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Effects of Ranitidine and Pantoprazole on Ventilator-Associated Pneumonia: A Randomized Double-Blind Clinical Trial

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Background: Acid suppressive medications are used to prevent stress ulcers in critically ill patients. Few studies have been done to evaluate the effect of ranitidine and pantoprazole on stress ulcers. We aimed to compare the effects of ranitidine and pantoprazole on Ventilator Associated Pneumonia (VAP).

Materials and Methods: In this double-blind randomized controlled trial, we enrolled 120 traumatic patients with trauma admitted to the intensive care unit (ICU) of Besat Hospital in Hamadan Province located in northwest Iran. The patients were divided into two equal groups receiving either intermittent intravenous ranitidine or pantoprazole to prevent stress ulcers. The incidence of VAP, duration of tracheal intubation, length of ICU stay, duration of hospital stay, and the outcome of treatment including mortality or hospital discharge were compared in both groups.

Results: The incidence of VAP was 10% and 30% in patients receiving ranitidine and pantoprazole, respectively (P=0.006). There was no significant difference between the two groups with respect to the duration of tracheal intubation. However, the patients treated with pantoprazole stayed at the hospital two days longer than the other patients (P=0.027). Although patients with VAP stayed at the hospital for 12 more days, the two groups had almost equal mortality rates (P=0.572).

Conclusion: ICU patients using pump inhibitors have a three-fold increased risk of developing VAP in comparison to H2-blocker receivers. Thus, prevention of stress ulcers should be limited to its own specific indications.

Key words: Ventilator-associated pneumonia, Intensive care unit, Ranitidine, Pantoprazole, Randomized controlled trial

INTRODUCTION

Acid-suppressive medications such as proton pump inhibitors and histamine type 2 (H2) receptor antagonists are used to prevent stress ulcers. Theoretically, the inhibition of gastric acid secretion can be associated with increased gastric colonization as well as retrograde colonization of the pharynx leading to VAP with potential micro-aspiration. Some studies have reported that the incidence of hospital-acquired pneumonia increases by 30% following pharmacological stress ulcer prophylaxis (1-3). Considering their different mechanisms of action, it is assumed that these drugs have different effects on the incidence of VAP. Various studies have evaluated the effect of different medications on VAP. It was demonstrated that sucralfate, which does not raise gastric pH compared with other conventional prophylactic agents such as H2 blockers, did not increase the incidence of VAP

and seemed more favorable for preventing stress ulcers (4-7).

Currently, pantoprazole is administered widely for stress ulcer prophylaxis because of its greater efficacy in maintaining a constant elevated gastric pH (8). Pantoprazole inhibits gastric acid secretion more effectively in patients admitted to the ICUs and may lead to higher bacterial colonization (9). Some other studies have shown that pantoprazole is associated with increased rates of community-acquired pneumonia compared with ranitidine (10-12), while other studies have not confirmed such findings (13).Higher risk of hospital acquired pneumonia in patients on pantoprazole without mechanical ventilation has also been reported (3). We only found a historical cohort study in the literature comparing the effect of ranitidine and pantoprazole and reporting the incidence of VAP to be three times higher in patients receiving pantoprazole (14). In a meta-analysis, no statistically significant difference was observed between pantoprazole and ranitidine in prevention of gastrointestinal bleeding, risk of VAP or mortality. The researchers ultimately recommended the conduction of more randomized clinical trials in this regard (15).

We aimed to compare the effects of ranitidine and pantoprazole on VAP.

MATERIALS AND METHODS

In this double-blind randomized controlled trial, we enrolled trauma patients admitted to the intensive care unit (ICU) of Besat Hospital in Hamadan Province, located in northwest Iran, from July 2011 to July 2012. The study was approved by the Ethics Committee of Hamadan University of Medical Sciences. Written informed consent was obtained from the legal guardians of the patients. We included intubated patients who were older than 18 yrs. and had an Acute Physiology and Chronic Health Evaluation score (APACHE II) of less than 25. Patients who had pneumonia or gastrointestinal bleeding upon ICU admission, those with a history of gastrectomy, anticipated need for tracheal intubation in less than 48 hours, and known sensitivity to the studied medications were excluded from our study.

A total of 146 patients were chosen to participate in this study. Of them, 120 patients meeting the inclusion criteria were examined. All patients were followed up until discharge. The patients were randomized using online random allocation software (www.allocationsoftware.com). The patients and the attending intensivists responsible for data collection were blinded to the assigned groups.

Following admission to the ICU, 50 mg intravenous ranitidine (Ranitidine 50 mg, Caspian Tamin Co, Rasht, Iran) was administered three times daily to one group of patients during NPO time to prevent stress ulcers. Thereafter, the day after oral feeding initiation, 150 mg oral ranitidine tablets (Ranitidine 150 mg, Daroupakhsh, Tehran, Iran) were administered twice daily until the end of the study. The second group received 40 mg intravenous pantoprazole (PEPTICARE 40 mg Ronak Pharmaceutical Co, Saveh, Iran) once daily during NPO time. The day after oral feeding initiation, it was replaced with 40 mg pantoprazole tablets (E.C. Tablet Pantoprazole 40 mg, Osveh, Tehran, Iran) once a day for stress ulcer prophylaxis until the end of the study. GI prophylaxis continued till ICU discharge. Other treatments were similarly administered to both groups according to the ICU protocol.

The patients received care based on the available facilities and the guidelines for preventing VAP. After tracheal intubation, the patients underwent chest radiography which was repeated at least twice a week. Upon admission to the unit, daily complete blood count, urine samples and two separate sets of blood cultures from two different sites were obtained from the patients. If possible, samples from pulmonary secretions were obtained using the mini-bronchoalveolar lavage (mini-BAL) method. During treatment, if symptoms of systemic inflammatory response syndrome (SIRS) occurred, cultures

would be taken again. Moreover, daily chest radiography was done until the patients' symptoms subsided and did not fulfill the SIRS criteria.

The incidence of VAP was considered as the primary outcome of our study. VAP was confirmed if a score of 7 out of 14 was obtained according to clinical pulmonary infection score (CPIS). Duration of tracheal intubation, length of ICU stay, duration of hospital stay, and the outcome of treatment including mortality or hospital discharge were compared in both groups as secondary outcomes. Baseline variables included sex, age, reason for admission, APCHE II and the day VAP developed.

Data were analyzed using SPSS version 15 software. $P<0.05$ was considered as significant.

RESULTS

The mean (±SD) age of the participants was 40.15(±20.40) years; 71.7% of patients were men and the mean (±SD) APACHE II score was 15.21(±1.98). We found no statistically significant difference between the two groups regarding baseline characteristics such as age, sex or APACH II (Table 1).

Table 1. Comparison of baseline characteristics between the two groups

Variable	Receiving ranitidine (n=60)	Receiving pantoprazole (n=60)	P value
Age (years)	50.63 (±20.78)	43.67 (±19.58)	0.118
Sex (women/men)	44/16	42/18	0.420
APACHEII	15.30 (±1.34)	15.30 (±1.34)	0.252
VAP incidence (%)	10	30	0.006

The patients receiving ranitidine experienced VAP one day earlier than those who received pantoprazole (P=0.683, Table 2). The incidence of VAP was 10% and 30% in patients receiving ranitidine and pantoprazole, respectively (P=0.006). There was no significant difference between the two groups with respect to the duration of tracheal intubation. However, the patients treated with pantoprazole stayed at the hospital two days longer than the other patients (P=0.027). Although there was an evident difference in the rate of mortality between the two groups, we found no significant difference in the hospital mortality rate between the two groups (P=0.245).

Table 2. Comparison of dependent variables between the two groups

Variable	Receiving ranitidine (n=60)	Receiving pantoprazole (n=60)	P value
VAP incidence (days)	7.33 (±1.96)	8.17 (±2.59)	0.683
Hospital stay (days)	15.67 (±7.11)	17.58 (±7.90)	0.027
Duration of intubation	14.17 ±6.70)	14.10(±5.84)	0.613
Hospital mortality (%)	5	10	0.245

Table 3 shows comparison of patients with respect to the incidence of VAP. As shown, no significant difference was observed between patients with and without VAP with respect to their age, sex, and APACH II scores. VAP patients stayed at the hospital for 12 more days during the treatment process (P=0.000), and tolerated mechanical ventilation for 8 more days (P=0.000) compared to non-VAP patients. However, the two groups had almost similar mortality rates (P=0.572).

Table 3. Comparison of patients with and without VAP with respect to some variables

Variable	With VAP (n=24)	Without VAP (n=96)	P value
Age (years)	45.41 (±21.11)	47.58 (±20.30)	0.644
Sex (women/men)	20/4	66/30	0.159
APACHEII	15.12 (±1.82)	15.24 (±2.03)	0.801
Days of intubation	20.41 (±7.39)	12.56 (±4.83)	0.000
Hospital stay (days)	26.12 (±7.43)	14.25 (±5.42)	0.000
Hospital mortality (%)	8.3	7.3	0.572

DISCUSSION

Studies on the association of pharmacological stress ulcer prophylaxis with pneumonia incidence date back to 1987 (17). Several studies have stated that pharmacological stress ulcer prophylaxis with sucralfate is safer than H2 blockers respecting VAP (16, 17). Proton pump inhibitors are more effective in causing community-acquired

pneumonia (CAP) and HAP in patients without mechanical ventilation (3, 10). Minao and colleagues conducted a cohort study to compare pantoprazole and ranitidine in the development of VAP. They reported that the incidence rate of VAP was significantly higher in patients who received pantoprazole (10, 14). However, a meta-analysis showed no statistically significant difference between pantoprazole and ranitidine in preventing gastrointestinal bleeding, risk of VAP or mortality. Conduction of more clinical trials was also recommended (15). To the best of our knowledge, our study was the first double-blind randomized controlled trial comparing the effect of these two commonly used medications for preventing stress ulcers in causing VAP.

We found that the incidence of VAP was 10% and 30% in patients receiving ranitidine and pantoprazole, respectively. We observed no significant difference between the two groups regarding the duration of tracheal intubation. However, the patients treated with pantoprazole stayed at the hospital for two more days compared with those receiving ranitidine. The rate of hospital mortality was not significantly different between the two groups.

In a historical cohort study on 1,682 patients who underwent cardiac surgery in the United States, the incidence rates for VAP were 9.3% and 1.5% in patients receiving pantoprazole and ranitidine for the prevention of stress ulcers, respectively (14). The researchers of the mentioned study suggested that this relationship needs to be further assessed in a randomized controlled trial.

In a clinical trial conducted by Somberg and colleagues (2008), intravenous pantoprazole was compared with intravenous cimetidine in 202 patients admitted to the ICU. No difference was found in the incidence rates of pneumonia between the patients (18). Since the patients who required mechanical ventilation for more than 24 hours were excluded from the study, the definition of VAP did not apply to the mentioned.

In another study, omeprazole and ranitidine were compared with respect to gastrointestinal bleeding. No difference was detected in the incidence rate of VAP as a secondary outcome. In the mentioned study, 150 mg ranitidine was administered intravenously and compared with 40 mg pantoprazole administered orally (19). However, this dosage differed from the one we used in our study.

In a clinical trial in 2004, researchers compared the effects of omeprazole (40mg), famotidine (40mg), sucralfate (1g) and a placebo on gastrointestinal bleeding. They reported that gastric pH and gastric colonization were higher in patients who received omeprazole and famotidine, while the incidence rates of pneumonia were equal in both groups (20). In another clinical trial in 2005, immediate-release omeprazole oral suspension was compared with intravenous cimetidine in preventing stress ulcers. No difference was observed in the incidence of VAP between the two groups (21). However, the drug administration method in both mentioned trials differed from ours.

In a review article, possible mechanisms of increased VAP incidence using proton pump inhibitors were discussed including increased bacterial colonization of the stomach and delayed gastric emptying. The authors stated that the use of proton pump inhibitors could only increase the incidence of aspiration pneumonia, with no effect on other types of pneumonia (22).

Based on the findings of a large hospital-based cohort study, HAP occurred in 3.5% of the studied population and pantoprazole was ordered in 52% of ICU admissions, hence the risk of HAP while receiving proton pump inhibitors could be calculated as 0.9%. Moreover, by considering a mortality rate of 18% for HAP, we could prevent 33,000 deaths annually by restricting the use of proton pump inhibitors to specific indications (3).

Patients treated with mechanical ventilation are at a higher risk for VAP because microorganisms can enter the lower respiratory tract as a result of impairment of the mucociliary clearance and micro-aspiration. Therefore, treatment strategies should focus on decreasing bacterial colonization of the oropharynx. In this regard, frequent

hand washing by healthcare providers, semi-recumbent positioning of patients and frequent suctioning of subglottic secretions could be effective. These factors along with some others have been mentioned in VAP prevention guideline and reviewed regularly (23).

We did not assess the success rate of the two understudy medications in reducing gastrointestinal bleeding. Proton pump inhibitors prove to be more successful than H2 blockers in decreasing the incidence of gastrointestinal bleeding induced by the stress ulcers because of better gastric acid suppression and gastric pH elevation (8, 9). It should be noted that mortality rates are much lower in patients with VAP compared to patients with gastrointestinal bleeding. However, stress ulcer prophylaxis is still a controversial issue. 40-70% of admitted patients receive stress ulcer prophylaxis, 70% of which are at a low risk of developing stress ulcers. Therefore, these medications should be administered with care and upon indication (24).

In conclusion, patients in ICUs have a three-fold increased risk of developing VAP using pump inhibitors in comparison with H2-blockers. Therefore, the prevention of stress ulcers should be limited to its own specific indications. Such indications for the use of prophylactic drugs should be developed for administering these two medications for specific cases and limit the use of proton pump inhibitors to the patients at a high risk for gastrointestinal bleeding.

REFERENCES

1. du Moulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. *Lancet* 1982; 1 (8266): 242- 5.
2. Donowitz LG, Page MC, Mileur BL, Guenthner SH. Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. *Infect Control* 1986; 7 (1): 23- 6.
3. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009; 301 (20): 2120- 8.
4. Driks MR, Craven DE, Celli BR, Manning M, Burke RA, Garvin GM, et al. Nosocomial pneumonia in intubated patients given sucralfate as compared with antacids or histamine type 2 blockers. The role of gastric colonization. *N Engl J Med* 1987; 317 (22): 1376- 82.
5. Prod'hom G, Leuenberger P, Koerfer J, Blum A, Chiolero R, Schaller MD, et al. Nosocomial pneumonia in mechanically ventilated patients receiving antacid, ranitidine, or sucralfate as prophylaxis for stress ulcer. A randomized controlled trial. *Ann Intern Med* 1994; 120 (8): 653- 62.
6. Thomason MH, Payseur ES, Hakenewerth AM, Norton HJ, Mehta B, Reeves TR, et al. Nosocomial pneumonia in ventilated trauma patients during stress ulcer prophylaxis with sucralfate, antacid, and ranitidine. *J Trauma* 1996; 41 (3): 503- 8.
7. Cook D, Walter S, Freitag A, Guyatt G, Devitt H, Meade M, et al. Adjudicating ventilator-associated pneumonia in a randomized trial of critically ill patients. *J Crit Care* 1998; 13 (4): 159- 63.
8. Hsu TC, Su CF, Leu SC, Huang PC, Wang TE, Chu CH. Omeprazole is more effective than a histamine H2-receptor blocker for maintaining a persistent elevation of gastric pH after colon resection for cancer. *Am J Surg* 2004; 187 (1): 20- 3.
9. Thorens J, Froehlich F, Schwizer W, Saraga E, Bille J, Gyr K, et al. Bacterial overgrowth during treatment with omeprazole compared with cimetidine: a prospective randomised double blind study. *Gut* 1996; 39 (1): 54- 9.
10. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; 292 (16): 1955- 60.
11. Gulmez SE, Holm A, Frederiksen H, Jensen TG, Pedersen C, Hallas J. Use of proton pump inhibitors and the risk of community-acquired pneumonia: a population-based case-control study. *Arch Intern Med* 2007; 167 (9): 950- 5.

12. Eurich DT, Sadowski CA, Simpson SH, Marrie TJ, Majumdar SR. Recurrent community-acquired pneumonia in patients starting acid-suppressing drugs. *Am J Med* 2010; 123 (1): 47-53.
13. Beaulieu M, Williamson D, Sirois C, Lachaine J. Do proton-pump inhibitors increase the risk for nosocomial pneumonia in a medical intensive care unit? *J Crit Care* 2008; 23 (4): 513- 8.
14. Miano TA, Reichert MG, Houle TT, MacGregor DA, Kincaid EH, Bowton DL. Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. *Chest* 2009; 136 (2): 440-7.
15. Lin PC, Chang CH, Hsu PI, Tseng PL, Huang YB. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. *Crit Care Med* 2010; 38 (4): 1197- 205.
16. Barletta JF, Erstad BL, Fortune JB. Stress ulcer prophylaxis in trauma patients. *Crit Care* 2002; 6 (6): 526- 30.
17. Daschner F. Stress ulcer prophylaxis and the risk of nosocomial pneumonia in artificially ventilated patients. *Eur J Clin Microbiol* 1987; 6 (2): 129- 31.
18. Somberg L, Morris J Jr, Fantus R, Graepel J, Field BG, Lynn R, Karlstadt R. Intermittent intravenous pantoprazole and continuous cimetidine infusion: effect on gastric pH control in critically ill patients at risk of developing stress-related mucosal disease. *J Trauma* 2008; 64 (5): 1202- 10.
19. Levy MJ, Seelig CB, Robinson NJ, Ranney JE. Comparison of omeprazole and ranitidine for stress ulcer prophylaxis. *Dig Dis Sci* 1997; 42 (6): 1255- 9.
20. Kantorova I, Svoboda P, Scheer P, Doubek J, Rehorkova D, Bosakova H, et al. Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial. *Hepatogastroenterology* 2004; 51 (57): 757- 61.
21. Conrad SA, Gabrielli A, Margolis B, Quartin A, Hata JS, Frank WO, et al. Randomized, double-blind comparison of immediate-release omeprazole oral suspension versus intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill patients. *Crit Care Med* 2005; 33 (4): 760- 5.
22. Fohl AL, Regal RE. Proton pump inhibitor-associated pneumonia: Not a breath of fresh air after all? *World J Gastrointest Pharmacol Ther* 2011; 2 (3): 17- 26.
23. Prescott HC, O'Brien JM. Prevention of ventilator-associated pneumonia in adults. *F1000 Med Rep* 2010; 2. pii: 15.
24. Quenot JP, Thiery N, Barbar S. When should stress ulcer prophylaxis be used in the ICU? *Curr Opin Crit Care* 2009; 15 (2): 139- 43.