

Determinants of the Effectiveness of Antimicrobial Prophylaxis among Neurotrauma Patients at a Referral Hospital in Kenya: Findings and Implications

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Abstract

Background: Surgical site infections can occur adding to morbidity, mortality and costs, and can be particularly problematic in low and middle income countries. This includes infections in neurosurgical patients following surgery despite antimicrobial prophylaxis. The study aimed at measuring the incidence of surgical site infections (SSIs) and identifying factors that influence the effectiveness of antimicrobial prophylaxis in a leading hospital in Kenya.

Methods: Prospective cohort study from April to July 2015 in the Neurosurgical ward of a leading referral hospital in Kenya. Adult head injury patients were recruited by universal sampling. Data was collected on prophylactic antibiotics and the occurrence of SSIs. Risk factors for infection were identified by logistic regression.

Results: Eighty four patients were recruited, with 69 patients eventually analysed. The incidence of SSIs was 37.7% (n=26). The most common antibiotic used for prophylaxis was ceftriaxone. Patients on prophylaxis were less likely to be infected than those who did not receive prophylaxis; however, this was not statistically significant (RR 0.87, 95% CI 0.40-1.893). The presence of epidural haematoma was a risk factor for the development of SSIs (Crude RR 2.456, 95% CI 1.474-4.090). Overall, antimicrobial prophylaxis was effective only in patients who underwent evacuation of hematoma by craniotomy (risk reduction, 62.5% (CI, 29.0%-96.0%).

Conclusion: Evacuation of haematomas through craniotomy increased the effectiveness of prophylaxis, and should be considered in the future. The rationale will be explored further to see if antibiotic prophylaxis can reduce SSIs in other patients with neuro trauma.

Keywords: Antimicrobial prophylaxis; Neurosurgery; Surgical site infections; Epidural hematoma; Craniotomy; Kenya

Background

Surgical site infections (SSIs) increase morbidity, mortality and costs, and can be particularly problematic in low and middle income countries (LMICs) [1-5]. They are a common cause of hospital acquired infections, and can be common after certain surgical procedures [6,7]. The estimated global incidence ranges from 1.2 or lower to 23.6 or higher per 100 surgical procedures, with higher rates seen in developing countries and for some colorectal procedures [1-3,7,8]. Concerns with SSIs and their implications has resulted in a number of guidelines and other documents to reduce future rates [3,9], including examination of potential risk factors [7], with potentially up to 50% of SSIs preventable [3,10-13]. Surveillance of SSIs is seen as critical to reduce future rates through providing information on the possible risk factors and the effectiveness of existing infection control procedures [2,7,14].

In neuro trauma, patients with penetrating brain injuries are more likely to develop serious infections as opposed to those with blunt trauma, with the recommended use of antimicrobial agents to appreciably reduce a high risk of secondary infection [15,16]. The most common infective organism in these cases is *Staphylococcus aureus*, although gram negative organisms may be implicated [17]. Currently, the use of pre and perioperative prophylaxis is largely empiric in neuro trauma. However, prophylactic antibiotic use may not always be beneficial in patients with traumatic brain injury [18]. In some settings, the use of prophylactic antibiotics in neuro trauma can potentially increase the risk of hospital acquired pneumonia [19,20]. Despite these concerns, there exist several guidelines that promote the routine use of antimicrobial prophylaxis in neurosurgery, although the 2007 guidelines on management of severe traumatic brain injury (TBI) did not [18]. These guidelines advocated that where there is an infection, clinicians must choose an antibiotic at their own discretion [18].

Typically, the choice of antibiotics for prophylaxis depends on knowledge of the infecting bacteria, local antimicrobial susceptibility

patterns, safety and cost issues of potential antibiotics [21]. Synthesis of recent evidence suggests the use of first and second generation cephalosporins for prophylaxis in neurosurgery, with metronidazole for anaerobic cover [12].

For effective prophylaxis, several principles should be adhered to. Firstly, antibiotics should be given 30 min to 60 min before the initial incision to allow for the drug tissue concentration to rise above the minimum inhibitory concentration [13,22,23], although others have suggested within the first 120 min [4]. Additional doses of prophylactic antibiotics may be required for procedures longer than 3 h [20]. Prophylaxis should be stopped within 24 h for clean procedures; however, for patients with contaminated and dirty wounds, antibiotics should be given for the treatment duration. A single antimicrobial agent is typically sufficient for prophylaxis as opposed to use of multiple agents [12]. Antimicrobial prophylaxis alone may not prevent SSIs. Other pre-operative and intraoperative infection control procedures such as disinfection and hair removal are extensively described in current guidelines for the prevention of SSIs [3,9,23].

However, little is known about SSIs especially those following neuro trauma in LMICs such as Kenya, where it is known such infections could be more problematic. Consequently, the objective of this study was to measure the incidence of SSIs in patients with neuro trauma in the neurosurgical ward of a leading referral hospital in Kenya, building on previous epidemiological studies [24]. Secondly, ascertain factors that could affect the effectiveness of antimicrobial prophylaxis. The findings of the study will form the baseline for monitoring the effectiveness of existing infection control measures, as well as plan future measures in this and other hospitals in Kenya to improve future antibiotic use in hospitals.

Methods

Study design, site and population

Prospective cohort study following up neuro trauma patients admitted in the Neurosurgical wards of Kenyatta National Hospital (KNH) between April and July 2015 for the development of SSIs. KNH was chosen for this initial study as it is the largest teaching and referral hospital in Kenya. Consequently, can provide direction and guidance to other hospitals in Kenya.

Inclusion and exclusion criteria

Inclusion criteria were: adult patients over 18 y old, who sustained traumatic injury through road traffic accidents, assault, falls or any other cause; those who were admitted at the neuro-intensive care unit for elective; and emergency neurosurgery in the study period. Exclusion criteria were all other patients with neuro trauma not meeting these criteria

Sampling and participant recruitment strategies

A previous study carried out at a neurosurgical unit for elective neurosurgical patients [24] found an incidence of SSIs of 7.5%. Using this incidence, a sample size of 100 patients was estimated using the formula for prospective incidence studies [25]. Participants were recruited in the afternoons after the main ward rounds. Consent forms were completed either by the participants or their care givers.

Data collection

All the patients were followed up daily for the admission period for the development of SSIs, which was diagnosed by the operating surgeon as per the CDC guidelines [9]. The following data was abstracted from patient files: patient demographics, antimicrobial treatment, surgical and medical history. Additional information was obtained from patients or their caregivers.

Case definition

As mentioned, guidelines have indicated that prophylactic antibiotics should be given at least one hour before surgery, although others have indicated longer, and stopped 24 h after the initial incision [4,22,23]. In case of contaminated and dirty wounds, presumptive treatment should be undertaken [21].

For the purposes of this study, antimicrobial prophylaxis was defined as administration of antibiotics for a period of 24 h before surgery and up to 3 days after surgery. This is because in our study, there were no local guidelines for antimicrobial use and prophylaxis, making it difficult to distinguish between prophylaxis and presumptive treatment. Any antimicrobials given for longer than three days were considered presumptive treatment for infection. Evidence of SSIs was obtained from the patient records. The attending surgeons examined the wounds during the ward rounds and documented evidence of infection, as per current guidance [2,9,23].

Variables

The main outcome of interest was the development of a SSI. The main predictor of interest was antimicrobial prophylaxis. Other covariates included patient demographic characteristics and the cause of injury (road traffic accident, assault, accidental falls or any other type of trauma). The number, type and duration of surgery were also included as potential co-variables.

Data analysis

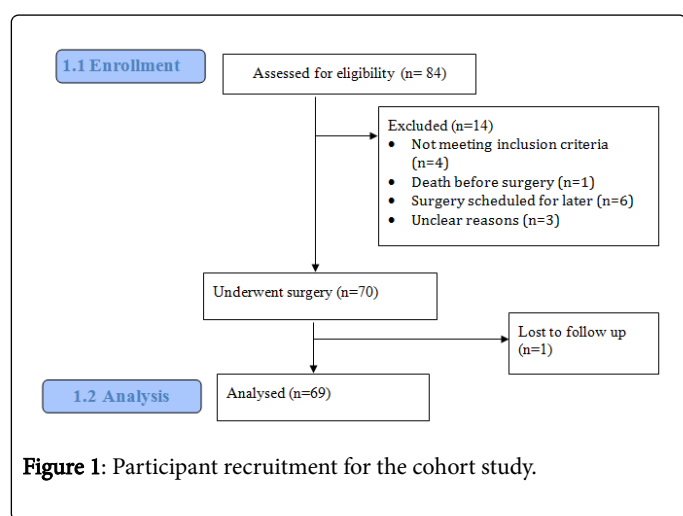
All variables were subjected to descriptive analysis. For normally distributed variables, the mean and standard deviation were reported. For those which were not normally distributed, the median and interquartile ranges were reported. Categorical variables were summarized as counts and proportions. The Wilcoxon Rank Sum test was used to compare continuous variables across the group. The Fischer exact Chi Square test was used to compare the distribution of categorical variables. To identify risk factors for SSIs, logistic regression was conducted. Bivariable analysis was initially conducted to obtain the crude measure of association between predictor variables and the main outcome.

To adjust for confounding, multivariable analysis was conducted by using two or more predictor variables. Model building was done using a manual forward stepwise model building approach. The last step of model building entailed testing for statistical interaction between key variables. Data analysis was done using STATA version 13 software. The level of significance was set at 0.05.

RESULTS

Patient recruitment, causes of trauma and indications for surgery

Out of the 84 patients who were recruited in this study, 83.3% (n=70) underwent surgery. Eleven patients did not undergo surgery for several reasons as outlined in Figure 1. It was unclear whether three patients had undergone surgery or not. Of those who underwent surgery, one had missing records and could not be included in the analysis, making a total of 69 patients analysed. The most common cause of trauma amongst those who underwent surgery was assault (44%), followed by road traffic accidents (33%), falls (18%) and unknown blunt trauma (5%). The number of patients whose data was finally analysed was 69 (Figure 1).



Indications for the patients who underwent surgery included evacuation of haematomas (n=34), repair of skull fractures (n=13), drainage of intracranial abscesses (n=15), repeat surgery for patients who developed post craniotomy complications (n=1), the management of brain contusion (n=2) and surgery for multiple injuries on the brain and other body parts (n=4).

Baseline characteristics of the cohort and incidence of surgical site infections

Most patients were males and the majorities were aged below 35 years. Nearly equal numbers had primary or secondary education. Out of 69 patients who underwent surgery, 37.7% (n=26) developed surgical site infections. In Table 1 compares the traits of those who developed surgical site infections and those who did not. There were no statistically significant differences between these two groups.

Most of the patients who developed infections were male (92.3%, n=24). Of the patients who were in theatre once, the incidence of infection was 73.0% (OR 0.73, 95% CI 0.42, 1.27). Of the patients who were aged below 35 years, 43.2% developed an infection as opposed to older patients of whom only 29% developed infections. Patients with secondary and tertiary education had the highest incidence of SSIs at 37.5% and 55.6% respectively. Patients with epidural haematoma had a higher risk of developing infections (77.8%) compared to those with subdural haematoma (31.2%).

Demographic characteristics	No Infection, n (%)	Infection, n (%)	Total (n)	Risk Ratio (95% Confidence interval)	P value
Sex					
Male	41 (63.1%)	24 (36.9%)	65	0.73 (0.26, 2.07)	0.600
Female	2 (50.0%)	2 (50.0%)	4		
Age group					
Age <35 yrs	21 (56.8%)	16 (43.2%)	37	0.67 (0.34, 1.30)	0.226
Age >35 yrs	22 (71.0%)	9 (29.0%)	31		
Education level					
Unknown	4 (40.0%)	6 (60.0%)	10	1.743 (0.944, 3.218)	0.123
No education	2 (66.7%)	1 (33.3%)	3	0.872 (0.171, 4.443)	0.864
Primary	18 (78.3%)	5 (21.7%)	23	0.474 (0.206, 1.092)	0.005
Secondary	15 (62.5%)	9 (37.5%)	24	0.979 (0.521, 1.841)	0.948
Tertiary	4 (43.4%)	5 (55.6%)	9	1.566 (0.798, 3.072)	0.246
Patient co-morbidities					
Other cardiovascular disease	2 (100.0%)	0 (0.0%)	2	-	0.214
Hypertension	2 (100.0%)	0 (0.0%)	2		
Neurointensive care unit admission	0 (0.0%)	2 (100.0%)	2	-	0.103
Neurointensive care unit					

Table 1: Demographics of patients who developed infection and those who did not.

The types of injuries and surgical procedures patients underwent are presented in Table 2. These characteristics were compared among those who developed SSIs and those who did not. The most important cause of injury was assault (49.3%). Most patients had one injury (74.3%). The most common injury was a haematoma (68.1%) of which the most common seen was a subdural haematoma. Several patients, 13 (18.8%), sustained skull fractures. For most patients, the severity of head injury was not scored. Only 6 (8.7%) patients had their injury scored (Table 2). Most patients underwent only one surgical procedure.

The majority of the patients 47 (68.1%) had a diagnosis of haematoma (Table 2). Out of these, 30 (63.8%) underwent a craniotomy while 7 (14.9%) underwent burr hole procedures. For 10 (21.3%) patients, it could not be established from their records the type of evacuation procedure they had undergone, with their records simply indicating that they had undergone an evacuation procedure.

For the 13 patients (18.8%) who had a diagnosis of skull fracture, all underwent craniotomy except for one patient who underwent an open reduction internal fixation of the fracture (ORIF). None of the patients with a skull fracture underwent a burr whole procedure. Five of these also underwent evacuation of haematomas. One of the patients with a craniotomy also underwent surgical toilet and elevation of skull fracture.

Skull fracture				
No skull fracture	37 (66.1%)	19 (33.9%)	56 (81.2%)	0.194
Skull fracture	6 (46.2%)	7 (53.8%)	13 (18.8%)	
Extracranial Haemorrhage				
	1 (100.0%)	0 (0.0%)	40 (58.0%)	0.385
Surgical Procedures				
Number of surgical procedures per patient				
1	25 (62.5%)	15 (37.5%)	25 (36.2%)	0.840
2	17 (68.0%)	8 (32.0%)	3 (4.3%)	0.338
3	1 (33.3%)	2 (66.7%)	1 (1.5%)	-
4	0 (0.0%)	1 (100.0%)		-

Table 2: Surgical procedures, patterns of injury in patients with and without infection.

Trauma	No infection, n(%)	Infection, n (%)	Total	P value
Cause of trauma				
Assault	20 (58.8%)	14 (41.2%)	34 (49.3%)	0.600
RTA	12 (66.7%)	6 (33.3%)	18 (26.1%)	0.635
Fall	8 (66.7%)	4 (33.3%)	12 (17.4%)	0.713
Blunt trauma	3 (100.0%)	0 (0.0%)	3 (4.3%)	0.166
Unknown cause	0 (0.0%)	2 (100.0%)	2 (2.9%)	
Total no of injuries				
1	34 (65.4%)	18 (34.6%)	52 (74.3%)	0.526
2	9 (56.3%)	7 (43.8%)	16 (22.9%)	
3	1 (50.0%)	1 (50.0%)	2 (2.8%)	
Type of hematoma				
Subdural	22 (68.8%)	10 (31.2%)	32 (46.4%)	0.023
Epidural	2 (22.2%)	7 (77.8%)	9 (13.04%)	
Intracerebral	1 (100.0%)	0 (0.0%)	1 (1.4%)	
Position of hematoma not indicated				
Unknown	4 (100.0%)	0 (0.0%)	4 (5.8%)	
Unknown	0 (0.0%)	1 (100.0%)	1 (1.4%)	
Total number with haematoma			47 (68.1%)	
Head injury (Glasgow coma Score)				
Mild (13-15)	3 (75.0%)	1 (25.0%)	4 (66.8%)	0.274
Moderate (8-12)	1 (100.0%)	0 (0.0%)	1 (1.6%)	
Severe (<8)	0 (0.0%)	1 (100.0%)	1 (1.6%)	

Patterns and effects of antimicrobial prophylaxis

Eighteen patients (26.1%) received antibiotics for prophylaxis. The most commonly used antibiotic for prophylaxis was ceftriaxone, (78%, n=14). The duration of prophylaxis from the onset of surgery ranged from 1 to 3 days.

Patients on prophylaxis were slightly less likely to be infected than those who did not receive prophylaxis (RR 0.87, CI 0.40-1.893). This was equivalent to a risk reduction of 4.0% (CI 26.12 to -18.0%, p=0.790). Patients on amoxicillin-clavulanate and cefuroxime prophylaxis did not develop surgical site infections. The use of ceftriaxone prophylaxis was associated with an increased risk of development of infection (RR 1.12, 95% CI 0.55-2.27); however, this was not statistically significant (p=0.759).

Risk factors for surgical site infections- logistic regression analysis

Logistic regression analysis was performed to identify key risk factors associated with the development of surgical site infections. On bivariable analysis, the only variable that was significantly associated with risk of surgical site of infections was the presence of an epidural haematoma (RR 2.456, 95% CI 1.474-4.090). Out of the 9 patients with epidural haematoma, 77.8% (n=7) developed a surgical site infections. For the other patients who did not have epidural haematoma (n=60), only 33.0% (n=19) developed a surgical site infection (Table 3). The presence of an epidural haematoma was the most important independent risk factor for occurrence of SSIs (Table 3). Evacuation procedures were negatively associated with SSIs. Assault was positively associated with SSIs. None of the known risk factors for SSI such as duration of surgery was a significant risk factor.

Determinants of the effectiveness of antimicrobial prophylaxis–effect measure modification

In the last step of model building, the presence of a statistical interaction was evaluated. The most parsimonious model showed there was a two way interaction between craniotomy and prophylaxis. The most parsimonious model is presented in Table 3.

Variable	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Patient Demographics				
Sex	0.63 (0.08, 4.79)	0.657	-	-
Age	0.99 (0.96, 1.03)	0.635	-	-
Cause of Trauma				
Assault	1.08 (0.41, 2.86)	0.882	-	-
Road traffic accidents	0.86 (0.27, 2.72)	0.794	-	-
Falls	0.82 (0.21, 3.13)	0.771	-	-
Pattern of Injury				
No. of injuries	1.43 (0.55, 3.68)	0.462	-	-
Epidural haematoma*	7.368 (1.396, 38.894)	0.019	-	-
Chronicity of hematoma	1.00 (0.99, 1.01)	0.375	-	-
Site of injury	0.99 (0.77, 1.29)	0.965	-	-
Skull fracture	1.28 (0.74, 2.21)	0.384	-	-
Surgical Procedure				
Burr hole	0.68 (0.19, 4.01)	0.864	-	-
Evacuation of hematoma	0.50 (0.18, 1.38)	0.180	-	-
Craniotomy	1.54 (0.52, 4.52)	0.434	3.556 (0.848, 14.91)	0.083

Table 3: Association between Selected Variables and Surgical Site Infection.

Interaction between antimicrobial prophylaxis and craniotomy on surgical site infections

Figure 2 summarizes the interaction of craniotomy and prophylaxis. Overall, antimicrobial prophylaxis was more effective in patients who underwent craniotomy. The risk of developing an infection was reduced by 45.2% among those who underwent craniotomy and were on prophylaxis, as opposed to only 27.1% among those who underwent craniotomy and were not on prophylaxis. This was statistically significant (p=0.05). Craniotomy had a protective effect. Patients who did not undergo craniotomy but received antimicrobial prophylaxis had a high risk of infection.

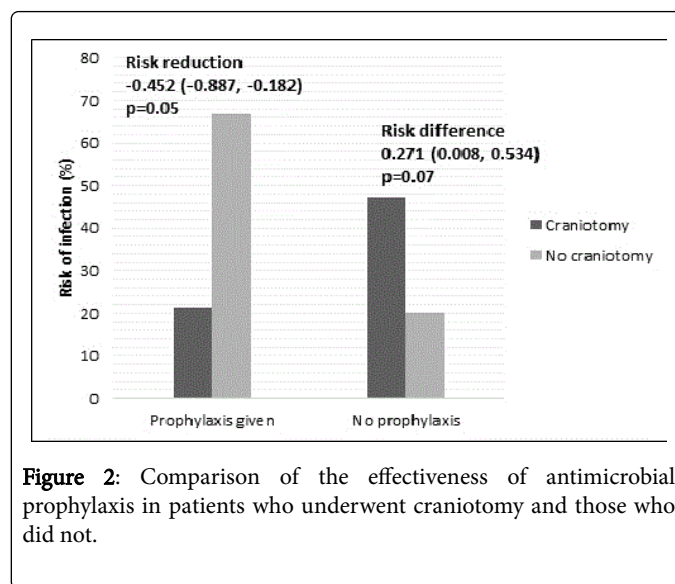


Figure 2: Comparison of the effectiveness of antimicrobial prophylaxis in patients who underwent craniotomy and those who did not.

The effects of duration of the surgical procedure on the effectiveness of antimicrobial prophylaxis

The difference in the effectiveness of antimicrobial prophylaxis could have been attributed to the differences in duration of surgical procedures. In general, the duration of the surgery for patients who underwent craniotomy was longer when compared to patients who underwent other surgical procedures. The median duration of surgery for patients who underwent craniotomy was 3 h with a range of 2 to 6 h (n=49). On the other hand, the median duration of surgery for patients who underwent other surgical procedures was 2 h with a range of 2 to 7.5 h (n=33). The difference in the duration of surgery was statistically significant (p<0.001).

The duration of surgery was also dependent on the total number of procedures a patient underwent while in theatre (p=0.001). When the duration of surgery was added to the parsimonious model, the interaction term became insignificant. In longer surgical procedures, a second dose of prophylactic antibiotic was often administered.

Discussion

In our study, the incidence of SSIs was very high at 37.7%, which is at the upper range of reported incidences acknowledging SSIs are more common and more problematic in LMICs [1-3]. This compares with an earlier study at the same hospital reporting a much lower infection rate of 7.5% [24]. Several other studies conducted in LMICs have also recorded similar SSI rates of 5-10% [26,27]; however, this is not universal [1]. Typically though these studies mainly recruited patients undergoing clean neurosurgical procedures, whilst this study recruited patients who had sustained injury through trauma, with clean contaminated, contaminated to dirty wounds. As a result, the neuro trauma patients in our study are more likely to be infected.

Patients who had epidural haematomas were the most likely to develop an infection, with epidural haematomas developing in trauma that results in skull fractures and stripping off the dural membrane from bone [28]. Additionally, epidural haematomas tend to accumulate very fast. The skull fractures and rapidly expanding haematomas could contribute to colonization of the injured areas by normal flora, causing

infection [28]. This may help explain why patients with epidural haematomas were more likely to develop infection.

The most common surgical procedure was craniotomy, followed by burr hole procedures. The highest infection rates were recorded among patients who underwent craniotomy alone, followed by those who underwent burr hole drainage procedures. Those who underwent evacuation of hematomas were less likely to develop infection; in fact, evacuation of haematomas reduced the risk of surgical site infections. Studies have shown that infections that develop after craniotomy are a major problem in neurosurgery, and are associated with high morbidity and mortality rates [26].

The risk of development of infection in our study was dependent on a combination of two different variables: type of procedures and prophylaxis. Prolonged duration of surgical procedures is a major risk factor for development of neurosurgical site infections [27,29]. In this study, the median duration of surgical procedures was 3 h, although studies have recorded durations of 3 to 5 h or longer [26,30]. Procedures that last more than two to four h have been associated with an increase in the incidence of SSIs, because of an increase in the time of wound contamination as well as reduced efficacy of antibiotics administered for prophylaxis [20].

The duration of the surgical procedure performed typically depends on the type of procedure. From the results, the duration was longer for the patients who underwent craniotomy than those who underwent other procedures. This can be an issue as prolonged surgery increases the chances of contamination of the surgical wound and the surgical field from normal flora and bacteria from the environment [30]. In addition, the minimum inhibitory concentration of antibiotics reduces with time, and this affects their effectiveness as prophylaxis. To address this, in KNH, patients undergoing long procedures receive a second dose of antimicrobial prophylaxis. This may explain why craniotomy had a reduced risk of infection when antibiotics were given prophylactically (Table 3 and Figure 2), and endorses the need for intraoperative re-dosing for patients undergoing long procedures [20].

Overall, antimicrobial prophylaxis alone did not seem to be effective in preventing SSIs in our patient population. The exception was craniotomy where antimicrobial prophylaxis reduced subsequent SSIs (Figure 2), potentially due to the prolonged procedure and additional prophylaxis. There appear to be no published studies to date which explains this particular finding in patients with this neuro trauma. It may be that the infection control procedures performed during craniotomy in our hospital, coupled with undertaking evacuation of haematoma procedures such as disinfection of the site and other intraoperative sterile procedures, contributed to a reduction of SSIs in our patients undergoing craniotomy. We will be following this up in future studies.

Our study had several limitations. These included the fact that some of the patient data was missing from patient files, which is typical for this type of analysis. As a result, since there was no clear distinction between antimicrobial prophylaxis and presumptive treatment for infection in our patients due to a lack of local guidelines, we assumed prophylaxis to be antibiotic use for up to three days. In addition, the sample size was small. However, we believe our findings are robust and do provide future direction as KNH is a national referral hospital.

The findings of this study imply that there is need for more intense infection control for patients with epidural haematomas. Secondly, intra-operative infection control measures that are undertaken during craniotomy may need to be applied to other patients with neuro

trauma to reduce the risk of SSIs in these patients with potentially contaminated wounds. We will be exploring this further as part of the Kenyan National Action Plan (NAP) for the prevention and containment of antimicrobial resistance (AMR) in Kenya through the improved use of antibiotics [31]. Kenya has recently formulated its multisectoral and interdisciplinary NAP anchored in five key strategic objectives. These are (i) to improve awareness and understanding of AMR; (ii) to strengthen knowledge through surveillance and research; (iii) to reduce the incidence of infection; (iv) to optimize the use of antimicrobial agents and (v) to ensure sustainable investment in countering AMR. The NAP provides a regulatory and implementation framework to establish and strengthen systems to contain the emergence and spread of AMR. Data from this study contributes directly to the strategic objectives of the NAP through providing data that will be invaluable in the efforts to reduce the future incidence of infection in Kenya, and to optimize the use of antimicrobial agents particularly in surgical patients. There will be greater follow-up of this type of research in the future to achieve the goals established in the NAP.

Conclusion

In conclusion, the presence of epidural haematoma was an independent risk factor in the development of infection among our neuro trauma patient cohort. Antimicrobial prophylaxis alone appeared not effective in preventing SSIs in patients with neuro trauma with the exception of craniotomy procedures and evacuation of haematomas. Further studies should be carried out in Kenya and other hospitals in Africa and wider to establish why craniotomy and evacuation procedures increased the effectiveness of prophylaxis in these neuro trauma patients, and potentially transfer the learnings to other patients. More studies may also be required to determine how the type of surgical procedure in patients with neuro trauma may also affect the effectiveness of antibiotic prophylaxis to improve future use. We will be pursuing these studies in the future.

Acknowledgement and Conflicts of Interest

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Ethical Consideration

The study was approved by the Kenyatta National Hospital-University of Nairobi Research and Ethics Committee (Approval Number P76/02/2014).

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