

A study of the changes in the cause of peptic ulcer bleeding

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peptic ulcer bleeding changed from *H. pylori* infection to use of NSAIDs over the 7-year period of study. It seems that the number of low-dose aspirin users has increased with the increase in the proportion of vascular disease. It is necessary to take measures to prevent peptic ulcer bleeding among NSAIDs and low dose aspirin users.

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Key words: Peptic ulcer bleeding; Gastroduodenal ulcer; *Helicobacter pylori*; Nonsteroidal antiinflammatory drugs; Low-dose aspirin

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Abstract

AIM: To clarify the frequency of and changes in the cause of peptic ulcer bleeding.

METHODS: This study retrospectively evaluated the out- and inpatients who underwent endoscopy between 2002 to 2008. The subjects were patients presenting with peptic ulcer bleeding. The details of these patients were obtained from their endoscopic reports and medical records.

RESULTS: The rates of *Helicobacter pylori* (*H. pylori*) infection were significantly low ($P = 0.039$), while the proportion of nonsteroidal antiinflammatory drugs (NSAIDs) users and vascular disease significantly increased over the period studied ($P = 0.034$ and $P = 0.04$, respectively). However, there was no significant difference in the proportion of low-dose aspirin users ($P = 0.832$).

CONCLUSION: It's found that the primary cause of

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection and the use of nonsteroidal antiinflammatory drugs (NSAIDs) are two of the major risk factors for peptic ulcers and ulcer complications^[1]. *H. pylori* infection has been recognized in more than 87% of patients with gastric ulcers and about 96% of patients with duodenal ulcers^[2]. The incidence of peptic ulcers has steadily decreased in Western countries, and this decrease is thought to result from both the widespread eradication of *H. pylori* and the decreasing prevalence of *H. pylori* infection in the population as a result of the improvement in hygienic conditions^[3,4].

On the other hand, the use of NSAIDs is associated with an increased risk of major upper gastrointestinal complications, including bleeding and perforation^[5-7]. With the increase in the elderly population, which has led to an increase in musculoskeletal and joint disorders, it seems that the consumption of NSAIDs has increased. In addition, antiplatelet therapy with low-dose aspirin (75-325 mg) reduces the risk of vascular events in patients with cardiovascular and cerebrovascular diseases^[8-10]. Although low-dose aspirin has the advantages of being both highly effective and inexpensive, they pose a significant risk for developing peptic ulcer bleeding^[11-13]. The aim of this study is to clarify the frequency and trends of peptic ulcer bleeding over the past seven years.

MATERIALS AND METHODS

Patients

This study retrospectively evaluated the 199 994 of out- and inpatients who underwent endoscopy at Toyama University Hospital between January 2002 and December 2008. We collected the following details of patients with peptic ulcer bleeding from their endoscopic reports and medical records: age, gender, symptoms, *H. pylori* infection, NSAIDs intake, low-dose aspirin intake, previous ulcer history, cardiovascular and cerebrovascular diseases, endoscopic findings, and interventions. The rate of gastroduodenal ulcer (GDU) and peptic ulcer bleeding, average age, body proportions, hematemesis, melena, and previous ulcer histories, rate of *H. pylori* infection, rate of cardiovascular and cerebrovascular diseases and proportion of NSAIDs and low-dose aspirin users were calculated and compared from 2002 to 2008 based on this information. The subjects were checked for *H. pylori* infection using the ¹³C-urea breath test (UBT) and/or rapid urease test (RUT). *H. pylori* status was defined as *H. pylori*-negative when UBT was negative and *H. pylori*-positive when either UBT or RUT were positive. Peptic ulcer bleeding was defined as a clinical presentation of hematemesis and/or melena, and endoscopic examination showed a peptic gastric and/or duodenal ulcer. However, we also anticipated the presence of upper gastrointestinal tract neoplasm, erosive gastritis, erosive duodenitis, Mallory-Weiss syndrome, and esophagogastric varices.

Statistical analysis

The following details of peptic ulcer bleeding patients were obtained from their endoscopic reports and medical records: age, gender, symptoms, *H. pylori* status, NSAIDs intake, low-dose aspirin intake, previous ulcer history, endoscopic findings, and interventions. The rate of peptic ulcer and/or peptic ulcer bleeding, average age, body proportions, hematemesis, melena, previous ulcer histories, rate of *H. pylori* infection, rate of cardiovascular and cerebrovascular diseases and rate of NSAIDs, low-dose aspirin users were calculated and compared from 2002 to 2008 based on this information.

Changes in each parameter over the period studied were analyzed using the chi-square test. Differences were considered to be statistically significant when $P < 0.05$.

RESULTS

The details of subjects were showed in Table 1. The rate of GDU decreased from 16.9% to 11.3% over the period studied, and there were significant changes ($P < 0.001$). The rate of peptic ulcer bleeding significantly increased from 4.87% to 9.03% during the first three years ($P < 0.001$) and significantly decreased from 9.03% to 5.95% during the last three years ($P < 0.05$). The clinical details of those patients who presented with peptic ulcer bleeding are shown in Table 2. Age and gender did not change significantly over the period studied. The rate of GDU decreased. Cardiovascular and cerebrovascular diseases significantly increased from 29.2% to 61.9% over the period studied ($P = 0.04$). The risk factors of peptic ulcer bleeding are shown in Table 3. *H. pylori* infection rate was 84.2% in 2002, 72.6% in 2005, and 71.4% in 2008, which demonstrates a significant decrease ($P = 0.048$). The greatest cause of peptic ulcer bleeding was the use of gastrointestinal injury drugs, such as NSAIDs and low-dose aspirin. The proportion of NSAIDs users significantly increased ($P = 0.034$), but there were no significant changes in the proportion of low-dose aspirin users ($P = 0.832$). The proportion of NSAIDs (including low-dose aspirin) users significantly increased over the period studied ($P = 0.021$).

DISCUSSION

In this study, it was found that the number of peptic ulcer bleeding cases significantly increased during the first three years. One explanation for this is that while the *H. pylori* infection rate decreased over this period, the main cause of peptic ulcer bleeding changed from *H. pylori* infection to use of NSAIDs, including low-dose aspirin. NSAIDs were associated with approximately 30% of the bleeding peptic ulcers diagnosed in Japan, which shows a significant increase from the figures of previous reports. One reason of the increased number of NSAIDs users is that it is used in treating back and joint pain, which has shown an increased incidence among the increasing elderly population^[14,15]. In the United States, hospitalization and death due to NSAID-related gastrointestinal events have been estimated at 103 000 and 16 500 patients per year, respectively^[16]. In a population-based retrospective case-control study, the adjusted relative risk (RR) of upper gastrointestinal bleeding (UGIB) associated with NSAIDs use was 5.3 [95% confidence interval (CI): 4.5-6.2]^[17]. In our study, NSAIDs use was significantly associated with an increased risk of bleeding ulcer, and the rate of *H. pylori* infection was significantly lower throughout the observed period. Nonetheless, the number of peptic ulcer bleeding was decreased during the last three years. As one of the possibilities, a

Table 1 The incidence of peptic ulcer bleeding

	2002	2005	2008
Number	2910	3023	3121
No. of GDU	493	421	353
Rate of GDU (%)	16.9	13.9	11.3
No. peptic ulcer bleeding	24	38	21
Rate of peptic ulcer bleeding (%)	4.87	9.03	5.95

The rate of GDU significantly decreased during the period studied ($P < 0.001$). The rate of peptic ulcer bleeding significantly increased during the first three years and significantly decreased during the last three years. GDU: Gastroduodenal ulcer.

Table 2 Clinical characteristics of patients with peptic ulcer bleeding

	2002	2005	2008	<i>P</i> value
Cases	24	38	21	
Age (average \pm SD)	63.1 \pm 17.6	69.1 \pm 15.8	65.9 \pm 15.2	0.738
Male <i>n</i> (%)	18 (75.0)	25 (84.8)	15 (71.4)	0.75
Gastric ulcer <i>n</i> (%)	20 (83.3)	31 (81.6)	16 (76.2)	0.824
Haematemesis <i>n</i> (%)	10 (50.0)	10 (30.3)	7 (33.3)	0.433
Melena <i>n</i> (%)	13 (65.0)	26 (78.8)	14 (66.7)	0.534
Vascular disease <i>n</i> (%)	7 (29.2)	13 (34.2)	13 (61.9)	0.048

Clinical characteristics of patients with peptic ulcer bleeding. There was significantly increased in vascular disease over the period studied.

study of the Swedish population from 1974-2002 was reported that the increasing the amount of proton pump inhibitor (PPI) has reduced the incidence of peptic ulcer complications^[18]. In fact that gastroesophageal reflux disease is increasing and the usage of PPI is actually increasing in Japan^[19].

Low-dose aspirin is also one of the causes of drug-induced peptic ulcer bleeding. It is widely used because it reduces the risk of cardiovascular events and death in patients with coronary and cerebrovascular diseases. It seems likely that the number of low-dose aspirin users will increase in the future because coronary and cerebrovascular diseases have increased in recent years. However, the use of aspirin, even at a low dose for secondary prevention of cardiovascular events, remains a risk factor for developing UGIB. In addition, more than a few epidemiological studies have suggested that *H. pylori* infection increases the risk of UGIB in patients taking low-dose aspirin^[20,21]. Taha *et al.* reported that the increase in UGIB associated with the use of gastrointestinal toxic drugs increased in subjects treated with low-dose aspirin between 1996 and 2002^[22]. A recent study indicates that the relative risk of UGIB after exposure to low-dose aspirin is 3.7 (95% CI: 3.0-4.5)^[17]. In our study, we found that the proportion of low-dose aspirin users also increased from 8.3% in 2002 to 14.3% in 2008. In addition, our data showed the significant increasing of cardiovascular and cerebrovascular diseases. Therefore, the proportion of low-dose aspirin users will be increased in future. Recently it was suggested that the damaging effect of

Table 3 Risk factors of peptic ulcer bleeding

	2002	2005	2008	<i>P</i> value
<i>Helicobacter pylori n</i> (%)	20/24 (83.3)	20/38 (72.6)	15/21 (71.4)	0.039
NSAIDs <i>n</i> (%)	3 (12.5)	11 (28.9)	10 (47.6)	0.034
Low-dose aspirin <i>n</i> (%)	2 (8.3)	5 (13.2)	3 (14.3)	0.832
NSAIDs and/or	5 (16.7)	16 (42.1)	13 (61.9)	0.021
Low-dose aspirin <i>n</i> (%)				

The *H. pylori* infection rate significantly decreased. On the other hand, the proportion of NSAIDs users was significantly increased. The proportion of low-dose aspirin users demonstrated no significant changes. NSAIDs: Non-steroidal anti-inflammatory drugs.

aspirin alone on the gastric mucosa might be less potent than the effect of NSAIDs^[23]. In a case-control study by Hallas *et al.*, the age- and sex-adjusted odds ratios associating drug use with UGIB were 1.8 (1.5-2.1) for low-dose aspirin, 1.1 (0.6-2.1) for clopidogrel, 1.9 (1.3-2.8) for dipyridamole, 1.8 (1.3-2.4) for vitamin K antagonists, 7.4 (3.5-15) for clopidogrel and aspirin, 5.3 (2.9-9.5) for vitamin K antagonists and aspirin, and 2.3 (1.7-3.3) for dipyridamole and aspirin. These results suggest that combined antithrombotic therapy with low-dose aspirin is associated with an increased risk of UGIB^[24]. We also found that the proportion of NSAIDs and low-dose aspirin users was significantly increasing over the period studied. The odds ratio of a combination of NSAIDs and low-dose aspirin was reported as 12.7 (95% CI: 7.0-23.0). Furthermore, the concurrent use of non-aspirin antiplatelet agents with traditional NSAIDs also potentiated the risk of UGIB^[17]. In a meta-analysis of randomized, placebo-controlled trials of low-dose aspirin, prior gastrointestinal events, older age, and the use of other injurious medications, such as NSAIDs, anticoagulants, and corticosteroids seemed to be factors associated with an increased risk for UGIB^[25].

In the future, it will be necessary to prevent the association between UGIB and the use of NSAIDs and low-dose aspirin because it is expected that the more the proportion of the elderly population increases, the more coexisting diseases, such as cardiovascular disease, cerebrovascular disease, and musculoskeletal disorders will increase. The use of both NSAIDs for the treatment of musculoskeletal pain and low-dose aspirin as an anti-thrombotic therapy has increased recently. This tendency has been deduced from our data, which reveals that cardiovascular and cerebrovascular diseases have increased from 2002 to 2008. In addition, it is useful to note that few patients complained of epigastric symptoms in our study. In fact, most NSAIDs-associated GDU are asymptomatic^[26,27]. In low-dose aspirin users, there were no significant differences between the ulcer and non-ulcer groups in the frequency and severity of symptoms, such as nausea, acid regurgitation, and heartburn^[28]. Moreover, there were more patients without symptoms than with abdominal pain among NSAIDs users, since NSAIDs have an analgesic effect. On the contrary, peptic ulcers treated with NSAIDs and low-dose aspirin develop sud-

denly by hematemesis and melena. In fact, those patients taking NSAIDs and low-dose aspirin became serious cases because they had a coexisting disease, such as cardiovascular or cerebrovascular disease.

The prevention of peptic ulcers related to the use of NSAIDs and/or low-dose aspirin will become an important issue in the future. It is suggested that those patients who need NSAIDs treatment use the prostaglandin analogue misoprostol^[29] or acid-suppressive agents, such as high-dose H₂ receptor antagonists^[30] and PPI^[31]. Switching from non-selective NSAIDs to cyclooxygenase-2 inhibitors^[32] is also a choice. In the prevention of ulcers caused by NSAIDs and/or low-dose aspirin, the effectiveness of *H. pylori* eradication therapy has been reported^[33]. In naive NSAIDs users, it has been suggested to receive *H. pylori* eradication therapy before NSAIDs use. A similar strategy has also been suggested for naive aspirin users^[34]. In chronic NSAIDs/aspirin users, the recommendations may depend on the risk for peptic ulcer complications. Those who continue taking NSAIDs/aspirin, being at high-risk for peptic ulcer complication, should be tested for the presence of *H. pylori* infection and, if positive, receive *H. pylori* eradication therapy, as well as long-term therapy with a PPI^[35-37].

Where the elderly population is increasing, it seems likely that the consumption of NSAIDs and low-dose aspirin will also increase in the future. Therefore, it is necessary to make guidelines for the use of NSAIDs and low-dose aspirin with the cooperation of gastroenterologists, neurologists, cardiologists, and orthopedic surgeons.

COMMENTS

Background

Helicobacter pylori (*H. pylori*) infection and non-steroidal anti-inflammatory drugs (NSAIDs) including low dose aspirin are two of the major risk factors for peptic ulcers. With the increase in the elderly population, which has led to an increase in musculoskeletal and joint disorders, ischemic heart disease and cerebrovascular disease, it seems that the incidence of NSAID-related peptic ulcer has increased. The aim of this study is to clarify the frequency and trends of peptic ulcer bleeding over the studied period.

Research frontiers

In Western countries, *H. pylori* infection rate is low and the cause of peptic ulcer was NSAIDs. Since the same tendency was recognized in Japan, it is necessary to investigate about changes in the cause of peptic ulcer.

Innovations and breakthroughs

In this study, it was found that the number of peptic ulcer bleeding case was increased and *H. pylori* infection rate was decreased over the studied period, the main cause of peptic ulcer bleeding changed from *H. pylori* infection to use of NSAIDs, including low-dose aspirin.

Applications

In fact that gastroesophageal reflux disease is increasing and the usage of proton pump inhibitors (PPI) is actually increasing in Japan. The results suggest that peptic ulcer will be decreased in the future.

Terminology

Peptic ulcer bleeding: Defined as a clinical presentation of hematemesis and/or melena, and endoscopic examination showed a peptic gastric and/or duodenal ulcer bleeding.

Peer review

This paper describes the rate of peptic ulcer bleeding and the change in the causes of that. Although *H. pylori* infection and the use of NSAIDs were adopted as a risk factor, it was indicated that other factors (i.e., corticosteroid, warfarin and clopidogrel) should also have been examined. Though we find that frequency on gastrointestinal bleeding has been subsequently decreasing recent years, it was reported that the increase in the usage of PPI is related. To investigate the cause by which the peptic ulcer bleeding is decreased will be desired from now on.

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