

Characteristics of Hemorrhagic Peptic Ulcers in Patients Receiving Antithrombotic/Nonsteroidal Antiinflammatory Drug Therapy

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Background/Aims: Antithrombotic/nonsteroidal antiinflammatory drug (NSAID) therapies increase the incidence of upper gastrointestinal bleeding. The features of hemorrhagic peptic ulcer disease in patients receiving antithrombotic/NSAID therapies were investigated. **Methods:** We investigated the medical records of 485 consecutive patients who underwent esophagogastroduodenoscopy and were diagnosed with hemorrhagic gastroduodenal ulcers. The patients treated with antithrombotic agents/NSAIDs were categorized as the antithrombotic therapy (AT) group (n=213). The patients who were not treated with antithrombotics/NSAIDs were categorized as the control (C) group (n=263). The clinical characteristics were compared between the groups.

Results: The patients in the AT group were significantly older than those in the C group ($p<0.0001$). The hemoglobin levels before/without transfusion were significantly lower in the AT group (8.24 ± 2.41 g/dL) than in the C group (9.44 ± 2.95 g/dL) ($p<0.0001$). After adjusting for age, the difference in the hemoglobin levels between the two groups remained significant ($p=0.0334$). The transfusion rates were significantly higher in the AT group than in the C group ($p=0.0002$). However, the outcome of endoscopic hemostasis was similar in the AT and C groups. **Conclusions:** Patients with hemorrhagic peptic ulcers receiving antithrombotic/NSAID therapies were exposed to a greater risk of severe bleeding that required transfusion but were still treatable by endoscopy. (**Gut Liver 2012;6:423-426**)

Key Words: Peptic ulcer; Hemorrhagic ulcer; Antithrombotic therapy; Anti-inflammatory agents, non-steroidal; Endoscopic

hemostasis

INTRODUCTION

Increasing numbers of patients are given antithrombotic agents for vascular protection. The mainstay of such antithrombotic therapy (AT) is low dose aspirin (LDA).¹ However, LDA is an ulcerogenic agent that inhibits cyclooxygenase, thus increasing the risk of peptic ulcers and upper gastrointestinal bleeding (UGIB).²⁻⁵ In addition, antithrombotic therapies are becoming more aggressive, and dual antiplatelet therapies, mainly combinations of LDA with clopidogrel, have become standard treatment for preventing stent thrombosis in patients with coronary artery diseases who undergo coronary stenting with drug-eluting stents.⁶ Importantly, combined antithrombotic therapies further increase the threat of UGIB, compared with antiplatelet monotherapies.⁷⁻⁹ Much attention has been paid to the gastrointestinal risks of antithrombotic therapies, and a statement regarding the prevention of upper gastrointestinal complications during AT has recently been published.¹⁰ In addition, use of nonsteroidal antiinflammatory drugs (NSAIDs) is also known to increase the risk of UGIB.^{3,8} Although an increase in the incidence of UGIB during antithrombotic/NSAID therapies has been extensively described, comparisons between the characteristics of hemorrhagic peptic ulcers in patients with and without such therapies are scarce, in particular regarding whether they are associated with an increased risk of massive bleeding and whether they can be treated endoscopically. Therefore, we retrospectively analyzed the data from recent hemorrhagic peptic ulcer patients, and compared the outcomes between antithrombotic drug users

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and non-users.

MATERIALS AND METHODS

We conducted a retrospective study of 485 consecutive patients who underwent esophagogastroduodenoscopy and were diagnosed with hemorrhagic gastric and/or duodenal ulcers between April 2008 and March 2010 in the Department of Medicine and Bioregulatory Science, Kyushu University Hospital, Aso Ilzuka Hospital, Saiseikai Fukuoka General Hospital, Kyushu Medical Center, Harasanshin Hospital, and Fukuoka-Higashi Medical Center. We reviewed the medical records of these patients to determine their baseline demographics and clinical characteristics, including age, sex, presence, or absence of *Helicobacter pylori* infection, history of peptic ulcer disease, current smoking habit, use of LDA, use of antithrombotic agents, use of NSAIDs, use of anti-ulcer drugs, hemoglobin levels at endoscopy (before transfusion, if performed), success or failure of endoscopic hemostasis and number of attempts, Forrest classification, localization of ulcers, and outcome of treatment. *H. pylori* infection was diagnosed by serum levels of anti-*H. pylori* antibodies, urea breath test, rapid urease test, or the culture of *H. pylori* from gastric mucosal biopsy samples. Of the 485 patients, the use of antithrombotic agents was unknown in eight, and the ulcerative lesion in one further patient was finally diagnosed as duodenal cancer. These patients were excluded from the analysis. Of the remaining 476 patients, 213 were treated with antithrombotic agents and/or non-aspirin NSAIDs (NA-NSAIDs), and were allocated to AT group. The remaining 263 patients who received no antithrombotic agents or NA-NSAIDs were allocated to control (C) group. Antithrombotic agents included antiplatelet agents such as LDA, clopidogrel, and ticlopidine, and anticoagulants such as vitamin K antagonists. In the AT group, 87 patients received LDA, 12 received clopidogrel, 10 received ticlopidine, 36 received warfarin, 106 received NA-NSAIDs, and 16 received other antithrombotic agents. The AT group was further subdivided into patients taking only one antithrombotic agent/NSAIDs (single therapy [ST] group) and those who were treated with two or more antithrombotic agents/NSAIDs (combined therapy [CT] group). Of the 213 AT group patients, 167 were allocated to the ST group and 46 to the CT group. The ST group was subdivided into patients taking only an antithrombotic agent (antithrombotic alone [ATA] group) and those who took only a NA-NSAID (NA-NSAID alone [NSA] group). Of the 167 ST group patients, 81 were allocated to the ATA group and 86 to the NSA group. This study was carried out in accordance with the World Medical Association Declaration of Helsinki.

For statistical analysis, the Mann-Whitney U test and chi-square test were used to compare numerical and categorical data between two groups, respectively. The Kruskal-Wallis H test was applied for the comparison of numerical data among three groups. When statistical significance was reached among

three groups, the Mann-Whitney U test with Bonferroni correction was used to compare between each category. For comparison of hemoglobin levels with adjustment for age, multiple regression analyses were performed. Statistical analysis was carried out using JMP software (SAS Institute, Cary, NC, USA). A value of $p < 0.05$ was considered to be statistically significant. However, for the Mann-Whitney U test with Bonferroni correction, $p < 0.05/\text{number of groups to compare}$ was considered to be significant.

RESULTS

The baseline demographics of the patients are described in Table 1. The mean ages of patients in the AT and C groups were 70.9 and 59.5 years, respectively ($p < 0.0001$). The C group was more male predominant than the AT group ($p = 0.0351$). The frequency of *H. pylori*-negative patients was significantly higher in the AT group than in the C group ($p < 0.0001$). A past history of peptic ulcers was significantly less frequent in the AT group, compared with the C group ($p = 0.0405$), and the percentage of smokers was significantly lower in the AT group than in the C group ($p = 0.0135$). Significantly more patients in the AT group received prophylactic anti-ulcer drugs, compared with the C group ($p < 0.0001$).

The characteristics of the peptic ulcers in each group are shown in Table 2. Number of duodenal ulcer patients was smaller in the AT group than in the C group ($p = 0.0029$). In terms of gastric ulcers, more ulcers were located in the lower part of the stomach in the AT group than in the C group ($p = 0.0337$). The mean hemoglobin levels at first endoscopy without/before transfusion were 8.24 and 9.44 g/dL in the AT and C groups, respectively ($p < 0.0001$). Transfusion was given more frequently in the AT group than in the C group ($p = 0.0002$). Endoscopic hemostasis was performed in 174 of 213 patients in the AT group and 234 of 263 patients in the C group, with success

Table 1. Demographics of Hemorrhagic Peptic Ulcer Patients Treated with and without Antithrombotic Agents

Demographic	AT group (n=213)	C group (n=263)	p-value
Age, mean (SD), yr	70.9 (11.8)	59.5 (16.3)	<0.0001
Range	33-97	13-95	
Sex, female/male	74/139	68/195	0.0351
<i>Helicobacter pylori</i> infection, positive/negative	96/45	179/30	<0.0001
Past history of peptic ulcer, yes/no	59/151	97/165	0.0405
Smoking, yes/no	74/126	122/129	0.0135
Prophylactic use of anti-ulcer drug, yes/no	66/142	28/235	<0.0001

AT, antithrombotic therapy; C, control; SD, standard deviation.

Table 2. Clinical Features of Hemorrhagic Peptic Ulcer Patients Treated with and without Antithrombotic Agents/NSAIDs

Feature	AT group (n=213)	C group (n=263)	p-value
Gastric ulcer/duodenal ulcer	163/50	168/95	0.0029
Localization (upper/mid/lower) of gastric ulcer	41/81/36	54/91/20	0.0337
Hemoglobin level, mean (SD), g/dL	8.24 (2.41)	9.44 (2.95)	<0.0001
Range	3-15.6	2.1-16.7	
Transfusion, performed/not performed	127/86	112/151	0.0002
Endoscopic hemostasis, performed/not performed	174/39	234/29	0.0239
Outcome of endoscopic hemostasis, success/failure	172/2	225/9	0.0963
No. of endoscopic hemostasis procedures, 1/>1	151/22	202/32	0.7781
Forrest classification, Ia or Ib/others	72/141	93/169	0.6999
Outcome, recovered or death due to other diseases/death due to UGIB	208/5	259/4	0.5103

NSAID, nonsteroidal antiinflammatory drug; AT, antithrombotic therapy; C, control; SD, standard deviation; UGIB, upper gastrointestinal bleeding.

rates of 98.8% and 96.2%, respectively. The rates of endoscopic hemostasis were unexpectedly higher in the C group. However the success rates and the number of endoscopic procedures performed per patient were similar in the two groups. The percentages of ulcers with active bleeding (Ia and Ib according to Forrest classification) were similar in the two groups. Regarding the treatment outcomes, number of death due to hemorrhagic peptic ulcer were similar in the AT and C groups.

It was considered patients in the AT group had more severe bleeding than those in the C group as hemoglobin levels were significantly lower in the AT group than in the C group. However, it might be because AT group patients were significantly older than C group patients. With adjustment for age, there were still significant difference in hemoglobin levels between the AT and C groups ($p=0.0334$).

To clarify whether combined antithrombotic therapies further increased the severity of bleeding compared with single antithrombotic agent therapies, the AT group patients were subdivided into the ST and CT groups. Hemoglobin levels in both the ST (mean, 8.28 g/dL; standard deviation [SD], 2.48; range, 3 to 15.6 g/dL) and CT groups (mean, 8.08 g/dL; SD, 2.13; range, 3.7 to 13.5 g/dL) were significantly lower than in the C group (mean, 9.44 g/dL; SD, 2.95; range, 2.1 to 16.7 g/dL) ($p<0.0001$ and 0.0027, respectively), but hemoglobin levels in the CT group were not significantly lower than those in the ST group ($p=0.8457$). To know whether there is a difference between patients who take an antithrombotic agent and those who take a NA-NSAID in the severity of hemorrhage, the ST group was subdivided into the ATA and NSA groups. Hemoglobin levels of the ATA group (mean, 8.36 g/dL; SD, 2.47; range, 4.1 to 15.6 g/dL) and the NSA group (mean, 8.22 g/dL; SD, 2.51; range, 3 to 15.5 g/dL) were not significantly different ($p=0.8189$).

DISCUSSION

Considerable attention has recently been paid to antithrom-

botic/NSAID therapy as a cause of UGIB. In this study, we clarified the characteristics of hemorrhagic peptic ulcers in patients receiving antithrombotic/NSAID therapy, by comparing the clinical data for patients with and without antithrombotic agents/NA-NSAIDs. Regarding the patient demographics, patients in the AT group were significantly older than those in the C group, which is understandable, because older patients would potentially have had more reasons to take antithrombotic agents for vascular protection or NSAIDs for pain relief. The proportion of patients with *H. pylori* infection was lower in the AT group than in the C group, suggesting that most peptic ulcers in the C group were caused by *H. pylori* infection, while most in the AT were caused by ulcerogenic agents, such as LDA or NA-NSAIDs. The proportion of patients with a past history of peptic ulcers was higher in the C group than in the AT group. This could be because most patients in the C group had not received *H. pylori* eradication therapy and thus had persistent *H. pylori* infection and the risk of recurrent disease, while patients with a history of peptic ulcers who were receiving antithrombotic/NSAID therapy were more likely to have been given prophylactic anti-ulcer drugs. Indeed, more patients in the AT group received anti-ulcer drugs, compared with the C group. More patients in the C group than the AT group had a smoking habit, suggesting that smoking could be a trigger for peptic ulcer disease in *H. pylori*-positive patients, while ulcerogenic medicines themselves may be enough to induce peptic ulcers.

The percentage of hemorrhagic duodenal ulcers was lower in the AT group than in the C group, in line with previous reports showing a trend for gastric ulcers to be more frequently observed than duodenal ulcers in LDA users.^{2,11} In the case of gastric ulcers, ulcers associated with antithrombotic/NSAID therapy were more likely to occur in the lower region of the stomach than those in patients without antithrombotic/ulcerogenic agents. Hemoglobin levels in the AT group were significantly lower than those in the C group. As patients in the AT group were significantly older than those in the C group, this

may be due to the older age rather than the use of antithrombotic/ulcerogenic medicine. To clarify this point, we conducted multiple regression analyses and showed hemoglobin levels in the AT group was still significantly lower than those in the C group with the adjustment for age. It was thus clearly demonstrated that, once a hemorrhagic ulcer occurs, patients receiving antithrombotic/NSAID therapy are exposed to a greater risk of severe bleeding than patients not taking antithrombotics/NSAIDs. Significantly more patients in the AT group required transfusions, compared with the C group. However, peptic ulcer bleeding during AT appeared to be treatable endoscopically. The rate of endoscopic therapy was unexpectedly even lower in the AT group than in the C group. The outcome of endoscopic therapy was similar between the two groups. Fortunately, the frequency of death due to peptic ulcer disease was no higher in the AT group than in the C group. Although CT with more than one antithrombotic agent, or an antithrombotic agent with an NA-NSAIDs, has been shown to be associated with an increased incidence of UGIB, compared with treatment with a single antithrombotic agent,^{7,8} this study found no evidence that CT was associated with more severe bleeding than ST. It was likely that the severity of hemorrhage was not significantly different between the patients with an antithrombotic agent and those with a NA-NSAID.

It is of interest whether underlying diseases such as diabetes mellitus, ischemic heart disease or chronic renal disease influence the severity of bleeding from peptic ulcer. This issue was not analyzed in this study and larger sample size may be required to clarify such points. Therefore, further studies are thus awaited to address these questions.

In summary, once hemorrhagic peptic ulcer disease occurs in patients receiving antithrombotic/NSAID therapy, they are exposed to an increased risk of severe hemorrhage, which may require transfusion. Thus, patients who require antithrombotic/NSAID therapy, and are considered to be at high risk of developing peptic ulcers with ulcerogenic agents, should receive prophylactic treatment with anti-ulcer agents. However, like hemorrhagic ulcers in patients without antithrombotics/NSAIDs, peptic ulcer bleeding under antithrombotic/NSAID therapy can still be successfully treated by endoscopic hemostasis.

CONFLICTS OF INTEREST

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