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Prevention of Stress Related Mucosal Disease with Intermittent Intravenous Pantoprazole and Ranitidine in Critically Ill Patients

Farshid Rahimi Bashar[1], Alireza Rastgouyhaghi[2], Saadat Torabian[3], Mohammad Reza Hajiesmaeili[4*], Alireza Sedaghat[5], Shahram Seifi[6], Mahdis Solhjoo[7]

[1] Assistant Professor, Department of Anesthesiology, School of Medicine, Hamedan University of Medical Sciences, Hamedan, Iran.
[2] Assistant Professor, Department of Pathology, School of Medicine, Hamedan University of Medical Sciences, Hamedan, Iran.
[3] Assistant Professor, Department of Community Medicine, School of Medicine, Hamedan University of Medical Sciences, Hamedan, Iran.
[4] Fellow in Critical Care Medicine, Parsian Hospital, Tehran, Iran.
[5] Assistant Professor, Department of Anesthesiology, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.
[6] Assistant Professor, Department of Anesthesiology, School of Medicine, Babol University of Medical Sciences, Babol, Iran.
[7] General practitioner, Qazvin University of Medical Sciences, School of Medicine, Qazvin, Iran.

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ABSTRACT

Background: This study aimed to compare intermittent intravenous (IV) pantoprazole and ranitidine for control of gastric acid secretion and the possible prevention of Upper Gastrointestinal Bleeding (UGIB) in critical care patients.
Methods: This was a randomized, double blind clinical trial study of IV pantoprazole (40 mg every 12 hour) or intermittent IV ranitidine (50 mg bolus every 8 hour) in patients at risk for UGIB. The primary endpoint was gastric pH. UGIB was measured as secondary endpoint.
Results: ninety two Critical care patients were enrolled. Gastric pH was well controlled by two study drugs. Gastric pH increased in pantoprazole group than in the ranitidine group (4.40±0.39 versus 3.32±0.28; P=0.000). Upper GI bleeding was higher in ranitidine group than pantoprazole group (4/46 versus 2/46; P=0.404).
Conclusion: This study indicates that intermittent IV pantoprazole compared with bolus IV ranitidine, more effectively controls gastric pH and may prevent UGIB in high risk critical care patients without the development of tolerance.

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Introduction

Stress-Related Mucosal Disease (SRMD) is common in Intensive Care Units (ICU) and up to 100% of severely injured ICU patients have endoscopic evidence of SRMD within the first 72 hours after ICU admission (1, 2). Gastric mucosa ischemia, disruption of the mucosal barrier, back-diffusion of hydrogen ions, mucosal damage, ulceration and bleeding may occur as a consequence of SRMD (2).

The role of gastric acid in the development of SRMD and need for early prevention of possible UGIB have led to the prophylactic use of antacid agents in ICU patients.

Hastings et al., (3) found that maintenance of gastric pH above 3.5, by antacids, was effective in preventing UGIB because of SRMD.

Martin et al., (4) found that continuous intravenous (IV) infusion of H2-Receptor Antagonists (H2RA) was effective for increasing gastric pH and reduction of SRMD

* *Corresponding Author*: Dr Mohammad Reza Hajiesmaeili
Address: Parsian Hospital, Tehran, Iran.
Email: mr-hajiesmaeili@razi.tums.ac.ir

Table 1. Baseline characteristic of patients.

	Pantoprazole 40 mg q 12 h (n=46)	Ranitidine 50 mg q 8 h (n=46)	P Value
Age (yrs), mean (SD)	43.17 (1.99)	41.69 (2.15)	0.734
Gender, n (male/total)	31/46	32/46	0.825
APACHE II score, mean (SD)	13.93 (2.89)	14.93 (2.15)	0.063
Gastric pH, mean (SD)	2.048 (0.13)	2.0761(0.13)	0.331

APACHE**:** Acute Physiology and Chronic Health Evaluation.

and UGIB in ICU patients. Several studies conducted in a critical care setting indicate that the proton-pump inhibitors might be more potent gastric PH controlling than the H2RAs (5, 6).

This study aimed to compare intermittent intravenous (IV) pantoprazole and ranitidine for control of gastric acid secretion and the possible prevention of UGIB in critical care patients.

Patients and Methods

Ninety two traumatic critical care patients were enrolled into this double-blind, randomized clinical trial, between the dates of June 2009 and September 2011 at ICU ward, "Besat" hospital, Hamedan University of Medical Sciences. The study was approved by the institutional ethical committee and was conducted according to the Declaration of Helsinki and its amendments and written, informed consent was obtained from patient's legal representative before enrollment.

Inclusion criteria of study participants were traumatic patients, over than 18 years old age, mechanical ventilation over than 48 hour, Acute Physiologic and Chronic Health Evaluation II (APACHE II) less than 25, and ability to tolerate the nasogastric/orogastric (NG/OG) tube. When intervention was initiated, the patients were nothing by mouth (NPO) for at least 48 hours. Exclusion criteria included any of the following: (1) Coagulopathy: a platelet count<50,000 mm^3 or an increased international normalized ratio or partial thromboplastin time >1.5 times than upper normal limit; (2) Known hypersensitivity to pantoprazole and ranitidine; (3) Pregnancy; (4) History of a gastrectomy or an upper gastrointestinal lesion with the potential for hemorrhage or a hypersecretory condition such as Zollinger Ellison syndrome; peptic ulcer disease within the past 1 year; (5) Recipients of (a) H2 Receptor Antagonists <12 hours, (b) sucralfate <24 hours, (c) Gastrointestinal promotility agents <24 hours, or, (d) proton pomp inhibitors <72 hours before the study enrolment. All patients remained NPO for the duration of the study. Gastric aspirations were obtained every 8 hours via NG/OG tubes for measurement of gastric pH and UGIB detection. Gastric pH was analyzed with a Fisher Scientific standardized pH meter.

Eligible patients randomly enrolled into the study groups and received study drug based on accidental number table. One of the groups received intravenous ranitidine 50 mg every 8 hours and in the other group received intravenous pantoprazole 40 mg every 12 hours. In each patient the gastric PH was measured before starting study drugs and after that every 8 hours for 2 days. Also the rate of UGIB was estimated via nasogastric tube in each group for 48 hours. UGIB used in this study defined as; hematemesis or bright red blood in gastric aspirate that did not clear after adjustment of nasogastric or orogastric tube and a 5 to 10 min lavage with iced water or saline, persistent coffee ground material for 8 consecutive hours that did not clear with a 100 CC lavage, or was accompanied by a 5% decrease in hematocrit, a decrease in hematocrit requiring one or more transfusions that occurred in the absence of any obvious source and required further diagnostic studies, melena or frank bloody stools from an upper gastrointestinal source.

The evaluation included the following items: (1) demographic data; (2) Acute Physiology and Chronic Health Evaluation (APACHE) II score; (3) a gastric aspiration pH and UGIB Criteria. The primary endpoint was the gastric aspirates pH and secondary endpoint included assessment of the incidence of UGIB. One physician blinded to the patient's treatment assignment and pH data assess patient for serious adverse events and need to premature discontinuation of study drugs. All patients had continuous special monitoring including collection of adverse events, review of concurrent treatments, laboratory assessments (hematology, serum electrolytes, serum creatinine, and blood oxygenation assessment), and Glasgow Coma Scale score.

The sample size of 46 patients per group was chosen to provide this study with a sufficient sample to analyze reasonable estimates of the pH response associated with each treatment group based on 80% power to detect a mean difference of 20% for the treatment group. Differences across the treatment groups in the effect of study drug on

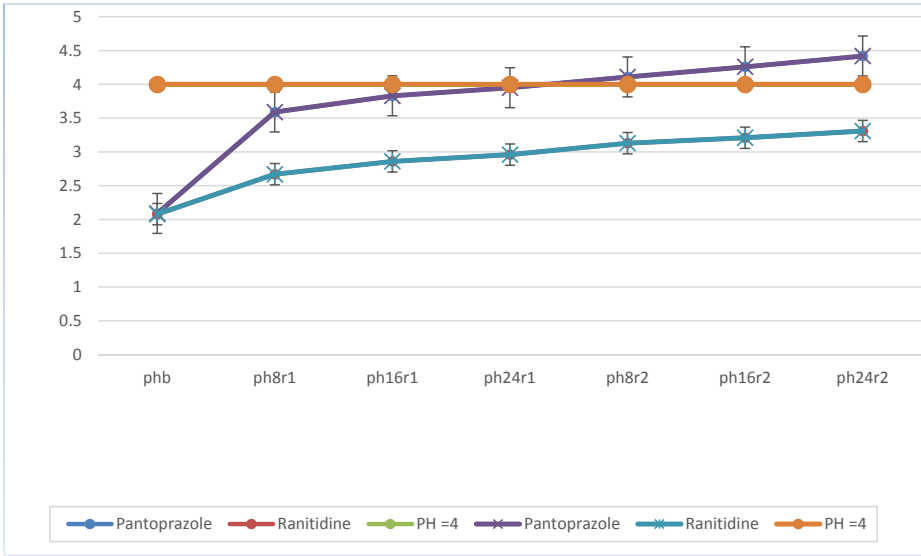

Figure 1. Mean percentage gastric aspirates pH.

gastric pH were assessed among the study groups using analysis of variance.

Results

The patient population was prescreened using the selection criteria were 102. Ten patients were excluded. The reasons for non-selection were lack of an NG/OG tube (4 patients), use of H2RA or PPI medications within specified pre-study time frame (3 patients), stay in ICU less than 48 hours (2 patients) and stress-related UGIB (1 patients).

A total of 92 patients who met the inclusion criteria were enrolled, randomized, and received study intervention (46 in each group).

The baseline characteristics of the patient population per treatment groups were similar (Table 1). The mean (SD) age of study population was 42.43(20.67) years and 68.2% of the total population were male. For the total population, the baseline means (SD) APACHE II score were 14.43 (2.59). The baseline gastric pH was similar among groups, with a mean (SD) pH for the total population of 2.06 (1.33).

There was statistical significance observed among the treatment groups for the primary endpoint of mean percentage of gastric pH at 8, 16 ,24 ,32 ,40 and 48 hours after intervention (Figure 1) and pantoprazole patients have statistically significant higher gastric pH than ranitidine group (4.40±0.39 versus 3.32±0.28; P= 0.000).

Four patients in ranitidine group and 2 patients in pantoprazole group exhibited protocol defined UGIB. This observed difference is statistically non significant (4/46 versus 2/46; P=0.404).

Discussion

Based on findings of this study, intermittent IV pantoprazole therapy demonstrated more effective than intermittent IV ranitidine for control of gastric pH and UGIB for the 2 days of the trial.

Although gastric pH is not as concise as gastric acid output in evaluating acid secretion, but pH can serve as a surrogate for determining the appropriate acid control needed to prevent UGIB (3).

All patients in both study groups, showed the sufficient effects on percent time pH>4.0. Thus finding of this study suggested that patients might be adequately controlled with a treatment using a 40 mg dosing regimen pantoprazole q12 hour and 50 mg ranitidine q 8 hours.

Further studies evaluating these pantoprazole dosing regimens are warranted. In this study, 6 patients (4 patients in ranitidine group and 2 patients in pantoprazole group; P= 0.404) experienced protocol-defined UGIB. These findings are similar to previously study with IV PPI therapy in an ICU population (1).

One of the limitations of our study design was that our patients were not monitored for the development of pneumonia. Because of rising the gastric pH may allow bacterial proliferation, subsequent regurgitation and pulmonary aspiration may result in hospital acquired pneumonia (7). Although In a meta-analysis, Cook et al., concluded that prevention of SRMD with antacids or H2RAs did not increase the incidence of pneumonia compared with placebo or control therapy (8), Although Somogi et al., concluded that prophylactic treatment with acid-suppressing agents does not increase the risk of pneumonia (1).

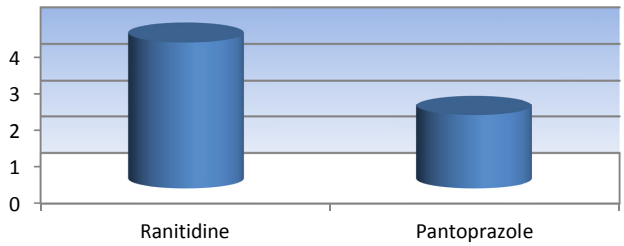

Figure 2. Comparison of Upper Gastrointestinal Bleeding between

We don't observed apparent development of tolerance in patients receiving ranitidine and pantoprazole but Somogi et al., have unexpected observation in their study patients and observed the apparent development of tolerance in patients receiving cimetidine (1). Researcher reported that; by day 2 of treatment, acid control in the ranitidine group had decreased compared with proton pomp inhibitors and, acid control was statistically significant increased from day 1 to day 2 in all pantoprazole treatment groups. Thus, in volunteers receiving high oral dose of H2 blocker or PPI, tolerance developed by day 2 in subjects receiving H2 blocker, whereas acid suppression in the PPI-treated group increased during the course of the study (9-11).

Martin et al., found that up to 50% of the H2 blocker treated patients required up-titration of their dose because of tolerance of gastric acid secretion within 1 to 2 days on study (4).

In conclusion, these findings suggest that intermittent IV pantoprazole can maintain gastric pH measurements at 4.40 in NPO ICU patients at high risk of developing an UGIB event but IV intermittent ranitidine maintain gastric pH measurements at 3.32.

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