

## Clinical Study

# Adherence to stress-related mucosal damage prophylaxis guideline in patients admitted to the Intensive Care Unit

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## ABSTRACT

**Objective:** Concern about adverse effects of the inconsistent use of stress-related mucosal damage prophylaxis in intensive care unit (ICU) is increasing. Hence, this study was designed to prospectively evaluate the rate of inappropriate stress ulcer prophylaxis (SUP) administration upon ICU admission, at ICU discharge and determine the adherence to American Society of Health-System Pharmacists (ASHP) guideline during ICU stay.

**Methods:** In this study, 200 patients were randomly selected from all ICU admissions during 9 months. Risk factors of stress ulcer were recorded daily during ICU stay and appropriateness of SUP administration was assessed according to the ASHP criteria.

**Findings:** Of all 160 (80%) patients who received SUP, 44.4% did not have indication; and among 95 patients with an indication for SUP administration, 6.3% did not receive it upon ICU admission. Consequently, 77 (38.5%) of 200 patients received inappropriate prophylaxis on ICU admission. In addition, 53.5% of patients had appropriate adherence to ASHP guideline during all days of ICU stay (44% and 2.5% of patients received SUP more than 120% and <80% of appropriate SUP duration, respectively). Moreover, 81.2% were continued on inappropriate prophylaxis upon transfer from the ICU.

**Conclusion:** We concluded that although SUP administration included both overutilization and underutilization in this ICU, but high prevalence of SUP overutilization caused unnecessary hospital costs, personal monetary burden, and may increase adverse drug reactions. Therefore, educating physicians and cooperation of clinical pharmacists regarding implementing standard protocols could improve patterns of SUP administration.

**Keywords:** Intensive Care Unit; stress ulcer prophylaxis; stress-related mucosal damage

## INTRODUCTION

Gastrointestinal (GI) stress ulcer are common in critically ill patients who require admission to

Intensive Care Unit (ICU), whereas 75–100% of ICU patients experience mucosal injury as early as the first 24 h of ICU admission.<sup>[1,2]</sup> Moreover, occult bleeding

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occurs in 15–50% of critically ill patients and 5–25% of these patients experience overt bleeding if they do not receive stress ulcer prophylaxis (SUP).<sup>[3]</sup>

Therefore, prophylaxis of stress-related mucosal damage (SRMD) in ICU patients became routine care from many years ago, and guidelines such as American Society of Health-System Pharmacists (ASHP) guideline were developed and used for SUP administration in critically ill patients according to different risk categories.<sup>[4]</sup>

High morbidity and mortality of stress ulcer-related bleeding and concerns about cost and adverse effects of SUP administrations such as pneumonia and *Clostridium difficile* infections, provoked different studies to determine the pattern of SUP prescription in ICU and non-ICU patients.<sup>[2-13]</sup>

Proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H<sub>2</sub> blockers), and sucralfate are usually used for acid suppression therapy in ICU patients.

Some evidence have illustrated that there is an increased risk for overutilization of these medications in such patients. In 2014, Frandah *et al.* prospectively studied the pattern of SUP administration for patients admitted to ICU. The authors found that of the 99 new ICU admissions, 82% received SUP without any indication. Moreover, 53% either received underutilization or overutilization of SUP.<sup>[2]</sup>

Another study retrospectively studied all ICU admissions for 4 months. Among 210 studied patients, 87.1% received SUP, whereas 68.1% of them did not have any risk factor.<sup>[14]</sup>

Previous studies have addressed the issue of the inconsistent use of SUP in the ICU patients which includes both underutilization and overutilization, however, there is not enough information regarding this concern in developing countries. On the other hand, to the best of our knowledge, there is not any information about adherence to SUP guideline during ICU stay. Therefore, this study was designed to prospectively evaluate the rate of inappropriate SUP administration upon ICU admission and determine the adherence to ASHP guideline (prevalence of overutilization or underutilization of SUP administration) during ICU stay.

## METHODS

We prospectively evaluate the patterns of SUP administration in patients admitted to the ICU at an 800 tertiary referral academic medical center during 9 months (January to October 2014). This general, medical and surgical ICU has 63 beds affiliated with residency and fellowship program in Isfahan province.

ICU adult patients were selected by simple randomization from all ICU admissions with at least 72 h ICU stay. Patients admitted for diagnosis of GI bleeding or bleeding within the first 24 h were excluded because they received treatment of disease rather than prophylaxis. We assign a consecutive number to each individual, and then 200 random numbers were generated using the SPSS for Windows, version 15 (SPSS, IBM, Somers, NY) random number generator.

In addition, we tried to avoid treatment bias induced by physician awareness.

Demographic data, admission diagnosis, time spent from ICU admission to start SUP, type of SUP medication received upon admission and during the ICU stay, duration of ICU and hospital stay, and type of SUP medication at ICU discharge were recorded. Moreover, required data regarding SUP medications, dose, route, duration, and associated risk factors (according to ASHP guideline) were gathered, and patients were followed carefully for GI problems. Acute Physiology and Chronic Health Evaluation-II score<sup>[15]</sup> and sepsis-related organ failure assessment score<sup>[16]</sup> were also calculated for all 200 patients.

Indications for SUP were evaluated upon ICU admission and thereafter daily during ICU stay. Prescription patterns of SUP were also prospectively studied according to the ASHP criteria.

ASHP guideline recommended prophylaxis in ICU patients with coagulopathy or those requiring mechanical ventilation for more than 48 h. In addition, prophylaxis is also suggested in ICU patients with a history of GI ulceration or bleeding within 1 year before admission and in patients with at least two of the minor risk factors mentioned in Table 1.<sup>[17]</sup>

We categorized patients according to our primary aim, into the following groups: eligible for SUP administration upon ICU admission (met criteria for SUP administration according to ASHP guideline), and not eligible for SUP administration upon ICU admission.

Thereafter, percent of days which SUP was administered according to ASHP guideline was calculated as “number of days which SUP administered according to guideline during ICU stay/duration of ICU stay × 100.”

After that, patients were stratified in three groups based on the calculated percent: Appropriate duration of SUP administration (80–120%), underutilization (<80%), and overutilization (>120%).

Descriptive statistics (mean and standard deviation) were used to report these results.

The study protocol was approved by the Ethical Committee of Isfahan University of Medical Sciences.

The sample size of 200 patients was calculated as adequate for this study, with 95% level of confidence and 60% expected proportion of SUP administration with the desired precision of 6.6% ( $d = 0.11 \times P$ ).

$$n = P \times (1 - P) \times z^2/d^2.$$

## RESULTS

A total of 203 patients were randomly selected and enrolled in this study. Three patients were excluded from the current study because of GI bleeding on admission or within the first 24 h.

Demographic and baseline characteristics of the patients were listed in Table 2. The mean age of included patients was 54 years (range = 23–89) with 53% male. Most of the patients were admitted to ICU for surgical problems and SUP was used for six patients before ICU admission.

Eighty percent of patients (160 out of 200) received prophylaxis for stress gastritis on admission date while 59.4% (95 out of 200) had indication for SUP according to ASHP criteria. Patients received SUP for  $13.3 \pm 20.2$  days during ICU stay.

Stratification of patients in groups based on risk factors and number of patients who received prophylaxis upon ICU admission is illustrated in Table 3. This table also outlines the number indications for SUP.

Major ASHP risk factors were occurred frequently in critically ill patients upon ICU admission; whereas, 29.5% of patients had at least 1 of the major ASHP criteria. In addition, a nearly equal percent of cases (32.5%) received prophylaxis of stress gastritis according to minor ASHP criteria.

Among 160 patients who received SUP, 71 (44.4%) did not have indication upon ICU admission, whereas, 6 (6.3%) of 95 patients did not receive SUP when it was indicated according to ASHP criteria [Table 3]. Consequently, 77 (38.5%) of 200 patients did not receive appropriate prophylaxis upon ICU admission.

Patients were also followed up daily during prophylaxis administration, and the results revealed in 88 patients SUP was prescribed without adequate criteria for  $3.8 \pm 4.9$  days.

Moreover, 14 patients met criteria for prophylaxis but did not receive it for  $1.2 \pm 0.4$  days during ICU stay.

Overall, 53.5% of patients had appropriate adherence to ASHP guideline during all days of ICU stay. While 88 (44%) of 200 patients received SUP medications in more than 120% of days which were indicated during

**Table 1: Major and minor risk factors for stress-related bleeding according to American Society of Health-System Pharmacists guideline\***

Major risk factor	
Coagulopathy defined as a platelet count lower than 50,000 or INR higher than 1.5 or a PTT higher than two times the control value	
Respiratory failure requiring mechanical ventilation for longer than 48 h	
History of GI ulceration or GI bleeding during past year	
Minor risk factor	
Head trauma or spinal cord injury	
Burn >35% BSA	
Sepsis	
ICU admission lasting >1 week	
Occult GI bleeding lasting >6 days	
Renal insufficiency	
Hepatic failure	
Heart failure	
Use of warfarin	
Multiple trauma	
History of use of NSAID >3 months	
Prolonged NPO status lasting >5 days with GI pathology or after major surgery	
Glucocorticoid therapy (>250 mg hydrocortisone or the equivalent)	
Use of heparin with therapeutic dose	

\*Prophylaxis is recommended in patients with one of the major risk factor or at least two minor risk factors. INR=International normalized ratio, PTT=Partial thromboplastin time, GI=Gastrointestinal, BSA=Body surface area, ICU=Intensive Care Unit, NSAID=Nonsteroidal anti-inflammatory drugs, NPO=Nil per os

**Table 2: Demographic and baseline characteristics of patients completed the study**

Characteristic	Value
Age (years)	54.4±18.7
Gender	
Male	106 (53)
Female	94 (47)
Admission APACHE-II score	10.58±6.6
SOFA score during ICU stay	4.38±2.7
Medical diagnosis	
Surgical	109 (54.5)
Medical	59 (29.5)
Trauma	32 (16)
Nutrition	
Oral	96 (48)
Gavage	84 (42)
NPO	20 (10)
Chronic organ insufficiency at the time of admission	
Kidney	7 (3.5)
Heart	43 (26.5)
Duration of taking SUP (days)	13.3±20.2

Data presented as numbers (%) or mean±SD, where applicable. SD=Standard deviation, APACHE-II=Acute Physiology and Chronic Health Evaluation II, SOFA=Sepsis-related organ failure, ICU=Intensive Care Unit, NPO=Nil per os, SUP=Stress ulcer prophylaxis

ICU stay, but only 5 (2.5%) patients received <80% of SUP medications according to ASHP guideline.

Moreover, 81.2% were continued on inappropriate prophylaxis upon transfer from the ICU.

PPIs and H<sub>2</sub> blockers are pharmacological options prescribed for SUP in our ICU. However, H<sub>2</sub> blockers were more frequently prescribed than PPI upon ICU admission in our study (49% versus 33.5%, respectively) but PPIs were considered the most administered SUP medications at ICU discharge (57%). Table 4 summarizes the medications used for prophylaxis upon ICU admission and at ICU discharge in these patients. During follow-up period, SUP of 33 patients was changed from H<sub>2</sub> blockers to PPI. Attending physicians declared the following reason for these modifications: Adverse drug reactions related to ranitidine use, such as thrombocytopenia (42.2%), starting enteral nutrition (39.4%), and clinical deterioration of patients (18.2%).

In addition, all patients continued SUP upon ICU transfer to other wards. Among all 200 patients, 9 (4.5%) cases experienced GI complication; however, only one patient experienced underutilized, and the remained eight patients received appropriate prophylaxis. The mean ICU and hospital stay were 15.1 ± 21.9 and 25.4 ± 35.6 days, respectively. Moreover, hospital and ICU mortality rate of patients were 16.5% (33 of 200 patients) and 12% (24 of 200 patients), respectively.

## DISCUSSION

SUP administration was inappropriate in 38.5% of our patients, and this irrational prescribing had been continued during ICU stay and upon transfer from ICU, which is consistent with the previous reports in literature.<sup>[2,4,9,12,18]</sup>

Prevention of SRMD by medical care is an important consideration because of its associated morbidity and mortality in critically ill patients.<sup>[19,20]</sup> However, a recent study showed that clinically significant GI bleeding was rare in ICU patients (<3%) because of acid suppressants overuse, but mortality increased by 1.7-fold in these patients when adjusted with other factors.<sup>[21]</sup>

Barletta *et al.* evaluated all GI medications orders written in 37 ICUs in the United States (US) during 24-h period. They concluded SUP was the most common indication for prescription of GI medications, and PPIs were the most frequent medications used for off-label indication in the ICU with poor level of evidence.<sup>[22]</sup> The recent survey also showed US critical care prescribers most frequently chose H<sub>2</sub> blockers (58.4%) and PPIs (39.6%) for SUP.<sup>[23]</sup>

However, in our study, ranitidine was the most prescribed SUP upon ICU admission, but

**Table 3: Frequency of eligible patients for stress ulcer prophylaxis on Intensive Care Unit admission**

Risk factor	Number (% out of 200 patients)
Major ASHP criteria	
Coagulopathy	41 (20.6)
Mechanical ventilation for longer than 48 h	19 (9.5)
History of GI ulceration or GI bleeding during past year	15 (7.5)
Patients with at least 1 of the major ASHP criteria	59 (29.5) <sup>a</sup>
Minor ASHP criteria	
Head trauma or spinal cord injury	27 (13.6)
Burn >35% BSA	-
Sepsis	18 (9)
ICU admission lasting >1 week	-
Occult GI bleeding lasting >6 days	-
Renal insufficiency	15 (7.5)
Hepatic failure	1 (0.5)
Heart failure	42 (21)
Use of warfarin	15 (7.5)
Multiple trauma	25 (12.5)
History of use of NSAIDs >3 months	7 (3.5)
Prolonged NPO status lasting >5 days with GI pathology or after major surgery	6 (3)
Glucocorticoid therapy <sup>b</sup>	84 (42)
Use of heparin with therapeutic dose	27 (13.5)
Patients meeting at least 2 of the minor ASHP criteria	65 (32.5) <sup>a</sup>
Patients received stress ulcer prophylaxis when it was not indicated upon ICU admission	71 (44.4) <sup>c</sup>
Patients did not receive stress ulcer prophylaxis when it was indicated upon ICU admission	6 (6.3) <sup>d</sup>

<sup>a</sup>This number is less than the sum of total patients meeting ASHP major criteria because some patients had >1 criteria, <sup>b</sup>>250 mg hydrocortisone or the equivalent, <sup>c</sup>Among 160 patients who received SUP, <sup>d</sup>Among 95 patients who indicated for SUP. ICU=Intensive Care Unit, ASHP=American Society of Health-System Pharmacists, GI=Gastrointestinal, BSA=Body surface area, NSAIDs=Nonsteroidal anti-inflammatory drugs, NPO=Nil per os, SUP=Stress ulcer prophylaxis

**Table 4: Stress ulcer prophylaxis administration at the beginning, and during the study**

Medication, dose and route	Patients receiving medications on ICU admission, n (%)	Patients receiving medications at ICU discharge, n (%)
Ranitidine		
Tablet	18 (9)	41 (20.5)
Solution injection	80 (40)	45 (22.5)
Omeprazole		
Capsule	-	5 (2.5)
Pantoprazole		
Tablet	22 (11)	76 (38)
Powder for solution for injection	45 (22.5)	33 (16.5)
Did not receive SUP medication	40 (20)	-

ICU=Intensive Care Unit, SUP=Stress ulcer prophylaxis

pantoprazole was considered the most prescribed SUP at ICU discharge. Since most patients did not



tolerate oral medications upon ICU admission; intravenous route was considered the most frequent route for SUP administration. On the other hand, most included patients were admitted for surgical purposes and attending physicians believed that moderate SUP administration ( $H_2$  blocker rather than PPI) was adequate to prevent stress ulcer for some of these patients.

Consequently, with clinical deterioration of patients, SUP medications had been changed to more potent SUP medications (PPIs). Moreover, with adequate tolerance of enteral nutrition, most intravenous medications altered to oral dosage forms. However, thrombocytopenia of ranitidine was also reported another reason to change  $H_2$  blockers to PPIs, but in fact, the prevalence of this adverse reaction is rare.<sup>[24]</sup>

A retrospective chart review of 394 ICU patients during 2 months reported that 90% patients received SUP during ICU stay, and SUP was continued in 80% upon transfer from the ICU. However, 60% of the prescribed SUPs were inappropriate.<sup>[12]</sup>

In another study in 2006, Farrell *et al.* retrospectively studied the prescription patterns for SUP in 210 ICU adult patients over the 4-month period. The authors noted that 87.1% of ICU patients received SUP. Although 68.1% placed on prophylaxis when they did not have adequate indication and 60.4% were continued on inappropriate treatment upon transfer from the ICU.<sup>[4]</sup>

Inappropriate use of SUP was reported in 20–70% of patients upon ICU admission in literature which is consistent with our study. Moreover, overutilization is the most frequent inappropriate pattern of SUP administration in all previous studies.

However, the higher percent of inappropriate SUP administration upon ICU discharge in our ICU (81.2%) may be related to differences in adherence to guideline and risk factors of admitted patients compared to other conducted studies.

In addition, study design may be another variable could have an effect on the results. It seems prospective design for evaluation of drug utilization is more appropriate than retrospective, but there are only two studies conducted prospectively to evaluated SUP administration in ICU setting.<sup>[2,9]</sup>

In one of prospective study, prescription patterns for SUP among 99 new ICU admissions in Texas showed that 53% of patients received inappropriate SUP. In fact, SUP was not prescribed for 10 out of 48 patients (21%) when it was indicated whereas, 82% (42 out of 51) received SUP when it was not indicated.<sup>[2]</sup>

In another prospective study in 2008, the pattern of Intravenous PPI use was evaluated by 4-month

period in 255 patients in ICU and non-ICU setting in Saudi Arabia. The results of this study showed that inappropriate use of IV PPI was significantly lower in ICU (19.8%) compared to non-ICU (71.7%) patients ( $P = 0.01$ ).<sup>[9]</sup> The inappropriate use of SUP was also more prominent in non-ICU compared to ICU patients that lead to waste hospital resources.

Previous studies in similar institutions in Iranian non-ICU setting also showed the higher incidence of inappropriate use of SUP (60–90%) than our study in ICU setting (38.5%).<sup>[25,26]</sup> It may be related to higher risk of ICU patients to develop SRMD than non-ICU patients.

SUP is an important issue not only on ICU admission but also during ICU stay.<sup>[27]</sup> Our study is the first prospective study that revealed results regarding SUP administration not only upon ICU admission and discharge but also during ICU stay and calculate adherence to ASHP guideline during the follow-up period. Since, there was not any related information to assess adherence to SUP guideline, 80–120% considered appropriate adherence in our study.<sup>[28-30]</sup>

High percent of overutilization during all stages of our study revealed that, or attending physicians may not be sufficiently aware of adverse effects of inappropriate use of SUP medications, or the complications of GI bleeding had more influence on the decision for prescribing SUP.

Although evaluation about the risk factors for SRMD and prescription pattern of SUP was initiated from decades ago but it still continued until now. However, all conducted studies used ASHP criteria to evaluate and report the results of SUP administration but, the cross-sectional survey in 2012 showed controversy among the US critical care prescribers regarding risk factors of SRMD and prescribing patterns for SUP.<sup>[23]</sup>

In 2015, Krag *et al.* described SUP practices in 97 adult ICUs in 11 countries to show variations in patient selection for SUP administration both within and between countries. It is interesting that all except one ICU used prophylaxis for SRMD but many did not report having a guideline for the use of SUP (36%).<sup>[19]</sup>

It seems necessary to establish and use of SUP guideline and registry-based information of SUP particularly in ICU setting to collect process of care and outcome data relevant to SUP.

Moreover, since many factors other than adherence to SUP guideline could impact on patients' outcome and adverse reactions of SUP such as pneumonia and infection of *C. difficile*, the association of these parameters was not evaluated in our study.

## AUTHORS' CONTRIBUTION

NR carried out the literature review, performed data collection and data entry process, and helped to draft the manuscript. SA participated in the study design and manuscript reviewing and editing. SF participated in the literature review and study design, performed final revision of the manuscript, and supervised the whole project. MM participated in the study design and statistical analysis. PA participated in the study design and manuscript reviewing and editing.

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## Conflicts of interest

There are no conflicts of interest.

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Rafinazari, *et al.*: Stress ulcer prophylaxis of patients admitted to the Intensive Care Unit

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