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Intravenous pantoprazole versus famotidine for epigastric pain in the emergency department: A triple-blind randomized clinical trial

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ABSTRACT

Objective: To compare the therapeutic efficacy of intravenous pantoprazole and famotidine for the treatment of epigastric pain in patients presenting to the emergency department.

Methods: In this triple-blind randomized clinical trial, eligible patients presenting with epigastric pain were randomly assigned to receive intravenous pantoprazole or famotidine. Block randomization was used, and patients, treating physicians, and outcome assessors were blinded to treatment allocation. Pain intensity was assessed at baseline and at 30 and 60 minutes after drug administration.

Results: Eighty patients were enrolled, with a mean age of 36.6 years (SD, 15.0), and 42.5% were male. Mean pain scores decreased significantly over time in both treatment groups. In the pantoprazole group, pain scores declined from 8.02±1.28 at baseline to 4.75±1.31 at 30 minutes and 1.62±1.29 at 60 minutes, whereas in the famotidine group scores decreased from 8.12±1.48 to 5.37±1.23 and 2.35±1.54, respectively. There was no significant difference in baseline pain scores between groups ($P=.92$). Pantoprazole resulted in greater pain reduction compared with famotidine at both 30 minutes ($P=.04$) and 60 minutes ($P=.05$).

Conclusions: Both medications were effective in relieving epigastric pain; however, pantoprazole provided greater and more sustained pain reduction, supporting its preferential use in emergency settings.

KEYWORDS: Pantoprazole; Famotidine; Epigastric pain; Dyspepsia; Emergency department

Summary

Question: Does intravenous pantoprazole provide more effective and rapid pain relief than intravenous famotidine in patients presenting to the emergency department with epigastric pain?

Findings: In a randomized clinical trial of 80 patients, both medications reduced pain at 30 and 60 minutes; however, pantoprazole resulted in greater pain reduction at both time points ($P=.04$ and $P=.05$, respectively).

Meaning: Pantoprazole may be preferred over famotidine in emergency settings when prompt and sustained relief of epigastric pain is clinically desired.

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1. Introduction

Dyspepsia is a common gastrointestinal disorder characterized by epigastric pain, postprandial fullness, and early satiety. According to the Rome IV diagnostic criteria, dyspepsia is classified into two subtypes based on symptomatology and presumed pathophysiology: postprandial distress syndrome and epigastric pain syndrome[1]. Although the exact mechanisms remain poorly understood, both PDS and EPS are thought to be associated with delayed gastric emptying, visceral hypersensitivity, *Helicobacter pylori* infection, and psychosocial stressors[2]. Further investigation is needed to better understand these associations.

Abdominal pain is among the most frequent presenting complaints in emergency departments worldwide, with epigastric pain accounting for nearly 25% of cases[3]. Rapid and effective symptom management is thus a clinical priority in acute care settings.

Proton pump inhibitors (PPIs) remain the mainstay of treatment for acid-related disorders, including peptic ulcer disease, gastroesophageal reflux disease, non-erosive reflux disease, and hypersecretory states such as Zollinger–Ellison syndrome. They are also frequently used in combination with antibiotics to eradicate *H. pylori*[4]. PPIs act by irreversibly inhibiting the H^+/K^+ -ATPase enzyme in gastric parietal cells, resulting in profound acid suppression. However, their efficacy may vary due to factors such as food intake, as shown by Tytgat et al., who demonstrated that PPI bioavailability is significantly influenced by fasting state[5].

Pantoprazole is a widely used PPI in both inpatient and outpatient settings. It is FDA-approved for the treatment of erosive esophagitis and pathological hypersecretory conditions, including Zollinger–Ellison syndrome.

Famotidine, a third-generation histamine-2 receptor antagonist, suppresses both basal and stimulated gastric acid secretion. It is commonly used to treat duodenal and gastric ulcers, gastroesophageal reflux disease, and hypersecretory states. Compared with earlier histamine-2 receptor antagonist such as cimetidine and ranitidine, famotidine has a more favorable pharmacokinetic profile and fewer side effects. Its mechanism involves the inhibition of gastric volume and acidity, including acid secretion triggered by food, caffeine, and insulin[6].

Given that both pantoprazole and famotidine are effective in controlling upper gastrointestinal symptoms, they are frequently used in emergency departments, where patients are typically fasting and intravenous administration is preferred. Historically, injectable forms of ranitidine and pantoprazole were widely used for this indication. However, after the Food and Drug Administration withdrew ranitidine from the market due to safety concerns, injectable famotidine has gained popularity as an

alternative.

Despite the widespread clinical use of both medications, few studies have directly compared the efficacy of intravenous pantoprazole and famotidine in managing epigastric pain in emergency settings. Therefore, this triple-blind randomized clinical trial was conducted to compare the therapeutic efficacy of intravenous pantoprazole versus famotidine in patients presenting with epigastric pain to the Emergency Department of Khatam-al-Anbia Hospital. This study is strengthened by its rigorous triple-blind design, the direct comparison of two commonly used intravenous agents in a fasting emergency population, and its practical relevance to real-time decision-making in acute care settings.

2. Patients and methods

2.1. Study Setting

This triple-blind randomized clinical trial was conducted at the Emergency Department of Khatam-al-Anbia Hospital between January and December 2024. The study started in January 2024, and the first patient was enrolled in the same month. Recruitment continued until December 2024.

2.2. Inclusion and exclusion criteria

Eligible participants were adults presenting to the emergency department with epigastric pain, with no clinical or paraclinical evidence of non-gastrointestinal causes of pain, and who provided written informed consent to participate in the trial.

Exclusion criteria were: age under 18 or over 60 years old, pregnancy, hemodynamic instability, recent administration (within two hours prior to emergency department admission) of antacids, H₂-receptor antagonists, or proton pump inhibitors, known hypersensitivity to the study medications, history of gastric or duodenal ulcer, regular use of PPIs within the past 30 days, and suspected alternative diagnoses such as myocardial infarction, cholecystitis, aortic dissection, or other undifferentiated conditions not yet ruled out.

2.3. Data Collection

Based on prior comparable randomized studies, a total sample size of 80 patients (40 per group) was considered appropriate. To ensure balanced allocation, block randomization was applied using permuted blocks of four participants. A total of 20 blocks were required to randomize the full sample. Block sequences were generated using computer software through random sampling

with replacement from six possible permutations of two-treatment sequences. For example, the first block selected was BBAA, assigning the first two patients to drug B and the next two to drug A. The subsequent block was ABAB, allocating the fifth to eighth patients to drugs A, B, A, and B respectively. This process continued until all 80 participants were assigned to their respective treatment groups.

Eligible patients who consented to participate and met none of the exclusion criteria were enrolled. After clinical confirmation of epigastric pain by the attending physician, each patient was assigned a code according to the predefined randomization table by the triage nurse. The nurse was blinded to the medication corresponding to each code. The emergency department pharmacist, who had access to the allocation table, prepared the corresponding medication based on the code. In addition, patients, treating physicians, and outcome assessors were blinded to group allocation, ensuring a rigorous triple-blind design. Each patient received either 40 mg of intravenous pantoprazole (Exir Pharmaceutical Co.) or 40 mg of intravenous famotidine (Caspian Tamin Pharmaceutical Co.), both diluted in 100 mL of normal saline and administered via intravenous infusion over 2 to 4 minutes. Both medications were identical in color and appearance, maintaining blinding for the administering nurse. The patients were also blinded to the treatment they received.

As part of the initial clinical evaluation, patients underwent routine history-taking and medication review, including assessment of previously used drugs. However, for the purpose of this study, only recent use (within the past 30 days) of PPIs and H₂-receptor

antagonists was formally recorded and applied as exclusion criteria. All other clinical examinations, investigations, and treatment procedures were conducted in accordance with standard emergency department protocols.

Pain severity was evaluated at baseline (time zero), and again at 30 and 60 minutes post-infusion using the Visual Analog Scale ranging from 0 (no pain) to 10 (worst imaginable pain).

The primary outcome of the study was the change in pain intensity measured by the Visual Analog Scale (VAS) at 30 minutes after drug administration. Secondary outcomes included pain intensity at 60 minutes, comparison of pain reduction between treatment groups over time, and the occurrence of adverse drug reactions.

Treatment failure was defined as persistent pain with a VAS score ≥ 5 at 60 minutes post-administration. In such cases, intravenous morphine at a dose of 0.1 mg/kg was administered as rescue analgesia.

The average time from emergency department arrival to drug administration was approximately 15 minutes. Associated symptoms such as nausea, vomiting, or bloating were not predefined study outcomes and therefore were not systematically assessed during patient enrollment.

2.4. Statistical Analysis

Upon completion of data collection, all data were analyzed using SPSS version 22. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. As the data were

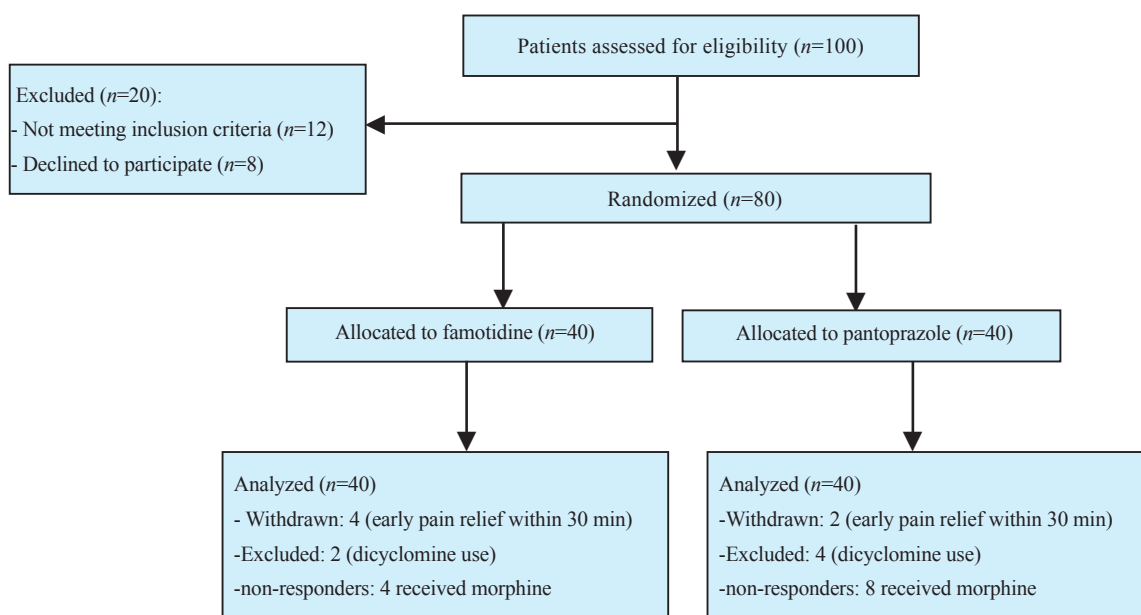


Figure 1. The study flowchart.

normally distributed, continuous variables were expressed as mean±standard deviation (SD), with 95% confidence intervals where appropriate.

An independent samples *t*-test was used to compare mean pain scores between the pantoprazole and famotidine groups. A $P<0.05$ was considered statistically significant. Participants were assured that their personal information would remain confidential and would be used solely for research purposes.

3. Results

3.1. Patient baseline characteristics

A total of 80 participants were randomized, with 40 assigned to receive intravenous famotidine and 40 assigned to receive intravenous pantoprazole. Despite withdrawals and exclusions, the final analyzed sample remained 40 in each group, as replacements were made to preserve the predetermined sample size. The patient enrollment and analysis process are detailed in Figure 1, presented in accordance with the CONSORT guidelines. 4 Patients (10%) experienced rapid symptom relief within the first 30 minutes and voluntarily withdrew before the final pain assessment. Additionally, 2 patients (5%) received dicyclomine during the observation period and were excluded from analysis due to protocol violation. Among the remaining participants, treatment failure occurred in 4 patients (10%), who subsequently received intravenous morphine (0.1 mg/kg). In the pantoprazole group, 2 patients (5%) withdrew early due to complete symptom resolution within 30 minutes, while 4 patients (10%) were excluded after receiving dicyclomine during the study period. Among the remaining participants, treatment failure occurred in 8 patients (20%), who required rescue analgesia with intravenous morphine.

Among the 80 enrolled participants, the mean age was 36.6 ± 15.0 years, and 42.5% were male. Baseline age and sex distributions were comparable between the pantoprazole and famotidine

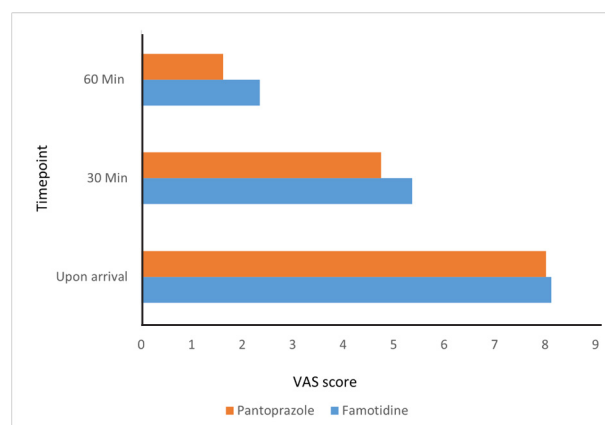


Figure 2. Pain intensity trends by drug type over time in patients receiving pantoprazole and famotidine at three different timepoints.

groups, with no significant differences in sex ($P=.64$) or age group allocation ($P=.98$), indicating well-balanced baseline characteristics.

3.2. Efficacy outcomes

In the famotidine group, the mean pain score decreased from 8.02 at baseline to 5.37 at 30 minutes and 2.35 at 60 minutes. In comparison, the pantoprazole group showed a reduction from 8.02 to 4.75 at 30 minutes and to 1.62 at 60 minutes (Table 1). Both medications were effective in reducing epigastric pain over time. There was no statistically significant difference in baseline pain scores between the pantoprazole and famotidine groups ($P=.92$); however, pantoprazole resulted in greater pain reduction at 30 minutes ($P=.04$) and 60 minutes ($P=.05$).

VAS scores in the pantoprazole group decreased from 8.02 ± 1.28 at baseline to 4.75 ± 1.31 at 30 minutes and 1.62 ± 1.29 at 60 minutes. In the famotidine group, corresponding scores declined from 8.12 ± 1.48 to 5.37 ± 1.23 and 2.35 ± 1.54 , respectively. Both treatment groups demonstrated a consistent reduction in pain intensity over time.

As shown in Table 2, no statistically significant differences were observed in mean pain scores between male and female participants at any assessed timepoint within either treatment group.

These analyses were performed as exploratory subgroup analyses, while the primary comparison between treatment groups is presented in Table 1.

As illustrated in Table 3, both pantoprazole and famotidine produced statistically significant reductions in mean pain scores across all three timepoints within each age group ($P<.001$).

Age-group analyses were conducted as exploratory subgroup analyses and were not defined as primary study outcomes.

Table 1. Baseline characteristics by treatment group.

Variables	Pantoprazole (n=40)	Famotidine (n=40)
Age, years (Mean±SD)	36.8±15.1	36.4±14.9
Under 25 years	14	13
25–35 years	13	14
Over 35 years	13	13
Sex		
Male	16	18
Female	24	22
Baseline VAS score (Mean±SD)	8.02±1.28	8.12±1.48

Table 2. Subgroup analysis of mean Visual Analog Scale scores by sex and timepoint.

Timepoint	Group	Male	Female	<i>P</i> (M vs. F)
Baseline	Pantoprazole	8.31±1.66	7.83±1.68	.35
	Famotidine	7.88±1.27	8.31±1.28	.23
30 min after drug	Pantoprazole	4.87±1.54	4.66±1.16	.68
	Famotidine	5.22±0.94	5.50±1.43	.97
60 min after drug	Pantoprazole	1.93±1.28	1.66±1.16	.27
	Famotidine	2.00±1.28	2.63±1.70	.35

While baseline pain intensity did not differ significantly among age groups for either medication, a significant difference was observed at the 30-minute timepoint in the pantoprazole group ($P=.02$), with patients under 25 years of age showing a faster and more pronounced response to treatment. In contrast, patients over 35 years treated with famotidine experienced a relatively greater reduction in pain at the 60-minute mark ($P=.21$), suggesting a delayed but sustained therapeutic effect in older individuals.

Overall, pantoprazole demonstrated a more rapid onset of analgesic action, whereas famotidine showed a graconsistent reduction in pain intensity over time, highlighting potential age-related differences in therapeutic response to acid-suppressive therapy.

Table 4 presents the significance of differences in mean pain intensity across three timepoints following the administration of pantoprazole and famotidine, as well as the interaction effect between drug type and timepoint. The results of this table indicate that the overall mean pain intensity significantly differed across the three measurement timepoints. However, the interaction between drug type and timepoint was not statistically significant. Additionally, the main effect of drug type was not statistically significant, indicating no overall difference in pain intensity between treatment groups across timepoints.

Figure 2. Estimated marginal means of pain intensity in patients receiving pantoprazole and famotidine at three different timepoints: baseline, 30 minutes, and 60 minutes after drug administration. Figure 2 demonstrates a consistent decline in pain intensity over time in both treatment groups. However, the reduction is more pronounced in the pantoprazole group compared to the famotidine

group, particularly at the 60-minute mark.

3.3. Safety outcomes

Adverse drug reactions were observed in 10 patients (12.5% of the study population), including nausea, headache, and dizziness. Five adverse events occurred in the pantoprazole group—three cases of vomiting, one case of headache, and one case of dizziness—while the famotidine group accounted for five additional events, including one case of vomiting, two cases of headache, and two cases of dizziness. Vomiting was managed with ondansetron, and betahistine was administered for dizziness. All reported headaches were mild, self-limited, and did not require pharmacologic intervention. No other adverse effects were documented.

4. Discussion

In this randomized clinical trial, 80 patients were enrolled, including 26 males (39.4%) and 54 females (60.6%), with a mean age of 36.6 ± 15.0 years. Based on our findings, both famotidine and pantoprazole significantly reduced pain intensity at 30 and 60 minutes after intravenous administration compared to baseline values. Pantoprazole, however, demonstrated superior efficacy in providing faster and more sustained pain relief.

Few studies in the past decade have directly compared these two agents in acute emergency settings. A study by Hosseinzadeh Hamzeh *et al.* evaluated oral pantoprazole and famotidine in

Table 3. Subgroup analysis of Visual Analog Scale scores across age groups by treatment and timepoint.

Age group	Drug	Baseline	30 min after	60 min after	<i>P</i> (within group)
Under 25 years	Pantoprazole	7.21±1.88	4.00±1.03	1.42±1.06	< .001
	Famotidine	8.00±1.00	4.84±0.80	2.23±1.42	< .001
25–35 years	Pantoprazole	8.46±1.26	5.07±1.32	1.92±0.95	< .001
	Famotidine	8.00±1.56	5.50±1.55	2.92±1.77	< .001
Over 35 years	Pantoprazole	8.02±1.67	4.75±1.31	1.53±1.26	< .001
	Famotidine	8.12±1.28	5.76±1.09	1.84±1.28	< .001
<i>P</i> (between age groups)	Pantoprazole	.12	.02	.45	—
	Famotidine	.65	.12	.21	—

Table 4. Results of repeated measures ANOVA and interaction effects in mean pain intensity across three timepoints.

Source	df	Sum of squares	Mean square	F	P	Effect size
Timepoint	2	1482.358	741.179	742.131	<.001	0.905
Drug type	1	14.017	14.017	3.609	.48	0.442
Interaction (Drug×Time)	2	4.508	2.254	2.257	.11	0.028

patients undergoing elective surgery. This prospective, double-blind, randomized controlled trial of 120 patients divided subjects into three groups: placebo, pantoprazole, and famotidine. Their results indicated that pantoprazole more effectively increased gastric pH, while famotidine was superior in reducing gastric volume. These findings support the superior acid-suppressive effect of pantoprazole observed in our study[7].

Masoumi *et al.* conducted another relevant study comparing pantoprazole and ranitidine in the prevention of postoperative gastrointestinal complications after coronary artery bypass graft surgery. Their findings indicated no significant difference between the drugs in preventing complications; however, ranitidine was considered more cost-effective. Although the study addressed a different clinical setting, its conclusions align partially with ours in suggesting comparable efficacy between agents[8].

A third study, conducted by Engin Senay and colleagues in 2016, assessed intravenous pantoprazole versus ranitidine for epigastric pain in the emergency department. This double-blind, randomized trial measured pain scores at baseline, 30 and 60 minutes post-administration. Both medications significantly reduced pain, and no significant differences were observed by age or gender. The authors concluded that pantoprazole and ranitidine were equally effective. Although these findings share some similarities with our results—particularly in pain reduction at 30 and 60 minutes—our study suggests that pantoprazole achieves a more pronounced and sustained reduction in pain intensity, indicating a slight divergence in clinical implications[9].

Interestingly, our subgroup analysis revealed age-related variations in treatment response. Patients under 25 years of age experienced greater pain reduction with pantoprazole, whereas those over 35 showed better outcomes with famotidine. This pattern may reflect physiological and pharmacological differences across age groups. Younger patients tend to have higher gastric acid secretion and faster gastric emptying, potentially enhancing the effectiveness of proton pump inhibitors. In contrast, older adults may exhibit altered receptor sensitivity and slower drug metabolism, favoring a more pronounced response to H₂-receptor antagonists. Although our findings are preliminary, they highlight the potential importance of age as a factor in personalized acid-suppressive therapy and warrant further investigation in larger, multicenter studies.

This study has several limitations that should be acknowledged.

First, although the sample size was sufficient for statistical analysis, it was relatively small and limited to a single-center emergency department, which may affect the generalizability of the findings. Second, the assessment of pain relied on self-reported Visual Analog Scale scores, which, while widely used, are inherently subjective and may be influenced by individual pain perception. Third, due to ethical considerations and clinical protocols, patients experiencing severe pain were treated with rescue analgesia (morphine), which may have introduced variability in the outcome measurements. Finally, long-term follow-up was not performed, limiting the ability to evaluate sustained therapeutic effects or recurrence of symptoms. Despite these limitations, this study has several strengths. The strengths of this study include its rigorous triple-blind randomized design, the head-to-head comparison of two widely used intravenous agents in fasting emergency patients, and its direct applicability to real-time decision-making in acute care settings. These features enhance the robustness of our findings and underline their relevance for clinical practice.

Conflict of interest statement

The authors report no conflict of interest.

Ethical statement

The research protocol was reviewed and approved by the Research Council of the Faculty of Medicine and subsequently received ethical clearance from the Ethics Committee of Zahedan University of Medical Sciences (Approval Code: IR.ZAUMS.REC.1401.360). The study was conducted in full compliance with institutional ethical standards under the supervision of Zahedan University of Medical Sciences.

Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

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This study received no extramural funding.

Authors' contributions

AB developed the study concept, conducted the literature review, and acquired the data. AB and MK designed the study protocol and performed data analysis. SY contributed to patient recruitment and sample collection. All authors contributed to defining intellectual content, conducting the study, and preparing, editing, and reviewing the manuscript.

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