Original Article

# High-Versus Low Dose Pantoprazole for Optimal Inhibition of Gastric Acid in Patients with Peptic Ulcer Bleeding

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## ABSTRACT

***Background:*** Proton-pump inhibitor (PPI) was used to treat patients with peptic ulcer bleeding. There was no standardized effective dosing regimen, so various doses of PPI were used to treatment for peptic ulcer bleeding. The aim of this study was to evaluate the efficacy of various doses of PPI on the intragastric pH in Thai patients

***Methods:*** A prospective randomized study was conducted in 60 patients with peptic ulcer bleeding. Patients were randomized into two groups to receive a high-dose intravenous PPI regimen (80 mg bolus followed by 8 mg/hr) or a low-dose intravenous PPI regimen (40 mg bolus twice a day). The primary endpoint was 24 hr intragastric pH. Secondary end points were the antisecretory effect on 24 hr intragastric pH levels in relation to *H. pylori* infection and the rebleeding rate within 7 days.

***Results:*** The mean 24 hr intragastric pH values did not differ significantly between low dose pantoprazole group and high-dose pantoprazole group and demonstrated the similar effect on acid inhibition regardless of the absence or presence of *H. pylori.*

***Conclusion:*** In patients with peptic ulcer bleeding, pantoprazole 40 mg bolus twice a day or high- dose pantoprazole regimen was not significantly different in 24 hr intragastric pH in Thai patients.

**Key words :** Proton-pump inhibitor, pantoprazole, peptic ulcer bleeding

*[Thai J Gastroenterol 2012; 13(3):166-170.]*

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## Introduction

Upper gastrointestinal bleeding is an emergency condition that found around the world. In The United state of America reported the incidence rate of this condition about 102 persons per 100,000 population per year[1] and in the United Kingdom reported the same incidence rate[2]. This condition was seen more frequent in male and the elderly. And acute form was more common than chronic form. Mortality rate in upper gastrointestinal bleeding was about 10%[3]. Peptic ulcer is the most common cause of upper gastrointestinal bleeding which found about 50% of cases. For patients with peptic ulcer bleeding that display major endoscopic stigmata of recent hemorrhage, a combination of endoscopic and pharmacologic therapy is the current standard management. Proton pump inhibitors (PPI) was used widely to treat patients with bleeding peptic ulcers. The coagulation system and platelet aggregation are sensitive to changes in intragastric pH. Keeping intragastric pH value above 4 promotes platelet aggregation and keeping intragastric pH value above 6 promotes clot stability. Thus, inhibition of gastric acid to maintain intragastric pH above 4 and 6 should stabilize blood clot and prevent recurrent bleeding[4]. Peptic ulcer rebleeding is related to a failure in maintain optimal pH. In Caucasian, high doses of PPI (pantoprazole 80 mg bolus followed by continuous doses of 8 mg/hr) have been reported to keep intragastric pH greater than low doses of PPI[5-7]. However, in Asian patients study showed that low doses of PPI achieved optimal intragastric acidity as effectively as high doses PPI[8-12]. The reasons of differences in the response between ethnic groups were that Asian patients had smaller parietal cell mass,[13] higher prevalence of a slow metabolizer phenotype of PPI and higher presence of *Helicobacter pylori* infection. Ishizaki T, et al reported the prevalence of a slow metabolizer phenotype of PPI was about 2-6% in Caucasian and 15-20% in Asians[14,15]. In Thai populations reported prevalence of poor metabolizer 15.7%, intermediate metabolizer 47.1% and extensive metabolizer 37.2%[16]. Therefore, we hypothesized that 24 hr intragastric pH was not significantly different between the low-dose pantoprazole and the high-dose pantoprazole group. We conducted a head-to-head study, the effect on intragastric acidity comparing two strategies for intravenous pantoprazole administration in Thai patients with peptic ulcer bleeding.

## Patients and Methods

We enrolled patients who had peptic ulcer bleeding between Febuary 2010 and Febuary 2011. In high risk bleeding stigmata had been treated successfully with endotherapy either with epinephrine diluted in normal saline or a hemoclip. The exclusion criteria were followed as, patients who used PPI or $H_2$-receptor antagonists within 7 days prior enrolled, a history of gastrointestinal surgery, severe concomitant disease, abnormal kidney function (serum creatinine(2.0 mg/dL, severe coagulopathy (INR>1.5), thrombocytopenia (platelet <100,000), inability to give informed consent, and pregnancy.

## Study Design

A prospective randomized study was conducted at Bhumibol adulyadej hospital; the tertiary care hospital of Royal Thai Air Force, Bangkok, Thailand. All patients provided written informed consent, and the study was conducted according to the revised Declaration of Helsinki. The study was approved by the Hospital's Ethics Committee.

All patients with upper GI hemorrhage underwent EGD within 24 hr. Low risk and high risk bleeding stigmata were enrolled in this study. After successful endoscopic diagnosis and treatment, all patients were randomized by computer-generated list using block of four to receive one of the following intravenous regimens for 24 hr.: (i) pantoprazole 40 mg. bolus twice daily (40 mg bid); or (ii) pantoprazole 80 mg bolus followed by continuous doses of 8 mg/hr. The injection was started within 1 hr after endoscopy. A pH catheter was introduced through the patient's nostril to reach the fundus of stomach and pH was monitored for 24 hr. We used an ambulatory pH recorder catheter (ohmega; medical measurement system USA, Inc.) to measure the intragastric pH. Patients were not allowed to eat or drink during the pH monitoring. After the 24 hr intragastric pH measurement, all patients were treated following standard guideline. The results of intragastric pH were compared between two study groups. Recurrent bleedings were reported in both treatment groups at 1 week after the study. The presence of *H. pylori* was identified by biopsy specimen for rapid urease test.

## Study endpoints

The primary endpoint was the assessment of mean

and median 24 hr. intragastric pH in each pantoprazole treatment group. A secondary endpoints were assessed the antisecretory effect of different doses of pantoprazole on 24 hr. intragastric pH levels in relation to *H. pylori* infection and rebleeding within 7 days

## Statistical analysis

A sample size of 30 patients per treatment group was considered in this study. The $X^2$ test was used to analyze differences between sex, frequency of *H. pylori* infection and distribution of diseases in each treatment group. Independent *t*-test was used to compare the data for age, body mass index (BMI), mean and median intragastric pH within each group. A *p*-value of less than 0.05 was considered to a significant value.

## RESULTS

Sixty patients completed the study. Fifteen patients with high risk bleeding stigmata of gastric ulcers following successful endotherapy and 45 patients were low risk bleeding stigmata of duodenal and gastric ulcers. The demographic data of our study showed in Table 1. The age, sex, BMI, the presence of *H. pylori* infection and distribution of peptic ulcers did not differ between groups. There were no adverse events

**Table 1.** Patient characteristics.

| | **Pantoprazole 40 mg. twice daily (n = 30)** | **Pantoprazole 80 mg. bolus and continuous drip 8 mg/hr (n = 30)** |
|---|---|---|
| **Age (years) (mean, SD)** | 61.13 ± 11.39 | 58.56 ± 13.22 |
| **Sex** | | |
| Male (n, %) | 13 (43.30) | 12 (40.00) |
| Female (n, %) | 17 (56.70) | 18 (60.00) |
| **BMI (mean ± SD)** | 22.30 ± 4.38 | 22.15 ± 3.26 |
| **NSAIDS** | | |
| absent (n, %) | 2 (6.70) | 8 (26.70) |
| present (n, %) | 28 (93.30) | 22 (73.30) |
| **Smoke** | | |
| Absent (n, %) | 19 (63.30) | 17 (56.70) |
| Present (n, %) | 11 (36.70) | 13 (43.30) |
| **Alcohol** | | |
| Absent (n, %) | 19 (63.30) | 15 (50.00) |
| present (n, %) | 11 (36.70) | 15 (50.00) |
| **HP** | | |
| Positive (n, %) | 19 (63.30) | 19 (63.30) |
| Age (years) (mean, SD) | 62.78 ± 9.77 | 58.78 ± 9.86 |
| Negative (n, %) | 11 (36.70) | 11 (36.70) |
| Age (years) (mean, SD) | 58.27 ± 13.79 | 58.18 ± 18.21 |
| **Risk** | | |
| Low (n, %) | 24 (80.00) | 21 (70.00) |
| High (n, %) | 6 (20.00) | 9 (30.00) |
| **Diseases** | | |
| Clean base GU (n, %) | 7 (56.70) | 15 (50.00) |
| Adherent clot (n, %) | 4 (13.30) | 2 (6.70) |
| NBVV (n, %) | 2 (6.70) | 7 (23.30) |
| DU (frequency, %) | 7 (23.30) | 6 (20.00) |
| Rebleeding rate (n, %) | 0 (0.00) | 0 (0.00) |

related to the drug, and no patients died or rebled.

## Intragastric pH

The mean and median intragasrtric pH did not differ significantly between the low-dose pantoprazole group and the high-dose pantoprazole group ($p$= 0.08) (Table 2, Figure 1). Therefore, acid inhibition did not differ significant between the low-dose pantoprazole group and the high-dose pantoprazole group.

## Helicobacter pylori

Of the 60 patients, 22 were confirmed as positive for *H. pylori* (36.66%) The *H. pylori* positive group as the same age as *H. pylori* negative group (mean age 60.78 ± 9.89 in *H. pylori* negative group and mean age 58.22 ± 15.76 in *H. pylori* positive group; $p$-value = 0.84). A positive result of testing for *H. pylori* infection was found in 11 of 30 patients in the low-dose pantoprazole group and 11 of 30 patients in the high-dose pantoprazole group. The low-dose pantoprazole group and high-dose pantoprazole group demonstrated similarly effective acid inhibition regardless of the absence or presence of *H. pylori* (Table 3.)

**Table 2.** Mean 24 h intragastric pH.

| | Pantoprazole 40 mg bid | Pantopprazole 80 mg + 8 mg/hr |
|---|---|---|
| Number of patients | 30 | 30 |
| Mean pH ± SD | 5.56 ± 0.93 | 5.96 ± 0.86 |
| Median pH | 5.80 | 6.35 |
| (min, max) | (3.9,7.5) | (4.1,7.4) |

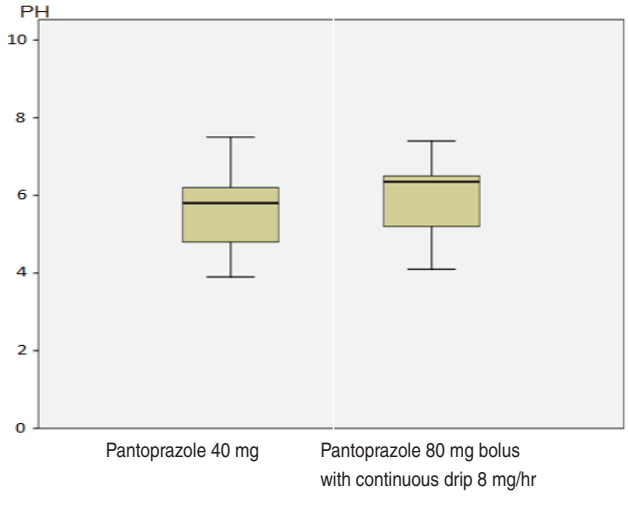


**Figure 1.** Median 24 h intragastric pH in patients treated with the different regimens of pantoprazole. Box plots represent interquartile renge (25 - 75%) and the median is shown as a line across the box.

**Table 3.** Mean and median 24 hr. intragastric pH of patients treated with different pantopazole regimens according to *H. pylori* infection status.

| | HP | Low dose pantoprazloe | High dose pantoprazole |
|---|---|---|---|
| Mean pH ± SD | Positive | 5.55±0.97 | 6.11±0.84 |
| | Negative | 5.57±0.90 | 5.70±0.87 |
| Median pH | Positive | 5.80 (4.01,7.50) | 6.40 (4.10,7.40) |
| (min, max) | Negative | 5.80 (3.90,7.40) | 6.10 (4.30,6.70) |

## Discussion

In patients with peptic ulcer bleeding, our study showed that 40 mg of pantoprazole twice daily and high-dose pantoprazole could effectively raise intragastric pH without significant differences in gastric acid inhibition.

In non-Asian populations, the high-dose PPI regimen currently uses to maintain intragastric pH because the low dose PPI regimen is ineffective in these populations. In contrast to Western studies, Asian studies suggested that low-dose PPI could maintain intragastric pH as good as high dose PPI regimen.

The definitive cause of these interethnic differences in response to PPI is uncertain. It may relate to smaller parietal cell mass, the CYP 2C19 genotype or *H. pylori* infection status.

The prevalence of the CYP 2C19 genetic polymorphism in Asians was more likely than Caucasians to be poor metabolizer; for example, the prevalence of the poor metabolizer genotype was 18.8% in Japanese, 14.6% in Chinese, 15.7% in Thai but only 3.3% in Swedish Caucasians.

Furthermore, in Asian populations had higher prevalence of *H. pylori* infection. This organism may be cause of atrophic gastritis in infected persons. Low acid production in patients with *H. pylori* infection was expected. Thus, the efficacy of PPI was higher in infected persons than in non-infected persons. In our study showed that the high-dose pantoprazole group with *H. pylori* infection had a greater acid inhibition

than a high-dose pantoprazole group without *H. pylori* (mean pH = 6.11 in *H. pylori* positive versus mean pH = 5.70 in *H. pylori* negative; *p*-value = 0.22). These findings suggested that *H. pylori* effected on the efficacy of PPI.

This study, there was no rebleeding rate in both treatment groups. These results could not translation into the real-life clinical practice because of the limitation of a small sample size and more frequently in low-risk bleeding stigmata. (75% of patients were clean base GU.)

Thailand is developing country. Cost of intravenous PPI therapy is expensive. Thus our study results suggested that high-dose pantoprazole infusion could be replace with a 40 mg pantoprazole twice daily, supporting the use of a low-dose regimen for its cost-saving potential.

This study was limited by a small sample size. The sample size which needed to show statistical difference of intragastric pH between both groups was 69 in each group.

## CONCLUSIONS

In patients with peptic ulcer bleeding, pantoprazole 40 mg bolus twice a day or high-dose pantoprazole regimen (80 mg bolus followed by an infusion of 8 mg/hr) was not significantly different in 24 hr intragastric pH in Thai patients.

## REFERENCES

1. Longstretch GE. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population based study. Am J Gastroenterol 1995; 90:206-10.
2. Rockall TA, Logan RF, Devlin HB, *et al*. Incidence and mortality from acute upper gastrointestinal hemorrhage in the United Kingdom. Steering committee and member of the National Adult of Acute upper Gastrointestinal Hemorrhage. Br Med J 1995; 311:222-6.
3. Yavorski RT, Wong RK, Maydonovitch C, *et al*. Analysis of 3294 cases of upper gastrointestinal bleeding in military medical facilities. Am J Gastroenterol 1995; 90:568-73.
4. Green FW Jr, Kaplan MM. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal hemorrhage. Gastroenterology 1978; 74:38-43.
5. Brunner G, Luna P, Hartmann M, *et al*. Optimizing the intragastric pH as a supportive therapy in upper GI bleeding. Yale J Biol Med 1996; 69:225-31.
6. Van Rensburg CJ, Hartmann M, Thorpe A, *et al*. Intragastric pH during continuous infusion with pantoprazole in patients with bleeding peptic ulcer. Am J Gastroenterol 2003; 98:2635-41.
7. Udd M, Toyry J, Miettinen P, *et al*. The effect of regular and high doses of Omeprazole on the intragastric acidity in patients with bleeding peptic ulcer treated endoscopicall y: a clinical trial with continuous intragastric pH monitoring. Eur J Gastroenteral Hepatol 2005; 17:1351-6.
8. Khuroo Ms, Yattoo GN, Javid G, *et al*. A comparison of omeprazole and placebo for bleeding peptic ulcer. N Engl J Med 1997; 336: 1094-8.
9. Javid G, Masoodi I, Zargar SA, *et al*. omprazole as adjuvant therapy to endoscopic combination injection sclerotherapy for treating bleeding peptic ulcer. Am J Med 2001; 111:280-4.
10. Kaviani MJ, Hashemi MR, Kazemifar AR, et al. Effect of oral omeprazole in reducing re-bleeding in bleeding peptic ulcer: a prospective, double. blind, randomized, clinical trial. Aliment pharmacol Ther 2003; 17:211-16.
11. Oh JH, Choi MG, Dong MS, *et al*. Low-dose intravenous pantoprazole for optimal inhibition of gastric acid in Korean patients. J Gastroenterol Hepatol 2007; 22:1429-34.
12. Andriulli A, Loperfido S, Focareta R, *et al*. High-versus low-Dose Proton Pump Inhibitors After Endoscopic Hemostasis in Patients with peptic ulcer Bleeding. Am J Gastroenterol 2008; 103:3011-18.
13. Naik SR, Bajaj SC, Goyal RK, *et al*. Parietal cell mass in healthy human stomach. Gastroenterology 1971; 61:682-5.
14. Sohn DR, Kusaka M, Ishizaki T, *et al*. Incidence of s-mephenytoin hydroxylation deficiency in a Korean population. Clin Pharmacol ther 1992; 52:160-9.
15. Bertilsson L, Lou YQ, Du YL, *et al*. Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxyla of S-mephenytoin. Clin Pharmacol Ther 1992; 51:388-97.
16. Yamada S, Onda M, Kato S, *et al*. Genetic difference in CYP2C19 single nucleotide polymorphisms among four Asian populations. J Gastroenterol 2001; 36:669-72.