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VENTILATOR-ASSOCIATED PNEUMONIA IN CRITICALLY ILL AFRICAN PATIENTS ON STRESS ULCER PROPHYLAXIS
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VENTILATOR-ASSOCIATED PNEUMONIA IN CRITICALLY ILL AFRICAN PATIENTS ON STRESS ULCER PROPHYLAXIS

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ABSTRACT

***Background*: Stress ulcer prophylaxis is an integral part of the care of the critically ill. Agents that alter gastric pH may predispose these patients to gastric colonisation, with subsequent pneumonia and/or sepsis. Cytoprotective agents such as sucralfate preserve gastric acidity and may be protective.**
***Objective*: To determine whether African patients on sucralfate as stress-ulcer prophylaxis have a lower incidence of gastric colonisation and ventilator-associated pneumonia than those on ranitidine.**
***Design*: Randomised case-control study**
***Setting*: Kenyatta National Hospital Intensive Care Unit**
***Subjects*: Patients on ventilatory support for 48 hours or more**
***Interventions*: Sixty-eight critically ill patients were randomly assigned to either ranitidine or sucralfate as stress ulcer prophylaxis. Paired samples were taken from gastric and tracheal aspirates at admission, 48 hours and day six. Pneumonia was diagnosed using the Clinical Pulmonary Infection Score.**
***Main outcome measures*: Death or the development of pneumonia.**
***Results*: Although gastric colonisation rates were similar in the two groups, the incidence of pneumonia was lower in the sucralfate group (17.6% vs. 23.5%, p=0.4). In 63.6% of patients with both gastric colonisation and airway infection, the same organism was isolated from the two sites (p<0.01). The majority of the organisms isolated were multi-drug resistant.**
***Conclusion*: Compared with ranitidine, sucralfate did not offer significant reduction in either gastric colonisation or ventilator-associated pneumonia in critically ill African patients.**

INTRODUCTION

Pneumonia is the leading cause of death from hospital-acquired infections (1). Infections are classified as nosocomial if there is no evidence that they were present or incubating at the time of admission to hospital. They generally occur after 48 to 72 hours of admission or within ten days of discharge. Ventilator-associated pneumonia is nosocomial pneumonia in patients who have been on mechanical ventilation for 48 hours or more, and is the second most common hospital-acquired infection (1-3).

Nosocomial pneumonia affects more than 250,000 acute care patients every year in the United States, accounting for up to 18% of all nosocomial infections (1,4). The incidence is 20 times greater in critically ill patients and 21 times more common in the intubated patient (5). A study based in the Kenyatta National Hospital ICU in 1993 found a 35.7% incidence of pneumonia among intubated patients (8). Although ICUs make up only 5% of hospital beds and care for less than 10% of hospital patients, infections in these units account for more than 20% of hospital-acquired infections (5).

VAP that occurs within 48 to 72 hours of tracheal intubation is termed early-onset pneumonia. It often results from aspiration at the time of intubation. The organisms responsible are often antibiotic-

sensitive bacteria such as Haemophilus influenza, *Streptococcus pneumoniae* and coagulase-negative *Staphylococcus aureus*. VAP that occurs after 72 hours is called late-onset pneumonia, commonly due to antibiotic-resistant organisms including *Pseudomonas aeruginosa,* Methicillin-Resistant *Staphylococcus aureus* (MRSA), Acinetobacter and Enterobacter species. The European Prevalence of Infection in Intensive Care (EPIC) study found that VAP was responsible for an estimated 45% of all infections in ICUs across Europe (6). The German National Infection Surveillance System (KISS) of 2012 established that a significant number of nosocomial infections in European ICUs were attributable to multi-drug resistant gram-negative organisms (4,7).

Nosocomial pneumonia prolongs the critically ill patient's stay in ICU, lengthens the duration of mechanical ventilation and ultimately increases the cost of care (4). Mortality rates are notably high in patients with nosocomial pneumonia, ranging from 20-60%, depending on the severity of the underlying disease (9,10).

The mortality in mechanically ventilated patients treated with pH-altering agents has been found to be up to 1.6 times greater than predicted mortality, based on ICU mortality scoring systems such as APACHE II (9). This has been attributed to the development of higher rates of VAP and septicaemia in these patients. The use of cytoprotective agents such as sucralfate, rather than pH-altering agents such as ranitidine, has been shown to lower the incidence of nosocomial pneumonia from 20% to as low as 5% in one study (11) and from 36% to 10% in a different study (12). It has also been shown to reduce gastric colonisation from 48% to 28%. In addition, sucralfate is a much cheaper alternative than ranitidine, an important consideration for a resource-limited country.

In health, equilibrium exists between pathogens, the environment and natural host defence mechanisms. For infection to occur, this equilibrium will have been disrupted. Critical illness leads to an acquired immunodeficiency state, largely due to the severity of the underlying disease or injury. The organisms most frequently isolated in critically ill patients with airway colonisation and/or infection are gram-negative, with a total frequency of 62.5%. Often, these are organisms from the patient's own gastric contents. The presence of a nasogastric tube, as is commonly found in intubated patients, impairs the function of the gastro-oesophageal sphincter. Passive gastro-oesophageal reflux of infected contents therefore occurs, with micro-aspiration and subsequent pneumonia. Gastric colonisation and VAP rates have not been established in critically ill African patients.

Enhanced bacterial pathogenicity in critical care units, coupled with the numerous invasive diagnostic and therapeutic procedures performed there that bypass local host defence mechanisms, also predispose these patients to nosocomial infections. Endotracheal tubes prevent the clearing of the airway by the mucocilliary apparatus, facilitating bacterial colonisation of the tracheobronchial tree. Further, pooling of contaminated secretions above the endotracheal tube cuff leads to aspiration of contaminated secretions. Other variables that are independently associated with nosocomial pneumonia include age greater than 70 years, underlying disease, shock, depressed consciousness, re-intubation, smoking, obesity and malnutrition. Artificial ventilation alone as an exogenous risk factor for nosocomial infection contributes 27.6% to that risk.

There is no standard test for the diagnosis of VAP and no standard method to exclude pulmonary infections in mechanically ventilated patients with fever and multi-organ dysfunction. The Clinical Pulmonary Infection Score (CPIS) is commonly employed, although this scoring system has been criticised as being of low specificity. Bronchoscopically directed techniques have specificity rates of 78-89% and positive predictive values of 83-91%. Cost however is still the greatest limiting factor to the widespread use of bronchoscopy to diagnose pneumonia in ICUs in the developing world.

Main Objective

To compare the incidence of ventilator-associated pneumonia (VAP) in mechanically ventilated critically ill African patients on ranitidine as stress ulcer prophylaxis versus sucralfate.

Specific Objectives

1. To compare the incidence of VAP in patients on sucralfate and those on ranitidine on the basis of the CPIS scoring system.
2. To compare the degree of gastric colonisation in the two groups of patients.
3. To determine whether there is any association between the organisms present in gastric aspirates and those causing pneumonia in the two groups of patients.

Justification of the Study

Stress ulcer prophylaxis with pH-altering agents such as ranitidine is routinely carried out on ventilated patients in the Kenyatta National Hospital ICU. Sucralfate however, is a much cheaper alternative. The fact that sucralfate may also serve to reduce the incidence of VAP would have far-reaching implications as it would lead to a reduction in ventilator days and a reduction in the need for expensive antibiotics, reducing morbidity as well as lowering the cost of care.

MATERIALS AND METHODS

This was a prospective, randomised case-control study, based at the Kenyatta National Hospital ICU. Critically ill patients who had been on ventilatory support for a minimum of 48 hours were eligible for inclusion into the study. Exclusion criteria included patients with any respiratory tract infection at admission, positive bacterial cultures from baseline tracheal aspirates, patients on treatment for peptic ulcer disease, documented upper gastrointestinal bleeding, previous gastrectomy, patients without nasogastric tubes, patients transferred from other ICUs and patients who had been on antibiotics prior to admission.

Statistical methods: We estimated that 31 patients per group would provide an 80% power for a two-sided test to detect a 20% reduction in gastric colonisation rates between the two groups, at the 0.05 level. Results were analysed using the Statistical Package for Social Sciences (SPSS) software. Categorical variables were expressed as numbers and frequencies and compared using Chi-squared tests for significance. Logistic regression was used to test for confounders. Probability levels of <0.05 were considered statistically significant.

Recruitment: This study was approved by the Kenyatta National Hospital Ethical and Research Committee. Written informed consent was obtained from guardians or next-of-kin. Consecutive patients admitted to the Kenyatta National Hospital ICU for mechanical ventilation were randomly assigned to receive either intravenous ranitidine 50mg eight-hourly or sucralfate 1gram via nasogastric tube six-hourly (for patients below 12 years of age, ranitidine 0.5mg/kg eight-hourly or sucralfate 10-20mg/kg six hourly was given). Only patients still on mechanical ventilation 48 hours later were included in the study, remaining in the assigned treatment group.

Each patient had a thorough history and physical examination on admission. They then had tracheal aspirate cultures, gastric aspirate cultures, full blood counts and chest X-rays on admission, at 48 hours and on day six. All tracheal and gastric samples were taken to the KEMRI Nairobi lab for microbiological analysis. VAP was diagnosed using the CPIS score which includes new and persistent infiltrates on chest X-ray, temperature greater that 38.5°C or less than 36°C, white cell counts above 2,000/ul or below 4,000/ul, purulent tracheobronchial secretions, a PaO2/FIO2 ratio less than 250 and the absence of alternative sources of infection. Mortality prediction was performed within 24 hours of admission using the APACHE II scoring system.

RESULTS

There were 447 admissions during the study period. 80 patients admitted to the Kenyatta National Hospital ICU who met the inclusion criteria were recruited into the study, and randomly assigned to receive either ranitidine or sucralfate. Twelve patients were subsequently excluded for the following reasons: Five died before 48 hours, three were extubated before 48 hours and four had positive bacterial cultures in the baseline tracheal aspirate. The remaining 68 were evenly split into 34 in the sucralfate group and 34 in the ranitidine group.

Table 1
Baseline Demographics

	Ranitidine (n=34)	Sucralfate (n=34)	p-value
Sex – no (%)			NS
Male	18 (52.9%)	19 (55.9%)	NS
Female	16 (47.1)	15 (44.1)	NS
Age - yrs			
Mean	28.9 (24.6-33.2)	23 (19-27)	NS
Median	27	19.5	NS
Range	2-80	4-85	NS
Admission diagnosis – no (%)			
Medical	14 (41.2%)	14(44.1%)	NS
Surgical (non-trauma)	11 (32.4%)	5(14.7%)	NS
Trauma	9 (26.5%)	14(41.2%)	NS

APACHE II score			
Mean	10 (4-15)	10 (5-16)	NS
Median	9	10	NS
Range	3-24	2-25	NS

NS = Not Significant

Eighteen (26.5%) of 68 patients had new and persistent infiltrates reported on Chest X-ray during the 6-day period. Only 14 (82.4%) of these satisfied the other diagnostic criteria for VAP. The other patients had lung collapse, ARDS and a haemothorax. This therefore translated to a 20.6% incidence of VAP within six days.

At intubation, all 68 patients had clear tracheal aspirates. Within 48 hours, 29 patients, 17 (50%) in the ranitidine group and 12 (35.3%) in the sucralfate group had either whitish or purulent secretions. By day six, less than half of the ranitidine patients still had clear secretions. However, only 14 (56%) of those with purulent secretions were diagnosed with pneumonia based on their CPIS score.

Fifty four (79.4%) of 68 patients were normothermic on admission. The other 14 were febrile, eight of whom were randomised to the ranitidine group and six to the sucralfate group. Ten (71.4%) of these did not acquire any airway infection during the six days of follow-up. 23(42.6%) of the normothermic patients developed fever during the study period. nine (39.1%) of these were found to have pneumonia. Two patients who were febrile at admission later had a temperature rise of at least 1.5°C above baseline and were also diagnosed to have VAP.

Table 2
Clinical and Demographic Characteristics of Patients with Pneumonia

Characteristic	Ranitidine (n=8)	Sucralfate (n=6)	p-value
Sex – no(%)			
Male	3 (37.5)	4 (66.7)	NS
Female	5 (62.5)	2 (33.3)	NS
Age –yrs			
Mean	37.1	41	NS
Median	27	30	NS
Admission diagnosis			
Medical	4 (50)	3 (50)	NS
Surgical (non-trauma)	1 (12.5)	0 (0)	NS
Trauma	3 (37.5)	3 (50)	NS
APACHE II score			
Mean	11	11	NS
Median	10	10	NS
Mean temperature	38.6	38.8	NS
PaO2/FIO2 ratio	223.8	229.7	NS
WBC count	14.1	13	NS
Mortality	3 (37.5)	2 (33.3)	NS

NS= Not significant

Thirty three (24.3%) of 136 gastric aspirates were found to be positive after an initial negative culture at intubation. These represented 24 (35.3%) of the 68 study patients, an equal number of whom were on ranitidine as were on sucralfate. Eighteen (26.5%) patients had gastric colonisation at 48 hours. Gastric colonisation at 48 hours occurred more commonly in patients on ranitidine than those on sucralfate, but this difference was not statistically significant (29.4% vs. 23.5%, p=0.3). The total number of those with

colonised gastric secretions had risen to 24 (35.3%) of 68 patients by Day six.

Twenty two (16.2%) of 136 paired samples taken at 48 hours and on Day six were found to have bacterial growth in both tracheal and gastric aspirates. Of these, 14(63.6%) had the same organism isolated from both tracheal and gastric aspirates. These organisms were Methicillin-Resistant *Staphylococcus aureus* (MRSA) in 9(64.3%), *Klebsiella* in 4 (28.6%) and *Acinetobacter* in 1 (7.1%). Seventy seven point two percent (77.2%) of positive cultures were found to have an association between the organism isolated from gastric contents and that isolated from the airways ($p<0.01$).

Tracheal aspirates from 32 (47%) of 68 patients were positive for bacterial growth at 48 hours. Of these, there was colonisation in 19 (27.9%) patients, tracheobronchitis in 19 (27.9%) and pneumonia in 14(20.6%). By Day six, the number of patients with a positive tracheal aspirate number had risen to 52(76.5%). 25(73.5%)of these were on ranitidine and 27(79.4%) on sucralfate, a difference that was not statistically significant. The organisms isolated at 48 hours were mainly MRSA and *Klebsiella*. By Day six, the organisms isolated were mainly MRSA, *Klebsiella* and *Acinetobacter*.

Table 3
Airway infection in study patients

Diagnosis	At 48 hrs (n=68)	By Day 6 (n=68)	Ranitidine (n=34)	Sucralfate (n=34)
Colonisation	16(23.5)	19(27.9)	9 (26.5)	10 (29.4)
Tracheobronchitis	12(17.6)	19(27.9)	8 (23.5)	11 (32.4)
VAP	4(5.9)	14(20.6)	8 (23.5)	6 (17.6)
Total	32(47.1)	52(76.5)	25(73.5)	27(79.4)

Positive tracheal aspirates

Figures in parentheses represent percentages

Table 4
Organisms isolated from study patients

	Positive gastric aspirates (n=32)	Positive tracheal aspirates (n=53)	At 48 hrs (n=32)	On day 6 (n=23)
MRSA	15 (45.5)	22 (41.5)	15(46.9)	8(34.8)
Streptococcus pneumoniae	0 (0)	1 (1.9)	1 (3.1)	0 (0)
Klebsiella	6 (18.2)	15 (26.4)	9 (28.1)	6 (26.1)
Acinetobacter	4 (12.1)	10(18.9)	3 (9.4)	6 (26.1)
Citrobacter	0 (0)	2(3.8)	1 (3.1)	1 (4.3)
Proteus mirabilis	1 (3.0)	2 (3.8)	1 (3.1)	1 (4.3)
Pseudomonas	0 (0)	1 (1.9)	1 (3.1)	0 (0)
E.coli	2 (6.1)	1 (1.9)	0 (0)	1 (4.3)
Enterobacter	5 (15.2)	0 (0)	0 (0)	0 (0)

Early VAP occurred in 4(28.6%) of 14 patients with pneumonia. Causative organisms were equally distributed between MRSA and *Klebsiella*. Late-onset VAP occurred in 10 (71.4%) of 14 patients, the main causative organisms being *Acinetobacter* in 4 (40%), MRSA in 2 (20%), *Klebsiella* in 2 (20%) and *Citrobacter* in 1 (10%).

The majority of the organisms isolated were resistant to first line antibiotics. The highest resistance rates were found with penicillin (95.2%) while the lowest resistance rates were found with ciprofloxacin (27.4%). Resistance rates to cefotaxime, a third-generation antibiotic were 50%.

Table 5
Antibiotic resistance patterns of bacterial isolates

	n	X-PEN	CAF	GENT	Co-TRIM	CEPHAL	CEFOT	CIPRO
MRSA	36	36(100)	9(25)	18(50)	16(44.4)	14(38.9)	15(41.7)	12(33.3)
Strep pneumo	1	1(100)	1(100)	1(100)	1(100)	0(0)	0(0)	0(0)
Klebsiella	19	18(94.7)	12(63.2)	7(36.8)	9(47.4)	12(63.2)	5(26.3)	3(15.8)
Acinetobacter	14	11(78.6)	14(100)	10(71.4)	8(57.1)	14(100)	12(85.7)	4(28.6)
Enterobacter	5	5(100)	3(60)	4(80)	4(80)	5(100)	4(80)	0(0)
E. Coli	3	3(100)	2(66.7)	2(66.7)	2(66.7)	3(100)	2(66.7)	1(33.3)
Proteus	3	3(100)	3(100)	2(66.7)	3(100)	3(100)	2(66.7)	2(66.7)
Citrobacter	2	2(100)	2(100)	2(100)	2(100)	2(100)	1(50)	0(0)
Pseudomonas	1	1(100)	1(100)	0(0)	1(100)	1(100)	1(100)	1(100)
TOTAL	84	80(95.2)	47(56.0)	46(54.8)	46(54.8)	54(64.3)	42(50)	23(27.4)

Key: X-PEN Crystalline penicillin; CAF chloramphenicol; GENT gentamicin; CEPHAL cephalothin; CEFOT cefotaxime; CIPRO ciprofloxacin, CO-TRIM Co-trimoxazole
n= total number of isolates
Figures in parentheses represent percentages

Twenty two (32.4%) of the 68 patients in the study died within six days in ICU. The overall mortality in the KNH ICU during this period was 33.6%. There was a 17.7% higher mortality rate in patients on sucralfate versus those on ranitidine (41.2% vs. 23.5%, p=0.5). This difference however was not statistically significant. There was no statistically significant difference between the two groups in terms of age, sex, APACHE II score, degree of gastric colonisation or any airway infection in those who died. Fourteen (63.6%) of the 22 patients who died had acquired airway colonisation, tracheobronchitis or VAP while in ICU.

Table 6
Characteristics of the patients who died

Characteristic	Patients who died (n=22)	Mortality by group Ranitidine (n=8)	Sucralfate (n=14)
Mean age, range (yrs)	32.5	36.8 (17.8-55.8)	30.3 (4.4-56.2)
Males – no. (%)	11(50)	5 (62.5)	6 (42.9)
Mean APACHE II score	12	12 (6-18)	12 (6-18)
Medical cases – no. (%)	10(45.5)	2 (25)	8 (57.1)
Trauma cases – no. (%)	7(31.8)	3 (37.5)	4 (28.6)
Gastric colonisation – no. (%)	9(40.9)	4 (50)	5 (35.7)
Any airway infection –no. (%)	14(63.6)	5 (62.5)	9 (64.3)

DISCUSSION

This study showed that the rate of bacterial infection in intubated patients at the KNH ICU is high, occurs early and rapidly progresses to more severe infection.

Within 48 hours of admission, nearly half the study patients had airway colonisation, tracheobronchitis or pneumonia. By Day 6, 76.5% of patients had positive bacterial cultures on tracheal aspirate.

The incidence of early-onset VAP was low (5.9%), which compared well with other studies. Although three times as many patients on ranitidine had acquired VAP as compared to those on sucralfate, this was not statistically significant. However, the presence of MRSA and gram-negative organisms such

as *Klebsiella* at 48 hours was unusual and would imply that the source of these organisms is contaminated airway management equipment within the ICU.

There was a causal relationship between bacteria isolated from gastric secretions and those found in patients' airways. Selective decontamination of the digestive tract (SDD) has for this reason been advocated in some centres as being invaluable in preventing gastric colonisation and subsequent pneumonia and/or sepsis in intubated patients. This has not been universally accepted however, as it may lead to the development of antibiotic-resistant organisms in critical care units (13).

Sixty eight point two percent (68.2%) of patients who died had airway colonisation, tracheobronchitis or pneumonia. Although the mortality in the sucralfate group was almost 9% higher than that in the ranitidine group, this was not statistically significant. Of note however is the fact that 22.7% of the patients who died had been diagnosed with VAP. Mortality rates in patients with pneumonia in the two groups were approximately equal (33.3% of those on sucralfate and 37.5% of those on ranitidine).

The organisms isolated from these patients were multi-drug resistant. Very few were sensitive to first-line antibiotics and as such the use of these antibiotics in critically ill patients presenting to this unit needs to be reviewed. A previous study conducted in the KNH ICU had identified the third generation antibiotic ceftazidime as proving the best broad-spectrum cover. The lack of sensi-discs for this antimicrobial however meant that sensitivity patterns to ceftazidime were not tested. There was a worryingly high rate of Methicillin-Resistant *Staphylococcus aureus* (MRSA), a virulent organism with a high morbidity and mortality in infected patients, which requires stringent infection control measures to prevent and control.

Colonisation, tracheobronchitis and pneumonia rates were similar between patients on sucralfate and those on ranitidine. In addition, the rates of gastric colonisation were the same in both treatment groups (23.5%). This study therefore failed to demonstrate any protective effect of using sucralfate as stress ulcer prophylaxis. The common use of enteral feeds in the KNH ICU may have been a potential confounder, as it would result in an alteration in gastric pH levels. This was not adjusted for in the analysis.

Despite the lack of a protective effect on gastric colonisation or VAP in critically ill African patients, stress ulcer prophylaxis with sucralfate may still be a viable alternative for stress ulcer prophylaxis in resource-limited countries, due to its lower cost.

LIMITATIONS OF THE STUDY

Fungal and viral pneumonias were not accounted for, as the cultures for these would have been too costly to perform. The use of tracheal aspirate samples and the CPIS scoring system are of low specificity in diagnosing VAP. Bronchoscopically directed techniques may have increased the proportion of positive cultures, but these were however not available at the Kenyatta National Hospital ICU. Previous unreported antibiotic use may also have interfered with culture results.

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