

NSAID, antiaggregant, and/or anticoagulant-related upper gastrointestinal bleeding: Is there any change in prophylaxis rate after a 10-year period?

Dinç Dinçer¹, Ece Ulukal Karancı², Mete Akın¹, Haydar Adanır¹

¹Department of Gastroenterology, Akdeniz University School of Medicine, Antalya, Turkey

²Department of Internal Medicine, Akdeniz University School of Medicine, Antalya, Turkey

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ABSTRACT

Background/Aims: Using proton-pump inhibitor (PPI) is a protective option for patients who require long-term non-steroidal anti-inflammatory drugs (NSAIDs) and antiaggregants. In our previous study, the rate of PPI use in prophylaxis was found to be 2%. Here we aimed to investigate whether there is a change in PPI use in prophylaxis in a similar patient group after 10 years.

Materials and Methods: The patients who followed up with upper gastrointestinal (GI) bleeding diagnosis between January 01, 2016 and December 31, 2017 were retrospectively evaluated. Patients who had malignancy or variceal hemorrhage were excluded. Ninety-six patients, who had taken NSAIDs, antiaggregants, or anticoagulants that were considered as the possible cause of bleeding, were included in the study. Risk groups for NSAID GI toxicity and PPI use rates in these patients were evaluated.

Results: Twenty (21%) of all patients with upper GI bleeding were using PPI. According to the pre-bleeding risk factor assessment, 86% of the patients were found to have moderate to high risk for NSAID-related GI bleeding, and 81% of these patients were not using PPI. PPI prophylaxis was not provided to 15 (75%) of the 20 patients with previous history of peptic ulcer bleeding.

Conclusion: Despite many studies and recommendations on risk factors and prophylaxis for NSAID-related bleeding, prophylactic PPI use is still largely ignored by physicians. The rate of PPI use in the patient group of this study was found still quite insufficient.

Keywords: Upper gastrointestinal bleeding, prophylaxis, proton-pump inhibitors, NSAID, antiaggregants

INTRODUCTION

Upper gastrointestinal (GI) system bleeding is a common medical condition worldwide. Although the frequency of bleeding due to peptic ulcer has decreased in recent years, it can still be associated with a mortality rate of 2%-10% (1,2). Non-steroidal anti-inflammatory drugs (NSAIDs) might be associated with several GI problems, including particularly dyspeptic symptoms, peptic ulcer, and GI bleeding. NSAIDs consist of a commonly prescribed drug group. In Turkey, according to the International Medical Statistic (IMS) data, 120 million NSAIDs were prescribed in 2013. No association is available between the severity of dyspeptic symptoms and the presence of NSAID-related erosive or ulcerative lesions in the stomach or duodenum. In prophylaxis of NSAID-related GIS toxicity, the risk factors and the risk groups should be taken into consideration (Table 1) (3).

Currently, the use of proton-pump inhibitor (PPI) is the safest and protective option for patients who require

long-term NSAIDs and/or aminosalicic acid (ASA) or clopidogrel use. In our previous study, the rate of PPI use in prophylaxis was found to be 2%, even in the high-risk group for GI bleeding due to NSAID use (4). Here, in this study, we aimed to investigate whether there is a change in PPI use in prophylaxis in a similar patient group after 10 years.

MATERIALS AND METHODS

The patients who followed up with upper GI bleeding diagnosis between January 01, 2016 and December 31, 2017 were retrospectively evaluated. The patients under the age of 18 years and found to have malignancy or variceal hemorrhage were excluded from the study, and 128 patients with a diagnosis of upper GI bleeding were included. The study included 96 patients (75% of all patients) with upper GI bleeding who had taken NSAIDs, antiaggregants, or anticoagulants, which were considered as the possible cause of bleeding, at most one week prior to the bleeding. The data regarding age; sex; comor-

Corresponding Author: Dinç Dinçer; dinc@akdeniz.edu.tr

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Table 1. Risk factors associated with NSAIDs related to GI toxicity.

High Risk

1. History of complicated ulcer (recently in particular)
2. Multiple (more than two) risk factors

Moderate Risk

1. Age >65
2. High-dose NSAID treatment
3. History of uncomplicated ulcer
4. Concomitant ASA (low doses included), glucocorticoid, or anti-coagulant use

Low Risk

1. Without any risk factors

NSAID: non-steroidal anti-inflammatory drug; ASA: aminosalicic acid.

bid diseases; use of NSAIDs, antiaggregant, and/or anti-coagulants; PPI; history of peptic ulcer and ulcer-related bleeding; *Helicobacter pylori* status; the length of hospital stay; the management of bleeding; and the amount of erythrocyte suspension transfused were retrospectively recorded.

The presence of *H. pylori* was determined by the CLO (Campylobacter-like organism) test. Risk groups for NSAID GI toxicity were determined according to the criteria given in Table 1. All patients underwent endoscopy within the first 24 hours of bleeding. Endoscopy was performed with Fujinon EG-530 WR (Tokyo, Japan) or Olympus GIF-H170 (Tokyo, Japan) gastroscopes. Forrest classification was used to classify ulcers (5,6). Patients with visible vascular signs at the base of the ulcer, active leakage, or spouting hemorrhage were treated with diluted epinephrine (1/10000) injection around the lesion together with endoscopic intervention with a heater probe (by using 10F probes with an Olympus HPU-20 brand device) or argon plasma coagulation (with an Erbe VIO 200 S brand device with the power/gas flow adjustment at 50 W and 1.8 L/minute). All patients were monitored with a similar medical treatment protocol after undergoing endoscopy (pantoprazole intravenous 80 mg bolus followed by intravenous 40 mg every 12 hours until alimentation).

Ongoing bleeding despite blood transfusions more than five units within 24 hours and more than 12 units within 48 hours, and recurrent hemorrhages in the hospital

accompanied by shock in spite endoscopic intervention were considered as emergency surgical criteria. In-hospital deaths were defined as early mortality.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences package program, version 20 (IBM Corp.; Armonk, NY, USA). Our study is a descriptive study; and descriptive data were expressed as mean±standard deviation for continuous variables and as number of cases and percentage for categorical variables.

RESULTS

The median age of 96 patients with NSAID and/or anti-coagulant-associated upper GI bleeding was 70.5/year, and 63 (66%) were male. Of these, 93 patients were using NSAIDs and/or antiplatelet (ASA or clopidogrel); 21 patients were additionally using anticoagulants (warfarin, low molecular weight heparin (LMWH), rivaroxaban); and three patients were using anticoagulants alone. For 44 (46%) patients, medications were prescribed by cardiologists. Of all patients, 20 (21%) were using PPI. Eighty-one (83%) patients had comorbid diseases. Erosive gastritis was the most common cause of bleeding (33%). While in 84 patients (87.5%) the bleeding stopped spontaneously, in 12 patients (12.5%) endoscopic or surgical procedure was applied. Endoscopic therapy was successful in 11 of 12 patients. Surgical treatment was required in one patient who had failed endoscopic therapy. Second look endoscopy was performed in two patients, who had initially ulcer with spurting hemorrhage, and bleeding was found to be under control and no additional approach was required. A 78-year-old female patient, who was diagnosed with heart failure and hypertension and was on hemodialysis due to chronic renal failure, had died in the follow-up period due to hypotension and cardiorespiratory arrest during hemodialysis, despite the absence of bleeding symptoms. Two of eleven patients (18.2%) who underwent CLO were found to be *helicobacter* positive. These findings are presented in Table 2. The median length of hospital stay was four days. The median of erythrocyte suspension delivered during this period was one unit. According to the pre-bleeding risk factor assessment, 86% of the patients were found to have moderate to high risk for NSAID-related GI bleeding, and 81% of these patients were not using PPI. PPI prophylaxis was not provided to 15 (75%) of the 20 patients with previous ulcerative bleeding history. The distribution of patients according to risk group, risk factors, and rate of PPI use are presented in Table 3. Cardiol-

Table 2. Patient characteristics and medicine used.

	n	%
Sex		
Women	33	34
Men	63	66
Comorbid disease		
No	15	16
Yes	81	84
Causes of bleeding		
Erosive gastritis	33	34
Gastric ulcer	28	29
Duodenal ulcer	22	23
Duodenal+gastric ulcer	8	8.5
Other	5	5.5
Forrest classification of ulcers		
Spurting hemorrhage	2	3
Oozing hemorrhage	4	7
Non-bleeding visible vessel	4	7
Adherent clot	5	9
Hematin covered lesion	8	14
Clean based	35	60
Medicine used		
NSAID alone	16	17
NSAID plus ASA	3	3.1
NSAID plus clopidogrel	2	2.1
NSAID plus anticoagulant	9	9.3
ASA alone	33	34
ASA plus clopidogrel	4	4.2
ASA plus anticoagulant	7	7.3
Clopidogrel alone	14	14.6
Clopidogrel plus anticoagulant	5	5.2
Warfarin alone	2	2.1
Rivaroxaban alone	1	1.1
The division medicine prescribed in		
Internal medicine	7	7.2

	n	%
Physical therapy and rehabilitation	3	3.1
Cardiology	44	46
Neurology	8	8.3
Cardiovascular surgery	8	8.3
Chest diseases	3	3.1
General practitioner	6	6
Patients' own use	16	17
Unknown	1	1
PPI use prior to bleeding	20	21
<i>Helicobacter pylori</i> positive*	2	18
Mortality	1	1

NSAID: non-steroidal anti-inflammatory drug; ASA: aminosalicic acid; LMWH: low molecular weight heparin; PPI: proton-pump inhibitor. *CLO test was performed in 11 of 96 patients and positive in 2 of 11 patients (%18).

Table 3. Risk factors, risk groups, and PPI use ratios.

	n	%
Risk group		
Low	13	14
Moderate	53	55
High	30	31
Risk factors		
History of ulcerative bleeding	20	21
History of peptic ulcer	24	25
Age >65	67	70
High dose of NSAID use	22	23
Medication use together with NSAIDs	15	16
PPI use ratio according to risk level		
Low risk	4	31
Moderate to high risk	16	19

NSAID: non-steroidal anti-inflammatory drug; PPI: proton-pump inhibitor.

gists were the specialists who prescribed the medicine in 34 (51%) of 66 patients with moderate to high risk not on PPI (Table 4).

Table 4. The division medicine prescribed in for patients with moderate to high risk and not using PPI.

	n	%
Cardiology	34	51.5
Patients' own use	11	17
Neurology	8	12
Internal medicine	4	6
Cardiovascular surgery	3	4.5
General practitioner	3	4.5
Physical therapy and rehabilitation Chest diseases	2	3
	1	1,5

PPI: proton-pump inhibitor.

DISCUSSION

NSAIDs are one of the most prescribed drug groups in the world (7). The use of antiplatelet therapy has also significantly increased because of the increase in coronary artery diseases (8). Although mostly being asymptomatic for the first three months of NSAID use, the incidence of gastric ulcer was reported to be 10%-40%, and the incidence of duodenal ulcer was reported to be between 4% and 15% in endoscopic studies (9). The use of low-dose ASA in patients requiring long-term cardiovascular protection was associated with increased risk of GI bleeding or death from GI complications independent of other risk factors. In the studies, gastric erosion was found to be 63% and peptic ulcer approximately 10% in long-term ASA users (10).

A meta-analysis of 14 randomized controlled trials revealed a twofold increase of relative risk approximately for GI bleeding in patients receiving ASA between 75 mg and 325 mg, and it was reported that the risk was higher in patients with multidrug use and co-morbidity, particularly in older patients (11). Clopidogrel, placed on the market due to the low GI side effects, was found to have lower GI bleeding rate (1.99% vs. 2.66%), severe GIS bleeding risk (0.49% vs. 0.71%), and GI side effects (27.1% vs. 29.8%) compared to ASA in the phase studies (12). However, in current studies, the risk of GI bleeding with clopidogrel use was found to be similar with ASA, anticoagulant, or NSAID use. Furthermore, while GI bleeding risk associated with ASA use alone was 0.6%-1%, clopidogrel inclusion to the treatment was reported to be associated with an additional 1% increase in the risk (13). Moreover, studies have shown that high doses of NSAIDs cause a

significant relative risk increase in GI toxicity compared to lower doses (14).

Effective strategies for the prevention of NSAID or antiplatelet-induced peptic ulcers and their complications include medication property-based measures such as using enteric-coated or buffered ASA preparations and selective COX-2 inhibitors; however, the most preferred strategy is the addition of gastric mucosa protecting agents to the treatment. Identification of the patients with GI and cardiovascular risk factors is an appropriate strategy. The use of COX-2 selective NSAIDs or the inclusion of PPI or misoprostol in the treatment has been suggested to reduce the incidence in high-risk groups. While COX-2 selective NSAIDs reduce the incidence of peptic ulcer by 71%, the use of PPI reduces the incidence of peptic ulcer in these patients by 69% (15,16). In a Cochrane systematic review of 40 randomized controlled trials comparing the efficacy of misoprostol, PPI and H2-receptor antagonists in the prevention of NSAID-related gastric and duodenal ulcers, PPIs significantly reduced the risk of both gastric and duodenal ulcers and significantly improved dyspeptic symptoms. PPIs were found to be more effective than standard-dose H2-receptor antagonists in this respect; and it was emphasized that they were better tolerated than misoprostol, and side effect incidence was significantly lower (17).

Despite the established risk factors and the proven protective effect of PPI therapy, the number of patients provided prophylaxis is still insufficient even in risky groups. Morneu et al. (18) investigated the GI prophylaxis in patients receiving dual antiplatelet therapy with aspirin and clopidogrel, and 56.4% of patients with prophylaxis indication were found not to use PPI3. Ruiz et al. (19) demonstrated that only PPI prophylaxis in effective dose was effective together with treatment adherence in reducing the risk of NSAID or antiplatelet drug-associated upper GI bleeding in Spain in a multicenter case control study. However, in the same study, the rate of patients on PPI with full adherence and effective dose was reported as 4.85%.

In our previous study conducted in our center in 2006, only 2% of patients were found to be using PPI, who were followed up due to upper GI bleeding and had moderate to high risk of NSAID-related GI toxicity before bleeding. We think that the history of NSAID-related peptic ulcer bleeding is a condition that should be questioned and should not be ignored by physicians in these patients. However, in our previous study, it was determined that

NSAIDs were prescribed by physicians in approximately half of the patients with a history of NSAID-related peptic ulcer bleeding, and that only one of them was taking PPI prophylaxis (4). In the current study involving a similar patient group, prophylactic PPI use rate was found to be 21% overall and 19% in moderate- to high-risk patients. Only 5 (25%) of 20 patients with a history of NSAID-related peptic ulcer bleeding had been given PPI prophylaxis. Although there was a 17-point (2% vs. 19%) increase in the rate of PPI use in this patient group after 10 years, this increase is still quite insufficient because 81% of patients who need to take PPI are not taking medication. Despite many studies and recommendations on risk factors and prophylaxis in the guidelines of various divisions, risk factors for NSAID-related bleeding are still largely ignored by physicians, and prophylactic PPI treatment is not started for these patients. NSAIDs and/or antiplatelet/anticoagulant drugs have been observed to be prescribed in various departments, especially in cardiology, and started by patients themselves. When all patients were considered, it was determined that the group of physicians who started these therapies were mostly cardiologists; furthermore, 34 of 44 patients (77%) who were given treatment by cardiologists were not on PPI even though they had moderate to high risk of GI toxicity. The fact that patients with peptic ulcer and its complications are mostly evaluated and followed up by gastroenterology seems to result in low awareness among other physicians about these complications. To increase the prophylaxis rate and reduce the risk of complications, it is obvious that increased awareness is required among both patients and physicians.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of the Akdeniz University School of Medicine (Decision Date: December 26, 2018; Decision Number: 923).

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

Peer-review: Externally peer-reviewed.

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