Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 2, 2022, pp.845-857.

Bulletin of Pharmaceutical Sciences
Assiut University
Website: http://bpsa.journals.ekb.eg/
e-mail: bullpharm@aun.edu.eg

BULL. PHARM. SCI. Assiut Univ.

EVALUATION OF CURRENT PRACTICE OF STRESS ULCER PROPHYLAXIS IN PATIENTS ADMITTED TO INTENSIVE CARE UNITS IN THE GAZA STRIP- PALESTINE

Hala Z.I Alagha* and Nasaem Ramadan Mohammed Al Mabhouh

Department of Pharmacology and Medical Sciences, Faculty of Pharmacy, Al Azhar University of Gaza, Palestine P.O Box: 1277

This study aimed at assessing the degree of adherence of Stress ulcer prophylaxis (SUP) practice to the American Society of Health-System Pharmacists (ASHP) guidelines in intensive care units (ICUs) at three hospitals in the Gaza Strip, Palestine. This was a prospective study that utilized chart review methodology for data collection. Four aspects of SUP practice were assessed: indication, dose, route of administration and duration. The study enrolled 442 ICU patients with a median (Interquartile range, IQR) age of 49.0 (36.6) years. More than half the patients (55.7%) were males. Coagulopathy was the most common major risk factor for stress ulcer, presented in 73 (16.5%) patients, while the use of corticosteroid therapy was the most common minor risk factor presented in 93 (21%) patients. SUP was administered to 426 (96.4%) patients, of which 86.9% received ranitidine and 13.1% received PPIs. Overall adherence and indication adherence rates to guidelines were 16.7% and 36.4%, respectively. Appropriate dose, route and duration of SUP were found in 63.6%, 68.2%, and 88.1% of the evaluated doses, respectively. Of the 426 patients prescribed SUP, 48 (11.3%) developed adverse effects. This study revealed suboptimal SUP practice in the investigated hospitals and the need to apply strategies to improve SUP use patterns.

Keywords: *Stress ulcer, ASHP guidelines, prophylaxis, Intensive care unit, Adherence*

INTRODUCTION

Stress-related mucosal disease (SRMD) is the broad term used to describe the pathology attributed to the erosive, inflammatory insult to the upper gastrointestinal tract associated with critical illness[1]. SRMD can be asymptomatic superficial gastrointestinal lesions found incidentally during endoscopy, or it may progress into gastrointestinal bleeding (GIB). GIB may be occult, overt or clinically important bleeding (CIB)[1&2]. CIB is associated with several undesirable outcomes including prolonged hospital stay and increased mortality risk, particularly in critically ill patients[3&4].

Endoscopic studies from decades ago confirmed the presence of gastric mucosal changes in most critically ill patients[5]. Endoscopic evaluation has revealed that more than 75% of extremely critically ill patients develop gastric lesions within 72 h of admission to the intensive care unit (ICU)[1&6&7]. Lesions are most often superficial, and cause subepithelial hemorrhages and erosions[8&9]. The clinical relevance of these lesions may be limited, as only a small number of these ulcerations progress to overt and clinically important GIB[10]. The true incidence of GIB due to stress ulcerations in ICU patients varies widely in the literature. The reported incidence of overt GIB ranges between 2-10%. However, the overall incidence of CIB appears to be low, ranging from 0.6% to 3.5% [2&6&10-13].

The exact mechanism of SRMD is not completely understood, but is believed to be related to disruption of protective mechanisms against gastric acid, increased acid production, splanchnic hypoperfusion, reperfusion injury, and oxidative injury to the GI tract[14&15]. A number of risk factors are known to increase

Received in 13/5/2022 & Accepted in 8/6/2022

*Corresponding author: Hala Z.I Alagha, E-mail: Dr.halagha@gmail.com

the risk of SRMD and CIB in critically ill patients. These include, but are not limited to, mechanical ventilation, coagulopathy, shock, sepsis, increased length of ICU stay and older age. In addition, acute and chronic hepatic disease, acute kidney injury, corticosteroid use and acute myocardial infarction have been proposed as other important risk factors[4&8&10&11].

Stress ulcer prophylaxis (SUP) is commonly administered to critically ill patients to prevent GIB. Different pharmacological agents are used to provide SUP, with proton pump inhibitors (PPIs) and histamine 2 receptor antagonists H2RAs being the most widely used agents[10-11]. Yet, the use of SUP is not without risks, and complications -particularly infectious complications- such as nosocomial pneumonia and Clostridium difficile infection (CDI) are associated with its use[16-17]. Thus, the decision to administer SUP must be individualized and only considered in patients who are at high risk for stress ulcer–related CIB. A number of guidelines have been published over the past years in an effort to optimally direct acid suppression use for preventing SRMD[15&18-20]. Yet, a considerable body of evidence has demonstrated suboptimal SUP practice worldwide, with adherence rates to guidelines ranging from 30-70% [21-31]. Studies from the Arab world have reported inappropriate and excessive use of SUP. A study conducted in a Jordanian hospital found that 86% of patients started SUP that was unnecessary and should be avoided[29]. Another study evaluated SUP practice in Lebanese hospitals showed that 67% of patients did not have an indication for SUP according to the American society of health system pharmacists (ASHP) based guidelines[32]. Moreover, Khudair *et al.*,[33], in a medication use evaluation (MUE) study conducted in Qatar assessing the prescribing pattern of acid-suppressive medications in medical inpatients, found that the use of SUP was unjustified in 66% of patients. According to our research knowledge; no information about SUP use patterns in Palestine (West bank/Gaza strip) is available and it is unknown whether SUP practice in Gaza Strip hospitals follows international guidelines or not.

Aim

The main aim of this study was to assess the degree of adherence of SUP practice to the *ASHP guidelines on stress ulcer prophylaxis* in the main three governmental hospitals in the Gaza Strip, Palestine. In addition, the study aimed at determining the prevalence of SUP prescriptions, types of pharmacological agents used for SUP and the contribution of each type to overall SUP prescriptions in the investigated ICUs.

Ethics approval

The study received ethical approval from the Al-Azhar University ethical review board, followed by an approval from the general directorate for human research in the Ministry of Health. The institutional review board of each of the involved hospitals granted approval for the study. The informed consent for this type of study was waived as the study was not interventional, didn't involve collection of biological materials from patients, and collected information was anonymized.

METHODS

Study design and setting

The present study is a prospective study utilizing chart review methodology and was carried out in the Gaza Strip-Palestine in the period from 11th April 2019 to 27th October 2019. A multicenter design was used where three hospitals participated in this study: Al Shifa medical complex (SMC), Nasser medical complex (NMC) and European Gaza hospital (EGH).

Patients

Sample size was calculated using the formula $n = Z^2 P (1-P) / d^2$ [34], based on the following assumptions: a) for the level of confidence of 95%, which is conventional, Z value is 1.96, b) adherence rate to SUP guidelines (p) is 36%[29&32&33&38], c) the precision (d) is 5%. The minimum sample size required was 354 patients. In our study we included all eligible adult patients admitted to the ICU during the study period. Patients were excluded from data collection if they had any of the following: 1) An active GIB or an active gastric or duodenal ulcer at the time of admission or during their hospital stay; 2) Patients on acid suppressive therapy (AST) for treatment of GI disease (gastroesophageal reflux disease, esophagitis etc.); 3) Patients who were taking any AST as home medication. Patients admitted twice during the study period were not re-included.

Data collection

A chart review method was utilized for data collection. In this method, medical records and medication sheets of patients were reviewed during their ICU stay until they were discharged from ICU. Data was collected using a special data sheet for medical chart data abstraction, which included the following six sections: 1) Patient's demographics: general characteristics of the patients such as age, gender and length of ICU stay; 2) Disease state: including cause of admission, prescribed medications, past medical history and past medication history; 3) Stress ulcers risk factors: the recommendation for prophylaxis was based on the risk factors for CIB according to the ASHP guidelines (Table 1)[18]; 4) Lab tests including complete blood count (CBC), liver function tests, kidney function tests or other tests to assess the eligibility of patients for SUP[35&36]; 5) SUP regimen (agents used, dose, frequency, route of administration and duration) (Table 2); 6) Adverse drug reactions: This section of the data sheet determines if the patients developed complications of SUP, namely nosocomial pneumonia or CDI[21&32].

Table 1: Risk factors for stress ulcer and indications for stress ulcer prophylaxis[18]**.**

Stress ulcer prophylaxis is indicated in the presence of at least one of the following:
1. Respiratory failure: mechanical ventilation >48 hours
2.Coagulopathy: platelet count <50 000 per mm^3, international normalized ratio (INR) >1.5 or partial thromboplastin time >2.0 times the control value
3. History of gastric ulceration or bleeding during year before admission
4. Head injury with Glasgow coma score (GCS) of ≤10 or inability to obey simple commands
5. Thermal injury involving >35% of body surface area
6. Partial hepatectomy
7. Multiple trauma with injury severity score (ISS) of ≥16
8. Hepatic or renal transplantation
9. Hepatic failure: any two of the following: a serum bilirubin concentration >8.8 mg dL^{-1}, a serum aspartate aminotransferase level >500 U L^{-1}, a serum albumin level <41 g L^{-1} and clinical signs and symptoms of hepatic coma
10. Spinal cord injury
11. Renal failure: a creatinine clearance rate < 40 mL $minute^{-1}$ or a serum creatinine concentration >2.8 mg dL^{-1}
Or, in the presence of at least two of the following:
1. Sepsis: core temperature >38.5 or < 35.0°C, a white cell count >15 000 or < 3000 per mm^3 and a positive blood culture
2. Intensive care unit stay of more than 1 week
3. Occult bleeding or overt bleeding (haematemesis, gross blood or 'coffee grounds' material in a nasogastric aspirate, haematochezia or melaena) for ≥ 6 days
4. Corticosteroids therapy (>250 mg hydrocortisone or equivalent daily)

Table 2: Dosage regimens for agents used for stress ulcer prophylaxis[32].

Cimetidine	300 mg *qid* po, NG, or iv or 50 mg/h by continuous iv infusion
Famotidine	20 mg *bid* po, NG, or iv or 1.7 mg/h by continuous iv infusion
Ranitidine	150 mg *bid* po or NG, 50 mg every 6-8 h iv, or 6.25 mg/h by continuous iv infusion
Sucralfate	1 g *qid* po or NG
Omeprazole	40 mg LD then 20-40 mg daily po, NG or iv
Lansoprazole	15 mg daily po, NG or iv
Esomeprazole	20-40 mg daily po, NG or iv
Pantoprazole	40 mg daily po or NG or iv

qid: Four times daily; p.o: per oral; NG: Nasogastric tube; i.v: intravenous; *bid*: Twice a day; LD: Loading dose.

Assessment of SUP practice

Practice of SUP was classified as either adherent or non-adherent to practice guidelines[18] taking into consideration the following parameters: 1) Indication for SUP based on the presence or absence of risk factors as shown in Table 1, 2) Dose and frequency as shown in Table 2, 3) Route of administration (Parenteral therapy should only be used in patients without enteral feeding access or those with "nothing by mouth" status), 4) duration of the prophylaxis (SUP should be discontinued once the risk factors are resolved). Overall adherence rate was calculated as (Number of patients needed SUP and prescribed it in concordance with guidelines for all parameters + Number of patients did not need SUP and were not prescribed it) divided by the total number of patients. *Indication* adherence rate was calculated as (Number of patients needed SUP and prescribed it + Number of patients did not need SUP and were not prescribed it) divided by the total number of patients. Finally, adherence rate of other parameters of SUP use (dose, duration of use, route of administration) was calculated by dividing the number of patients delivered SUP correctly with respect to that specific parameter by the number of patients delivered SUP when it was indicated.

Table 3: General characteristics of patients.

Variables	**N=442**
Gender n (%) • Male • Female	 246 (55.7) 196 (44.3)
Age (year): Median (IQR) [a]	49 (36)
Length of ICU stay (Day): Median (IQR) [a]	2 (3)
Number of drugs / patient: Median (IQR) [a]	7 (3)
Cause of admission	
Post-operative (Colectomy, thyroidectomy, abdominal exploration, heart surgery...etc.)	91 (20.6)
Respiratory disorders (COPD, P.O., P.E., DPLD, OSA, pneumonia, asthma, lung empyema, lung abscess ....etc.)	89 (20.4)
Miscellaneous (Head trauma, SLE, near drowning, snake bite, polytrauma, vocal cord paralysis)	44 (9.9)
Cardiovascular disorders (IHD, MI, CVA, Post CPR, AF, HTN crises, IVH, air embolism ....etc.)	43 (9.7)
Endocrine system disorders (DKA, hypothyroidism, pituitary apoplexia)	40 (9.1)
Sepsis and shock	38 (8.6)
Renal disorders (AKI, CKD, electrolyte imbalance, pyelonephritis)	29 (6.6)
Gastrointestinal disorders (Acute pancreatitis, spleen injury, cholangitis, colon cancer, drug poisoning ...etc.	22 (5.0)
CNS disorders (Brain tumor, spinal cord injury, GBS, meningitis, meningoencephalitis ...etc	21 (4.8)
Pregnancy associated disorders (Preeclampsia, septic abortion, hyperemesis gravidarum, post caesarean bleeding ...etc.)	15 (3.4)
Liver disorders (Hepatitis, acute liver failure, hepatic encephalopathy, hepatorenal syndrome)	6 (1.4)
Skin disease (Burns, stab wounds)	4 (0.90)

N: Total number of patients, n (%): Percentages are given within parentheses with the total number of patients as denominator. [a] The median was reported since these variables were positively skewed. IQR: Interquartile range, ICU: Intensive Care Unit. COPD: Chronic obstructive pulmonary disease, P.O.: Pulmonary oedema, P.E.: Pulmonary embolism, DPLD: Diffuse pulmonary lung disease, OSA: Obstructive sleep apnea, SLE: Systemic lupus erythematous, IHD: Ischemic heart disease, MI: Myocardial infarction, CVA: Cerebrovascular accident, CPR: Cardiopulmonary resuscitation, AF: Atrial fibrillation, HTN: Hypertension, IVH: Intraventricular hemorrhage, DKA: Diabetic ketoacidosis, AKI: Acute kidney injury, CKD: Chronic kidney disease, CNS: Central nervous system, GBS: Guillain-Barre syndrome.

Data analysis

Data entry process was done by giving a serial number for each report form for each patient, coding variables, then designing a data entry model using EXCEL software. Then, data were entered to statistical package for the social science (SPSS) version 22 program. Summary statistics, including frequency, percent, median and IQR were calculated to summarize the data. Continuous variables (age, length of ICU stay, number of drugs given to each patient, duration of SUP regimen) were assessed for normality using Shapiro-Wilk and Kolmogorov-Smirnov tests. These variables were expressed as median and IQR as they violated the assumption of normality, and compared among hospitals using Kruskal-Wallis test. Categorical data (gender, risk factors, drug used, route of administration, side effects of SUP, etc.) were expressed as frequency and percentages and compared among hospitals using Chi-square test. In addition, SUP practice was compared across different hospitals. Differences in adherence rates among different hospitals were tested using the Pearson chi-square test. The results were considered to be statistically significant if P-values ≤ 0.05.

RESULTS AND DISCUSSION

Results

A total of 442 patients were included in the study. The characteristics of all patients are shown in (Table 3). Two hundred forty six (55.7%) patients were males. Median (IQR) age of patients was 49.0 (36.0) years old. The most common causes of admission to the ICU were post-operation (20.6%) and respiratory disorders (20.4%). Of the 442 patients included in the study, 196 (44.3%) patients did not have risk factors for stress ulcer while 246 (55.7%) patients have one or more risk factors. Coagulopathy was the most common major risk factor found in 16.5 % of all patients while the use of corticosteroid therapy was the most common minor risk factor reported in 21% of all patients (Table 4).

Of all patients included in the study; 426 (96.4%) patients received SUP. Proton pump inhibitors (PPIs) and Histamine-2 receptor antagonists (H2RAs) were the only pharmacological options prescribed for SUP in the current study, with H2RAs being more frequently prescribed. Of the 426 patients received SUP, 370 (86.9%) patients received H2RAs of which ranitidine was the only agent used, and 56 (13.1%) patients received PPIs of which omeprazole was the most commonly used (83.92%). Moreover, 391 (91.8%) patients were administered the drug parenterally while 35 (8.2%) patients were administered the drug enterally (oral or through nasogastric tube) (Table 5).

Adherence of SUP practice in this study to the ASHP guidelines for all aspects of SUP use (indication, dose, route of administration and duration) was fulfilled in 74 cases only (16.7%). *Indication* adherence rate to ASHP guidelines was 36.4%. No significant differences were found among hospitals in the *overall* or *indication* adherence rates (Table 6).

Adherence rates for each SUP parameter (dose, route, duration) in patients to whom SUP was indicated and administered (N= 151) are shown in (Table 6). The dose was concordant with guidelines in 96 (63.6%) of the 151 evaluated cases. Significant differences were shown among hospitals with the highest *Dosing* adherence rate was shown in SMC (82.5%) (P-value < 0.001). SUP was given to 103 (68.2%) patients in an appropriate route. Yet, in 48 (31.8%) patients SUP was administered parenterally while patients were able to tolerate enteral route (where they were taking other drugs via enteral route). Significant differences were shown among hospitals with the highest *route* of *administration* adherence rate observed in EGH (81.6%) (P-value = 0.002). With regard to SUP *duration*, SUP was administered for the appropriate duration (i,e until the risk factors were resolved) in 133 (88.1%) patients. No significant differences were shown among hospitals (P-value = 0.351) (Table 6).

In this study; 16 (3.6%) patients did not receive SUP and did not develop adverse effects. Of the 426 patients prescribed SUP, 48 (11.3%) patients developed adverse effects, 15 patients (31.25%) had nosocomial pneumonia, 24 (50%) patients had Clostridium difficile infection (CDI) and 9 (18.75%) patients had both infections (Fig. 1).

Table 4 : Risk factors for SRMD**.**

Variables	Total N=442 n (%)	SMC N=163 n (%)	EGH N=153 n (%)	NMC N=126 n (%)	P-value [a]
Major risk factors					
Coagulopathy [b]	73 (16.5)	25 (15.3)	36 (23.5)	12 (9.5)	0.006 [c]
Renal failure [d]	63 (14.3)	17 (10.4)	10 (6.5)	36 (28.6)	< 0.001 [c]
Respiratory failure: MV > 48 hours	46 (10.4)	16 (9.8)	14 (9.2)	16 (12.7)	0.598 [c]
Head injury with GCS of ≤10	29 (6.6)	19 (11.7)	8 (5.2)	2 (1.6)	0.002 [c]
Hepatic failure [e]	12 (2.7)	4 (2.5)	3 (2)	5 (4)	0.571 [c]
History of gastric ulceration or bleeding during year before admission	8 (1.8)	3 (1.8)	5 (3.3)	0 (0)	0.125 [c]
Multiple trauma with ISS of ≥16	7 (1.6)	4 (2.5)	3 (2)	0 (0)	0.228 [c]
Hepatic or renal transplantation	3 (0.7)	1 (0.6)	0 (0)	2 (1.6)	0.273 [c]
Spinal cord injury	2 (0.5)	2 (1.2)	0 (0)	0 (0)	0.179 [c]
Thermal injury involving >35% of body surface area	1 (0.2)	1 (0.6)	0 (0)	0 (0)	0.424 [c]
Partial hepatectomy	1 (0.2)	1 (0.6)	0 (0)	0 (0)	0.424 [c]
Minor risk factors					
Corticosteroids therapy [f]	93 (21)	34 (20.9)	33 (21.6)	26 (20.6)	0.980 [c]
Sepsis [g]	69 (15.6)	18 (11)	26 (17)	25 (19.8)	0.105 [c]
ICU stay of more than 1 week	20 (4.5)	10 (6.1)	5 (3.3)	5 (4)	0.443 [c]

N: Number of patients in each group, n (%): Percentages are given within parentheses with the total number of patients in each group as denominator.

[a] P-value ≤ 0.05 was considered significant, [b] Coagulopathy: platelet count <50 000 per mm^3, international normalized ratio >1.5 or partial thromboplastin time >2.0 times the control value, [c] Chi-Square Test, [d] Renal failure: a creatinine clearance rate < 40 mL $minute^{-1}$ or a serum creatinine concentration >2.8 mg dL^{-1}, [e] Hepatic failure: any two of the following: a serum bilirubin concentration >8.8 mg dL^{-1}, a serum aspartate aminotransferase level >500 U L^{-1}, a serum albumin level <41 g L^{-1}, and clinical signs and symptoms of hepatic coma, [f] Corticosteroids therapy (>250 mg hydrocortisone or equivalent daily), [g] Sepsis: core temperature >38.5 or < 35.0°C, a white blood cell count >15 000 or < 3000 per mm^3 and a positive blood culture. SMC: Al Shifa Medical Complex, EGH: European Gaza Hospital, NMC: Nasser Medical Complex, MV: Mechanical ventilation, GCS: Glasgow coma score, ISS: injury severity score.

Table 5: SUP use patterns**.**

Variable	Total	SMC	EGH	NMC	P-value [a]
Prevalence of SUP use n (%)[b]	426 (96.4)	162 (99.4)	145 (94.8)	119 (94.4)	0.035 [c]
Pharmacological agents used n (%)[d]					
H2RA (Ranitidine)	370 (86.9)	156 (96.3)	138 (95.2)	76 (63.9)	
PPIs	56 (13.1)	6 (3.7)	7 (4.8)	43 (36.1)	
Omeprazole	47 (11.0)	6 (3.7)	5 (3.4)	36 (30.2)	< 0.001 [c]
Esomeprazole	7 (1.6)	0 (0)	0 (0)	7 (5.9)	
Pantoprazole	2 (0.5)	0 (0)	2 (1.4)	0 (0)	
Route of administration n (%)[d]					
Parenteral	391 (91.8)	159 (98.1)	142 (97.9)	90 (75.6)	< 0.001 [c]
Enteral	35 (8.2)	3 (1.9)	3 (2.1)	29 (24.4)	
Duration of AST (Day): Median (IQR) [e]	2 (3)	2 (3)	2 (2)	3 (3)	0.028 [f]

n (%): Percentages are given within parentheses with the total number of patients in each group as denominator.

[a] P-value ≤ 0.05 was considered significant, [b]Denominator as total number of patients (442 in all hospitals, 153 in EGH, 163 in SMC, 126 in NMC), [c] Chi-Square Test, , [d] Denominator as number of patients received SUP (426 in all hospitals, 145 in EGH, 162 in SMC, 119 in NMC), [e] The median was reported since these variables were positively skewed, [f] Kruskal-Wallis test. AST: Acid suppressant therapy, SUP: Stress ulcer prophylaxis, SMC: Al Shifa Medical Complex, EGH: European Gaza Hospital, NMC: Nasser Medical Complex, IQR: Interquartile range.

Table 6: Adherence of SUP practice to ASHP Guidelines**.**

	All hospitals	EGH	SMC	NMC	P-value[a]
Overall **adherence n (%)[b]**	74 (16.7%)	26 (17)	30 (18.4)	18 (14.3)	0.645
Indication **adherence n (%)[b]**	161 (36.4)	55 (35.9)	57 (35)	49 (38.9)	
Indicated and administered n (%)[b]	151 (34.1)	49 (32)	57 (35)	45 (35.7)	
Not indicated and not administered n(%)[b]	10 (2.3)	6 (3.9)	0 (0)	4 (3.2)	0.213
Indication **non-adherence n (%)[b]**	281 (63.6)	98 (64.1)	106 (65)	77 (61.1)	
Indicated but not administered n (%)[b]	6 (1.4)	2 (1.3)	1 (0.6)	3 (2.4)	
Not indicated but administered n (%)[b]	275 (62.2)	96 (62.8)	105 (64.4)	74 (58.7)	
Dosing **adherence n (%)[c]**	96 (63.6)	28 (57.1)	47 (82.5)	21 (46.7)	<0.001
Route of administration **adherence n (%)[c]**	103 (68.2)	40 (81.6)	41 (71.9)	22 (48.9)	0.002
Duration **adherence n (%)[c]**	133 (88.1)	41 (83.7)	50 (87.7)	42 (93.3)	0.351

[a] Chi-square test was used for comparisons. P-values ≤ 0.05 were considered significant.
n (%) percentages are given within parentheses with the total number of patients in each group as the denominator.
[b] Denominator as total number of patients (442 in all hospitals, 153 in EGH, 163 in SMC, 126 in NMC)
[c] Denominator as number of patients for whom SUP was indicated and administered (151 in all hospitals, 49 in EGH, 57 in SMC, 45 in NMC).

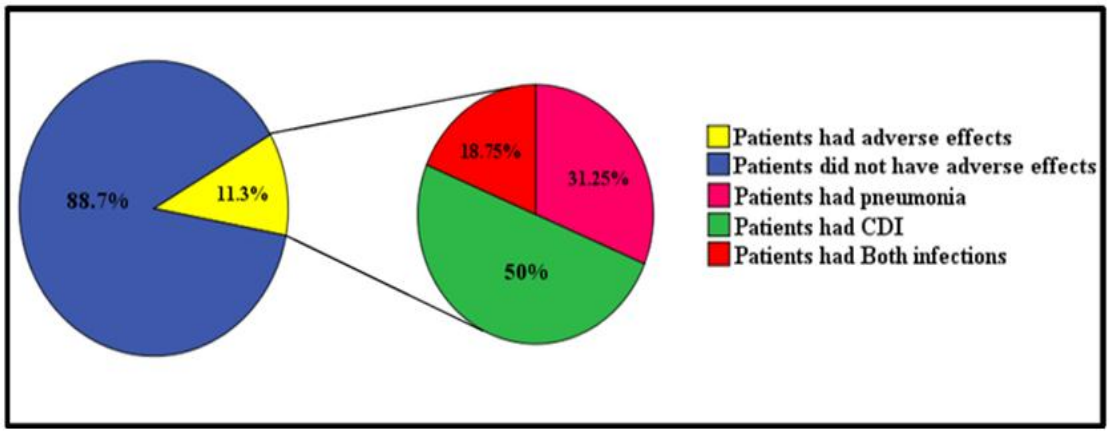

Fig. 1: Prevalence of SUP adverse effects . Total number of patients = 426. Of the 426 patients prescribed SUP, 48 (11.3%) patients developed adverse effects, 15 patients (31.25%) had nosocomial pneumonia, 24 (50%) patients had CDI and 9 (18.75%) patients had both infections. CDI: *Clostridium difficile* infection.

Discussion

This study represents the first attempt to assess the degree of adherence of current SUP practice in our hospitals to the international standards, namely the ASHP guidelines. It is an important step in developing strategies to improve the rational use of gastric acid suppressive therapy in Gaza Strip hospitals.

The current study involved 442 ICU patients in the largest governmental hospitals in the Gaza strip. We found that 96.4% of the patients received SUP. Similar results were

obtained by a number of studies worldwide[25&35&37]. Retrospective observational studies from Switzerland and Germany found that 92.9% and 91.3% of ICU patients received SUP, respectively[25&37]. In Iran, a prospective interventional study found that 81.2% of patients received prophylactic treatments[35]. Lower SUP use rates (73%), however, were found in an international survey carried out in 97 adult ICUs in 11 European countries[38].

Regarding the choice of SUP drugs; H2RAs and PPIs were the only drug classes prescribed in our study, with H2RAs being much more frequently used (in 86.9% of patients). Similarly, Rafinazari *et al.,*[39] found that ranitidine was the most prescribed agent for SUP upon ICU admission in Isfahan, Iran. In their study, as in ours, most patients were surgically operated patients so physicians might have believed that moderate SUP administration (H2RAs not PPIs) was sufficient. In our hospitals, the availability of intravenous PPIs is limited due to cost issues. This may explain why ranitidine was the most commonly used agent for SUP considering that most SUP were delivered by the intravenous route. Our results are also consistent with those of a survey by Preslaski *et al.,*[40]. They found that US critical care physicians used either H2RAs or PPIs for SUP with a preference for H2RAs. Some studies, however found PPIs were more commonly prescribed[37& 41& 42]. In the current study, other agents such as antacids, misoprostol and sucralfate, were not used. Those agents are generally less commonly used for SUP worldwide. Antacids are no longer considered a viable treatment option due to frequent dosing and potential side effects[43]. For misoprostol, the profile of drug interactions, side effects, lack of overall efficacy and availability of alternatives preclude its use in current medical practice[32]. Sucralfate is considered comparable to H2RAs in the prevention of SRMD[44]. However, its potential for drug-drug interactions and the availability of intravenous H2RAs and PPIs limits its use[1].

In the current study , only 74 patients were eligible for SUP and received it in the appropriate dose, route of administration and duration. Thus, overall adherence rate was 16.7%. Comparing those results to other studies was challenging as most of the studies investigating SUP use assessed mainly the eligibility of patients to SUP (indication adherence), with much less emphasis on the appropriateness of other aspects of SUP use such as dosing and route of administration. A study from Lebanon assessed those aspects, yet, it involved patients from medical, surgical wards in addition to the ICUs. Nevertheless, the reported overall adherence rate to ASHP guidelines in the study was 12.4%[32]. In our study, among different aspects of SUP use, adherence rate was lowest for *indication* (36.4%), while 62.2% of patients received SUP which was not indicated for them. Those results were comparable to other studies from Lebanon and Qatar where SUP was indicated in only 33% and 34% of patients receiving SUP, respectively[32&33]. Better indication adherence was observed in Iran (61.5%)[39], while a lower indication adherence rate was observed in a Jordanian study (14%)[29]. Many reasons might have contributed to the high degree of inappropriate use of SUP in our study. One of them could be the absence of written guidelines for SUP in the different study settings. From researcher observations, practitioners were unaware of the different international guidelines. Another reason for suboptimal SUP practice could be the absence of clinical pharmacists in our hospitals. Active involvement of clinical pharmacists in the healthcare team became essential, especially where medications that need a great degree of attention are dealt with as in the ICUs[45]. Clinical pharmacists in the ICUs were shown to improve adherence to practice guidelines and reduce inappropriate SUP prescriptions with subsequent significant cost savings[46& 47].

With regard to other aspects of SUP use; *Dosing*, and *duration* were appropriate in 63.6%, and 88.1% of patients, *respectively*. In addition, *route of administration* was appropriate in 68.2% of patients, yet, 31.8% patients were administered drugs parenterally while they were able to tolerate enteral route. Such inappropriate practice may be due to the misconception that parenteral medications are more effective than oral ones[32]. However, several studies have shown comparable efficiencies of intravenous and oral routes of administration in suppressing gastric acid secretion[48-49]. Thus, to minimize the adverse effects and additional costs of parenteral administration, the parenteral route should be reserved for patients who cannot tolerate oral medications.

When interpreting the findings of the current study, it is worth mentioning some

limitations that we would like to point out. First, this study evaluated the SUP practice in ICUs only and did not evaluate the adherence rate in other departments. Second, the study was conducted in governmental hospitals only and did not include non-governmental hospitals. Finally, in this observational study we cannot assess the correlation between the use of SUP and the occurrence of adverse effects such as nosocomial pneumonia and CDI due to the small number of patients who did not take SUP (3.6% compared with 96.4% of the other group who took SUP), so unbiased comparison was not allowed.

Conclusion

Little is known about SUP practice in Palestine. This study assessed the appropriateness of SUP practice by comparing it with the ASHP guidelines at three governmental hospitals in the Gaza Strip, Palestine. Adherence rates to standards of practice were extremely low. The results of this study highlighted a need for implementing correction measures such as establishing and practice within Palestinian hospitals, their own guidelines. As well as , the need of active participation of clinical pharmacists in critical care settings.

REFERENCES

1. M.P. Plummer, A.R. Blaser, and A.M. Deane, "Stress ulceration: prevalence, pathology and association with adverse outcomes", ***Crit Care,*** 18(2), 213 (2014).
2. S. Marker, M. Barbateskovic, A. Perner, J. Wetterslev, J.C. Jakobsen, M. Krag, A. Granholm, C.T. Anthon and M.H. Møller, "Prophylactic use of acid suppressants in adult acutely ill hospitalised patients: a systematic review with meta-analysis and trial sequential analysis", ***Acta Anaesthesiol Scand,*** 64(6), 714-728 (2020).
3. S. Chumnumwat, P. Dilokpatanamongkol, T. Wiriyanont, T. Sricholwattana, N. Lekpittaya, P. Sa-ngasoongsong and P. Sumritpradit, "Compliance with Guidelines for Stress Ulcer Prophylaxis in Surgical and Orthopedic Units at Ramathibodi Hospital", ***J Med Assoc Thai,*** 101(1),58-62 (2018).
4. R.D. Collins, "Stress Ulcer Prophylaxis in the Critically Ill Oncology Population", ***Oncol Crit Care,*** 137-151 (2020).
5. M. Alshahrani, and W. Alhazzani, "Stress ulcer prophylaxis: Back to square one", ***Saudi Crit Care J,*** 1(6), 31-33 (2017).
6. A. Alshami, S.V. Barona, J. Varon and S. Surani, "Gastrointestinal stress ulcer prophylaxis in the intensive care unit, where is the data?", ***World J Meta-Anal,*** 7(3), 72-76 (2019)
7. A.C. Faust, K.L. Echevarria, R.L. Attridge, L. Sheperd and M.I.Restrepo, "Prophylactic acid-suppressive therapy in hospitalized adults: indications, benefits, and infectious complications", ***Crit Care Nurse,*** 37(3), 18-29 (2017)
8. M. Barbateskovic, S. Marker, J.C. Jakobsen, M. Krag, A. Granholm, C.T. Anthon, A. Perner, J. Wetterslev and M.H. Møller, "Stress ulcer prophylaxis in adult intensive care unit patients - a protocol for a systematic review", ***Acta Anaesthesiol Scand,*** 62(6),744-755 (2018)
9. M. Bardou, , J.P. Quenot, and A. Barkun, "Stress-related mucosal disease in the critically ill patient", ***Nat Rev Gastroenterol Hepatol,*** 12(2), 98-107 (2015)
10. M. Krag, A. Perner, J. Wetterslev, M.P. Wise, M. Borthwick, S. Bendel, C. McArthur, D. Cook, N. Nielsen, P. Pelosi, F. Keus, A.B. Guttormsen, A.D. Moller, M.H. Møller and SUP-ICU Collaborators, "Stress ulcer prophylaxis in the intensive care unit: an international survey of 97 units in 11 countries", ***Acta Anaesthesiol Scand,*** 59(5), 576-585 (2015)
11. J.F. Barletta, M.S. Buckley, and R. MacLaren, "The SUP-ICU trial: does it confirm or condemn the practice of stress ulcer prophylaxis?", ***Hosp Pharm,*** 55(2), 96-101 (2020).
12. L. Cholin, T. Ashour, A. Mehdi, *et al.*, "Proton-pump inhibitor vs. H2-receptor blocker use and overall risk of CKD progression", ***BMC Nephrol,*** 22(1), 264 (2021).
13. A. Granholm, L. Zeng, J.C. Dionne, A. Perner, S. Marker, M. Krag, R. MacLaren, Z. Ye, M.H. Møller, W. Alhazzani and GUIDE Group, "Predictors of

gastrointestinal bleeding in adult ICU patients: a systematic review and meta-analysis", ***Intensive Care Med,*** 45(10), 1347-1359 (2019)

14. M. Krag, A. Perner, J. Wetterslev and M.H. Møller, "Stress ulcer prophylaxis in the intensive care unit: is it indicated? A topical systematic review", ***Acta Anaesthesiol Scand,*** 57(7), 835-47 (2013)
15. A. Rhodes, L.E. Evans, W. Alhazzani, *et al.,* "Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016", ***Intensive Care Med,*** 43(3), 304-377 (2017)
16. J.F. Barletta, J.J. Bruno, M.S. Buckley and D.J. Cook, "Stress ulcer prophylaxis", ***Crit Care Med,*** 44(7), 1395-1405 (2016)
17. R. MacLaren, L.E. Kassel, T.H. Kiser and D.N. Fish, "Proton pump inhibitors and histamine-2 receptor antagonists in the intensive care setting: focus on therapeutic and adverse events", ***Expert Opin Drug Saf,*** 14(2), 269-280 (2015)
18. ASHP, "ASHP Therapeutic Guidelines on Stress Ulcer Prophylaxis. ASHP Commission on Therapeutics and approved by the ASHP Board of Directors on November 14, 1998*",* ***Am J Health Syst Pharm,*** 56(4), 347-379 (1999).
19. Z. Ye, A. Reintam Blaser, L. Lytvyn, *et al.,* "Gastrointestinal bleeding prophylaxis for critically ill patients: a clinical practice guideline", ***BMJ,*** 368,l6722 (2020).
20. O.D. Guillamondegui, J. Gunter, L.Oliver, J. A. Bonadies, J. E. Coates, S. J. Kurek, M.A. De Moya and A.J. Sori, *"Practice management guidelines for stress ulcer prophylaxis",* ***Eastern Association for the Surgery of Trauma,*** (2008). https://www.east.org/education-career-development/practice-management-guidelines/details/stress-ulcer-prophylaxis
21. C. Bez, N. Perrottet, T. Zingg, E.L. Leung Ki, N. Demartines and A. Pannatier, "Stress ulcer prophylaxis in non-critically ill patients: a prospective evaluation of current practice in a general surgery department", ***J Eval Clin Pract,*** 19(2), 374-378 (2013).
22. B.A. Horsa, , Y. Ayele, and M.B. Ayalew, "Assessment of pharmacologic prophylaxis use against stress ulcer in the medical wards of University of Gondar Hospital", ***SAGE Open Med,*** 7, 2050312119827409 (2019).
23. S.M. Masoompour, R. Kasaee, and H. Mahdavi azad, "Evaluation of adherence to American Society of Health-System Pharmacists guidelines*",* ***Gastroenterol Nurs,*** 40(6), 491-495 (2017)
24. A.L. Oh, A.G. Tan, H.S. Phan, *et al.*, "Indication of acid suppression therapy and predictors for the prophylactic use of protonpump inhibitors vs. histamine-2 receptor antagonists in a Malaysian tertiary hospital", ***Pharm Pract,*** 13(3), 633 (2015).
25. M. Franchitti, J. Piubellini, F. Sadeghipour, P. Eckert, P. Voirol, and A.G. Schneider, "Adequacy of stress ulcer prophylaxis prescription in the intensive care unit: an observational study", ***Swiss Med Wkly,*** 150,w20322 (2020).
26. W. Frandah, J. Colmer-Hamood, K. Nugent and R. Raj, "Patterns of use of prophylaxis for stress-related mucosal disease in patients admitted to the intensive care unit", ***J Intensive Care Med,*** 29(2), 96-103 (2014)
27. Y. Santos, M. S .Younes-Ibrahim, L. L. Crozatti, D. Raglione, L.Cardozo Junior, B. Besen, L. U Taniguchi, M. Park, and P.V. Mendes, "Adherence to a stress ulcer prophylaxis protocol by critically ill patients: a prospective cohort study", ***Rev Bras Ter Intensiva,*** 32(1), 37–42 (2020).
28. F. Shahbazi, H. Karimpur, and E. Hosseini, "Implementation of stress ulcer prophylaxis (SUP) in an intensive care unit (ICU)", ***J Pharm Res Int,*** 31(6),1-7, (2019).
29. M.A.Y. Alqudah, S. Al-azzam, K. Alzoubi, M. Alkhatatbeh and N. Rawashdeh, "Overuse of proton pump inhibitors for stress ulcer prophylaxis in Jordan", ***Int J Clin Pharmacol Ther,*** 54(8), 597-602 (2016).
30. M.S. Alsultan, A.Y. Mayet, A.A. Malhani and M.K. Alshaikh, "Pattern of intravenous proton pump inhibitors use in ICU and Non-ICU setting: a prospective

observational study", ***Saudi J Gastroenterol,*** 16(4), 275-279 (2010).
31. I.A. Issa, O. Soubra, H. Nakkash, and L. Soubra,"Variables associated with stress ulcer prophylaxis misuse: a retrospective analysis", ***Dig Dis Sci,*** 57(10), 2633-2641 (2012).
32. A. Zeitoun, M. Zeineddine, and H. Dimassi, "Stress ulcer prophylaxis guidelines: Are they being implemented in Lebanese health care centers?", ***World J Gastrointest Pharmacol Ther,*** 2(4), 27-35 (2011)
33. I. F. Khudair, N.D. Sadik, and Y.I. Hanssens, "Prescribing pattern of acid suppressive medications for medical inpatients in a teaching hospital in Qatar", ***Saudi Med J,*** 30(1), 125-129 (2009).
34. W.W. Daniel, editor, "*Biostatistics: a foundation for analysis in the health sciences"* 7th ed, John Wiley & Sons, New York 1999.
35. L. Mahmoudi, , R. Mohammadi, and R. Niknam, "Economic impact of pharmacist interventions on correction of stress-related mucosal damage prophylaxis practice", ***Clinicoecon Outcomes Res,*** 11, 111-116 (2019).
36. L. L.M anning-Dimmitt, S.G. Dimmitt, and G. R. Wilson, "Diagnosis of gastrointestinal bleeding in adults", ***Am Fam Physician,*** 71(7), 1339-1346 (2005).
37. L. Buendgens, J. Bruensing, M. Matthes, H. Dückers, T. Luedde, C. Trautwein, F. Tacke and A. Koch, "Administration of proton pump inhibitors in critically ill medical patients is associated with increased risk of developing Clostridium difficile-associated diarrhea", ***J Crit Care,*** 29(4), 696, e11-696.e15 (2014).
38. M. Krag, A. Perner, J. Wetterslev, M.P. Wise, M. Borthwick, S. Bendel, C. McArthur, D. Cook, N. Nielsen, P. Pelosi, F. Keus, A.B. Guttormsen, A.D. Moller, M. H. Møller and SUP-ICU Collaborators, "Prevalence and outcome of gastrointestinal bleeding and use of acid suppressants in acutely ill adult intensive care patients", ***Intensive Care Med,*** 41(5), 833-845 (2015)
39. N. Rafinazari, S. Abbasi, S. Farsaei, M. Mansourian and P. Adibi, "Adherence to stress-related mucosal damage prophylaxis guideline in patients admitted to the Intensive Care Unit", ***J Res Pharm Pract,*** 5(3), 186-192 (2016).
40. C.R. Preslaski, S.W. Mueller, T.H. Kiser, D.N. Fish and R. MacLaren, "A survey of prescriber perceptions about the prevention of stress-related mucosal bleeding in the intensive care unit", ***J Clin Pharm Ther,***39(6), 658-662 (2014).
41. J.F. Barletta, S. Kanji, R. MacLaren, I. Lat and B.L. Erstad, American-Canadian consortium for Intensive care Drug utilization (ACID) Investigators. "Pharmacoepidemiology of stress ulcer prophylaxis in the United States and Canada", ***J Crit Care,*** 29(6), 955-960 (2014).
42. A. Kochar, P. Palabindela, C. Patel, S. Shaikh, D. Tager, S. Kemper, H. Mohamed and B. McJunkin, "Assessing the Appropriateness of Stress Ulcer Prophylaxis in Critically Ill ICU Patients at CAMC", ***Am J Gastroenterol,***113, S317-S317 (2018).
43. M.J. Spirt, "Stress-related mucosal disease: risk factors and prophylactic therapy", ***Clin Ther,*** 26(2), 197–213 (2004).
44. M. Tryba, "Sucralfate versus antacids or H2-antagonists for stress ulcer prophylaxis: a meta-analysis on efficacy and pneumonia rate", ***Crit Care Med,*** 19(7), 942–949 (1991)
45. C.R. Preslaski, I. Lat, R. MacLaren and J. Poston. "Pharmacist contributions as members of the multidisciplinary ICU team", *Chest*, 144(5), 1687-1695 (2013).
46. M.S. Buckley, A.S. Park, C.S. Anderson, J.F. Barletta, D.S. Bikin, R.D. Gerkin, C.W. O'Malley, L.M. Wicks, R. Garcia-Orr and S.L. Kane-Gill, "Impact of a clinical pharmacist stress ulcer prophylaxis management program on inappropriate use in hospitalized patients", ***Am J Med,*** 128(8), 905-913 (2015)
47. U. Masood, A. Sharma, Z. Bhatti, J. Carroll, A. Bhardwaj, D. Sivalingam and A.S. Dhamoon, "A Successful Pharmacist-Based Quality Initiative to Reduce Inappropriate Stress Ulcer Prophylaxis Use in an Academic Medical Intensive

Care Unit", ***Inquiry,*** 55, 46958018759116 (2018).

48. A. Tringali, R. Manta, M. Sica, G. Bassotti, R. Marmo and M. Mutignani, "Comparing intravenous and oral proton pump inhibitor therapy for bleeding peptic ulcers following endoscopic management: a systematic review and meta-analysis", ***Br J Clin Pharmacol,*** 83(8), 1619-1635 (2017).
49. K. Tsoi , H. Hirai and J. Sung, "Meta-analysis: comparison of oral vs. intravenous proton pump inhibitors in patients with peptic ulcer bleeding", ***Aliment Pharmacol Ther,***38(7), 721-728 (2013).

Bull. Pharm. Sci., Assiut University, Vol. 45, Issue 2, 2022, pp. 845-857.

نشرة العلوم الصيدليـــــة
جامعة أسيوط

BULL. PHARM. SCI. Assiut Univ.

تقييم استخدام أدوية الوقاية من قرحة الإجهاد لدى مرضى العناية المركزة في قطاع غزة / فلسطين

هلا زكريا إبراهيم الأغا* – نسائم رمضان محمد المبحوح

قسم علم الأدوية و العلوم الطبية ، كلية الصيدلة ، جامعة الأزهر، غزة، فلسطين، صندوق بريد ١٢٧٧

تهدف هذه الدراسة إلى تقييم درجة الالتزام بالمبادئ التوجيهية للعلاج الوقائي من قرحة الإجهاد للجمعية الأمريكية لصيادلة النظام الصحي (ASHP) لدى مرضى العناية المركزة في المستشفيات الحكومية الرئيسية الثلاث في قطاع غزة – فلسطين.

الدراسة الحالية هي دراسة مستقبلية، تمت من خلال متابعة السجلات الطبية للمرضى البالغين في وحدات العناية المركزة على مدى ستة أشهر. وقد تم فيها تقييم استخدام أدوية الوقاية من قرحة الإجهاد من النواحي التالية: اتخاذ القرار المناسب باستخدام هذه الأدوية من عدمه ، الجرعة الدوائية ، طريقة إعطائها ، و مدة استخدامها.

شملت الدراسة 442 مريضًا. تم إعطاء ٤٢٦ منهم (٩٦.٤%) أدوية الوقاية. كان أكثر الأدوية استخدامًا هو الرانتيدين وريدياً بنسبة (٨٦.٩%). تم تحقيق الالتزام الشامل للمبادئ التوجيهية للعلاج الوقائي في٧٤ حالة فقط بنسبة (١٦.٧%). أقل معدل للالتزام بالمبادئ التوجيهية كان يخص اتخاذ القرار المناسب باستخدام أدوية الوقاية من عدمه وكان بنسبة (٣٦.٤%)، بينما كان أعلى معدل التزام(٨٨.١%) يخص مدة استخدامها ، يليه طريقة الإعطاء(٦٨.٢%) ، ثم الجرعة (٦٣.٦%) . من بين ٤٢٦ مريضًا وصفت لهم أدوية الوقاية ، أصيب٤٨ مريضًا (١١.٣%) بآثار جانبية.

لقد أظهرت الدراسة الحالية ضعف الالتزام بالمبادئ التوجيهية للعلاج الوقائي من قرحة الإجهاد في مستشفيات قطاع غزة مما يستدعي اتخاذ استراتيجيات مناسبة لضمان الاستهلاك الرشيد لهذه الأدوية .