Stress ulcer prophylaxis use in critical care units at public hospitals in Johannesburg, South Africa

N Biyase,1 MB ChB, DA (SA), FCA (SA), MMed (Anaes); OrcID 0000-0002-2120-0162; H Perrie,1 MSc; OrcID 0000-0002-9890-7887; J Scribante,2 PhD; OrcID 0000-0002-2221-5024; M Mutsche,1 MB ChB, MSc; OrcID 0000-0002-8593-3592; S Chetty,2 MB ChB, DCH (SA), DA (SA), FCA (SA), Cert Crit Care, PhD; OrcID 0000-0002-9878-5488

1 Department of Anaesthesiology, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
2 Department of Anaesthesiology and Critical Care, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

Corresponding author: N Biyase (nana.biyase@yahoo.com)

Background. Stress ulcer prophylaxis (SUP) is part of the management of critically ill patients in intensive care units (ICUs). However, inappropriate use of these drugs has important clinical implications such as ventilator-associated pneumonia and Clostridium difficile-associated gastrointestinal tract infections. The overuse of proton pump inhibitors (PPIs) as SUP is a rapidly growing problem globally.

Objective. To describe the use of SUP in three selected ICUs in Johannesburg, South Africa (SA).

Methods. A retrospective, descriptive, contextual study design was used. Data were collected from ICU records of adult patients admitted into these units during the study period (1 August 2013 - 31 October 2013).

Results. A total of 174 patients were included in the study. Of these, 156 were on SUP and only 38.5% (n=60/156) were appropriately treated with SUP according to the American Society of Health-System Pharmacists guidelines. There was an inappropriate use of SUP in over 50% of those who were treated. The most frequently prescribed SUP was histamine-2 receptor antagonist (H2RA) (51.3%; n=80/156), followed by PPIs (30.8%; n=48/156), sulcalfate (17.3%; n=27/156), and a combination of PPI and H2RA (0.6%; n=1/156).

Conclusion. The study demonstrated overuse of SUP. The most commonly used drug for SUP was H2RA and not PPIs. This study demonstrates that the problem of SUP overuse internationally also exists locally. The development of local guidelines may help to improve the practice of SUP in SA.

Keywords: stress ulcer prophylaxis, critically ill, proton pump inhibitors, gastrointestinal bleeding

South Afr J Crit Care 2021;37(1):16-20. https://doi.org/10.7196/SAJCC.2021.v37i1.439

Contribution of the study. This study showed overuse of SUP and should encourage doctors to critically evaluate why they prescribe SUP and whether it is really indicated. This should help in the adoption of practices towards appropriate use of SUP.

Stress ulcer-related gastrointestinal (GI) mucosal bleeding was a common occurrence in critically ill patients in the past; however, over the years, the prevalence has decreased. This has been attributed to the advancement of medical practice, a better understanding of the conditions that predispose patients to GI stress ulceration and adoption of preventive measures. Stress ulcer prophylaxis (SUP) is one of the cornerstones of the preventive measures used to treat GI ulcers in the critically ill. This has regrettably led to the international trend of SUP overuse.

The physiological stress associated with critical illness leads to GI hypoperfusion, accumulation of acid and micro-ischaemia of the upper GI mucosal lining. These changes result in stress-related mucosal disease, which includes erosions, occult bleeding and clinically significant bleeding (CSB). The occurrence of CSB increases the length of hospital stay, medical cost and transfusion requirements.

Mechanical ventilation (MV) for at least 48 hours and coagulopathy are the two proven independent major risk factors for developing CSB. Interventions with acid suppressive therapy (i.e. proton pump inhibitors (PPIs) and histamine-2 receptor antagonist (H2RA)) in the high-risk groups can decrease the occurrence of CSB by 50%. The use of SUP in this group of patients is therefore recommended. However, there is a widespread inappropriate use of SUP in patients with low risk of CSB, with the most frequently used agent being PPIs.

There is growing international concern over the overuse of SUP, especially PPIs, as they have been implicated in hospital-acquired infections such as ventilator-associated pneumonia (VAP) and Clostridium difficile-associated GI infections. In a landmark study by Cook et al., MV for at least 48 hours and coagulopathy were associated with a 3.7% chance of CSB, whereas patients without these risk factors had only 0.1% risk of developing CSB. The American Society of Health-System Pharmacists (ASHP) guidelines recommended that only patients with one major, or two or more minor risk factors should receive SUP. Use outside of these guidelines is therefore deemed as inappropriate in this study. In South Africa (SA), there are no national guidelines governing the prescription of SUP.

The overuse of PPIs as SUP is well described in the literature; however, the use of PPIs for SUP in SA has not been described. The objectives of this study were to describe the use of SUP in three selected intensive care units (ICUs) in Johannesburg, and to identify the risk factors that necessitated
the initiation of SUP therapy. The study also sought to describe the use of SUP in accordance with the ASHP guidelines. In addition, we also aimed to determine what constitutes appropriate use of PPIs.

Methods

All complete and legible ICU charts of adult patients admitted into the ICUs of the three selected hospitals affiliated to the University of the Witwatersrand (referred to as ICU A, B and C) were included. We excluded those with existing upper GI bleeding, previous total gastrectomy, on pre-existing PPI therapy prior to ICU admission, patients who died, and those who were discharged 24 hours after admission to ICU. A consecutive and convenience sampling method was used and the number of patients admitted into the ICUs over a 3-month study period (1 August 2013 - 31 October 2013) determined the sample size. These are closed ICUs with both medical and surgical patients.

A data collection sheet was compiled following an extensive literature review ensuring content validity. The data collection sheet captured the following data: patient characteristics, risk factors for CSB, SUP received in ICU, and time to commencement of enteral feeds after starvation. In the current study, the following definitions were adopted: major risk factors were MV for more than 48 hours and coagulopathy (platelet <50 000/mm$^3$; international normalised ratio (INR) >1.5); minor risk factors were acute renal failure, acute hepatic failure, sepsis, hypotension, history of upper GI bleeding, burns >35% of body surface area, hydrocortisone >250 mg/d or equivalent and major surgery: and CSB was overt bleeding associated with haemodynamic changes and decrease in haemoglobin in 24 hours.\textsuperscript{[4]}

The data were collected by NB and entered into a Microsoft Excel spreadsheet (Microsoft, USA). Appropriate use of SUP was regarded as the initiation of SUP in the presence of one or more major risk factors, or the presence of two or more minor risk factors.\textsuperscript{[4,5]} SUP was regarded as inappropriate in the presence of only one minor risk factor or the absence of risk factors. For the purpose of this study, omission of treatment in patients who qualified for SUP was classified as inappropriate SUP therapy.

Approval to conduct the study was obtained from the University of the Witwatersrand Human Research Ethics Committee (ref. no. M130104) and other relevant authorities. A retrospective, descriptive, contextual study design was used.

Stata software version 14 (Stata Corp., USA) was used to analyse data in consultation with a biostatistician. The continuous variables were not normally distributed and were described with medians and interquartile range (IQR). Pearson’s $\chi^2$ test and Fisher's exact test were used for comparison of appropriate and inappropriate use of SUP. The Mann-Whitney U-test and Wilcoxon rank-sum test were used for independent and dependent samples, respectively. A $p$-value <0.05 was considered to be statistically significant.

Results

A total of 174 patients were included in the study. The patients’ demographic data are presented in Table 1. A combination of major and minor risk factors were the reasons for the initiation of SUP in the majority (35.6%; n=62) of cases at the three ICUs (Fig. 1). MV was the most frequent major risk factor at the three ICUs (ICU A: n=47/56; ICU B: n=19/23; ICU C: n=24/30). Only 4 patients (ICU A: n=1/56; ICU C: n=3/30) were initiated on SUP because of coagulopathy. There were only 15 patients (ICU A: n=8/56; ICU B: n=4/23; ICU C: n=3/30) initiated on SUP for a combination of both major risk factors.

The practice of SUP in the three ICUs is presented in Table 2. A total of 156 patients were on SUP. The characteristics of the patients on SUP and the relationship between the appropriateness of SUP and drugs used are shown in Table 3. PPI use is higher in the inappropriate category (Table 3).

The comparison of prescription practices among the three ICUs shows that the facility influenced the drug prescribed. Inappropriate PPI use was associated with patients from internal medicine, general surgery and orthopaedics/trauma ($p<0.001$). Of the 174 patients included in the study, 10.3% (n=18) had risk factors for developing CSB and did not receive any prophylaxis.

Discussion

The routine use of SUP in patients who are not at risk of developing CSB is reported to be on the rise in ICUs across the world, with PPIs being the commonly prescribed agents.\textsuperscript{[6]} Factors such as costs, availability of stock and local guidelines influence the prescription practices of SUP agents in the ICU.\textsuperscript{[7]}

Table 1. Demographic data

| Characteristics | ICU A, n (%) | ICU B, n (%) | ICU C, n (%) | Total, n (%) |
|-----------------|-------------|-------------|-------------|-------------|
| Age (years) | Median | 37.5 | 49 | 47.5 | 41.5 |
| (IQR) | (27 - 54) | (37.5 - 62) | (30.5 - 63.5) | (30 - 58) |
| 18 - 29 | 29 | 27 | 56 | 60 |
| 30 - 39 | 27 | 25.5 | 27 | 32 |
| 40 - 49 | 16 | 15.1 | 16 | 15.1 |
| 50 - 59 | 21 | 19.8 | 5 | 19.8 |
| ≥60 | 13 | 12.2 | 9 | 12.2 |
| Sex | | | | |
| Female | 55 | 51.9 | 15 | 53.6 | 19 | 47.5 | 89 | 51.2 |
| Male | 51 | 48.1 | 13 | 46.4 | 21 | 52.5 | 85 | 48.8 |
| Discipline | | | | |
| ENT | 5 | 4.7 | 1 | 3.6 | 0 | 3.6 |
| General surgery | 27 | 25.5 | 6 | 21.4 | 13 | 32.5 | 46 | 26.4 |
| Internal medicine | 20 | 18.9 | 18 | 64.3 | 22 | 55 | 60 | 34.5 |
| Neurosurgery | 3 | 2.8 | 0 | 0 | 3 | 1.7 |
| Obs & Gynae | 15 | 14.2 | 0 | 0 | 15 | 8.6 |
| Orthopaedics | 5 | 4.7 | 1 | 3.6 | 1 | 2.5 | 7 | 4 |
| Trauma | 24 | 22.6 | 1 | 3.6 | 4 | 10 | 29 | 16.7 |
| Urology | 1 | 0.9 | 3 | 3.57 | 0 | 2 | 1.2 |
| Vascular surgery | 6 | 5.7 | 0 | 0 | 6 | 3.5 |

ICU = intensive care unit; IQR = interquartile range; ENT = ear, nose and throat; Obs & Gynae = obstetrics and gynaecology.

*Unless otherwise specified.

Fig. 1. Risk factors of the patients in the study.
PPIs have been proven to be highly effective at suppressing gastric acid secretion by elevating gastric pH. They have also been shown to be the most effective drugs for the prevention of CSB; hence, their widespread use as the agents of choice. There are however other studies stating the contrary, and the ability of PPIs to increase gastric pH may lead to GI bacterial proliferation, which is associated with increased risk of developing infectious complications. Similarly, we showed in the present study that the most commonly prescribed SUP agent was H2RA and not PPIs. It is evident from the results that locality influenced practice, with ICU A using predominantly H2RA, ICU B using PPIs and ICU C using sucralfate.

A comparison of inappropriate prescription practices among the three ICUs followed similar trends, whereby the facility significantly influenced the drug prescribed inappropriately. ICU A had the highest proportion of these incidents, followed by ICU C. In general, H2RA accounted for the highest proportion of inappropriately used drugs, followed by PPIs and then sucralfate. Internationally, it is reported that the most commonly prescribed SUP agent was H2RA and not PPIs. It is evident from the results that locality influenced practice, with ICU A using predominantly H2RA, ICU B using PPIs and ICU C using sucralfate.

These locality/facility-related practices are likely to be influenced by drug costs, as our study was conducted in public sector ICUs, where formulations are predominantly driven by price. In addition to the drug costs, as our study was conducted in public sector ICUs, where formulations are predominantly driven by price.

**Table 2. SUP practice in ICUs**

| Treatment | ICU A, n (%) | ICU B, n (%) | ICU C, n (%) | Total, n (%) |
|-----------|--------------|--------------|--------------|--------------|
| Duration (days), median (IQR) | 3 (2 - 4) | 3 (2 - 3) | 3 (2 - 3) | 3 (2 - 4) |
| Range | 1 - 23 | 2 - 5 | 1 - 17 | 1 - 23 |
| Stress ulcer prophylaxis drug | 80 (75.5) | 0 | 0 | 80 (51.3) |
| H2RA | 22 (20.8) | 11 (91.7) | 15 (39.5) | 48 (30.8) |
| PPI | 1 (0.9) | 0 | 0 | 1 (0.6) |
| H2RA + PPI | 3 (2.8) | 1 (8.3) | 23 (60.5) | 27 (17.3) |
| Route of administration | 35 (55.6) | 3 (4.7) | 35 (39.6) | 63 (40.4) |
| Oral | 67 (84.8) | 8 (10.1) | 4 (5.1) | 79 (50.6) |
| IV bolus | 4 (28.5) | 1 (7.1) | 9 (64.3) | 14 (8.9) |
| IV infusion | 0 | 0 | 0 | 0 |
| Day enteral feeds commenced | 0 | 0 | 0 | 0 |
| 0 | 0 | 0 | 7 (18.4) | 7 (4.9) |
| 1 | 43 (53.7) | 25 (100) | 26 (68.4) | 94 (65.7) |
| 2 | 19 (23.8) | 0 | 2 (5.3) | 21 (14.7) |
| 3 | 13 (16.3) | 0 | 3 (7.9) | 16 (11.2) |
| 4 | 3 (3.7) | 0 | 0 | 3 (2.1) |
| 5 | 2 (2.5) | 0 | 0 | 2 (1.4) |

**Table 3. Characteristics of patients on SUP**

| Characteristics | Appropriate (n=60), n (%) | Inappropriate (n=96), n (%) | p-value |
|----------------|---------------------------|-----------------------------|--------|
| Age (years), median (IQR) | 40 (27 - 58.5) | 42 (31 - 54.5) | 0.686 |
| Duration of treatment (days), median (IQR) | 2 (1 - 3.5) | 3 (2 - 5) | 0.005 |
| Sex | Female | 37 (61.7) | 42 (43.8) | 0.029 |
| Male | 23 (38.3) | 54 (56.3) |
| Discipline | ENT | 2 (3.3) | 3 (3.1) | <0.001 |
| General surgery | 22 (36.7) | 22 (22.9) |
| Internal medicine | 7 (11.7) | 39 (40.6) |
| Neurosurgery | 1 (1.7) | 2 (2.1) |
| Obs & Gynae | 10 (16.7) | 5 (5.2) |
| Orthopaedics | 5 (8.3) | 2 (2.1) |
| Trauma surgery | 7 (11.7) | 22 (22.9) |
| Urology | 1 (1.7) | 0 |
| Vascular surgery | 5 (8.3) | 1 (1) |

**Table 4. Characteristics of patients on SUP**

| Characteristics | Appropriate (n=60), n (%) | Inappropriate (n=96), n (%) | p-value |
|----------------|---------------------------|-----------------------------|--------|
| Age (years), median (IQR) | 40 (27 - 58.5) | 42 (31 - 54.5) | 0.686 |
| Duration of treatment (days), median (IQR) | 2 (1 - 3.5) | 3 (2 - 5) | 0.005 |
| Sex | Female | 37 (61.7) | 42 (43.8) | 0.029 |
| Male | 23 (38.3) | 54 (56.3) |
| Discipline | ENT | 2 (3.3) | 3 (3.1) | <0.001 |
| General surgery | 22 (36.7) | 22 (22.9) |
| Internal medicine | 7 (11.7) | 39 (40.6) |
| Neurosurgery | 1 (1.7) | 2 (2.1) |
| Obs & Gynae | 10 (16.7) | 5 (5.2) |
| Orthopaedics | 5 (8.3) | 2 (2.1) |
| Trauma surgery | 7 (11.7) | 22 (22.9) |
| Urology | 1 (1.7) | 0 |
| Vascular surgery | 5 (8.3) | 1 (1) |

SUP = stress ulcers prophylaxis; ICU = intensive care unit; IQR = interquartile range; PPI = proton-pump inhibitor; IV = intravenous; H2RA = histamine-2 receptor antagonist.

SUCC March 2021, Vol. 37, No. 1

RESEARCH
A concerning factor in this study was that 10.3% of patients who were eligible for SUP according to the guidelines did not receive them. The omission of treatment has a potential of increasing morbidity, mortality and the cost of care. The simultaneous presence of overuse and underuse of SUP reinforces the importance of setting up guidelines or following internationally described guidelines. It is also important that audits of practice be performed regularly to inform these guidelines. Influencing practice in this way will further reduce risk and improve patient care.

In the group that was on SUP, 78% of patients were receiving enteral nutrition from day two of ICU admission. The early introduction of enteral nutrition is an important protective mechanism to maintain gut integrity and reduce the risk of CSB. SUP is not indicated in patients who are on full enteral nutrition.20,21 Adherence to recommendations to stop pharmacological SUP in patients on full enteral nutrition can therefore further reduce the negative consequences of inappropriate SUP in the critically ill.

Study limitations
We did not look at the rate of occurrence of CSB, which might have provided a more comprehensive view into the use of SUP in our setting. This study was conducted in three selected public sector ICUs affiliated to the University of the Witwatersrand and the findings may not be applicable in the private sector, as drug costs and availability may have a greater influence on the choice of SUP therapy in the public sector. In addition, the contextual nature of this study prohibits its use in describing generalised practices in SA. A national study of practices in the public and private sector ICUs would achieve this endpoint. The implied trend of inappropriately prescribed SUP therapy from our data is however of concern and should encourage discussion and further national research in this area.

This study would also have been able to auditing rates of VAP and Clostridium difficile infection, and their association with SUP use. The literature highlights growing concerns in the association of PPIs and H2RA use with VAP and Clostridium difficile infection in critically ill patients.12-20 In contrast, a study by Krag et al.14,15 found that the number of clinically important events such as CSB, pneumonia and Clostridium difficile infection were similar between those who received 40 mg of pantoprazole and those given placebo as SUP, while the effects of PPI and H2RA on acquiring these infections were inconclusive in another study.20

The estimated per case cost of VAP and Clostridium difficile infections in adult in-patient population was USD40 144 and USD11 285 in the USA, respectively.26 We did not find published data in SA evaluating the cost of hospital-acquired infections. There was also paucity of data reporting SUP and PPI practice in the intensive care environment in SA. In addition, no national practice guidelines for SUP in ICU have been published.

Conclusion
SUP therapy is a well-established intervention for at-risk patients in the ICU. The inappropriate use of these therapies is associated with increased healthcare costs and morbidity in the ICU. Therefore, judicious use of these agents, in line with internationally accepted guidelines, is very important to reduce adverse events.

We identified inappropriate SUP prescription in three ICUs in Johannesburg, SA. Not only should the prescription practices of these university-affiliated ICUs be reviewed, but a larger national study on the use of SUP therapy also needs to be conducted to determine if the identified trend is a national problem. Although the incidence of CSB, VAP and Clostridium difficile infections in relation to SUP were not in the scope of this study, an investigation into this would be invaluable.

The development of a local set of guidelines more suitable to the SA healthcare sector would also be beneficial.

Declaration. This research was done in partial fulfilment of a MMed degree.

Acknowledgements. We would like to thank Dr Palesa Motshabi, academic Head of the Department of Anaesthesis at the University of the Witwatersrand for assisting with the editing of the manuscript.

Author contributions. SC, HP, JS, NB conceptualised the study. NB collected data and MM analysed the data. NB wrote the manuscript and SC, HP, JS and MM revised the manuscript. All the authors approved the manuscript for publication.

Funding. None.

Conflicts of interest. None.
24. Linsky A, Gupta K, Lawler EV, Fonda JR, Hermos JA. Proton pump inhibitors and risk for recurrent Clostridium difficile infection. Arch Intern Med 2010;170(9):772-778. https://doi.org/10.1001/archinternmed.2010.73

25. Tariq R, Singh S, Gupta A, Pardi DS, Khanna S. Association of gastric acid suppression with recurrent Clostridium difficile infection: A systematic review and meta-analysis. JAMA Intern Med 2017;177(6):784-791. https://doi.org/10.1001/jamainternmed.2017.0212

26. Kwok C, Arthur AK, Amhuzee CI, Singh S, Cavallazzi R, Loke YK. Risk of Clostridium difficile infection with acid suppressing drugs and antibiotics Meta-analysis. Am J Gastroenterol 2012;107(7):1011-1019

27. Krag M, Marker S, Perner A, et al. Pantoprazole in patients at risk for gastrointestinal bleeding in the ICU. N Engl J Med 2018;379(23):2199-2208. https://doi.org/10.1056/NEJMoai174939

28. Barbateskovic M, Marker S, Granholm A, et al. Stress ulcer prophylaxis with proton pump inhibitors or histamine-2 receptor antagonists in adult intensive care patients: A systematic review with meta-analysis and trial sequential analysis. Intensive Care Med 2019;45(2):143-158. https://doi.org/10.1007/s00134-019-05526-4

29. Zimlichman E, Henderson D, Tamir O, et al. Health care associated infections: A meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013;173(22):2039-2046. https://doi.org/10.1001/jamainternmed.2013.9763

Accepted 6 January 2021.