due to the inhibition of cyclooxygenase (COX) activity, resulting in the reduction of mucosal regeneration due to the inhibition of the production of major gastroprotective prostaglandins E (PGE_2) and prostacyclin (PGI_2); which causes the activation of white blood cells and proinflammatory cytokines, the reduction of gastric microcirculation, an increase in lipid peroxidation, and a stimulation of gastrointestinal motility [12-16].

Therefore, NSAIDs should be used with caution in the elderly, especially those who have gastrointestinal diseases. When absolutely necessary, co-administration of acid suppressing drugs or gastric mucosal protective agents is recommended [10]. Due to gastrointestinal dysfunction, vascular sclerosis and hemorrhage of the upper digestive tract are often associated with more serious consequences in the elderly. In addition, in patients older than 60 years old, the risk of rebleeding has been shown to be double of that of younger patients [17].

The association between corticosteroid use and gastrointestinal adverse effects including bleeding or perforation has been a source of debate since the 1950s [18-20]. Even though many gastroenterologists consider corticosteroids as not having ulcerogenic properties, a recent survey has shown that corticosteroids are still currently considered ulcerogenic by a majority of physicians, and that a majority of practitioners would treat corticosteroid users with ulcer prophylaxis [21]. A study has shown that corticosteroid use was associated with increased risk of gastrointestinal bleeding and perforation. This increased risk is statistically

significant for hospitalized patients only. For patients in ambulatory care, the total occurrence of bleeding or perforation is very low, and the increased risk was not statistically significant [22].

Recently, adverse reactions of traditional Chinese medicines have been reported, especially with regard to liver and kidney damage [23, 24]. However, specific digestive tract, particularly gastric mucosal damage by traditional Chinese medicine, has not been reported. It is possible that gastrointestinal adverse reactions induced by Chinese herbal medicines are often overshadowed by the primary disease, and neglected as a possible cause.

Conclusion

In conclusion, in this study, we found that aspirin, corticosteroids and Chinese herbal medicines are associated with the increased risk of gastrointestinal bleeding. In-hospital mortality from gastrointestinal bleeding due to varices is nearly double of the mortality due to ulcers. However, there was no higher risk of rebleeding that required a repeat esophagogastroduodenoscopy (EGD). This indicates that patients who presented with variceal UGIB remains at risk of death on their index hospitalization due to the decompensation of their underlying illness, even if their bleeding is successfully controlled. There are a number of the limitations of this study. This study is a retrospective study, and the methods of hemostasis, as well as the types and doses of therapy, could not be controlled. In addition, this is a single center study; thus, the results may not necessarily reflect the entire national population. Finally, the lack of exclusion of patients who had had pervious UGIB complicates the conclusions regarding the age of onset of the particular causes of UGIB. Further large, multicenter prospective trials would be needed to confirm these current observations.

Disclosure of conflict of interest

None.

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