RESEARCH ARTICLE

# Evaluation of Ventilator-Associated Pneumonia According to Stress Related Mucosal Disease Prophylaxis Regimen in the Intensive Care Unit

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**Background:** Ventilator-associated pneumonia (VAP) increases the cost of intensive care unit (ICU) treatment and the chance of mortality. Due to the increasing use of proton pump inhibitors (PPI) and H2 receptor inhibitors for stress ulcer prophylaxis, the purpose of the study was to investigate the differences of VAP in two groups of patients receiving PPI or H2 blocker.

**Methods:** In the retrospective cross sectional study, from September 2011 to September 2012, 43 patients who had positive pulmonary cultures (PC) were studied. These patients had a clinical pulmonary infection score (CPIS) ≥6 for more than 48 hours after receiving stress related mucosal diseases prophylaxis (SRMD). Patients whose SRMD prophylaxis was changed within 72 hours before obtaining the PC samples were excluded. Patients were divided into two groups. One group received pantoprazole (20 cases) and the other group received ranitidine (23 cases). Between the groups, age, sex, APACHE II score, predicted mortality, type of used SRMD prophylaxis drug, duration of prophylaxis prior to PC sampling, interval time between ICU admission and VAP manifestation, the type of bacterial causes of VAP, gastrointestinal bleeding, ICU length of stay and actual mortality were compared.

**Results:** The APACHE II score and predicted mortality were higher in the pantoprazole group (P=0.173, 0.167). We found that 30% of the ranitidine group suffered from upper GI bleeding. In the pantoprazole group, 21.74% suffered from upper GI bleeding (P<0.001). Patients receiving ranitidine had a higher mortality rate and a worse prognosis (P< 0.001).

**Conclusion:** Although there were more critically ill patients with a higher predicted mortality in the pantoprazole group, the ranitidine recipients turned out to have a higher mortality rate.

**Keywords:** ventilator-associated pneumonia; stress related mucosal diseases; prophylaxis; intensive care unit

Ventilator-associated pneumonia (VAP) is a type of nosocomial pneumonia (NP) that occurs in patients who have been intubated for more than 48 hours. NP is the second most common type of nosocomial infection. VAP is the main cause of death in intensive care units (ICU). It has a crude mortality rate of 30 to 70% [1]. Furthermore, VAP causes prolonged stays in hospitals and ICUs. It also increases the chances of mortality, as well as the cost of hospital treatment [1].

In ICU patients, stress ulcers are the most common causes of GI bleeding. To prevent stress ulcers, proton pump inhibitors (PPI) and H2 receptor inhibitors are used. These inhibitors decrease the gastric acidity. A decrease in bacterial growth, especially in the gram-negative bacteria of the upper GI tract, is one of the underlying causes of VAP [2-3]. The different mechanisms of these two gastric acid inhibitors, especially in their pH values, resulted in the growth of various bacteria. Thus, in the gastrointestinal tract, multifarious strains of bacteria are colonized [4]. In cases of VAP, micro-aspiration should be considered. This is because different bacterial strains can impact the course of treatment, prognosis and more. Nowadays, pantoprazole is increasingly used in SRMD prophylaxis. It is known that PPIs are effective in reducing stomach acidity and controlling the secretion of gastric acid [5]. In the inhibition of gastric acid secretion, a further effect of pantoprazole has been

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demonstrated in ICU patients. ICU patients have an increased bacterial colonization in their stomachs [6]. Previous studies have shown that pantoprazole increases the risk of community-acquired pneumonia, compared with ranitidine [7-10].

In a clinical trial study conducted by Thorens and colleagues, 53% of patients treated with PPI had an overgrowth of bacteria, compared with 17% of patients who were being treated with H2 blocker [6]. The stomach PH in patients treated with PPI was equal to 4.2. In H2 blocker recipients, it was 2. It is important to note that the pH differences in patients suffering with bacterial overgrowth were greater than in the uninfected group (5.1 vs. 4.2). Furthermore, the purpose of the study was to investigate the differences of VAP in two groups of patients receiving PPI or H2 blocker.

## Methods

In the retrospective cross-sectional study, microbiologic data of the pulmonary cultures were extracted. The extraction was taken from patients in the medical and surgical ICU, Rasool Akram Medical Center, Iran University of Medical Sciences (IUMS), Tehran, Iran, from September 2011 to September 2012. During the period, 248 patients were admitted to the ICUs and 391 sputum culture sampling were obtained. Of these patients, only 86 were positive. From the 86 positive cultures, 43 patients whose pulmonary culture samples were obtained less than 48 hours after receiving stress related mucosal diseases prophylaxis were included and 6 patients who received SRMD prophylaxis less than 48 hours, 11 patients whose prophylactic medication was changed, 12 patients who were not intubated and 14 patients who were intubated less than 48 hours, were excluded. Furthermore, data of 20 patients in pantoprazole (Nycomed Exir Pharmaceutical Co., Broojerd, Iran) and 23 in ranitidine (Kimi) groups from records and archives were extracted and analyzed (Figure 1). The study questionnaire was approved by the Department of Intensive Care, Iran University of Medical Sciences. According to the current institutional ICU guideline, the patients' sputum culture samplings were obtained and sent when they had a clinical pulmonary infection score (CPIS) ≥6 (including temperature, blood leukocytes, airway secretion, compared Pao2 / FIO2, chest X-ray protests, protests of CXR progress, audio protests lung, etc.). Sputum culture was obtained using a mini-ball technique and sent in the standard setting to the institutional microbiology laboratory. After 48 hours, the microbiology laboratory reported the culture and antibiogram results. According to the current treatment protocol for stress ulcer prophylaxis in ICUs, patients initially receive a single dose of 80 mg pantoprazole. If gastrointestinal bleeding occurs, an infusion pump of pantoprazole (8 mg/hour) is started. Hence, patients who received continuous infusions of pantoprazole or ranitidine were considered as cases of gastrointestinal bleeding.

By online APACHE II software, age, sex, APACHE II score and predicted mortality were calculated. SRMD prophylaxis data included the type of drug used and the duration of prophylaxis prior to sampling for VAP diagnosis. VAP related data included the time interval between admission to the ICU and VAP creation, as well as the type of bacterial causes of VAP. Moreover, mortality and ICU length of stay were considered as primary and secondary outcomes.

For data analysis, patients were divided into two groups. The results were analysed using the SPSS16 software. P Values less than 0.05 were considered statistically significant.

## Results

The results of the study showed that there was no statistical significant difference between age, APACHE II, predicted mortality percent, and SRMD prophylaxis before VAP in two groups; then, two groups were identical from this view. This is while that two groups from sex variable perspective, had statistical significant difference (P<0.0001). The mean and standard deviation of age between two groups were 66.65±1.84 and 59.52±2.47, respectively (Table 1).

According to the age variable, patients in pantoprazole group than patients in ranitidine group had more risk for stress ulcer, however, there were no statistical significant difference between two groups from APACHE II (P=0.173), predicted mortality percent (P=0.167), and SRMD prophylaxis before VAP days (P=0.566), respectively (Table 1).

From the 43 studied cultures, Acinetobacter in 23 cases, Klebsiella in six cases and other bacteria including pseudomonas and entrobactor in 14 cases were found (Table 2).

The results of the table 3 revealed that two groups from primary outcome variable perspective (ICU mortality) had statistical significant difference (P<0.0001) but from secondary outcome variable view (ICU stay) had no statistical significant difference (P=0.99) (Table 3). The risk percent of UGI bleeding between two groups were significant (P<0.0001) as the percent in ranitidine group was approximately 8.26 % more than the pantoprazole group (Table 3).

As a general result, in the study, two kinds of the mortalities after VAP were reported that were actual and attributable with the numbers 68.2% and 33.53%, respectively.

## Discussion

In this study, the average APACHE II score and predicted mortality percent of the patients were 19.21±6.65 and 34.67±18.94, respectively. Furthermore, actual mortality after the course of VAP was 68.2% and attributable morality to VAP was 33.53%. In similar studies, the actual mortality and attributable mortality of VAP has been reported as 24-76% and 20-30%, respectively [1]. In the current study, the observed mortality was approximately 8.5% higher. A comparison between the APCHE II score's of the two study groups indicates that the physician colleagues prescribed PPI for the prevention of stress ulcers in patients with critical condition in the study units [11].

Despite more critically ill patients and a higher predicted mortality in the pantoprazole group (about 8%), the ranitidine recipients had a higher mortality rate (13.9%) compared to the pantoprazole recipient patients. Thus, the sum of the observed differences was 21.9%. This observed difference in mortality leads us to conclude this hypothesis that PPI recipients (resistant against the development of VAP) have a lower predicted mortality than H2 receptor

inhibitor recipients.

Figure 1- Patient's Flowchart

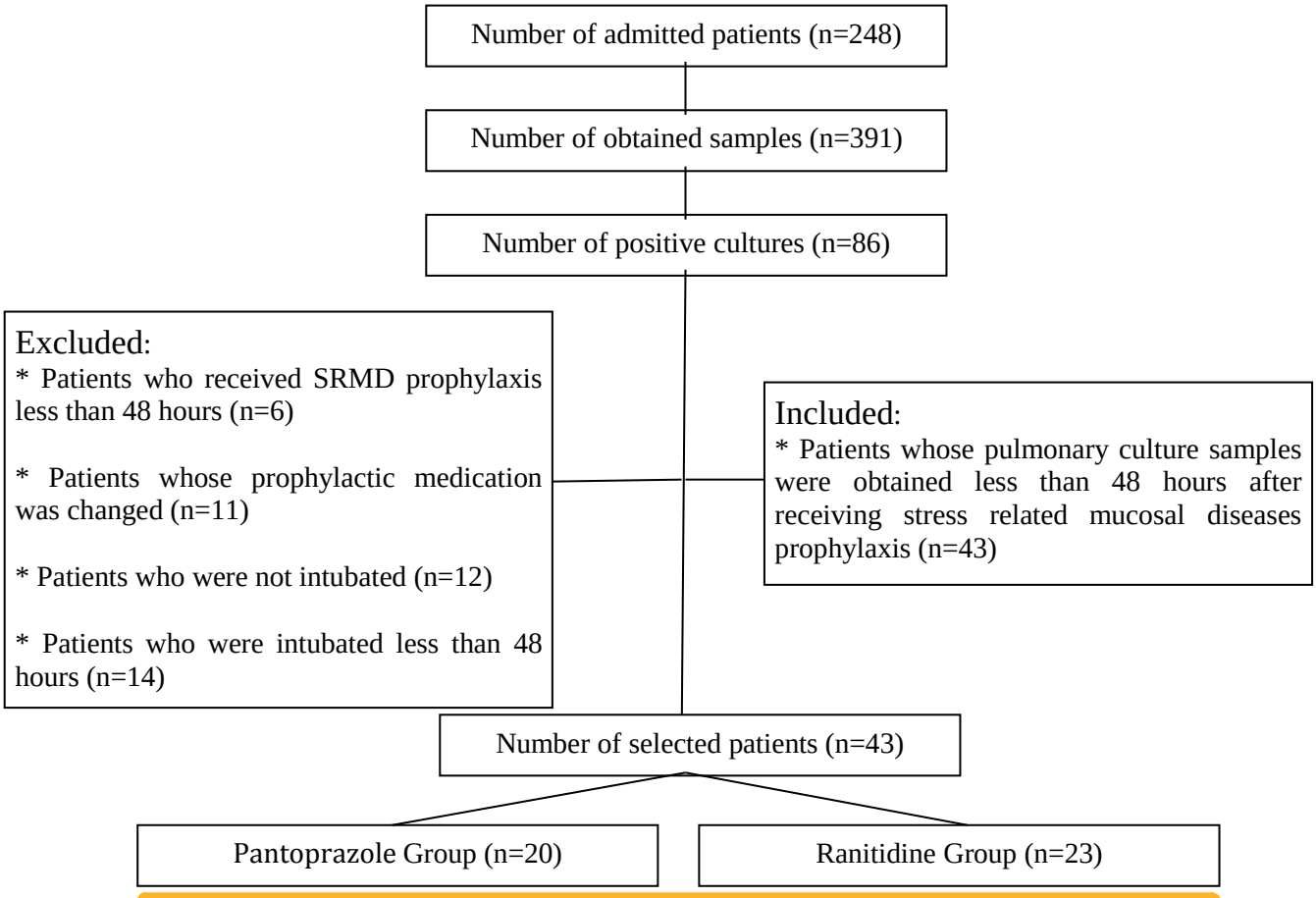


Table 1- Comparison of variables between the two study groups

| Variables | Pantoprazole (n=20) | Ranitidine (n=23) | P- Value |
|---|---|---|---|
| Age (year) | 66.65±1.84 | 59.52±2.47 | 0.296 |
| Sex (male %) | 45 | 60 | <0.0001 |
| APACHEII | 20.70±7.53 | 17.91±5.62 | 0.173 |
| Predicted Mortality (%) | 38.96±21.22 | 30.92±16.27 | 0.167 |
| SRMD prophylaxis before VAP (day) | 14.35±13.49 | 16.65±15.88 | 0.566 |

Table 2- Comparison of tracheal fluids culture findings between the two study groups

| Variables | Pantoprazole (n=20) | Ranitidine (n=23) | P- Value |
|---|---|---|---|
| Acinetobacter | 12 | 11 | 0.196 |
| Klebsiella | 6 | 0 | 0.654 |
| Others | 8 | 6 | 0.376 |
| Total | 26 | 17 | 0.761 |

Table 3- Comparison between the two study groups in terms of UGI bleeding, ICU stay, and ICU mortality

| Variables | Pantoprazole (n=20) | Ranitidine (n=23) | P Value |
|---|---|---|---|
| UGI bleeding (N)% | 21.74% (5) | 30% (6) | <0.0001 |
| ICU stay | 41.9±28.39 | 42.00±22.26 | 0.99 |
| ICU mortality | 60% | 73.9% | <0.0001 |

As it has been shown in authors' recently published studies the prevalence of gastrointestinal bleeding is higher in ranitidine recipients than in PPI group [12-13]; other studies also demonstrated how PPI medications inhibit the growth

of microorganisms. In this regards, Sasaki et al. demonstrated that lanaprazole inhibits the growth of rhinoviruses in the tracheal endothelial cells by reducing the production of cytokines and Intercellular Adhesion Molecule-1 (ICAM-1) [14]. Several previous studies have also revealed that PPIs can exert an anti-inflammatory effect by inhibiting the neutrophils adhesion to endothelial cells through ischemia reperfusion inhibition. Subsequently, they also inhibit the production and presentation of free oxygen radicals [15]. Moreover, other mechanisms of PPI medications have been found to inhibit the sodium potassium pump, as well as anti-oxidants and anti-apoptosis functions.

The results of the study showed that upper gastrointestinal bleeding occurred in 25% of the patients. The difference between the two study groups was statistically significant (P<0.0001). Moreover, GI bleeding in patients receiving ranitidine was higher (8.36%) than in those receiving pantoprazole. The results are different from the Somberg et al. study. One possible reason for the difference among the results can be explained by the ICU patients in Somberg et al. study weren't from specific subgroups of the ICU patients.

VAP as a hospitalization outcome in the ICU, deteriorated the patient's situation and consequently, there is an increase in ICU complications and GI bleeding. In addition, the prescribed doses to the patients in the two compared studies were different. In current study, 150 mg intravenous ranitidine was given twice a day and in the Somberg et al. study, 300 mg cimetidine was given per hour. As well as this, the same subject can have a role in the mentioned difference [16].

Another important point is that the incidence rate of GI bleeding is approximately 1% in ICU patients. In our case study subgroup, despite chemoprevention, GI bleeding was 25-27% and reported over 25 times, compared to the reported amount in ICU patients. However, the amount reported was not related to the VAP patient. On the other hand, considering the 3-14% of mortality rate of GI bleeding, the increased mortality of patients receiving ranitidine with a greater incidence of GI bleeding cannot be justified in our studied patients [17].

## Conclusion

Despite more critically ill patients and a higher predicted mortality in the pantoprazole group, the ranitidine recipients had a higher mortality rate.

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