Indexed by : DOAJ Google Crossref Dimension sinta GARUDA

J.Biomed.Transl.Res
ISSN: 2503-2178

JOURNAL OF BIOMEDICINE AND TRANSLATIONAL RESEARCH

Available online at JBTR website: https://jbtr.fk.undip.ac.id

Original Research Article

Rationality of Use and Effectiveness of Stress Ulcer Prophylaxis in Critically Ill Patients: An Experience from A Tertiary Intensive Care Unit

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Article Info
History
Received: 17 Nov 2022
Accepted: 15 Dec 2022
Available: 30 Dec 2022

Abstract

Background: Stress-related mucosal disease (SRMD) frequently develops in critically ill patients, increasing mortality and length of intensive care unit (ICU) stay. There is limited data on stress ulcer prophylaxis (SUP) on critically ill patients in Indonesia.

Objective:

Methods: This is a retrospective cohort study of patients admitted to the ICU from January 1, 2015, to December 31, 2017. The subjects were all ICU patients who used proton pump inhibitor (PPI) and histamine-2 receptor antagonist (H2RA) as SUP therapy**.**

Results: A total of 315 patients were included, and the mean age was 48 years. Approximately 55.2% were women, and 62.8% of patients were admitted to ICU following high-risk surgery. PPI was given to 187 patients (59.4%) and H2RA to 128 patients (40.6%), with an average usage of 5 days. The incidence of SRMD was 15.9% (n = 50), and the mean length of stay in the ICU was 6 days. Gender, age, duration of SUP, and ICU length of stay of the PPI and H2RA groups were not statistically different ($p > 0.05$) and did not affect the GI event ($p > 0.05$). The use of rational SUP was 98.4%. The Major American Society of Health-System Pharmacists (ASHP) risk factor criteria was ventilator use (86.8%), while the minor ASHP criteria was anticoagulant therapy (22.2%). The incidence of GI events was significantly lower in PPI group than in H2RA group ($p < 0.05$).

Conclusions: The use of SUP is rational with an average use of 5 days. PPI is superior to H2RA for SRMD prophylaxis.

Keywords: *upper gastrointestinal bleeding, critically ill, risk factors, proton pump inhibitor, ICU*
Permalink/ DOI: https://doi.org/10.14710/jbtr.v8i3.16387

INTRODUCTION

Stress-related mucosal disease (SRMD) and subsequent stress ulcer bleeding frequently occur in critically ill patients as a result of both underlying disease and therapeutic intervention, increasing mortality and length of ICU stay.[1] Mucosal damage was found in 75% to 100% of ICU patients within the first 24 hours of admission.[2,3] An international prevalence study by Krag et al. reported that 27 of 1,034 patients (2.6%) developed clinically important gastrointestinal (GI) bleeding, and 49 patients out of 1,034 (4.7%) experienced at least one incident of overt GI bleeding while they were in the ICU.[4] Each episode of gastrointestinal bleeding causes an increase in the length of ICU stay, additional laboratory tests, additional blood product transfusions, and hospital costs. Complications of gastrointestinal bleeding that affect hemodynamics increase mortality up to four times.[2]

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Table 1. Demographic characteristics and patient baseline

Variable	Frequency	%	Mean ± SD	Median (min – max)
Sex				
Male	141	44.8		
Female	174	55.2		
Age			48.79 ± 15.19	51 (18 – 85)
≤ 25	32	10.2		
26 – 35	36	11.4		
36 – 45	49	15.6		
46 – 55	77	24.4		
56 – 65	84	26.7		
> 65	37	11.7		
GI event				
Yes	50	15.9		
No	265	84.1		
Stress ulcer prophylaxis (SUP)				
PPI	187	59.4		
H2RA	128	40.6		
Duration of SUP administration			5.23 ± 4.50	4 (0 – 47)
1 – 7 days	269	85.4		
8 – 14 days	36	11.4		
> 14 days	10	3.2		
ICU stay			6.09 ± 3.50	5 (1 – 30)
1 – 7 days	253	80.3		
8 – 14 days	49	15.6		
> 14 days	13	4.1		
ICU admission indication				
Surgical	198	62.8		
Medical	117	37.1		

Table 2. Risk factor of stress-related mucosal disease

Variable	Frequency	%	Mean ± SD	Median (min – max)
Major risk factor				
1. Coagulation disorders				
Yes	52	16.5		
No	263	83.5		
2. Duration of mechanical ventilator use			4.82 ± 2.99	4 (2 – 22)
1 – 7 days	243	86.8		
8 – 14 days	27	9.6		
> 14 days	10	3.6		
Minor risk factor				
1. Severe head trauma	6	1.9		
2. Hepatic failure	6	1.9		
3. Renal insufficiency	53	16.8		
4. Sepsis	23	7.3		
5. Hypotension	24	7.6		
6. High dose corticosteroid	45	14.3		
7. Anticoagulation therapy	70	22.2		
8. Thermal injury > 35 %	0	0		
9. Major surgery > 4 hours	16	5.1		
10. Acute lung injury	69	21.9		

Practice guidelines have consistently recommended prophylaxis for patients in the ICU with bleeding risk factors. SUP is commonly used in the ICU and is recommended internationally.[5] According to several risk classifications, the American Society of Health-System Pharmacists (ASHP) guidelines are devised and applied when providing SUP to critically ill patients. Acid suppression therapy is frequently administered using PPI, H2RA, and sucralfate.[6]

However, the evidence base for SUP is extremely limited and outdated. This has raised many key questions about the medications used and the overall benefit of SUP. Concerns about the side effects of SUP have increased with the inconsistent use of SUP in the ICU. Some evidence has shown that there is an increased risk of overuse of these drugs in ICU patients. Frandah et al. conducted a prospective study about SUP administration for SRMD in patients admitted to the ICU. The authors discovered that 82% of the 99 newly admitted ICU patients received SUP without indication, and 53% either received underuse or overuse of SUP.[3] Furthermore, the adverse effects of taking SUP, like pneumonia and Clostridium difficile infection, prompted many investigations to evaluate SUP prescribing in ICU patients.[2,7,8,9,10]

Although there are international guidelines about SUP use, previous studies have addressed the problem of inconsistent use of SUP in ICU patients involving both underutilization and overutilization. Moreover, there is insufficient research regarding SUP use evaluation on ICU patients in Indonesia. Therefore, this retrospective study was conducted to examine the administration of SUP, including the rationality, duration, and effectiveness of the type of SUP in ICU patients at Dr. Kariadi Hospital Semarang.

MATERIALS AND METHODS

The sample size was determined using a consecutive and convenient sampling technique based on the number of patients admitted to the ICU over the three-year study period (January 1, 2015–December 31, 2017). Data collection was carried out for 3 months from medical records of ICU patients. These were closed ICU with both medical and surgical patients. During that period, a total of 692 patients were admitted to the ICU of Dr. Kariadi Hospital. This retrospective observational cohort study included 315 subjects who met the inclusion and exclusion criteria. The research subjects were all ICU patients who received PPI or H2RA therapy as prophylactic therapy for SRMD. Patients admitted with gastrointestinal bleeding and patients receiving combination therapy with both PPI and H2RA or changing regimens in the middle of treatment were excluded. This study was approved by the Health Research Ethics Committee of Dr. Kariadi General Hospital Semarang (number 1006/EC/KEPK-RSDK/2022). This study aimed to evaluate the rationality of administering SUP to critically ill patients, including the type, duration of administration, and its effect on GI events.

The inclusion criteria were based on ASHP guidelines: age ≥ 18, been treated in the ICU of Dr. Kariadi Hospital within 2 days with at least one of the major criteria for coagulopathy (including treatment of induced coagulopathy, platelet count < 50,000 mm3, INR > 1.5, or PTT > 2× normal value) or respiratory failure using a mechanical ventilator for 48 h, or two minor criteria, i.e., spinal cord injury, multiple trauma, liver failure (AST > 150 U/L, ALT > 150 U/dl or total bilirubin level > 5 mg/dl), head trauma with GCS 10 or unable to perform simple commands, history of gastric ulcer or gastrointestinal bleeding for 1 year before hospital admission, sepsis/septic shock (using vasopressors and/or positive culture of suspected microorganism), duration of ICU stay > 1 week, major surgery > 4 hours (including abdominal surgery but gastric surgery was excluded), acute lung injury, thermal injury > 35% and high-dose corticosteroid therapy (250 mg/day).

Patient characteristics, risk factors for SRMD, SUP obtained in ICU, duration of SUP use, and GI event were all recorded on the data collection sheet. GI events were defined as upper and lower gastrointestinal mucosal injuries that we observed as GI bleeding with evidence of hematemesis, melena, hematochezia, coffee ground emesis, or nasogastric aspiration of blood. Appropriate use of SUP was defined as beginning SUP administration in the presence of two or more minor risk factors or one or more major risk factors. According to ASHP recommendations, prophylaxis is advised for ICU patients with coagulopathy or those who need mechanical ventilation for longer than 48 h. In addition, prophylaxis is also advised for ICU patients with a history of GI ulcer or bleeding within 1 year prior to admission.[6]

The data were collected and entered into a Microsoft Excel spreadsheet. Data were performed by SPSS software (IBM statistic 21.0) and described for categorical data (with frequency, percentage, mean ± SD) and displayed in tabular form. Pearson's Chi-square analysis was performed to test patient characteristics and therapy effectiveness.

RESULTS

In this study, 692 patients were hospitalized in the ICU from January 2015 to December 2017. A total of 377 patients were excluded because they received a combination therapy of gastric acid suppressants PPI and H2RA. Of 315 samples of this study, 187 received PPI therapy, and 128 received H2RA.

Table 1 lists the demographic and baseline characteristics of the patients. The mean age was 48 years (range = 25–65), and 55.2% were women. Most patients were admitted to the ICU for surgical indications, and the widely prescribed SUP was a PPI with an average use of 5 days. There were 50 patients (15.9%) who experienced the incidence of SMRD. The average length of ICU stay was 6 days.

Table 2 presents the major ASHP risk factors that often occur in critically ill patients when entering the ICU. In our study, the most common factors for the incidence of SMRD included mechanical ventilator use (86.8%) with the longest duration of ventilator use being 4 days on average, in the range of 1–7 days, and coagulation disorders (16.5%). In addition, the six highest minor risk factors were the use of anticoagulant therapy (70 samples, 22.2%), acute lung injury (69 samples, 21.9%), renal insufficiency (53 samples, 16.8%), the use of high-dose corticosteroids (45 samples,

14.3%), hypotension (24 samples, 7.6%), and sepsis (23 samples, 7.3%).

Table 3. Rationalization of SUP use

Variabel	Total	%
Rationalization of SUP use		
Appropriate	310	98.4
Inappropriate	5	1.6

As presented in Table 3, 310 samples (98.4%) received SUP rationally according to the ASHP criteria, while 5 samples (1.6%) did not meet the indications of SUP according to the ASHP criteria. Samples that did not meet the indications of SUP came with a diagnosis of NSTEMI, which is a minor risk factor for SMRD and requires an anticoagulant therapy which according to ASHP criteria does not require SUP administration.

As presented in **Table 4**, the characteristics of gender, age, duration of SUP use, and length of ICU stay between the PPI and H2RA groups are not statistically significant ($p > 0.05$). **Table 5** presents the relationship between patient's characteristics and GI events. It is known that gender, age, duration of SUP use, length of ventilator use, and length of stay do not affect GI events ($p > 0.05$).

The results of this study (Table 6) show that the incidence of GI events was significantly lower in PPI group than H2RA group ($p < 0.05$). The PPI group obtained 11 (22%) incidences of GI events, while H2RA had 39 (78%) incidences where the PPI group had more samples than the H2RA.

DISCUSSION

In this research, no statistically significant difference was found between the PPI and H2RA groups in terms of gender, age, length of ICU stay, and duration of SUP use ($p > 0.05$). Similarly, a cluster randomized clinical trial conducted at 50 ICUs in 5 countries involving patients requiring invasive mechanical ventilation within 24 h of ICU admission concluded that hospital lengths of stay were not significantly different in the PPI and H2RA groups.[11]

ASHP is the only therapeutic guideline stating that it is necessary to use SRMD prophylaxis in patients admitted to the ICU with major categories in the form of coagulopathy and respiratory failure followed by the use of mechanical ventilators for 48 h, as well as several minor categories.[6] An observational study conducted by Marilena et al. presented that mechanical ventilation was the most common indication for SUP.[12] Our findings are also in line with Marilena's research that ventilator use is the most common risk factor in ICU patients who experienced SRMD.

The interaction between critical illness and mechanical ventilation is complex. Among several mechanisms suggested to explain how mechanical ventilation unfavorably affects the GI tract, splanchnic hypoperfusion appears to be particularly important. The state of gastric mucosal hypoperfusion results in an imbalance between oxygen supply and demand which eventually leads to gastrointestinal complications such as SRMD.[13,14] Therefore, SUP (particularly PPI) should be advised for patients with obvious risk factors such as prolonged mechanical ventilation of at least two days.[1] According to a national survey conducted in Canada, SUP was the primary medication provided by doctors in the majority of ICUs (80%). It is currently unknown the effect and safety of long-term use of SUP on patients with risk factors.[8,15]

Stress related mucosal disease is associated with morbidity and mortality in critically ill patients, the prevention of SRMD is an important consideration.[9] Clinically important upper gastrointestinal bleeding was reported in 1.3% of the PPI group and 1.8% of the H2RA group.[11] A study by Krag et. al regarding the prevalence and outcome of gastrointestinal bleeding in acutely ill adult intensive care patients found that 7.3% of patients experienced GI bleeding during the ICU stay.[4] In our study, the incidence of SMRD was higher than the previous study, i.e., 3.5% in PPI group and 12.4% in H2RA group. This difference could be due to the different subject characteristics in our study compared to Krag's study. In our study, subjects on mechanical ventilation were 86.8% vs. 52.6% in Krag's study. Patients with coagulation disorders were also found to be more common in our study at 16.5% vs. 12.4% in the previous study. The use of anticoagulant therapy, which is a minor risk factor, was also higher in our sample at 22.2% vs. 13.0% in the previous study.

According to a recent meta-analysis, SUP by PPIs or H2RAs is only beneficial and recommended in patients with a high risk of gastrointestinal bleeding. The bleeding was reduced to 20–49 per 1000 patients in patients with high bleeding risk (>4%). However, neither PPIs nor H2RAs significantly decreased the incidence of gastrointestinal bleeding in patients with low (2%) and moderate (2%–4%) risk levels. Compared to H2RAs or sucralfate, the reduction in PPIs group was greater.[16]

The administration of SUP has been recommended for high-risk patients in the ICU, but its inappropriate use increases the burden of health care costs and morbidity.[17] A prospective study of SUP administration pattern for patients admitted to the ICU by Frandah et al. discovered that 82% of the 99 newly admitted ICU patients received SUP without indication. In addition, 53% obtained underutilization or overutilization of SUP.[3] Meanwhile, in a retrospective study in Iran, the administration of SUP did not comply with the ASHP guidelines in about 93.1% of cases in noneducational hospitals and 84.6% of cases in teaching hospitals.[18] In this study, the inappropriate administration of SUP was only 1.6%, and this irrational prescribing was different from previous reports in the literature.[3,18]

Table 6. Relationship between Stress ulcer prophylaxis (SUP) and GI events

Variabel	GI event				P
	Yes		No		
	n	%	n	%	
Stress ulcer prophylaxis (SUP)					
PPI	11	22.0	176	66.4	0.003
H2RA	39	78.0	89	33.6	

Table 4. Relationship between characteristics and stress ulcer prophylaxis

Variable	*Stress Ulcer Prophylaxis*				P
	PPI		H2RA		
	n	%	n	%	
Sex					
Male	82	43.9	59	46.1	0.694
Female	105	56.1	69	53.9	
Age					
≤ 25	13	7.0	19	14.8	0.264
26 – 35	20	10.7	16	12.5	
36 – 45	32	17.1	17	13.3	
46 – 55	48	25.7	29	22.7	
56 – 65	53	28.3	31	24.2	
> 65	21	11.2	16	12.5	
Duration of SUP administration					
1 – 7 days	158	84.5	111	86.7	0.548
8 – 14 days	24	12.8	12	9.4	
> 14 days	5	2.7	5	3.9	
ICU stay					
1 – 7 days	154	82.4	99	77.3	0.432
8 – 14 days	25	13.4	24	18.8	
> 14 days	8	4.3	5	3.9	

Table 5. Relationship between characteristics and GI event

Variable	GI event				P
	Yes		No		
	n	%	n	%	
Sex					
Male	25	50.0	116	43.8	0.417
Female	25	50.0	149	56.2	
Age					
≤ 25	3	6.0	29	10.9	0.399
26 – 35	4	8.0	32	12.1	
36 – 45	12	24.0	37	14.0	
46 – 55	14	28.0	63	23.8	
56 – 65	11	22.0	73	27.5	
> 65	6	12.0	31	11.7	
Duration of SUP administration					
1 – 7 days	45	90.0	224	84.5	0.601
8 – 14 days	4	8.0	32	12.1	
> 14 days	1	2.0	9	3.4	
Duration of mechanical ventilator use					
1 – 7 days	39	88.6	204	86.4	0.868
8 – 14 days	4	9.1	23	9.7	
> 14 days	1	2.3	9	3.8	
ICU stay					
1 – 7 days	41	82.0	212	80.0	0.944
8 – 14 days	7	14.0	42	15.8	
> 14 days	2	4.0	11	4.2	

Another retrospective study by Alqudah et al. reported the frequency of inappropriate prescription of PPI for SUP during hospitalization in 236 patients in a Jordanian tertiary hospital. Their study found that 86% of the patients did not require SUP because they did not have at least one major or two minor indications.[19]
Barletta et al. assessed all prescriptions for GI drugs in 37 ICUs in the United States over a 24-h period. They found that the majority of GI drugs were prescribed for stress ulcer prophylaxis, and 76% of GI drugs used as SUPs were PPIsPPI provides more potent acid inhibition than H2RAs.[20]

The usage of PPIs has increased in other parts of the world. Based on a recent survey of 97 ICUs in 11 countries, intensivists stated that PPIs were preferred as SUP agents (66%) over H2RAs (31%).[21] This study is consistent with our research where PPIs were more widely used as SUP.

Oral PPIs have been shown in numerous studies to be superior to H2RA for SUP, whereas intravenous PPIs have not been widely evaluated. In a meta-analysis comparing the efficacy and safety of PPI and H2RA for the upper GI bleeding prevention of ICU patients, PPI was more effective in reducing overt GI bleeding (RR 0.35; 95% CI 0.21–0.59; $p < 0.0001$; I 2 = 15%) and clinically important GI bleeding (RR 0.36; 95% CI 0.19–0.68; $p = 0.002$; I 2 = 0%) than H2RA.[15] Another study reported that PPIs were superior to H2RA in reducing the risk of overt GI bleeding (RR 0.48; 95% CI 0.34, 0.66; $P < 0.0001$; I2 = 3%) and clinically important GI bleeding (RR 0.39; 95% CI 0.21, 0.71; $P = 0.002$; I2 = 0%,).[8] The authors concluded that PPIs are clinically feasible, effective, and safe for SUP in ICU patients. In line with the studies mentioned above, our study also showed that the incidence of GI events was significantly lower in PPI group than in H2RA group.

The duration of SUP administration is quite varied. In a previous study examining the use of SUP in cardiac surgery patients, the duration of PPI use was 4–7 days, while H2RA was 4–8 days.[22] The average use of SUP in our research was 5 days, which was slightly longer than the latest study in South Africa which was 3 days.[23]
There are few limitations to our study. Patient follow-up was not done until the patient was discharged, the misuse of SUP after discharge was unknown, and we have no reports on whether our patients experienced any of the SUP overuse health-related issues during the follow-up period. Our findings suggest that SRMD is common in critically ill patients with higher rates than in previous studies; therefore, SUP administration is crucial but must remain rational. With the high proportion of patients being treated with acid suppressants, future large-scale studies are needed to explore the potential benefit versus harm of this prophylaxis.

CONCLUSION

The use of SUP agents in the ICU of Dr. Kariadi Hospital Semarang has met the ASHP criteria. PPIs are the most frequently used drugs as SUP. PPI agents are superior to H2RA for SRMD prophylaxis. The use of SUP to prevent the occurrence of SMRD is rational with an average use of 5 days.

ACKNOWLEDGMENTS

Thank you to dr. Debby Vania as a research assistant of Internal Medicine at RSUP Dr. Kariadi Semarang who helped this publishing process.

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