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A retrospective study demonstrating properties of nonvariceal upper gastrointestinal bleeding in Turkey

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Background/aims: *Helicobacter pylori infection, non-steroidal anti-inflammatory drugs and peptic ulcer are considered as the major factors for upper gastrointestinal system bleeding. The objective of the study was to determine the sociodemographic and etiologic factors, management and outcome of patients with non-variceal upper gastrointestinal system bleeding in Turkey.* ***Methods:*** *Patients who admitted to hospitals with upper gastrointestinal system bleeding and in whom upper gastrointestinal endoscopy was performed were enrolled in this retrospective study. The detailed data of medical history, comorbid diseases, medications, admission to intensive care units, Helicobacter pylori infection, blood transfusion, upper gastrointestinal endoscopy, and treatment outcome were documented.* ***Results:*** *The most frequent causes of bleeding (%) were duodenal ulcer (49.4), gastric ulcer (22.8), erosion (9.6), and cancer (2.2) among 1,711 lesions in endoscopic appearances of 1,339 patients from six centers. Seven hundred and four patients were evaluated for Helicobacter pylori infection and the test was positive in 45.6% of those patients. Comorbid diseases were present in 59.2% of the patients. The percentage of patients using acetylsalicylic acid and/or other non-steroidal anti-inflammatory drug was 54.3%. Bleeding was stopped with medical therapy in 66.9%. Only 3.7% of the patients underwent emergency surgery, and a 1.1% mortality rate was determined.* ***Conclusions:*** *Patients with upper gastrointestinal system bleeding were significantly older, more likely to be male, and more likely to use non-steroidal anti-inflammatory drugs. Though most of the patients were using gastro-protective agents, duodenal and gastric ulcers were the contributing factors in more than 70% of the upper gastrointestinal bleeding. The extensive use of non-steroidal anti-inflammatory drug is a hazardous health issue considering the use of these drugs in half of the patients.*

Key words: Non-steroidal anti-inflammatory drugs, acetylsalicylic acid, gastrointestinal bleeding, gastrointestinal endoscopy, *Helicobacter pylori,* peptic ulcer

Türkiye'de varis dışı üst gastrointestinal kanamayı gösteren retrospektif bir çalışma

Amaç: *Helikobakter pilori enfeksiyonu, non-steroid antiinflamatuvar ilaçlar ve peptik ülser gastrointestinal sistem kanama nedenlerinin başında gelmektedir. Çalışmanın amacı ülkemizdeki varis dışı üst üst gastrointestinal sistem kanamalarında sosyodemografik ve etyolojik faktörlerin, tedavi özelliklerinin ve prognozun değerlendirilmesidir.* ***Yöntem:*** *Bu retrospektif çalışmaya üst gastrointestinal sistem kanaması nedeniyle hastaneye yatırılıp üst gastrointestinal sistem endoskopisi yapılan olgular alınmıştır. Öykü, komorbidite, kullanılan ilaçlar, yoğun bakım ünitesine yatırılma, Helikobakter pilori enfeksiyonu, kan nakilleri, üst gastrointestinal sistem endoskopisi ile uygulanan tedavilerin etkinliği retrospektif olarak değerlendirilmiştir.* ***Bulgular:*** *Altı merkezin 1339 hastasının verilerinden toplanan 1711 lezyon içerisinde en sık kanama yerleri (%) duodenal ülser (49.4), gastrik ülser (22.8), erozyon (9.6), kanser (2.2) olarak bulunmuştur. Helikobakter pilori varlığı 704 olguda değerlendirilerek %45.6 oranında pozitif bulunmuştur. Komorbid hastalık oranı %59.2 ve non-steroid anti-inflamatuvar ilaç ve/veya aspirin kullanımı %54.3'dür. Kanama olguların %66.9'unda medikal tedavi ile durmuştur. Olguların %3.7'sinde hasta cerrahiye verilmiş ve %1.1'i kaybedilmiştir.* ***Sonuç:*** *Üst gastrointestinal sistem kanaması bulunan olgular istatistiksel olarak anlamlı olacak şekilde daha yaşlı, erkek cinsiyette ve non-steroid anti-inflamatuvar ilaçlar kullanmaktadır. Olguların çoğu gastroprotektif ilaç kullanmakla birlikte, kanama nedeni olguların %70'den fazlasında duodenum veya mide ülseridir. Olguların yarısından fazlasının non-steroid anti-inflamatuvar ilaç kullanması, bu ilaçların halk sağlığı yönünden ciddi bir sorun yarattığını göstermektedir. Mortalitenin ve Helikobakter pilori varlığının anlamlı olarak düşük olması dikkat çekicidir.*

Anahtar kelimeler: Steroid olmayan antiinflamatuvar ilaçlar, asetil salisilik asit, gastrointestinal kanama, gastrointestinal endoskopi, *Helikobakter pilori,* peptik ülser

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INTRODUCTION

Acute upper gastrointestinal bleeding represents a major problem in public health despite advances in the diagnosis of contributing diseases and the introduction of new treatment approaches (1). In recent years, neither the incidence nor mortality has changed due to the increasing mean age of the population (2-4). Peptic ulcer remains the most common cause; other causes of upper gastrointestinal bleeding include erosions, esophagitis, Mallory-Weiss tears, and malignancy (5). The increase in *Helicobacter pylori* (*Hp*) infection, extensive use of non-steroidal anti-inflammatory drugs (NSAIDs), poor health, and poor hygiene status have been considered in recent years as the main factors that increase the incidence of upper gastrointestinal system bleeding (3, 4, 6, 7). The data about upper gastrointestinal bleeding in eastern Mediterranean countries such as Turkey are poorly described. This region exhibits a high rate of *Hp* infection (countrywide prevalence is 75% with urea breath test [UBT]; Bor et al. unpublished data) and different sanitary conditions and health care facilities. The prescription rates and over-the-counter (OTC) availability of NSAIDs are relatively high, and combination of more than one drug in the prescription is common. Turkey is particularly important since the east part of the country reflects the eastern-type lifestyle while the western part mimics the westernized type lifestyle. For all these reasons, it might be interesting to evaluate the relative contribution of two major pathogenetic factors, namely *Hp* and NSAIDs, to upper gastrointestinal bleeding in this particular country.

The objective of the study was to determine the sociodemographic and etiologic factors, management and outcome of non-variceal upper gastrointestinal system bleeding in Turkey.

MATERIALS AND METHODS

Patients and Design of the Study

This study was designed as a multicenter retrospective study. The patients who admitted to the hospital with non-variceal upper gastrointestinal system bleeding between January 1995 and December 2001 were enrolled into the study. All patients were examined with upper gastrointestinal system endoscopy for the evaluation of underlying disease. The medical history, presence of comorbid diseases, use of NSAIDs, gastro-protective drugs, steroid and anticoagulant agents, hospitalization, admission to intensive care units, presence of *Hp* infection, requirement of blood transfusion, and findings of upper gastrointestinal endoscopy were documented retrospectively. The definitive outcome was also noted in all.

Patients were accepted to the study if a lesion was detected with upper gastrointestinal system endoscopy accompanied with any of the following:

- active bleeding,
- the presence of hematemesis and/or melena,
- positive stool occult blood test and a falling in hematocrit (5%) or orthostatic hypotension,
- The presence of hematemesis and accompanying lesions on endoscopy,
- Even the presence of varices, if the bleeding lesion is identified as due to a nonvariceal reason.

Exclusion criteria were as follows:

- Variceal bleedings;
- Inability to identify the bleeding site and suspected lower gastrointestinal bleeding;
- The presence of melena without any lesion that can explain the bleeding on upper endoscopy.

Hp positivity included positivity of any of the following: gastric biopsy and pathology, rapid urease test, CLO test, or C13 UBT.

Definitions

NSAIDs/aspirin-related ulcer: The ulcer possibly related with NSAIDs usage, as common as five times per week and at least for a two-week period.

NSAIDs/aspirin-related upper gastrointestinal bleeding: use of NSAIDs at least once and/or aspirin one week before the upper gastrointestinal bleeding.

Ulcer: At least 5 mm long with deep lesions in the esophagus, stomach and duodenum.

Erosion: Smaller and superficial lesions in the esophagus, stomach and duodenum.

Statistical Analysis

Sociodemographic and clinical characteristics of the patients, the findings of endoscopic evaluation and treatment interventions and outcome were defined by descriptive statistical methods (mean, median, percent, standard deviation, minimum, maximum).

RESULTS

Clinical and Demographic Characteristics

A total of 1,339 patients were enrolled into the study from six different centers. The male to female ratio was 2.6/1. Most of the patients were in the 5th, 6th or 7th decade, and 47% were over 60 years (Figure 1). A history of previous gastrointestinal bleeding was present in 34.3% of the patients. Comorbid diseases were reported in 59.2% of the patients; the most common were cardiovascular disease, diabetes mellitus and cancer (Table 1).

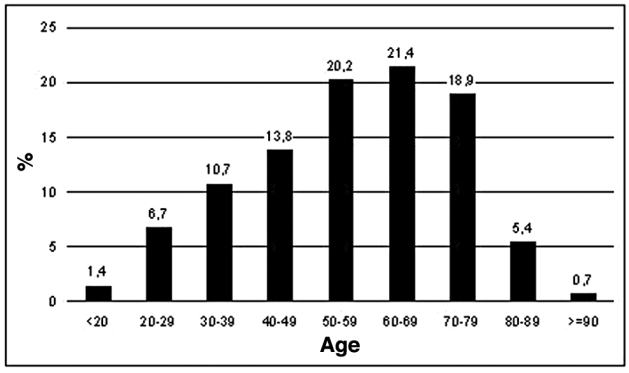

Figure 1. The distribution of patients according to age groups

Table 1. The distribution of comorbid diseases

Comorbid disease	Number of the paitents	%
Cardiovascular diseases	489	36.5
Respiratory diseases	54	4.7
Type II Diabetes	135	10.1
Cancer	105	7.8
Rheumatic diseases	72	5.4
Other	123	30.3
Total	**793**	**59.2**

The percentage of patients using acetylsalicylic acid and/or other NSAIDs was 54.3. Of patients using acetylsalicylic acid, it was prescribed as an antiaggregant agent in 69.2% and interestingly for analgesic purposes in the rest (30.8%). None of the patients received cyclooxygenase-2 inhibitors. Gastro-protective agents were being used in 32.7%. At the time of upper gastrointestinal bleeding, 43.2% of the patients were using acetylsalicylic acid or other NSAIDs, 1.7% were using corticosteroids, and 6.6% were using anticoagulant medications. Medical history revealed that 8% of the patients were consuming alcohol on a regular basis. No difference was found in these parameters according to the geographic regions of the country.

Endoscopic Diagnosis

All patients were examined with upper gastrointestinal system endoscopy to detect the source of hemorrhage and an attempt was made to achieve endoscopic homeostasis in patients with clinically significant upper gastrointestinal hemorrhage. It was revealed that 98% of the patients had pathologic lesions, and 1,711 distinctive lesions were identified with endoscopy. The most common causes of bleeding were duodenal and gastric ulcer, erosions and cancers (Table 2). Anatomically, the lesions were localized in the esophagus in 6.8%, gastric in 41.6%, duodenum in 63.2%, and in the region of anastomosis in 3.2%. Active bleeding was present in 24.3% of the patients in the endoscopic evaluation.

Table 2. The distribution of lesions according to upper gastrointestinal endoscopy findings

Lesions	Number of lesions	%
- Ulcer	1288	75.3
• Duodenal	846	49.4
• Gastric	391	22.8
• Esophageal	17	1.0
• Anastomotic	34	2.0
- Erosion	165	9.6
- Acute hemorrhagic gastropathy	14	0.8
- Polyp	23	1.3
- Cancer	38	2.2
- Non-variceal vascular lesions	22	1.3
- Mallory-Weiss tears	39	2.3
- Esophagitis	19	1.1
- Other	103	6.0
Total	**1711**	**100**

Hp test was not done routinely for each patient with acute upper gastrointestinal bleeding during the study period in each hospital. A total of 704 patients were evaluated with UBT or biopsy, or both, and the result was positive with any of these techniques in 45.6% (Table 3).

Treatment and Outcome

Of the patients admitted to hospitals, 91.6% were hospitalized and 63.5% of them were admitted to intensive care units. The mean duration of the hospital stay was 7.0±5.7 (0-90) days and of intensive care unit stay was 2.2±3.2 (0-65) days. The details of duration of stay in the hospital and in-

Table 3. The distribution of lesions according to upper gastrointestinal endoscopy by the positivity of *Hp* test

Lesions	Number of lesions in all patients	Number of lesions in *Hp* test (+) patients	%
Ulcer	743	346	46.6
Duodenum	512	264	51.6
Epigastrium	211	75	35.5
Esophagus	5	3	60.0
Anastomosis	15	4	26.7
Erosion	66	31	46.9
Acute hemorrhagic gastropathy	5	1	20.0
Polyp	11	5	45.4
Cancer	11	4	36.4
Non-variceal vascular lesions	7	3	42.8
Mallory-Weis tears	15	6	40.0
Esophagitis	6	3	50.0
Other	34	16	47.1
Total	**898**	**415**	**46.3**

tensive care unit are given in Table 4. Blood transfusions were required in 54.2% of the patients. The mean number of transfused blood cells was 3.5±3.0 (0-30) units. Bleeding was stopped with medical therapy in 66.9%. An endoscopic intervention was attempted in patients if the bleeding was not stopped with medical therapy: Sclerotherapy was used in 25.8% and heater probe in 5.3% (available only at one center). Of the 425 patients treated endoscopically, the source of bleeding was localized and initial homeostasis was achieved successfully in 88.2%; emergency surgery was needed in 9.2% of the patients after failed response to therapeutic endoscopy. Only 3.7% of the patients underwent emergency surgery without endoscopic intervention due to massive bleeding. The mortality was determined as only 1.1%.

Subgroup Analysis in Patients with Comorbidities

Hospitalization and admission to the intensive care unit was required in 93.9% and 64.2% of the patients without comorbid diseases and in 89.9% and 62.2% of those with comorbid diseases, respectively. The duration of stay in the hospital and intensive care unit of ≥8 days was 20.9% and 1.4% without comorbid diseases and 35.5% and 4.8% with comorbid diseases, respectively. Active bleeding was present in 24.9% with comorbid diseases and in 23.7% without comorbid diseases. Blood transfusions were required in 47.3% without comorbid diseases and in 58.8% with comorbid diseases. None of these comparisons were significantly different (p>0.05). Gastro-protective agents were used in 30.2% without comorbid diseases and in 34.4% with comorbid diseases, and interestingly, proton pump inhibitors (PPIs) were used in 13.4% without comorbid diseases and in 22.8% with comorbid diseases.

Table 4. The duration of stay in hospital and intensive care unit

Number of days	Hospital		Intensive care unit	
	n	%	n	%
1-3	259	19.3	495	37.0
4-7	571	42.6	242	18.1
8-14	307	22.9	32	2.4
≥15	89	6.6	9	0.7
Total	**1226**	**91.6**	**778**	**58.2**

n: Number of patients

DISCUSSION

Upper gastrointestinal system bleeding is a life-threatening complication of gastrointestinal diseases resulting in most of the hospital admissions requiring immediate treatment. Despite the introduction of new diagnostic and therapeutic approaches, the incidence is not decreasing and the mortality has not changed in recent years (2, 4, 5, 8). With the introduction of endoscopy, the efficacy of diagnosis and treatment has been greatly improved. In case of massive bleeding or failure to respond medical and endoscopic treatment, emergency surgery should be established (9, 10).

Turkey, which is similar to some other developing countries, has its own cultural and health care characteristics, such as the high prescription rates, OTC availability of NSAIDs, combination of

more than one drug in the prescription, and high rate of *Hp*. A recent survey was performed and reported the prevalence of *Hp* in Turkey as 75% with UBT (Bor et al. unpublished data). In addition, the eastern and western parts of the country reflect different lifestyles, health care facilities, food habits, etc. Studies from developing countries might help in the identification of the differences between the developed countries versus others and facilitate the development of better ways of using the limited sources and more practical means of management. The impact of the presence of *Hp* could be more easily identified in these high-prevalence countries.

In our study, upper gastrointestinal bleeding was observed mainly in the elderly, and the more than two-fold increase in male cases was similar to other studies (3, 5, 11). The presence of comorbidity is a well-known cause of increased incidence for upper gastrointestinal system bleeding, and accordingly, nearly 60% of our patients had comorbid diseases (3, 12). Peptic ulcer remains the most common cause of upper gastrointestinal bleeding, representing approximately half of all cases; other less common but appreciably frequent causes of non-variceal upper gastrointestinal bleeding include erosions, esophagitis, Mallory-Weiss tears, and malignancy (1, 3, 5, 9, 11). In this retrospective study, we confirmed that endoscopy contributed to identification of the bleeding site in nearly all the patients. Similar to other surveys, the most common source of upper gastrointestinal system bleeding was duodenal ulcer, representing 49.4% of all cases. Bleeding from gastric ulcer is the next most common diagnosis, following erosions of the upper gastrointestinal tract. The pathogenic role of *Hp* in the development of peptic ulcer is a well-established phenomenon. The prevalence of *Hp* infection is reported to be higher in developing countries and it may influence the etiology of upper gastrointestinal system bleeding (6, 7). The test was positive in 51.6% of duodenal ulcer, 35.5% of gastric ulcer and 46.9% of erosion patients. The prevalence was lower compared to the prevalence rate of the general population of the country. However, this data should be interpreted carefully because it is known that the presence of blood in the stomach and PPI usage change the *Hp* tests, especially rapid urease test (13). Some patients might have received eradication therapy previously because of the dyspepsia. The prevalence of the *Hp* infection could not be determined for the whole group in this retrospective study, since tests were not routinely done for the entire group of patients during the study period in each hospital. No difference was found according to the geographical areas for any major parameters.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most frequently prescribed medications worldwide. The main factor limiting use of NSAIDs is the concern about their gastrointestinal side effects, and the use of NSAIDs is a well-established risk factor for upper gastrointestinal bleeding (6, 14, 15). However, the majority of patients are not aware of the risks of these medications (16). The elderly are especially susceptible to NSAIDs-induced gastrointestinal system bleeding. Although the bleeding risk increases with increasing NSAID dose, it is a well-known fact that any amount can cause bleeding. Additionally, anticoagulants may unmask or aggravate hemorrhage from preexisting lesions (17, 18). This survey confirms the extremely high incidence of NSAIDs use in patients with upper gastrointestinal system bleeding. It is important to be cautious in prescribing NSAIDs with risk factors particularly in the elderly and patients having comorbid diseases. Although one-third of the patients were using gastro-protective agents, prevention of gastrointestinal bleeding was not achieved.

A variety of endoscopic and pharmacological modalities are effective in achieving and maintaining homeostasis. In case of failure in medical treatment, early endoscopic intervention is the cornerstone of diagnosis and management. Endoscopic therapy is a well-established procedure in the management of gastrointestinal bleeding and can be used as an effective tool for selected patients (2, 9). In our study group, endoscopic treatments were done in 425 patients in an attempt to stop bleeding, and treatment was successful in 88.2% of the cases.

In conclusion, gastrointestinal system bleeding remains a common complication of gastrointestinal diseases, with a mortality rate that has remained unchanged over the past five decades despite changing usage patterns of NSAIDs and gastroprotective medications. However, in our study, the mortality was only 1.1%. One of the possible reasons is the selection criteria for patients. Patients for whom upper gastrointestinal endoscopy could not be performed because of severe condition were not included. Patient demographics indicated that patients with upper gastrointestinal system bleeding were significantly older, more likely to be ma-

le, and more likely to use NSAIDs and anticoagulants. Duodenal and gastric ulcers were the contributing factors in more than 70% of the upper gastrointestinal bleeders. Most of the patients were hospitalized, 54.1% received blood transfusions, and 31.1% received endoscopic therapy. It can be concluded that extensive use of NSAIDs is a hazardous health issue considering the use of these drugs in half of the patients. The prevention of bleeding is of significant importance. The data from a developing country with high occurrence of *Hp* did not have any influence on these characteristics of the population except with respect to the mortality rate.

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