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Research Article

# Investigating and Comparing the Severity and Prevalence of Ventilator-Induced Pneumonia in Patients Taking Famotidine and Pantoprazole in the Intensive Care Unit: A Clinical Trial

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**ABSTRACT**

**Background:** Patients admitted to the intensive care unit (ICU) are at high risk of gastrointestinal (GI) mucosal injury and stress ulcers, which may lead to gastrointestinal bleeding, due to their critical condition and use of mechanical ventilation. Stress ulcer prophylaxis drug regimens, including proton pump inhibitors (PPIs) and histamine type 2 receptor antagonists (H2RAs), are commonly used to prevent these complications. However, there are concerns about the side effects of these drugs, including an increased risk of ventilator-associated pneumonia (VAP). This study aimed to compare the effects of pantoprazole and famotidine on clinical outcomes and the risk of VAP in patients admitted to the ICU.

**Methods:** This study was designed as a single-center randomized clinical trial conducted in the Intensive Care Unit (ICU). The study population included 138 patients admitted to the ICU who required mechanical ventilation. The treatment regimens studied included two groups: group 1 received intravenous pantoprazole (40 mg daily), and group 2 received intravenous famotidine (20 mg twice daily). The study's primary outcome measure was the incidence of VAP, which was assessed according to ATS/IDSA and CDC guidelines. Other clinical variables included ICU length of stay, APACHE score, and incidence of adverse events.

**Results:** The results showed that in the famotidine group, ICU length of stay and APACHE II score were significantly shorter than in the pantoprazole group. However, no statistically significant differences were observed in variables such as age, weight, drug administration duration, and intubation duration. In addition, the frequency of death and pneumonia incidence in the famotidine group was lower than in the pantoprazole group, although this difference was not statistically significant.

**Conclusion:** This study showed that both famotidine and pantoprazole are effective in the prophylaxis of stress ulcers in critically ill ICU patients, but famotidine may be associated with more favorable clinical outcomes, including reduced length of stay and severity of illness. Also, the use of gastric acid suppressant drugs is associated with an increased risk of VAP, which requires more attention to drug selection and patient management. The findings of this study can help in better decision-making regarding the use of SUP drugs in ICU patients.

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## Introduction

Ventilator-associated pneumonia (VAP) is a serious hospital-acquired infections, and it is defined by the occurrence of pneumonia after 48 hours of patient being mechanically ventilated and is a leading cause of ICU mortality [1-3]. VAP increases ICU stay by about four days and has an attributable mortality of 20–30% [3]. VAP is a serious and prevalent complication in ICUs, occurring in 5–40% of mechanically ventilated patients [4-5]. High morbidity and mortality, including respiratory failure, prolonged ICU stays, and increased healthcare costs, are consequences of VAP [6-8].

Early and accurate diagnosis of VAP is critical for effective management, yet it remains challenging due to the clinical overlap with other pulmonary conditions [9-10]. No single clinical manifestation is sufficient to diagnose VAP [11]; however, chest X-rays and clinical signs such as fever, high leukocyte count, or pulmonary manifestations are valuable indicators to VAP diagnosis [12-13]. Clinical Pulmonary Infection Score (CPIS) is an important diagnostic tool to improve diagnostic accuracy [14], and a score > 6 suggests VAP [15-16].

Based on research conducted, primarily through observational studies, two key risk factors for VAP are identified: colonization of bacteria in the stomach [17-20] and the use of medications that alter gastric acid levels, such as histamine-2 receptor antagonists and antacids [21-22]. Furthermore, experimental studies provided evidence of gastric contents being aspirated into the trachea. This aspiration was found to be particularly prevalent when patients were supine, suggesting that body position plays a significant role in the risk of developing VAP [1, 23].

Critically ill patients are at high risk of stress-related gastrointestinal (GI) bleeding, which is associated with increased mortality and prolonged ICU stays [24-25]. Stress ulcer prophylaxis (SUP) is administered to these patients in ICUs [26]. Common agents include proton pump inhibitors (PPIs) such as pantoprazole and histamine-2 receptor antagonists (H2RAs) such as famotidine [26-28]; however, pantoprazole is frequently used in critically ill patients for stress ulcer prophylaxis [29]. There is growing concern that acid-suppressing medications, particularly PPIs, may increase the risk of nosocomial infections, including VAP and Clostridium difficile infections [30-31]. This association is thought to result from the suppression of gastric acid, which facilitates bacterial colonization of the upper GI tract and subsequent aspiration into the lungs [32-33].

The relationship between SUP and VAP remains controversial [34], with limited comparative data on the risks associated with different prophylactic agents [35-37]. This study aimed to investigate the incidence of VAP in critically ill patients receiving SUP with either famotidine or pantoprazole. By comparing these two commonly used agents, we seek to provide evidence-based guidance on optimizing SUP strategies to minimize the risk of VAP while effectively preventing stress ulcer-related complications.

## Methods

### Experimental

This experimental clinical trial was conducted using a randomized, double-blind, single-center design. The study population consisted of 138 patients admitted to the ICU of Bouali Hospital in Tehran in 2024 who required mechanical ventilation. Eligible patients were selected via a convenience sampling approach and were randomly assigned to two treatment groups (each group 69 patients) using block randomization with a block size of four. This study sought to evaluate the effectiveness of two different classes of medications in the prevention of stress ulcers and to examine the treatment-related outcomes, including the risk of acquiring VAP. According to reputable IDSA/ATS (30), the regimens for gastrointestinal ulcer prophylaxis include the following medications:

- H2 receptor antagonists (such as famotidine and cimetidine)
- Proton pump inhibitors (PPIs) (such as pantoprazole and omeprazole)

Previous studies have shown no significant difference in reducing upper gastrointestinal bleeding when these medications are compared to placebo. However, concerns have been raised regarding the side effects of these medications, including pneumonia and Clostridium difficile infection [38]. In this study, we compared the effectiveness of pantoprazole and famotidine in stress ulcer prophylaxis while maintaining standard therapeutic practices for ICU patients. The intervention treatment regimens were as follows:

- Group 1: Intravenous pantoprazole, 40 mg daily
- Group 2: Intravenous famotidine, 20 mg twice daily

The risk of acquiring VAP was defined as the primary outcome, assessed based on the ATS/IDSA and CDC guidelines.

### Setting

Patients receiving mechanical ventilation in the ICU of BouAli Hospital in Tehran in 2024 were enrolled as the target population for this study. Clear inclusion and exclusion criteria were defined for the patient selection process.

Inclusion criteria for patients range from 18 to 80 years old in the ICU who have been on mechanical ventilation for at least 48 hours. The exclusion criteria were patients with a history of elevated creatinine levels,

immunosuppression, active liver or kidney disease, or pulmonary infections.

Those requiring further interventions or who are lost to follow-up are excluded. Sensitivity analysis indicates that patients with active gastrointestinal bleeding will not be included in the study.

### Participants

Based on preliminary calculations, 62 patients should be allocated to each group. Based on the study by Bashar et al. and the incidence of pneumonia in the ranitidine group (p = 0.10) and the pantoprazole group (p = 0.30), the required sample size was estimated using G*Power software. With a 95% confidence level and a statistical power of 80%, the calculated sample size was 62 patients per group, resulting in a total of 124 patients for the study [32] (Figure 1).

However, to enhance the statistical power of the study and ensure reliable results, the final number of patients in each group was increased to 69 (the allocation ratio is 1:1), resulting in a total of 138 patients participating in the study. (Figure 2) illustrates the patient selection process and randomization.

**z tests -** Proportions: Difference between two independent proportions

| | | | |
|---|---|---|---|
| | A priori: Compute required sample size | | **Analysis:** |
| Two | = | Tail(s) | **Input:** |
| 0.1 | = | Proportion p2 | |
| 0.3 | = | Proportion p1 | |
| 0.05 | = | α err prob | |
| .80 | = | Power (1-β err prob) | |
| 1 | = | Allocation ratio N2/N1 | |
| -1.9599640 | = | Critical z | **Output:** |
| 62 | = | Sample size group 1 | |
| 62 | = | Sample size group 2 | |
| 124 | = | Total sample size | |
| 0.8025989 | = | Actual power | |

**Figure 1- Sample size calculation**

### Sampling Method

Sampling was performed using block randomization with a block size of four. This method was employed to ensure a balanced distribution of patients between the two groups and to reduce bias in treatment assignment.

### Ethical Consideration

This study was conducted with approval from the Islamic Azad University of Tehran Medical Sciences (Pharmaceutical Branch)'s ethics committee (IR.IAU.PS.REC.1402.655) and was registered at the Iranian Clinical Trials Center database (IRCT20231220060484N2).

The written informed consent was obtained from the patient's guardians before their enrollment in the study. All patient data were kept confidential and were used solely for research purposes.

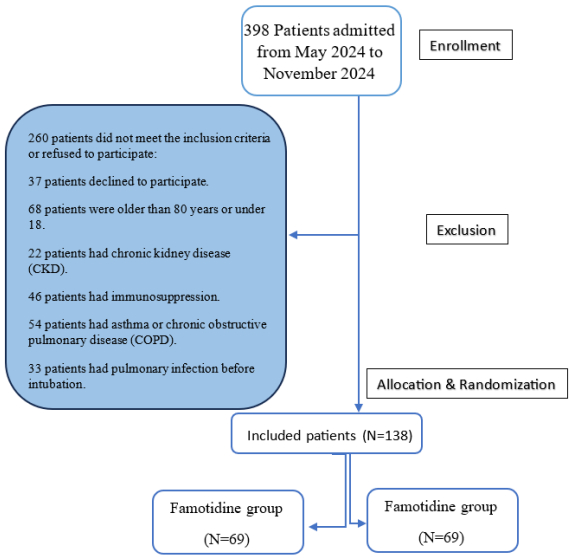


**Figure 2- Consort diagram of participants.**

## Results

### Participant Flow and Baseline Characteristics

A total of 138 patients requiring stress ulcer prophylaxis (SUP) were enrolled in this single-center, double-blinded, randomized clinical trial. (Table1) Participants were equally allocated into two groups:

- Pantoprazole group: 69 patients (50.0%)
- Famotidine group: 69 patients (50.0%)

**Table 1- Participant Flow**

| | Frequency | Percent | Cumulative Percent |
|---|---|---|---|
| Pantoprazole | 69 | 50.0 | 50.0 |
| Famotidine | 69 | 50.0 | 100.0 |
| Total | 138 | 100.0 | |

### Reasons for ICU Admission

The distribution of patients based on the Primary clinical condition necessitating ICU admission is shown in (Table 2). Neurological conditions were the most frequently reported reason for ICU admission in both groups (30 patients in the famotidine group and 27 in the pantoprazole group). The pantoprazole group included one patient admitted for cardiac disease, which was not observed in the famotidine group. Orthopedic admissions were slightly higher in the pantoprazole group (22 vs. 20 patients).

### Main Outcomes

### Comparison of Quantitative Variables

Normality was tested using the Shapiro-Wilk method. Only height followed a normal distribution; thus, the independent samples t-test was used for this variable.

Non-normally distributed variables were compared using the Mann-Whitney U test.

As shown in (Table 3), the famotidine group had a significantly shorter ICU length of stay compared to the pantoprazole group (13.84 vs. 17.20 days, p=0.001). The APACHE II score as the disease severity tool was found to be significantly lower in the famotidine group (14.38 vs. 16.16, p=0.038). No significant differences in age, weight, height, or intubation time were found between the two groups.

**Secondary Outcomes**

**Incidence of Pneumonia and Mortality**

As indicated in Table 4, the chi-square test revealed no statistically significant difference in pneumonia incidence was observed between the two groups (p=0.382). However, the famotidine group had a lower incidence of pneumonia (8.7% vs. 15.9%). Mortality rates did not differ significantly between the groups, according to Fisher's exact test (p=0.562). The famotidine group had a lower mortality rate (7.2% vs. 11.6%).

**Pathogens and Treatment Regimens**

No significant differences were observed in the distribution of pathogens causing pneumonia (p>0.05). The most common pathogen was Acinetobacter (5.8% in the pantoprazole group vs. 4.3% in the famotidine group). (Table 5). The distribution of pneumonia treatment regimens among the study participants is summarized in (Table 6). In the pantoprazole group, 84.1% of patients (n=58) did not develop ventilator-associated pneumonia (VAP), while 7.2% (n=5) were treated with colistin-meropenem, 7.2% (n=5) with meropenem-levofloxacin, and 1.4% (n=1) with Gram-positive-targeted therapy. In the famotidine group, 91.3% of patients (n=63) did not develop VAP, while 4.3% (n=3) were treated with colistin-meropenem, 4.3% (n=3) with meropenem-levofloxacin, and 0.0% (n=0) with Gram-positive-targeted therapy. Overall, 87.7% of patients (n=121) across both groups did not develop VAP, while 5.8% (n=8) were treated with colistin-meropenem, 5.8% (n=8) with meropenem-levofloxacin, and 0.7% (n=1) with Gram-positive-targeted therapy. The most effective treatment regimens for VAP were colistin-meropenem and meropenem-levofloxacin, with no significant differences detected between the two groups.

**Table 2- Reasons for ICU Admission**

| Reason for Admission | Famotidine Group (n=69) | Pantoprazole Group (n=69) |
|---|---|---|
| Neurological conditions | 30 (43.5%) | 27 (39.1%) |
| Sepsis (excluding pneumonia) | 15 (21.7%) | 13 (18.8%) |
| Abdominal surgery | 4 (5.8%) | 6 (8.7%) |
| Orthopedic conditions | 20 (29.0%) | 22 (31.9%) |
| Cardiac disease | 0 (0.0%) | 1 (1.4%) |

**Table 3- Quantitative Variables**

| Variable | Pantoprazole Group (n=69) | Famotidine Group (n=69) | P value |
|---|---|---|---|
| Age (years) | 65.67 ± 14.76 | 66.62 ± 12.63 | 0.937 |
| Height (cm) | 170.67 ± 8.44 | 170.61 ± 8.03 | 0.966 |
| Weight (kg) | 73.14 ± 12.26 | 71.09 ± 11.02 | 0.320 |
| APACHE II score | 16.16 ± 3.68 | 14.38 ± 5.85 | **0.038** |
| Intubation time (days) | 8.38 ± 4.72 | 7.88 ± 4.89 | 0.505 |
| ICU length of stay (days) | 17.20 ± 6.55 | 13.84 ± 7.96 | **0.001** |

**Table 4- Incidence of Pneumonia and Mortality**

| Outcome | Pantoprazole Group (n=69) | Famotidine Group (n=69) | P value |
|---|---|---|---|
| Pneumonia incidence | 7 (10.1%) | 3 (4.3%) | 0.382 |
| Mortality | 8 (11.6%) | 5 (7.2%) | 0.562 |

**Table 5- Pathogens detected**

**strain Crosstabulation**

| | | | Strain | | | | Total |
|---|---|---|---|---|---|---|---|
| | | | No VAP | Acinetobacter | Klebsiella | Gram+ | |
| Group | Pantoprazole | Count | 62 | 4 | 2 | 1 | 69 |
| | | % within | 89.9% | 5.8% | 2.9% | 1.4% | 100.0% |
| | Famotidine | Count | 66 | 3 | 0 | 0 | 69 |
| | | % within | 95.7% | 4.3% | 0.0% | 0.0% | 100.0% |
| Total | | Count | 128 | 7 | 2 | 1 | 138 |
| | | % within | 92.8% | 5.1% | 1.4% | 0.7% | 100.0% |

**Table 6- Treatment Regimens**

| pneumonia treatment Crosstabulation * | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | Pneumonia treatment | | | | Total |
| | | | No VAP | colistin-meropenem | meropenem.levofloxacin | Gram+ | |
| Group | Pantoprazole | Count | 58 | 5 | 5 | 1 | 69 |
| | | % within | 84.1% | 7.2% | 7.2% | 1.4% | 100.0% |
| | Famtidine | Count | 63 | 3 | 3 | 0 | 69 |
| | | % within | 91.3% | 4.3% | 4.3% | 0.0% | 100.0% |
| Total | | Count | 121 | 8 | 8 | 1 | 138 |
| | | % within | 87.7% | 5.8% | 5.8% | 0.7% | 100.0% |

These findings suggest that both regimens are equally effective in managing VAP in critically ill patients, regardless of the stress ulcer prophylaxis (SUP) agent used.

**Clinical Pulmonary Infection Score (CPIS)**

The CPIS score, a measure of VAP severity, was compared between the two groups using the Mann-Whitney U test, which revealed no statistically significant differences ($p>0.05$) (Table 7).

**Table 7- CPIS score**

| Group | N | Mean CPIS Score | Std. Deviation |
|---|---|---|---|
| Pantoprazole | 11 | 6.45 | 2.02 |
| Famotidine | 6 | 7.83 | 2.04 |

## Discussion

PPIs or H2R are common agents for stress ulcer prophylaxis regimens in critically ill patients. PPIs are effective in increasing gastric pH and reducing the risk of clinically important bleeding compared to H2RAs [39-42]. This double-blinded, randomized clinical trial compared pantoprazole and famotidine in 138 ICU patients, with no significant differences in demographic variables such as age and weight between the two groups. The identified VAP-specific risk factors align with the findings from recent studies, emphasizing the multifaceted nature of VAP risk [43-45].

This study found the prevalence of neurological conditions as the primary reason for ICU admission in both the famotidine and pantoprazole groups, pointing to neurologic causes as a key risk factor for VAP. This is consistent with the understanding of several studies that neurological conditions can impair protective reflexes and increase aspiration risk [46-48].

The present study showed the APACHE II score, as an indicator of disease severity [49-50], lower in the famotidine group, which is consistent with a study conducted by Fook-Hong Ng in 2010; they found that famotidine may have a protective effect in some patients hospitalized in the ICU [51]. This suggests that famotidine may be linked to improved overall patient outcomes in this context, consistent with a multi-center randomized clinical trial in 2020, which found that famotidine may offer a protective benefit in some patients admitted to the intensive care unit [31]. Also, the reduction in length of stay in the famotidine group suggests that Famotidine may potentially improve the management of ICU patients. However, this finding contrasts with the latter study, indicating the need for further investigation [31].

In the present study, although there was no significant difference in the incidence of pneumonia between the two groups, pneumonia occurred less frequently in patients receiving famotidine. This result is consistent with a study investigating the effects of gastric acid secretion inhibitors for VAP that found no significant difference in pneumonia incidence between H2RAs and PPIs that have shown that PPIs may increase the risk of VAP [36], although the meta-analysis conducted by Eom et al. indicates that the use of proton pump inhibitors is related to an increased risk of pneumonia [52].

A lower mortality rate was observed in the famotidine group; this difference was not significant, which is in line with the study conducted by Song et al., which demonstrated no significant difference in mortality between the H2RA and PPI groups [26].

Both famotidine and pantoprazole demonstrated a favorable safety profile, with no significant differences in adverse events. This is consistent with previous studies reporting mild side effects and good tolerability for both drug classes. [39-40, 53]

No statistically significant differences were observed in CPIS or pneumonia criteria between the two groups. Several studies support this finding and reported similar outcomes for H2RAs and PPIs in terms of pneumonia-related criteria [28, 54].

Pathogen prevalence varies by location, antibiotic use, and intubation time [55]. Acinetobacter was the most common pathogen in VAP in the current study, with a prevalence of 9.8% in the pantoprazole group and 9.3% in the famotidine group, showing no significant difference ($p > 0.05$). This aligns with literature identifying Acinetobacter baumannii as a major VAP pathogen, especially in late-onset cases, with multidrug resistance rates reaching 79.9% in some regions [55-56]. Other frequent pathogens include Pseudomonas aeruginosa, Klebsiella pneumoniae, and MRSA [56-58].

The observed effectiveness of colistin-meropenem and meropenem-levofloxacin in managing VAP aligns with current clinical guidelines, which emphasize the importance of selecting antibiotics based on local resistance patterns and patient-specific risk factors for resistant pathogens (IDSA/ATS guidelines) [59-60]. Our findings suggest that both regimens are similarly effective in treating VAP, regardless of the SUP agent used. This is consistent with previous studies indicating that the choice of SUP does not significantly impact VAP incidence or treatment outcomes [36, 61].

## Conclusion

This study suggests that famotidine may be associated with more favorable clinical outcomes, including reduced ICU length of stay and disease severity, compared to pantoprazole. Famotidine may represent a suitable alternative for stress ulcer prophylaxis in ICU patients, particularly those with less severe illness. However, further research with a greater number of participants and a more sophisticated study design is needed to confirm these findings and optimize clinical decision-making.

### Limitations

The limitation of the current study was the small sample size, which may have limited the ability to detect small but clinically significant differences. The generalizability of the findings may be limited by single-centered data collection. The study did not account for other medication regimens or comorbidities that could influence outcomes.

Studies should include larger sample sizes and multicenter designs to enhance the generalizability and robustness of the findings. Investigate the long-term effects of famotidine and pantoprazole in ICU patients, including their impact on morbidity and mortality.

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