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ORIGINAL ARTICLE

The Role and Importance of Antiagregan, Anticoagulant Drugs in the Etiology of Upper Gastrointestinal System Bleeding in Elderly

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Abstract

Introduction: In this study, we aimed to determine the role of anticoagulants and antiagregan medications in the etiology and prognosis of the upper gastrointestinal system (GIS) bleeding in elderly patients.

Methods: One hundred and eighty-four patients who were admitted to the emergency department with the complaints of upper GIS bleeding between January and December 2016 were evaluated retrospectively regarding the age, gender, complaints, drugs, endoscopy findings, intensive care requirement and mortality.

Results: The mean age of 184 patients was 78.3±7.9 years. 112 (60.9%) of them were male and 72 (39.1%) of them were female. 128 (69.6%) of the patients applied with only melena, 32(17.4%) with only hematemesis and 24 (13%) were admitted with both hematemesis and melena. Of the patients, 139 (75.9%) were treated in the internal medicine clinic and 31 (16.8%) were treated in the intensive care unit and 12 (6.5%) were expired. The most commonly used drug was acetylsalicylic acid (ASA) (31.5%) and the most common endoscopic finding was peptic ulcer (55.4%). The mean age of the patients treated in the intensive care unit was 81±7.2years, and 18 (58.1%) of those patients were male. The most common endoscopic finding was peptic ulcer- Forrest 2A (16.2%) and ASA (35.5%) was also the most common drug in that group. The mean age of the 12 patients who were expired was 75.3±7.2 years and 8 (66.7%) of them were male. In 12 patients, the most common endoscopic finding was the peptic ulcer and the most frequent drug was warfarin (33%).

Discussion and Conclusion: Antiagregan, anticoagulant, NSAI drugs have significant effects on etiology and prognosis of the upper GIS bleeding in the elderly. Gastroprotective drugs should be added to the treatment of patients using these drugs.

Keywords: Antiagregan drugs; anticoagulant drugs; elderly; GIS bleeding.

Upper gastrointestinal bleeding (GIS) is an important cause of mortality and morbidity [1]. Its incidence is 103/100.000 per year and constitutes 80-85% of all GIS bleedings. Although 80% of bleedings in patients spontaneously stop, 20% of them are severe. Although there have been many improvements in modern surgical techniques, intensive care treatments, endoscopic diagnosis and treatments in recent years, mortality is still high and it is around 2-10% [2, 3]. The incidence and mortality rates of GIS bleeding increase with age.

Especially patients over 60 years of age account for 35-45% of all the cases with upper gastrointestinal bleedings [4]. The incidence of upper GIS bleeding in patients older than 70 years is 20-30 times higher than 30-year-old patients. Furthermore, the mortality rate due to GIS bleeding in patients in this age group is 12-25% [5]. Multiple drug use is common in the elderly population due to chronic diseases. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most important cause of GIS bleeding in this age group. In addition, the use of antiaggregant and/or anticoagulant

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drugs frequently due to concomitant cardiovascular, cerebrovascular diseases increases the risk of GIS bleeding in these patients [4].

In this study, we aimed to determine the role of anticoagulant and antiaggregant drugs in the etiology and prognosis of upper gastrointestinal bleeding in patients aged 65 years and older.

Materials and Methods

A total of 184 patients aged 65 years and over who were admitted to the emergency internal medicine department of our hospital between January and December 2016 with complaints of hematemesis and melena and followed up with the diagnosis of upper GIS bleeding were evaluated retrospectively. Patients were evaluated in terms of age, gender, admission complaints, drug use and type (NSAIDs, antiaggregants, anticoagulants), endoscopy findings, need for intensive care, and mortality.

Approval of the Ethics Committee of our hospital was obtained for this study (B.10.1.TKH.4.34.H.GP.0.01/71). Statistical analyzes were performed using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013). Descriptive statistics were used to define continuous variables (mean, standard deviation, minimum, median, maximum) Statistical significance level was determined as p=0.05.

Results

A total of 184 patients with upper gastrointestinal bleeding were included in this study. The mean age of the patients was 78.3±7.9 years. Of these, 112 (60.9%) were male and 72 were female. When the age and sex distribution of the patients were examined, 66 (58.9%) of the patients between the ages of 65-75 were male, and 10% (13.9%) of them were female, while 34 male (30.4%), and 30 (41.7%) female patients were in the age group of 75-85 years. However, 12 (10.7%) of them were male, and 32 (44.4%) of them were female patients in the age bracket of 85-95 years. Upper GI bleeding was most frequently seen in the 6-7 decades (Table 1).

The patients were admitted to the hospital with the complaints of only melena (n=128: 69.6%), hematemesis (n=32 :17.4%), and both with hematemesis and melena (n=24: 13%).

The most common findings in upper GIS endoscopy were peptic ulcer (55.4%), gastritis (25%), esophageal variceal bleeding (7.6%), and gastric cancer (7.6%). When the patients with peptic ulcer were examined according to Forrest classification most frequently (63.7%) Forrest 3 peptic ulcer was observed followed by Forrest 2B (15.6%), Forrest 2A (8.8%), and Forrest 1A (7.8%) peptic ulcer in decreasing order of frequency (Table 2). When the gender distribution

Table 1. Demographic data

	n	Mean±SD	Median (Min-Max)		
Age (year)	184	78.3+7.9	79 (65-95)		
	Male		Female		Total
	n	%	n	%	n
65-75	66	58.9	10	13.9	76
75-85	34	30.4	30	41.7	64
85-95	12	10.7	32	44.4	44
	n	%			
Sex					
Male	112	60.9			
Female	72	39.1			

Table 2. Distribution of parameters

	n	%
Complaints		
Hematemesis	32	17.4
Hematemesis+Melena	24	13.0
Melena	128	69.6
Endoscopic		
Gastritis+Esophagitis	2	1.1
Findings		
Gastritis	46	25.0
Gastric Ca	14	7.6
Normal	2	1.1
Esophagitis	2	1.1
Esophageal Ulcer	2	1.1
Esophageal varices	14	7.6
Peptic ulcer	102	55.4
Forrest 1A	8	7.8
Forrest 1B	2	1.9
Forrest 2A	9	8.8
Forrest 2B	16	15.6
Forrest 2C	2	1.9
Forrest 3	65	63.7
Number of drugs used		
0	50	27.2
1	108	58.7
2	26	14.1
ASA	58	31.5
NSAD	38	20.7
Clopidogrel	24	13.0
Warfarin	14	7.6
Rivaroxaban	12	6.5
Apixaban	6	3.3
Dabigatran	6	3.3
Enoxaparin	2	1.1
Prognosis		
Ex	12	6.5
Discharge	2	1.1
Hospitalisation	139	75.6
Intensive care	31	16.8

was examined according to the endoscopy findings, it was observed that 51.7% of men and 61.1% of women had peptic ulcers (Table 3).

When the patients were evaluated in terms of the drugs they used, 134 (72.8%) of the patients were using drugs that could cause GIS bleeding, 108 (58.7%) were one kind of medication, and 26 (14.1%) patients were taking two drugs at the same time. In order of decreasing frequency the drugs used were acetylsalicylic acid (ASA) (31.5%), NSAID (20.7%), clopidogrel (13%), warfarin (7.6%), rivaroxaban (6.5%), apixaban (3.3%), dabigatran (6%), and enoxaparin sodium (1.1%). When the drug distributions were examined according to the endoscopy findings, in users of NSAIDs, ASA or dabigatran most frequently peptic ulcer (79%, 62 %, 67%, respectively) was seen, while gastritis was most often (57.1%) observed in warfarin users (Table 4).

Of these 184 patients presenting with complaints of upper GIS bleeding, 139 (75.9%) were treated in the internal medicine clinic, 31 (16.8%) in the intensive care unit and two in emergency observation room (Table 2). The mean age of 31 patients who were in need of intensive care was 81±7.2 years, while 58% of them were male, and 42% of them were female. Most frequently (16.2%) Forrest 2A peptic ulcer was found in endoscopy findings and 35.5% of these patients were using ASA (Table 5).

The mean age of 12 deceased patients was 75.3±7.2 years,

Table 3. Endoscopic findings and their distribution between genders

	Male		Female	
	n (112)	%	n (72)	%
Endoscopic Findings				
Gastritis+ Esophagitis	0	0.0	2	2.8
Gastritis	28	25.0	18	25.0
Gastric Ca	10	8.9	4	5.6
Normal	0	0.0	2	2.8
Esophagitis	2	1.8	0	0.0
Esophageal Ulcer	2	1.8	0	0.0
Esophageal Varices	10	8.9	4	5.6
Peptic Ulcer	58	51.7	44	61.1
Forrest 1A	4	3.6	4	5.6
Forrest 1B	0	0.0	2	2.8
Forrest 2A	9	8.1	0	0.0
Forrest 2B	10	8.9	6	8.4
Forrest 2C	0	0.0	2	2.8
Forrset 3	35	31.3	30	38.9

Table 4. Distribution of drugs used according to endoscopic findings

Endoscopic findings	NSAİDs		Warfarin		Dabigatran		Rivaroxaban		Apixaban		ASA		Clopidogrel		Enoxaparin	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Gasritis+Esopphagitis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	3.4	0	0.0	0	0.0
Gastritis	2	5.3	8	57.1	2	33.3	6	50.0	4	66.7	18	31	4	16.7	2	100.0
Gastritis Ca	0	0.0	0	0.0	0	0.0	0	0.0	2	33.3	0	0.0	0	0.0	0	0.0
Normal	2	5.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	8.3	0	0.0
Esophagitis	2	5.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Esophageal Ulcer	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Esophageal Varices	2	5.3	0	0.0	0	0.0	0	0.0	0	0.0	2	3.4	2	8.3	0	0.0
P. ulcer	30	79	6	43	4	67	6	50	0	0	36	62	9	37.5	0	0.0
P. ulcer F1A	2	5.3	0	0.0	2	33.3	0	0.0	0	0.0	2	3.4	0	0.0	0	0.0
P. ulcer F1B	0	0.0	0	0.0	2	33.3	0	0.0	0	0.0	0	0.0	2	8.3	0	0.0
P. ulcer F2A	6	15.8	0	0.0	0	0.0	0	0.0	0	0.0	13	22.3	5	20.8	0	0.0
P ulcer F2B	4	10.5	0	0.0	0	0.0	0	0.0	0	0.0	2	3.4	0	0.0	0	0.0
P. ulcer F2C	2	5.3	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
P. ulcer F3	16	42.1	6	42.9	0	0.0	6	50	0	0.0	19	32.7	9	37.5	0	0.0

while 66.7% of them were male and 33.3% of them were female. Two of these 12 patients had gastric cancer. The other 10 (83%) patients had GIS bleeding due to peptic ulcer detected during their endoscopic examination. These patients were using warfarin (33%), rivaroxaban (16%), or an NSAID (16%) (Table 6).

Discussion

In the last century, with the prolongation of human life, an older society started to emerge and digestive system diseases of the elderly population started to be seen more frequently. Despite all the improvements in diagnosis and treatment, acute GIS bleeding still exists as a serious and fatal clinical problem. Especially, 90% of deaths caused by acute gastrointestinal bleeding consisted of elderly patients [4].

NSAIDs are widely used for chronic pain in older people. In addition, secondary to the frequent use of antiaggregant and anticoagulant drugs for the treatment of cardiovascular and cerebrovascular diseases, the incidence of GIS bleeding increases. Mortality also increases in this age group due to other accompanying diseases [6]. NSAIDs show analgesic, antipyretic and anti-inflammatory effects by inhibiting cyclooxygenase (COX) enzyme. Aspirin is the prototype of this group of drugs which is defined as non-

Table 5. Characteristic features of the patients who need intensive care

	n	Mean±SD	Median (Min-Max)
Age (year)	31	81.4+7.2	82 (70-95)
		n	%
Gender			
Male		18	58.1
Female		13	41.9
Complaints			
Hematemesis		7	22.6
Hematemesis+Melena		8	25.8
Melena		16	51.6
Endoscopic findings			
Gasritis+ Esophagitis		0	0.0
Gastritis		4	12.9
Gastric Ca		4	12.9
Normal		0	0.0
Esophagitis		2	6.5
Esophageal Ulcer		0	0.0
Esophageal Vari		0	0.0
Peptic ulser		19	48.5
Forrest 1A		4	12.9
Forrest 1B		2	6.5
Forrest 2A		5	16.2
Forrest 2B		0	0.0
Forrest 2C		0	0.0
Forrest 3		4	12.9
ASA		11	35.5
NSAID		9	29.0
Dabigatran		6	19.4
Apixaban		2	6.5
Clopidogrel		2	6.5
Rivaroxaban		0	0.0
Warfarin		0	0.0
Enoxaparin		0	0.0

Table 6. Clinical characteristics, and endoscopic findings of deceased patients

	n	Mean+SD	Median (Min-Max)
Age (year)	12	75.3+7.2	74 (67-86)
		n	%
Gender			
Male		8	66.7
Female		4	33.3
Complaints			
Hematemsis		4	33.3
Hem+Mel		2	16.7
Melena		6	50.0
Endoscopic			
Gastritis+Esophagitis		0	0.0
Findings			
Gastritis		0	0.0
Gastric Ca		2	16.7
Normal		0	0.0
Esophagitis		0	0.0
Esophageal Ulcer		0	0.0
Esophageal Varices		0	0.0
Peptic ulcer		10	83.4
Forrest 1A		2	16.7
Forrest 1B		0	0.0
Forrest 2A		2	16.7
Forrest 2B		0	0.0
Forrest 2C		0	0.0
Forrest 3		6	50
Warfarin		4	33.3
Rivaroxaban		2	16.7
NSAIDs		2	16.7
Apixaban		0	0.0
Dabigatran		0	0.0
ASA		0	0.0
Clopidogrel		0	0.0
Enoxaparin		0	0.0

steroidal anti-inflammatory drugs (NSAIDs). NSAIDs affect the gastrointestinal system mucosa negatively and cause damage. Local and systemic mechanisms in combination play a role in this effect.

With direct effect on stomach and duodenum mucosa, they may lead to epithelial damage and superficial petechia, with resultant occult, and massive bleedings. NSAIDs also inhibit the synthesis of cytoprotective prostaglandins by inhibiting the COX enzyme.

The cytoprotective effects of prostaglandins include increasing bicarbonate release and increasing resistance to superficial epithelium against injury, enhancing mucosal regeneration and mucosal blood flow. NSAIDs inhibit all these mucosal protective mechanisms of prostaglandins and cause GIS bleeding [7–9].

Yalçın et al. reported that 52.6% of the patients who had GIS bleeding used ASA and NSAID. In the study of Günşar et al., and Şimşek et al. [10, 11], 74.6%, and 31.5 % of the patients with complaints of GIS were using these drugs, respectively. In our study, ASA was used in 31.5% and NSAID in 20.7% of the patients. In other words, 52.2% of our patients were using NSAIDs and/or ASA.

In our study, 60.9% of the patients were male and 39.1% of them were female. The male/female ratios differed in various studies (Fleischer et al. [12] 2.19/1, Paspatis et al. [13] 2.4/1 and Zaltman et al. [14] 1.7/1. In our study, the male/female ratio was 1.5/1, which was consistent with the literature. It has been reported in many previous studies that male gender is an independent risk factor for upper GI bleeding [15].

The use of endoscopy in upper GIS bleeding is the most appropriate method for both correct diagnosis and interventional treatment [16]. In a study published in JAGS in the year 2010 on 113 patients over 65 years of age, the most common cause of upper GIS bleeding was reportedly gastritis and duodenal ulcer (66%) [17]. Yalçın et al. also reported causes of upper gastrointestinal bleeding as a peptic ulcer (63.2%), erosive gastroduodenitis (16.3%) and esophageal varices (9.4%).

Also, in our study, the most common causes of upper GIS bleeding in this age group were peptic ulcer (55.4%), gastritis (25%) and esophageal varices (7.6%). Mortality rates in acute upper gastrointestinal bleeding are still high, despite medical treatment and interventional treatment mortality rates range between 2 and 10%. When the mortality rates in the literature are examined, in a study conducted by Clason et al., [18] mortality rates of 3% and 35% were reported in patients under and over 60 years of age, respectively. In the studies of Aksöz et al., Ercan et al., Ünsal and Şimşek et al. mortality rates of 7.4%, 6.2%, and 6% were repoprted, respectively [19]. In our study, the mortality rate was 6.5% in accordance with the literature. When we examined our twelve deceased patients in our study, we found gastric cancer in two, and upper gastrointestinal bleeding due to peptic ulcer in 10 patients. In addition, these deceased patients were using oral anticoagulants (warfarin and rivaroxaban) more frequently. This condition suggests us that the presence of other concomitant diseases as cerebrovascular diseases, atrial fibrillation, and cardiovascular diseases that require the use of oral anticoagulants contribute considerably to mortality rates, and in some cases, we thought that the patients died not from GIS bleeding but from other concomitant diseases.

Morbidity and mortality rates increase with age in patients with upper gastrointestinal bleeding. The presence of concomitant diseases, the amount, and recurrence of bleeding, the success in achieving endoscopic hemostasis, the characteristic feature of the lesion causing the bleeding are factors that affect the prognosis. When we examined the characteristics of the patients treated in the intensive care units in our study, we found that these patients were relatively older (mean age, 81.4±7.2 years), and the most common cause of bleeding (16.2%) was Forrest 2a- peptic ulcer.

Conclusion

ASA, clopidogrel, NSAIDS and oral anticoagulant drugs play an important role in the etiology of upper gastrointestinal bleeding seen in the elderly. Therefore, these drugs should be used with caution in the elderly patient population, and their indications should be well-reviewed. Addition of gastric protective drugs should not be neglected if necessary for the treatment of patients using ASA and NSAID. Especially very old people with concomitant systemic disease(s) should be treated under intensive-care conditions.

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