Changing patterns of upper gastrointestinal bleeding over 23 years in Turkey

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Cite this article as: *Danış N, Tekin F, Akarca US, Ünal NG, Işık Erdoğan E, Akat K, et al. Changing patterns of upper gastrointestinal bleeding over 23 years in Turkey. Turk J Gastroenterol 2019; 30(10): 877-82.*

ABSTRACT

Background/Aims: *This study aimed to compare the causes of nonvariceal upper gastrointestinal bleeding (NVUGB), demographics, risk factors, and outcomes of patients during two periods between 1993 and 2016 in a tertiary health-care center in Turkey.*

Materials and Methods: *We compared the causes of NVUGB and clinical outcomes in 421 patients hospitalized between January 1993 and December 1995 with those of 231 patients with NVUGB hospitalized between January 2015 and September 2016. We also compared epidemiological characteristics, risk factors, and the rates of endoscopic hemostatic procedures.*

Results: *We observed significant increases in patients' mean age, in the percentage of patients with comorbid conditions, and in the percentage of patients who received direct-acting oral anticoagulants before bleeding. We also observed a statistically nonsignificant increase in the diagnoses of gastric ulcer, along with a significant concordant decrease in diagnoses of duodenal ulcer as a cause of bleeding. The use of emergency surgical hemostasis decreased among cases of peptic ulcer bleeding. The overall rate of mortality from bleeding did not significantly change between the two periods.*

Conclusion: *Over the 23 years studied, the causes of NVUGB changed, probably because the population was increasingly elderly population and because of the use of anticoagulants and better therapeutic approaches to chronic duodenal ulcers. The use of emergency surgical hemostasis reduced, but mortality rate did not significantly change between the two specific periods.*

Keywords: *Antiaggregants, anticoagulants, endoscopy, gastrointestinal bleeding, nonsteroidal anti-inflammatory drugs*

INTRODUCTION

Nonvariceal upper gastrointestinal bleeding (NVUGB) remains a life-threatening emergency with high rates of mortality and morbidity, despite the use of very potent drugs such as proton pump inhibitors, eradication of *Helicobacter pylori* (*H. pylori*), and application of endoscopic therapeutic procedures. As in Western populations, the proportion of elderly people in Turkey has increased (1). As life expectancy has increased, so have the comorbidities and the use of medications such as acetylsalicylic acid, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral anticoagulants (2). Despite the decline in incidence of NVUGB and the advances in diagnostic procedures, resuscitation, medical and endoscopic treatment, and intensive care, the rate of mortality remains unchanged (3). One recent study showed that the increased use of anticoagulants did not affect the incidence of NVUGB, but the bleeding episodes became more severe (4). This study aimed to compare the causes of NVUGB, demographics, risk factors, and rates of mortality among patients with NVUGB in a tertiary health-care center in Turkey during two distinct periods since the 1990s.

MATERIALS AND METHODS

Patients hospitalized between January 2015 and September 2016 with hematemesis or melena, or both, as well as other clinical or laboratory evidence of acute bleeding from the upper gastrointestinal tract, were enrolled. Patients with variceal bleeding were excluded from the study. Each patient's age, gender, clinical characteristics, predisposing factors (smoking, use of NSAIDs, anticoagulants, or antiaggregants), causes of bleeding, clinical outcomes, comorbidities, endoscopy, laboratory findings, history of blood transfusion and medical, endoscopic, surgical treatments were obtained from the patient's records, and these data were compared with the data of a previous study period involving patients hospitalized from January 1993 to December 1995 for the same reasons (5).

The clinical management of patients those involved in study 1 was detailed in reference 5. In our department, endoscopic sclerotherapy was the only hemostatic method in those years. For the patients involved in study 2, the initial management of admitted patients with symptoms

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Received: ***March 25, 2019*** *Accepted:* ***May 23, 2019*** *Available online date:* ***June 26, 2019***

DOI: ***10.5152/tjg.2019.19239***

of NVUGB was fluid resuscitation and acid supapression therapy with pantoprazole (80 mg intravenous bolus, followed by continuous infusion of 8 mg/h). In accordance with our clinical practice, in these patients, emergency endoscopy was performed within the first 24 hours of admission or immediately after resuscitation in patients with massive bleeding. Olympus GIF-Q150 and GIF-H190 video endoscopes were used in the endoscopic procedures. Topical lidocaine spray was administered with midazolam, and the dose of midazolam for sedation was customized for each patient. For patients hospitalized in the gastroenterology clinic, intravenous pantoprazole infusion was continued for 72 h. Second-look endoscopy was performed if evidence of active bleeding persisted after the infusion.

Stigmata of active or recent bleeding was classified according to the Forrest classification: active spurting bleeding (Ia), active oozing bleeding (Ib), nonbleeding visible vessel (IIa), adherent clot (IIb), dark base/hematin-covered lesion (IIc), and clean ulcer base (III) (6,7). All patients in whom active bleeding or a visible vessel was found on endoscopy underwent endoscopic hemostasis. In Forrest Ia and Ib lesions, diluted epinephrine (1:10,000) was injected into four quadrants of the ulcer (maximum, 12 mL). Thereafter, either 1% to 3% polidocanol was injected into the vessel or endoscopic hemoclip treatment was performed until the vessel was effectively grasped. In Forrest IIa lesions, either 1% to 3% polidocanol was injected into the visible vessel or endoscopic hemoclip treatment was performed until the vessel was effectively grasped. Hemoclips with an arm length of 7.5 mm and a jaw angle of 135° (Olympus EZClip HX-610-135) were used to perform endoscopic hemoclip treatment. If an angiodysplastic lesion showed evidence of prior or active bleeding, it was treated with argon plasma coagulation. Malignant lesions were subjected to endoscopic sclerotherapy with polidocanol or endoscopic hemoclip treatment, or argon plasma coagulation. Otherwise, the patient either was sent to surgery or underwent boost radiotherapy to achieve the hemostasis. For Mallory-Weiss lesions, endoscopic hemoclip treatment was performed if it was necessary. Erosive esophagitis and Forrest IIb, IIc, and III lesions were treated with intravenous pantoprazole, as previously described.

Erythrocyte suspensions were transfused in eligible patients to keep patients' hemoglobin levels in the range of 7-8 g/dL. Hemoglobin level was maintained between 9 and 10 g/dL in patients with significant comorbidities such as cardiovascular disease, cerebrovascular disease, and chronic obstructive lung disease. The criteria for emergency surgical hemostasis in NVUGB were (1) continuing bleeding despite adequate transfusion of more than 5 units in 24 h or 12 units in 48 h; (2) rebleeding in hospital with hemodynamic evidence of shock (systolic pressure<100 mmHg, pulse rate>100/min); and (3) failure of endoscopy to achieve hemostatic copic sufficiency. Early mortality was defined as death during the hospitalization period. Endoscopic and hemostatic procedures, management, and resuscitation protocols were the same in both study periods.

Statistical analysis

As this was a retrospective study, no sample size was calculated. Results were determined through an intent-to-treat analysis with descriptive statistics. Continuous variables were expressed as means and standard deviations or as minimums-maximums, as appropriate, and descriptive variables are expressed as frequencies and percentages. Categorical variables were analyzed via the chi-square test or with Fischer's exact test. For quantitative variables, group differences were analyzed with Student's *t* test. Values of p lower than 0.05 were considered significant.

RESULTS

The study included 652 patients: 421 patients with NVUGB between January 1993 and December 1995 (period 1), and 231 patients between January 2015 and September 2016 (period 2).

Patients' characteristics

We observed a statistically significant increase in the mean ages of patients, from 53.6±0.7 years in period 1 to 65.2±14.5 years in period 2 (p<0.001). Most of the patients were men in both periods (75.3% vs. 68%). From period 1 to period 2, the use of NSAIDs decreased significantly (50% vs. 25%, respectively; p<0.001) and the use of anticoagulants, including direct-acting oral anticoagulants (DOACs), increased significantly (2% vs. 19%, respectively; p<0.001). There was, however, no significant difference in bleeding related to use of acetylsalicylic acid (p=0.85). In patients in period 2, we observed that combination use of antiaggregants and anticoagulants was 15.1%. In addition, of interest in period 2 was that the drug suspected of causing NVUGB in two patients was regorafenib, which is used in treatment of metastatic colon cancers and of unresectable and metastatic gastrointestinal stromal tumors. Coexisting diseases were tremendously common in period 2 in comparison with period 1 (47% vs. 85%, respectively; p<0.001), and

Table 1. Clinical characteristics of patients with nonvariceal upper gastrointestinal bleeding

Characteristics	Period 1 number		Period 2 number		p
	421		231		
Age (in years±SD)	53.6±0.7		65.2±14.5		<0.0001
Male/female	317/104	75.3/24.7	157/74	68/32	0.0446
NSAID use	211	50%	58	25%	<0.0001
Anticoagulant use	10	2%	44	19%	<0.0001
Coexisting diseases overall	194	46%	198	85%	<0.0001
Cardiovascular diseases	122	25.3%	106	45.9%	<0.0001
Respiratory disease	16	3.1%	13	5.5%	0.2794
Type 2 diabetes mellitus	34	6.7%	38	16.5%	0.0011
Previous peptic ulcer bleeding	158	37.6%	26	11.3%	<0.0001

NSAID: nonsteroidal anti-inflammatory drug

Table 2. Causes of nonvariceal upper gastrointestinal bleeding

	Study 1		Study 2		
Cause	Number	%	Number	%	p
Duodenal ulcer	227	53.9	63	27.4	<0.0001
Gastric ulcer	89	21.1	58	25.1	0.2465
Erosive gastritis	35	8.3	11	4.8	0.0905
Anastomotic ulcer	5	1.2	12	5.2	0.00355
Erosive bulbitis	5	1.2	3	1.3	1
Gastric cancer	7	1.7	13	5.7	0.007724
Mallory-Weiss tear	9	2.1	4	1.7	1
Esophagitis	9	2.1	10	4.3	0.14318
Dieulafoy lesion/angiodysplasia	3	0.7	8	3.5	0.000002
No identifiable source	21	5	18	7.8	0.149
Others	11	2.6	23	10	0.000134
Total	421	100	231	100	

atherosclerotic cardiovascular diseases were the most common comorbidities in both periods (31.7% vs. 45.9%, respectively) (Table 1). The research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013). Written informed consent was obtained from the patients who participated in this study.

Causes of bleeding

In both periods, the most common cause of NVUGB was peptic ulcer. We observed a statistically nonsignificant increase in diagnoses of gastric ulcer (21.1% vs. 25.1%, respectively; p>0.05) and a concordant decrease in diagnoses of duodenal ulcer (53.9% vs. 27.4%, respectively; p<0.001) as the cause of bleeding (Table 2). The frequency of erosive bulbitis, however, did not change between

Table 3. Emergency endoscopic/surgical hemostasis and mortality in patients with acute upper nonvariceal gastrointestinal bleeding

Procedure	Number	%	Number	%	p
Blood transfusion (patients)	290	69	165	71.4	ns
Blood transfusions (mean±SD)	2.2±0.13		4.1±3.7		<0.001
Emergency endoscopic hemostasis	364	86.4	202	87.4	0.7224
Endoscopic sclerotherapy	92	21	66	29	0.0557
Emergency surgical hemostasis	27	6	2	0.8	0.00052
Overall mortality	14	3	15	6	0.0607

ns: non-significant

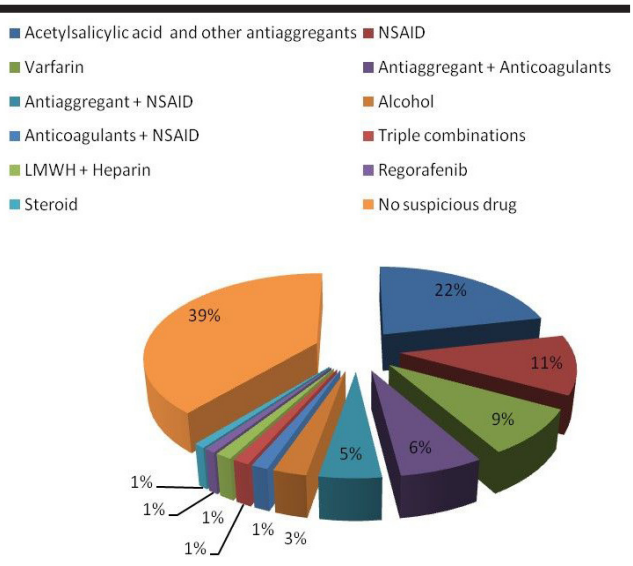

Figure 1. The use of risky drugs
LMWH: low molecular weight heparin; NSAID: nonsteroidal anti-inflammatory drug

the two periods. In period 2, the rate of *H. pylori* infection, as confirmed by the finding of *H. pylori* antigen either in stool or in pathological specimens, was 43.6% in 117 patients in whom *H. pylori* could be tested (51/117). We also observed from period 1 to period 2 gradual increases in the percentages of patients with vascular lesions, such as Dieulafoy lesions and angiodysplasia (0.7% vs. 3.5%, respectively; p<0.001), anastomotic ulcer (1.2% vs. 5.2%, respectively; p=0.00355) and gastric cancer (1.3% vs. 5.6%, respectively; p=0.0077). In period 2, 130 ulcers were categorized by the Forrest classification: 5 (3.8%) were type Ia, 6 (4.6%) were type Ib, 38 (29.2%) were type IIa, 15 (11.5%) were type IIb, 4 (3.1%) were type IIc, and 62 (47.7%) were type III. Eleven patients in period 2 had more than one lesion that could cause bleeding. Eight patients were given double antiaggregants, and seven patients were given DOACs. The use of risky drugs in this study is summarized in Figure 1.

Emergency endoscopy and surgery

Twenty-seven patients (6%) underwent surgery for continuing or recurrent bleeding in period 1, whereas two patients (0.8%) underwent to surgery in period 2 (p<0.001). The percentage of emergency endoscopic procedures did not change distinctly between the periods, but there was a nonsignificant increase in the use of sclerotherapeutic hemostasis (p=0.0557). There was a remarkable increase from period 1 to period 2 in mean amount of erythrocyte suspension transfused to the patients (2.2 vs. 4.1, respectively).

Mortality

A total of 14 patients (3%) died in period 1, whereas 15 (6%) died in period 2 (p=0.06) (Table 3). All patients who died in period 2 had serious comorbidities such as cardiovascular diseases, respiratory diseases, cerebrovascular diseases, or malignancy; only 2% of patients died as a result of bleeding.

DISCUSSION

Nonvariceal upper gastrointestinal bleeding is a common medical problem and a major cause of morbidity and mortality. Many different lesions of variable prognostic importance may cause bleeding. The main cause of NVUGB remained peptic ulcer in both periods of this study. We observed a statistically significant decrease in duodenal ulcers and an increase in gastric cancer, as well as a nonsignificant increase in gastric ulcer. Similar results (decrease in duodenal ulcer and increase in gastric ulcer) were observed in Theocharis et al. (8) study in 2008. It has been suggested that the decrease in the incidence of duodenal ulcer over time could be a result of the decrease in prevalence of *H. pylori* because the bacterium has been

widely eradicated, as well because of the greater use of proton pump inhibitors in patients treated by NSAIDs or acetylsalicylic acid (8). Although the prevalence of *H. pylori* could not be compared between the two periods in this study, it is obvious that both overall seroprevalence and infection with *H. pylori* decreased in Turkey from the 1990s to the 2000s (9).

Rate of malignancies, especially gastric cancer, as a cause of NVUGB differs by age, according to the literature. For instance, Hearnshaw et al. (10) found that among patients with NVUGB who were younger than 60 years, 1.1% of newly admitted patients and 1.3% of hospitalized patients had malignancies, whereas among patients with NVUGB who were 60-79 years of age, 5.3% of newly admitted patients and 3.3% of hospitalized patients had malignancies. These findings were similar to those in the first and second periods of our study. In period 1 of our study, the mean age of patients was 53.6 years, and the prevalence of gastric cancer was 1.7%; whereas in period 2, the mean age of patients was 65.2 years, and the prevalence of gastric cancer was 5.7%. Nahon et al. (11) also found gastric cancer as a cause of acute NVUGB in 2% of patients younger than 75 years and in 5% of patients older than 75 years.

In our study, NVUGB occurred more often in men in both periods, but other epidemiological characteristics of patients changed remarkably. Both the number of elderly patients and the prevalence of diseases such as diabetes mellitus, cardiovascular diseases, or chronic respiratory diseases that coexisted with NVUGB increased markedly. Cardiovascular diseases, diabetes mellitus, and chronic respiratory diseases are known to be related to gastrointestinal problems. Although the incidences of NVUGB and peptic ulcer bleeding are decreasing in the general population overall, rates of hospitalization because of ulcer complications are increasing among elderly people (12). This paradoxical situation is thought to be the result of longer life expectancy in Turkey, as well as in Western populations, which also has led to increased occurrence of cardiovascular diseases. We were surprised to observe a gradual decline in use of NSAIDs. However, in period 1, data about acetylsalicylic acid and NSAID use were available from several sources; in period 2, the data about the use of NSAIDs was collected via the Medula software used by the Turkish Social Security Institution. This means that we could not account for the use of NSAIDs bought from drugstores.

We also observed a dramatic increase in the use of anticoagulants. According to a 2015 review, the relative risk of adverse events with anticoagulant use was 12.7, whereas the relative risk of adverse events with high-dose NSAID use was 5.8 (13). Use of anticoagulants was the second most frequent predictor of bleeding, after prior bleeding history. The gastrointestinal bleeding (GIB) risk associated with warfarin use appears to arise from its systemic anticoagulant effects through inhibition of vitamin K-dependent clotting factors. The anticoagulant effect can be local or systemic, and DOACs may inhibit gastrointestinal mucosal healing. In comparison with warfarin, dabigatran and rivaroxaban are associated with an increase in only GIB, but they have not been demonstrated to increase bleeding in other organs, such as intracranial hemorrhage (14). After oral ingestion, dabigatran and the factor Xa inhibitors appear to be incompletely absorbed; thus their oral bioavailability is more limited than that of warfarin. Indeed, unabsorbed dabigatran etexilate, the prodrug of dabigatran, can be activated intraluminally during transit through the gastrointestinal tract. This off-target activation may explain the predisposition for lower gastrointestinal bleeding with this agent. In summary, factor Xa inhibitors and dabigatran have direct topical anticoagulant effects; in addition to these effects, resulting from intraluminal activation by the prodrug, dabigatran is also associated with a predisposition for colorectal bleeding.

In period 2, we observed that combination of antiaggregants and anticoagulants was used by 15.1% of the patients. Use of these drugs in combination is also a well-recognized risk factor for GIB (15). For instance, among patients who take dabigatran, concomitant antiplatelet use was associated with a 30%-50% higher risk for GIB (16,17). Of the various indications for DOAC use, acute coronary syndrome carried the highest risk for GIB (odds ratio: 5.21). DOACs are coprescribed with antiplatelet agents for this disorder (14); in our study, cardiovascular diseases were the most common comorbidities in patients with NVUGB. Accumulating data indicate that single or dual antiplatelet therapy should be limited in patients taking anticoagulants, in view of the particularly high rates of GIB with combination regimens (18). We think that the remarkable increase in mean amount of erythrocyte suspension transfused to the patients in period 2 was probably related to concomitant use of antiaggregants and anticoagulants.

According to the literature, the rate of mortality from acute NVUGB upper gastrointestinal bleeding changed from 8% to 14% between 1996 and 2000 (19). In our study, the mortality rate seemed to increase in period 2, but most of these deaths were not related to the NVUGB

alone (only 2% of mortality was due to bleeding). Of patients with NVUGB, 85% had comorbid diseases, and patients were significantly older in period 2 than in period 1. The major reasons for mortality were the comorbid diseases, not bleeding. The emergency treatment of bleeding peptic ulcer has also changed over the time. Surgical treatment has been replaced by endoscopic treatment (8,20). We also detected a decrease in the use of emergency surgical hemostasis from 6% to 0.8%; the use of sclerotherapeutic hemostasis was increasing.

In conclusion, NVUGB is still a life-threatening disease, especially among elderly people. Surgical treatment has been replaced by endoscopic treatment. Among patients with NVUGB, death is usually due to older age, comorbidities, and more frequent use of DOACs for particularly cardiovascular diseases.

Ethics Committee Approval: The authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - N.O., F.T., U.S.A., N.G.Ü., F.G.; Design - N.O., F.T., U.S.A., N.G.Ü., Ö.Ö.; Supervision - E.I.E., K.A., Z.K., İ.T., R.V.; Resources - N.O., F.T., U.S.A., N.G.Ü.; Materials - E.I.E., K.A., Z.K. İ.T.; Data Collection and/or Processing - E.I.E., K.A., Z.K. İ.T.; Analysis and/or Interpretation - Ü.D., N.O., A.A., G.E.; Literature Search - Ü.D., N.O., A.A., G.E.; Writing Manuscript - F.T., N.D., R.V., Ö.Ö., F.G., Ü.D., N.O.; Critical Review - R.V., Ö.Ö., F.G., A.A., G.E.; Other - N.D., F.T.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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