African Journal of Pharmacology and Therapeutics Vol. 3 No. 2 Pages 51-61, 2014
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Research Article

Risk Factors and Management of Stress Ulcers in the Critical Care Unit in a Kenyan Referral Hospital

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Background: Stress ulcers develop due to extreme physiological stress among critically ill patients. Data on it management is scant in resource limited settings.

Objectives: To determine the incidence, risk factors and management of stress ulcers among adult patients admitted to the Critical Care Unit of a Kenyan referral hospital, Kenyatta National Hospital. The outcome of the prophylaxis was also evaluated.

Methodology: This was a retrospective cohort study among 186 critically ill adult patients admitted between January and December, 2012. The data was extracted from patient files. Logistic regression was performed to determine the risk factors for development of stress ulcers by manual forward stepwise model building.

Results: Ninety percent of the patients received prophylaxis and this was done within 72 hours of admission. Twenty patients did not qualify for prophylaxis but received it. Most (76.4%) patients received prophylaxis with histamine 2 receptor blockers. The incidence of stress ulcers was 36.6% which was mainly treated with ranitidine (57.4% of cases) and omeprazole (38.8% of cases). The only diagnostic criteria were presence of the following clinical signs: epigastric tenderness (60 patients, 36.6%) and melena (3, 4.4%) and hematemesis (5, 7.4%). Mechanical ventilation of patients was the most important risk factor for stress ulcer development (adjusted OR: 43.76, 95% CI [5.067, 377.9]; followed by hospital stay for more than 7 days (adjusted OR: 11.88, 95% CI [3.923, 36.9]). Antibiotics (adjusted OR: 0.044, 95% CI [0.002, 0.936]) and benzodiazepines (adjusted OR: 0.074, 95% CI [0.013, 0.419] appeared to confer protection. Prophylaxis with histamine receptor antagonists did not seem to confer protection.

Conclusion: The incidence of stress ulcers was high and methods for prophylaxis of stress ulcer need to be improved.

Key words: Stress ulcers, Critical care, antibiotics, benzodiazepines, antibiotics, CNS depressants

Received: April, 2014
Published: June, 2014

1. Introduction

Stress ulcers (SU) are gastrointestinal lesions that develop as a result of major physiological stress. They occur in the fundus of the stomach and proximal duodenum and are caused by localized ischemia, tissue acidosis and the presence of bile salt in the stomach of patients with decreased gastrointestinal motility (Porth, 2009). Stress ulcers are a challenge in management of critically ill patients. Seventy five (75%) of intensive

 ISSN 2303-9841

care unit patients develop ulcers within 72 hours of admission (Zuckerman et al, 1988). Physiologic stress causes deterioration of gastric mucosa and results in stress ulceration (Cosen-Binker et al, 2004).

Changes in gastrointestinal mucosal integrity, motility, nutrition and effect of gastric acid are amongst the factors are involved in the pathophysiology of stress ulcers (Salzman 1995). Physiologic stress decreases gastrointestinal (GI) pH and also causes hypoperfusion. These combined factors lead to stress related mucosal damage and bleeding (Dive et al, 1994).

Patients with low risks do not benefit from prophylactic therapy (Dive et al, 1994). In critically ill patients, the main risk factors for stress ulcers are mechanical ventilation and patients with a coagulopathy (Cook et al, 1994). Prophylaxis reduces resultant gastrointestinal bleeding and associated morbidity and mortality. Gastrointestinal lesions are usually asymptomatic. The clinical signs of stress ulcers are occult or overt bleeding (Dive et al, 1994).

Gastroduodenoscopy is the gold standard for diagnosis although it is not suitable for all critically ill patients. Alternatively, angiography can be used if endoscopy fails (Oscar et al, 2008). Diagnosis is often done after overt bleeding has occurred.

There are no published management guidelines for stress ulcer management in Kenya and the rest of Africa. According to the Eastern Association for the Surgery of Trauma (EAST) practice management guidelines for stress ulcer, patients should receive prophylaxis if they have selected risks factors (EAST, 2008). Pharmacological agents used for management and prophylaxis of stress ulcers include proton pump inhibitors (PPIs), histamine-2- receptor antagonists and cytoprotective agents. None, however, confers complete protection (Basso et al, 1981).

Data from Western countries show increased cases of stress ulcers, with varied levels of prophylaxis (Dive et al, 1994). In Africa, Kenya included, there is lack of data on current preventive strategies and their effectiveness. It is probable that stress ulcers are not being effectively managed. Consequently, standard prophylaxis may be inadequate in high-risk patients, while it may be over prescribed for low-risk patients (Grube et al, 2007).

Additionally, there is unexplained and continued increase in the use of acid suppressive therapy, particularly proton pump inhibitors and histamine two receptor antagonists (H_2RAs) (Hunfeld et al, 2007). Cessation of proton pump inhibitor after prolonged used causes rebound hypersecretion of gastric acid which could cause harm (Sing et al, 1992). Use of PPIs should therefore be limited to patients who have established risk factors (Lødrup et al, 2013).

The objective of this study was to determine the incidence, risk factors for and management of stress ulcers in the Critical Care Unit (CCC) of Kenyatta National Hospital. The outcomes of the prophylaxis were also evaluated.

2. Methods

2.1 Study Design, Site and Population

The study design was a retrospective cohort study of patient records. Target population was adult patients admitted between January and December, 2012 in CCU. The study was carried out in the Critical Care Unit (CCU) the largest referral hospital in East and Central Africa, Kenyatta National Hospital. It has a bed capacity of 20

Table 1: Baseline characteristics of sampled patients

Parameter	Number (%)
Age In years	
18- 30	64 (34.4)
31- 40	46 (24.7)
41- 65	53 (28.5)
>65	20 (10.8)
Unknown	3 (1.6)
Gender	
Male	107 (57.5)
Female	79 (42.5)
Marital status	
Single	47 (27.7)
Married	116 (68.1)
Widowed	7 (4.1)
Reason for CCU admission	
[1]Accident and trauma	108 (58.1)
[2]CVS complications	52 (28.0)
[3]CNS complications	13 (7.0)
[4]Metabolic complications	10 (5.38)
[5]Respiratory complications	3 (1.1)
Duration (days) of CCU stay (Median, IQR)	4 (2-10)
Patient outcome	
Discharged	95 (51.08)
Died	91 (48.92)

[1] ***Accident and trauma****: Traumatic brain injury, post surgical care, burns.*

[2] ***CVS conditions****: Myocardial infarction, congestive cardiac failure, eclampsia, venous thrombosis, hypertension, sepsis*

[3] ***CNS conditions****: Spinal cord injury, Guillen Barre syndrome, status epilepticus, brain tumor, cerebral aneurysm, hydrocephalus*

[4] ***Metabolic conditions****: Hepatic failure, goiter, renal failure*

[5] ***Respiratory conditions****: Chronic obstructive pulmonary disease, asthma, tuberculosis*

 ISSN 2303-9841

2.2 Inclusion and Exclusion criteria

The patients who were included in the study were aged 18 and above and were admitted during the study period. Patients with gastrointestinal bleeding secondary to direct abdominal trauma or cancer were excluded.

2.3 Sample Size Determination and sampling procedure

The sample size was calculated using the Fischer's formula. The desired sample size was a minimum of 168 patients. This was sufficient to detect an incidence of 0.875 with a power of 80% and an alpha of 0.05. Files for patients admitted to CCU during the study period were obtained from the KNH records department. Only those files that met the eligibility criteria were selected. A final study sample of 186 was then selected randomly from the list of eligible patients.

2.4 Data Collection

The data collection tool was modified after a pilot study. The files were abstracted for the patient demographic characteristics, dates of admission, diagnosis and drug administration, risk factors for stress ulcers, concurrent medication, anti-ulcer drugs, date anti-ulcer drugs were stopped, outcomes of treatment and the prescriber level of education.

2.5 Case definition

Patients who had a record of any the following clinical signs were considered to have stress ulcers: hematemesis, hematochezia, melena stools or 'coffee-ground' vomitus. Occult bleeding was defined as the presence of blood in stools. Overt bleeding was defined as melena stools, hematemesis or bloody nasogastric aspirate (Alhazzani et al, 2012). Prophylaxis was defined as administration of any antiulcer medication in the absence of any clinical signs. Management was defined as any therapy with anti-acid drugs instituted after onset of the clinical signs of stress ulcers.

2.6 Data analysis

Continuous variables were summarized as either the mean and standard deviation of the mean or as the median and the inter quartile range. Categorical variables were summarized as frequencies and proportions. Logistic regression with manual forward stepwise model building was performed to determine the risk factors for development of stress ulcers. The presence of stress ulcer was the dependent variable and covariates of interest were: prophylaxis treatment, patient demographic characteristics, concomitant drugs, and known risk factors such as parenteral nutrition, multiple trauma, mechanical ventilation and coagulopathy. Data was analyzed using STATA version 9 software. P-values of 0.05 or less were considered statistically significant.

2.5 Ethical considerations

Approval to carry out the study was granted by the Kenyatta National Hospital/University of Nairobi Ethics and Research Committee (KNH/UoN ERC) as per the letter referenced **KNH-ERC/A/188** dated 5th July 2013. Confidentiality was maintained by using codes instead of patient names. All data were kept under lock and key.

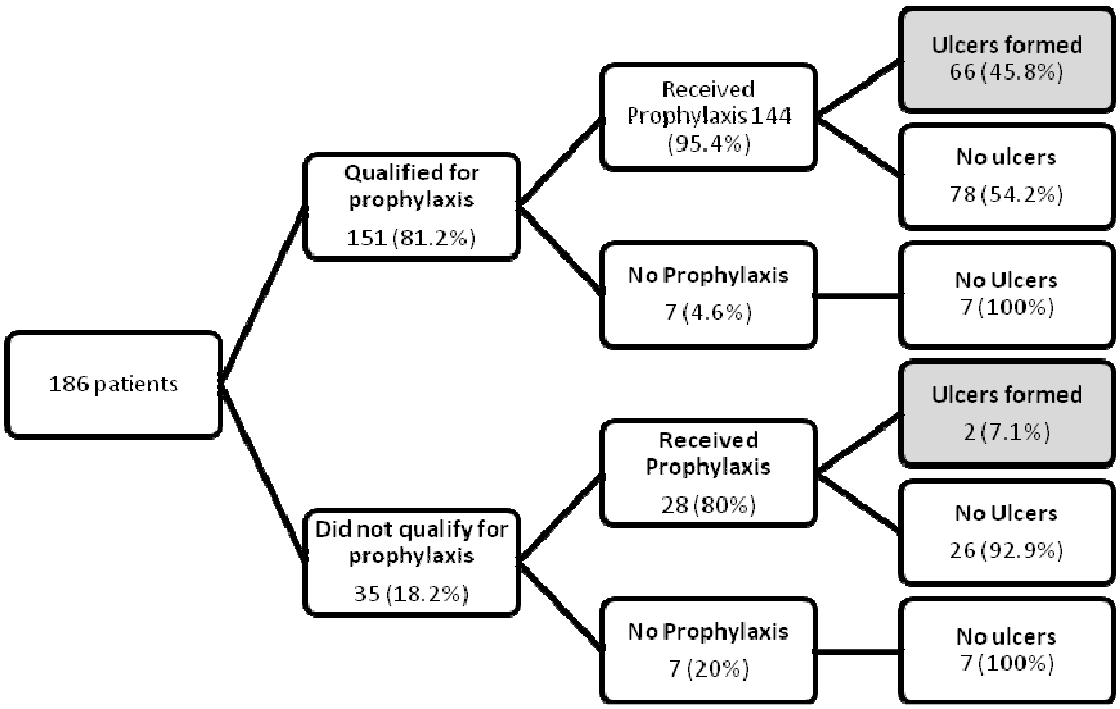

Figure 1: Proportions of patients who qualified for and received prophylaxis and developed stress ulcers

 ISSN 2303-9841

3. Results

3.1 Baseline characteristics of the study population

In 2012, there were 764 admissions in the Critical Care Unit (CCU). The characteristics of the 186 patients included in this study are described in **Table 1**. Most of the study patients were males (57.5%), and the rest were females. The median age of the patients was 40.4 years (IQR 18 - 80 years).

Twenty eight patients (15.1%) stayed in the critical care unit for only one day. Most of the patients stayed for between 1- 6 days. About half of the admitted patients (51.1%) were discharged while the rest (48.9%) died.

Each patient received a mean of 8 drugs. The types of drugs patients received are listed in Table 2. Antibiotics were administered to 172 (92.5%) of the patients, with ceftriaxone being the most frequently antibiotic. It was prescribed to 93 (50%) of the patients. One hundred and fifteen patients115 (61.8%) received ulcerogenic medications of which dexamethasone, diclofenac were the most commonly administered, representing 39.8% of ulcerogenic drugs used (**Table 2**).

3.2 Prophylaxis, Diagnosis, Incidence and Management of stress ulcers

Patients were assessed for eligibility for prophylaxis using the criteria set out in the guidelines (EAST, 2008). About 80% of the patients were eligible for prophylaxis, and out of these, 95.4 % received prophylaxis (Figure 1). Twenty patients were not eligible for prophylaxis but still received it.

Stress ulcer prophylaxis was initiated on 172 (92.5%) patients. This was done within 72 hours of admission for 170 (98.8%) of these patients, while only two received prophylaxis after 72 hours of admission. The median duration of prophylaxis was 8.9 days (range 3, 10).

Table 2: Drugs used by patients administered to patients in the Critical Care Unit

Drug	n, (%)	**Drug**	n, (%)
Antibiotics		**Ulcerogenic drugs**	
Coamoxiclav	24 (12.9)	Complexed iron	7 (3.8)
Ceftriaxone	93 (50)	Warfarin	2 (1.1)
Ceftazidime	8 (4.3)	Dexamethasone	18 (9.7)
Cotrimoxazole	8 (4.3)	Potassium citrate	13 (7.0)
Clindamycin	1 (0.5)	Ibuprofen	10 (5.4)
Metronidazole	3 (1.6)	Diclofenac	16 (8.6)
Cefuroxime	16 (8.6)	Aspirin	4 (2.2)
Benzyl penicillin	3 (1.6)	Prednisone	4 (2.2)
Meropenem	11 (5.9)		
Flucloxacillin	3 (1.6)		
Levofloxacin	3 (1.6)	**Gastrointestinal drugs**	
Ciprofloxacin	1 (0.5)	Metoclopromide	147 (79.0)
		Ondansetron	8 (4.3)
Narcotic analgesics		Lactulose	6 (3.2)
Tramadol	124 (66.7)		
Morphine	10 (5.8)	**Central Nervous System**	
Pethidine	1 (0.5)	Anesthetic agents	45 (24.2)
		Anticonvulsants	30 (16.1)
Cardiovascular drugs		Benzodiazepines	35 (18.8)
Diuretics	20 (10.8)		
Calcium channel blockers	18 (9.7)		
Beta blockers	7 (3.8)		

 ISSN 2303-9841

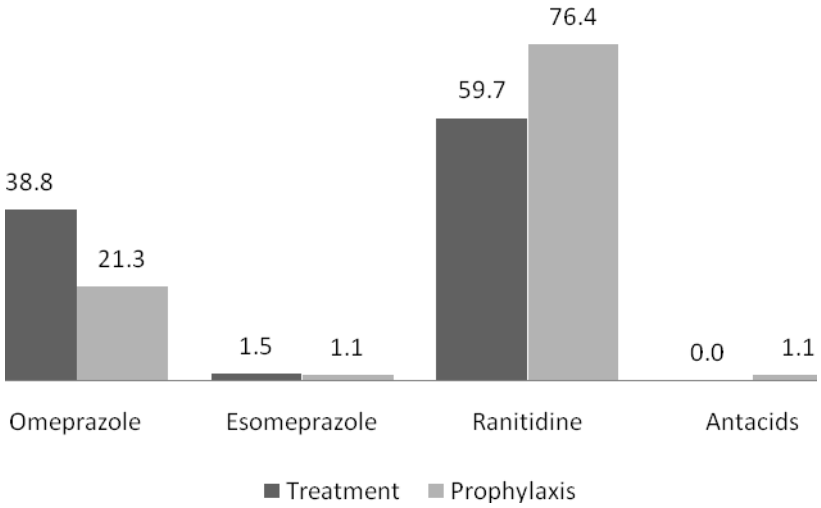

Figure 2: Drugs used for prophylaxis and treatment of stress ulcers

The histamine receptor antagonist, ranitidine was the most the most frequently used prophylactic agent (Figure 2). Ranitidine was administered to 133 (76.4%) patients. The rest of the patients received PPIs which include omeprazole 37 (21.3%) and esomeprazole 2 (1.1%). Antacids were also used for prophylaxis in two patients. Enteral feeding is a prophylactic measure which administered to 51 (27.4%) of the patients studied.

The incidence of stress ulcers was 36.6% (68 patients) (**Figure 1**) in the whole cohort. The incidence of stress ulcers was lowest amongst patients who did not quality to receive prophylaxis (7.1%) and was highest amongst those who qualified to receive prophylaxis (45.8%). All the patients who did not receive prophylaxis did not develop stress ulcers.

The only diagnostic method used was physical examination and the presence of clinical signs. The clinical signs were: epigastric tenderness (60 patients, 88.2%); melena (3 patients, 4.4%); and hematemesis (5 patients, 7.4%).

Ranitidine was also the most widely used drug for the treatment of confirmed stress ulcers. It was administered to 59.7% of cases (**Figure 2**). Omeprazole was administered to 26 (38.8%) patients who developed ulcers.

3.3 Risk factors for stress ulcers

Table 3 presents the bivariable analysis between the occurrence of stress ulcers and covariates of interest. The following variables were not statistically significant on bivariable analysis: sex, time taken to initiate prophylaxis, type of prophylactic agent, prescriber's level of training and specific diagnosis such as sepsis and head injury (**Table 3**). There was no association between stress ulcers and mortality.

Variables that were statistically significant on bivariable analysis were subsequently used to determine the key predictors by forward stepwise model building. The results are presented in **Tables 4**. On adjusting for confounding, most of the variables remained statistically significant.

The length of CCU stay was a significant predictor of stress ulcer development (p=0.02; adjusted odds ratio (OR): 5.214 (95% confidence interval (CI) [1.288, 21.11]). This was particularly true for patients who were admitted for more than one week of whom slightly more than two thirds (67.7%) developed stress ulcers. Mechanical ventilation for more than 48 hours was an important risk factor for developing stress ulcers. The strength of association between mechanical ventilation and stress ulcer was very strong (p=0.002; adjusted OR: 75.51, 95% CI [5.134, 1110]. The number of drugs prescribed was a very strong predictor for developing stress ulcers (p=0.01; adjusted OR 1.481 [1.170, 1.897]). Use of more than 8 drugs increased the risk of developing stress ulcers.

On bivariable analysis, there was a statistically significant positive association between use of prophylactic acid lowering drugs and stress ulcers. The odds of developing ulcers amongst those who received prophylaxis were about 9 times the odds of those who did not receive prophylaxis. On adjusting for confounding, the association remained positive but was not statistically significant. The duration of prophylaxis on the other hand was negatively associated with the development of stress ulcers (p=0.04; adjusted OR 0.823 [0.685, 0.990]). Patients who were eligible for prophylaxis were more likely to develop stress ulcers but this was not significant on adjusting for confounding. A high International Normalized Ratio (INR) value also increased the risk of developing stress ulcers (p=0.06; adjusted OR 5.481 [0.922, 32.594]).

There was a negative association between use of anticonvulsants and benzodiazepines which implied they had a protective effect. These two class of drugs act on the central nervous system. The effect of benzodiazepines was statistically on multivariable analysis (p=0.04: adjusted OR 0.058 95% CI [0.008, 0.398]).

 ISSN 2303-9841

Table 3: Comparison of the traits of patients who developed ulcers and who did not

	No ulcers (n, %)	Ulcers developed (n, %)	Crude Odds Ratio (95% CI)	P Value
Overall	118 (63.4)	68 (36.6)	-	-
Sex				
Male	64 (59.8)	43 (40.2)	0.689 [0.374, 1.270]	0.23
Female	54 (68.4)	25 (31.7)		
Prophylaxis status				
Did not receive	14 (100)	0	-	**0.00**
Received	104 (60.47)	68 (39.5)		
Time taken to initiate prophylaxis after admission				
Within 72 hours	103 (60.6)	67 (39.4)	1.537 [0.0945, 24.999]	0.76
After 72 hours	1 (50)	1 (50)		
Prophylatic drugs given				
Antacids	1 (50)	1 (50)	1.016 [0.718, 1.439]	0.64
Ranitidine	82 (61.7)	51 (38.3)		
Omeprazole	21 (56.8)	16 (43.2)		
Esomeprazole	2 (100)	0		
Eligibility for Prophylaxis				
Eligible	85 (56.3%)	66 (43.7%)	-	**0.00**
Non Eligible	33 (94.3%)	2 (5.7%)		
Time in CCU (days)	-	-	1.119 [1.064, 1.176]	**0.00**
Reasons for Admission				
CVS complication	34 (65.4)	18 (34.6)		
CNS complication	9 (69.2)	4 (30.7)		
Resp. Syst. complication	1 (33.3)	2 (66.7)		
Trauma/accident	69 (63.9)	39 (36.1)	1.036 [0.989, 1.085]	**0.01**
Metabolic disease	5 (50)	5 (50)		
Other drugs used				
Antibiotics	110 (63.9)	62 (36.1)	1.09 [0.991, 1.197]	0.47
Ulcerogenic drugs	70 (60.9)	45 (39.1)	1.024 [0.937, 1.119]	0.33
GIT acting drugs	100 (62.1)	61 (37.9)	1.23 [0.723, 2.114]	0.60
Narcotic analgesic	86 (64.2)	48 (35.8)	1.02 [0.594, 1.750]	0.70
Antihypertensives	40 (65.6)	21 (34.4)	0.946 [0.765, 1.169]	0.88
CNS acting	73 (66.4)	37 (33.6)	0.747 [0.568, 0.983]	**0.03**
Duration prophylaxis	-	-	1.103 [1.050, 1.159]	**0.00**
INR Value	-	-	2.299 [0.967, 5.468]	**0.06**
CCU stay > 1 week	20 (32.3)	42 (67.7)	7.915 [3.986, 15.717]	**0.00**
Severe head injury	29 (64.4)	16 (35.6)	0.944 [0.469, 1.901]	0.87
Spinal cord injury	1 (50)	1 (50)	1.746 [0.107, 28.375]	0.69
NSAID use	30 (69.8)	13 (30.2)	0.693 [0.333, 1.443]	0.33
Sepsis	13 (81.3)	3 (18.8)	-	
Patient outcome				
Discharged	61 (64.2)	34 (35.8)	1.034 [0.768, 1.394	0.82
Died	57 (62.6)	34 (37.4)		
Prescriber's level of training				
Consultant	12 (70.6)	5 (29.4)	1.426 [0.480, 4.238]	0.52
Registrar	106 (62.7)	63 (37.3)		

 ISSN 2303-9841

Table 4: Multivariable analysis – Association between stress ulcer development and medication administered

	Crude OR [95% CI]	P value	Adjusted OR [95% CI]	P value
Length of stay in CCU	7.915[3.986, 15.72]	**0.00**	5.214 [1.288, 21.113]]	**0.02**
Length hospital stay			1.212 [1.020, 1.442]	**0.03**
Mechanical ventilation	12.42 [3.680, 41.9]	**0.00**	75.505 [5.134, 1110]	**0.00**
Number of drugs used	1.388[1.180, 1.634]	**0.00**	1.481 [1.170, 1.897]	**0.01**
INR value	2.299 [0.967, 5.468]	0.06	5.481 [0.922, 32.594]	0.06
Ulcerogenic drugs				
No ulcerogenic drug	-	-	-	-
Complexed iron	5.217 [0.940, 28.94]	**0.06**	6.760 [0.496, 92.197]	0.15
Warfarin	2.087 [0.125, 34.87]	0.61	19.452 [0.002, 189875]	0.53
Dexamethasone	1.670 [0.582, 4.791]	0.34	3.497 [0.469, 26.058]	0.22
Potassium citrate	0.928 [0.258, 3.331]	0.91	1.576 [0.184, 13.480]	0.68
Ibuprofen	0.894 [0.212, 3.779]	0.88	1.985 [0.285, 13.846]	0.49
Diclofenac	0.482 [0.125, 1.858]	0.29	0.681 [0.057, 8.113]	0.76
Aspirin	0.696 [0.686, 7.058]	0.76	0.016 [0.000, 1.458]	**0.07**
Paracetamol	1.543 [0.693, 3.433]	0.29	2.598 [0.574, 11.755]	0.22
Prednisone	6.261 [0.617, 63.53]	0.12	26.362[0.000, 1579642]	0.56
CNS drugs				
No CNS drugs	-	-	-	-
Anesthetic agents	1.388 [0.661, 2.917]	0.39	1.534 [0.333, 7.061]	0.58
Anticonvulsants	0.363 [0.133, 0.991]	**0.05**	0.369 [0.075, 1.826]	0.22
Benzodiazepines	0.502 [0.207, 1.218]	0.13	0.058 [0.008, 0.398]	**0.00**
Antibiotics				
No antibiotic	-	-	-	-
Amoxycillin/clavulanic	0.549 [0.139, 2.175]	0.39	1.190 [0.096, 14.957]	0.89
Ceftriaxone	0.635 [0.202, 1.994]	0.44	0.470 [0.060, 3.679]	0.47
Ceftazidime	0.444 [0.065, 3.028]	0.41	0.242 [0.010, 5.891]	0.38
Cotrimoxazole	0.889 [0.111, 7.107]	0.91	0.013 [0.000, 0.337]	**0.01**
Metronidazole	2.667 [0.193, 36.76]	0.46	0.046 [0.001, 2.585]	0.13
Cefuroxime	1.714 [0.403, 7.292]	0.47	0.458 [0.329, 6.391]	0.56
Benzyl penicillin	0.667 [0.484, 9.189]	0.76	1.388 [0.009, 217.7]	0.90
Meropenem	0.5 [0.092, 2.730]	0.42	0.107 [0.005, 2.276]	0.15
Flucloxacillin	2.667 [0.193, 36.76]	0.46	0.524 [0.000, 5678]	0.89
Levofloxacin	2.667 [0.193, 36.76]	0.46	25.432 [0.128, 5042]	0.23
Received prophylaxis	-	-	5.749 [0.812, 40.678]	0.78
Duration prophylaxis	1.103 [1.050, 1.159]	**0.00**	0.823 [0.685, 0.990]	**0.04**
Eligibility for prophylaxis	.361 [0.178 0.733]	**0.01**	1.321 [0.032, 55.036]	0.88
Reasons for admission	1.036 [0.989, 1.085]	**0.01**	1.037 [0.938, 1.147]	0.48
Age above 65	0.505[0.158, 1.615]	0.24	0.099 [0.009, 1.081]	**0.06**

 ISSN 2303-9841

The association between antibiotics and stress ulcers was not statistically significant on bivariable analysis. However on multivariable analysis, selected antibiotics were protective against stress ulcer development. Most antibiotics such as ceftriaxone, ceftazidime and metronidazole conferred a protective effect which was not statistically significant. The only agent that had statistically significant protective effect was cotrimoxazole (p=0.01; adjusted OR 0.013, 95% CI [0.000, 0.337]). All patients on cotrimoxazole and ciprofloxacin did not develop stress ulcers. Unlike all other antibiotics, there was a very strong positive association between levofloxacin and stress ulcers (p=0.23; 25.43 95% CI [0.128, 5042]). Though this association was very strong, it was not statistically significant.

Use of ulcerogenic drugs was not a statistically significant predictor of stress ulcers. There was, however, a positive association between use of individual agents such as iron preparations and potassium citrate. In the case of warfarin and corticosteroids such as prednisone, the strength of association was very high with adjusted odds ratios greater than 25. On adjusting for confounding, warfarin was not a statistically significant predictor for GI bleeding though the measure of association was very strong (p=0.57; adjusted OR: 19.452, 95% CI [0.002, 189876]), indicating that it could be a clinically significant predictor for GI bleeding.

Non steroidal anti-inflammatory drugs with the exception of ibuprofen conferred protection on both bivariable and multivariable analysis. However, this effect was not statistically significant. In the case of low dose aspirin, this protective effect was very strong significant (p=0.07; adjusted OR 0.016 [0.000, 1.458]).

There was no statistically significant association between use of antihypertensive drugs, narcotic analgesics and other gastrointestinal acting drugs and development of stress ulcers on bivariable analysis.

4. Discussion

Stress ulcers and gastrointestinal bleeding are common complications in intensive care hospitalization and cause mortality. The incidence of stress ulcers in this cohort was lower (36.6%) than that reported in the United States of America, where the incidence is up to 75% (Cosen-Binker et al, 2004). This wide disparity could have been because of differences in the diagnostic criteria in the two clinical settings and mix of patient characteristics. In the Kenyatta National Hospital, assessment of clinical signs was the main diagnostic criterion while in clinical settings in USA, diagnosis is mainly by endoscopy. Endoscopy is the most accurate diagnosis for stress ulcers (Moody and Cheung, 1976).

Proper identification of patients for prophylaxis is necessary to avoid unnecessary costs and minimize adverse effects (Moody and Cheung 1976; Gill et al, 2004). Using the criteria set out in the EAST guidelines (EAST, 2008), 28 patients (15.1%) did not qualify to receive stress ulcer prophylaxis but still received it.

It is notable that the incidence of stress ulcer was very low amongst patients who were not eligible for prophylaxis. Twenty six of these patients (92.9%) patients did not develop stress ulcers. This indicates that the EAST guidelines for initiation for prophylaxis are a useful tool minimizing wasteful administration of antiulcer agents. This may have resulted in unnecessary medical cost. Adoption of the EAST guidelines may minimize unnecessary administration of prophylaxis.

All the 14 patients who did not receive prophylaxis did not develop stress ulcers. Half this number was eligible for prophylaxis. This indicates that clinicians could have used rational judgment to withhold prophylaxis. It would be useful to conduct a qualitative study to determine reasons why clinicians in the CCU withhold prophylaxis and incorporate these into treatment guidelines.

Long duration of CCU stay and mechanical ventilation were the most significant risk factor for stress ulcers. Patients who are on mechanical ventilation and stay long in CCU are often very ill and experience a high degree of physiological stress. This predisposes them to stress ulcers. This finding is consistent with findings in other studies (Stollman and Metz, 2005). Data was not collected on whether mechanical ventilation was performed on conscious, sedated or anesthetized. It is plausible that patients who are conscious and are on mechanical ventilation may experience more stress.

Administration of multiple drugs was an important predictor for stress ulcers. This could have been caused by drug interactions or the direct corrosive effects of multiple drugs on the gastrointestinal tract.

Other known risk factors for developing stress ulcers such as low platelet counts, sepsis, head injury, thromboprophylaxis and ulcerogenic drugs are significant predictors of stress ulcer development (Stollman and Metz, 2005). This was however not the case in this study. This may be attributed to the small sample size. It is notable however that those with coagulopathy had greater risks of developing stress ulcers (adjusted OR: 43.76, 95% CI [5.067, 378]), and thus require prophylaxis. This is consistent with what is reported in literature (Stollman and Metz, 2005). The confidence interval of the association between coagulopathy was wide and this could have been attributed to the small sample size.

Our study reports for the first time that antibiotic use may confer protection from stress ulcers in critically ill patients. This could be as a result of eradication *Helicobacter pylori*. A positive *H. pylori* serology is aetiologically associated with stress ulcers in critically ill patients (Ellison et al, 1996). Benzodiazepines could have conferred protection by ameliorating the psychogenic pathways involved in the pathogenesis of stress ulcers (Dive et al, 2000). Benzodiazepines reduce the formation of gastric ulcers in stressed rats (File and Pearce, 1981). A study of the effects of benzodiazepines in ulcer formation in critically ill patients has not been conducted.

Aspirin and other non steroidal anti-inflammatory drugs (NSAIDs) are known ulcerogenic agents and cause gastrointestinal disturbances such as nausea, dyspepsia and vomiting (Edwards et al, 1999). A surprising finding in this study was that aspirin and other NSAIDS reduced the odds of developing stress ulcers. This finding was not statistically significant. The

 ISSN 2303-9841

stress ulcer protective properties of NSAID were surprising and this contrary to what is known. A larger study is warranted to determine whether NSAIDs reduce the risk of stress in critically ill patients. This observation could be attributed amelioration of inflammatory reactions that lead to gastrointestinal bleeding in critically ill patients (Hsieh et al, 2006). Studies done on experimental rats found that non acidic NSAIDs drugs, nabumetone and dipyrone, reduced stress ulcer formation. (Yıldırım et al, 2013). It is probably therefore that NSAIDs may confer protection by reducing gastrointestinal inflammation.

Prophylaxis for stress ulcers should be initiated as soon as possible or within 72 hours of CCU admission on eligible patients (Moody and Cheung 1976). In this study, 98.8% of those that received prophylaxis got it within 72 hours of admission, which is in agreement with accepted standards of practice. However, 1.2% of patients received prophylaxis after 72 hours of admission.

The choice of drugs for prophylaxis in KNH CCU was consistent with recommendations of the EAST practice management guidelines (EAST, 2008). Ranitidine and omeprazole were the preferred choices for prophylaxis. Antacids were however used for prophylaxis (1-2%), contrary to recommendations. The use of antacids such as calcium and management based alkaline compounds for stress ulcer prophylaxis is complicated by frequent dosing, monitoring and drug interactions (Klebl and Schölmerich 2007). Moreover, antacids have also been implicated in increased mortality caused by electrolyte imbalance. Antacid salts are therefore not recommended for use (Flannery and Tucker 2002).

Ranitidine and omeprazole were the most commonly used drugs for prophylaxis. There was no statistically significant difference in the incidence of stress ulcer in patients who received these drugs. This concurs with a meta-analysis that compared the protective effects of omeprazole and ranitidine (Lin et al, 2010). Two other meta-analysis of randomized control trials found that omeprazole has a superior protective effect compared to ranitidine in critically ill patients (Levy et al, 1997; Alhazzani et al, 2013). It is probable that our study was not sufficiently powered to detect a difference in the effectiveness of histamine two receptor blockers and proton pump inhibitors.

Our study showed that use of acid lowering prophylactic agents did not confer any protection. Although this conclusion regarding the lack of efficacy of stress ulcer prophylaxis correlate with those of some studies (Schutzer et al, 1984; Reusser et al, 1990), it differs from the results of others (Khan et al, 1981, Friedman et al, 1982, Martin et al, 1993). A meta-analysis of 10 clinical trials on the efficacy of acid lowering agents as prophylactic agents found that they had beneficial effects when compared to the placebo (Cook et al, 1996).

Many published studies that suggest that anti ulcer drugs have a beneficial prophylactic effect are more than 10 years old. Because of improvements in CCU care, the conclusions of these older studies may no longer be applicable. Current literature suggests that both the incidence and severity of stress ulcers have decreased independent of the use of prophylaxis (Cook et al, 1991). It has been suggested that enteral feeding should replace pharmacological prophylaxis (Pilkington et al, 2012). Factors thought to contribute to the decreasing incidence of stress-related gastritis include more aggressive shock management and improved methods of ventilatory support.

The duration of use of prophylactic agents was, notably, is negatively associated with stress ulcers. This strongly suggests that prophylaxis with acid lowering antiulcer drugs plays a critical role in prevention of stress ulcers. Studies that report lack of a beneficial effect have probably not considered the duration of use.

The study was retrospective and was affected by missing records and reliance on records. The records may have been incomplete and information on medications used by patients before admission was not available. Verification of information in the patient's files was not always possible. A second limitation of this study was assessment of the clinical significance of gastrointestinal bleeding was not done. Clinically significant bleeding is often accompanied by hypotension or increased pulse (Alhazzani et al, 2012). The effects of other known risk factors such as a history of alcohol abuse and hepatic disease were not investigated.

We recommend that protective role of benzodiazepines, NSAIDS and antibiotics should be investigated using randomized control studies.

5. Conclusion

The incidence of gastrointestinal bleeding in this setting was 36.6%. The true incidence may be higher if endoscopy was used as the diagnostic criteria. The key risk factors for development of stress ulcers are duration of hospitalization, mechanical ventilation for more than 48 hours and use of many drugs. Antibiotics and benzodiazepines were protective. Patients on anticoagulants and steroidal agents had a high risk of developing ulcers. Further research is required into the possibility of using benzodiazepines and antibiotics for stress ulcer prophylaxis.

Conflict of Interest declaration

The authors declare no conflict of interest

Acknowledgements

Writing of this paper was supported by Medical Education Partnership Initiative (MEPI) and Partnership in Innovative Medical Education in Kenya (PRIME-K) under National Institute for Health (NIH) grant number R24 TW008889-02. The authors also acknowledge the invaluable support and the suggestions made by Prof. PAO Odhiambo and Prof CF Otieno who proof read the manuscript and gave very useful insights and comments.

 ISSN 2303-9841

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 ISSN 2303-9841