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BRIEF ARTICLE

Comparative study of therapeutic effects of PPI and H2RA on ulcers during continuous aspirin therapy

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Abstract

AIM: To compare the therapeutic effects of proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) on gastroduodenal ulcers under continuous use of low-dose aspirin.

METHODS: Sixty patients who had a gastroduodenal ulcer on screening endoscopy but required continuous use of low-dose aspirin were randomly assigned to receive PPI (lansoprazole 30 mg, *n* = 30) or H2RA (famotidine 40 mg or if famotidine had been administered before assignment, ranitidine 300 mg, *n* = 30). The therapeutic effects were evaluated by endoscopy after 8-wk treatment. The presence or absence of *Helicobacter pylori* (*H. pylori*) was determined by urea breath test before treatment. Abdominal symptoms were compared with the gastrointestinal symptom rating scale (GSRS) questionnaire before and after treatment.

RESULTS: Twenty-six patients in the PPI group and 26 patients in the H2RA group, excluding dropouts, were analyzed. There were no significant differences in median age, sex, underlying disease, smoking status, *H. pylori* infection, prevalence of ulcers before treatment, and lesion site between the two groups. The therapeutic effects were endoscopically evaluated as healed in 23 patients (88.5%) and not healed in 3 patients in the PPI group and as healed in 22 patients (84.6%) and not healed in 4 patients in the H2RA group. Abdominal symptoms before treatment were uncommon in both groups; the GSRS scores were not significantly reduced after treatment as compared with before treatment.

CONCLUSION: The healing rate of gastroduodenal ulcers during continuous use of low-dose aspirin was greater than 80% in both the PPI group and the H2RA group, with no significant difference between the two groups.

Key words: Low-dose aspirin; Proton pump inhibitors; Histamine 2 receptor antagonists; Gastric ulcer

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INTRODUCTION

As the population of Japan ages, the use of low-dose aspirin has increased to prevent cerebral and myocardial infarction. Many reports from Japan and overseas showing evidence that low-dose aspirin is useful for prevent-

ing thrombosis have been published. However, low-dose aspirin use raises concern about its adverse effects such as gastrointestinal mucosal injury[1,2]. Low-dose oral aspirin (300 mg or less) is reportedly associated with a 2.6- to 3.0-fold increased risk of ulcers[3] and a 1.59-fold increased risk of gastrointestinal bleeding[4]. The prevalence of low-dose (200 mg or less) aspirin-associated gastroduodenal ulcers was 11.9% to 15.7% in Japanese patients treated for ischemic heart disease[5], and another case-control study has shown that low-dose aspirin is associated with a 5.5-fold increased risk of gastrointestinal bleeding[6]. However, low-dose aspirin is administered for the purpose of secondary prevention of cardiovascular events, and because drug suspension due to gastrointestinal injury would increase the risk of thrombosis, it is frequently difficult to discontinue the use of low-dose aspirin. In fact, when long-term users of low-dose aspirin suspended the use of the drug, the risk of thrombosis increased[7,8]. Therefore, gastrointestinal injury should be treated under continuous use of low-dose aspirin. Previous studies from Western countries have shown that proton pump inhibitors (PPI) are first-line drugs for the treatment of gastrointestinal injury associated with non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin[9-11]. However, there are no prospective studies focusing on low-dose aspirin, nor are there studies from Japan where *Helicobacter pylori* (*H. pylori*) infection rate is high.

We conducted a prospective, multicenter controlled study to compare the therapeutic effects of ordinary dose of PPI and histamine 2 receptor antagonists (H2RA) on gastroduodenal ulcers during continuous use of low-dose aspirin.

MATERIALS AND METHODS

Patients

Two hundred twenty-nine low-dose aspirin users developed an endoscopy-proven gastrointestinal ulcer between May 2006 and November 2009 at the Hokkaido University Hospital and associated facilities. Out of these patients, 78 patients who did not meet inclusion criteria were excluded. Patients were excluded from the study if they had gastrointestinal bleeding as a complication, underwent gastrectomy, had a serious complication, had been taking non-aspirin NSAIDs regularly, or were under 20 years or over 80 years old. Patients who administered non-aspirin NSAIDs on an as-needed basis were included.

One hundred fifty-one patients were recruited to this study. All of them wished to continue taking low-dose aspirin and gastric acid secretion inhibitors, because they had no vascular events after aspirin therapy. However, the majority of patients rejected a second endoscopy after 8 wk. Finally, 60 patients who provided written informed consent and required continuous use of low-dose aspirin were entered into the study.

This study was approved by the ethics committee of each facility. Written informed consent was obtained from each participant in this study.

Methods

Enrolled patients were randomly assigned to the PPI group (lansoprazole 30 mg, $n = 30$) or the H2RA group (famotidine 40 mg, $n = 30$) by Central Registry *via* the Internet. If patients who had been treated with famotidine before randomization were assigned to the H2RA group, they were treated with ranitidine 300 mg instead.

The presence of *H. pylori* was determined by urea breath test before treatment. An exhaled-breath sample was collected 20 min after patients took ^{13}C-urea 100 mg orally, and the cut-off value was set at Δ^{13}C 2.5‰[12].

Therapeutic effects were based on endoscopic findings obtained at the end of 8 wk treatment. Endoscopy was performed before and after treatment by a single endoscopist at each facility using GIF-XQ 240 (Olympus Corporation, Tokyo, Japan). Mucosal defects were measured with biopsy forceps and an ulcer was defined as a mucosal defect when it was 3 mm or more in diameter. Photographs of lesions were taken before and after treatment and therapeutic effects were evaluated by a single physician. Complete disappearance of a mucosal defect was defined as healed, reduction of mucosal defect as reduced, no change in mucosal defect as unchanged, enlargement of mucosal defect as aggravated.

Patients were instructed to record abdominal symptoms using gastrointestinal symptom rating scale (GSRS) just before the first and the second endoscopic examinations. The GSRS scores were compared before and after treatment to evaluate the improvement of abdominal symptoms.

Statistical analysis

Endoscopic healing rate and self-improvement rate using GSRS were statistically determined by Wilcoxon test. The statistical software used was the SPPS 15.0. A level of $P < 0.05$ was considered statistically significant.

RESULTS

Four patients in the PPI group and 4 patients in the H2RA group dropped out of the study because they refused to undergo endoscopy when their symptoms disappeared or they were moved to another hospital. Medication compliance rate was as high as 80% or more among patients excluding dropouts. Twenty-six patients in the PPI group and 26 in the H2RA group qualified for analysis.

Buffered aspirin tablets (Bufferin 81) and enteric coated tablets (Bayaspirin 100) were continuously used by 11 and 15 patients, respectively, in the PPI group and by 10 and 16 patients, respectively, in the H2RA group. Two patients in each group had used NSAIDs as needed for headache (diclofenac sodium in 3 patients and zaltoprofen in 1 patient). H2RA had been used before enrollment in 3 patients in the PPI group (usual dose of ranitidine, usual dose of nizatidine, and half dose of famotidine respectively) and in 4 patients in the H2RA group (usual dose of famotidine, usual dose of ranitidine, usual dose of nizatidine, and half dose of nizatidine respectively). No patients

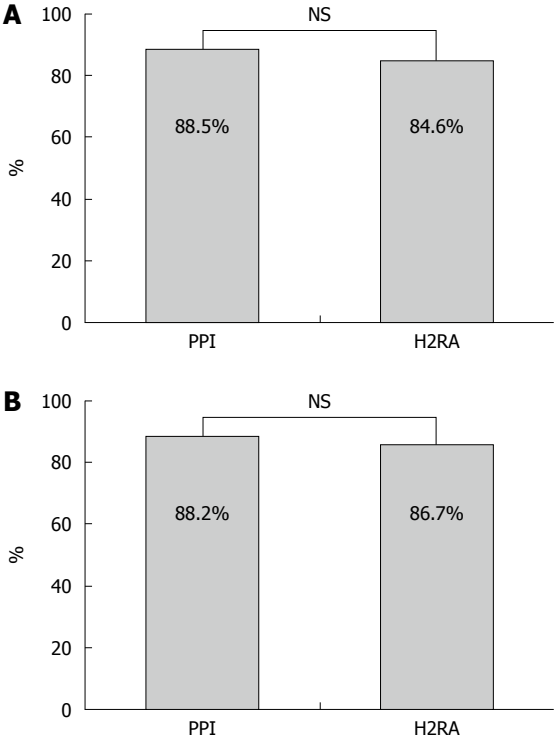

Figure 1 Gastroduodenal ulcer healing was endoscopically achieved in proton pump inhibitors and histamine 2 receptor antagonists group patients. A: Gastroduodenal ulcer healing was endoscopically achieved in 88.5% of proton pump inhibitors (PPI) group patients and in 84.6% of histamine 2 receptor antagonists (H2RA) group patients. There was no significant difference between the two groups; B: Gastroduodenal ulcer healing in patients with non-pangastritis was endoscopically achieved in 88.2% of PPI group and in 86.7% of H2RA group. There was no significant difference between the two groups. NS: Not significant.

Table 1 Background of patients *n* (%)

	PPI group (*n* = 26)	H2RA group (*n* = 26)	*P* value
Median age (yr)	67.2 ± 8.7	71.1 ± 6.9	NS
Male	19 (73.1)	19 (73.1)	NS
Ischemic heart disease	15 (57.7)	13 (50.0)	NS
Smoking	11 (42.3)	8 (30.8)	NS
Helicobacter pylori (+)	13 (50.0)	12 (46.2)	NS
Ulcer size > 5 mm	13 (50.0)	12 (46.2)	NS
Location of mucosal defect			
Stomach	24	23	NS
Duodenal	2	3	
Aspirin			
Buffered	10	10	NS
Enteric-coated	16	16	

PPI: Proton pump inhibitors; H2RA: Histamine 2 receptor antagonists; NS: Not significant.

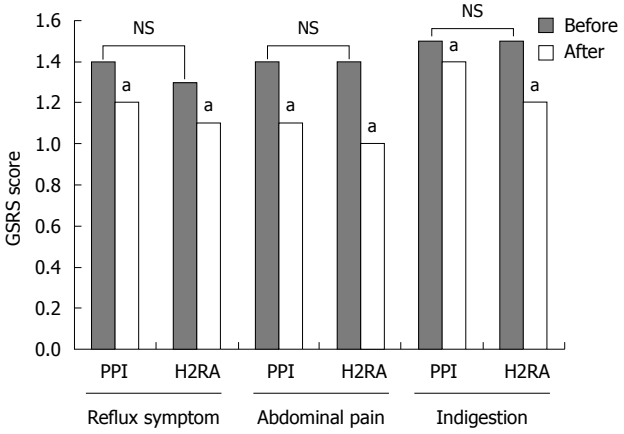

Figure 2 Improvement of abdominal symptoms was evaluated using gastrointestinal symptom rating scale scores. The scores were not significantly reduced after treatment as compared with before treatment in both proton pump inhibitors (PPI) and histamine 2 receptor antagonists (H2RA) groups. [a]NS *vs* before. NS: Not significant.

had used PPI before enrollment. If patients assigned to the H2RA group had a history of famotidine use, they were administered ranitidine 300 mg.

There were no significant differences in median age, sex, underlying disease, smoking status, *H. pylori* infection, prevalence of ulcers before treatment, or lesion site between the PPI group and the H2RA group (Table 1).

The therapeutic effects were endoscopically evaluated as healed in 23 of 26 patients in the PPI group and in 22 of 26 patients in the H2RA group, with no significant difference between the groups (Figure 1A).

Three patients in the PPI group were evaluated as not healed, including 2 evaluated as reduced and 1 evaluated as unchanged. In the 2 patients evaluated as reduced, multiple ulcers were observed at the antrum of the stomach and ulcers 10 and 5 mm in maximum diameter were reduced to 3 and 2 mm, respectively, after treatment. In the patient evaluated as unchanged, the use of 100 mg aspirin enteric coated tablets was continued for the treatment of angina pectoris, endoscopy revealed a solitary ulcer 5 mm in diameter at the body of the stomach, and there was no evidence of *H. pylori* infection.

Four patients in the H2RA group were evaluated as not healed, including 3 evaluated as reduced and 1 evaluated as unchanged. In the 3 patients evaluated as reduced, solitary ulcers 15 mm at the antrum of the stomach, 15 mm at the body of the stomach, and 3 mm at the antrum of the stomach were all reduced to 2 mm after treatment. In the patient evaluated as unchanged, the use of 162 mg buffered aspirin tablets was continued for the treatment of old myocardial infarction, multiple ulcers were observed at the antrum of the stomach 3 mm in maximum diameter on endoscopy, there was no evidence of *H. pylori* infection, diclofenac sodium was prescribed as needed, and usual dose of ranitidine had been administered before assignment to treatment group.

Improvement of abdominal symptoms was evaluated after treatment by comparing the GSRS scores before and after treatment. Pretreatment scores indicated that abdominal symptoms were uncommon in both the PPI group and the H2RA group. The scores were not significantly reduced after treatment as compared with before treatment in either group (Figure 2). No side events were observed in either group.

For research about influence of acid secretion, both groups were subdivided into 2 groups based on whether the patient had pangastritis or not. There were 17 patients in the PPI group with pangastritis and 15 in the H2RA

group. The therapeutic effects were not significantly different between the non-pangastritis groups (Figure 1B).

DISCUSSION

One of the major adverse events associated with low-dose aspirin is gastrointestinal bleeding. However, screening endoscopy is widely used in Japan and peptic lesions are frequently pointed out on screening endoscopy before the development of overt gastrointestinal bleeding. Therefore, the subjects of this study were those found to have gastroduodenal lesions on endoscopy without gastrointestinal bleeding as a complication.

Low-dose aspirin-induced mucosal defect is commonly 5 mm or less[3]. Considering that lesions 5 mm or less in size can cause bleeding, and if left untreated, may be enlarged, we believe that small ulcers should be treated. Thus, patients with ulcers 3 mm or more were included in this study.

Controlled studies of the therapeutic effects of PPI *vs* H2RA for NSAIDs-associated gastric ulcers have shown that the healing rate after 8 wk treatment was significantly higher in the PPI group than in the H2RA group[9-11].

A recent controlled study investigated the preventative effects of PPI *vs* H2RA on the occurrence of bleeding ulcers associated with low-dose aspirin in patients not infected with *H. pylori* and concluded that PPI are significantly more effective than H2RA in preventing the occurrence of bleeding ulcers and abdominal symptoms[13]. However, the results of their preventative effects against ulcers cannot be extrapolated to the healing of ulcers. On the other hand, it was reported that patients who take H2RA with low-dose aspirin had fewer peptic ulcers than patients who take placebo[14].

In the present study, the healing rate of gastroduodenal ulcers associated with low-dose aspirin was similar in the PPI group and the H2RA group. This may be explained by the facts that half of the subjects included in this study were infected with *H. pylori,* the subjects were limited to the Japanese, and they had a lower ability to secrete gastric acid. Previous studies involving patients with duodenal ulcers have shown that average maximum gastric acid secretion was 21.9 mEq/h for Japanese men and 43.2 mEq/mL for American men[15,16]. However, a retrospective study from Western countries investigated the effects of H2RA (famotidine 20-40 mg or ranitidine 150-300 mg) and PPI (omeprazole 20 mg) on lowering the risk of gastrointestinal bleeding in low-dose aspirin users and concluded that both drug classes have similar effects on preventing bleeding[17]. Further studies are needed to evaluate the therapeutic effects of both PPI and H2RA on low-dose aspirin-induced ulcers.

One patient evaluated as unchanged in the H2RA group developed an ulcer 3 mm in diameter, was not infected with *H. pylori*, and had a history of diclofenac sodium on an as-needed basis. One other patient in the PPI group had used diclofenac sodium as needed before assignment, but the ulcer was healed after 8 wk treatment. PPI are also reported to be effective when combined with low-dose aspirin and NSAIDs[18]. The combined use of low-dose aspirin and NSAIDs is known to be associated with an increased risk of gastrointestinal bleeding[3]. When low-dose aspirin is used alone, H2RA is expected to heal ulcers, but it may be better to choose PPI in high risk cases in which low-dose aspirin and NSAIDs are combined. Even in these cases, PPI are considered to be more effective than H2RA for 4 wk treatment[11,18].

The patient evaluated as unchanged in the PPI group had an ulcer 5 mm in size and was not infected with *H. pylori*. This case indicated that some ulcers are not healed even when treated with PPI. Such cases require further investigation for their appropriate treatment.

In this study, none of the patients were treated with combined aspirin and other antiplatelet drugs. However, recently use of combinations of low-dose aspirin and other antiplatelet drugs (e.g. clopidogrel and ticlopidine) have been increased, especially after coronary bypass graft surgery. PPI decrease clopidogrel's inhibitory effect on platelets[19]. It may be better to choose H2RA when low-dose aspirin and clopidogrel are combined. On the other hand, clopidogrel is not associated with an increased risk of gastrointestinal bleeding when used alone, but is associated with a 7.7-fold increased risk when used in combination with low-dose aspirin[20]. Further studies are required to investigate the preventive and therapeutic effects of PPI and H2RA on gastrointestinal events in the presence of combined aspirin and other antiplatelet drugs.

In conclusion, the healing rate of gastroduodenal ulcers was greater than 80% after 8-wk treatment with PPI or H2RA during continuous use of low-dose aspirin, with no significant difference between the two groups.

COMMENTS

Background

The use of aspirin has increased in the aging population. Aspirin increases the risk of gastrointestinal injury. The strategy to treat ulcers during low-dose aspirin treatment is not clear.

Research frontiers

It was reported that proton pump inhibitors (PPI) are more effective than histamine 2 receptor antagonists (H2RA) in prevention of aspirin-induced ulcers.

Innovations and breakthroughs

In this study, the healing rate of aspirin-induced ulcers was greater than 80% in both the PPI and the H2RA groups, with no significant difference between groups.

Applications

This study may be useful for considering changes in treatment of aspirin-induced ulcer.

Peer review

This article demonstrates some interesting points that compare the effects of PPI and H2-blocker in patients taking continuous low dose aspirin. The paper is well written, design is appropriate for end-points stated and patient number is nearly enough to draw conclusions.

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