American Journal of Emergency Medicine (2012) **30**, 1737–1742

The American Journal of Emergency Medicine

www.elsevier.com/locate/ajem

Original Contribution

A randomized controlled trial of adding intravenous pantoprazole to conventional treatment for the immediate relief of dyspeptic pain ☆

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Received 15 November 2011; revised 30 January 2012; accepted 1 February 2012

Abstract

Introduction: Acute, severe dyspeptic pain is a common condition in the emergency department. Despite the traditional "GI cocktail" (GI indicates gastrointestinal), an intravenous (IV) proton pump inhibitor (PPI), a novel acid-lowering drug, has recently been used to treat this condition. The aim of this study was to evaluate the immediate effect of IV pantoprazole in addition to the conventional GI cocktail in the relief of severe dyspeptic pain.

Methods: This double-blind, randomized, controlled study was conducted in the emergency department of an urban tertiary-care hospital from January 2011 to October 2011. Selected patients with severe dyspeptic pain were randomized to treatment with a placebo, antacid, and antispasmodic (conventional group) or IV pantoprazole, antacid, and antispasmodic (pantoprazole group). The self-reported 100-mm visual analog scale score, adverse effects, and overall satisfaction were evaluated in 15-minute intervals for 60 minutes.

Results: Eighty-seven eligible cases were enrolled in the study. Forty-four and 43 patients were randomized in the conventional group and pantoprazole group, respectively. There was no difference in the mean 60-minute visual analog scale scores between the treatment groups. The rate of "responders," additional drug use, adverse effects, and patient satisfaction were similar between the groups.

Conclusion: Intravenous PPI provides no additional benefit over the conventional GI cocktail in the relief of acute, severe dyspeptic pain. Because of its neutral effect and higher cost, the use of IV PPI to treat such conditions should be discouraged in general clinical practice.

☆ Conflict of interest: M.K. received one third of the total amount of intravenous pantoprazole from Merck Sharp & Dohme. The company did not provide other forms of financial support to the study and was not involved in any part of the study design, patient enrollment, data collection and analysis, or manuscript drafting. The authors declared no conflicts of interest. This study was funded by Rachadapiseksompoch Fund Grant No. RA6/54(1), Faculty of Medicine, Chulalongkorn University.

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0735-6757/$ – see front matter.
http://dx.doi.org/10.1016/j.ajem.2012.02.001

1. Introduction

Functional and acid-related dyspepsia is common among the general population [1-4], and approximately 15% of these patients have severe symptoms [5]. Therefore, epigastric pain or other acid-related symptoms (eg, gastroesophageal reflux disease [GERD]) often lead these patients to the emergency department (ED). "Gastrointestinal, GI cocktails" were widely used in the ED during the recent decades to relieve this acute pain [6]. Treatment mostly comprises liquid antacids, antispasmodics, and viscous lidocaine. Moderate improvement in the pain severity score has been demonstrated in several studies [7-9].

Intestinal acidification and acid hypersensitivity were shown to contribute to acute dyspeptic symptoms in a number of studies [10-13]. Proton pump inhibitors (PPIs) are effective in reducing epigastric pain in GERD [14] as well as a certain subgroup of patients with functional dyspepsia [15-17] over both the short and long terms. Pantoprazole, a Food and Drug Administration–licensed PPI, reaches its peak concentration within the first hour after the first intravenous (IV) infusion. The acid-lowering effect also occurred within the first hour after the first IV infusion [18-22]. Thus, the drug theoretically has a rapid onset and a prolonged effect on acid reduction. Although IV PPIs are not yet considered a well-approved approach to treatment, they are frequently used in an attempt to alleviate severe dyspeptic pain in recent clinical practice. However, patients suitable of oral PPIs (eg, GERD and nonulcer dyspepsia) with a nil-by-mouth status were considered to benefit from the IV PPI [23,24]. No previous study that evaluates the immediate relief of severe dyspeptic pain has been published. Thus, the primary aim of our study was to evaluate the immediate effect of pantoprazole and the conventional GI cocktail compared with the GI cocktail alone in the relief of this condition. Our secondary end point was to evaluate the duration of the effect and the overall degree of patient satisfaction with the treatment. The results of our study may elucidate whether IV PPIs alleviate acute pain in GERD and dyspepsia among patients in the ED.

2. Patients and methods

2.1. Study design and setting

We conducted this prospective randomized, double-blind controlled study in the ED of King Chulalongkorn Memorial Hospital, an urban 1500-bed, university-affiliated, tertiary-care hospital. This ED treats more than 45 000 new cases per year. The hospital institutional review board approved this study. Written informed consent was obtained from each participant. Enrollment began in January 2011 and finished at the end of October 2011. The study was registered with ClinicalTrials.gov (identifier NCT01281501).

2.2. Patient selection

Patients ranging in age from 15 to 50 years who presented to the ED with severe reflux "heartburn" or dyspeptic epigastric pain were prospectively enrolled in this study. The eligibility assessment was completed by the treating ED physicians. Reflux symptoms such as heartburn and regurgitation were generally regarded as typical symptoms of GERD. *Dyspeptic epigastric pain* was defined by pain or burning of at least moderate severity localized to the epigastrium [25]. Patients who had been through the investigation of related symptoms (eg, endoscopy) as well as those who had not been investigated were evaluated for eligibility. Then, simple symptom-based questions adapted from those of Armstrong et al [26], which had been translated into the local (Thai) language, were posed to the patients:

1. Did you experience heartburn during this visit? (Heartburn)
2. Did you experience an acid or sour taste in the back of your throat or mouth during this visit? (Acid regurgitation)
3. Did you experience pain or aching in the stomach region during this visit? (Epigastric pain)
4. Did you experience bloating (a feeling of stomach distension) during this visit? (Bloating)
5. Did you experience nausea or a feeling of sickness during this visit? (Nausea)
6. Did you experience a feeling of fullness or slow digestion lasting 2 hours after a normal-sized meal during this visit? (Slow digestion)
7. Did you have burping or belching? (Burping)

The patients were classified as having "reflux-like" dyspepsia if they had symptoms 1 and 2; "ulcer-like," symptom 3; and/or "dysmotility-like," symptoms 4 to 7. Patients with primary nonpainful conditions (eg, globus, dysphagia, vomiting, and belching) were not included in the study. The diagnoses of GERD or dyspeptic epigastric pain were carefully made using an appropriately detailed history and a physical examination profile.

Patients were excluded if they had the following conditions: (1) pretreatment 100-mm linear visual analog scale (VAS) pain score less than 50 mm; (2) known cases of malignancy or terminal illness; (3) known cases of major medical problems (eg, any evidence of active structural or functional abnormality of the hearts, *chronic renal failure* defined as calculated creatinine clearance <60 mL min^{-1} 1.73 m^{-2} at least 3 months, *liver cirrhosis* defined as the cirrhosis of Child-Pugh classification B or C, or diseases that may significantly confound the diagnoses of GERD or dyspeptic pain); (4) allergy to the drugs studied; (5) contraindication to hyoscine butylbromide (HB) (glaucoma, myasthenia gravis, paralytic ileus, pyloric stenosis, prostatic enlargement, porphyria); (6) received agents to inhibit the secretion of acid (PPIs or histamine-2 receptor antagonists),

antispasmodics, nonsteroidal anti-inflammatory drugs, aspirin, or steroids within 5 days or antacids within 4 hours before the ED visit (those who consumed alcohol within 5 days were also excluded from the study); (7) receiving clopidogrel, statins, iron therapy, warfarins, and antiretroviral agents, which may exhibit serious drug interactions with the PPIs; (8) receiving drugs that have strong anticholinergic activities (eg, acetylcholinesterase inhibitors for Parkinson or Alzheimer diseases, antihistamines, antispasmodics, antipsychotics, skeletal muscle relaxants, and tricyclic antidepressants) or decongestants (eg, phenylephrine), which may exhibit serious drug interactions with HB; (9) diarrhea more than 2 times within the past 24 hours; (10) being suspected to have other ED diagnoses (eg, gut obstruction, biliary colic, pancreatitis, hepatitis, or localized hepatobiliary infections); (11) being pregnant or breast-feeding; and (12) inability to comprehend the VAS evaluation.

2.3. Intervention

All patients were treated with 30 mL of open-labeled antacid (containing 1.32 g of aluminum hydroxide, 0.72 g of magnesium hydroxide) and 20 mg of IV HB as baseline treatment. We did not include the viscous lidocaine in the regimen because of the potential for serious adverse effects [27,28]. The patients were allocated to receive either the placebo (control group) or 80 mg IV pantoprazole (pantoprazole group). In our protocol, we used 10 mL of 0.9% normal saline as the placebo. To set up the blind randomization list, we prepared the operational packets, which were serially labeled according to the preplanned computer-generated randomization. Each packet contained demographic data and a form with a 100-mm VAS as well as vial(s) of the trial drug. All supplies were provided by noninvestigators and stored elsewhere.

When an eligible patient was identified by the ED physicians and informed consent was obtained, every participant was numbered and then treated with antacid, IV HB, and either the study drug or the placebo. The preparation of the IV pantoprazole included 10 mL of clear compatible solvent, which was provided in a format such that the amount and physical appearance were the same as that of the placebo. Then, the drugs were administered to the patients by trained registration nurses who were not involved in the study. At the beginning of the treatment, demographic data and the pretreatment VAS (VAS_0) results were recorded immediately. For the VAS, "100 = unbearable pain" and "0 = no pain" are marked on the higher and lower ends, respectively, of a 100-mm line. During the observation, VAS evaluations were consecutively performed at 15, 30, 45, and 60 minutes after the treatment to assess the pain response. The potential adverse effects were also recorded. The patients were asked to self-mark their pain scores on the lines and were not permitted to compare the current VAS assessment with their previous evaluation. Additional symptomatic relievers such as IV metoclopramide were used to relieve the residual symptoms as indicated. Ancillary treatment with stronger analgesics (eg, opioid derivatives) was prohibited until the end of the 60-minute pain assessment. If more serious alternative diagnoses were suspected anytime during or at the end of the study period, the patients were withdrawn from the study and then fully observed and treated.

At the end of the study, we asked the participants to assess their satisfaction, reflected by whether they would or would not like to be treated with the same regimen if they experienced similar attacks. The patients were discharged with 40 mg oral pantoprazole once daily and other symptomatic relievers (eg, antispasmodics, antiemetics, or antiflatulence agents). We advised the patients to take the acid-lowering tablet more than 2 hours before or after the beginning of the IV regimen. Finally, the patients were scheduled for outpatient follow-up over the next 7 to 14 days.

2.4. Outcome measurement

Pain assessment was performed every 15 minutes. The mean VAS of the 60-minute posttreatment pain score was the primary outcome evaluation. For the purpose of post hoc analysis, we categorized the pattern of the treatment response at the end of the study to 2 groups:

1) "Non-responders" were the patients who had less than 50% decreases in posttreatment VAS compared with the pretreatment evaluation or posttreatment scores greater than 40 mm at the end of the study.
2) "Responders" defined the patients who had 50% decreases or greater in posttreatment VAS compared with the pretreatment evaluation and posttreatment scores of 40 mm or less at the end of the study.

The number of patients in each group was compared between the treatment arms. The overall patient satisfaction at the end of the study was assessed by a simple, self-reported yes/no questionnaire.

2.5. Statistical analysis

According to previous studies [8,9], the mean reduction in VAS scores after the administration of the GI cocktail for the treatment of dyspeptic symptoms was 20 ± 20 mm. We postulated that the pantoprazole arm would display at least a 10-mm improvement on the VAS, as assessed either preoperatively or postoperatively when compared with the conventional GI cocktail arm. Such a trend would have been clinically significant. A standard deviation (SD) of the difference in VAS scores of 20 mm was used in our estimation. The sample size was calculated with G∗power version 3.1 software (Düsseldorf, Germany). The calculation was based on a 2-tailed independent t test with an α error

probability of .05 and a power of analysis of 0.80. Consequently, 65 eligible patients should have been enrolled in each study arm. The total number of participants necessary was 130.

We analyzed the data for all enrolled patients with the intention-to-treat principles. We used SPSS software version 16.0 for Windows (Chicago, IL) for all analyses. Normally distributed continuous data such as the mean differences in VAS results were analyzed by 2 independent *t* tests. The χ^2 test was used to compare the nonparametric proportions. All tests were 2 sided; a *P* values less than .05 was considered statistically significant.

3. Results

In total, 254 patients were evaluated with respect to the eligibility criteria. This evaluation revealed that 87 eligible cases were preliminarily enrolled before the targeted recruitment: 44 and 43 patients were randomized to the conventional arm and pantoprazole arm, respectively. During the study period, 3 patients in the conventional group had other serious diseases: 1 patient had a high fever diagnosed as a systemic infection with hepatic involvement, 1 patient had acute appendicitis, and 1 patient had persistent vomiting and eventually underwent endoscopy with a final diagnosis of pyloric stenosis due to peptic stricture. One patient in the pantoprazole group participated in the study, but her treatment allocation was accidentally revealed during therapy. However, the data of these patients were then analyzed using their corresponding treatment arm. The schematic flowchart of the patients in both groups is shown in Fig. 1. The demographic data of the patients are shown in Table 1. There was no significant difference in patient characteristics between the treatment groups.

For the pain response after treatment, there was no difference in the VAS score between the treatment groups in any posttreatment intervals (Fig. 2). The rates of responders, additional drug use, adverse effects, and patient satisfaction were similar between the groups (Table 2).

4. Discussion

Severe dyspeptic pain is frequently observed in the ED. The administration of an IV PPI is typically performed in the clinic to "reduce acid" and, therefore, "reduce the pain." Although long-term acid suppression of an oral PPI is responsible for the improvement of acid-related dyspeptic pain [14-17], no previous study demonstrating the efficacy of IV administration in the relief of acute dyspeptic pain was published. As the preliminary results were analyzed, we

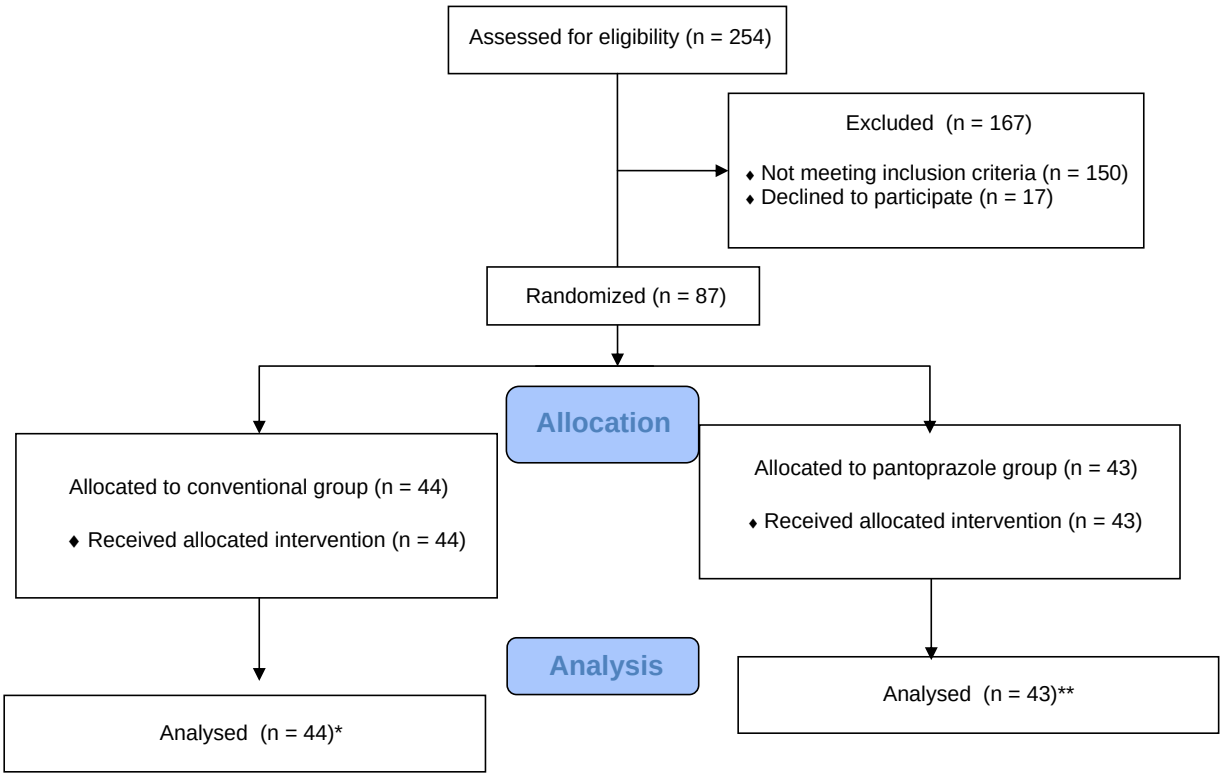

Fig. 1 The CONSORT diagram shows the serial case numbers of the 2 treatment groups during the study period. Notes: * included patients with systemic infection (n = 1), appendicitis (n = 1) and suspected pyloric stenosis (n = 1). ** included a patient whose her treatment allocation was accidentally revealed to the investigators (n = 1).

Table 1 Demographic data for the 2 treatment groups

Patient characteristics	Conventional group, n = 44 (100%)	Pantoprazole group, n = 4 (100%)	*P*
Female sex, n (%)	33 (75.0)	35 (81.4)	.34
Age (y), means ± SD	29.8 ± 8.1	29.4 ± 9.2	.81 (*t* test)
Onset of the symptoms (h), means ± SD	4.6 ± 7.1	3.9 ± 3.1	.57 (*t* test)
Symptom categorization, n (%)			
Reflux-like	36 (81.8)	29 (67.4)	.17
Ulcer-like	36 (81.8)	37 (86.0)	.94
Dysmotility-like	43 (97.7)	39 (90.7)	.28
VAS_0 (mm), mean ± SD	64 ± 13	64 ± 16	.91 (*t* test)

Table 2 Pain response after treatment, rates of rescue drug use, adverse effects, and overall satisfaction

Parameters	Conventional group, n = 44 (100%)	Pantoprazole group, n = 43 (100%)	*P*
VAS scores [a] (mm), (*t* test) mean ± SD			
VAS_0	64 ± 13	64 ± 16	.90
VAS_{15}	40 ± 24	35 ± 25	.32
VAS_{30}	27 ± 23	28 ± 23	.73
VAS_{45}	20 ± 24	25 ± 23	.34
VAS_{60}	17 ± 24	19 ± 23	.60
Responders, n (%)	36 (81.8)	32 (74.4)	.40
Additional drugs, n (%)	11 (25.0)	9 (20.9)	.65
Metoclopramide	7 (15.9)	3 (7.0)	.19
Tramadol	0 (0)	1 (2.3)	–
Morphine	1 (2.3)	1 (2.3)	.99
Ranitidine	4 (9.1)	6 (14.0)	.48
Liquid antacid	0 (0)	2 (4.7)	–
Minor adverse effects [b]	31 (70.5)	30 (69.8)	.92
Patients satisfied with the treatment	34 (77.3)	34 (79.1)	.84

[a] VAS_{15}, VAS_{30}, VAS_{45}, VAS_{60} indicate VAS score at 15, 30, 45, and 60 minutes after treatment, respectively.

[b] Minor adverse effects included transient blurred vision, dry mouth, dizziness, headache, palpitation, and nausea.

believed that no additional benefit of the study drug was likely to be found even if we achieved the target numbers, and thus, we terminated the recruitment before achieving the end goal of 130 eligible patients. Our study results do not demonstrate an additional positive effect of an IV PPI compared with the use of the conventional GI cocktail alone, which implies that the IV PPI treatment should not be used for this condition. The findings of this study validated the inappropriateness of IV PPI when used to relieve acute acid-related abdominal pain [23,24]. Although most of the study patients were placed in the acid reflux-like subgroup (having heartburn or a sense of acid regurgitation), their symptoms may not correlate with PPI-responsive pathologic acid reflux [29-31]. Proton pump inhibitors, as well as other drugs that prevent the secretion of acid, may not mediate the immediate reduction in pain. The neutralization of excessive acid as well as the visceral analgesic and antispasmodic properties of the GI cocktail may be adequate for immediate dyspeptic pain relief. Moreover, the unnecessary use of IV PPI may lead to the recurrence of pain due to rebound acid hypersecretion [32,33] as well as financial burdens.

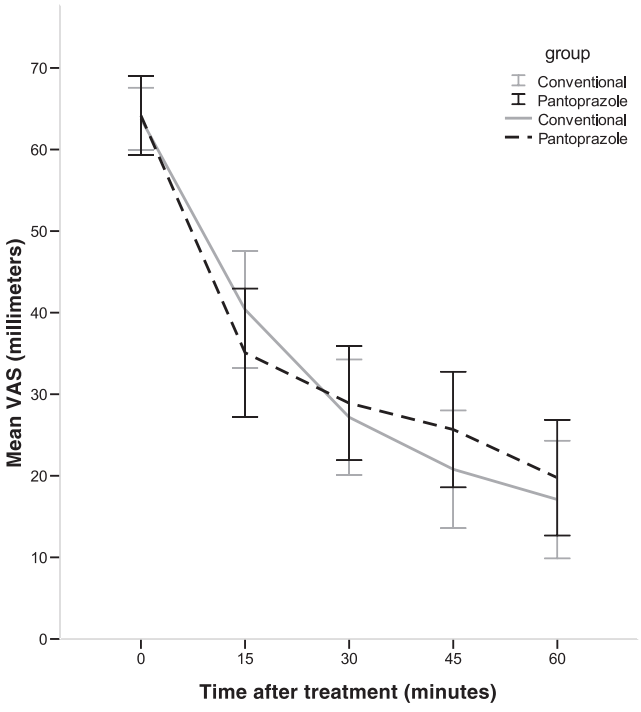

Fig. 2 The line graph demonstrates the mean VAS scores over time after treatment in both treatment groups. (Note: error bars represent ± 2 SD).

We believe that patient factors such as alternative diagnoses or self-treatment with acid-modifying drugs did not confound our results because of the rigorous eligibility criteria. Furthermore, the blinding protocol was used such that major biases were unlikely to occur. Unfortunately, our study has some limitations. First, this was a small, single-centered study, so the included patients do not represent the general population. Second, a self-evaluation of the pain score may have resulted in exaggerated values among patients presenting to the ED because of patients' belief that IV treatment was therapeutic, regardless of whether the placebo or the drug was used. The physician's expectation of a "good outcome" when caring for a patient may also have biased the report. These biases were minimized by the randomized, double-blind methodology and comparison of the self-reported pain evaluations. Moreover, we did not study the short-term recurrence of the pain, which may have resulted from reduced drug potency or rebound acid hypersecretion.

5. Conclusion

In general ED practice, the use of IV PPI provides no additional benefit over the conventional GI cocktail in the relief of acute, severe dyspeptic pain. Because of its neutral effect and higher cost, the use of IV PPI to treat such conditions should be discouraged.

Acknowledgment

We would like to thank Associate Professor Suthep Kolchanwit, MD, from the Gastrointestinal Unit, Department of Medicine, for helpful discussion; Mr Nirun Intarut from the Clinical Research Center, Faculty of Medicine, Chulalongkorn University, for helpful statistical suggestions and figure creation; and all the personnel at the ED of King Chulalongkorn Memorial Hospital and patients who participated in this study.

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