Comparative Study of 24-Hour versus Five-Day Prophylactic Antibiotic Use in Gustilo II Open Tibia Fractures at Kenyatta National Hospital

A dissertation submitted in part fulfillment for the requirements of the degree of Master of Medicine (M.Med) in Orthopedic Surgery of the University of Nairobi.

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H58/70490/2011

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DECLARATION

I hereby declare that this study is my original work and has not been presented for a degree at any other university.

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ACKNOWLEDGEMENT

I would like to express my heartfelt appreciation to the following for their contribution in this study.

1. My supervisors Prof. J.E.O Ating'a and Dr. Bwana Ombachi for their guidance throughout the study.
2. All lecturers in the department of orthopedic surgery, University of Nairobi, for their mentorship while in the department
3. My fellow orthopedic registrars for their assistance throughout the study.
4. Dr. Moses Masika (Tutorial Fellow, Microbiology department, UoN) for his advice and data analysis
5. The secretary, department of orthopedic surgery, nurses in all clinical areas involved for their unwavering support throughout the study.
6. The staff of trauma theatre for their cooperation in quick debridement of the patients.
7. My family and friends for their support and understanding throughout the study.
8. Our creator, for through Him only do things happen at the right time.

LIST OF ABBREVIATIONS

A &E	Accident and Emergency
AWSS	Asepsis Wound Scoring System
IMN	Intramedullary Nailing
KNH	Kenyatta National Hospital
KNH/ERC	Kenyatta National Hospital ethical and Research Committee.
NINSS	Nosocomial Infection National Surveillance Scheme
PAU	Prophylactic Antibiotic Use
S.D	Standard Deviation
UoN	University of Nairobi

1.0 ABSTRACT

Background: Open fractures have been a challenge to clinicians for centuries and this scenario persists in the 21st century. Management protocols have been devised over the years including among others prophylactic antibiotic use (PAU). Optimum duration of antibiotic use has been extensively researched but still remains unresolved although most studies have recommended 24 to 72 hours of prophylaxis. Furthermore, no protocol exists on PAU in our set up and most clinicians prescribe for five days to several weeks. Therefore, there is need for further research in the quest to improve the effectiveness of prophylactic antibiotic use and its adoption in developing countries like Kenya.

Objective: To determine the difference in infection rate between 24 hours versus five days of prophylactic antibiotic use for the management of Gustilo II open tibia fractures.

Design: Prospective randomized comparative interventional study.

Setting: Accident and Emergency department, orthopedic wards and orthopedic outpatient clinics at KNH.

Patient and methods: The study involved patients aged 18 to 80 years admitted in the orthopedic wards at KNH through A & E department with Gustilo II acute traumatic open tibia fractures and subsequent follow up in the clinics. These were randomized into either the 24 hour or five day group and antibiotics (Cefuroxime and Gentamycin) started at A &E department and continued for 24hours or five days after surgical debridement. Patient demographics, wound characteristics and fracture pattern were recorded after informed consent then antibiotics started. The wounds were exposed and scored using ASEPSIS wound scoring system for any infection after 48 hours, 5 days and at 14 days.

Outcome measures: The main outcome measure was the presence of infection as determined at day 2, 5 and 14 days. Antibiotics were restarted for those who developed infection as per the diagnostic criteria.

Results: There was no significant difference in infection rates between 24-hour and 5-day groups with infection rates of 23% (9/40) vs. 19% (7/37) respectively (p = 0.699). The infection rate was significantly associated with time lapsed before administration of antibiotics (p = 0.004). Participants who received antibiotics less than 12 hours after admission were less likely to develop infection than those who received antibiotics after 12 hours; 11% (5/45) vs 52% (11/21) respectively. Infection rate was related to the time lapsed before debridement but the association was not statistically significant ($p = 0.08$). Out of 13 patients who underwent debridement within 12 hours, 2 (15%) developed infection as compared to 14 (29%) out of 48 patients who underwent debridement after 12 hours, (chi-sq, $p = 0.72$). Both groups had similar culture growth rates with *Staphylococcus aureus* as the commonest isolate followed by *pseudomonas aeruginosa*

Conclusion: In the use of prophylactic antibiotics for the management of Gustilo II traumatic open tibia shaft fractures, there is no difference in terms of infection rate between 24 hours and five days regimen. Time to debridement and fracture stabilization method does not seem to influence infection rate but time to antibiotic administration correlates with infection rate.

2.0 INTRODUCTION

The management of open fractures has presented a long standing challenge to health care practitioners. Faced with such a daunting challenge of open fractures, surgeons and other clinicians have sought various antibiotic regimens to prevent infection and achieve healing. Some of the regimens employed include use of single or combined antibiotic therapy for a varied duration of time depending on the Gustilo classification. It is generally accepted that antibiotic prophylaxis in grade I and II fractures should not be administered for more than 24 hours(1, 2) to 48 hours(2). However, some guidelines recommend a maximum of 72 hours (3). The minimum duration for grade III fractures varies between one and ten days (1, 2, 4, 5). Although this has achieved remarkable results it has not been adopted in most developing countries (6) including our set up.

In the management Gustilo II and III open fractures, the aim is to achieve early primary or secondary wound closure and subsequent bone healing without infection (7). This requires hospital admission in our setting, early institution of antibiotics and adequate debridement with bone stabilization. To prevent infection various studies have demonstrated the crucial role of prophylactic antibiotic use. Studies focused on short duration of PAU have shown similar outcome compared with longer duration of PAU (8). However, longer duration of PAU than necessary has disadvantages including emergence of resistant organisms (9), extra cost to the patient and unwarranted side effects (10). Recent clinical trials and guidelines suggest that 24 to 48 hours of PAU for Gustilo II open fractures is adequate to prevent wound infection and chronic osteomyelitis (1, 2).

In our institution, PAU protocol is non-existent with clinicians prescribing antibiotics for the duration ranging from five days to several weeks in an attempt to maximize infection prevention. In a nearby country, Uganda, a Study done by Kigera et al (6) in Mulago Hospital

found the average duration of PAU in open fractures to be 7.3 days. Unfortunately this may be posing extra unnecessary burden to the hospital and the patient especially cost and side effects.

Considering that longer duration of PAU is the norm in most hospitals in our set up and there are no studies for or against the practice in these set ups, there is need for a randomized study to compel habit change. To limit the number of variables this study zeroed on Gustilo II open tibia fractures and aimed to find out whether there is any difference in infection rate if prophylactic antibiotics are administered for 24hours or five days.

3.0 LITERATURE REVIEW

The management of open fractures has a long history and has provided a challenge to humanity through ages. Throughout history open fracture has been greatly feared due to the high incidence of infection leading to death. Until the beginning of the twentieth century the most dependable way of avoiding such an unhappy result was to carry out early amputation.(11)

Classification system of open fractures has undergone evolution over the years. The most accepted is that of Gustilo and Anderson developed in 1976 based on prospective and retrospective study of 1025 patients (4). This was later refined by Gustilo who subdivided type III fractures into three subtypes (12, 13). Although various studies have questioned the Gustilo classification due to its poor inter-observer reliability (5, 14, 15), it has been found to be an important predictor of infection rate and bone union (16, 17). It divides open tibia fractures into types I, II, and III based on four parameters; fracture pattern, degree of soft tissue damage, contamination and neurovascular status.

• Grade I — open fracture with a skin wound less than 1 cm long

-there is minimal soft tissue contamination

-fracture pattern is simple with minimal or no periosteal stripping of bone

-closure can be primarily achieved

• Grade II — open fracture with a laceration more than 1 cm long,

-there is moderate soft-tissue damage,

-fracture pattern is simple or with mild comminution.

-bone is easily covered primarily.

• Grade III —is a high velocity injury with open segmental fracture, an open fracture with extensive soft-tissue damage, or a traumatic amputation. The infection rate for grade III fractures is at least 24%, (12, 13) which is so high that these fractures were further classified as follows:

• Grade IIIA — adequate soft tissue coverage of a fractured bone, despite extensive soft tissue laceration or flaps, or high-energy trauma, irrespective of the wound.

• Grade IIIB — extensive soft tissue loss with periosteal stripping and bone exposure, usually associated with massive contamination.

• Grade IIIC — open fracture associated with arterial injury, often requiring repair.

Dunkel et al noted that infection in open fractures is related to extent of tissue damage (Gustilo grade) not duration of prophylactic antibiotic therapy hence the reason for studying one Gustilo grade to reduce the number of variables (8)

Bowen and Widmaier's study of 174 patients with open fractures of long bones found that besides Gustilo and Anderson classification, a number of compromising comorbidities are also significant predictors of infection especially immune system compromising factors (17). The study reported 14 comorbidities that increase infection besides the Gustilo grade. Among them include; tobacco use, diabetes mellitus, pulmonary insufficiency, age more than 79 years, renal failure, malignancy and corticosteroid use.

Dellinger et al in their series of patients with open fractures (18), explicitly excluded patients with chronic health problems, such as diabetes, peripheral vascular disease or steroid use. Similarly, the LEAP study excluded patients older than 69 years and patients with a documented psychiatric disorder or mental retardation (19). This forms the basis for the exclusions from this study

Review of current management guidelines

Treatment of open tibia fractures has been extensively researched with elaborate guidelines.

All open fractures, no matter how trivial they may seem, must be assumed to be contaminated and judicious management is required to prevent infection. The four essentials are antibiotic prophylaxis, urgent wound and fracture debridement, stabilization of the fracture and early definitive wound cover (20).

Of these early surgical debridement and antibiotic use are the most important preventive tools against infection (21). In Patzakis et al's study on factors influencing infection rate in open fracture wounds, they concluded the single most important factor in reducing the infection rate to be early administration of antibiotics that provide antibacterial activity against both gram-positive and gram-negative microorganisms (16).

3.1 Antibiotic prophylaxis

Use of antibiotic therapy in open tibia fractures raises three questions; how useful are they? Which antibiotics? And for how long?

Antibiotic usefulness; the value of antibiotic therapy in open wounds and its beneficial effect has been well documented in literature.

Intravenous antibiotics have been considered the standard of care since 1974, when Patzakis et al (21) reported their randomized controlled trial of cephalothin, a first generation cephalosporin, for the management of open fractures.

This study by Patzakis et al on the role of antibiotics in the management of open fractures in a controlled study, appropriate antibiotic(s) were demonstrated to be useful in significantly reducing infection rates. He analyzed 363 open tibia fractures irrespective of Gustilo grade divided into four groups. The first group received no antibiotics, second group received

penicillin and streptomycin, third group received only first generation cephalosporin and fourth group received a cephalosporin and aminoglycoside. The highest infection rate was in open tibia fractures receiving no antibiotics at 24%, and the lowest was in the fourth group receiving a cephalosporin and an aminoglycoside at 4.5%.

A Cochrane review published in 2004 by Gosselin et al confirmed that antibiotics reduced the incidence of infection in open fractures of the limbs by 59% and concluded placebo controlled randomized trials cannot be justified (22). This unparalleled usefulness of prophylactic antibiotic use in open fractures has been reported by other investigators (23-25)

Antibiotic choice; the choice of antibiotic depends mainly on the contaminating organisms and resistance patterns.

Robinson et al study on microbiologic flora contaminating open fractures found positive wound cultures in 83% of all the fractures with Gustilo grade I, II, and III giving 70.4%, 88.5%, and 90% positive cultures respectively (26). A total of 84 strains of bacteria were isolated. Of the organisms isolated, more than 90% were sensitive to routine antibiotics. Three strains of staphylococcus aureus and two strains each of staphylococcus epidermidis and pseudomonas aeruginosa were resistant. In this study most wounds contaminated by bacteria that were resistant to first antibiotic given on arrival became infected later. Study by Benson et al came up with similar findings (27).

Studies have reported an increasing number of gram negative organisms isolated (7, 28, 29). They increase the likelihood of infection (13, 30). However, out of the different organisms isolated, staphylococcus aureus is the commonest (31, 32).

Study done by Dinda et al at Agha Khan university hospital Nairobi Kenya on organisms involved in surgical site infections isolated staphylococcus aureus as the commonest organism (33). This was followed by pseudomonas aeruginosa and E. coli

First generation cephalosporin are very active against gram positive cocci including staphylococci and cefazolin is the drug of choice against surgical prophylaxis. Second generation cephalosporin are active against organisms covered by first generation but in addition they have extended gram negative coverage e.g. klebsiella but not pseudomonas or enterococci. (34)

Several recommendations for antibiotic prophylaxis exist (1, 3, 5). In general:

Gustilo Grade I - first-generation cephalosporin

Gustilo Grade II - first-generation cephalosporin +/- an aminoglycoside, depending on the level of contamination.

Gustilo Grade III - first-generation cephalosporin with an aminoglycoside.

All farm injuries and heavily soil contaminated injuries ensure adequate anaerobic cover, add Metronidazole or Benzyllpenicillin to cover for Clostridium and other anaerobes.

The Latest guideline by Councils of the British Association of Plastic, Reconstructive and Aesthetic Surgeons and the British Orthopaedic Association (3) on the Standards for the management of open fractures of the lower limb recommends as follows;

Antibiotics should be administered as soon as possible after the injury, and certainly within three hours.

The antibiotic of choice is Co-Amoxiclav (1.2g 8 hourly), or a cephalosporin (eg cefuroxime 1.5g 8 hourly), and this should be continued until first debridement.

At the time of first debridement, Co-Amoxiclav (1.2g) or a cephalosporin (such as cefuroxime 1.5 g) and gentamicin (1.5 mg/kg) should be administered and Co-

amoxiclav or cephalosporin continued until soft tissue closure or for a maximum of 72 hours, whichever is sooner.

Patients with anaphylaxis to penicillin should receive clindamycin (600mg IV pre-op/qds) in place of co-amoxiclav or cephalosporin. For those with lesser allergic reactions a cephalosporin is considered to be safe and is the agent of choice.

Duration of antibiotics; when compared with the duration of preoperative antibiotic prophylaxis in surgery for closed fractures where a single parenteral dose is sufficient (9, 35), open fractures remain one of the few surgical fields where antibiotics are administered for a varied duration and usually prolongs if wound closure is delayed (36)**.**

Dunkel et al in their retrospective case-control study to assess the clinical variables associated with infections in open fractures remarked; Infection in open fractures is related to the extent of tissue damage (Gustilo grade) but not to the duration of prophylactic antibiotic therapy (8). Even for grade III fractures, a one-day course of prophylactic antibiotics might be as effective as prolonged prophylaxis. In their findings there was no threshold in the duration of total antibiotic treatment beneath which the infection risk was enhanced. Likewise, there was no linear, quadratic or logarithmic relationship between antibiotic duration and infection risk.

Most studies have shown that 24 hour administration of prophylactic antibiotics is adequate for infection control in grade I and II fractures (1, 2, 35). However, the minimum duration for grade III fractures varies between one and ten days (1, 2, 37), or even several weeks (36). Guidelines based on expert opinion and common practice advocate a maximum of 48 hours (1) to 72 hours (5) for grade III fractures. The British Association of Plastic, Reconstructive and Aesthetic Surgeons and the British Orthopedic Association standards for the management of open fractures of the tibia recommend parenteral Co-amoxiclav or cefuroxime for 72 hours or

definitive wound closure, whichever is sooner. The association's recommendations are general without reference to Gustilo grade.

Despite the abundance of literature advocating short duration of PAU, this has not been adopted in most African setting. Study by Kigera et al (6) in a neighboring country at Mulago Hospital in Uganda found the average duration of PAU for open tibia fractures to be 7.3days. Literature search did not reveal any randomized studies that have been done in East Africa to establish the appropriate duration of PAU in open fractures. In our set up at KNH there is no protocol on prophylactic antibiotics in open fractures.

Therefore, by selecting Gustilo type II open tibia fractures and using the similar instruments as from previous randomized studies, the intention was to find out if 24hours of PAU will have similar or different outcomes to that of five day PAU.

Oral versus intravenous antibiotic prophylaxis

A study done by Knapp et al (38) in patients with extra-articular fractures of long bone from a low-velocity gunshot found oral prophylactic antibiotic therapy does not increase prevalence of infection compared with intravenous antibiotic therapy. A study by Nungu KS et al (39) reported similar findings. Using the same principle, patients on the five day group were given oral antibiotics as from 24 hours after debridement

3.2 Surgical debridement

Wound care in open tibia fractures raises concerns of timing to debridement and closure of the wound. Traditionally, initial debridement has been recommended to be done as early as possible preferably within the six hour 'golden period' (40). This has been disputed by most studies.

Bednar et al(41) found no difference in infection rate for open fractures which were debrided within 8 hours and those which were debrided after 8 hours. This holds true for most studies especially those done after the year 2000 (5, 42).

Study done by Harley et al noted that time to debridement is not a significant factor in predicting either nonunion or infection (43). Reuss et al's study showed up to 48 hours delay to operative debridement of open tibia fractures does not adversely affect infection and nonunion rates (44).

A study done in a typical district hospital in the UK by Spencer et al (42) found no statistically significant difference in infection rates between patients debrided within 6 hours and those debrided after 6 hours. In their opinion, it is better for the emergency team to provide intravenous antibiotics, basic wound care and splintage awaiting formal care during normal working hours. Other similar studies like one by Skaggs et al (45) have reported similar findings though some studies disagree (46).

Study done by Asif on effect of delay in initial debridement on the rate of infection in open fractures of tibia shaft at Kenyatta National Hospital, found that in Gustilo type II fractures, time to debridement did not have an effect on infection (47). However, in Gustilo type III fractures, there was an increase in infection rate for those debrided after 12 hours.

3.3 Fracture stabilization

Stabilization of open fractures is one of the most important preventive tools against infection (21). It limits infection and systemic inflammatory response to major trauma (39).

Methods of stabilizing open tibia fractures include cast application, plate and screws, Intramedullary Nailing (IMN), external fixators and calcaneal pin (48). IMN and external fixators are currently thought to provide the best infection prevention with IMN being superior including Gustilo grade 3B open tibia fractures(49).

However study done by Bach and Hansen et al(50) in their randomized trial comparing plates versus external fixation concluded that external fixation should be regarded as the primary method of stabilization for grades II and III open tibia shaft fractures because of lower infection risk.

Study done by Asif Adman in 2011 at KNH found long leg cast to be the treatment modality in 83% which compares poorly with figures between 12.5 – 20% reported in other studies. This may be one of the reasons for the high overall infection rate of 50% reported in Admani's study compared to other centers reporting infection rate of 10-30%.(4, 22, 51)

3.4 Timing of wound closure

Whether to do primary or secondary closure has been a subject of debate and still remains contentious. Study by Delong et al (52) revealed no statistically significant difference in infection rates between immediate and delayed closures of open fracture wounds. They concluded that immediate primary closure of open fracture wounds after a thorough debridement by an experienced fracture surgeon appears to cause no significant increase in infections or delayed union/nonunion. In addition, early closure may decrease the requirement for subsequent debridement and soft-tissue procedures, thereby minimizing surgical morbidity, shortening hospital stays, and reducing cost (52). Besides, primary closure decreases risk of subsequent wound contamination, maintains viability and decreases desiccation of underlying tissues. Patients with Gustilo II open fractures recruited in this study will have wounds primarily closed after debridement.

3.5 WOUND INFECTION SCORING

Determining wound infection is very subjective and this provides a big challenge to researchers in getting an objective measure. To overcome this, different wound scores have been developed such as the Asepsis Wound Scoring System (AWSS) and Southampton score.

There are several definitions of wound infection/surgical site infection. The three definitions cited as commonly used include;

The United States Centers for Disease Control & Prevention (CDC)

The English Nosocomial Infection National Surveillance Scheme (NINSS)

Asepsis Wound Scoring System (AWSS)

Studies on the three most widely used definitions/score conclude that:

- CDC criteria is subjective and on psychometric evaluation has been shown to be unreliable (53)
- Reproducibility of NINSS is low (54)
- ASEPSIS wound scoring method is objective and repeatable (55)

As a tool for wound assessment, scoring methods provide more detailed information than CDC and NINSS but are more time consuming and costly (56).

A study done at University College London hospital recommended the use of the ASEPSIS scoring method and found Both CDC and NINSS to be unreliable (57)

In this study ASEPSIS wound scoring system (AWSS) will be used to assess presence of wound infection.

3.6 ASEPSIS wound scoring

ASEPSIS wound scoring will be adopted in this study because it has been demonstrated to be objective and repeatable (55).

ASEPSIS is a mnemonic for the seven parameters assessed in the score

A- **A**dditional treatment (Antibiotics, Drainage of pus or Debridement)

S- **S**erous discharge

E- **E**rythema

P- **P**urulent exudate

S- **S**eparation of deep tissues

I- **I**solation of bacteria

S- **S**tay in hospital over 14 days

Each of these parameters are scored on wound assessment (**appendix II**). Total score is out of 65. The interpretation is as depicted below (57)

SCORE	**MEANING**
0 – 10	No infection Normal healing
11 – 20	Disturbance of healing
21 – 30	Minor infection
31 – 40	Moderate infection
≥ 41	Severe infection

In this study a score of 20 will be the cut off for infection.

4.0 STUDY QUESTION

Is there difference in infection rate between 24 hours and five days of PAU in Gustilo II open tibia fractures at KNH?

5.0 STUDY JUSTIFICATION

Infection following open fractures still poses a challenge to all clinicians despite current treatmeint modalities. Prophylactic antibiotic use has revolutionized open fracture management and its role in reducing infection rate is immense.

The majority of the studies have recommended short duration of PAU for 24hours in Gustilo type I and II fractures or 72 hours in type III or 24 hours after wound closure, whichever comes earlier.

Long duration of PAU has dangers of super-infection and the emergence of resistant pathogens besides the extra cost and drug toxicity to the patient yet has no effect on reducing rate of infection

Some centers especially in developing countries continues to administer prophylactic antibiotics for a prolonged duration. Study by Kigera et al(6) in Mulago Hospital Uganda found the average duration of PA for open tibia fractures to be 7.3 days. This unfortunate state is the reality in our set up.

In our hospital a single 750mg dose of cefuroxime and 240mg of gentamycin costs about Kshs. 300. 24-hour dose will cost kshs.780. If prophylaxis is continued for five days this pushes the cost five times more besides the risk of antibiotic resistance and side effects to the patient. It also adds unnecessary load to the already strained manpower and limited consumables like syringes and needles.

While PAU has been widely adopted in the developed countries, there are limited published studies in sub-Saharan Africa on the same and it has not been widely adopted in our health system. Therefore, more studies are necessary to improve PAU and aid guideline formulation.

Open tibia fractures is a common injury seen at A/E department in KNH. The institution attends to an average of 35 patients per week with open tibia fractures. Study done by Asif in KNH found Gustilo II open tibia fractures to constitute about 32% of all open tibia fractures (47). These fractures require admission and early antibiotic administration with debridement hence need to develop better and cheaper ways to manage them.

6.0 STUDY OBJECTIVES

6.1 MAIN OBJECTIVE

To determine the difference in infection rate between 24 hour and five day use of prophylactic antibiotics in Gustilo II open tibia fractures at KNH.

6.2 SPECIFIC OBJECTIVES

1. To determine difference in infection rate between the two groups.
2. To determine effect of time to antibiotic administration on infection rate
3. To determine the effect of time to debridement on infection rate
4. To determine effect of fracture stabilization method on infection rate.

- **HYPOTHESIS**

  There is no difference in infection rate between 24 hour and five day use of prophylactic antibiotics in Gustilo II open tibia fractures.

7.0 METHODOLOGY

7.1 STUDY DESIGN

Prospective randomized interventional comparative study

7.2 STUDY SETTING

KNH A&E department, orthopedic wards and outpatient orthopedic clinics. KNH is the national referral and teaching hospital with 2000 bed capacity located in the capital city Nairobi, Kenya. It serves Nairobi, its environs and the country as whole through the referral system.

7.3 STUDY POPULATION

All the patients aged above 18 years and less than 80 years with Gustilo grade II open tibia fractures as determined at A & E department and during debridement.

7.4 SAMPLE SIZE

This was done for comparison of two proportions, with the infection rate as the endpoint. Infection in the control was estimated as 20% while that in the intervention group, it was assumed to be 50%. The power of test was set at 80% and the level of significance was 95%.

We used the following formula(58)

$$n = [(Z_{\alpha/2} + Z_{\beta})^2 \times \{(p1\ (1-p1) + (p2\ (1-p2))\}]/(p1 - p2)^2$$

n = sample size required in each group,

p1 = Infection rate in control group = 0.20,

p2 = Infection rate in intervention group = 0.5,

p1-p2 = Margin of error = 0.3

$Z_{\alpha/2}$ = Critical value for a 5% level of significance = 1.96

Z_{β} = critical value for a power of 80% = 0.84

Based on above formula the sample size required per group is 38. Hence total sample size required is 76

Correction for drop-outs by adding 10% (8) to obtain a total sample size of 84.

7.5 INCLUSION CRITERIA

- Patients with isolated Gustilo grade II open tibial fractures.
- Patients who are above 18 years of age and less than 80 years. Pediatric patients excluded because of fixed dosage regimen
- Patients who will consent for the study

7.6 EXCLUSION CRITERIA

- Gustilo grade I and III open tibial fractures to reduce number of variables
- Gustilo II open tibial fractures whose wounds cannot be closed primarily after debridement
- Fractures not debrided within 24 hours of injury
- Non – traumatic open tibia fractures e.g pathological fractures
- Cigarette smokers.
- Patient with diabetes mellitus, HIV/AIDS, psychosis or chronic renal failure.
- Patients on corticosteroids or chemotherapy.
- Patients who come as referrals from other medical facilities where they have already received any form of treatment
- Patients who refuse to give consent.

7.7 SAMPLING PROCEDURE

Patients were recruited into the study by the principal researcher and two trained assistants by convenient sampling procedure.

7.8 ALLOCATION OF TREATMENT

The patients were received in A and E department, assessed and managed according to ATLS protocol. If the patient satisfied the inclusion criteria he/she was recruited into the study after consent.

Block randomization was used to allocate one of the two arms of treatment to the patients after they consented to participate in the study. The patients were considered in blocks of four at a time which would then give 6 possible ways of allocating treatments. Block **A** for 24-hours and **B** for 5 days. The six possible options were be as follows:

1. AABB 2. BBAA 3. ABAB. 4. BABA 5. ABBA 6. BAAB.

A list of random numbers were then computer generated and the numbers between 1 and 6 selected until a total of 21 random numbers were obtained. The blocks were assigned to the random numbers to obtain an allocation sequence which was used to allocate patients to the two different treatments (Appendix VII).

The patient's open tibia fracture were assessed and temporarily splinted with but not limited to POP back slab or Thomas splint if not done yet.

Information collected on first inspection included:

- Demographics
- Mechanism of injury
- Grade of open fracture according to the Gustilo classification i.e. (Gustilo Grade II fractures were recruited pending confirmation during debridement)

- Site of the fracture; proximal, mid-, or distal shaft
- Pattern of fracture
- Size of wound

The wound was then covered with sterile dressing and patient taken to treatment room for antibiotic administration followed by X-ray and baseline blood tests. If the patient certified the inclusion criteria consent was obtained then he/she recruited into the study.

7.9 ANTIBIOTIC ADMINISTRATION

- An intravenous catheter was inserted.
- 240mg of Gentamycin and 1.5g of Cefuroxime were administered intravenously by the principal investigator, assistants or a nurse.
- For the 24-hour group, Gentamycin single dose was only repeated if debridement delayed more than 24 hours and cefuroxime 750mg intravenously was repeated every 8 hours until 24hours after debridement and wound closure. Gentamycin was only administered if patient was hemodynamically stable with no renal compromise
- For the 5-day group, Gentamycin 240mg was administered intravenously every 24 hours for five doses and cefuroxime 750mg intravenously every 8hours for 24hours after debridement and wound closure then converted to oral cefuroxime 500mg twice daily for four more days
- Other medications e.g. analgesics and tetanus toxoid as prescribed by the doctor were administered

The patients were prepared for emergency debridement in operating theatre by any of the four selected orthopedic surgery residents. All the surgeons were assumed to follow a standard debridement protocol as summarized below;

Initially, the limb is washed with a soapy solution (59)

The limb was then ‘prepped’ with antiseptic solution

Wound extensions done along the Fasciotomy lines

The tissues were assessed systematically in turn, from superficial to deep (skin, muscle, bone) and from the periphery to the Centre of the wound. Non-viable skin, fat, muscle and bone were excised (3)

Wound irrigation was then done with 6 liters for Gustilo type II fractures (60) using low pressure pulse lavage (61, 62). 20 or 50 milliliter syringe was used for pulse lavage.

Definitive fracture stabilization was done depending on surgeon preference and implant availability.

This was followed by primary wound closure without tension

If casting was the fracture stabilization method chosen, the wound was closed, dressed then casting done. Cast window created after 24-hours at the wound site.

After debridement data was collected on:

a. Gustilo grade in case of any post-debridement modification
b. Method of tibia fracture stabilization used.
c. Wound closure; whether closed primarily or left open

If Gustilo grade changed or wound was left open, patient was excluded from the study. Five patients were excluded on this basis.

7.10 OUTCOME MONITORING

All wounds were inspected at 2, 5 and 14 days.

Assessment of wound healing and infective complications were made using a modified version of the ASEPSIS wound scoring system (63) (**appendix II**) as recommended by the surgical infection study group(46). The maximum score is 65. It is objective and repeatable with high sensitivity(55). For the purpose of this study, a score of 0 to 20 was taken as normal wound healing and a score of more 20 as wound infection. The score was recorded at day 2, day 5 and day 14 following debridement. The highest score for each patient was adopted as determined at days 2, 5 and 14.

Patients who were found to have infection and had completed the antibiotic regimen under study were treated empirically initially and then as per the culture results.

7.11 CULTURE PROTOCOL

Wound was cleaned prior to culturing. Culturing purulent or necrotic debris or drainage over hard eschar were avoided.

Wound was cleansed by removing excess debris from wound base with normal saline

Wound was thoroughly flushed with sterile saline.

Excess saline from wound bed was gently blotted with sterile gauze.

Soiled gloves were removed and clean ones applied.

The following procedure was then be followed to obtain a swab specimen for culture.

a. Sterile culture collection/transport kit containing Amies or Stuarts transport medium was opened and swab removed.

b. If wound is dry, tip of swap was moistened with transport fluid at the bottom of the transport sleeve or sterile preservative-free saline. If wound was moist after cleaning, this was not necessary.
c. Without touching swab to surrounding wound edges or skin, Levin technique was used to obtain specimen (tip of swab was rotated over a 1 cm area at the center of the open wound for 5 seconds)
d. Sufficient pressure was applied to cause tissue fluid to be expressed. It is the bacteria in the tissue fluid that was desired for culture
e. Swab was placed in culture transport sleeve making sure swab tip is not contaminated.
f. Culture collection/transport kit was labelled with study number, age, specimen source, date and time of culture.

Contaminating outside of the culture collection/transport kit was avoided.

Specimens were submitted to KNH Microbiology Laboratory within one hour of collection for culture.

The specimens were cultured within one to two hours after delivery to the laboratory. Sheep or chocolate blood agar was used for culture incubated at 35 to 38 degrees celcius for 18 hours followed by further 18 hours of sensitivity testing if growth was obtained. Only aerobic culture was done.

7.12 DATA COLLECTION AND MANAGEMENT

Data was collected using a standard data sheet. Data collected included:

- Patient demographics
- Fracture and wound characteristics/status(pre- and post-debridement)
    - Size of wound
    - Location of fracture
    - Fracture pattern
    - Gustilo grade
- Duration of prophylactic antibiotics
- ASEPSIS score which includes culture results

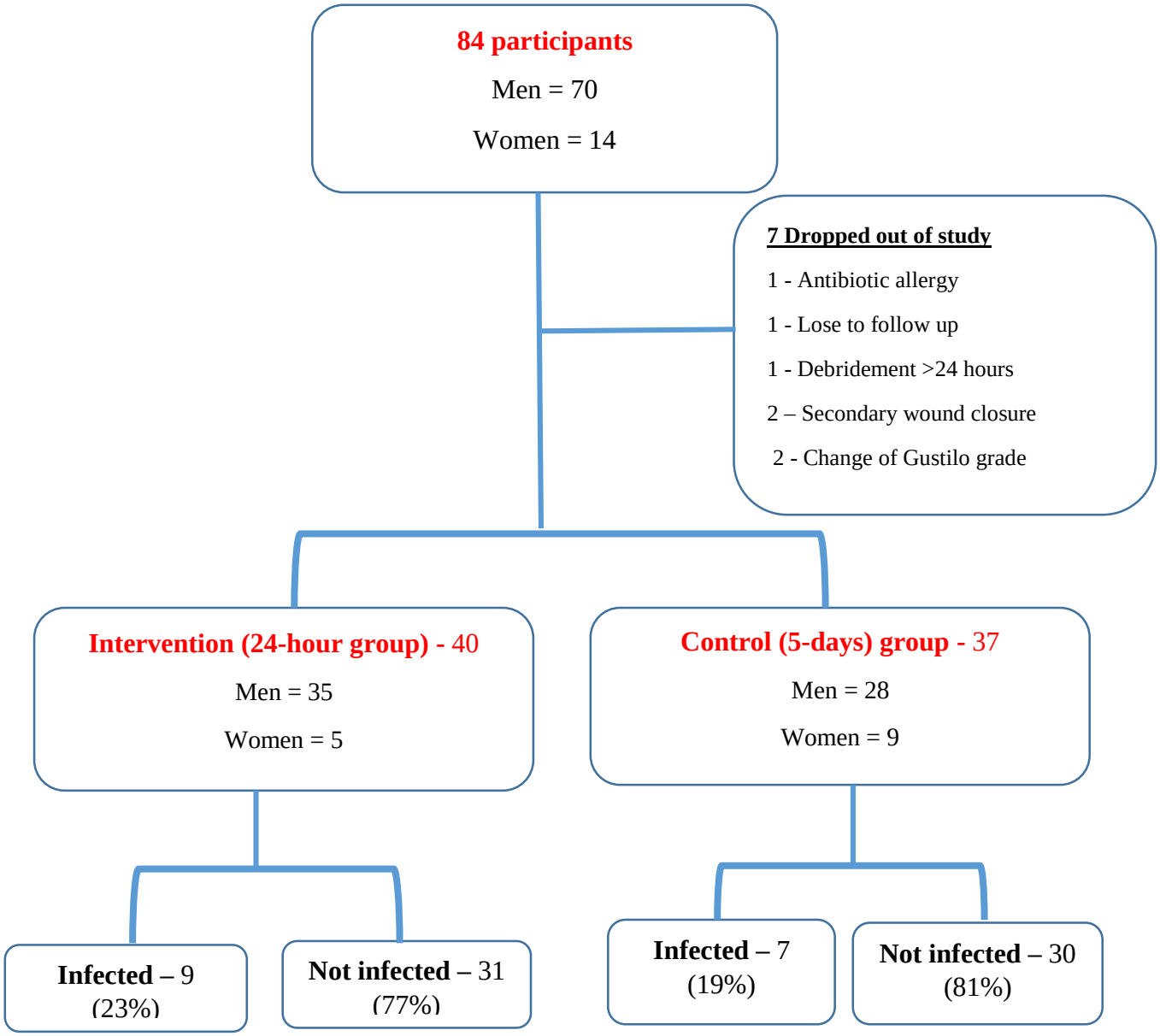
Data was coded and entered in SPSS version 20.0 for analysis. The baseline characteristics were summarized and presented as means/medians and proportions. Associations were tested using chi square test for categorical variables (proportions) and student t-test for continuous variables (means).

Relative risk was calculated to estimate the likelihood of patients presenting with any of the outcomes among the intervention group. All statistical tests were performed at 5% level of significance (95% confidence interval)

8.0 RESULTS

Between September 2014 to March 2015 eighty four patients with Gustilo II open tibia fractures eligible for the study were recruited. Two patients in the 24 hour group and five patients in the 5 day group dropped from the study because of antibiotic allergy (one), lose to follow up (one), failure to debride within 24 hours (one), failure to achieve primary wound closure (two) and post-debridement change of Gustilo grade (two). The data from the remaining seventy seven patients was analyzed as summarized in fig. 1 below.

Figure 1. Summary of patient allocation



8.1 Baseline characteristics

Table 1. Summary of the baseline characteristics

CHARACTERISTIC		INTERVENTION GROUP		Total
		24 hours	5 days	
	Sample size	**40**	**37**	**77**
Sex	Male	35 (88%)	28 (76%)	**63 (82%)**
	Female	5 (13%)	9 (24%)	**14 (18%)**
Age	Mean (years)	34.1	33.1	**33.6**
	SD	12.7	12.2	**12.4**
Age group	18 - 25 years	12 (30%)	10 (27%)	**22 (29%)**
	26 – 40 years	19 (48%)	20 (54%)	**39 (51%)**
	Over 40 years	9 (22%)	7 (19%)	**16 (21%)**
Cause of injury	Pedestrian	27 (68%)	17 (46%)	**44 (57%)**
	Motorcycle	7 (18%)	9 (24%)	**16 (21%)**
	Fall from height	2 (5%)	7 (19%)	**9 (12%)**
	Assault	4 (10%)	2 (5%)	**6 (8%)**
	Others	0 (0%)	2 (5%)	**2 (3%)**
Fracture site	Proximal leg	10 (25%)	7 (19%)	**17 (22%)**
	Mid-leg	19 (48%)	16 (43%)	**35 (46%)**
	Distal-leg	11 (28%)	14 (38%)	**25 (32%)**
Side injured	Left	21 (53%)	18 (49%)	**39 (51%)**
	Right	19 (48%)	19 (51%)	**38 (49%)**
Fracture pattern	Transverse	8 (20%)	13 (35%)	**21 (27%)**
	Oblique	14 (35%)	16 (43%)	**30 (39%)**
	Spiral	8 (20%)	5 (14%)	**13 (17%)**
	Comminuted	10 (25%)	3 (8%)	**13 (17%)**
Fracture stabilization	Plaster cast	26 (65%)	29 (78%)	**55 (71%)**
	External fixation	13 (33%)	8 (22%)	**21 (27%)**
	Intramedullary nail	1 (3%)	0 (0%)	**1 (1%)**
Hours to ABx administration	Mean	11	10.5	**10.7**
	SD	4.2	5.1	**4.6**
Hours to debridement	Mean	18.4	18.5	**18.4**
	SD	5.1	5.7	**5.3**
Wound size	Mean (cm)	5.3	5	**5.2**
	SD	2.1	2.1	**2.1**

Summary of the baseline characteristics for the two groups

The main parameters between the two groups were analyzed for any statistical difference as shown in table 2 below

Table 2. Summary of the baseline characteristics and statistical difference

Parameter	Measures	24 hour group	5 day group	P value
Age (years)	Mean (SD)	34.1 (12.7)	33.1 (12.2)	**0.734**
	Median (IQR)	31.0 (24.0-40.0)	32.0 (24.0-38.5)	
	Range	18.0-73.0	18.0-77.0	
Sex	Male Female	35 (87.5%) 5 (12.5%)	28 (75.7%) 9 (24.3%)	**0.184**
Time to antibiotic administration (hours).	Mean (SD)	10.98 (4.2)	10.46 (5.1)	**0.629**
	Median (IQR)	11.5 (8.3 – 13.8)	11.0 (5.5 – 14.0)	
	Range	3.0 – 20.0	2.0 – 22.0	
Time to debridement (hours).	Mean (SD)	18.4 (5.1)	18.5 (5.7)	**0.945**
	Median (IQR)	19.1 (15.1 – 22.0)	20.0 (12.5 – 23.0)	
	Range	5.0-24.0	5.0-24.0	
Fracture Stabilization method	Plaster cast	26 (65.0%)	29 (78.4%)	**0.155**
	External fixator	13 (32.5%)	8 (21.6)	
	Intramedullary nail	1 (2.5%)	0	

NB: SD = standard deviation.

IQR = interquartile range.

There was no statistically significant difference between the two patient groups in all the baseline characteristics. All the p-values are more than 0.05.

8.2 Infection

Presence of infection was assessed at days 2, 5, and 14 using ASEPSIS wound scoring system incorporating both clinical assessment and culture results.

With ASEPSIS score cut-off of 20 for infection, the infection rate is summarized below (figure 2).

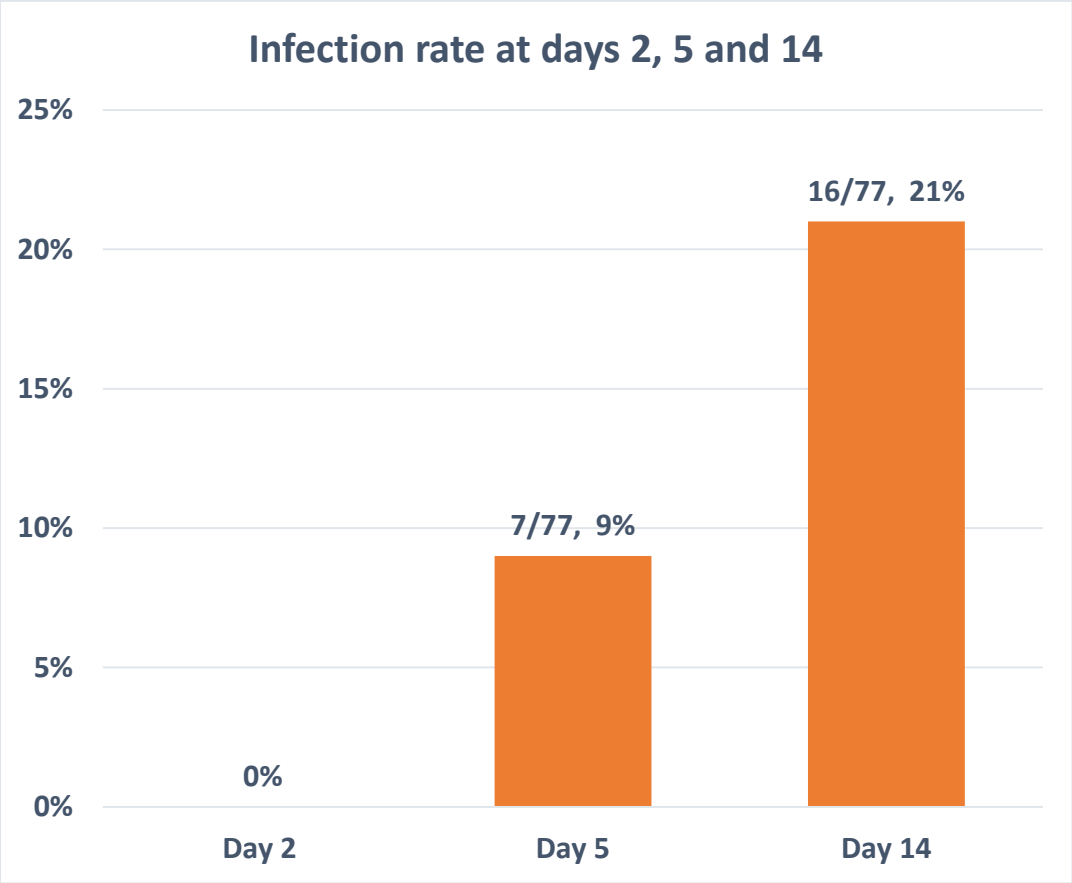


Figure 2 infection rate at days two, five and fourteen.

No patient had infection at day 2. At day 5, there was 9% infection rate (7/77) and 21% at day 14 (16/7). All infected cases at day 5 continued to day 14. Those infected were restarted on antibiotics guided by the culture results

Infection rate between 24-hour group and 5-day group

ASESPSIS scores at day 14 were used for subsequent analysis and comparison between the two groups as summarized below (figure 3).

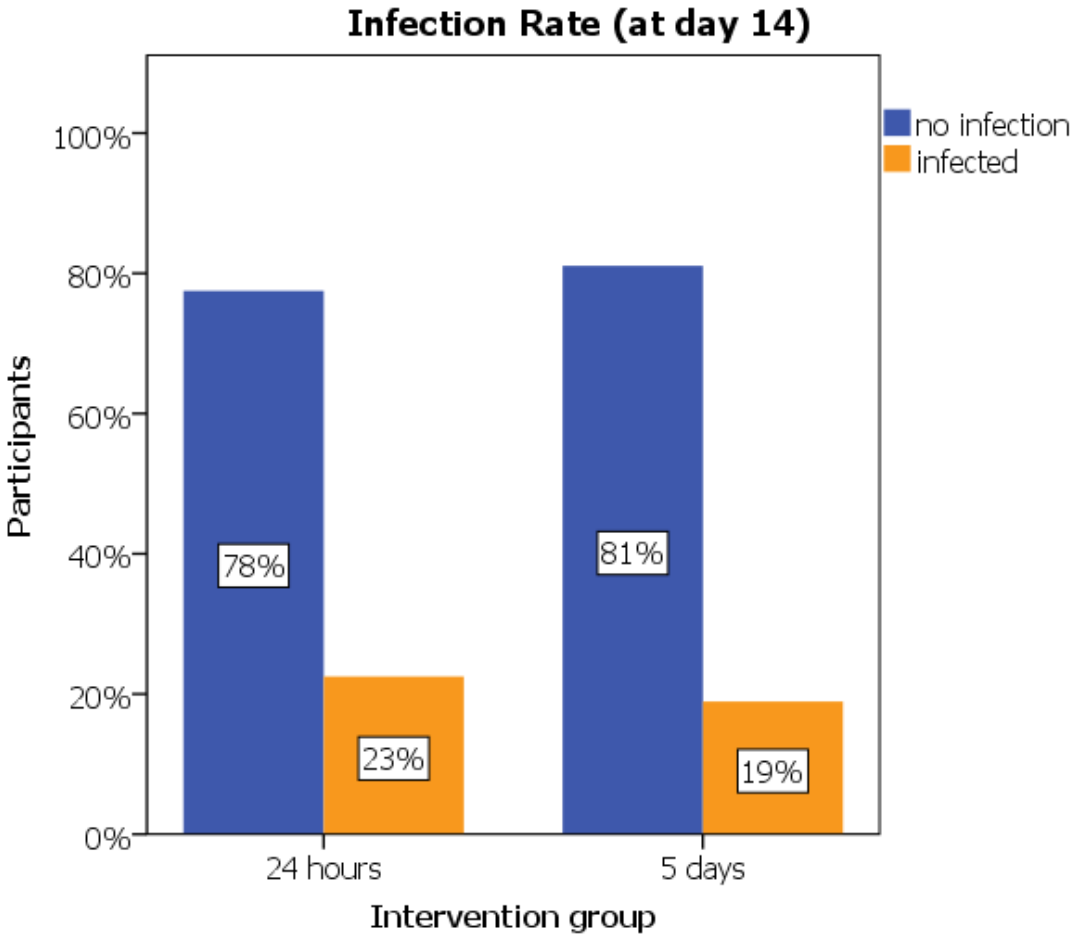


Fig. 3. Comparison of infection rate between the two groups at day 14

There was no significant difference in infection rates between 24-hour group and 5-day group, 23% (9/40) versus 19% (7/37) respectively (p = 0.699).

Effect of time to antibiotic administration, debridement and fracture stabilization method on infection rate

The effect of time to antibiotic administration, time to debridement and fracture stabilization method on infection rate is shown in table 3 below

Table 3. Summary of the infection rate results

Parameter	Measures	No infection	Infected	P value
Time to antibiotic administration (Hours)	12 hours or less	40	5	**0.013**
	Over 12 hours	21	11	
Time to debridement (Hours)	12 hours or less	13	2	**0.723**
	Over 12 hours	48	14	
Fracture stabilization method	Plaster cast	41	14	**0.11**
	External fixation	19	2	
	Intramedullary nail	1	0	

Time to antibiotic administration had statistically significant association with infection rate ($p = 0.013$). Time to debridement and fracture stabilization method had no association with infection rate ($p > 0.05$)

Time to antibiotic administration and infection rate

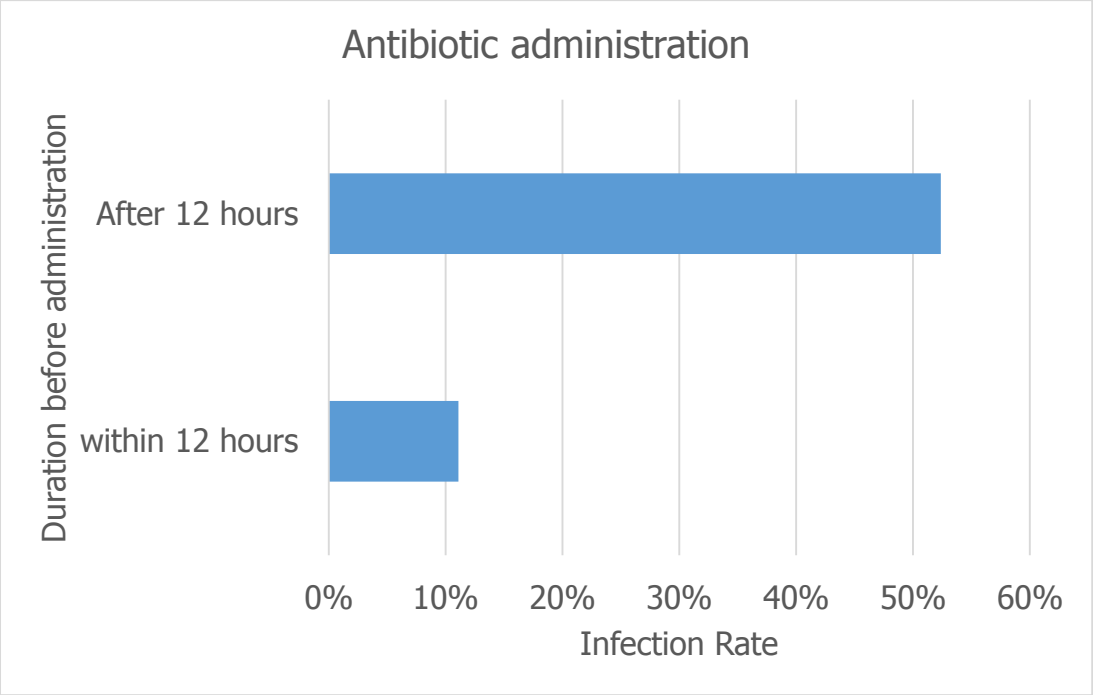


Figure 4 Infection rate and time before antibiotic administration

The infection rate was significantly associated with time lapsed before administration of antibiotics (p = 0.004). Participants who received antibiotics within 12 hours after admission were less likely to develop infection than those who received antibiotics after 12 hours; 11% (5/45) vs 52% (11/21) respectively, (p = 0.013) (Table 4 above).

Time to antibiotic administration comparing the two groups

Table 4. Time to antibiotic administration on infection rate

	24 hour group			5 day group		
	Presence of infection		**P value**	**Presence of infection**		**P value**
	Yes	No		Yes	No	
Mean time to antibiotic administration(hours)	14.0	10.1	0.012	13.1	9.83	0.125

The time taken to antibiotic administration had positive correlation with infection rate in the 24-hour group (p=0.012) but did not have statistical significance in the 5-day group (p=0.125). These results are summarized in table 4 above and illustrated in figure 5 below. ASEPSIS score at day 14 was used in the linear regression analysis which correlates with the infection rate.

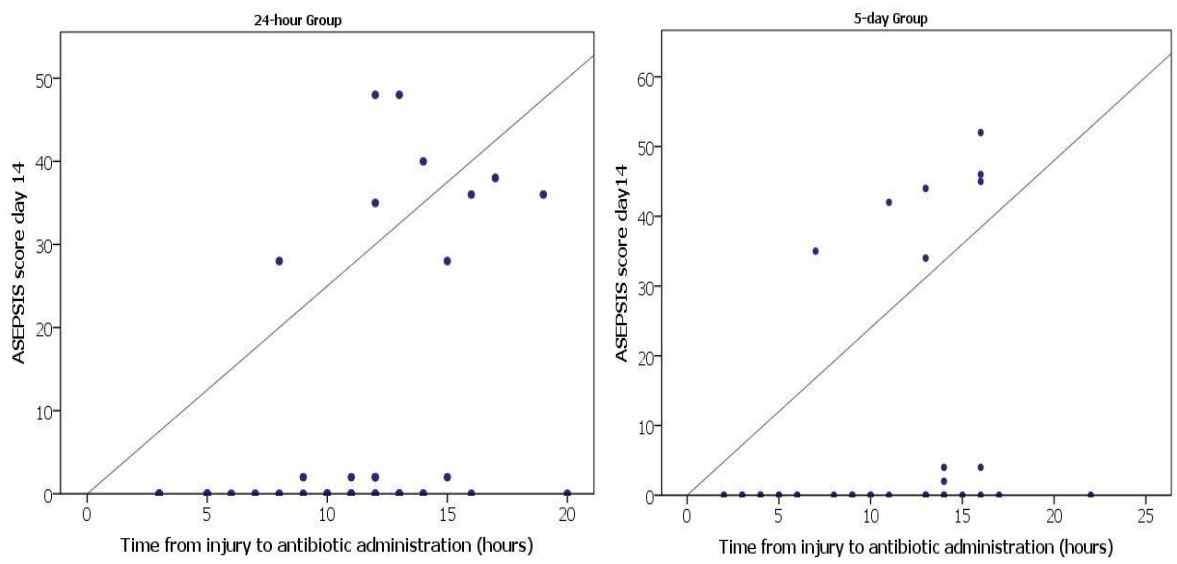


Figure 5 Scatter plot showing time to antibiotic administration versus ASEPSIS Score.

Time to debridement on infection rate

All patients were debrided within 24 hours. One patient whose debridement delayed longer than 24 hours was excluded from the study.

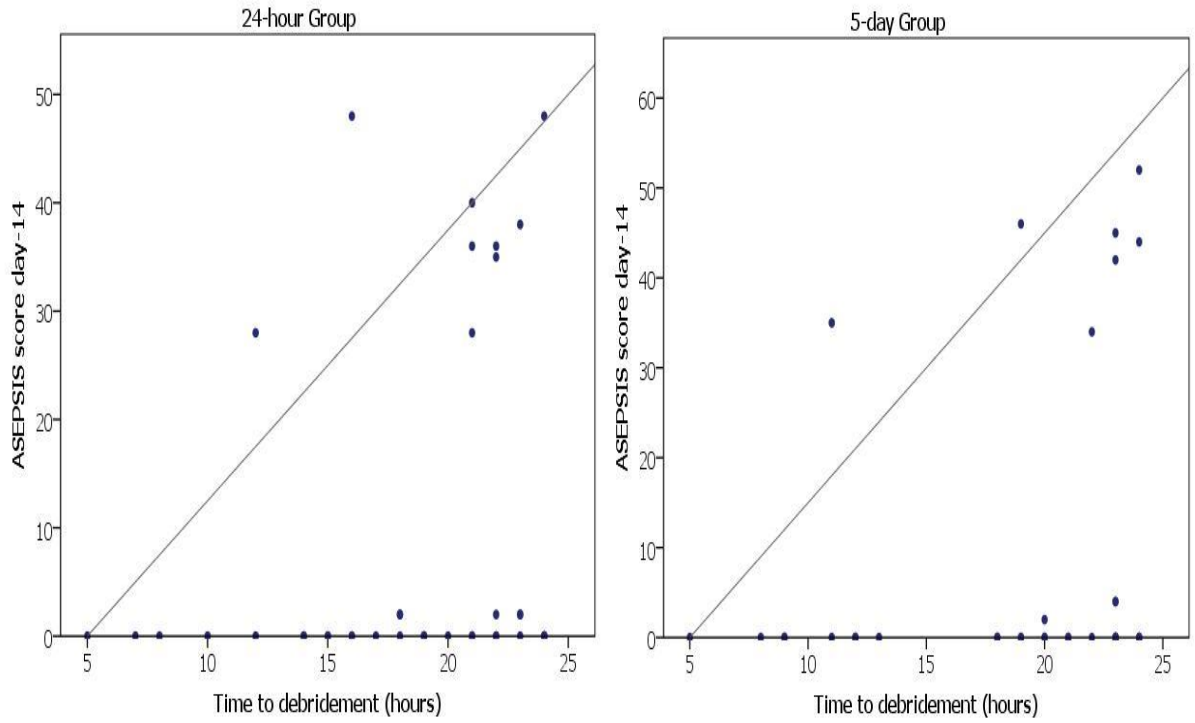


Figure 6 Scatter plot showing time to debridement versus ASEPSIS Score (infection rate).

Infection rate was related to the hours lapsed before debridement but the association was not statistically significant (p = 0.08). Out of 13 patients who underwent debridement within 12 hours, 2 (15%) developed infection as compared to 14 (29%) out of 48 patients who underwent debridement after 12 hours, (chi square, p = 0.72). this is illustrated in figure 6 above

Fracture stabilization method and infection rate

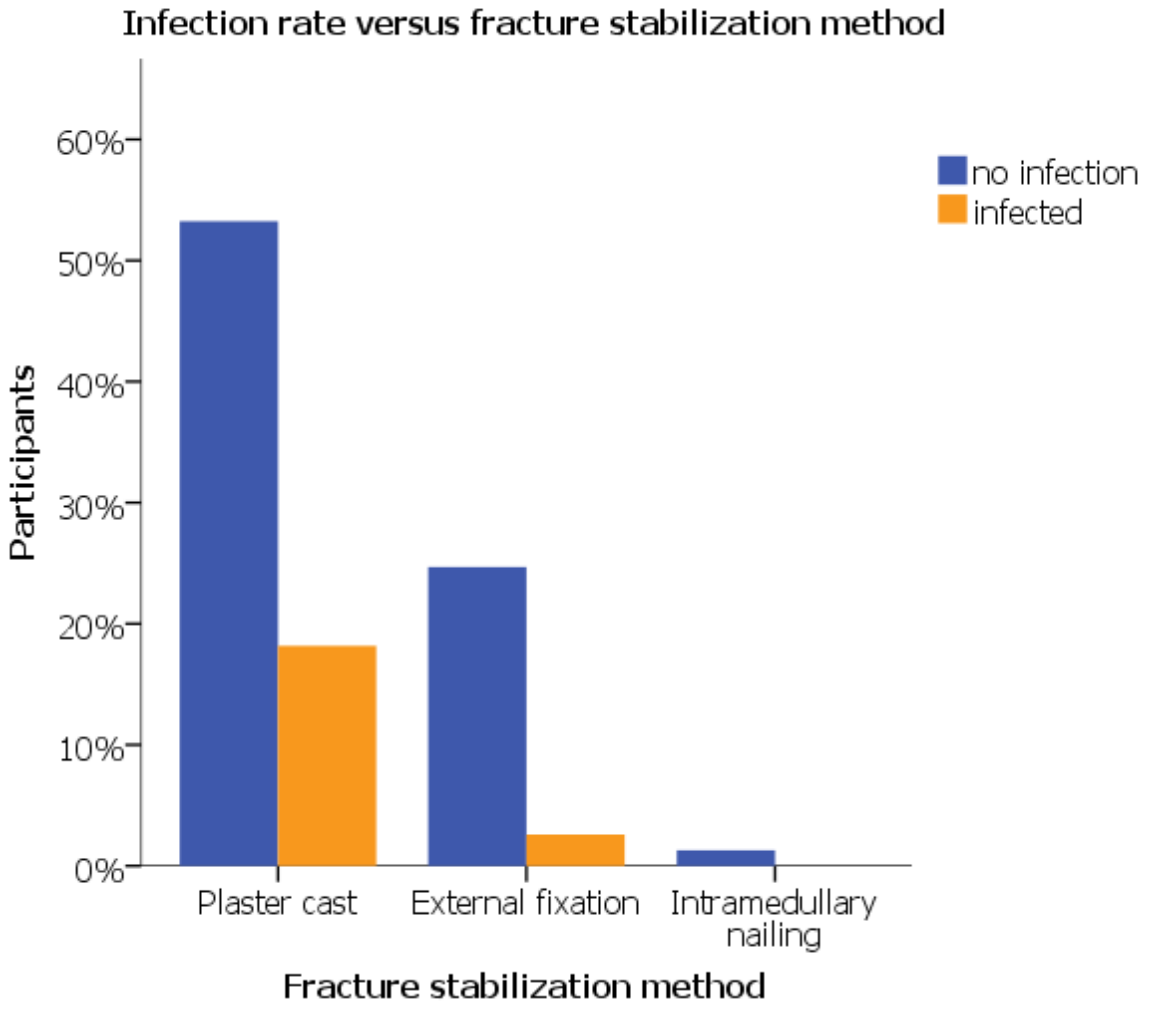
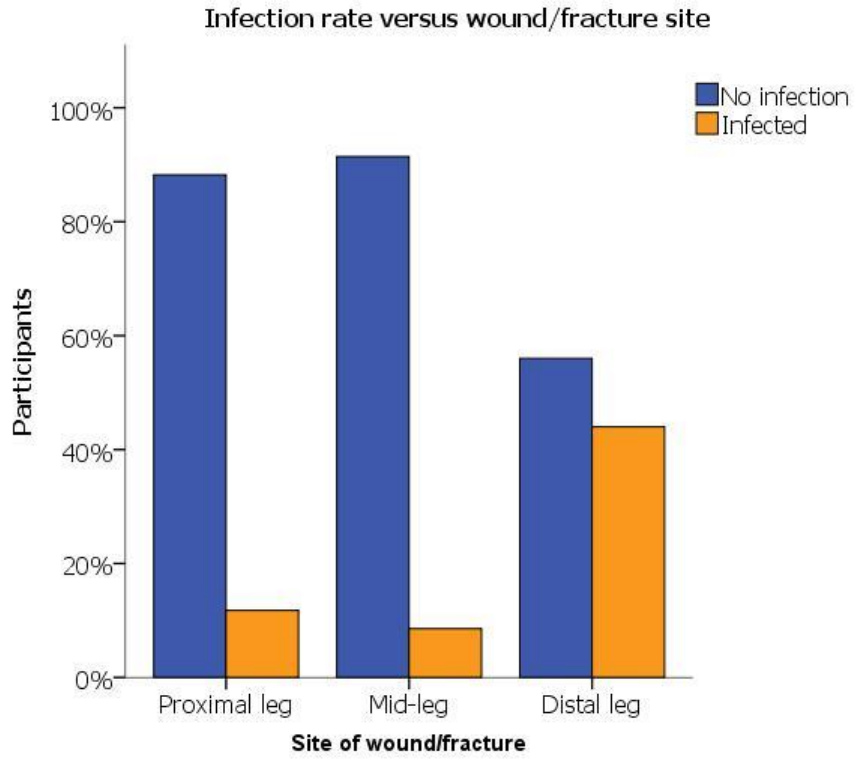


Figure 7 **Fracture stabilization method and infection rate**

There was a difference in infection rate between those stabilized with plaster cast and external fixator/intramedullary nail, this was not statistically significance (figure 7 above). Only one patient had intramedullary nailing hence this was combined with external fixators then compared with plaster cast in statistical analysis (*p = 0.11)*

Wound/fracture site for the two groups and infection rate

Figure 8. Bar charts on wound site in the two groups and infection rate



Patients with injuries in the distal leg were more likely to be infected than those with injuries in the mid or upper leg; 11/14 (79%) vs 5/47 (11%), (chi-sq, $p < 0.001$) as illustrated in the figure 8 above.

8.3 Culture growth

Both groups had similar culture growth rates; 20% (8/40) of participants in the 24-hour group yielded a positive culture growth as compared to 19% (7/37) in the 5-day group (p – 0.91).

Table 6 bacterial organisms isolated

Organism	**Number of isolates**	%
Staphylococcus aureus	9	50%
Pseudomonas aeruginosa	4	22%
Proteus mirabilis	2	11%
Acinetobacter baumannii	1	6%
Providencia stuartii	1	6%
Morganella morganii	1	6%
TOTAL Isolates	**18**	100%

Out of the 16 infected cases, 15 had culture growth, 13 with one organism, one with two organisms and one with three organisms, there was a total of 18 isolates (table 6 above).

8.4 Resistance pattern

All 18 Isolates had some resistance as summarized in table 8.

Table 8. Resistance pattern of the microbial isolates

Antibiotic	Number of Isolates tested	Resistance			
		Overall	***S aureus***	***P aeruginosa***	***P mirabilis***
Ciprofloxacin	9	**33%**		0%	50%
Levofloxacin	9	**11%**	11%	-	-
Moxifloxacin	9	**0%**	0%	-	-
Cefuroxime	14	**86%**	78%	-	100%
Cefoxitin	1	**0%**	-	-	0%
Ceftriaxone	9	**100%**	-	100%	100%
Cefotaxime	9	**100%**	-	100%	100%
Ceftazidime	9	**67%**	-	25%	100%
Cefepime	9	**67%**	-	25%	100%
Gentamicin	9	**78%**	-	50%	50%
Amikacin	9	**0%**	-	0%	0%
Tetracycline	9	**22%**	22%	-	-
Erythromycin	9	**0%**	0%	-	-
TrimethoprimSulfamethoxazole	14	**79%**	67%	-	100%
Ampicillin-Sulbactam	9	**78%**	78%	-	-
AmoxicillinClavulinate	4	**75%**	-	-	50%
Piperacillin-Tazobactam	9	**33%**	-	100%	0%
Imipenem	9	**78%**	78%	-	-
Meropenem	9	**11%**	-	0%	0%
Clindamycin	9	**0%**	0%	-	-
Linezolid	9	**0%**	0%	-	-
Teicoplanin	9	**0%**	0%	-	-
Vancomycin	9	**0%**	0%	-	-

There was high microbial resistance to Cefuroxime and Gentamycin and low resistance pattern to fluoroquinolones. Cephalosporins have the highest resistance including 4th generation. Ceftriaxone has 100% resistance. There was no resistance to Vancomycin and Linezolid.

9.0 DISCUSSION

This study was undertaken at Kenyatta National Hospital. Patients with acute traumatic Gustilo grade II open tibia fractures recruited and randomized into either 24 hours or 5 days of antibiotic prophylaxis with main outcome measure being infection rate.

This study results show that in the management of acute traumatic open tibia fractures, there is no difference in infection rate between 24 hours and five days of antibiotic administration (p=0.699). Infection rate was associated with duration to antibiotic administration (p=0.004). Duration to debridement had no effect on infection rate. Mean hours to debridement was 17.87 hours in the non-Infected group and 20.05 hours in the infected group. This demonstrated no clear difference (P= 0.079). Fracture stabilization method had no statistically significant effect on infection rate (14 out of 16 in plaster group and 2 out of 16 in external fixator/intramedullary nail, P=0.11).

The time taken to antibiotic administration had positive correlation with infection rate in the 24-hour group (p=0.012) but did not have statistical significance in the 5-day group (p=0.125). This suggests when longer duration of antibiotics are used, effect of time to antibiotic administration on infection rate diminishes.

To our knowledge, this is the first local randomized controlled study on duration of prophylactic antibiotics in open tibia fractures. However, there are many randomized experimental studies especially from the west comparing infection rates between short and long duration of antibiotic prophylaxis. They are all in favour of short duration of antibiotic prophylaxis. Dunkel et al in their retrospective case-control study to assess the clinical variables associated with infections in open fractures concluded that infection in open fractures is related to Gustilo grade but not the duration of prophylactic antibiotic therapy (8).

This study confirms the same as there was no statistically significant difference in infection rate between 24 hours and 5 days of antibiotic prophylaxis.

Study done by Asif in 2011 at KNH found overall infection rate of 50% in open tibia fractures(47). Similar study in the same set up by Mogire in 1995 found a higher infection rate of 85% in fresh traumatic open tibia fractures (64). In this study, done in the same environment as above two we found a much lower overall infection rate of 20.8%. This may be explained by two main factors;

First is the *Recruited study population sample*. This study recruited only Gustilo II isolated open tibia fractures without comorbidities. This is in contrast to above two studies which recruited all open tibia fractures irrespective of Gustilo grade including patients with co-morbidities.

Second is the *Study design.* Unlike above two studies which were observational, this was an interventional study with strict protocol hence better patient management. This included strict antibiotic and debridement regime.

However, infection rate in this study compares well with other centers which have reported infection rates of 10 – 30% (4, 22, 51). This could be due to more advanced and better patient management protocols in this centers close to our study.

Our current study did not demonstrate any correlation between hours to debridement and infection rate. There was no statistically significant difference in infection rate between those debrided within 12 hours, and after 12 hours, ($p = 0.72$). Other studies on open fractures have reported similar findings (5, 41, 42). Study done by Harley et al noted that time to debridement is not a significant factor in predicting either nonunion or infection (43). In Reuss et al's study, up to 48 hours delay to operative debridement of open tibia fractures did not adversely affect infection and nonunion rates (Reuss 2007). Locally, study done by Asif at KNH found no

correlation between time to debridement and infection rate for Gustilo type I and II fractures(47). However, in Gustilo type III fractures, he found an increase in infection rate for those debrided after 12 hours. This finding could not be compared in our study because Gustilo type III patients were excluded.

In 1974 Patzakis reported Stabilization of open fractures as one of the most important preventive tools against infection (21). Schandelmaier et al found IMN and external fixators to provide the best infection prevention in open tibia fractures with IMN being superior(49). In our study only 9% (2/22) of those stabilized with external fixator and IMN got infected versus 25% (14/56) in those stabilized with plaster cast. In Asif's study done in KNH, the high infection rate of 50% was partially attributed to use of plaster cast in high proportion of patients (80%). Although this compares well with our study with 71% use of plaster cast, infection rate was lower. Therefore, fracture stabilization method is not a major infection prevention tool.

Incidentally, patients with injuries in the distal leg were more likely to be infected than those with injuries in the mid or upper leg; 79% versus 11% of the infected cases respectively ($p < 0.001$). In our literature search no studies reporting similar finding were identified. This can be explained by poor soft tissue cover in the distal leg hence poor blood supply.

Culture of the infected wounds obtained 18 isolates. Staphylococcus aureus was the commonest isolate at 50% followed by pseudomonas aeruginosa (22%). Other studies on surgical site infections or open fracture wounds have reported similar finding. Study done by Dinda et al at Agha Khan university hospital Nairobi Kenya on organisms involved in surgical site infections isolated staphylococcus aureus as the commonest organism followed by pseudomonas aeruginosa.(33). Studies on microbial isolates in open fractures have equally reported staphylococcus aureus as the most common organism (31, 32)

Robinson et al study on microbiologic flora contaminating open fractures found a high rate of positive wound cultures in 83% of all the fractures(26). Of the organisms isolated, more than 90% were sensitive to routine antibiotics. In our study there is high resistance pattern to routine antibiotics mainly cephalosporins and penicillins ranging between 70 – 100%. This could due to the different times of obtaining specimen for culture. In Robinson's study specimen for cultures were obtained from open fracture wounds at initial assessment before antibiotic initiation unlike in this study where culture was done days after initiation of antibiotic prophylaxis.

One complication was noted in this study. One patient in the 5 day group developed an allergic reaction to Cefuroxime. He was dropped out of the study with antibiotic change to Clindamycin.

The traditional practice of long prophylactic antibiotics is associated with medical and economic implications and an increased risk of complications. In an era of cost containment, it is important to shorten the duration unless clinically indicated. We hope the findings of this study will inculcate practice change. 24-hour antibiotics dose used in this study costs kshs.780 at KNH. Prophylaxis for five days pushes the cost five times more besides the risk of antibiotic resistance and side effects to the patient. Considering that there is no difference in infection rate and shorter antibiotic duration is more convenient and cost effective, its general adoption in open fractures is economically sound.

This study had limitations. First, there was no blinding between the two groups since the researcher knew patients allocated to each group. This may cause bias in some observations like ASEPSIS wound scoring. Secondly, ASEPSIS scoring had its limitations like assessing deep soft tissue separation and erythema in dark skin. Third, the study sample size was not adequate to assess secondary outcomes. Fourth, the study did not consider osteomyelitis which

may manifest long after the wound has healed. Wound infection was determined by clinical assessment and bacteriological cultures done for only those with ASEPSIS score of more than 20. ASEPSIS score of 10 to 20 implying healing disturbance may be an early sign of infection as suggested from the study findings.

10.0 CONCLUSION

This study provides evidence that there is no difference in the infection rate between the use of 24 hours and 5 days of antibiotics in the management of acute traumatic open tibia fractures. Prophylaxis beyond one day does not seem to add any additional benefit to infection prevention. Early antibiotic administration significantly reduces infection rate.

11.0 RECOMMENDATIONS

1. Shorter duration of antibiotic administration should be adopted in the management of acute traumatic open tibia fractures as opposed to longer duration.
2. Management protocols should be developed guiding physicians on the short duration of PAU especially in the resource constrained developing world
3. Prophylactic antibiotics should be administered earliest possible
4. Further research with larger sample size and follow up of patients to complete fracture healing is necessary to find out if there is any difference in outcome between the two groups especially late osteomyelitis.
5. If confirmed in prospective trials, what is already known for grade I or II fractures could be extended to grade III fractures

12.0 ETHICAL CONSIDERATIONS

Approval for the study was obtained from the department of orthopedic Surgery, University of Nairobi and the KNH ethics and research committee (KNH/ERC) before commencement.

Informed consent was obtained from the patients who accepted to participate in the study (See appendix IV and V).For those who did not consent; they were managed as per the regular open tibia management protocol in the hospital.

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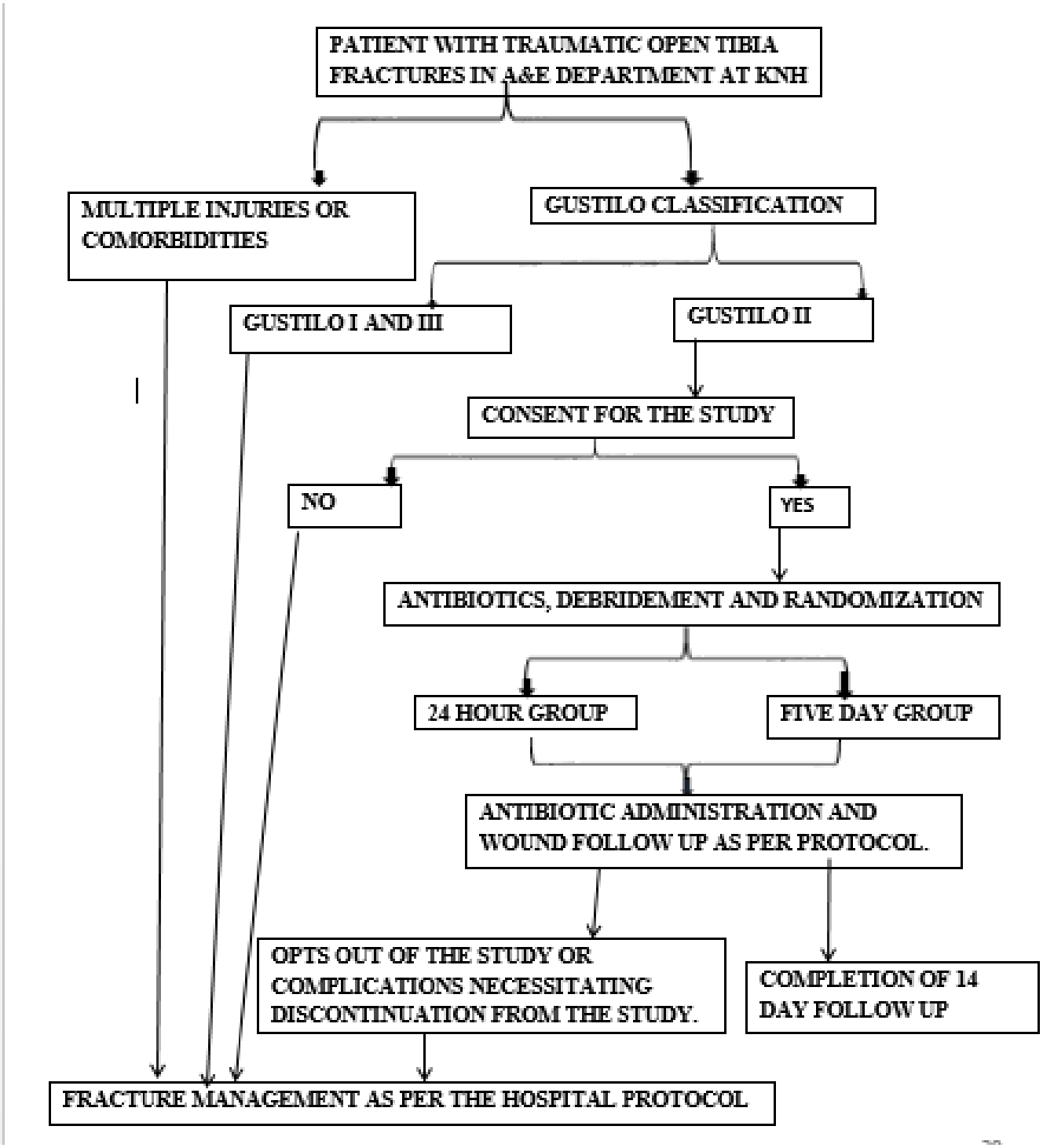
14.0 APPENDIX

14.1 PATIENT FLOW DIAGRAM



APPENDIX II

14.2 ASEPSIS WOUND SCORING SYSTEM

Adopted from journal of bone and joint surgery British edition article (57)

Table II. Points scale used to calculate total ASEPSIS score

Criterion	Points
Additional treatment	
Antibiotics	10
Drainage of pus under local anaesthetic	5
Debridement of wound under general anaesthetic	10
Serous discharge	0 to 5
Erythema	0 to 5
Purulent exudate	0 to10
Separation of deep tissues	0 to 10
Isolation of bacteria	10
Stay in hospital over 14 days	5

Table III. Points scale for ASEPSIS daily wound inspection

	Proportion of wound affected (%)					
	0	> 0 to 19	20 to 39	40 to 59	60 to 79	80 to 100
Serous exudate	*0*	*1*	*2*	*3*	*4*	*5*
Erythema	*0*	*1*	*2*	*3*	*4*	*5*
Purulent exudates	*0*	*2*	*4*	*6*	*8*	*10*
Separation of deep tissues	*0*	*2*	*4*	*6*	*8*	*10*

Table IV. Breakdown of ASEPSIS scores

Score	Meaning
0 to10	No infection Normal healing
11 to 20	Disturbance of healing
21 to 30	Minor infection
31 to 40	Moderate infection
≥ 41	Severe infection

APPENDIX III

14.3 DATA COLLECTION SHEET.

Study number……..

Group: 24 hours ☐

Five days ☐

PATIENT DATA

1. Inpatient number…….
2. Age in years …….
3. Sex : M ☐
   F ☐
4. Date of injury ……time of injury……..
5. Hours from the time of injury to antibiotic administration……
6. Date of debridement ……time of debridement…….
7. Hours from the time of injury to debridement……...

FRACTURE/WOUND DATA

1. Cause of injury
   a. Automobile/pedestrian ……
   b. Motorcycle……...
   c. Bicycle ……
   d. Industrial injury……
   e. Fall from height……
   f. Fallen on by weight……..
   g. Assault …….
   h. Farm injury ……..
   i. Sport injury ……..
2. Site of the fracture and wound
   a. Proximal leg ……
   b. Mid-leg…….
   c. Distal Leg…….
3. Gustilo grade
   a. grade I ☐
   b. Grade II ☐
   c. Grade III ☐
4. Size of Wound……..cm

5. Fracture pattern
    a. Transverse……
    b. Oblique……..
    c. Spiral……
    d. Comminuted……..

POST-DEBRIDEMENT DATA

1. Gustilo grade ……..

2. Method of fracture stabilization

    a. Reduction + long plaster cast……

    b. External fixation……

    c. Intramedullary nailing……

    d. Plating……

ASEPSIS SCORE

1. 2nd day……
2. 5th day……..
3. 14th day……

CULTURE (WHEN ASEPSIS SCORE >20)

1. Growth (specific organism if yes)
    a. Yes…….
    b. No……..
2. Sensitivity testing……
3. Resistance pattern……

Any adverse event……

APPENDIX IV

14.4 CONSENT FORM

Study number…….

My name is Dr. Joshua Nyaribari Ondari a master's of orthopaedic surgery student at the University of Nairobi, department of orthopaedic surgery. I am carrying out a six months study on the management of open tibia fractures using prophylactic antibiotics for 24hous or five days. This will involve selected patients seen at A/E department and admitted in the orthopaedic surgical wards at Kenyatta national hospital. This study has been approved by the University of Nairobi and Kenyatta national hospital ethical and research committee. The aim of the study is to find out whether there is any difference in infection rate if antibiotics are administered for 24 hours or five days following open tibia fractures. This information will help improve open fracture management in patients.

Antibiotic administration following open fractures is effective in preventing infection and should be started soonest possible. Short duration of prophylactic antibiotics is sufficient. Long duration can also be used and am seeking to find out its advantages and disadvantages compared to short duration. Your participation in this study is on a voluntary basis. It is not a must that you participate in this study and your decision will be respected. All the information collected will be kept strictly confidential and your name will not be used in any publication.

If you agree to be included in this study, you will be randomly allocated to either arm of antibiotic regimen. Measurements of the affected wound will be taken and information stored in a data collection sheet. Antibiotics will be administered, wound debrided and fracture stabilized. The antibiotics will be continued for 24hous or five days after theatre depending on the group you will be allocated. The wound will be examined on the second day after debridement and findings recorded. This will be repeated on the 5^{th} and 14^{th} day. The

management of the fracture or wound after this will be by the appropriate method selected by the ward or clinic doctors.

You are free to withdraw from the study at any time. This will not compromise the treatment you receive in the hospital. By signing below, you are agreeing to participate in this study voluntarily.

Name _____

Signature_____ Date_____

Witness_____

Signature_____Date_____

For further information, enquiries or complaints please contact;

1. Dr. Joshua NyaribariOndari mobile number 0722686298 – principal researcher.
2. Prof Ating'a mobile 0733737769 or Dr. Ombachi mobile 0722524948- supervisors
3. Chairman, UON/Kenyatta National Hospital ethics and Research committee on Tel 020-2726300 Ext 44355.

APPENDIX V

14.5 CHETI CHA KUKUBALI

Nambari ya kushiriki……

Jina langu ni daktari Joshua Nyaribari Ondari mwanafunzi wa shahada ya juu ya upasuaji wa mifupa katika chuo kikuu cha Nairobi. Nafanya utafiti kwa muda wa miezi sita kuhusu kutibu mifupa ya miguu iliyovunjiika ikiwa na vidonda pahala pa kuvunjika. Utafiti huu utahusisha wagonjwa watakaochaguliwa kushiriki ambao wamelazwa kwenye wodi za upasuaji ya mifupa katika hospitali kuu ya Kenyatta. Utafiti huu umeidhinishwa na kamati ya utafiti ya chuo kikuu cha Nairobi na hospitali kuu ya Kenyatta.

Utafiti huu unalenga kubainisha kama kuna tofauti kati ya siku moja na siku tano ya kutumia dawa zenye makali ya kuua viini vya vijaa sumu ili kuzuia kidonda na mfupa kupata usaha. Baada ya kuhusishwa kwa hii utafiti, utaanzishwa dawa kwa siku moja au tano, kidonda kuoshwa na kuvishwa. Kidonda kitafunguliwa siku ya pili, tano na ya kumi na nne. Matokeo hayo yatasaidia kuimarisha huduma za kutibu mifupa iliyovunjika na vidonda kwa wagonjwa wengi.

Uko huru kujitoa kwa utafiti huu wakati wowote na hii haitadhuru ile matibabu utapata kwa hii hospitali. Kuweka sahihi inamaanisha umekubali kuhusishwa kwa utafiti huu bila kushurutishwa.

Jina_____

Sahihi/Kidole_____ Tarehe_____

Shahidi_____

Sahihi_____Tarehe_____

Ikiwa unahitaji maelezo zaidi au una swali au malalamishi unaweza kuwasiliana na;

1. Mtafiti mkuu – Dkt. Joshua Nyaribari Ondari kupitia nambari ya simu 0722686298.
2. Wasimamizi – profesa J. E. O Ating'a nambari ya simu 0733737769 and Dr. Bwana Ombachi nambari 0722524948
3. Mwenye kiti wa kamati ya utafiti ya chuo kikuu cha Nairobi na hospitali kuu ya Kenyatta kupitia nambari ya simu 0202726300 ext 44355.

APPENDIX VI

14.6 INFORMATION AND CONSENT FORM

Study number…….

University of Nairobi Department of Orthopedic Surgery

Investigator: Dr. Joshua Nyaribari Ondari

Supervisors: Dr. Bwana Ombachi and Prof. J.E.O Ating'a

STUDY TITLE: comparative study of 24 hour versus five day prophylactic antibiotic use in Gustilo II open tibia fractures at Kenyatta National Hospital.

INFORMATION AND CONSENT FORM

Introduction & Purpose of Study:

My name is Dr. Joshua Nyaribari Ondari a master's of orthopaedic surgery student at the University of Nairobi, department of orthopaedic surgery. I am carrying out a six months study on the management of open tibia fractures using prophylactic antibiotics for 24hous or five days. This will involve selected patients seen at A/E department and admitted in the orthopaedic surgical wards at Kenyatta national hospital. The aim of the study is to find out whether there is any difference in infection rate if antibiotics are administered for 24 hours or five days following open tibia fractures.

Procedures:

If you accept to take part in this study, you will be randomly allocated to either arm of antibiotic regimen. Antibiotics will be administered, wound debrided and fracture stabilized. The antibiotics will be continued for 24hous or five days after theatre depending on the group you will be allocated. The wound will be examined on the second day after debridement and findings recorded. This will be repeated on the 5^{th} and 14^{th} day. The management of the fracture or wound after this will be by the appropriate method selected by the ward or clinic doctors

Risk

Participating in this study bears minimal risk. All procedures are part of usual management in patients with these injuries. Therefore all costs incurred will be paid by the patient as part of hospital bill.

Benefits:

This study has no direct benefit to you as an individual. The study will help change the practice by clinicians of giving antibiotics for long duration and help improve open fracture management in patients. Because of close follow up of study participants, your management in the hospital will be hastened with possible reduced length of hospital stay.

Voluntary Participation and Right to Withdraw from the Study:

Participation in this study is voluntary, you may refuse to participate or withdraw at any point in time. There will be no consequences if you refuse to participate or pull out of the study.

Confidentiality:

No personal identification information will be collected. Any report on this study will not include your name.

Ethical Approval:

To ensure that the study conforms to research ethics, it has been reviewed and approved by the Kenyatta National Hospital-University of Nairobi Ethical Review Committee. If you have any complains about the study please contact the committee chairperson, Prof. Anastacia Guantai on 020 2726300 or make an appointment to see her at the University of Nairobi School of Pharmacy.

Contacts:

If you need to contact the investigator on any matter relating to the study please call 0722686298 or email ondarijoshua@students.uonbi.ac.ke

Declaration:

I have read the above information and had the opportunity to ask questions to my satisfaction. I voluntarily consent to participate in the study.

APPENDIX VII

14.7 MAELEZO YA CHETI CHA KUKUBALI

Nambari ya kushiriki……

Chuo Kikuu Cha Nairobi Idara ya Upasuaji wa Mifupa

Mtafiti mkuu: Daktari Joshua Nyaribari Ondari

wasimamizi: Daktari Bwana Ombachi na Profesa J.E.O Ating'a

MAELEZO YA CHETI CHA KUKUBALI

Kianzisho na madhumuni ya utafiti

Jina langu ni daktari Joshua Nyaribari Ondari mwanafunzi wa shahada ya juu ya upasuaji wa mifupa katika chuo kikuu cha Nairobi. Nafanya utafiti kwa muda wa miezi sita kuhusu kutibu mifupa ya miguu iliyovunjika ikiwa na vidonda pahala pa kuvunjika. Utafiti huu utahusisha wagonjwa watakaochaguliwa kushiriki ambao wamelazwa kwenye wodi za upasuaji ya mifupa katika hospitali kuu ya Kenyatta. Utafiti huu unalenga kubainisha kama kuna tofauti kati ya siku moja na siku tano ya kutumia dawa zenye makali ya kuua viini vya bakteria ili kuzuia kidonda na mfupa kupata usaha.

Utaratibu

Baada ya kuhusishwa kwa hii utafiti, utaanzishwa dawa kwa siku moja au tano, kidonda kuoshwa na kuvishwa. Kidonda kitafunguliwa siku ya pili, tano na ya kumi na nne. Matokeo h0ayo yatasaidia kuimarisha huduma za kutibu mifupa iliyovunjika na vidonda kwa wagonjwa wengi.

Hatari

Hakuna hatari ya kushiriki katika huu utafiti. Matibabu yote yatakayotolewa katika huu utafiti ni kawaida kwa wagojwa wenye aina hii ya mifupa iliyovunjika. Kwa hivyo, gharama yote italipwa na mgojwa.

Faida

Hii utafiti haina faida ya moja kwa moja kwako. Utafiti utasaidia kubadilisha mazoea ya madaktari kupeana dawa za kuua viini vya bakteria kwa muda mrefu na kusaidia kuboresha matibabu ya haya maumivu. Sababu ya ufuatiliaji wa karibu wa washiriki wa utafiti,

usimamizi yako katika hospitali itakuwa haraka iwezekanavyo na kupunguza urefu wa kukaa hospitali.

Kushiriki hiari na haki ya kujitoa kwa utafiti:

Uko huru kujitoa kwa utafiti huu wakati wowote na hii haitadhuru ile matibabu utapata kwa hii hospitali.

Siri:

Hakuna habari ya siri kukuhusu itarekodiwa. Ripoti yoyote katika huu utafiti haitakua na jina lako.

Idhini kimaadili:

Utafiti huu umeidhinishwa na kamati ya utafiti ya chuo kikuu cha Nairobi na hospitali kuu ya Kenyatta.

Ikiwa unahitaji maelezo zaidi au una swali au malalamishi unaweza kuwasiliana na mwenyekiti wa kamati Profesa Anastacia Guantai nambari 020 2726300 ama umuone katika chuo kikuu cha Nairobi kitengo cha madawa.

Contacts:

Ikiwa unahitaji maelezo zaidi au una swali au malalamishi na mtafiti au wasimamizi unaweza kuwasiliana na;

1. Mtafiti mkuu – Dkt. Joshua Nyaribari Ondari kupitia nambari ya simu 0722686298.
2. Wasimamizi – Bwana Ombachi nambari 0722524948 au Profesa J. E. O Ating'a nambari ya simu 0733737769

Azimio:

Nimesoma huu ujumbe na kuuliza maswali yote nikatosheka. Ninakubali kwa hiari kushiriki katika utafiti huu.

APPENDIX VII

14.8 RAMDOMIZATION CHART

A Randomization Plan

From

http://www.randomization.com

1. A_____
2. B_____
3. B_____
4. A_____
5. A_____
6. B_____
7. B_____
8. A_____
9. A_____
10. B_____
11. B_____
12. A_____
13. A_____
14. B_____
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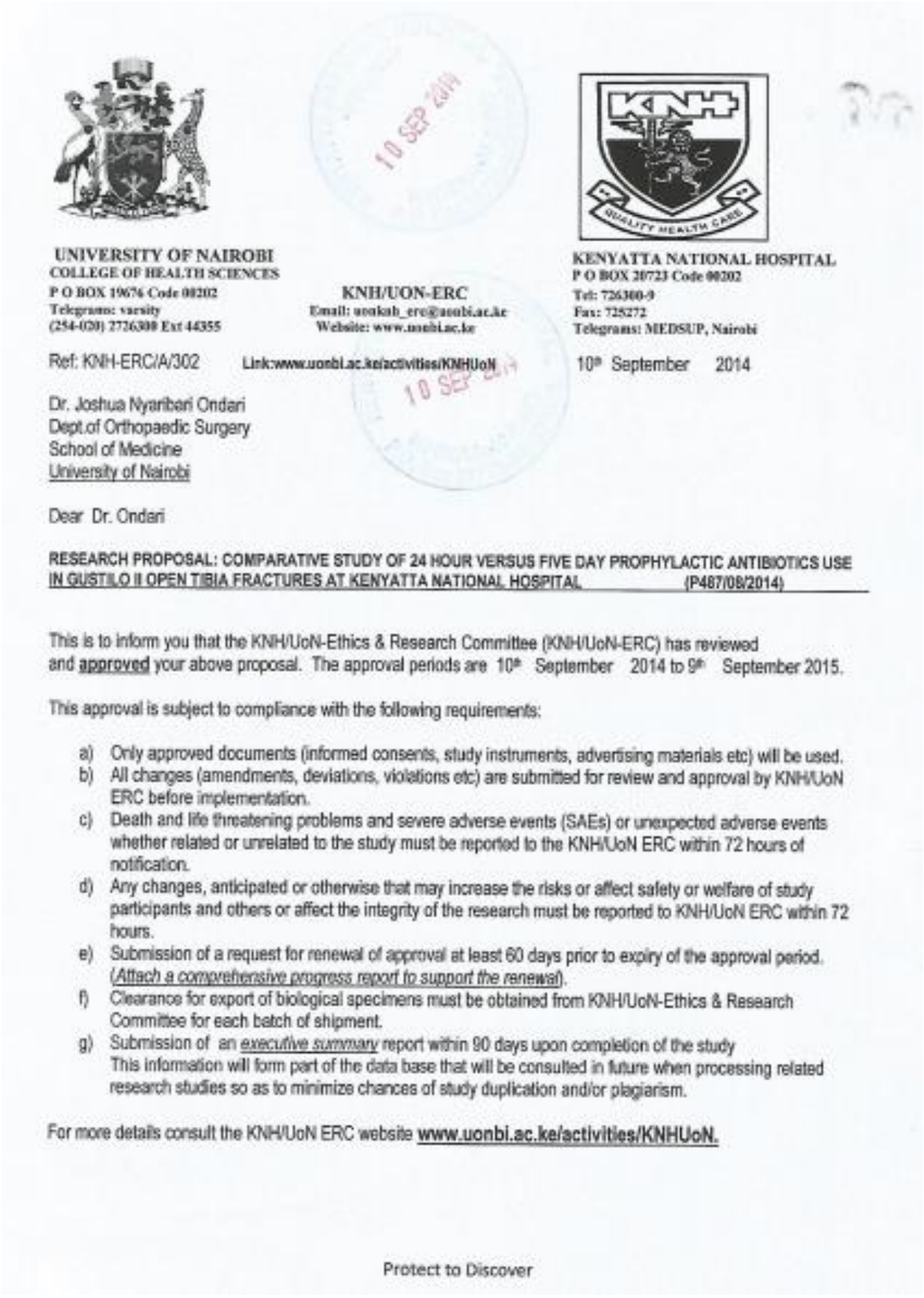
36. A_____
37. B_____
38. A_____
39. A_____

40. B_____
41. B_____
42. B_____
43. A_____
44. A_____
45. B_____
46. A_____
47. A_____
48. B_____
49. A_____
50. A_____
51. B_____
52. B_____
53. A_____
54. B_____
55. B_____
56. A_____
57. A_____
58. B_____
59. B_____
60. A_____
61. B_____
62. A_____
63. B_____
64. A_____
65. B_____
66. A_____
67. B_____
68. A_____
69. B_____
70. A_____
71. B_____
72. A_____
73. B_____
74. B_____
75. A_____
76. A_____
77. B_____
78. A_____
79. A_____
80. B_____
81. B_____
82. A_____
83. B_____
84. A_____

84 subjects randomized into 21 blocks
To reproduce this plan, use the seed 28161
Randomization plan created on 9/22/2014, 12:16:28 AM

APPENDIX VIII

14.9 ETHICAL APPROVAL



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Ref: KNH-ERC/A/302 Link:www.uonbi.ac.ke/activities/KNHUoN 10th September 2014

Dr. Joshua Nyaribari Ondari
Dept.of Orthopaedic Surgery
School of Medicine
University of Nairobi

Dear Dr. Ondari

RESEARCH PROPOSAL: COMPARATIVE STUDY OF 24 HOUR VERSUS FIVE DAY PROPHYLACTIC ANTIBIOTICS USE IN GUSTILO II OPEN TIBIA FRACTURES AT KENYATTA NATIONAL HOSPITAL (P487/08/2014)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and **approved** your above proposal. The approval periods are 10th September 2014 to 9th September 2015.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (*Attach a comprehensive progress report to support the renewal*).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an *executive summary* report within 90 days upon completion of the study This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website **www.uonbi.ac.ke/activities/KNHUoN.**

Protect to Discover

Yours sincerely

PROF.M.L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Chair, KNH/UoN-ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UoN
The Chairman, Dept.of Orthopaedic Surgery, UoN
Supervisors: Prof. J.E. O. Ating'a, Dr. Bwana Ombachi