

Original Article: Comparison of the effects of ranitidine and pantoprazole on incidence of ventilator-associated pneumonia

Sara Rozmina^a, Ahmad Bagheri Moghaddam^b, Sayyed Majid Sadrzadeh^a, Vida Vakili^c, Hamid Zamani Moghaddam^a, Morteza Talebi Doluee^{a,*}

^aDepartment of Emergency Medicine, Faculty of Medicine, Mashhad University of Medical sciences, Mashhad, Iran

^bDepartment of Anesthesiology and Critical care, Faculty of medicine, Mashhad University of Medical sciences, Mashhad, Iran

^cDepartment of Community Medicine, Faculty of Medicine, Mashhad University of Medical sciences, Mashhad, Iran



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ABSTRACT

Background and Aim: Patients with ventilator-associated pneumonia (VAP) have high morbidity and mortality. Some evidence suggests that aspiration of the colonized oropharyngeal and gastric contents can be a risk factor for the incidence of VAP in patients undergoing endotracheal intubation. In this study, we sought to compare the effects of ranitidine and pantoprazole on VAP incidence.

Subjects and Methods: In this double-blind clinical trial, 180 patients undergoing endotracheal intubation and mechanical ventilation were assigned to two groups based on the inclusion and exclusion criteria. Prophylaxis with pantoprazole and ranitidine was administered for the two groups (n=90 each), and then the patients were followed up for the detection of VAP and clinical signs of pneumonia. Finally, the patients' demographic and clinical data were analyzed in SPSS, version 18.

Results: Of the 180 patients enrolled in the study, 36 (20%) patients were diagnosed with VAP, 19 (52.7%) of whom belonged to the Ranitidine group, and 17 (47.2%) pertained to the Pantoprazole group (P=0.1). The daily risk for VAP in the two groups and each group separately was 1.7%.

Conclusion: Pantoprazole and ranitidine have similar effects on the incidence of pneumonia caused by endotracheal intubation. However, further studies are recommended due to the lack of convincing evidence.

*Corresponding Author: Morteza Talebi Doluee (TalebiDM@mums.ac.ir)

Introduction

The Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in intensive care units [1]. VAP typically occurs 24 to 48 hours following intubation and mechanical ventilation [2]. According to various studies, the prevalence of VAP and its mortality rate among hospitalized patients are about 30% and 50%, respectively [3].

Studies on the incidence of VAP in patients admitted to ICU have shown that the ultimate cause of this disorder is the aspiration of pathogenic bacteria of the gastrointestinal tract, especially the oropharynx [4]. This was drawn from the theory that acute diseases alter gastrointestinal flora, and the organisms that are commonly present in the gastrointestinal tract are activated by acute stress caused by the patient's ICU admission. They may colonize in the gastrointestinal tract, especially in the oropharynx, and enter the respiratory tract with intubation, ultimately leading to lung parenchyma infection [1]. Some evidence suggests that the aspiration of oropharyngeal and acidic contents may be a risk factor for VAP in patients undergoing endotracheal intubation [5, 6]. Theoretically, proton pump inhibitors (PPI) and histamine receptor antagonists (H2RA) can increase gastric colonization and lead to VAP with microaspiration potential [7]. So far, various studies have been conducted to investigate the effect of oral and intravenous antacids on VAP incidence [8-10].

Considering the importance of VAP prevention and the great use of the two mentioned drugs for the prevention of stress ulcers, addressing the difference between these drugs in the incidence of VAP can be a valuable guide for physicians to minimize the risk of VAP at least while using antacids. In this research study, we sought to compare the effects of ranitidine and pantoprazole on the incidence of VAP among intubated patients undergoing mechanical ventilation.

Patients and Methods

This randomized double-blind clinical trial was performed among 180 intubated patients under mechanical ventilation who presented no evidence of active pulmonary infection and were hospitalized for reasons other than pulmonary problems. The patients were allocated to two groups of treatment with ranitidine (n=90 patients) and treatment with pantoprazole (n=90 patients). The treatment of these patients was initiated on admission to the emergency department, and pantoprazole and ranitidine were continued until ICU discharge. The eligible patients for the study were allocated to two groups of pantoprazole and ranitidine after examination for the inclusion criteria and recording the baseline data in a randomized and 1: 1 form based on patient records.

In the pantoprazole group, treatment was initiated by the injection of pantoprazole at a dose of 40 mg twice daily. Then 40 mg of pantoprazole was administered orally through a nasogastric feeding tube in the form of intracapsular granules. In the ranitidine group, 50 mg of intravenous ranitidine was administered in three steps, followed by its oral administration at 150 mg twice daily. During this time, nutrition was provided through a nasogastric feeding tube. In addition, gastrointestinal bleeding was controlled daily.

The VAP diagnostic criteria included new infiltration in chest X-ray with two of the following three criteria: 1) fever higher than 38.5°C, 2) leukocytosis more than 10,000, and 3) presence of pus and secretions at the tip of the endotracheal tube. The data obtained from the patients with VAP diagnosis were analyzed by SPSS, version 18. Considering the double-blind design of the study, those prescribing the drugs and examining the occurrence of VAP and its presentations were two separate groups.

The eligible participants consisted of all the intubated patients admitted to the ICU of our hospital. The exclusion criteria were patients with a history of pulmonary infection before initiating the intervention, evidence of acute gastrointestinal bleeding at the outset of the study, signs of inherent or acquired immunodeficiency, history of antibiotics consumption, or any other risk factor for VAP.

We observed all the ethical considerations, such as obtaining informed consent from patients' next of kin, informing them that participation in the study was voluntary, and assuring them that patient's information will be kept confidential. We also attained the approval of the Ethics Committee of our university (IRCT2014112611956N3).

Results

Of the 36 patients with VAP, 19 (52.7%) patients were allocated to the ranitidine group and 17 (47.2%) patients to the pantoprazole group. Our results showed no significant difference in the incidence of VAP between the two groups ($P=0.1$). The risk of VAP incidence in both groups was 1.7% for each day of ICU stay.

The mean age of the patients was 45.45 ± 18.7 years. Of the 36 patients with VAP, 17 (47.2%) cases were male, and 19 (52.7%) were female; gender distribution in the two groups was similar ($P=0.121$). The demographic and clinical data of the patients with VAP are presented in Table 3. The mean duration of ICU stay was 16 ± 11.66 days. The mean interval from the onset of intubation until the occurrence of VAP and the mean interval from the onset of intubation until the initiation of antibiotic therapy were 7.3 ± 1.33 and 7.37 ± 1.61 days, respectively.

The demographic and clinical data of the 36 patients with VAP are presented in Table 4. The two groups had no significant difference in mean age ($P=0.417$) and gender distribution ($P=0.782$). No significant difference was observed between the two groups in terms of the mean interval from intubation until the incidence of VAP ($P=0.12$), the interval from the establishment of intubation until the initiation of antibiotics (pantoprazole group: 2.3 ± 1.76 vs. ranitidine group: 5.2 ± 1.46 ; $P=0.51$), the interval from intubation until the radiological detection of pneumonia (pantoprazole group: 8.1 ± 1.95 vs. ranitidine group: 6.1 ± 1.56 ; $P=0.233$), the interval from intubation until reduced oxygenation (pantoprazole group: 2.4 ± 1.39 vs. ranitidine group: 1.34 ± 1.3 ; $P=0.7$), and the mean interval from intubation until the increased level of white blood cells (WBCs); pantoprazole

group: 1.58 ± 1.2 vs. ranitidine group: 1.53 ± 1.2 ; $P=0.6$). The mean duration of ICU stay was not significantly different between the two groups (ranitidine: 12.08 ± 3.2 days vs. pantoprazole: 11.24 ± 8.1 days; $P=0.112$).

Discussion

The incidence rate of VAP in our study was 20%. Based on our findings, the incidence of VAP was not significantly different between the ranitidine and pantoprazole groups. Also, there was no significant difference between the pantoprazole and ranitidine groups in terms of duration of ICU stay, the interval from intubation until the incidence of VAP, interval from intubation until initiation of antibiotic therapy, the interval from intubation until the radiological detection of pneumonia, interval from intubation until hypoxemia, and the interval from intubation until the increased level of WBCs. Based on these findings, the type of prescription drug (pantoprazole or ranitidine) did not affect the incidence of VAP. Our results showed that the daily risk of VAP was similar in both groups of pantoprazole and ranitidine (1.7%).

In a study by Apt *et al.* (1992) on 34 patients with tetanus tracheotomy, 16 patients received intravenous ranitidine to maintain gastric acidity levels higher than 4, and 18 patients received no drugs (control group) [10]. They found that increased gastric pH with the assistance of medications elevates the odds of developing pneumonia in intubated and very ill patients (intubated patients treated with ranitidine develop pneumonia in a shorter time).

In a review conducted by Tryba *et al.* (1991) to investigate the effect of increasing gastric pH on the development of bronchopulmonary infection, it was noted that the risk of bacterial gastric colonization among ICU patients was significantly enhanced with higher gastric pH [8]. Based on a predefined explanation (the role of increasing gastric pH in promoting the incidence of VAP), various studies have been conducted to investigate the effects of oral and intravenous antacids on the incidence of VAP. Ryan *et al.* (1993) evaluated the effect of cimetidine (a stress ulcer prophylaxis drug) on

114 ICU patients who had developed VAP [12]. Their results indicated that using prophylaxis cimetidine does not increase the risk of nosocomial pulmonary infections.

Bonten *et al.* (1995) studied the effects of antacids on VAP in a double-blind study [11]. In that study, which was performed on 141 patients under mechanical intubation, it was found that none of the used antacids could prevent stress ulcer from predisposing endotracheal intubation to VAP.

Thomson *et al.* (1996) compared the incidence of nosocomial pneumonia among 242 patients with a severe physical injury who were allocated to two groups of patients treated with sucralfate and ranitidine [15]. Based on their results, no difference was observed in hospital-acquired pneumonia in trauma patients requiring mechanical ventilation during the first four days of stress ulcer prophylaxis with sucralfate or ranitidine. Pickworth *et al.* (1993) compared the incidence of VAP between two groups of trauma patients receiving sucralfate and ranitidine [16]. Of 92 patients undergoing mechanical ventilation, 39 patients received sucralfate, and 44 were administered intravenous ranitidine. The results of that study showed no significant difference in the incidence of VAP between the trauma patients receiving stress ulcer prophylaxis with sucralfate or ranitidine.

In a study by Mehedad *et al.* (2009) aimed at evaluating the incidence of VAP in two groups of intravenous ranitidine and oral omeprazole, it was found that although the difference between the two groups was significant in terms of incidence of gastrointestinal bleeding, there was no significant difference in the incidence of VAP between the two groups [17]. In a clinical trial carried out by Somberg *et al.* (2008), the incidence of nosocomial pneumonia was compared between patients receiving intravenous pantoprazole and those administered intravenous cimetidine [18]. In that study, no significant difference was noted in the incidence of pneumonia between the two groups of patients. As was noted in the mentioned studies and contrast with the presumption of the effect of antacids on the incidence of VAP and the different effects of

antacid drugs on the incidence of VAP in patients undergoing mechanical ventilation, Conrad did not find any association between the incidence of VAP and the use of antacid drugs [13]. The present findings aligned with those of previous studies showing the lack of effectiveness of pantoprazole and ranitidine in the incidence of VAP.

Contrary to our findings and the results as mentioned earlier, there has been some evidence on the effectiveness of some antacids in the incidence of VAP. In a retrospective cohort study conducted by Miano *et al.* (2009) on patients undergoing cardiothoracic surgery, the risk of nosocomial pneumonia was compared between pantoprazole prophylaxis users (n=377 patients) and patients receiving ranitidine (n=457 patients) [19]. In that study, 834 patients were examined. After analyzing the data, it was found that nosocomial pneumonia had occurred among 35 (9.3%) patients in the pantoprazole group and 7 (1.5%) cases in the ranitidine group. In the pantoprazole group, 31 (88.5%) of the 35 patients showed VAP, and the remainder were affected by hospital-acquired pneumonia. Moreover, in the ranitidine group, 5 (71.4%) out of 7 patients had VAP, and others showed hospital-acquired pneumonia. In that study, it was found that in patients undergoing cardiothoracic surgery, the use of pantoprazole for stress ulcer prophylaxis is associated with a higher risk for the incidence of nosocomial pneumonia compared to ranitidine.

A review study was conducted by Fohl *et al.* (2011) to investigate the possible mechanisms for increasing the incidence of VAP [20]. It was found that using PPIs could only affect the onset of pneumonia caused by aspiration, and this drug category does not affect other types of pneumonia. Rahimi *et al.* (2013) studied 120 ICU patients to compare the incidence of VAP between pantoprazole and ranitidine users [9]. In that study, a group of patients received 50 mg of intravenous ranitidine three times daily while fasting to prevent stress ulcer. Another group received 40 mg of intravenous pantoprazole once daily during NPO. Until the end of the study, oral administration of 150 mg of ranitidine twice daily in the ranitidine group and 40 mg of

pantoprazole daily in the pantoprazole group was continued. The occurrence of VAP was considered the primary result of the study. Based on the results, the incidence of VAP in the pantoprazole group was significantly higher than in the ranitidine group (statistical analysis showed a three-fold increase in the incidence of VAP in the pantoprazole group relative to the ranitidine group).

In conclusion, based on some evidence [7-10, 12], the use of antacids for stress ulcer prophylaxis can expose patients under endotracheal intubation to a higher risk for VAP; however, some other studies have yielded contradictory results [8, 11-13, 15-18] which highlights the need for further studies. Abundant studies are comparing the role of antacids in the occurrence of VAP. However, due to the lack of studies comparing the effects of pantoprazole and ranitidine, further studies are recommended for more comprehensive conclusions. Of limitations of our study were lack of long-term follow-up of the clinical status of patients (complete recovery, relative recovery, and death), lack of simultaneous evaluation of the patient groups, and failure to study the complications of VAP.

Conclusion

Pantoprazole and ranitidine have similar effects on the incidence of pneumonia caused by endotracheal intubation. However, further studies are recommended due to the lack of convincing evidence.

ORCID

Sara Rozmina

<https://www.orcid.org/0000-0002-0487-1191>

Ahmad Bagheri Moghaddam

<https://www.orcid.org/0000-0002-8890-6987>

Sayyed Majid Sadrzadeh

<https://www.orcid.org/0000-0002-7261-025X>

Veda Vakili

<https://www.orcid.org/0000-0002-5732-4407>

Hamid Zamani Moghaddam

<https://www.orcid.org/0000-0002-7506-7782>

Morteza Talebi Doluee

<https://www.orcid.org/0000-0003-2570-3733>

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

There are no conflicts of interest in this study

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