ORIGINAL RESEARCH

ANALYSIS OF THE PATIENTS ADMITTED TO MARMARA UNIVERSITY HOSPITAL WITH NON-VARICEAL UPPER GASTROINTESTINAL BLEEDING

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ABSTRACT

Objective: Non-variceal upper gastrointestinal bleeding (NVUGIB) remains an important cause of morbidity and mortality despite the availability of advanced endoscopic techniques for haemostasis. We have described clinical and endoscopic features of the patients with NVUGIB in a teaching hospital.

Method: Two hundred and fifty patients admitted between 1996 and 2001 with acute NVUGIB have been evaluated retrospectively.

Results: Mean age was 59 and 34.4% were women. Ingestion of aspirin/non-steroidal anti-inflammatory drugs, steroid or warfarin during the previous week was reported for 59.6%, 2.8%, 9.6% of the patients, respectively. Previous upper gastrointestinal bleeding was reported for 31.8% of the patients. The leading cause of bleeding was peptic ulcer (49.2%), followed by erosions (19.2%) and stomach tumors (10.8%). Lesions were located in the stomach (40%), duodenum (33.6%), at the gastrojejunostomy line (4.4%) and esophagus (4.4%). H. pyloric region was positive in 79.2% of the 48 patients investigated. Endoscopic treatment was applied to 33 patients. Seven cases (2.8%) including 3 which had failed endoscopic therapy had a surgical intervention. Six patients (2.4%) died.

Conclusion: The main cause of bleeding was peptic ulcer. The majority of patients had either an H. pylori infection or an offending drug use. Since the etiology of bleeding was amenable to treatment, the rate of endoscopic and surgical treatment and mortality were low in our patients.

Keywords: NSAID, aspirin, therapeutic endoscopy, mortality and morbidity

MARMARA ÜNİVERSİTESİ HASTANESİNE VARİS DIŞI ÜST GASTROİNTESTİNAL KANAMA İLE BAŞVURAN HASTALARIN DEĞERLENDİRİLMESİ

ÖZET

Amaç: Endoskopik tedavi çağında, varis dışı üst gastrointestinal kanama hala önemli bir mortalite ve morbidite nedenidir. Bu çalışmanın amacı, bir eğitim hastanesine varis dışı üst gastrointestinal kanamayla başvuran hastaları klinik ve endoskopik özellikleri açısından araştırmaktır.

Metod: Varis dışı üst gastrointestinal kanamayla 1996-2001 tarihleri arasında başvuran 250 hasta retrospektif olarak incelendi.

Bulgular: Hastaların ortalama yaşı 59 olup %34.4'ü kadındı. Hastaların %59.6'sında aspirin/non-steroidal anti-inflamatuar ilaç (NSAİİ), %2.8'inde steroid ve %9.6'sında varfarin kullanımı vardı. Vakaların %31.8'i daha önce de gastrointestinal sistem kanaması geçirmişti. En sık görülen lezyon peptik ülserdi (%49.2), bunu duodenal ve gastrik erozyonlar (%19.2) ile mide tümörleri (%10.8) izliyordu. Lezyonlar mide (%40), duodenum (%33.6), gastrojejunal bileşke (%4.4) ve özofagus (%4.4) yerleşimliydi. H. pylori varlığı 48 olguda araştırıldı, bunların %79.2'sinde pozitif bulundu. Aktif kanama belirtisi olan 33 hastaya endoskopik tedavi uygulandı. Endoskopik tedavisi başarısız olan 3 hastayla beraber 7 hastaya (%2.8) cerrahi işlem uygulandı. Hastaların 6'sı (%2.4) kaybedildi.

Sonuç: Çalışmamızda en önemli kanama nedeni peptik ülserdi. Hastaların büyük bir çoğunluğunda kanamaya neden olacak en az bir risk faktörü vardı (H. pilori veya ilaç kullanımı). Kanama nedenleri kolay tedavi edilebildiğinden, hasta grubumuzda endoskopik ve cerrahi tedavi oranı ile mortalite düşük bulundu.

Anahtar Kelimeler: NSAİİ, aspirin, endoskopik tedavi, morbidite ve mortalite

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INTRODUCTION

While potent acid suppressing medications have considerably decreased hospital admissions due to uncomplicated peptic ulcer disease, endoscopic therapies, on the other hand, have reduced hospital stays, the need for surgery and the number of blood transfusions for bleeding peptic ulcers. However, mortality rates of upper gastrointestinal bleeding (UGIB) have remained constant at 4-14 %.[1-5] High risk patients are elderly people with multi-systemic diseases, using multiple medications (anti-inflammatory drugs, aspirin, corticosteroids, warfarin, etc), who experience hemorrhagic episodes during hospitalization for other disorders (esp. ICU patients) or persistent bleeding/rebleeding during a hospital stay, and who are hemodynamically compromised upon their admission to the hospital.[1,4-7] The mortality rate due to bleeding among patients under 60 years and without an underlying disease is < 1 % whereas it ranges from 16 % to 42 % among high risk patients.[3-9] Therefore, an organized and aggressive approach to diagnose and treat patients with UGIB, especially those at the high risk category, is mandatory.

The aim of this study was to describe demographical, clinical and endoscopical features of the patients presenting with non-variceal upper gastrointestinal bleeding (NVUGIB) in a teaching hospital in Istanbul.

MATERIAL AND METHOD

The databases of upper gastrointestinal (GI) endoscopies done between 1996 and 2001 at Marmara University Hospital were reviewed retrospectively. Patients who had a history of GI bleeding and/or had endoscopically diagnosed NVUGIB lesions were enrolled into the study. Clinical data related to the endoscopic procedures were obtained from the patient registry and in cases of missing data, a telephone interview was done with the patient regarding the previous history of bleeding, medications, clinical course and outcomes of the bleeding episode. Two hundred and fifty patients [86 of whom were women with a mean age of 59 ± 17 years (range 18-92 years)] having UGIB were evaluated retrospectively. Since the reports of endoscopies did not mention explicitly whether the patients were referred as outpatients or inpatients, risk factors of hospitalization on bleeding, especially stress ulcers of critically ill patients, were not assessed. The presence of H. pylori was investigated in modified Giemsa stained slices if any biopsy had been taken during the upper GI endoscopy. Data were processed and analyzed by SPSS version 10.0.

RESULTS

The main complaint on hospital admission was melena in about half of the patients and this was followed by hematemesis in one-third, hypotension, anaemia and hematochezia in the rest (Fig.1). Drugs assumed to cause bleeding were reported in 61.2 % of all patients. Ingestion of aspirin and/or non-steroidal anti-inflammatory drugs (NSAIDs), steroids or warfarin during the previous week was reported in 59.6 %, 2.8 %, and 9.6 % of the patients, respectively. All steroid and 83.3 % of warfarin using patients were also taking either aspirin or NSAIDs or both. Ninety-seven patients (38.8 %) did not report any drug ingestion. The main reasons for NSAIDs and aspirin use were cardiac or cerebro-vascular diseases (42.3 %), alleviation of chronic pain (37.6 %) or a combination of both analgesia and anti-aggregation (8.7 %). The medical history was not clear regarding the rationale for NSAIDs/aspirin prescription in 11.4 %. Seventy-one of 223 patients (31.8 %) had experienced previous upper GI bleeding and 51 of them had had endoscopy, with the diagnosis of peptic ulcers in 40 patients. Co-morbidities were reported in 109 patients (43.6 %) and the most commonly encountered ones were malignancy of any origin, cardiac or cerebro-vascular diseases and musculo-skeletal diseases (Table I).

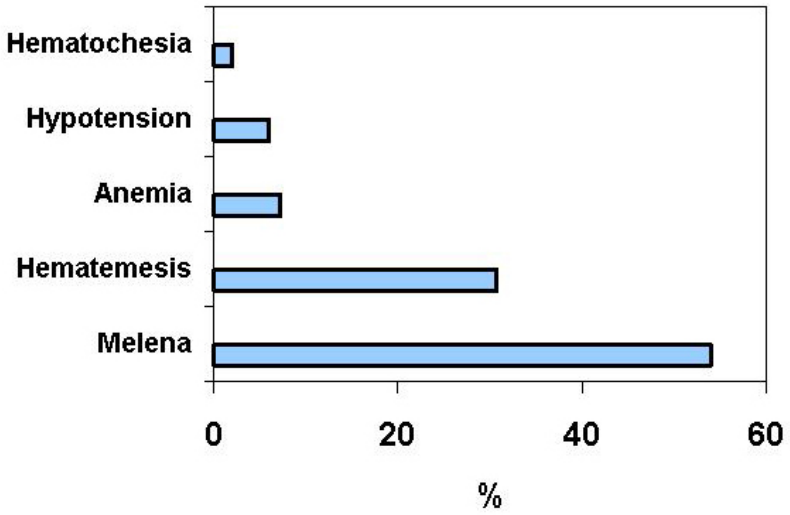

Figure I: Clinical presentations of gastrointestinal bleeding on hospital admission.
% denotes percentage of the patients with clinical presentations

Table I: Comorbidities of the patients presenting with non-variceal upper gastrointestinal bleeding.

Comorbidities	**number**	**%**
None	141	56.4
Malignancy of any origin	51	20.4
Cardiac/cerebro-vascular diseases	42	16.8
Musculo-skeletal diseases	7	2.8
Acute or chronic renal failure	3	1.2
Migraine	2	0.8
Others*	4	1.6
Total	**250**	**100**

*includes diabetes mellitus, trauma, bone marrow transplantation and cirrhosis, one patient for each disease.

All patients underwent upper GI endoscopy. The leading cause of bleeding was peptic ulcer (49.2 %). Other common lesions were gastric or bulbar erosions (19.2 %), tumors of the stomach (10.8 %) and Mallory Weiss tears (1.6 %) (Fig.2). Dual lesions were seen in 11.2 %. The origin of the bleeding could not be identified at endoscopy in 2 patients because of massive amount of fresh blood in the stomach and duodenum. The bleeding lesions were located within the stomach (40.0 %), duodenum (33.6 %), gastrojejunostomy line (4.4 %) and esophagus (4.4 %) (Table II). In 18.0% of the patients, lesions were located in more than one region of the upper GI tract. Fifty-one patients had malignancy of any origin, of which 32 were located within the stomach and only 27 of them were diagnosed as the source of the bleeding. The H. pylori status was investigated in biopsy specimens of only 48 patients, with positive results in 38 patients (79.2 %). Twenty-three (60.5 %) of H. pylori positive patients also reported ingestion of one of the drugs mentioned above. Of 10 patients having a negative H. pylori test, seven patients had no history of drug use while remaining three patients mentioned drug use.

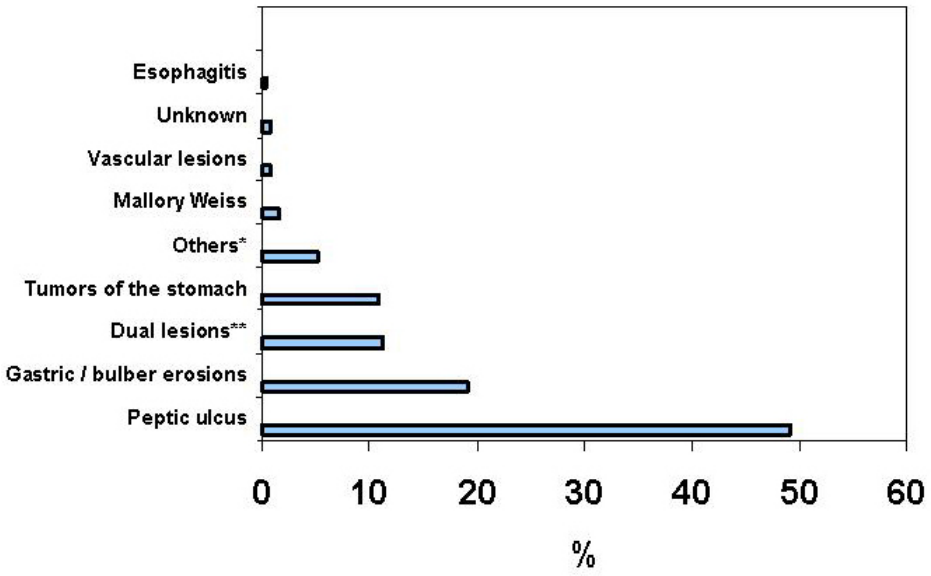

Figure II: Endoscopic diagnosis of the lesions causing bleeding

*Others include mucosal hyperemia, mucosal petechias, mucosal edema, salt–pepper appearance of the mucosa localized either in the stomach or in the duodenum
**Dual lesion denotes two types of lesions at the same time: erosion-esophagitis, erosion-ulcer.

Tablo II: Location of the lesions seen during upper GI endoscopy

Location of lesions	Number	%
Stomach	100	40
Duodenum	84	33.6
Gastrojejunostomy line	11	4.4
Esophagus	11	4.4
Dual lesions*	42	16.8
Unknown	2	0.8
Total	**250**	**100**

*denotes lesions affecting 2 parts of upper gastrointestinal system: stomach-duodenum, stomach-esophagus, esophagus-duodenum.

Thirty-four patients (13.6 %) had stigmata of active bleeding (visible vessel, adherent cloth or oozing) and all of them underwent endoscopic therapy except one patient who had massive active bleeding. Endoscopic therapies were heater probe in 27 cases, injection sclerotherapy in 4 cases and both in 2 cases. Seven cases (2.8 %) had urgent surgical intervention including 3 patients whose endoscopic therapies had failed. Two patients had iatrogenic bleeding triggered during endoscopic intervention which stopped spontaneously.

Six patients (2.4 %) died during the hospital stay; the reasons for death were malignancy related disseminated intravascular coagulation (2), ongoing GI bleeding (2), cardiac failure (1) and lympho-reticular malignancy (1). Bleeding related mortality was seen only in 2 patients (0.8 %); one had carcinoma of the stomach and bled postoperatively and the other had chronic renal failure. Advised prescriptions on hospital discharge were found for 215 of 250 patients (86 %). H. pylori eradication and acid suppression with proton pump inhibitors or H2 blockers were prescribed in 65.1 %, 33.5 % and 1.4 % of the patients, respectively.

DISCUSSION

The present study, based on 250 patients who had been referred to a university hosptai in İstanbul during five years period, reemphasizes that the leading cause of NVUGIB is peptic ulcer disease and the main localization of the lesions is the stomach. The most prevalent clinical presentation of NUUGIB, serious enough to require hospital admission, was melena followed by hematemesis. NSAIDs and/or aspirin use was detected in 59.6 % of the patients. Thirty-three patients needed endoscopic therapy and only 7 necessitated surgical interventions to control bleeding. The total mortality rate and the disease related mortality rate were 2.4 % and 0.8 %.

In the present study, 61.2 % of the patients were on some medication that can cause gastrointestinal bleeding and 59.6 % of the drug users took NSAIDs and/or aspirin during the week preceeding onset of the bleeding and this is comparable to the reports in the literature. NSAID users have a 3-10 times greater relative risk of developing serious adverse GI events, bleeding being the most important one.[1] The prevalence of NSAID use was reported to be between 38 % and 69 % in patients with UGIB.[10-13] The relative risk of UGIB among users of NSAIDs was documented as between 3.6 and 4.5.[14-17] The risk of GI bleeding in aspirin users is high and dose dependent as in NSAIDs users. It has been reported that daily use of 75 mg, 300 mg q.d., 600 mg b.i.d aspirin was associated with the relative risk of UGIB of 2.8, 3.3, and 6.4, respectively.[18,19] Doses as low as 10 mg / day of aspirin were shown to cause significant inhibition of gastric prostaglandin production to levels seen in patients taking 81 mg and 325 mg aspirin.[20] These data suggests that any dose of aspirin has the potential for inducing gastric lesions and GI complications.

In our study, ingestion of warfarin and corticosteroids was reported in 9.3 % and 2.8 % of the patients. All steroid and 83.3 % of warfarin using patients were also taking either NSAIDs or aspirin or both. Polypharmacy is one of the well-known risk factors for GI bleeding. In a case-control study of patients over 65, the relative risk for bleeding from ulcer in patients under anticoagulants was reported as 3.3 and the risk increased to 12.7 when patients were taking oral anticoagulants and NSAIDs concomitantly.[17] Likewise, in the study of Mellemkjaer et al., the risk of GI bleeding increased from 3.6 to 11.5 when NSAIDs were combined with anticoagulants.[14] Corticosteroid usage alone causes GI bleeding with a relative risk of 2.6[15] and concurrent use of corticosteroids with NSAIDs raises the risk to 7.2-9.[14,15] Similarly, the risk of bleeding which is 3.6 in NSAIDs monotherapy increases to 5.5 with NSAIDs and aspirin combination.[14]

Our finding that peptic ulcer is the major cause of bleeding (49.2%) is compatible with the results of other studies. Literally, peptic ulcer has been shown to account for 30-70 % of acute NVUGIB.[1,2,9,10,21,22] Although the incidence of peptic ulcer has decreased worldwide, probably due to the extensive use of potent acid suppressants, the incidence of bleeding from peptic ulcer disease has not changed.[23] This constant rate of bleeding may be explained by an increasing rate of NSAIDs, aspirin and warfarin usage which are all major predisposing risk factors.[1,14] Other risk factors associated with bleeding are

a previous history of ulcer disease or its complications, concomitant use of corticosteroids, major comorbidities and old age.[1] Due to comorbidities and extensive prescription of risky medications, elderly people are more susceptible to bleeding and its major complications.[1,24,25] It has been shown that the age of patients who presented with GI bleeding has increased over the years; it was 56.5±16,9 years between 1986-1987 and became 62.9±17,5 in 2000-2001.[13] After 2000, 47.2 % of patients who presented with GI bleeding were aged over 60.[13] Corroborating those figures, the mean age of our population in Turkey was 59 years and a previous UGIB history, the use of an offending drug and co-morbidities were reported for 31.8 %, 61.2 %, and 43.6 % of the patients, respectively.

The next common lesions were gastric or bulbar erosions. Gastric/bulbar erosion and hemorrhagic gastritis are well-known complications of NSAIDs and aspirin.[8,26] In the present study, 59.6 % of the patients reported NSAIDs/aspirin use. Not having enough information about the severely ill patients, we could not report the contribution of stress ulcers which are among the most common risk factors leading gastro-duodenal lesions.[8]

Erosions were followed by malignancy of the stomach and Mallory Weiss tears as causes of bleeding. In the literature, gastro-duodenal erosions, esophagitis or Mallory Weiss tears were reported in respectively 14-24 %,[22,25,27] 8-11 %[10,28] and 5-11%[10,27] of the patients who had undergone endoscopy to detect the source of bleeding. The lower prevalence of Mallory Weiss tears (1.6 %) and esophagitis (0.4 %) in our series when compared to similar studies conducted in western countries may be explained by the consumption of less alcohol in our society. Two other studies performed in Turkey revealed a similar order for the frequency of occurrence of lesions; peptic ulcer followed by erosions, tumors of the stomach, Mallory Weiss tears and esophagitis.[29,30] The frequency of Mallory Weiss tears in those studies was 1-2.6 % and of esophagitis was 0.5-1.6 %.

In this study, the number of malignant lesions of the stomach (10.8 %) was higher than figures reported in the literature which are between 1 % and 4 %.[8,24] The exact prevalence of stomach cancer in Turkey is not known, but various studies performed in gastroenterology clinics and endoscopy units suggest that it is more frequently observed in the Turkish population (between 2.2 % and 22 %) than in those who live in western countries.[29-31] The occurrence rate increases towards the eastern parts of the country as seen in Europe, probably, because of the poor environmental sanitation, increased prevalence of H. pylori infection, poor conservation and refrigeration of food, dietary habits, cooking style, consumption of salted food and genetic predisposition.[32-34]

In our study, the H. pylori status was investigated in only 48 patients and 38 of them (79.2%) were positive. This figure does not represent all participitants, but it is still high. The prevalence of H. pylori infection in developing countries may reach 90 % which is higher than the figures reported in developed countries (40 % or less).[35] Considering the prevalence of H. pylori infection in Turkey[36] which is 82.5 % as shown by urea breath test, the high incidence of H. pylori among patients who bled is not a surprise.

The mortality rate of the study (2.4 %) was lesser than the figures reported in the literature.[1-4] Since all patients had undergone immediate diagnostic endoscopy and the ones who had stigmata of active bleeding had endoscopic treatment, the mortality rate was low. If we could have used clips, a new treatment modality for upper gastrointestinal bleeding which was not available at our institution at that time, our mortality rate could be half of the current figure.[37] Lower mortality rates between 0.8 % and 3.1 % were also reported from other studies.[10,13,38] In a Greek study, the overall mortality rate in patients who bled was reduced from 5.2 %

between 1986-1987 to 3.1 % in 2000-2001 when therapeutic endoscopy had flourished.[13] Another risk factor for bleeding related mortality is advancing age. Mortality rate of UGIB increases with age; e.g, 0.4-3 %, 2-6 % and 11 % among patients < 60, 60-79, and ≥ 80 years old, respectively.[24] The mean age of our patients was lower than those of the studies reporting higher mortality rates.[2,3,9] The percentage of deaths (0.8 %) directly attributable to GI bleeding was quite low in our study. Both cases who died from GI bleeding had co-morbidities. Previous studies showed that death in bleeding patients is caused generally by underlying diseases such as cancer, sepsis, pneumonia or organ failure and bleeding related mortality was reported in less than 50 % of all causes of mortality.[2,27] In our study, complications related to endoscopic treatment were 0.8 % which is very close to the reported figures of 1 % and 2%.[39]

In conclusion, the most common cause of non-variceal upper GI bleeding was peptic ulcer in our series. The majority of the patients with GI bleeding had at least one of the risk factors; either H. pylori infection or ingestion of NSAIDs and aspirin or both. Probably, because the bleeding lesions were amenable to treatment, the rates of endoscopic intervention, surgical therapy and mortality were lower in our patients compared to the reports coming from western countries.

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