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Original Article

Appropriateness of Acid-suppressing Agents for Stress Ulcer Prophylaxis in Non-intensive Care Unit Setting in Saudi Arabia

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Abstract

Objective: To investigate the appropriateness of acid-suppressive therapy (AST) for stress ulcer prophylaxis (SUP) in noncritically ill hospitalized patients. **Materials and Methods:** A prospective, observational study with 384 subjects was conducted between October and December 2017 in the emergency and internal medicine departments. The Herzig clinical risk scoring system and the guidelines of the American Society of Health-System Pharmacists guidelines were used to assess risk factors and determine risk scores for gastrointestinal (GI) bleeding. **Results:** The mean age of subjects was 51.9 ± 19.4 years, and 220 (57.3%) of them were males. Among the absolute risk factors, coagulopathy was observed in 2 (0.5%) patients, mechanical ventilation in 15 (3.9%), and a history of GI bleeding in 1 (0.3%). Of 384 patients with SUP, 370 (96.4%) had a clinical risk score ≤ 9 and 14 (3.6%) had a risk score between 10 and 12 for nosocomial GI bleeding. A statistically significant relationship was found between the risk factor indication and demographics. **Conclusion:** SUP is frequently administered to noncritically ill hospitalized patients lacking risk factors for GI bleeding. Proton pump inhibitors are the overwhelming first choice of AST among prescribers. Practitioners should follow international guidelines when prescribing ASTs outside the critical-care setting.

Keywords: *Acid-suppressing agent, prophylaxis, stress ulcer*

Introduction

A stress ulcer is defined as a "superficial lesion of the mucosal layer of the stomach after a traumatic event."[1] Risk factors for developing stress-related ulcers include but are not limited to mechanical ventilation for more than 48 h, coagulopathy, hepatic dysfunction, sepsis, acute kidney dysfunction, and a history of gastrointestinal (GI) ulceration or bleeding.[2] More than 75 in every 100 intensive care unit (ICU) patients develop stress-related ulcers within the first 3 days of admission.[3,4] As patients with serious illnesses have a high risk of developing gastric ulceration and bleeding, acid-suppressive therapy (AST), such as proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs), is often used prophylactically to prevent gastric complications.[5] However, overutilization and inappropriate prescription of ASTs present a separate set of risks and long-term complications, including pneumonia and *Clostridium difficile* infection (CDI).[6] In 1999, the American Society of Health-System Pharmacists (ASHP) published therapeutic guidelines on stress ulcer prophylaxis (SUP). This publication provides authoritative guidance on the rational application of SUP.[7]

Because of the efficacy of PPIs, they have become clinicians' first choice for SUP.[3,8] According to a meta-analysis of 19 studies, PPIs were superior to H2RAs in preventing clinically important and overt

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GI bleeding without significantly increasing the risk of pneumonia.[9] However, a retrospective study of 1005 subjects in Korea found that PPIs significantly increased the risk of SUP-related CDIs compared to H2RAs.[10] Another observational study concluded that PPI use in hospitalized patients was associated with a higher risk of CDI and pneumonia compared to that of H2RAs.[11]

Despite the well-known and documented risks of using PPIs and H2RAs, these drugs are still unnecessarily prescribed and overused in hospitals to prevent stress ulcers in health-care settings.[12] A study conducted in a tertiary care setting in the Kingdom of Saudi Arabia (KSA) revealed that PPIs were inappropriately prescribed in 43% of patients without an approved indication.[13] Similarly, a retrospective study conducted in a tertiary care setting in Jordan found that more than 80% of patients were prescribed PPIs without an approved indication based on the ASHP guidelines.[14] Another retrospective study of 713 patients receiving intravenous PPIs for SUP found that more than half the patients did not have a proper indication.[15]

Similar to PPIs, H2RAs are overprescribed and inappropriately prescribed for SUP. A study in Iran reported that almost 85% of the SUP agents administered to hospitalized patients were inappropriately prescribed.[16] Another prospective study reported that ASTs had been prescribed for SUP to 44.4% of patients without an appropriate indication.[17] Herzig *et al.*[25] developed a stress ulcer–related GI bleeding risk score using a large cohort study that analyzed various risk factors for nosocomial GI bleeding in non-ICU patients, identifying patients who needed SUP based on their categorized risk groups. The Herzig scoring system provides a framework for the more selective use of ASTs for SUP.[18,19]

Globally, the misuse and overprescription of ASTs remain prevalent. As the incidence of stress ulcers and GI bleeding in non-ICU settings is extremely low, ASTs are being prescribed irrationally for SUP to non-ICU patients without assessing the patients' health status.[20,21] The objective of this study was to determine the appropriateness of AST administration for SUP in a non-ICU setting using the Herzig risk scoring system and the ASHP guidelines. The findings of this study will facilitate both a reduction in the inappropriate prescription of ASTs and the implementation of SUP guidelines, preventing adverse events related to the overutilization of ASTs in non-ICU settings.

Materials and Methods

This prospective, observational study sought to determine the percentage of noncritically ill patients who were administered ASTs for SUP from October 2017 to December 2017 in the emergency and internal medicine departments at the King Saud Medical City (KSMC), a large tertiary care Ministry of Health Hospital in the KSA. This hospital serves a broad range of patients drawn from a large population, several of whom present with complex medical comorbidities and are transferred from different regions of the KSA.

The data were collected from the patient files and the hospital's electronic health records Medical System (Medisys®) system. They were organized on data collection sheets, and the following variables were examined: age, gender, diagnosis, length of hospital stay, past medical history/past medical therapy, risk factors, the prescriber's department and specialty, the patient's discharge medications, laboratory tests (such as serum creatinine, blood urea nitrogen, coagulation tests, aspartate amino transferase, bilirubin, and albumin), and the patient's stress ulcer regimen (applied drugs, dose, frequency, route, duration, and indication). The appropriateness of the dose, route, duration of treatment, choice of AST agent, and indication were assessed using the ASHP guidelines, the textbook by DiPiro *et al.*,[26] and the Lexicomp database. If ASTs were prescribed for SUP with less than one absolute indication or less than two relative indications, the prescription was classified as inappropriate.

According to the ASHP guidelines, patients should have at least one absolute indication or two or more relative indications for the appropriate prescription of SUP.[7] The list of three absolute indications includes, for example, mechanical ventilation >48 h, coagulopathy (platelet <50,000 mm^3, international normalized ratio > 1.5, partial thromboplastin time two times the normal value), and a history of GI bleeding or peptic ulcer disease within 1 year. The relative indications include sepsis (core temperature >38.5°C or <35.0°C, white blood cell >15,000 or <3,000/mm^3, and a positive blood culture), renal insufficiency (creatinine clearance rate <40 mL/min or serum creatinine concentration >2.8 mg/dL), hepatic impairment (bilirubin >8.8 mg/dL, serum aspartate amino transferase >500 U/L, albumin <4 g/L, or signs and symptoms of a hepatic coma), enteral feeding, corticosteroid use (>250 mg/day of hydrocortisone or equivalent), unfractionated or low-molecular-weight heparin use, recent warfarin administration, nonsteroidal anti-inflammatory drug use (>3 months), an ICU stay of more than 1 week, occult bleeding lasting 6 days or longer, spinal cord injury, hepatic/renal transplantation, thermal injury >35% body surface area, partial hepatectomy, head injury with Glasgow Coma Scale ≤10 or inability to

obey simple commands, and multiple trauma with injury severity score ≥16.[7]

The Herzig risk score was also applied to the collected data to identify the patients' risk factors for nosocomial GI bleeding. The following risk factors were included in this scoring system: age more than 60 years, gender (male), acute renal failure, liver disease, sepsis, prophylactic anticoagulation, coagulopathy, and medicine service. The risk score for each patient was derived by summing the risk points for each applicable risk factor [Table 1]. SUP was deemed appropriate if the AST was administered to patients who were at medium-high risk and high risk for bleeding.

A consent statement was given to each potential research subject before his/her enrollment in the study. If a patient could not read, we read the form and took his/her verbal consent if he/she agreed to the consent statement. We did not recruit any subject without obtaining verbal consent. Adult (≥18 years) patients in the emergency and internal medicine departments were selected for eligibility. The following patients were excluded: those with active GI bleeding or active peptic ulcer disease and those who had taken AST medications at home or who had taken ASTs for specific indications (gastroesophageal reflux disease, peptic ulcer disease, dyspepsia, or recent acute or suspected GI bleeding). The sample size was determined using a Raosoft calculator (Seattle, Washington) with a 5% margin of error and a 95% confidence interval. This resulted in a target sample size of 377 study subjects. Data analysis was performed with the Statistical Package for the Social Sciences software, version 21.0 (IBM, Armonk, New York). Descriptive statistics were used to report the data, and normally distributed data were presented as mean ± standard deviation. This study was approved by the Institutional Review Board of KSMC (Reference number: H1RI-21-Aug17-01).

Table 1: Clinical risk scoring system[22] for nosocomial gastrointestinal bleeding in hospitalized patients outside of the intensive care unit

Risk factor	Points
Age >60 years	2
Male	2
Acute renal failure	2
Liver disease	2
Sepsis	2
Prophylactic anticoagulation	2
Coagulopathy	3
Medicine service[a]	3

[a]All services other than general surgery, surgical subspecialties, obstetrics and gynecology, neurology, and psychiatry

Results

This study enrolled 384 subjects. The male-to-female ratio was 1.3:1, where the mean age of male subjects was 52 ± 18.5 years and the mean age of female subjects was 51.9 ± 20.5 years. A statistically significant relationship was found between the risk factor indication and demographics [Table 2]. Among the 18 absolute risk indications, coagulopathy was observed in 2 (0.5%) patients, mechanical ventilation in 15 (3.9%), and a history of GI bleeding in 1 (0.3%). The risk factor indications are shown in Table 3.

Regarding the appropriateness of SUP use, PPIs were administered in 363 (94.5%) patients, whereas 21 (5.5%) received H2RAs. In the omeprazole group (n = 296), the inappropriateness of route and dose was observed in 176 (59.5%) and 4 (1.4%) patients, respectively, whereas in the ranitidine group (n = 21), an inappropriate frequency of administration was observed in 9 (42.9%) patients [Table 4]. Of the 384 patients with SUP, 370 (96.4%) had a low to low-medium clinical risk score, whereas only 14 (3.6%) patients had a medium-high

Table 2: Association between risk factor indications and study demographics (n = 384)

Demographics	Risk factor indication				*P*-value
	None (n = 79)	One relative (n = 214)	One absolute (n = 18)	Two or more absolutes (n = 73)	
Ward					<0.001
Internal medicine	15 (7.5%)	120 (60%)	5 (2.5%)	60 (30%)	
ER	64 (34.8%)	94 (51.1%)	13 (7.1%)	13 (7.1%)	
Gender					0.046
Male	35 (15.9%)	127 (57.7%)	13 (5.9%)	45 (20.5%)	
Female	44 (26.8%)	87 (53%)	5 (3%)	28 (17.1%)	
Age group					<0.001
≤50 years	52 (28%)	106 (57%)	7 (3.8%)	21 (11.3%)	
≥51 years	27 (13.6%)	108 (54.5%)	11 (5.6%)	52 (26.3%)	

ER = emergency

Row-wise data presented n (n%), chi-square test applied for statistical significance

to high clinical risk score for nosocomial GI bleeding [Figure 1].

Discussion

To the best of our knowledge, this study is the first in the KSA to assess the appropriateness of ASTs for SUP using ASHP-derived guidelines and the Herzig scoring system in a large tertiary care setting. On the basis of ASHP-derived internal guidelines, more than two-thirds of the non-ICU patients in this study were inappropriately prescribed SUP because of a lack of risk factors, whereas only 23.7% of the patients were prescribed ASTs in accordance with the ASHP guidelines. These results were consistent with earlier studies.[16,22] We relatively identified a large number of patients continuing SUP medication with lack of risk factors in emergency department than the patients admitted to the internal medicine department. These findings are similar to those obtained by Mohamad *et al.*,[23] who observed that approximately 57.8% of patients had no risk factors and received unjustified prophylaxis.[23] This is an important finding as inappropriate continuation of SUP may lead to adverse drug reactions, potential drug interactions, and polypharmacy problems, especially in a department where patients are admitted for an immediate care.[24]

When the study data were assessed using the Herzig clinical risk scoring system, only 3.6% of patients were appropriately prescribed SUP. However, it should be noted that our patient population did not have a similar risk stratification compared to that in the study conducted by Herzig *et al.*[25] (96.4% vs. 87.7% of patients scored ≤9; 3.6% vs. 12.6% of patients scored ≥10).[25]

Consistent with previous studies, we have shown that ASTs are being irrationally prescribed for SUP in ill patients who do not possess risk factors for GI bleeding and for whom the risk of bleeding is extremely low.[18,26] The significant independent risk factors of coagulopathy and mechanical ventilation were only found in 4.3% of the prescribed patients,[18,27] corroborating earlier findings regarding the low incidence of GI bleeding among non-ICU patients.[18] The risk of GI bleeding is directly proportional to the number of risk factors.[18] On the basis of current evidence and guidelines, there is no benefit to overprescribing ASTs for SUP in hospitalized noncritically ill patients.

It is critical that a proper medication reconciliation be performed at both hospital admission and discharge to ensure the rational prescription of ASTs in noncritically ill patients.[25] It is also imperative that AST prescription for patients admitted outside the ICU follows a targeted approach based on the level of risk. The risk scoring

Table 3: Risk factor indications (*n* = 384)

Risk factors	*n* (*n*%)
None	79 (20.6%)
One relative	214 (55.7%)
One absolute	18 (4.7%)
Coagulopathy	2 (0.5%)
Mechanical ventilation	15 (3.9%)
History of GI bleeding	1 (0.3%)
Two or more relative	73 (19%)
Sepsis	9 (2.3%)
Renal impairment	10 (2.6%)
Hepatic impairment	7 (1.8%)
LMWH or heparin or enoxaparin	66 (17.2%)
Warfarin	14 (3.6%)
ICU stay >1 week	9 (2.3%)

LMWH = low molecular weight heparin

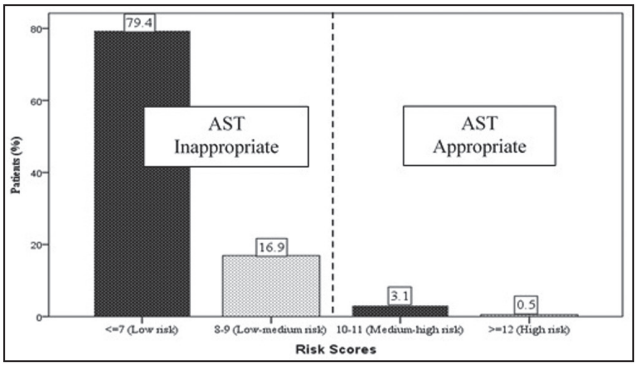

Figure 1: Percentage of patients with clinical risk scores for nosocomial gastrointestinal bleeding. Left side to dotted line indicates inappropriate AST (acid-suppressive therapy)

Table 4: Dose and route appropriateness of stress ulcer prophylaxis (*n* = 384)

Variable	Inappropriate dose	Inappropriate frequency	Inappropriate route
Omeprazole (*n* = 296)	4 (1.4%)	6 (2%)	176 (59.5%)
Pantoprazole (*n* = 57)	1 (1.8%)	5 (8.8%)	0
Esomeprazole (*n* = 10)	0	1 (10%)	1 (10%)
Ranitidine (*n* = 21)	0	9 (42.9%)	4 (19%)

Omeprazole: 20–40 mg (IV or NGT) once daily; pantoprazole: 20–40 mg (PO or IV) once daily; esomeprazole: 20–40 mg (PO) once daily; ranitidine: 150 mg (PO) twice daily, 50 mg (IV) every 6–8 h

NGT = nasogastric tube; PO = per oral; IV = intravenous

system and the ASHP guidelines should particularly be applied in clinical practice to avoid unnecessary AST administration. Inappropriate use of medications can lead to adverse drug reactions, potential drug interactions, polypharmacy problems, and unneeded costs.[23,27] This study revealed that PPIs were the first choice among practitioners for SUP, corroborating earlier findings.[18,28] In our study, 3.2% of patients received the wrong AST dose, which is also in line with earlier findings.[29] The ASHP guidelines and the Herzig risk scoring system should be implemented in clinical practice to prevent unnecessary AST exposure to patients with a low risk of stress ulcer bleeding.

Computerized ordering templates and automated reminders to discontinue SUP at discharge may reduce the overall indiscriminate use of ASTs, lower patients' prescription costs, and limit the occurrence of adverse effects.[27,29] The practice-based learning and improvement (PBLI) methodology is another approach that can be used to reduce inappropriate SUP administration and to improve guideline compliance among practitioners.[30] One study showed that PBLI successfully reduced inappropriate SUP (59% preintervention, 33% postintervention; $P < 0.007$) in a tertiary care setting in the United States.[30,31]

There were some limitations to this study. As it was conducted at a single tertiary care institution in the KSA, the results cannot be generalized to the entire population of the country. Therefore, these findings should be validated by a multicenter longitudinal study across KSA health-care settings.

Conclusion

SUP is frequently administered to noncritically ill hospitalized patients lacking risk factors for GI bleeding, and PPIs are the overwhelming first choice of AST among prescribers. Practitioners should be required to follow international guidelines when prescribing ASTs outside the critical-care setting.

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Conflicts of interest

There are no conflicts of interest.

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