LOW DOSE BOLUS PANTOPRAZOLE FOR ACUTE PEPTIC ULCER BLEEDING IS EFFECTIVE

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ABSTRACT

***Introduction**: Proton pump inhibitors are the most effective treatment for peptic ulcer bleeding. However, the PPI dose needed to prevent re-bleeding are not well established. We aimed to compare high-dose infusion of pantoprazole and low-dose bolus pantoprazole in patients given endoscopic treatment for control of peptic ulcer bleeding.*

***Materials and methods**: Patients admitted with peptic ulcer bleeding in which the bleeding was controlled by endoscopic intervention were randomized to high-dose and low dose groups. The primary endpoints were early re-bleeding, need for blood transfusion, surgery, mortality, and duration of hospitalization. Cost of treatment was also determined.*

***Results**: Re-bleeding occurred in 10 patients (27.8%) in the high-dose group and in 3 patients (8.1%) in the low-dose group (p = 0.028). Surgery, mortality, and duration of hospitalization were similar in the two groups. The pantoprazole cost per patient was 252.62 Turkish Liras (TL) in the high-dose group and 104.02 TL in the low-dose group.*

***Conclusion**: High-dose and low-dose pantoprazole treatment after endoscopic treatment had similar efficacy in the control of peptic ulcer bleeding in our study population. The low-dose treatment had lower costs and was easier to administer. Thus, low-dose bolus pantoprazole administration following successful endoscopic therapy should be considered for treatment of peptic ulcers.*

***Key words**: peptic ulcer bleeding, low dose, pantoprazole.*

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Introduction

Acute upper gastrointestinal system bleeding (AUGIB) is a serious condition that is associated with high morbidity and mortality. The annual incidence of AUGIB ranges from 50 to 172 per 100 000 and the mortality rate is 8-10%[1,2]. Peptic ulcer bleeding is responsible for approximately half of all AUGIB cases[1-10].

Peptic ulcer bleeding can stop spontaneously, but about 20% of patients experience continued bleeding or re-bleeding[3], an independent risk factor for mortality. If AUGIB is identified endoscopically as due to a bleeding peptic ulcer, the standard treatment is a combination of endoscopic and pharmacological therapies[11]. Controlled studies have demonstrated that re-bleeding, emergency surgery, and mortality rates were lower in patients given endoscopic treatment[12]. The aim of pharmacological treatment is to maintain a high intragastric pH in order to prevent pepsin activation; in addition, platelet aggregation is inhibited when pH is below 6, and fibrin clots are dissolved when pH is below 4[13]. In vivo studies indicated that high doses of proton pump inhibitors (PPIs) can maintain intragastric pH at near-neutral levels and that these drugs are more effective than infusional histamine-2 receptor blockers (H2RBs)[14-16].

Omeprazole is a PPI that effectively reduces production of gastric acid, but when given as standard therapy (20 mg/day), it takes up to five days to achieve an intragastric pH greater than 4[17]. Following endoscopic treatment, intravenous infusion of omeprazole (8 mg/h following an 80 mg bolus) significantly decreases the severity of bleeding, the need for surgery, and the need for a second

endoscopic treatment[18, 19]. Similar results were obtained with pantoprazole, a related PPI[20, 21]. Another study reported that intravenous (IV) infusion of omeprazole and pantoprazole had similar effects on 24-h intragastric pH[22]. A study of the treatment of bleeding ulcers reported no significant differences between omeprazole, pantoprazole, and rabeprazole in 72-h intragastric pH[23]. Compared with other PPIs, intravenous pantoprazole is associated with fewer drug interactions and does not require dose adjustment in the presence of renal failure or mild to moderate hepatic failure[20].

Many clinical studies have shown that treatment of peptic ulcer bleeding by high dose PPI was superior to placebo, and several studies have reported similar efficacies of high-dose and low-dose treatments[11, 21, 24-26]. Use of lower doses would result in fewer adverse effects and reduced costs. In this study, we compared the efficacy, safety, and costs of high dose infusion with low dose IV bolus pantoprazole therapy following endoscopic treatment for acute peptic ulcer bleeding.

Methods

Study Design

This study was a single-center, prospective, double-blind, double-dummy, randomized, comparative pilot study. The Ethics Committee of Mersin University Faculty of Medicine (Turkey) approved this study and all patients provided written informed consent.

Patients

Patients 18 years of age and older were admitted with complaints of hematemesis and/or melena, and underwent esophagogastroduodenoscopy. If a gastric or duodenal peptic ulcer was detected during endoscopy with indications of new bleeding (active bleeding ulcer, visible vessel on the ulcer or adherent clot [Forrest 1a, 1b, 2a, 2b]), then endoscopic treatment was performed and the patient was enrolled. The exclusion criteria were low risk for ulcer re-bleeding (Forrest 2c, 3), gastric malignancy, esophageal or fundal variceal bleeding, Mallory-Weiss bleeding, other reasons for bleeding, pregnancy, or bleeding that remained uncontrolled following endoscopic treatment.

Endoscopy and Treatment

Esophagogastroduodenoscopy was performed in all enrolled patients within 12 h of admission.

When a peptic ulcer was detected, injection sclerotherapy with diluted Epinephrine (1:10 000) was performed by the same investigator (E.U.) in order to maintain hemostasis at the periphery and bottom of the ulcer. Hemostasis is defined as cessation of active bleeding and flattening of the visible vessel. After this procedure, patients were randomized into two groups by a physician who was not a member of the study team. Patients were randomized in order of admission to hospital. The endoscopist and patients were both blinded with regard to PPI dose. The high-dose group was given Pantoprazole 80 mg IV bolus followed by 8 mg/h IV infusion for 72 h and the low-dose group was given Pantoprazole 80 mg IV bolus followed by 40 mg IV bolus every 12 h for 72 h. A double-dummy technique was used to keep the patients blinded, so all patients in the low-dose group received isotonic saline infusion for 3 days as placebo. After 3 days of treatment, all patients were given oral Pantoprazole (40 mg bid) until day-30.

Follow-up

Vital signs (blood pressure and pulse rate) and blood transfusions were recorded for all patients. Hemoglobin (Hb) was monitored every 8 h until discharge. A patient older than 60 years was given a blood transfusion if the Hb level was below 9.5 g/dL; a patient younger than 60 years was given a blood transfusion if the Hb level was below 8 g/dL. In cases of shock, blood transfusion was performed regardless of Hb level.

Re-bleeding was defined as the presence of hematemesis after endoscopic treatment, shock, orthostatic hypotension, or more than 2 g/dL decrease in Hb level despite blood transfusion. A patient with suspected re-bleeding was given endoscopy again (if medically applicable) and if the re-bleeding was confirmed, sclerotherapy was performed again.

Patients who did not have any symptoms or findings related to re-bleeding were monitored for at least 72 h and were discharged if they were hemodynamically stable and could tolerate oral feeding. At day-30, patients were asked to return to the hospital or information was collected via telephone to assess health status.

Endpoints

The primary endpoints were early bleeding recurrence (within 72 h), need for blood transfusion, surgery due to bleeding, mortality, and dura-

tion of hospitalization. The secondary endpoint was late bleeding recurrence (3-30 days). Cost analysis for PPI treatment was performed for each patient.

Statistical Analysis

Continuous measurements were tested for normality by the Shapiro-Wilk test and Student's t-test (independent samples t-test) was used to compare parameters with normal distributions, and the Mann-Whitney U test was used to compare parameters with non-normal distributions. Chi-square and likelihood ratio chi-square tests were used for analysis of categorical data. Descriptive statistics (mean, standard deviation, min-max, median, 25th and 75th percentiles), number, and percent, were given for all variables.

Results

Patient Characteristics

A total of 229 patients were admitted to our institution with AUGIB from December 2007 to August 2009. Among these 229 patients, 156 did not meet our inclusion criteria; 94 patients had non-peptic ulcer bleeding (variceal bleeding, malignancy and Mallory-Weiss syndrome) and 62 patients had Forrest 2c or Forrest 3 ulcer, bleeding that was uncontrolled with endoscopic treatment, late endoscopy, or refused to participate. We ultimately enrolled 73 AUGIB patients with peptic ulcer bleeding.

Table 1 shows the demographic, clinical, and endoscopic data of all enrolled patients. The male/female ratio was 50/23 and the mean age (±SD) was 59.1 years (±20.1). Forty-five patients had hematemesis, 27 patients had melena, and 1 patient had hypotensive shock. We detected melena in the patient with shock during the physical examination. All diagnoses were confirmed by upper gastrointestinal endoscopy. Thirty-five patients had a comorbid disease of the heart, lung, kidney, or liver. The mean Hb value at admission was 8.6 g/dL (±2.4). A total of 56 patients were using drugs associated with increased risk for bleeding (NSAID/aspirin or clopidogrel: 47 patients; steroid: 3 patients; warfarin: 2 patients; NSAID + warfarin: 4 patients). Classification of patients by Rockall score indicated that here were 42 low-risk patients (Rockall score = 0 to 5) and 31 high-risk patients (Rockall score > 5).

Following randomization, 36 patients were given high-dose infusional pantoprazole and 37 patients were given low-dose bolus pantoprazole therapy. There were no significant differences between the two treatment groups in age, gender, reason for admission, presence of comorbid diseases, Hb level at admission, drug use, smoking, alcohol use, and Rockall score.

Characteristic	Low-Dose (n=37)	High-Dose (n=36)	P
Mean age - years	56.11 (±22.52)	62.22 (±17.08)	0.195
Age group - n (%) ≥60 years <60 years	 18 (48.6) 19 (51.4)	 23 (36.1) 13 (63.9)	0.190
Gender - n (%) Male Female	 24 (64.9) 13 (35.1)	 29 (80.6) 7 (19.4)	0.130
Drug use associated with risk (%) (NSAID, Aspirin, Clopidogrel, Steroid, Warfarin)	30 (81.1)	26 (72.2)	0.371
Presence of comorbid disease (%)	14 (37.8)	21 (58.3)	0.08
Smoking (%)	15 (40.5)	19 (52.8)	0.295
Alcohol use (%)	4 (10.8)	6 (16.7)	0.466
Admission Hemoglobin (g/dl)	8.71 (±2.55)	8.47 (±2.35)	0.683
Systolic Blood Pressure - n (%) <100 mmHg ≥100 mmHg	 4 (10.8) 33 (89.2)7	 6 (16.7) 30 (83.3)	0.532
Type of Admission - n (%) Hematemesis Melena Shock	 27 (73.0) 10 (27.0) -	 18 (50.0) 17 (47.2) 1 (2.8)	0.081
Rockall score - n (%) ≤5 >5	 24 (64.9) 13 (35.1)	 18 (50.0) 18 (50.0)	0.199
Ulcer location - n (%) Stomach Duodenum Anastomotic	 11 (29.7) 24 (64.9) 2 (5.4)	 11 (30.6) 24 (66.7) 1 (2.8)	0.850
Ulcer Size - n (%) <20 mm ≥20 mm	 31 (83.8) 6 (16.2)	 26 (72.2) 10 (27.8)	0.233
Forrest classification - n (%) 1a 1b 2a 2b	 - 9 (24.3) 24 (64.9) 4 (10.8)	 2 (5.6) 13 (36.1) 17 (47.2) 4 (11.1)	0.196
Epinephrine amount ≤15 cc >15 cc	 25 (67.6) 12 (32.4)	 22 (61.1) 14 (38.9)	0.565

Table 1: Demographic, Clinical and Endoscopic Data of the Patients: Both low-dose and high-dose groups have similar characteristics.

Endoscopy Results

During the admission endoscopy, Forrest 1 lesion was detected in 24 patients (Forrest 1a in 2 patients and 1b in 22 patients) and Forrest 2 lesion was detected in 49 patients (2a in 41 patients and 2b in 8 patients). A total of 22 patients had stomach ulcers, 48 patients had duodenal ulcers, and 3 patients had anastomotic ulcers. The average ulcer size was 11.8 mm (±6.9), 57 patients had small ulcers (< 2 cm), and 21 patients had large ulcers (≥ 2

cm). There were no differences between the two groups in terms of Forrest classification, ulcer localization, or ulcer size (Table 1).

Endpoints

Early re-bleeding (within 3 days) occurred in 8 patients (22.2%) in the high-dose group and in 2 patients (5.4%) in the low-dose group (p = 0.032) and late re-bleeding (3-30 days) occurred in 2 patients (5.6%) in the high-dose group and in 1 patient (2.7%) in the low-dose group (p = 0.536). A total of 13 patients (17.8%) experienced re-bleeding, 10 patients (76.9%) in the high-dose group and 3 patients (23%) in the low-dose group (p = 0.028). Ten of the 13 re-bleeding patients had a second endoscopy. One of these 10 patients had an active spurting bleeding ulcer (Forrest 1a) that could not be stopped by endoscopic intervention, so surgery was performed; 1 patient with a Forrest 1b ulcer and 5 patients with Forrest 2a ulcers were given second endoscopic treatments; one patient with a Forrest 2c ulcer and 2 patients with Forrest 3 ulcers were given medical treatment to control bleeding. Three patients in the high-dose group could not be given a second endoscopy; 2 of these patients went directly into surgery and one did not accept a second endoscopy so was given medical treatment to stop the bleeding.

The mean blood transfusion dose was 4.5 (±4.2) units in the high dose group and 2.5 (±2.2) units in the low dose group (p = 0.040). Surgery was performed in 3 patients, 2 patients (5.6%) from the high-dose group and 1 patient (2.7%) from the low-dose group (p = 0.536).

Table 2 summarizes the endpoint data for our patients. There were 2 deaths (5.6%) in the high-dose group and 3 deaths in the low-dose group (8.1%) and the all-cause mortality rate was 6.8%. One patient in each group died due to re-bleeding and one patient in each group died due to a cardiac event. One patient in the low-dose group was diagnosed with type 4 Klatskin tumor at 20 days after discharge and died due to this condition. The two groups had no significant difference in mortality rate (p = 0.665). The overall mean duration of hospitalization was 5.3 (±4.4) days, and was 5.6 (±3.4) days in the high-dose group and 5.0 (±5.2) days in the low-dose group (p = 0.575).

Cost Analysis of PPI Medications

Patients in the high-dose group were given a mean dose of 656 mg pantoprazole in 3 days and patients in the low-dose group were given a mean dose of 280 mg pantoprazole in 3 days. The cost per patient in the high-dose group was 252.62 Turkish Liras (TL) (168.41 US Dollars, 114.82 Euro) and the cost per patient in the low-dose group was 104.02 TL (69.30 US Dollars, 47.28 Euro).

	Low-Dose (n=37)	High-Dose (n=36)	p
Rebleeding - n (%) Early (0-3 days) Late (3-30 days) Total	 2 (5.4) 1 (2.7) 3 (8.1)	 8 (22.2) 2 (5.6) 10 (27.8)	 ***0.032*** 0.536 ***0.028***
Blood transfusion - units	2.51 (±2.22)	4.53 (±4.21)	***0.04***
Surgery - n(%)	1 (2.7)	2 (5.6)	0.536
Death - n (%)	3 (8.1)	2 (5.6)	0.665
Duration of hospitalization - days	5.0 (±2.24)	5.58 (±3.39)	0.575

Table 2: Endpoint Characteristics of the Patients: Table shows that there was statistically significant difference in terms of re-bleeding and blood transfusion between two groups.

Adverse Effects

We observed no significant adverse effects.

Discussion

Endoscopic treatment is one of the most effective methods to stop the bleeding of peptic ulcers, decrease the probability of re-bleeding, and reduce morbidity and mortality rates. Pharmacological treatment in combination with endoscopic treatment provides even better outcomes. PPIs are the only group of medicines whose efficacy has been demonstrated for treatment of peptic ulcers. Following the study of Lau et al., high-dose PPI infusion has been recommended after endoscopic treatment of peptic ulcers[19]. The current guidelines of the British Society of Gastrointestinal Endoscopy Committee recommend high-dose omeprazole infusion for such patients[27]. Previous studies and meta-analyses have reported that high-dose PPI was significantly better than placebo in reducing the occurrence of re-bleeding[18-21, 28-30]. However, low dose PPIs also decrease re-bleeding[21, 31]. Thus, there is still no consensus on the most appropriate PPI dose for treatment of peptic ulcer bleeding.

Our results indicate that low-dose pantoprazole (80 mg bolus followed by 40 mg bolus every 12 h) was more effective than high-dose pantoprazole (80 mg bolus followed by 8 mg/h infusion for 72 h) when given after successful endoscopic treatment of acute peptic ulcer bleeding. In particular, the rates of

re-bleeding and blood transfusion requirements were significantly lower in the low-dose group. Similarly, Udd et al. compared high dose omeprazole (80 mg bolus followed by 8 mg/h for 3 days) and standard dose omeprazole (20 mg/day) following endoscopic treatment in a prospective randomized study of 142 patients and reported no significant difference in re-bleeding and mortality[24]. A multi-center study by Andriulli et al. compared high- and low-dose PPIs after endoscopic treatment, and reported no significant differences in bleeding rate[11]. Similar results have been obtained in studies from Turkey[25].

The aim of PPI treatment is to maintain a high intragastric pH and provide stability for blood coagulation. We did not measure intragastric pH in the present study. However, two previous studies[21, 23] reported that high dose and standard dose PPI regimens had similar effects on peptic ulcer bleeding and intragastric pH.

Most studies of peptic ulcer bleeding have been performed with IV PPIs, but other studies have shown that oral PPIs reduce re-bleeding and mortality rates[32-35]. In our study, the mortality rates and duration of hospitalization were similar in the high- and low-dose groups and similar to other comparative dose studies[11, 25]. Mortality from re-bleeding occurred in one patient from each group.

The mean requirement for blood transfusion in the high-dose group was 4.53 units (± 4.21) and that of the low-dose group was 2.51 units (± 2.22) units ($p = 0.040$). This difference can be explained by the higher re-bleeding rate in the high-dose group.

In Turkey, the price of a vial of pantoprazole (40 mg) is TL 14.86 (1 TL = 0.66 US Dollars, 0.45 Euro). The 3-day cost of the low-dose bolus treatment in our study was 104.02 TL (69.30 US Dollars, 47.28 Euro) whereas the cost of high-dose infusion was 252.62 TL (168.41 US Dollars, 114.82 Euro). Thus, the cost per patient is 148.6 TL (99.11 US Dollars, 67.54 Euro) more for the high-dose treatment. Moreover, administration of the low-dose treatment was much simpler.

Main weak points of our study were the limited number of patients and usage of just one kind of PPI.

In conclusion, our study showed similar efficacy for high dose pantoprazole infusion and low dose bolus pantoprazole after successful endoscopic treatment for acute peptic ulcer bleeding. However, low-dose treatment was less costly and easier to administer. Thus, low dose bolus PPI treatment following endoscopic therapy appears to be an effective, safe, and economic treatment for peptic ulcers. Further studies with larger number of patients and other PPIs are required to support our conclusions.

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