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Comparison of Intra-Venus Ranitidine with Pantoprazole in Patients with Epigastric Pain Referring to Emergency Department

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Abstract **Background and aim:** Epigastric pain episodes are one of the most common complaints of patients referring to the emergency departments worldwide. The purpose of this study was to compare the effects of ranitidine and pantoprazole on epigastric pain in the emergency department. **Materials and Methods:** This randomized clinical trial (RCT) study was performed on 100 patients (50 patients in each study arm) with epigastric pain complaints referred to emergency department of Imam Khomeini Educational Hospital in Sari in 2017. Patients older than 18 years of age with an epigastric pain with early diagnosis of dyspepsia and a visual acuity score of 20 mm high (VAS) were included. Patients were enrolled in two treatment groups: single venous dose of pantoprazole 40 mg and single dose of ranitidine 50 mg. The pain score was recorded 30 and 60 minutes after the intervention. **Results:** The findings showed that in the pantoprazole group: 9.4% dyspepsia and 37.5% pancreatitis and 12.5% gastroenteritis and 40.6% asymptomatic. Before the intervention, the pain group had a pain score of 10.8 and 8.16 in the pantoprazole group. There were no differences between the two groups ($P = 0.888$), but after treatment, significant difference were observed in each of the groups after the use ($P<0.001$). Also, the comparison of the two groups after treatment showed that there was a significant difference in pain severity between the two treatment groups ($P<0.001$). **Conclusion:** The results of this study have revealed that Ranitidine and Pantoprazole effectively improve initial epigastric pain, but ranitidine is more effective.

Keywords Ranitidine, Pantoprazole, Dyspepsia, Pain, Emergency

1. Introduction

Epigastric pain is one of the most common complaints in patients referring to emergency departments. It may have different reasons. The most important reasons are cardiac dysfunction and gastrointestinal disorders. Gastrointestinal epigastric pain has many symptoms including bloating, nausea, vomiting, heartburn, reflux, or a set of these symptoms. [1] The prevalence of symptoms in the western countries was reported 20- 30%. In several studies, especially endoscopic researches, only about 20- 30% of them were pathologically diagnosed, and the rest had no lesions. [2]

Papers have shown approximately 21% of people in Western countries have no ulcerative dyspepsia. In these patients, there is no structural dysfunction to justify the symptoms. [3] The pathogenesis of non-ulcerous dyspepsia is also unknown. [2, 4, 5] Recent researches focused on four factors: motor dysfunction, sensory impairment, Mucosa inflammation, Helicobacter infection, psychosocial and central nervous system changes [6].

Pantoprazole is a Proton pump inhibitor that is used to reduce gastric acid secretion in the treatment of acid-dependent disorders and indigestion. The use of this medicine is increasing. The reason is its greater effect on histamine receptor antagonists in the treatment of gastric acid-dependent disorders, including peptic ulcer. It has been recommended as the first treatment for most of the serious gastric acid diseases, such as erosive esophagitis, by the international guidelines. [1]

Ranitidine is a H2 receptor antagonist and it competitively inhibits the effect of histamine on H2 receptors in gastric wall cells. This effect prevents basic and nocturnal acid secretion. It also inhibits acid secretion result from histamine, food, amino acids, insulin and pantagastrin [1].

Kalantari and colleagues studied the effect of Omeprazole and Ranitidine in treating duodenal ulcer. This study showed that omeprazole was effectively better than ranitidine in improving duodenal ulcer. Omeprazole could reduce 60% of the prevalence of the ulcer while ranitidine could reduce 26% [6].

Mason and colleagues studied the effect of Ranitidine and Omeprazole on dyspepsia. The results showed that Omeprazole could improve 61% of the disorder while Ranitidine could improve 40% [7].

Serinken and colleagues compared the effect of 50 mg intravenous Ranitidine with 40 mg Pantoprazole. They concluded that the efficacy of intravenous pantoprazole was not significantly different from intravenous ranitidine in patients. The pain was reduced in both groups 30 and 30 minutes after the intervention [3].

Considering that the treatment of epigastric pain in emergency departments has not been studied in our region and despite of its high prevalence, therefore, the purpose of this article was to compare the analgesic effect of ranitidine and pantoprazole on epigastric pain in the patients referring to emergency department.

2. Method

This randomized clinical trial (RCT) was performed on 100 patients (50 patients in each group) with epigastric pain referring to emergency department of Imam Khomeini Hospital, Sari in 2017. The patients were divided to two groups randomly by computer. The patients and final evaluator were unaware of patient's allocation (double blinded). There was no possibility of masking for the doctor because the patients had emergent condition and emergent tests were needed.

According to Engin Senay [3] and colleagues' study (2016), sample size was calculated 50 patients for each group considering confidence interval of 95% and power of 80%.

$$N=2K*SD2/d2$$

$$N= 2 * 10.5 * 282 / 202 * 1.2 = 50$$

2.1. Inclusion and Exclusion Criteria

Study population was consisted of patients over 18 years old who were diagnosed with epigastric pain and early diagnosis of dyspepsia and a visual acuity score of 20 mm (VAS). The primary diagnosis of dyspepsia was done by Emergency Medicine Specialist. The placebo was provided by the pharmacy department of university and given to patients by blinded nurse.

The exclusion criteria were pregnancy, VAS score<20mm, other causes of dyspepsia such as acute cholangitis, acute myocardial infarction, and pancreatitis, unstable hemodynamic, history of anti-acid and H2 receptor blockers, and PPI one hour before admission in emergency department, having allergy to the medicines, dissatisfied with participating, and leaving the study.

The patients were divided into two groups A and B. group A received 40 mg intravenous pantoprazole which was diluted in 100cc Normal Saline and was infused during 2-4 hours. Group B received 50 mg intravenous Ranitidine diluted in 100cc Normal Saline and infused during 2-4 hours.

Data gathering was done using a questionnaire including demographic data such as age, sex, history of smoking, consuming analgesics, previous gastrointestinal diseases, and getting infected by H-pylori. Another questionnaire was used to record VAS score 30 and 60 minutes after intervention and side effects such as Headache, dizziness, blurred vision, rash, Diarrhea, palpitations, hypoglycemia, insomnia, anxiety, hyperglycemia, bloating, nausea and vomiting.

Data were analyzed by SPSS software 18. Quantitative data were described with mean and standard deviations and qualitative data with frequency and percentages. Studying data distribution was performed by histogram and Kolmogorov-Smirnov or Shapiro-Wilkes tests. Mean of VAS was calculated Using Mann-Whitney U Test and Independent T-Test. P value of less than 0.05 was defined as significant.

3. Results

This study was conducted to compare the effects of ranitidine and pantoprazole in patients with epigastric pain who referred to emergency department of Imam Khomeini Hospital (Sari, Iran) during 2017. One hundred patients over 18 years old were randomly entered into two groups. Non-parametric tests were used because of not being equal variances. Comparison between the groups was done using Mann-Whitney test and intra-group comparison was used to compare pain severity before and after treatment by Wilcoxon.

The mean age in Ranitidine group was 46.76±17.044 and in pantoprazole group was 48.88±16.184 (p-value=0.459).

Fisher's exact test was used for analyzing the qualitative data. For analyzing the quantitative data which had not normal distribution, nonparametric test was used. Comparison between groups was done using U-Mann-Whitney test and Wilcoxon test was used to compare pain severity before and after treatment.

Table 1 shows the results of comparison the variables between two groups.

Table 1. The results of comparison the variables between two groups

variables		Ranitidine		Pantoprazole		p-value
		frequency	percent	frequency	percent	
sex	Male	34	50	6	18.8	0.003
	female	34	50	26	81.3	
smoking	smoker	3	4.4	1	3.1	0.617
	Non-smoker	65	95.6	31	96.9	
Analgesic consumption	Yes	36	52.9	8	25	0.009
	no	32	47.1	24	75	
H-pylori infection	Yes	16	23.5	4	12.5	0.198
	no	52	76.5	28	87.5	
GI disorder	Yes	27	39.7	9	28.1	0.260
	no	41	60.3	23	71.9	
GI pain	Yes	68	100	32	100	-
	no	0	0	0	0	
headache	Yes	0	0	0	0	-
	no	68	100	32	100	
Dizziness	Yes	0	0	0	0	-
	no	68	100	32	100	
Blurred vision	Yes	0	0	0	0	-
	no	68	100	32	100	
Nausea and vomiting	Yes	14	20.6	10	31.3	0.316
	no	54	79.4	22	68.8	
Rash	Yes	0	0	0	0	-
	no	68	100	32	100	
Diarrhea	Yes	0	0	0	0	-
	no	68	100	32	100	
hypoglycemia	Yes	0	0	0	0	-
	no	68	100	32	100	
bloating	Yes	0	0	4	12.5	0.009
	no	68	100	28	87.5	
palpitation	Yes	0	0	0	0	-
	no	68	100	32	100	

According to table 1, two groups were not homogeneous in sex (p=0.003) there was also a significant difference between the groups in analgesic consumption which was higher in ranitidine group (p=0.009). According to similar situation about occurrence the GI pain, headache, dizziness, blurred vision, rash, diarrhea, hypoglycemia, and palpitation in both groups, therefore comparison was not possible.

Primary and secondary diagnosis is shown in table 2 using Fisher exact test.

Table 2. Primary and secondary diagnosis using Fisher exact test

diagnosis		Ranitidine		Pantoprazole		total		p-value
		frequency	percent	frequency	percent	frequency	percent	
Primary diagnosis	dyspepsia	68	100.0	24	75.0	92	92.0	<0.001
	pancreatitis	0	0.0	8	25.0	8	8.0	
	total	68	100.0	32	100.0	100	100.0	
Secondary diagnosis	dyspepsia	17	25.0	3	9.4	20	20.0	<0.001
	pancreatitis	0	0.0	12	37.5	12	12.0	
	gastroenteritis	4	5.9	4	12.5	8	8.0	
	No symptom	47	69.1	13	40.6	60	60.0	
	total	100	100.0	32	100.0	100	100.0	

The results showed that primary diagnosis for all participants of ranitidine group was dyspepsia, while the diagnosis changed into 25% dyspepsia, 5.9% gastroenteritis, and 69.1% no symptom after the intervention. In other group primary diagnoses were 75% dyspepsia and 25% pancreatitis. After the intervention the diagnoses were 9.4% dyspepsia, 37.5% pancreatitis, 12.5% gastroenteritis, and 40.6% no symptom. ($p<0.001$)

The pain score was compared before and after the intervention and the results is shown in table 3.

Table 3. Pain score before and after the intervention

Pain score	Ranitidine		Pantoprazole		p-value
	mean	SD	mean	SD	
Before intervention	8.10	2.11	8.16	2.03	<0.001
After intervention	1.35	1.44	3.88	2.63	

4. Discussion

This study was conducted to compare the effect of pantoprazole and ranitidine on epigastric pain induced by early dyspepsia in adult patients. They were randomly assigned to two groups: pantoprazole group with 52 patients 36.4 (0.91%) and ranitidine group with 43 patients (30.1%).

In this study, it was shown that pantoprazole was not better than ranitidine in controlling dyspeptic pain in emergency department. There are several therapeutic methods for primary gastritis and peptic ulcers such as SPPI, anti-acids, and H2 receptor blockers. But the response to the treatment is not clear enough.

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 and anti-acids [10]

Engin Senay and colleagues compared intravenous pantoprazole and ranitidine in patients with dyspepsia presented to the emergency department. They compared the effectiveness of 50 mg ranitidine and 40 mg pantoprazole, 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. They concluded that intravenous pantoprazole and ranitidine are not superior to each other in ceasing dyspeptic symptoms at 30 and 60 minutes in the ED. [3] our results are similar to this study.

Musikatalora and colleagues compared the effect of pantoprazole-anti-acid with pantoprazole-anti-spasmodic. 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. They showed that they were not different and better than each other [7]

In our study, the improvement in Ranitidine group was 24% while in pantoprazole group was 39%.

Vilke GM and colleagues studied viscous lidocaine versus benzocaine in a GI cocktail for dyspepsia. Patients 18 years or older were approached for participation when a GI cocktail was ordered by the Emergency Physician. Patients were randomized to equivalent doses of either Benzocaine or viscous Lidocaine in addition to 30 cc of Maalox and 10 cc of Donnatal. Assessment using a visual analog pain scale occurred at time intervals of 0, 5, 15, and 30 min. They showed no statistical differences between the Benzocaine and viscous Lidocaine groups in terms of the relief of symptoms at each of the assessment times. There were no adverse outcomes in either group [8] it was in line with our study.

According to our results, there was no headache, dizziness, hypoglycemia and nausea-vomiting in both groups, but floating was higher in pantoprazole group. Seray and colleagues showed similar result in their study [9].

Demetrashvili ZM and colleagues compared intravenous pantoprazole with intravenous ranitidine for prevention of rebleeding of peptic ulcers following initial endoscopic hemostasis. They investigated no statistically significant

differences between the groups with regard to need for emergency surgery (2,2% vs 6,8%), the length of hospital stay (6,7±3,3 vs 7,4±4,3 d) and mortality (0% vs 0%). After endoscopic treatment of bleeding peptic ulcers, intravenous pantoprazole is more effective than ranitidine for the prevention of rebleeding. [11]

Both PPIs and H_2 receptor blocker are generally accepted as safe drugs. Our study showed that pantoprazole and ranitidine are not superior in reducing epigastric pain in the ED, but each is safe to use in the ED. Cost might be a matter of choosing the appropriate treatment. Further studies are needed to discover the right ways.

5. Conclusions

The results of this study showed that both ranitidine and pantoprazole effectively improve initial episodes of pain, but ranitidine is more effective than pantoprazole in improving epigastric pain. Also, rash, headache, dizziness, hypoglycemia were not observed. It seems that ranitidine can control epigastric pain in emergency patients. Also, the accuracy of this study can be checked in future trials with more sample size. Further investigations are needed to confirm the outcomes.

Conflict of Interest

Authors declare that there are no conflicts of interest.

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