High Dose versus Low Dose Intravenous Pantoprazole in Bleeding Peptic Ulcer: A Randomized Clinical Trial

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ABSTRACT

BACKGROUND

The appropriate dose of proton pump inhibitors for treatment of patients with upper (GI) bleeding remains controversial. This study compares high-dose versus low-dose intravenous proton pump inhibitor (PPI) infusion for prevention of GI bleeding complications.

METHODS

A total of 166 patients with bleeding peptic ulcers underwent therapeutic endoscopy using concomitant therapy by argon plasma coagulation (APC) and diluted epinephrine injection. Patients were randomly divided into two groups: high-dose pantoprazole (80 mg bolus, 8 mg per hour) and low-dose pantoprazole (40 mg bolus, 4 mg per hour) infused for three days. Initial outcomes were rebleeding, need for surgery, hemoglobin drop more than two units, and hospitalization for more than five days. Secondary outcome included mortality rate.

RESULTS

Overall, 166 patients (83 patients per group) enrolled in the study. The average age of patients in the high-dose group was 59.5±15.6 years and 52.3±13.3 years in the low-dose group (p=0.58). Males comprised 69.7% of patients. In the high-dose group, the mean number of units of transfused blood was 3.3±1.71 and in the low-dose group, it was 2.82±1.73 (p=0.50). There were 36 (43.37%) patients in the high-dose group and 40 (48.19%) in the low-dose group who were hospitalized for more than 5 days (p=0.53). Rebleeding was observed in 27 (32.53%) patients in the high-dose group and in 21 (25.30%) in the low-dose group (p=0.30). There were no significant differences observed in drop in hemoglobin of more than two units (p=0.15), mortality (p=0.99) and surgery (p=0.75) between the two groups.

CONCLUSION

For controlling peptic ulcer bleeding, there is no difference between high dose and low dose pantoprazole infusion.

KEYWORDS
Pantoprazole; Bleeding peptic ulcer; Endoscopy

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INTRODUCTION

The most common etiology of upper gastrointestinal (GI) bleeding is peptic ulcer disease.[1] Various studies have reported the advantages of

pump proton inhibitor drugs (PPI) over histamine receptor blockers and placebo for lowering the complications of GI bleeding.[2]

The preference of PPI drugs in comparison with H_2 receptor antagonists is related to its long-term ability to maintain stomach pH levels greater than 6.[3,4] The advantage of high stomach pH is to maintain stability and resistance of platelets and blood clots created at the site of the peptic ulcers.[5] Currently, treatments for bleeding peptic ulcers include appropriate endoscopic therapy and prescription of pump inhibitor drugs. Prescription of pump inhibitor drugs following endoscopy lead to reductions in rebleeding and decreased need for surgery.[6-8] Studies have shown that the type of PPI has no effect on treatment outcome.[9-11]

The appropriate dose of pump inhibitor drugs for controlling bleeding has not been determined. The high-dose regimen is the most common method currently used for treating patients. In this regimen, patients receive an initial 80 mg bolus of pantoprazole followed by 8 mg per hour IV infusions for a three-day period. Advocates of the high-dose regimen believe that this regimen has superiority over low-dose by decreasing complications from bleeding such as mortality, surgery, and rebleeding.[12,13] Studies have shown that the low-dose regimen is as useful as the high-dose regimen for treating these patients.[14,15] The current clinical study has been designed to compare the efficacy of high and low dose pantoprazole in Khuzestan Province, Iran with a different racial combination in comparison with previous studies.

MATERIALS AND METHODS

This was a double-blind clinical trial conducted at Ahvaz Imam Hospital, a referral center. There were 166 patients assigned to the study groups by computer generated randomization (Figure 1). The treating physician and patients were unaware of the assigned dose of pantoprazole. Inclusion criteria included patients with symptoms of upper GI bleeding such as hematemesis, melena, hematochezia, or symptoms such as dizziness and light-headedness, and endoscopic confirmation of upper GI bleeding.

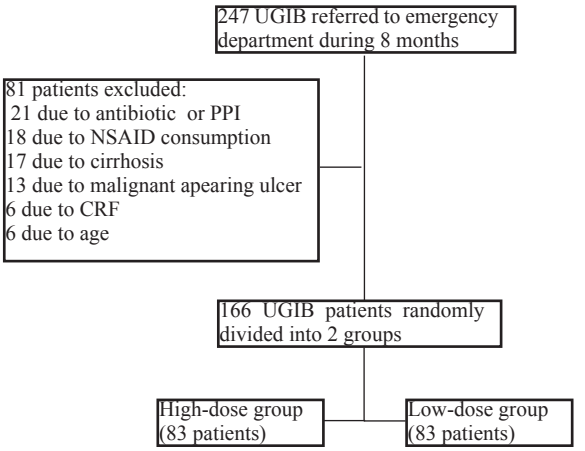

Fig.1: Flow chart of study design (UGIB: Upper gastrointestinal bleeding).

All patients underwent upper GI endoscopy within 6 hours after admission to the Emergency Department. The endoscopy was performed following stabilization of the patient's hemodynamic status. In this study we examined only high-risk ulcers such as adherent clot and visible vessel or oozing ulcer. Ulcers in these patients were treated by a combination of endoscopic therapy with argon plasma coagulation (APC) and a 15 cc injection of diluted epinephrine.

Exclusion criteria included: malignant ulcer, multiple ulcers visualized on endoscopy, cirrhotic patients with coagulative abnormalities and/or variceal bleeding, chronic renal failure, recent history of hospitalization and GI bleeding, those on maintenance doses of corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs), use of PPI or antibiotics during the previous month, history of peptic ulcer disease (PUD), and persons under 16 years and above 70 years of age. Exclusion of NSAID users was intended to prevent selection bias because NSAIDs have a higher fatality of bleeding among women.[16]

A number from 1 to 166 was randomly selected for each patient by SPSS version 14 software and the Random-Select program. Patients underwent treatment on the basis of whether this number belonged to the high- or low-dose group. This number was inserted in the information form of patients and

during hospitalization.

We observed patients for the development of rebleeding, need for re-endoscopy, surgery, and mortality. Primary and secondary results were analyzed in two groups by SPSS version 14. Patients in the high-dose group received an initial 80 mg bolus followed by 8 mg per hour infusion of pantoprazole over a three-day period. In the low-dose group, patients received an initial 40 mg bolus followed by 4 mg per hour infusion of pantoprazole over a three-day period. The researcher and patients were unaware of the selected regimen; follow-up of the patient during hospitalization was accomplished by other colleagues. We compared the primary results (rebleeding, drop of hemoglobin more than two units, infused blood, duration of hospitalization and need for surgery) and secondary results (mortality rate). A second look endoscopy was performed for patients who had evidence of further bleeding such as hematemesis, more than a 2 g drop in hemoglobin or hemodynamic instability. After discharge patients were followed for evidence of rebleeding, need for surgery and endoscopy, and mortality.

Statistical analysis

We considered results of previous studies[17] to calculate the sample size based on a 24% bleeding reduction in the high-dose group and 7% in the low-dose group. The formula for calculating the sample size to compare the ratio in both regimens was defined with α=5% and β=20%. Sample size in each group was 83 persons. Fisher's exact and chi-square tests, and survival analysis for the numerical variables such as hospitalization days were used for data analysis.

Ethical considerations

Patients initially received an explanation of the study after which they signed the written consent form. This research, as part of a thesis, was approved by the Ethical Committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS) with registration no. Eth-52 and recorded in IRCT with identification no. 2012022289166N1.

RESULTS

Overall, there were 166 patients with bleeding peptic ulcers who participated in this study. Demographic characteristics of patients were similar among the two groups (Table 1). We observed no statistically significant differences between groups in terms of hospital stay more than 5 days (p=0.53), rebleeding (p=0.3), mortality (p=0.99), and need for surgery (p=0.75). The mean units of blood transfused were 3.31±1.71 for the high-dose group and 2.82±1.73 for the low-dose group (p=0.50).

We compared two strategies of intravenous PPI administration in the prevention of rebleeding, surgery and death in patients with bleeding gastric and/or duodenal ulcers who achieved endoscopic homeostasis.

Following endoscopic homeostasis of the bleeding ulcers, there were 2 (6.3%) patients with gastric ulcers from the high-dose group and 2 (5.4%) from the low-dose group who underwent surgical intervention. There were 4 (7.8%) patients with duodenal ulcers in the high-dose group (p=0.99) and 3 (6.5%) patients with duodenal ulcers in the low-dose group (p=0.99) who underwent surgery.

The mortality rate was 1 (3.1%) for gastric ulcers in the high-dose group and 3 (8.1%) for gastric ulcers in the low-dose group (p=0.61). There were 3 (5.9%) patients with duodenal ulcers in the high-dose group and 2 (4.3%) with duodenal ulcers in the low-dose group who expired (p=0.99; Tables 2 and 3).

The mean numbers of transfused blood units were 3.45±1.85 for patients with gastric ulcers in the high-dose group and 2.94±1.45 for patients with gastric ulcers in the low-dose group (p=0.27). For patients with duodenal ulcers, there were 3.26±1.48 units transfused in the high-dose group and 3.26±1.48 units transfused in the low-dose group (p=0.11).

After the initial event, patients were followed for one month. Episodes of rebleeding occurred in 21 (25.3%) patients in the high-dose group and in 27 (32.5%) patients in the low-dose group (p=0.3). Additional bleeding occurred in 9 (10.8%) patients from the high-dose group and in 4 (4.8%) patients

Table 1: Demographic characteristics of patients.

Characteristics	High-dose group (n=83)	Low-dose group (n=83)
Mean age (years)	50.59±15.7	52.12±13.3
Mean weight (kg)	63.8±11.7	66.1±12.9
Male/female ratio	59/34	55/38
Smoking	17 (20.4%)	14 (16.8%)

from the low-dose group during one month (p=0.14). A total of 6 (7.2%) patients in the high-dose group and 5 (6%) in the low-dose group underwent surgery one week following discharge (p=0.75). There were 5 (6%) patients in the high-dose group and 4 (4.8%) from the low-dose group who died after one week of discharge (p=0.99; Table 4).

DISCUSSION

PPI drugs combined with appropriate endoscopic therapy are standard treatment for patients with bleeding peptic ulcers. In this treatment, the high-dose regimen PPI drugs are administered to patients. In this double-blind clinical trial we have found that among patients with bleeding from acute peptic ulcers, both high- and low-dose pantoprazole regimens have similar outcomes. Rebleeding (p=0.30), duration of hospitalization more than 5 days (p=0.53), hemoglobin drop of more than two units (p=0.15), mean amount of transfused blood (p=0.50), mortality (p=0.99) and surgery (p=0.75) have shown no significant differences. Low gastric pH can cause disaggregation of platelet plugs and prevent stabilization of the clot.[17] One of the concerns about low-dose regimens is the ability for maintaining the pH above 6. This matter has been investigated by Choi et al. who showed that the time intervals of pH >6 were equal in both regimens.[18] With regards to the PPI medications in terms of type of dose and pharmaceutical form, they have the same ability.[19] It is possible to generalize results of this investigation to other PPI drugs and their oral or injective forms. In a study conducted by Andriulli et al., 238 patients in the high-dose group and 236 patients in the low-dose group were examined. Rebleeding (p=0.34), mean units of transfused blood (p=0.32), duration of hospitalization (p=0.18) and surgery (p=0.03) were similar in both groups, but not significantly different. The ratio of rebleeding in this study was similar to the current study results (p=0.30)[20] and those of a study by Yao-chun et al. on 120 patients (p=0.1),[15] Wang et al. meta-analysis of 1157 patients,[21] Calvet et al.[22] and Liu-cheng et al. meta-analysis of 1345 patients.[23] We detected no difference between risk of rebleeding among patients with gastric and duodenal ulcers (p=0.84).There is concern about earlier discharge in the low-dose group so evaluation of rebleeding after 72 hours in Andriulli's study could not be an appropriate criterion for comparing two groups.[24] A retrospective study by Simon-Rudler et al. evaluated patients admitted between 1997 and 2001 in a low-dose group and from 2001 to 2004 in a high-dose group. In this historical cohort, sample sizes were 45 patients in one group and 69 in the next.[25] The high-dose regimen reported lower rebleeding (p=0.01), mortality (p=0.001) and need for surgery (p=0.05) rates than the low-dose group. However in this study, methods of endoscopic therapy were different in each group. On the other hand, the low number of patients and method of conducting the study were other pitfalls.

Of note, some studies have indicated that patients infected with *H. pylori* were less likely to respond to PPI. On the other hand, when there is *H. pylori* induced gastritis, the secreted interleukin-1 beta acts as a strong PPI.[26]

Chen et al. studied 93 patients in two groups: high- and low-dose. Each group consisted of 45 and 48 patients, respectively. In this study, rebleeding during four time periods (3, 7, 14 and 28 days) after initial bleeding was evaluated. At the end, bleeding rates were equal in all four time periods between the two groups (p=0.50).[27]

A retrospective study by Chih-Ming et al. showed that rebleeding, mortality and surgery rates in 477 patients who had a Rockall score of <6 did not significantly differ between the low- and high-dose groups (p=1.000) whereas higher rates of rebleeding occurred in patients who had a Rockall score ≥6 (p=0.001).[28] In this study, patients were treated only with epinephrine injections.

Table 2: Primary results based on ulcer type.

Results / Regimen	Rebleeding Numbers (%)	Rebleeding according to ulcer type		Drop in Hb >2 units	Drop in Hb >2units according to ulcer type		Hospitalization >5 days	Hospitalization <5 days according to ulcer type	
		Gastric ulcer[1]	Duodenal ulcer[2]		Gastric ulcer	Duodenal ulcer		Gastric ulcer	Duodenal ulcer
High-dose (n=83)	27(32.53)	11(34.4)	16(31.4)	29(34.9)	11(34.4)	18(35.3)	36(43.37)	16(50)	20(39.2)
Low-dose (n=83)	21(25.30)	8(21.6)	13(28.3)	38(45.8)	15(40.5)	23(50)	40(48.9)	23(62.2)	17(37)
p-value	0.30	0.23	0.73	0.15	0.59	0.14	0.53	0.30	0.81

1- Among the patients with gastric ulcers, 32 patients were in the high-dose group and 37 patients were in the low-dose group.
2- Among the patients with duodenal ulcers, 51 patients were in the high-dose group and 46 patients were in the low-dose group.

Table 3: Secondary results based on ulcer type.

Results / Regimen	Rebleeding Numbers (%)	Rebleeding according to ulcer type		Mortality Number (%)	Mortality according to ulcer type	
		Gastric ulcer[1]	Duodenal ulcer[2]		Gastric ulcer	Duodenal ulcer
High-dose(n=83)	6 (7.2)	2 (6.3)	4 (7.8)	4 (4.8)	1 (3.1)	3 (5.9)
Low-dose (n=83)	5 (6)	2 (5.4)	3 (6.5)	5 (6)	3 (8.1)	2 (4.3)
p-value	0.75	0.99	0.99	0.99	0.61	0.99

1-Among the patients with gastric ulcers, there were 32 patients in the high-dose group and 37 patients in the low-dose group.
2-Among the patients with duodenal ulcers, there were 51 patients in the high-dose group and 46 patients in the low-dose group.

Table 4: Results during one month follow-up.

Results / Regimen	Rebleeding Numbers (%)	Rebleeding according to ulcer type		Re-endoscopy Numbers (%)	Re-endoscopy on the basis of ulcer type	
		Gastric ulcer[1]	Duodenal ulcer[2]		Gastric ulcer	Duodenal ulcer
High-dose	4 (4.8)	0 (0)	4 (7.8)	8 (9.6)	5 (15.6)	3 (5.9)
Low-dose	9 (10.8)	5 (13.5)	4 (8.7)	10 (12)	4 (10.8)	6 (13)
p-value	0.14[3]	0.057	0.99	0.61	0.72	0.38

1-Among the patients with gastric ulcers, 32 patients were in the high-dose group and 37 patients were in the low-dose group.
2-Among the patients with duodenal ulcers, 51 patients were in the high-dose group and 46 patients were in the low-dose group.
3-OR=2.4 (95% CI: 0.7- 8.13)

We have studied 166 patients and more samples were investigated compared to previous studies. The double blind clinical trial method used in the current study is superior compared to an open-label trial, retrospective methods or historical cohorts. A separate survey of primary and secondary outcomes in gastric and duodenal ulcers in this study was a noteworthy point. We did not observe significant differences in results related to gastric or duodenal ulcers.

In some studies epinephrine injections were the only therapeutic treatment. However, the use of hemoclips and an epinephrine injection is the preferred method. Due to a local lack of access to Hemoclips our endoscopic method was the injection of epinephrine combined with APC. One of the advantages of our study was the inclusion of patients with high-risk stigmata. Within a month, we evaluated the study patients in terms of rebleeding, need for re-endoscopy, surgery and mortality–however these criteria have only been investigated in one other study.[27]

The current study has some limitations. First, it was better to select groups according to Rockall score. Second, if we had checked the pH of the stomach and assayed for *H. pylori* infection, we could have obtained more complete results for comparison between the two groups.

After endoscopic therapy, prescription of low-dose pantoprazole might be as effective as the high-dose. Thus, for economic reasons, the use of low-dose compared to high-dose regimen should be better. We suggest additional studies that enroll a larger sample size for further clarification of this issue.

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CONFLICT OF INTEREST

The authors declare no conflict of interest related to this work.

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