Original Article

Comparison of intravenous pantoprazole and ranitidine in patients with dyspepsia presented to the emergency department: a randomized, double blind, controlled trial

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BACKGROUND: This study aimed to compare pantoprazole, a proton-pomp inhibitors (PPIs), and ranitidine, a H_2 receptor antagonists (H_2RA), in ceasing dyspeptic symptoms in the emergency department (ED).

METHODS: This randomized, double-blinded study compared the effectiveness of 50 mg ranitidine (Ulcuran®) and 40 mg pantoprazole (Pantpas®), given in a 100 mL saline solution by an intravenous rapid infusion within 2–4 minutes in patients with dyspepsia presented to the ED. Pain intensity was measured at baseline, 30 and 60 minutes after the drug administration.

RESULTS: A total of 72 patients were eligible for the study. Of these patients, 2 were excluded from the study because the initial visual analogue scale (VAS) scores were under 20 mm and 4 were excluded from the statistical analysis because of being diagnosed as having other causes of epigastric pain despite being allocated to one of the study groups. Thirty-three patients in the pantoprazole group and 33 patients in the ranitidine group were analyzed ultimately. The mean age of the patients was 36.6±15 years, and 26 (39.4%) patients were male. Both of the groups reduced pain effectively at 30 [27.6±28 (18 to 37) vs. 28.3±23 (20 to 37), respectively] and 60 minutes [39.6±39 (26 to 53) vs. 42.3±25 (33 to 51), respectively]. There were 13 (39.4%) patients in the pantoprazole group and 8 (24.2%) patients in the ranitidine group who required additional drug at the end of the study (*P*=0.186).

CONCLUSION: Intravenous pantoprazole and ranitidine are not superior to each other in ceasing dyspeptic symptoms at 30 and 60 minutes in the ED.

KEY WORDS: Dyspepsia; Pantoprazole; Ranitidine; Emergency department

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INTRODUCTION

Dyspepsia is characterized as a discomfort or pain in the epigastric region that may be related to peptic ulcer, gastritis or functional dyspepsia, characterized by the negative results of endoscopy. The prevalence of dyspepsia in the USA is approximately 25% and the disease is the most common cause (6.8%) for emergency visits.[1] The high prevalence of dyspepsia leads to not only the workload of physicians but also high costs.[2,3]

Proton-pomp inhibitors (PPIs), H_2 receptor antagonists (H_2RAs) and anti-acids are the most common agents used for the treatment of dyspepsia, peptic ulcer and gastritis. A Cochrane meta-analysis reported that PPIs are more effective than H_2 receptor blockers (*RR* 0.63, 95%*CI* 0.47 to 0.85) and anti-acids (*RR* 0.72, 95%*CI* 0.64 to 0.80).[4] However, the DIAMOND study compared step-up (anti-

acids, H_2RA and PPIs respectively) and step-down strategies (reverse of the step-up strategy) in patients with dyspepsia in primary care patients and showed that there was no difference in six-month treatment success between the two groups (72% vs. 70%) but with lower costs.[5]

There is also little known about the effectiveness of PPIs and H_2RAs in patients with dyspepsia presented to the emergency department (ED).[6,7] This study aimed to compare pantoprazole, a PPI, and ranitidine, a H_2RA, in ceasing dyspeptic symptoms in the ED.

METHODS

Study design and setting

This single-center prospective randomized double-blind clinical trial was conducted between October 2012 and January 2013 in the ED of a tertiary care hospital with an annual census of 90 000 patients. We compared the efficacy of pantoprazole and ranitidine in patients with dyspepsia presented to the ED. A written inform consent was obtained from all patients. The study was registered to *clinicaltrials.gov* (*clinicaltrials.gov* ID: NCT01737840). Both the local ethics committee and central health agency approved the trial.

Selection of participants

Patients over 18 years old presented with epigastric pain suggestive of dyspepsia with visual analogue scale (VAS) score of over 20 mm were eligible for the study. They were enrolled into the study consecutively 24 hours a day, 7 days a week. The exclusion criteria from the study were as follows: patients diagnosed as having other possible causes of epigastric pain such as acute cholecytitis, pancreatitis, myocardial infarction at the end of the ED period or 24 hours after the ED discharge with a telephone follow-up, pregnancy, patients with unstable vital signs, receiving anti-acids, H_2 receptor blockers of PPI within one hour of ED visit, known allergy to the study agents, pain intensity with a VAS score under 20 mm, denied to give informed consent, and illiterate patients.

Attending physicians decided the patient eligibility between 08:00 and 24:00 and senior residents at the remaining time. The physicians were free of performing diagnostic tests during or after the study period for additional diagnosis.

Interventions

The patients received a single intravenous dose of 40 mg pantoprazole (Pantpas®, Nycomed) and 50 mg ranitidine (Ulcuran®, Abfar, Istanbul, Turkey). Both drugs were given in a 100 mL normal saline solution with a rapid infusion of 2–4 minutes. An assistant blinded to the study prepared randomization schedule. If a patient was suitable for the study, the study nurse got a folded paper displaying a study number which was also recorded to the study form from an opaque bag and prepared the study drug matched with the number. And another nurse with a blinded fashion administered the study drug. Both drugs were identical in color and appearance. Physicians, nurses administered the study drugs and patients were all blinded to the study drugs.

Methods of measurement

Pain intensity was measured by a 100-mm VAS (bounded by "no pain" and "worst pain") before the study drug, 30 and 60 minutes after the drug administration. Patients were blinded to the previous VAS scores. Adverse events such as nausea, vomiting or allergic reaction were recorded to the study form at the end of the study period. Patients diagnosed with another pathology causing epigastric pain rather than dyspepsia during the ED stay and 24 hours after the ED discharge with a telephone follow-up were also recorded.

Outcome measures

The primary outcome measure was the pain reduction recorded by VAS at 30 and 60 minutes. The secondary outcome measures were the need for additional drugs at 60 minutes and recurrence of pain at 24 hours after ED discharge.

Statistical analysis

The study data were analyzed with MedCalc 12 and SPSS 16.0. Because the numeric data were distributed normally, it was presented by mean±standard deviation with 95% confidence interval (*CI*). The categorical data were presented as rates. The normality analysis was performed by the Kolmogorov Smirnov test. For 25 mm standard deviation in patients presented with dyspepsia to the ED and a clinically significant difference of 20 mm in VAS, a minimum of 33 patients is needed for each group with 90% power. The statistical analysis was planned to be performed with an intention to treat analysis. All the hypotheses were constructed as two tailed and an alpha critical value of 0.05 was accepted as significant.

RESULTS

Seventy-two patients were enrolled in the study. Two of the 72 patients were excluded from the study because

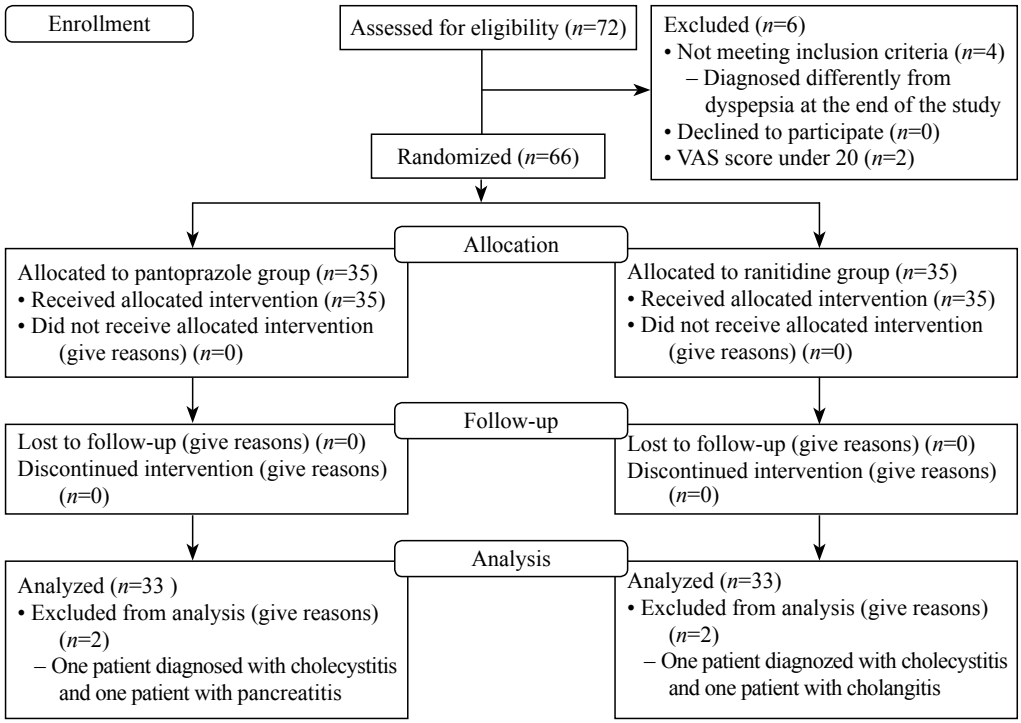

Figure 1. Patient flow chart.

Table 1. Pain outcomes at 30 and 60 minutes in the two groups [mean±SD (95%*CI*)]

Variables	Pantoprazole	Ranitidine
Visual analogue scale		
Baseline	69.0±23 (61 to 77)	60.9±19 (54 to 68)
30 minutes	41.4±27 (32 to 51)	32.6±21 (25 to 40)
60 minutes	29.4±32 (18 to 41)	18.6±19 (12 to 25)
Visual analogue change from Baseline		
30 minutes	27.6±28 (18 to 37)	28.3±23 (20 to 37)
60 minutes	39.6±39 (26 to 53)	42.3±25 (33 to 51)

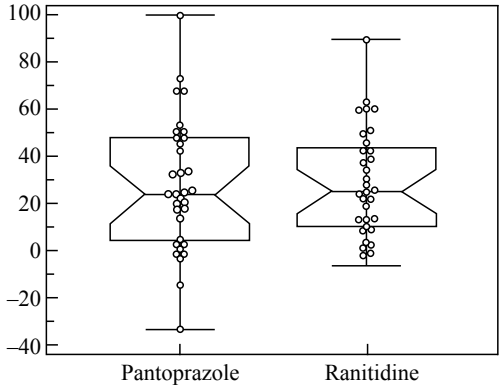

Figure 2. Pain reduction at 30 minutes in the two groups.

their initial VAS scores were under 20 mm, and 4 were excluded from the statistical analysis because of other causes of epigastric pain despite being allocated to one of the study groups (Figure 1). Thirty-three patients in the pantoprazole group and 33 patients in the ranitidine group were analyzed ultimately. The mean age of the patietns was 36.6±15 years, and 26 (39.4%) patients were male.

Main results

Both groups reduced pain effectively at 30 [27.6±28 (18 to 37) vs. 28.3±23 (20 to 37), respectively] and 60 minutes [39.6±39 (26 to 53) vs. 42.3±25 (33 to 51), respectively] (Table 1). There was no significant difference in the improvement of dyspepsia at 30 [0.76 (–12 to 13)] and 60 minutes [2.7 (–13 to 19)] between the two groups (Figures 2 and 3).

There were 13 (39.4%) patients in the pantoprazole group and 8 (24.2%) patients in the ranitidine group who required additional drugs at the end of the study period (P=0.186). There were seven patients (3 in the pantoprazole group and 4 in the ranitidine group) who cannot be reached by telephone follow-up at 24 hours. Nine (30%) patients in the pantoprazole group and 12 (41.4%) patients in the ranitidine group declared to have repeated pain (P=0.361). There was also no significant difference between the two groups [4 (13.3%) vs. 5 (17.2%), respectively, P=0.676] seeking for medical aid at 24 hours. No adverse effect was noted in both groups.

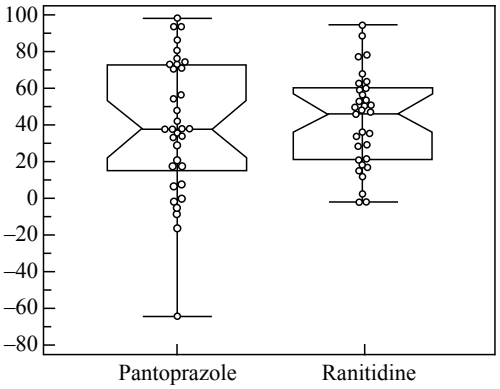

Figure 3. Pain reduction at 60 minutes in the two groups.

DISCUSSION

This study showed that pantoprazole is not better than ranitidine in ceasing dyspepsia in patients treated at the ED. There are many treatment modalities for peptic ulcers and gastritis such as proton pomp inhibitors, H_2 receptor blockers and anti-acids.[8-10] But the results of these madalities are not satisfactory in the treatment of dyspepsia in the ED. A Cochrane meta-analysis showed that PPIs are better than H_2 receptor blockers, anti-acids and prokinetics in the management of dyspepsia.[4]

There are few studies comparing the treatment modalities for dyspeptic symptoms in the ED. Although there are some methodological flaws, Musikatavorn et al[11] reported that combination of pantoprazole (80 mg IV), anti-acids and anti-spasmolytics (VAS_0=64±13 to VAS_{60}=17±24) was not superior to anti-acids and anti-spasmolytics combination (VAS_0=64±16 to VAS_{60}=19±23) at 60 minutes. They also found no difference in additional use of a drug between pantoprazole and placebo (25% vs. 20%). Despite the statistical insignificance, the rescue drug rate was 39% in the pantoprazole group and 24% in the ranitidine group in our study.

Welling et al[7] compared the oral anti-acids alone (n=34) with oral anti-acids and viscous lidocaine combination (n=39) in patients with dyspepsia presented to the ED. Pain reduction in 11 cm linear analogue scale was 9±29 mm in oral anti-acids group and 40±34 mm in oral anti-acids and viscous lidocaine combination group at 30 minutes (P<0.0001).

Berman et al[6] also found no difference between anti-acids, anti-acids+spasmolytics and anti-acids+spasmolytics+oral lidocaine combinations in ceasing dyspepsia at 30 minutes. Vilke et al[12] compared benzocaine (n=44) and lidocaine (n=38) in patients with dyspepsia, and found that after administration of oral anti-acids and oral anti-cholinergics there was no difference between the two groups at 30 minutes.

There are no adverse effects related to the study drugs. PPIs and H_2 receptor blocker are genrerally accepted as safe drugs. The present study showed that pantoprazole and ranitidine are not superior in ceasing dyspepsia in the ED, but each is safe to use in the ED. Cost might be a matter of choosing the appropriate treatment; however whether parenteral drugs for dyspepsia are superior to oral drugs such as anti-acids, local anesthetics and anti-cholinergics or their combinations is not clear. Further studies are needed to discover the right ways.

Limitations

This study has several limitations. This is a trial with a small sample size that is unable to conclude that both drugs are equal. A placebo might be added to the study, that may clarify the question whether parenteral drugs for dyspepsia in the ED are superior to the placebo.

There were no adverse effects in both groups in the present study but this finding doesn't mean that these drugs have no adverse effects as reported in previous trials. But it is troublesome to differentiate these effects from dyspepsia or drugs.

Dyspepsia is a symptom rather than a pathological diagnosis, and it can be diagnosed after ruling out other pathologies. There are no criteria for exclusive confirmation of dypepsia in the ED. Hence it may be a limitation to our study.

In conclusion, intravenous pantoprazole and ranitidine are not superior to each other in ceasing dyspeptic symptoms at 30 and 60 minutes in the ED.

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Conflicts of interest: The authors have no competing interests.

Contributors: Senay E, Eken C, Yildiz M, Yilmaz D and Alkan E are responsible for the study design, analysis and interpretation of data, and drafting. Akın M and Serinken M are responsible for revision of the intellectual content and final approval of the version. All the authors have read and approved the final version of the manuscript.

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