Intravenous pantoprazole versus ranitidine for prevention of rebleeding after endoscopic hemostasis of bleeding peptic ulcers

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Abstract

AIM: The role of intravenous pantoprazole in treatment of patients with high-risk bleeding peptic ulcers following endoscopic hemostasis remains uncertain. We therefore conducted the pilot prospective randomized study to assess whether intravenous pantoprazole could improve the efficacy of H2-antagonist as an adjunct treatment following endoscopic injection therapy for bleeding ulcers.

METHODS: Patients with active bleeding ulcers or ulcers with major signs of recent bleeding were treated with distilled water injection. After hemostasis was achieved, they were randomly assigned to receive intravenous pantoprazole or ranitidine.

RESULTS: One hundred and two patients were enrolled in this prospective trial. Bleeding recurred in 2 patients (4%) in the pantoprazole group (n = 52), as compared with 8 (16%) in the ranitidine group (n = 50). The rebleeding rate was significantly lower in the pantoprazole group (P = 0.04). There were no statistically significant differences between the groups with regard to the need for emergency surgery (0% vs 2%), transfusion requirements (4.9±5.9 vs 5.7±6.8 units), hospital days (5.9±3.2 vs 7.5±5.0 d) or mortality (2% vs 2%).

CONCLUSION: Pantoprazole is superior to ranitidine as an adjunct treatment to endoscopic injection therapy in high-risk bleeding ulcers.

BRIEF REPORTS

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INTRODUCTION

Bleeding is a common and potential life threatening complication of peptic ulcer diseases. Recently, endoscopic hemostasis has been the treatment of first choice for bleeding peptic ulcer, providing better outcomes compared with both medical and surgical therapies[1-4]. However, acute recurrent bleeding after initial hemostasis by therapeutic endoscopy has been reported to occur in 4% to 30% of cases, and the mortality rate in these patients is high[5-10].

In vitro studies have shown that clotting proceeds more efficiently and the dissolution of clots by proteolytic enzymes occurs more slowly at high pH levels[11,12]. Pepsin can digest blood clots overlying ulcer craters, and its activity is pH-related[13]. Additionally, the function of platelets is severely impaired at low pH in vitro[14]. A profound reduction of gastric acidity, therefore, could stabilize the clots over an ulcer and stop bleeding or prevent recurrent hemorrhage.

However, evidence of the effectiveness of H2-receptor antagonists in bleeding peptic ulcers is conflicting. Collins et al.[15] conducted a meta-analysis of 27 randomized studies and concluded that H2-receptor antagonists reduced the rate of continued bleeding, the need for surgery, and the mortality rate among patients with gastric ulcers. Nonetheless, a subsequent large trial of 1 005 patients with bleeding peptic ulcers demonstrated that intravenous famotidine treatment did not affect the rebleeding rate, the operative rate, and the mortality[16].

In vivo studies have shown that a regimen including a high dose of a proton pump inhibitor (PPI) can maintain intragastric pH at a nearly neutral level and inhibit acid production more effectively than does an infusion of an H2-receptor antagonist[17,18]. Thus, a high-dose PPI is theoretically better than an H2-receptor antagonist as a treatment to prevent rebleeding of peptic ulcers. A recent meta-analysis[19] disclosed that intravenous omeprazole was more effective than an H2-antagonist in preventing persistent recurrent bleeding from peptic ulcer, but this advantage seemed to be restricted to those patients who did not have adjunct sclerotherapy. Nonetheless, the authors emphasized that the data were too scarce and heterogeneous to draw definitive conclusions, and further comparative trials were clearly warranted.

Currently, intravenous omeprazole is available in Europe and other countries, but it is not available in the United States of America. Although pantoprazole was the first intravenous PPI marketed in the United States of America, it does not have an indication for treatment of upper gastrointestinal bleeding, mainly due to the lack of published clinically relevant outcome data. We therefore conducted this pilot, prospective, randomized study to compare the efficacy of intravenous pantoprazole and ranitidine for prevention of rebleeding of peptic ulcers following initial endoscopic hemostasis.

MATERIALS AND METHODS

Patients

From October 2002 to September 2003, all patients with hematemeses, melena, or both, had emergent upper endoscopy
performed within 24 h of admission to the emergency units of Kaohsiung Veterans General Hospital. Patients with active bleeding ulcers or ulcers with major signs of recent bleeding were treated with distilled water injection. Patients with successful initial hemostasis and who gave their consents were enrolled in this study. Criteria for exclusion included: the presence of other possible bleeding sites (for example, esophageal varices, gastric cancer), coexistence of an acute significant illness (for example, sepsis, stroke, acute myocardial infarction, acute respiratory failure, acute surgical abdomen), the presence of a systemic bleeding tendency (for example, platelets <50,000/mm³, prolonged prothrombin time >3 s, or use of an anticoagulant).

**Therapeutic endoscopy**

Upper gastrointestinal endoscopy was performed within 24 h of hospital admission. The equipments used were the Olympus GIF XV10, GIF XQ 200, and GIF IT20 (Olympus Corp., Tokyo, Japan). To improve the visual field, gastric lavage was carried out before endoscopy. Ulcers with stigmata were cleaned by water irrigation through the biopsy channel. We divided the ulcer lesions into six categories according to our previous study[20], clean base, red or black spot, adherent clot, nonbleeding visible vessel (NBVV), oozing visible vessel, and spurting visible vessel. An NBVV was defined as a raised red or bluish-red hemispheric lesion protruding from the ulcer base, without active bleeding. An adherent clot was defined as an overlying clot that was resistant to washing. If an adherent clot, NBVV or bleeding visible vessel was noted during the first examination, endoscopic local injection with distilled water was performed for hemostasis. Distilled water was injected in aliquots of 0.5-2 mL over and around the bleeding area, up to a total of 5.0-20.0 mL[63]. Once hemostasis was achieved, the bleeding site was observed for at least 5 min. Initial hemostasis was defined as no endoscopic evidence of bleeding during 5 min of observation after therapy.

We did not check *H pylori* status for our patients during acute bleeding episodes since previous studies[20,21] disclosed that biopsy-based tests had decreased sensitivities for the detection of *H pylori* in bleeding peptic ulcers. Besides, it would increase operating time to take gastric specimens in critical patients who required therapeutic endoscopies.

**Randomization**

Patients with successful initial hemostasis were randomly assigned to two groups. Randomization of eligible patients was carried out by a neutral individual who opened sealed envelopes containing the treatment assignments, derived from a table of random numbers. One group was treated with intravenous pantoprazole, with an initial dose of 40 mg and subsequently with 40 mg every twelve hours during the first three days, followed by 40 mg a day orally. The other group was treated with intravenous ranitidine, with an initial dose of 50 mg and subsequently every eight hours during the first three days, followed by 150 mg of oral ranitidine every 12 h. We chose the dose of intravenous ranitidine because it was commonly used in clinical practice. Previous studies[22] revealed that this dose of intravenous ranitidine could suppress gastric acid secretion by 83%. The study protocol was approved by the Medical Committee of Kaohsiung Veterans General Hospital.

**Follow-up**

During the stay in the hospital, patients received partial parenteral nutrition for 2 d. After a 48-h observation, patients were given soft diet for 48 h, and then a regular diet. The hemoglobin level was checked every day for 3 d, and a blood transfusion was given if the hemoglobin concentration fell below 8 gm/dL or if vital signs deteriorated.

A clinician independent of the endoscopist observed the patients for evidence of rebleeding. The definition of rebleeding was recurrent hemorrhage during an 8-wk observation period. Evidence of rebleeding included fresh hematemesis, aspiration of fresh blood from NG tube, or continuous melena with a pulse rate greater than 100 beats/min, a fall in systolic blood pressure exceeding 30 mmHg, or a decrease in hemoglobin of at least 0.2 g/L. When rebleeding was suspected, a second therapeutic endoscopy was performed immediately. If hemostasis could not be achieved, surgical intervention of uncontrolled rebleeding was performed.

After discharge, patients assigned to the pantoprazole group were treated with pantoprazole 40 mg daily for up to 8 wk, and those in the ranitidine group were treated with ranitidine 150 mg twice daily. All patients were requested to return to the outpatient clinic 14 d, 4 wk and 8 wk after initial hemostasis.

**Statistical analysis**

The sample size was calculated according to previous experiences[6,8,18,19]. The rebleeding rates following distilled water injection were 13% of patients treated with PPI[18,19] and 29% of patients treated with H₂ receptor antagonists[6,8]. A sample size of 46 was thus required for each group to achieve a statistical power of 80% at 10% type I error. The chi-square test with or without Yates’ correction for continuity and Fisher’s exact test were used when appropriate to compare the rates of rebleeding, emergency operation, and mortality between groups. A P value less than 0.05 was considered statistically significant.

**RESULTS**

During the study period, 236 patients were admitted due to bleeding peptic ulcers. Endoscopic treatment was not required in 136 patients who had ulcers with clean bases or flat pigments. Nineteen patients were excluded from this study for the presence of other possible bleeding sites (n = 5), coexistence of an acute significant illness (n = 9), association with a systemic bleeding tendency (n = 6). One hundred and nine patients with high-risk bleeding ulcers received endoscopic injection therapy. Initial hemostasis was not achieved in 7 patients who had profuse bleeding, and they underwent surgical treatment or further endoscopic hemostasis with thermocoagulation or hemoclipping.

The other 102 patients with successful endoscopic hemostasis were randomly assigned to either pantoprazole (n = 52) or ranitidine (n = 50) therapies. Data regarding the clinical characteristics of patients at entry are summarized in Table 1. The two groups had comparable clinical features, site and size of ulcers, and bleeding severity. At index endoscopy, 40% of randomized patients had bleeding visible vessels (spurting: 6%; oozing: 34%), 38% had NBVVs and 22% had adherent clots in the ulcer craters.

All patients were followed up through the eight-week period after initial endoscopy. Treatment results are shown in Table 2. Rebleeding developed in 2 patients in the pantoprazole group. One of the rebleeding patients underwent a second endoscopy, and hemostasis was controlled by local injection of diluted epinephrine. The other died of profuse rebleeding. Neither second endoscopic therapy nor surgical intervention was performed for him because of rapid deterioration of clinical course. In the ranitidine group, 8 patients developed rebleeding. In 7 of the 8 treatment failure patients, endoscopic retreatment by local injection (n = 5), heater probe (n = 1) and hemoclipping (n = 1) stopped the bleeding. The other patient underwent immediate surgery to control rebleeding after failure of second therapeutic endoscopy. None of the patients died of uncontrolled rebleeding, but one female patient died of heart attack.

The rebleeding rate of the pantoprazole group was significantly lower than that of the ranitidine group (3.8% vs 16.0%, P = 0.04). There were no statistically significant differences between the groups with regard to the need for emergency surgery (0% vs
Table 1 Base-line characteristics of the study patients with bleeding peptic ulcers n (%)

|                        | Pantoprazole group (n = 52) | Ranitidine group (n = 50) | P  |
|------------------------|-----------------------------|---------------------------|----|
| Age (yr) (SD)          | 63.2 (18.2)                 | 64.7 (13.8)               | 0.64|
| Gender (M:F)           | 41:11                       | 37:13                     | 0.56|
| Smoking                | 17 (32.7)                   | 16 (32.0)                 | 0.94|
| Alcohol abuse          | 7 (13.5)                    | 4 (8.0)                   | 0.37|
| NSAID use              | 14 (26.9)                   | 16 (32.0)                 | 0.57|
| History of ulcer       | 32 (61.5)                   | 28 (56.0)                 | 0.57|
| History of ulcer bleeding | 14 (26.9)               | 9 (18.0)                  | 0.28|
| Hypovolemic shock      | 3 (5.8)                     | 3 (6.0)                   | 1.00|
| Hemoglobin (g/dL) (SD) | 10.3 (3.0)                  | 10.0 (2.8)                | 0.68|

Table 2 Clinical outcomes of pantoprazole and ranitidine groups n (%)

|                        | Pantoprazole group (n = 52) | Ranitidine group (n = 50) | P  |
|------------------------|-----------------------------|---------------------------|----|
| Rebleeding             | 2 (3.8)                     | 8 (16.0)                  | 0.04†|
| Emergency operation    | 0 (0.0)                     | 1 (2.0)                   | 0.31|
| Hospital days (SD)     | 5.9 (3.2)                   | 7.5 (5.0)                 | 0.06|
| Units of Blood transfusion (SD) | 4.9 (5.8)           | 5.7 (6.8)                 | 0.42|
| Mortality              | 1 (1.9)                     | 1 (2.0)                   | 1.00|

†Significant difference.

DISCUSSION

The use of PPIs in patients with bleeding peptic ulcers has been evaluated in several studies. In a meta-analysis of 11 randomized trials[23,24], Gisbert et al. showed that PPIs were more effective than H2-receptor antagonists in preventing persistent or recurrent bleeding from peptic ulcers. However, meta-analysis had several limitations. For example, there was a marked variability between studies with respect to doses of PPIs and H2-receptor antagonists, schemes of administration of the drugs, Forrest classification of bleeding ulcers and concomitant endoscopic therapies. The authors thus concluded that the data were too scarce and heterogeneous to draw definite conclusions. In addition, it is important to point out that all the trials[23-26] analyzed by Gisbert et al. used omeprazole or lansoprazole as the test drug of PPIs.

To date, there are limited clinical outcome data on intravenous pantoprazole for the prevention of peptic ulcer rebleeding[27]. Furthermore, all the published data concerning the effects of intravenous pantoprazole on bleeding peptic ulcers were in abstract form[28], which has limited the ability to completely evaluate and generalize the suggested outcomes. We therefore designed the prospective randomized study to investigate the effects of intravenous pantoprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. The rebleeding rate of the pantoprazole and ranitidine groups in this study was 4% and 16%, respectively. The data suggest that pantoprazole is more effective than ranitidine for preventing rebleeding in high-risk bleeding ulcer patients.

However, it is important to note that continuous infusion of ranitidine was more effective to elevate intragastric pH than intermittent bolus injection[22]. Additionally, the percentage of intragastric pH value equal to or above 7.0 was significantly greater during high dose ranitidine infusion (300-mg/24 h) compared with conventional dose infusion (150-mg/24 h)[22]. Fered et al.[24] revealed that the efficacy of infusion of high dose ranitidine to prevent recurrent ulcer bleeding was similar to that of pantoprazole infusion.

Data from in vitro studies suggest that both acid and pepsin can alter coagulation by interfering with the coagulation system, fibrinogen polymerization, and platelet aggregation[12,13]. Therefore, profound acid suppression may improve the microenvironment at the bleeding point by keeping the gastric pH above the proteolytic range for pepsin to prevent clot lysis, and thus benefiting patients with bleeding peptic ulcers. Traditionally, pharmacological treatment for bleeding peptic ulcers has included H2-receptor antagonists, but these drugs have shown no effect at all when compared with placebo[16,19]. The lack of a clear beneficial effect of H2-receptor antagonists could be due to the limited control of gastric pH. This is because at the conventional recommended doses of these drugs, gastric pH could not be maintained higher than 4.0 for a long period in patients with a bleeding peptic ulcer[10]. On the other hand, intravenous PPIs could produce consistently high gastric pH values in patients with bleeding peptic ulcers[25,31]. Pharmacokinetic studies with PPIs have shown that a bolus of 80 mg pantoprazole or omeprazole followed by immediate continuous infusion of 8 mg per hour could result in an intragastric pH of 7 within 20 min[32]. Pisegna et al.[13] also demonstrated that a single intravenous dose of pantoprazole 80 mg suppressed pentagastrin-induced acid output by 99% for approximately 24 h and had an onset of action in less than 1 h. Its acid inhibition effect was much stronger than that of intravenous famotidine. The loss of effectiveness of famotidine might be due to tolerance (tachyphylaxis), which is known to occur in response to repetitive doses of H2-receptor antagonists[4,35], but has never been found with PPIs. Therefore, parenteral PPIs seem to be more effective than H2-antagonists in keeping the intragastric pH above the proteolytic range for pepsin to stabilize the clotting process.

In this study, there were no significant differences between the pantoprazole and ranitidine groups with regard to the need for emergency surgery, transfusion requirements, hospital stay or mortality. Several previous studies[18,19] also reported that PPIs were not more effective than H2-receptor antagonists for reducing surgery or mortality rates. However, the lack of differences in these parameters between study and control groups might be due to beta error since the numbers of cases in these studies were too small to draw definite conclusions to these parameters. In a large-scaled study of Liu et al.[7], a high-dose infusion of omeprazole was reported to decrease the hospital stay of patients following endoscopic treatment of bleeding ulcers.

Recently, the combinations of injection and thermal coagulation therapies have been applied in the treatment of high-risk bleeding peptic ulcers[36,37]. A meta-analysis by Calvet et al.[31] demonstrated that combined therapies were superior to injection therapies alone. It merits further studies to investigate whether combined therapies for high-risk bleeding ulcers will effectively control bleeding ulcers and change the results in the current study.

In conclusion, after endoscopic injection treatment of bleeding peptic ulcers, intravenous pantoprazole is more effective than ranitidine for the prevention of rebleeding.
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