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Research Article

Effects of Proton Pump Inhibitors versus Histamine-2 Receptor Antagonists on Gastric pH and Stress Ulcer Incidence in Mechanically Ventilated Patients with ARDS in the ICU

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ABSTRACT

Background: Acute Respiratory Distress Syndrome (ARDS) is associated with an increased risk of stress-related mucosal disease (SRMD) due to hypoxemia, systemic inflammation, and prolonged mechanical ventilation. Stress ulcer prophylaxis is routinely administered in the intensive care unit (ICU), most commonly using proton pump inhibitors (PPIs) or histamine-2 receptor antagonists (H2RAs). Although PPIs provide more potent gastric acid suppression, their use has been associated with a higher risk of infection, and evidence regarding their superiority over H2RAs remains inconclusive. This study aimed to compare the efficacy of PPIs and H2RAs in maintaining gastric pH and preventing stress ulcers in mechanically ventilated patients with ARDS.

Methods: This single-blind randomized controlled trial included 40 adult patients diagnosed with ARDS who required mechanical ventilation. Participants were randomly assigned to receive either intravenous omeprazole 40 mg once daily (PPI group) or intravenous ranitidine 50 mg every 12 hours (H2RA group) for three days. Gastric pH was measured at baseline (day 1) and on day 4 using nasogastric aspirates.

Results: The PPI group demonstrated a statistically significant increase in gastric pH from day 1 to day 4 ($p = 0.012$), whereas no significant change was observed in the H2RA group ($p = 0.528$). The between-group comparison showed a significant difference in pH changes over time ($p = 0.024$), with the PPI group exhibiting a mean increase of 0.65 ± 0.99, while the H2RA group showed a mean decrease of 0.18 ± 1.21. However, there were no significant differences between groups in absolute gastric pH values on day 1 ($p = 0.265$) or day 4 ($p = 0.117$), nor in the incidence of stress ulcers ($p = 1.000$). ARDS severity did not differ significantly between groups on day 1 or day 4 ($p = 0.058$ and $p = 0.655$, respectively), and the proportion of patients with worsening ARDS severity was also comparable (30% vs. 15%, $p = 0.451$).

Conclusion: Both PPIs and H2RAs were effective for stress ulcer prophylaxis in mechanically ventilated ARDS patients, with similarly low rates of stress ulcer bleeding. Although PPIs resulted in a greater increase in gastric pH, this did not translate into superior clinical outcomes. Therefore, the choice between PPIs and H2RAs should consider not only their acid-suppressive effects but also potential

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adverse events, including infection risk.

Introduction

Acute respiratory distress syndrome (ARDS) is a severe respiratory disorder characterized by dyspnea, hypoxemia, and non-cardiogenic pulmonary edema. Its definition is commonly based on the Berlin criteria, revised from the American-European Consensus Conference (AECC) guidelines. The reported incidence in Australia is 34 per 100.000 for acute lung injury (ALI) and 28 per 100.000 for ARDS [1]. Several factors are associated with increased mortality in ARDS, including advanced age, shock, liver failure, elevated dead space fraction, a low oxygenation index during the first week of illness, and multiple organ failure. ARDS may also predispose patients to stress ulcers due to the systemic effects of critical illness and prolonged mechanical ventilation, particularly when ventilation exceeds 48 hours. This condition can result in splanchnic hypoperfusion and disruption of the gastric mucosal barrier. In addition, the physiological stress response increases gastrin release and gastric acid secretion, thereby heightening the risk of mucosal injury and ulcer formation [2].

Stress-related mucosal disease (SRMD), commonly referred to as stress ulceration, represents one of the most frequent upper gastrointestinal complications among critically ill patients in the intensive care unit (ICU). SRMD encompasses a spectrum of gastric mucosal abnormalities, ranging from asymptomatic superficial erosions to clinically significant gastrointestinal bleeding. First described in 1969 based on post-mortem findings, subsequent endoscopic studies have demonstrated that approximately 74–100% of critically ill patients develop gastric mucosal lesions within the first 24 hours of ICU admission [3].

The pathophysiology of SRMD is primarily related to physiological stress, which creates an imbalance between aggressive factors such as excessive gastric acid secretion and impaired mucosal defense mechanisms. Gastric mucosal hypoperfusion, ischemia, and systemic inflammatory activation are key contributors to stress ulcer development. Patients requiring mechanical ventilation for more than 48 hours, those with coagulopathy or liver disease, and individuals receiving certain medications are at particularly high risk [4].

To reduce the incidence of upper gastrointestinal bleeding, stress ulcer prophylaxis (SUP) has become standard practice in the ICU setting. The two principal pharmacologic classes used are proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs). PPIs provide more potent and sustained gastric acid suppression than H2RAs; however, their use has raised concerns regarding potential adverse effects, particularly an increased risk of nosocomial infections such as ventilator-associated pneumonia and Clostridioides difficile–associated diarrhea [5]. A large cohort study involving more than 35,000 mechanically ventilated patients reported a higher incidence of pneumonia (38.6% vs. 27%) and C. difficile infection (3.8% vs. 2.2%) in patients receiving PPIs compared with those receiving H2RAs [6]. In contrast, the PEPTIC randomized clinical trial found no significant difference between the two groups in the incidence of pneumonia (6.5% vs. 5.8%) or C. difficile infection (0.3% vs. 0.43%). Similar findings were observed in the SUP-ICU trial comparing PPIs with placebo [7].

Patients with ARDS represent a particularly vulnerable population for the development of stress ulcers due to severe hypoxemia, systemic inflammation, and the frequent need for prolonged mechanical ventilation. Effective prophylaxis in this group is crucial to prevent gastrointestinal bleeding, which may further compromise clinical outcomes.

Although PPIs are widely used as first-line agents for stress ulcer prophylaxis, there remains no clear consensus regarding their superiority over H2RAs in terms of efficacy and safety, particularly among patients with ARDS. Therefore, this study aimed to compare the effectiveness of PPIs and H2RAs in maintaining gastric pH and preventing stress ulcer occurrence in mechanically ventilated ARDS patients in the ICU.

Methods

This study was a single-blind randomized controlled trial conducted among adult patients with Acute Respiratory Distress Syndrome (ARDS) who required mechanical ventilation at Wahidin Sudirohusodo Hospital, Makassar, between March and July 2025. The minimum required sample size was 40 patients, who were randomly allocated into two equal groups: the PPI group (omeprazole) and the H2RA group (ranitidine).

Eligible participants were patients aged 18–65 years who met the diagnostic criteria for ARDS. Exclusion criteria included pregnancy, disseminated intravascular coagulation (DIC), known hypersensitivity to the study drugs, or pre-existing major gastrointestinal complications such as active stress ulcers. Patients were withdrawn from the study if they developed a hypersensitivity reaction to the study medication, died during the study period, or were withdrawn by the treating physician or family.

Following insertion of a nasogastric tube (NGT), baseline gastric fluid samples were collected prior to the administration of prophylactic therapy for pH measurement. The PPI group received intravenous omeprazole 40 mg once daily, while the H2RA group received intravenous ranitidine 50 mg every 12 hours for

three consecutive days. On day 4, a second gastric fluid sample was collected for pH analysis. All laboratory examinations were performed according to standard operating procedures in the hospital's clinical pathology laboratory.

Throughout the study period, the occurrence of stress ulcers was assessed clinically based on evidence of hematemesis, melena, or the presence of blood in NGT aspirates. Demographic characteristics, nutritional status (body mass index, BMI), ARDS severity based on the PaO_2/FiO_2 ratio, and other relevant clinical data were obtained from patients' medical records.

Statistical analysis was performed using SPSS version 27. Normally distributed continuous variables were analyzed using paired and independent t-tests. Non-normally distributed data were analyzed using the Wilcoxon signed-rank test and the Mann–Whitney U test. Categorical variables were analyzed using Fisher's exact test or the likelihood ratio test, as appropriate. A p-value < 0.05 was considered statistically significant. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Hasanuddin University (No. 183/UN4.6.4.5.31/PP36/2025).

Results

This study included 40 ICU patients with ARDS, who were randomly divided into two groups based on stress ulcer prophylaxis: the PPI group (omeprazole) and the H2RA group (ranitidine). The sample characteristics are presented in (Table 1). Baseline characteristics such as age, sex, BMI, comorbidities, and ARDS severity were comparable between groups, with no significant differences ($p > 0.05$). In (Table 2), we presented the first and fourth day gastric pH. Intragastric pH analysis showed that PPI administration significantly increased gastric pH from day 1 to day 4 (median 6.0 to 6.5, $p = 0.012$). In the H2RA group, there was no significant difference between the first and fourth day gastric pH ($p=0.528$). The use of H2RA did not show significant changes in gastric pH in patients admitted to the ICU with ARDS. From (Table 3), it can be seen that direct comparison revealed no significant differences in gastric pH between groups on day 1 ($p = 0.265$) or day 4 ($p = 0.117$). However, the change in gastric pH was significantly greater in the PPI group compared to the H2RA group ($p = 0.024$). This suggests that the two ulcer prophylactic agents differ in affecting gastric pH changes as stress ulcer prophylactic agents in patients admitted to the ICU with ARDS. (Figure 1-3).

In (Table 4), we presented a comparison of the incidence of stress ulcers. The incidence of stress ulcers was equal in both groups, with three cases reported in each ($p = 1.000$). This indicates the selection of stress ulcer prophylactic agents is not associated with the incidence of stress ulcers in patients admitted to the ICU with ARDS.

In (Table 5), we presented a comparison of the incidence of ARDS progression from the administration of PPIs and H2RAs. ARDS severity did not differ significantly between groups on day 1 and day 4 ($p = 0.058$ for PPI, $p = 0.655$ for H2RA). This indicates that the use of PPI and H2RA agents for stress ulcer prophylaxis did not cause changes in the development of ARDS. (Table 6) showed the comparison of ARDS degree progression between the two groups. The trend of increasing ARDS degree was higher in PPI vs. H2RA group, 6 (30%) vs. 3 (15%). However, the difference was not statistically significant.

Table 1- Characteristics of research subjects

Characteristics	PPI group (n = 20)	H2RA group (n = 20)	P value
Age (years)	47.85 ± 13.02	46.90 ± 13.29	0.821[a]
Gender			
Male	8	7	1.000[c]
Female	12	13	
TB	155 (145-170)	160 (150-170)	0.221[b]
BB	56.2 ± 8.5	61.4 ± 12.3	0.128[a]
BMI (kg/m2)	22.60 ± 2.77	23.65 ± 3.84	0.330[a]
ARDS Degree			
Mild	9	10	0.237[d]
Moderate	9	10	
Severe	2	0	
Comorbidities			
Neoplasma	1	0	0.073[d]
Shock	1	0	
Burn	1	0	
Infection/Sepsis	9	4	
Trauma/Cerebrovascular Disease	7	11	
Renal Failure	1	2	

Autoimmune/Endocrine	0	3

Numerical data are displayed as mean, ± standard deviation, or median (min-max). Categorical data are displayed as frequency (n). [a]*Independent T test,* [b]*Mann-Whitney test,* [c]*Fisher's exact test,* [d]*likelihood ratio*.

Table 2- Effect of PPI and H2RA on gastric pH

Group	Gastric pH		P value
	Day 1	Day 4	
Proton Pump Inhibitor (PPI)	6.0 (5.0-8.0)	6.5 (5.0-8.5)	0.012[b]
H2 Receptor Antagonist (H2RA)	6.38 ± 1.13	6.20 ± 0.80	0.528[a]

Data were tested by [a]*Paired T test,* [b]*Wilcoxon Z test.*

Table 3- Comparison of the Effect of PPI and H2RA on Gastric pH

Gastric pH	PPI group	H2RA group	P value
First day	6.0 (5.0-8.0)	6.5 (5.0-8.5)	0.265[b]
Fourth day	6.63 ± 0.87	6.20 ± 0.80	0.117[a]
Gastric pH change	0.65 ± 0.99	-0.18 ± 1.21	0.024[a]

Data were tested by [a]*Independent t-test,* [b]*Mann-Whitney U test*.

Table 4- Comparison of the Effect of PPI and H2RA on Stress Ulcer Incidence

Stress Ulcer Incidence	PPI group	H2RA group	P value
Yes	3	3	1.000[a]
No	17	17	

Data were tested by [a]*Fisher's exact test*.

Table 5- Comparison of the Effect of PPI and H2RA on ARDS Development

Group	ARDS Severity Day 1	ARDS Severity Day 4	P value
Proton Pump Inhibitor (PPI)	2 (1-3)	2 (1-3)	0.058[a]
H2 Receptor Antagonist (H2RA)	1.5 (1-2)	2 (1-2)	0.655[a]

Data were tested by [a]*Wilcoxon Z test.*

Table 6- Comparison of the Effect of PPI and H2RA on ARDS Severity Progression

Group	Not Increased	Increased	P value
Proton Pump Inhibitor (PPI)	14	6	0.451[a]
H2 Receptor Antagonist (H2RA)	17	3	

Data were tested by [a]*Fisher's exact test*.

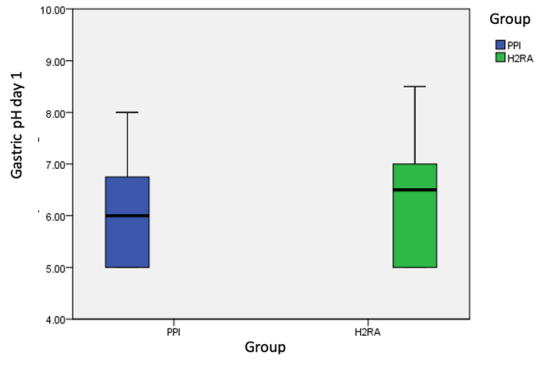

Figure 1- Comparison of gastric pH on day 1 between groups

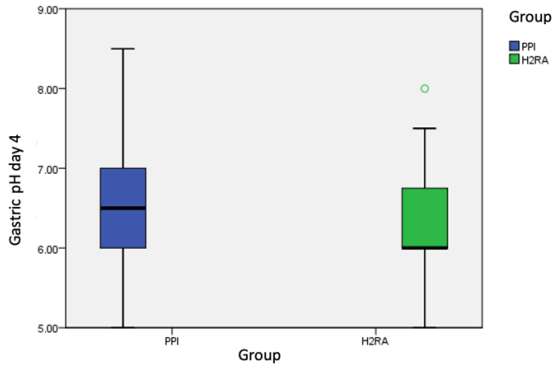

Figure 2- Comparison of gastric pH on day 4 between groups

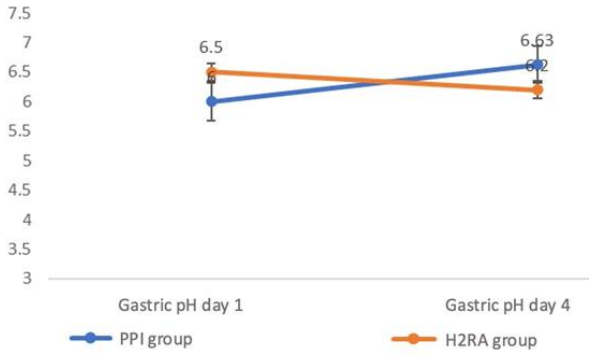

Figure 3- Comparison of gastric pH day 1 and day 4 changes between groups

Discussion

This study was conducted in 40 ICU patients diagnosed with ARDS who received stress ulcer prophylaxis (SUP) using two different classes of agents, namely proton pump inhibitors (PPIs) and H_2 receptor antagonists (H_2RAs). The baseline characteristics of the patients, including age, sex, body mass index, and comorbidities, showed no significant differences between the groups, indicating that they were comparable. This comparability strengthens the validity of assessing the effects of PPIs and H_2RAs on gastric pH and the incidence of stress ulcers during ICU admission.

The findings demonstrated that administration of PPIs for four days significantly increased gastric pH, from a median of 6.0 to 6.5. These results are consistent with the study by Stollman et al., which reported that intravenous omeprazole increased gastric pH to 7.1 from an initial mean pH of 3.5 within four hours of administration [8]. The elevation of gastric pH observed with PPIs reflects their superior ability to suppress gastric acid secretion in a more potent and sustained manner compared with other agents.

In contrast, the use of H_2RAs did not produce a significant change in gastric pH, with a mean pH of 6.38 on day one and 6.20 on day four. The study by Stollman et al. also suggested that the effectiveness of H_2RAs in maintaining intragastric pH above 4 remains uncertain, particularly when administered intermittently [8]. This may be attributed to the shorter half-life of H_2RAs compared with PPIs, resulting in less sustained acid suppression. Direct comparison between the groups revealed a significant increase in gastric pH only in the PPI group, whereas the H_2RA group showed a non-significant decline in pH.

A Cochrane meta-analysis of 18 studies concluded that PPIs are more effective than H_2RAs in suppressing gastric acid secretion. Furthermore, a study by Brett et al. confirmed that PPIs are more effective in increasing intragastric pH among critically ill patients. These differences in therapeutic response suggest distinct pharmacodynamic properties between the two drug classes, which have important clinical implications when selecting prophylactic agents for stress ulcers in ICU patients [9].

Nevertheless, excessive elevation of gastric pH may carry potential risks. It has been hypothesised that gastric alkalinisation associated with PPIs may promote colonisation by pathogenic microorganisms, thereby increasing the risk of ventilator-associated pneumonia (VAP). Consequently, the observed differences in gastric pH may warrant further investigation into the impact of PPIs and H_2RAs on the incidence of VAP and other clinical outcomes in critically ill patients.

Despite the differing effects on gastric pH, this study found no significant difference in the incidence of stress ulcers between the PPI and H_2RA groups. This finding is consistent with the study by Song et al., which compared the effectiveness of PPIs and H_2RAs in preventing gastrointestinal bleeding in ICU patients and reported comparable clinical outcomes in preventing clinically significant stress ulcers [10]. Similarly, a retrospective analysis by Kong et al. found no clear superiority of either H_2RAs or PPIs and emphasised the importance of considering individual patient characteristics and disease severity when selecting the most appropriate SUP regimen [11].

Changes in ARDS severity were also comparable between the groups, although there was a greater tendency towards clinical deterioration in the PPI group (30% vs 15%). This trend may be related to the higher gastric pH observed in the PPI group, which could predispose patients to VAP and potentially exacerbate ARDS.

This study has several limitations. It was conducted in a single academic centre, and the parameters assessed were limited to gastric pH and the incidence of stress ulcers. Additionally, the complex clinical conditions of ICU patients such as gastrointestinal hypoperfusion, the use of vasopressors, corticosteroids, anticoagulants, and

enteral nutrition may influence drug absorption and gastric pH levels, thereby complicating the interpretation of the specific effects of PPIs and H_2RAs.

Conclusion

Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs) demonstrated equivalent effectiveness in preventing stress ulcer events among mechanically ventilated patients with ARDS in the ICU. PPIs produced a significant increase in gastric pH, whereas H_2RAs did not result in a statistically significant change. These findings indicate that, although both agents provide comparable clinical outcomes in terms of stress ulcer prevention, PPIs achieve a greater degree of acid suppression. This difference should be carefully considered in light of potential risks, such as infection, when selecting the most appropriate prophylactic strategy.

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