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Effectiveness of Preoperative Intravenous Tranexemic Acid on Reduction of Perioperative Blood Loss in Open Intramedullary Nail Fixation of Femoral Shaft Fractures in Mulago

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Contents

ABBREVIATIONS

aPTT	-	ACTIVATED PARTIAL THROMBOPLASTIN TIME
DVT	-	DEEP VEIN THROMBOSIS
EMCA	-	EPISILON-AMINOCAPROIC ACID
ORIF	-	OPEN REDUCTION AND INTERNAL FIXATION
POD	-	POSTOPERATIVE DAY
PT/INR.	-	PROTHROMBIN TIME AND INTERNATIONAL NORMALIZED RATIO
SAE	-	SERIOUS ADVERSE EVENTS
NDA	-	NATIONAL DRUG AUTHORITY
SOMREC	-	SCHOOL OF MEDICINE RESEARCH AND ETHICS COMMITTEE
TXA	-	TRANEXEMIC ACID
UBTS	-	UGANDA BLOOD TRANSFUSION SERVICES

ABSTRACT

Background: Major Perioperative blood loos is one of the complications of open femoral shaft fracture intramedullary nailing surgery with average blood loss estimated at 1500mls. There is need for strategies to reduce on this blood loss. Antifibrinolytics such as tranexemic acid have been successfully used to reduce perioperative blood loss in other orthopaedic procedures.

However effectiveness oftranexemic acid use during open femoral shaft fracture intramedullary nailing surgery has not been studied in our setting.

Aim: To assess the effectiveness of intravenous tranexemic acid in reduction of perioperative blood loss, transfusion rates in patients undergoing open femoral shaft fracture intramedullary nailing surgery.

Methods: This will be an open label single arm study. Patients scheduled for open femoral shaft fracture intramedullary nail fixation surgery will receive preoperative tranexemic acid at 15mg/kg. Blood loss using difference between pre and post-operative hemoglobin, blood transfusion rates and adverse events in the peri operative period will be measured.

Utility: The results of this study will reveal effectiveness oftranexemic acid in reducing perioperative blood loss during open femoral shaft fracture surgery in this setting. This information will be useful in designing protocols for prevention of perioperative blood loss for femoral shaft fracture surgery.

OPERATIONAL DEFINITIONS

Peri-operative	- Period from start of surgery to 72 hours after the Surgery
ORIF	- Open intramedullary nailing of femoral shaft fractures.

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CHAPTER ONE

INTRODUCTION

1.1 Background

Major orthopaedic procedures are often associated with major blood loss.(1, 2) Open Reduction and Internal Fixation (ORIF) of femoral shaft fractures is one of major orthopaedic procedures associated with major perioperative blood loss estimated at 1500mls in a developing world operating theatre.(3)

Worldwide major blood losses cause hemodynamic instability and severe anaemia, hence a need for allogeneic blood transfusions that are associated with a number of complications such as (e.g., mismatched transfusion, allergic reactions, transmission of infections, and acute lung injury).(4-6) Furthermore, allogeneic transfusions are also associated with increasing costs such as prolonged hospital stay and the cost of processing, handling, administration of blood products.

Amount of perioperative blood loss during major orthopaedic procedures can be multifactorial with patient and institutional factors. Patient factors do include but not limited, inability to cauterize or coagulate bony surfaces resulting in uncontrollable hemorrhage and increased fibrinolysis as a result of surgical stress. (2, 7) On the other hand institutional factors include availability of electro cautery and fluoroscopy guided intramedullary fracture fixation are believed to reduce intraoperative blood loss.(3)

In the developed and under developed world the need to minimize perioperative blood loss during orthopaedic procedures has been a focus of multiple strategies addressing both patient and institutional factors. (e.g. Hypotensive epidural anesthesia (HEA), Platelet rich plasmapheresis, Acute normovolemic hemodilution (ANH), Cell salvage (scavenging), Anti-fibrinolytics, Fibrin sealants) (1, 8, 9)

Tranexemic acid (TXA) has been used to achieve hemostasis in a number of orthopaedic and non orthopaedic procedures. This is because TXA is an antifibrinolytic agent, a synthetic lysine product that competitively inhibits plasminogen activation to plasmin, and at much higher concentrations, a noncompetitive inhibitor of plasmin, i.e., actions similar to aminocaproic acid. This action prevents dissolution of the fibrin clots stabilizing the clots at the surgical site hence

achieving and maintaining hemostasis.(10-12). TXA has a wide therapeutic window and despite theoretical risk of thromboembolic events has been found to be safe for use in major orthopaedic procedures.(1, 12, 13)

Despite studies in developed countries showing intravenous administration ofTXA leads to significant reduction in perioperative blood loss and blood transfusion requirements in orthopaedic surgeries (Spine, Hip Arthroplasty, Knee Arthroplasty)(12, 14, 15) TXA use can be further extended to address need for reduction of perioperative blood loss in ORIF.

A study to determine efficacy of preoperative intravenous TXA on perioperative blood loss in patients undergoing Open intramedullary nail fixation of femoral shaft fractures in Mulago National Referral Hospital.

1.2 Problem Statement

Closed reduction intramedullary nail fixation under guidance of fluoroscopy is the most used treatment for femoral shaft fractures. However in resource limited settings with lack of standard theatre facilities, open intramedullary nailing is done with aid ofjig and target arm and this increases the risk of substantial peri-operative blood loss.(16) Kajja et al(3) in 2009 showed that ORIF in the resource limited settings leads to a substantial peri-operative blood loss of >1500ml.

This substantial peri-operative blood loss puts a stress on the limited hospital blood bank, financial and human resources, and limits access of the sparse blood units for others in need of blood transfusion. The costs to have a unit of safe blood delivered to the hospital have been estimated to be $45 in Uganda and$150 - $400 elsewhere (17-20).

TXA has been used to achieve hemostasis in number of orthopaedic and non orthopaedic procedures with significant reduction in peri operative blood loss and blood transfusions (12, 15, 21). In addition, TXA has a wide therapeutic window, is affordable and readily available compared to other strategies to minimize perioperative blood loss such as fibrin sealants. However TXA has not been applied in femoral shaft surgeries to reduce blood loss in our settings.

1.3 Study Justification

There is need for an affordable, readily available and safe method of reducing perioperative blood loss in ORIF such as TXA.

Use of TXA for this indication has not been assessed and its effect is unknown in our setting. This study will establish the role of TXA in ORIF in a resource limited theatres. Further providing clinicians a cheap and readily available option to use in reduction of blood loss during open femur shaft fracture Intra Medullary Nailing.

Institutions like hospitals and Ministry of health can use these findings to draw up protocols and guidelines for prevention of perioperative major blood loss in patients undergoing ORIF.

The study will set a baseline on which further studies on the use of Tranexemic Acid in other orthopaedic and non orthopaedic surgical procedures may be based.

1.4 Research Hypothesis

Intravenous Tranexemic acid given preoperatively at 15mg/kg before open femoral shaft fracture intramedullary nailing will reduce average perioperative blood loss of 3.31 g/dl and perioperative transfusion rates by 30%.

1.5 Research Question

What is the effectiveness of pre-operative intravenous Tranexemic acid in reduction of perioperative blood loss in open intramedullary nail fixation of femoral shaft fractures in Mulago Hospital?

1.6 Objectives

1.6.1 General Objective

To determine the effectiveness and safety of pre-operative intravenous Tranexemic Acid 15mg/kg on reduction of perioperative blood loss in adult patients undergoing open intramedullary nail fixation of femoral shaft fractures in Mulago National Referral Hospital.

1.6.2 Specific Objectives

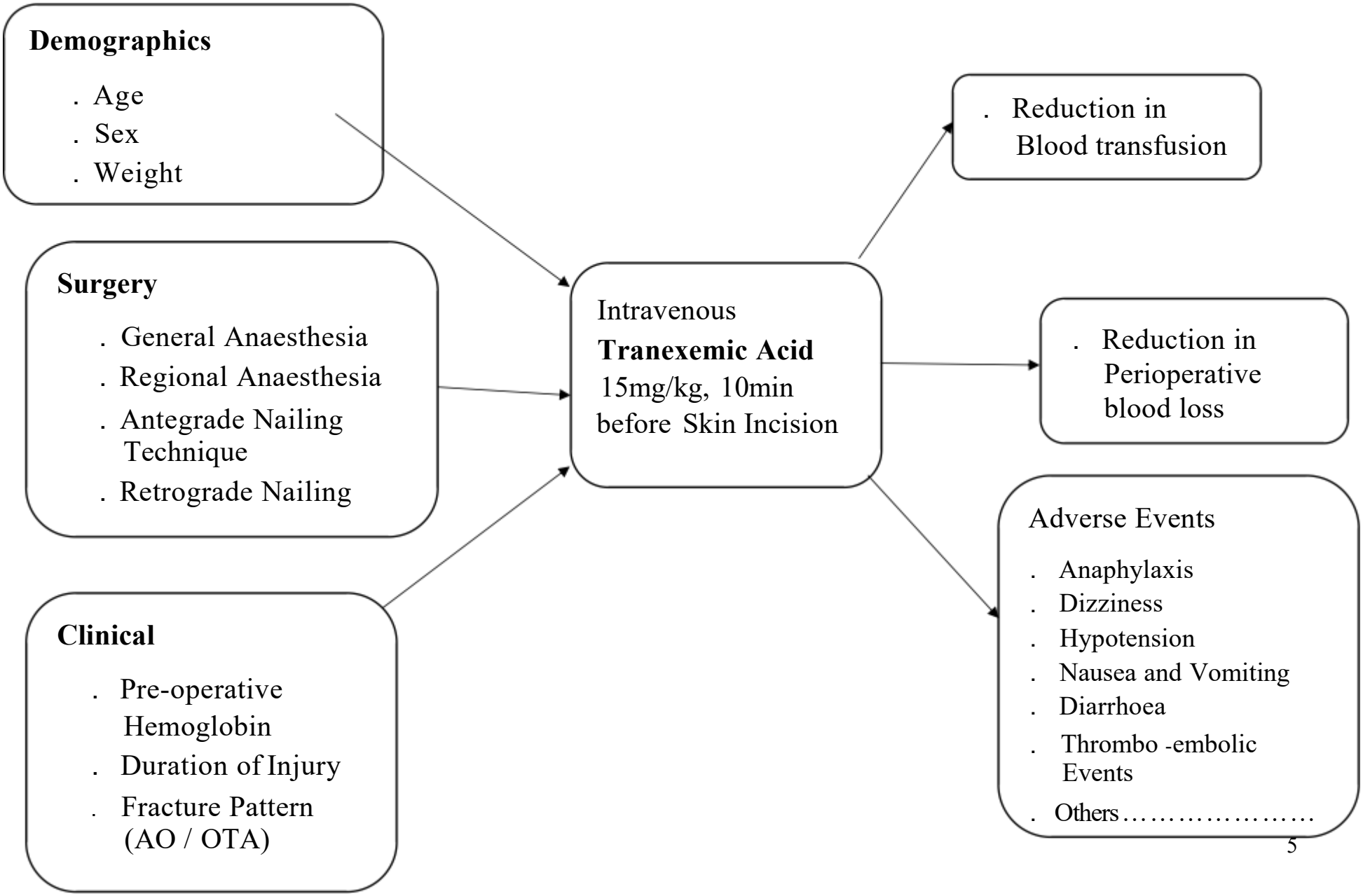
1.6.2.1 Primary Objective

1. To determine the effectiveness of pre-operative intravenous Tranexemic acid 15mg/kg reduction of perioperative blood loss as estimated by difference in 72 hour postoperative and 2 hour preoperative Hemoglobin concentration in patients undergoing open intramedullary nail fixation of femoral shaft fractures in Mulago National Referral Hospital.

1.6.2.2 Secondary Objectives

1. To determine effectiveness of pre-operative intravenous Tranexemic acid 15mg/kg on reduction of transfusion rates in patients undergoing open intramedullary nail fixation of femoral shaft fractures in Mulago National Referral Hospital.
2. To determine the safety of pre-operative intravenous Tranexemic acid 15mg/kg in patients undergoing open intramedullary nail fixation of femoral shaft fractures in Mulago National Referral Hospital.

1.7 Conceptual Framework



CHAPTER TWO

LITERATUE REVIEW

2.1 Introduction

The orthopaedic surgeon is faced with numerous perioperative complications arising from modern day orthopaedic surgery. Excessive intraoperative and postoperative blood loss, is a common occurrence attributed orthopaedic surgeries, being more invasive procedures as compared to other surgical specialties. Amongst the many strategies attempted to reduce perioperative blood loss in modern day orthopaedic procedures is use of antifibrinolytic agents such as Tranexemic Acid. (8)

2.2 Tranexemic Acid

Okamoto et al discovered trans-4-Aminomethyl-Cyclohexanecarboxylic Acid (Tranexamic acid) as a potent antifibrinolytic superior to the previously used antifibrinolytic lysine analogue Episilon-Aminocaproic Acid (EMCA).(22) TXA is an Antifibrinolytic Agent. TXA is a synthetic derivative of the amino acid lysine with antifibrinolytic activity. With strong affinity for the five lysine-binding sites of plasminogen, TXA competitively inhibits the activation of plasminogen to plasmin, resulting in inhibition of fibrinolysis ensuring stabilization of clot: at higher concentrations, this agent noncompetitively inhibits plasmin. This agent has a longer half-life, is approximately ten times more potent, and is less toxic than aminocaproic acid, which possesses similar mechanisms of action.(10)

Tranexemic acid has two formulations i.e. Oral tablet and injectable solution, however in surgery Injectable solutions have been mostly used due to the rapid distribution in intracellular and extracellular compartments. Despite several clinical studies proving the efficacy ofTXA with single or multiple boluses of different sizes with or without subsequent infusions, no consensus has been reached regarding the optimal regimen for intravenous TXA administration. Previous studies have established the need for a therapeutic plasma concentration of 10 ng/ mL and an 80% reduction in the activity of plasminogen activator for adequate suppression of fibrinolysis in

tissues, the dosage of 10-15mg/kg has been found to achieve this concentration within 10 mins of administration in the knee Arthroplasty surgeries. (23) (24) (25)

TXA has been reported to be a safe drug with a large therapeutic window and adverse effects mostly documented at high doses >20mg/kg. Some of the common adverse effects of intravenous TXA reported are.

- Hypotension, this is associated with rapid infusion, infusion rate of at most 1 mL per minute is recommended.
- Gastrointestinal disturbances (nausea, vomiting, diarrhea)
- Allergic dermatitis, giddiness
- The risk of thromboembolism among patients receiving TXA has been shown not to be different from those not receiving TXA (10, 23, 26)

2.3 Tranexemic Acid in orthopaedic surgery

2.3.1 Tranexemic acid in spine surgeries

Both intravenous and topical Tranexemic acid have been employed in spine surgery. Meta-analysis data analysis showed TXA reduced intraoperative, postoperative, and total blood loss by averages of 219, 119 (-141, - 98; p<00001), and 319 mL, respectively. 33% reductions in blood transfusion (0.54, 0.83; p<000001) and no apparent increase in Deep Venous Thrombosis (DVT) nor myocardial infarctions.(27)

Pradeep et al used intravenous TXA 10mg/kg versus placebo preoperatively in stabilization surgeries noted a significant decrease in intraoperative blood loss 1042ml in cases and 1149 in controls (p<0.033), thereby decreasing intraoperative transfusions however they noted that there was no major impact on postoperative blood loss 318ml in cases and 354 in controls. In their study they did not observe any thromboembolic events nor adverse effects.(15)

Ho Yong Choi et al also used intravenous loading dose ofTXA 10mg/kg in spinal deformity correction and noted use ofTXA can provide beneficial effects not only on reducing surgical bleeding (case 841 vs. controls 1336 mL, p=0.002), but also on decreasing transfusion requirements both intra- and postoperatively (cases 544 vs. control 812 mL, p=0.012; cases 193 vs. control 359 mL, p=0.034). They further noted no difference in the Incidence of

thromboembolic event and other complications did not show any differences between TXA and non-TXA groups.(28)

2.3.2 Tranexemic acid in Arthroplasty

In orthopaedics, TXA use has been explored most in field of hip and knee arthroplasty with both topical and intravenous routes of administration used however the most common route remains intravenous. However Topical administration ofTXA at an intra-articular and/or peri-articular soft tissue level is growing in popularity. With one of the advantages of topical use of TXA is the minimal systemic absorption hypothesizing less systemic adverse effects.(23, 29)

In hemi and total hip arthroplasty, most randomized placebo controlled trials clinical trial found that TXA administration safely reduced blood loss (TXA group was 242 mL lower on Postoperative Day (POD) 1 (731 vs. 973 mL, P = 0.01), 294 mL lower on POD 2 (830 vs. 1124 mL, P = 0.0002), and 305 mL lower on POD 3 (902 vs. 1205 mL, P = 0.0005) with a tendency for decreased transfusion rate (cases 17% vs. controls 26%) and total blood product consumption with no significant increase in the risk of thromboembolic event. This showing an 11% decrease in transfusion rates.(4, 12, 30)

In knee arthroplasty, study comparing routes of administration showed all routes had significant reduction of perioperative blood loss and transfusion needs with no superior route of administration.(4) (31)

Study comparing intravenous and topical TXA versus tourniquet showed intravenous TXA use without a tourniquet had less hidden blood loss, a lower ratio of postoperative knee swelling, less postoperative knee pain, lower levels of inflammatory biomarkers, better early knee function, and even better early satisfaction than those treated with a tourniquet.(32)

2.3.3 Tranexemic acid in femoral shaft fractures.

There is a paucity of literature on TXA use in femoral shaft fracture. Two literatures were addressing TXA use in femoral shaft fractures.

90 patient study in India looked at preoperative TXA 10mg/kg in femoral and hip surgeries, looked at postoperative drain volume (39.33± as compared to 91.11± in placebo) 56.8% less than placebo, postoperative heamoglobin on days 0 (2.99±3.457 in the study group as compared to 7.70±6.05 in the placebo a 61.1% difference that has P value 0.01) and 2 (0.3578±0.744 and in

the placebo was 2.7122±2.70, *P* value 0.000) a difference of 86.6% Results showed preoperative TXA caused a highly significant reduction in the blood loss in the first 24 hours in patients undergoing surgeries for hip and femoral fractures as well it caused a significant reduction in postoperative anemia and need for transfusion among these patients. In this study out of 45 patients, 18 patients (40%)who fell in the placebo group required blood transfusion and while 7 patients out of 45 (15%) in the study group needed a transfusion (*P*=0.01) a 25% difference in transfusion rates. This study recommended further investigation to determine the effectiveness of TXA in these surgeries.(33)

In Iran, double blinded randomized controlled clinical trial on role of preoperative TXA 15mg/kg versus placebo in intramedullary nailing of proximal femoral fracture shaft was done. With total of 40 patients, each study group was allocated 20 patients. Hemoglobin concentration was used to estimate blood loss, hemoglobin level was measured four hours before and after the surgeries. Blood transfusions observed and integrated into the blood estimation formula. Results showed No significant difference was observed between the groups in drain blood volume four hours after surgery. Mean fall in hemoglobin concentration in placebo group was higher than the TXA group, however, the difference was not statistically significant. (P= 0.570) A difference in transfusion rate between the placebo group (30%) and TXA group (5.6%) was also not statistically significant (P=0.06) a difference of 25%. Surgeon satisfaction level was also observed and noted to higher in the TXA group (94.4%) compared to the placebo group (80%), however the difference was not statistically significant. The study concluded that intravenous TXA before skin incision in patient undergoing proximal femoral shaft fractures surgery, may reduce intraoperative blood loss and hemoglobin fall however without significant reduction in postoperative anemia. This study recommended further investigations.(34)

CHAPTER THREE

METHODOLOGY

3.1 Study design

This will be an open label single arm trial involving adult patients undergoing open intramedullary femoral shaft nail fixation at Mulago National Referral Hospital.

3.2 Study Site

This study will be carried out in the Orthopaedic Department of Mulago National Referral Hospital.

Mulago National Referral Hospital is located on upper Mulago hill road, Kampala, the capital city of Uganda, in Kawempe Division, Mulago Parish. It is about 6 kilometers from city center. It has a bed capacity of about 1500 beds with an annual in-patient turnover in excess of 140,000 patients. It also serves as the teaching hospital for Makerere University, College of Health Sciences.

The Orthopaedic Department of Mulago National Referral Hospital is located in Old Mulago part of the Mulago Hospital Complex, it admits nearly 2000 patients with fractures annually. There are 3 in patient wards including spine ward (manages patients with spine deformities, fractures, infection and tumors), ward 7 (manages closed fractures, musculoskeletal deformities and tumors) and trauma ward (manages closed and open fractures, bone infections, ulcerative tumours) and 3 operating theatres including, spine theatre handles spine surgeries, Ward 7 theatre handles closed fractures, deformities, tumours arthroscopic and arthroplasty surgery, Trauma theatre handles open fractures, bone infections and ulcerative tumor surgery.

The study will be specifically carried out on ward 7, trauma ward and the ward 7 theatre. Patients scheduled for Femoral shaft fracture surgery pre operatively are assessed for their suitability to undergo surgery, Lab tests such as Complete Blood Count to assess hemoglobin levels are done, patients with Hemoglobin levels ≥ 10g/dl are considered fit for surgery other patients are optimized with blood transfusions. All patients preoperatively do have blood Grouping and

Cross matching done before surgery. Intraoperatively, excessive blood loss is prevented, however not always by use of intravenous Tranexemic acid, tourniquet, diathermy, intraoperative hypotension techniques, and occasionally topical / intramuscular adrenaline concoctions. Blood loss intraoperatively is estimated by anaesthesiologist and surgeon who use visual estimation assessing amount of bleeding at surgical site, blood volume in suction drain containers, soaking of the surgical mops, patient's vitals, level of consciousness and mucous membrane pallor. Intraoperatively blood transfusions are sanctioned by anaesthesiologist depending on visual estimation of blood loss, and patient's hemodynamic stability. Postoperatively patients receive intravenous fluids antibiotics, analgesia and are mobilized in and out of bed 12hours. Patients who are clinically aneamic and hemodynamically unstable have a complete blood count done and transfusions sanctioned by attending physician if necessary. DVT investigation and prophylaxis are not routinely done on patients post operatively however at the discretion of the primary surgeon and attending physician for patients at risk this is done.

3.3 Study Population

3.3.1 Target Population

All adult patients with femoral shaft fractures in Mulago National Referral Hospital Orthopaedic Department.

3.3.2 Accessible Population

Adult patients with isolated femoral shaft fractures scheduled for open intramedullary nail fixation at Mulago National Referral Hospital during the study period.

3.4 Study Duration

The study will be conducted over a period of 3 months from the date of ethical approval.

3.5 Selection Criteria

3.5.1 Inclusion Criteria

. All adult (≥ 18yrs) patients with isolated closed femoral shaft fractures scheduled for open intramedullary nail fixation in Mulago National Referral Hospital.

. Patients who will give informed consent to participate in the study

3.5.2 Exclusion Criteria

Patients presenting with

- More than one month after the injury
- Repeat surgery for a fractured femur
- Pathological fractures ofthe femur
- Undergoing Open Reduction and Internal Fixation of more than one fracture in peri operative period
- Known allergy to Tranexemic Acid
- History of a bleeding disorder
- Medical comorbidities (Diabetes Mellitus, Deep Venous Thrombosis, Pulmonary Thromboembolism)
- Patients already receiving anticoagulants.

3.6 Sample size estimation

3.6.1 Sampling Procedure

Comparison of Two Means (Minn M. Soe and Kevin M. Sullivan, Emory University)

$$n = \frac{(Z_1 + Z_2)^2\ 2(S)^2}{(u_1 - u_2)^2}$$

n = Sample size in each group

Z_1 = 1.96 for 95% confidence level

Z_2 = 0.84 for 80% power

S = Standard Deviation of Outcome in Control Group

$u_2 - u_1$ = minimum meaningful difference between means

In study done in Mulago by Kajja et al estimated blood loss in 93 patient who underwent open femur shaft fracture intramedullary nailing estimated 72 hours postoperative mean total blood loss at 3.31g/dl, (SD 1.56).

Tranexemic Acid is expected to give 30% reduction in Blood Loss

i.e. $\frac{u_1 - u_2}{} = 0.3$

$$\frac{u_1}{3.31 - u_2} = 0.3$$

$$\frac{}{3.31}$$

$$u_1 - u_2 = 0.993$$

$$n = \frac{(1.96 + 0.84)^2 \ 2x \ 1.56^2}{0.993^2}$$

$= 38.7$

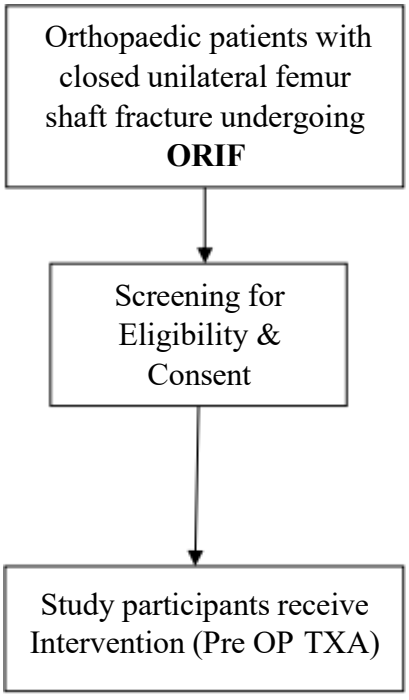
$n = 39$

Adjust for non-response = 39 /0.9

= 43.3 =43

N= 43

3.6.2 Allocation of intervention



3.7 Study Procedure

3.7.1 Participant recruitment

Participants who meet criteria for inclusion and exclusion will be recruited from two wards i.e. ward 7 and Trauma ward. Principle investigator and research assistant shall access patient's file and use screening tool to assess patient's eligibility for enrollment into the study. If patient is eligible participants will be educated on the study procedure and informed consent will be achieved. Participants will be clinically assessed for the Risk ofthromboembolic events and have hematological screening for thromboembolic events or bleeding dyscrasia with Prothrombin Time and International Normalized Ratio (PT-INR) and activated Partial Thromboplastin Time (aPTT) done prior to enrollment. Pre tested data collection tool will then be used by the principal investigator and his research assistants to collect participants demographics and clinical data.

3.7.2 Blood collection Procedure for hemoglobin Estimation.

The principal investigator or his research assistants will draw 2.0 mls of blood under aseptic conditions from the cubital vein of the participant, using a Becton Dickinson vacutainer® system containing EDTA-K3. The tube will be shaken to allow proper mixing of blood with the anticoagulant, legibly labeled with first and given name, age, sex and hospital number of the patient. A laboratory request form for hemoglobin determination will be filled by principal investigator or his research assistants and both the sample and the form delivered to the hospital central laboratory. Upon receiving the result the Hemoglobin concentration will be entered into the data collection tool as Preoperative Hemoglobin in g/dl.

Blood for hemoglobin concentration estimation will be collected 2 hours prior to surgery and 72 hours after surgery. Optimal timing for post-operative heamoglobin concentration monitoring still remains a challenge, however studies in orthopaedic surgeries have noted major variation in hemoglobin concentration estimations from day 0 to day 2 which is attributed to hemodilution with colloids and crystalloids together with ongoing hidden blood losses into the joint cavity and within soft tissue planes. From day 3 onwards minimal changes are noted and this is attributed to heamostabilistion. (35-37)

3.7.3 Tranexemic Acid other preoperative drugs.

Tranexemic Acid (Kapron, Egypt) 500mg / 5ml ampoule will be used. Drug will be prepared at 15mg/kg by the anaesthetist who will administer it for over 10mins to prevent drug induced hypotension, dizziness vomiting and nausea. 10mins before skin incision so as to achieve optimal plasma and interstitial concentrations.

All patients will receive pre-operative antibiotics, before the surgery.

3.7.4 Surgical Time

Time of skin incision and last skin suture will be documented to determine surgical time. It will be presented in minutes.

3.7.5 Surgical Technique

Qualified Orthopaedic surgeons will perform the surgeries and the surgical technique shall be as below:

The choice of ante grade or retrograde nailing can also be influenced by a number of factors including the patient's body habitus, the condition of the soft tissues, and concerns regarding positioning of the patient during anesthesia.

Ante grade Technique

This technique will be preferred for fractures ofthe proximal or middle third of the femur shaft as the centered starting point helps to ensure that the nail will be centered within the distal fracture fragment. Antegrade nailing will be performed with the patient in the lateral position. Open reduction of the fracture will be used. The length of the skin incision will depend primarily on the duration since the injury, the more the time the longer the incision as wider dissections are required to release the use a periosteal elevator to longitudinally separate the muscle fibers of the vastus lateralis down to the fracture site. Free up the callus and soft tissues with aid of periosteal elevators and osteotomes until each fracture fragment is free. Surgeon will preserve immature callus to fill the dead space. Once fragments are free, hand reaming will` performed through the fracture site until the full length of the isthmus had been reamed. Any bone retrieved from the flutes ofthe reamer will be saved for placement in the fracture site at the end of the procedure. Then the surgeon with aid of assistants and manual maneuvers will reduce the fracture ensuring

to line up the linea aspera on both sides of the fracture to accomplish rotational alignment. Accurate rotational alignment of the fracture site is an advantage of open reduction over closed reduction. Reduction will be held by bone holding clamps.

The proximal incision will be made and the proximal aspect of the femur was entered with use of a curved awl positioned at the tip of the greater trochanter or piriformis fossa between the posterior and middle thirds ofthe femur. Hand reamers will then be used to ream the segment of bone between the osseous entrance and the femur shaft. The reaming will also be used to determine the proper nail diameter, which is 2 mm less than the diameter of the reamer that will elicits ‘‘chatter’’ for a distance of approximately 6 cm.

The target arm will then be attached to the nail, and the longitudinal positions ofthe proximal and distal interlocking screws noted. The target arm will then be removed and the nail inserted, with rotation allowed during placement of the nail. After the nail is inserted, the target arm will be reattached to guide the placement of the interlocking screws. Two, three or four interlocking screws will be used. A window will be drilled in the near cortex at the position indicated by the target arm, and a specially designed cannulated slot finder will be placed through this cortical window into the slot of the nail. The hole in the far cortex will then be drilled through the cannulated slot finder, the length of the screw will be measured, and the interlocking screw will be placed. The proximal interlocking screws will be placed from lateral to medial or from anterior to posterior, with the direction depending on how the nail will be rotated during insertion, as the two orientations provide equal stability.

Retrograde Technique

This technique will be preferred for fractures ofthe distal third of the femur. Nailing will be performed with the patient in the supine position. As in the antegrade technique, the fracture site will be opened to allow for reduction as well as reaming through the fracture site. After the knee incision will be made, the femoral canal will be opened distally with use of an awl, and hand reaming will be performed. The nail will be inserted in a retrograde direction and the target arm will be used to place the interlocking screws with use of a technique similar to that described for antegrade technique.

Electro cautery will be used for all patients undergoing ORIF.

3.7.6 Blood use in the perioperative period

The decision to transfuse patients in the intraoperative period will be taken by the anaesthesiologist in concert with the primary surgeon, Basing on:

- Visual assessment of the extent of soaking of the surgical mops with blood.
- Extent of pallor of the finger nail beds, palms and mucous membranes.
- Patient with features of severe hemodynamic instability, tachycardia, hypotension, dizziness etc.
- Post op hemoglobin results of severe anaemia (≤ 6g/dl)

The decision to transfuse patients in the postoperative period will be taken by the primary surgeon or the residents on the wards basing on:

- Patient with features of severe hemodynamic instability, tachycardia, hypotension, dizziness, palpitations etc.
- Extent of pallor of the finger nail beds, palms and mucous membranes.
- Post op hemoglobin results of severe anaemia (≤ 6g/dl)

Intraoperative and postoperative transfusion guidelines shall be availed to the teams to guide on when to transfuse patients to reduce on bias.

Whole blood and packed red blood cell units will be used. 450mls of whole blood and 200mls of packed red blood cells will be estimated to be equivalent to 1g/dl rise in hemoglobin level.

3.7.7 Post-operative care

Patients in the immediate post-operative period will be monitored by the nurses on their primary wards noting vitals (Blood Pressure, Pulse Rate, Respiratory Rates and observe blood soiling of the surgical site dressing). Adequate analgesia will be given to the patients and mobilization in or out of bed will be instituted 12 hours following surgery with guidance of the physiotherapist as per patient tolerability.

Principal investigator together with the surgeons and residents on the primary wards will clinically review the patients daily as part of routine post-operative follow-up with emphasis on identifying and addressing post-operative complications such as thromboembolic phenomena e.g. DVT. Patients with features ofthromboembolic phenomena or develop other Serious Adverse

Events will be investigated thoroughly with blood work up PT-INR, aPTT and Doppler Studies for the lower limbs. They will receive treatment as per guidance of qualified physician.

Serious Adverse Events (SAE) shall be reported within 24hours of occurrence to Department Of Orthopaedics, SOMREC, and National Drug Authority (NDA) using National SAE reporting tools.

Patients shall be followed up for a period of 2 weeks post operatively.

3.7.8 Total blood loss

Total blood loss due to the surgical procedure will be represented by total hemoglobin loss in the perioperative period.

Pre-operative hemoglobin (Pre-opHb) will be taken off 2 hours prior to surgery. Post-operative (Post-opHb) hemoglobin will be done 72 hours after surgery, it will be assumed hemodynamic stability is restored at that time.

Total Blood Loss = Pre-opHb – (Post-opHb + Blood Units g/dl)

3.8 Study variables

3.8.1 Independent Variables

Demographics

- Age
- Sex
- Weight

Clinical

- Pre-operative Hemoglobin

Fracture

- Duration of Injury
- Fracture Pattern (AO / OTA)

Surgery

- General Anaesthesia
- Regional Anaesthesia
- Antegrade Nailing Technique

- Retrograde Nailing Technique
- Duration of Surgery

3.8.2 Outcome Variables

- Primary Outcome: Perioperative blood loss –Will be represented as difference in the 2 hour pre-operative and 72 hour post-operative hemoglobin concentration in g/dl.
- Secondary Outcome: Blood Transfusion – will be represented as the number of blood units. 450mls of whole blood will equate to 1 unit of whole blood. 200mls of packed cells will equate to 1 unit of whole blood.
- Secondary Outcome: Safety – Will be described as adverse events secondary to administration of Tranexemic Acid observed in patients in the study during the perioperative period.
    - Anaphylaxis
    - Dizziness
    - Hypotension
    - Nausea and Vomiting
    - Diarrhoea
    - Thrombo -embolic Events
    - Others……..

3.9 Data Collection

In this study, the principal investigator and research assistant will obtain data using a standardly developed data-collection tool.

3.10 Data Analysis

3.10.1 Interim analysis

This study will conduct two interim analysis and will be done at the midpoint of data collection and at 90% data collection by the DSMB which will be independent from the day to day staff working on the study which will meet at the midpoint of the study for Interim analysis and study progress review.

3.10.2 Data Safety Monitoring Board (DSMB)

A data safety monitoring board will be identified and they will ensure quality, subject safety and provide independent advice to the study team regarding progress and appropriateness of study continuation. It will be composed of 3 members: 1 Orthopaedic Surgeon 1 Pharmacologist, 1 Clinical Epidemiologist, and 1 Ethicist and will meet when 50% data collection completed and 90% completed to perform an interim analysis.

A Bonferroni approximation will be applied during the planned interim analysis for efficacy. For the interim analysis, the critical value for the 2-degree-of-freedom omnibus test will be set to have $\alpha = 0.0001$

3.10.3 Stoppage rules / discontinuation

These shall include the following

- Serious Adverse Events and toxicity data compromising participant safety.
- When noted a large efficacy effect.

The DSMB may recommend stopping the study based on their reviews. Because the DSMB could stop the trial for safety concerns as well as for a large efficacy benefit, there could be multiple opportunities to reject the null hypothesis.

3.11 Data Management

The data collected by the tool will be checked daily and edited for completeness. The data will be entered into the computerized system particularly in Epi Data version 3.1. Following entry, range and consistency checks will be run for each variable to identify inadmissible values. In some cases in which it is impossible to correct errors in the data, a missing value code will be assigned.

3.12 Statistical analysis

Data will then be exported into a SPSS version 19 system which will be used for analysis. We will summarise the study population. We will use descriptive statistics such as means (standard deviations) or median and interquartile range (IQR) for continuous variables and proportions for categorized variables. We will also conduct appropriate statistical tests such as chi square or Fischer's test for categorical variables and a one sample independent T-test or wilcoxon sum rank test for continuous variables.

Objective 1: *To determine the effectiveness of pre-operative intravenous Tranexemic acid 15mg/kg on reduction of perioperative blood loss as estimated by difference in 72 hour postoperative and 2 hour preoperative Hemoglobin concentration in patients undergoing open intramedullary nailfixation offemoral shaftfractures in Mulago National Referral Hospital*.

We will assess for the hypothesis that TXA reduces perioperative blood loss by at least 30% using one sample independent T-test

Objective 2: *To determine effectiveness ofpre-operative intravenous Tranexemic acid 15mg/kg on reduction oftransfusion rates by 30% inpatients undergoing open intramedullary nail fixation offemoral shaftfractures in Mulago National Referral Hospital.*

We will conduct univariate analysis and adjust for effect modification and confounding.

Objective 3: *To determine the safety ofpre-operative intravenous Tranexemic acid 15mg/kg in patients undergoing open intramedullary nailfixation offemoral shaftfractures in Mulago National Referral Hospital.*

We will assess for safety using descriptive statistics showing proportions of adverse events in the study group.

3.13 Study Limitations

Ward 7 theatre currently being used together with the spine team and hence reduced numbers of patients being worked on.

3.14 Ethical Considerations

The permission to carry out the study will be sought from the department of Orthopaedics, Makerere University and ethical Approval will be sought from the School of Medicine Research and Ethics Committee, Mulago Research Ethics Committee.

During the data collection, study identification numbers will be used on all study related documents to maintain confidentiality and privacy. Informed consent will be sought from all study participants before enrollment into the study.

3.15 Dissemination of results

Results from this study will be compiled into a dissertation and availed to the following:

. Department of Orthopaedic surgery, Makerere University.

. Sir Albert Cook Library, Makerere University.

. School of Post Graduate Studies, Makerere University.

. School of Medicine Research and Ethics Committee.

. A manuscript will be written for publication in peer reviewed journals.

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APPENDICES

APPENDIX I: ENROLLMENT SCREENING TOOL

Information to be picked from file of patient's with femoral shaft fractures awaiting surgery

Patient Initials: …… **Ward: ……..**

Inclusion Criteria: Individual should meet all criteria to qualify for enrollment.

	Circle what applies
Duration of Injury ≤30 days	**YES / NO**
Isolated Femoral Shaft Fracture	**YES / NO**
Patient Age ≥18yr	**YES / NO**
Patient scheduled for Intramedullary Nail Fixation	**YES / NO**

Exclusion Criteria: Presence of any below excludes individual from enrollment.

	Circle what applies
Known Allergy to Tranexemic Acid	**YES / NO**
History of bleeding disorder	**YES / NO**
Has received or is currently on Anticoagulant therapy	**YES / NO**
Deep Vein Thrombosis	**YES / NO**
Pulmonary Embolism	**YES / NO**
Myocardial Infarction	**YES / NO**
Diabetes Mellitus	**YES / NO**
Pathological fracture	**YES / NO**

Above individual is **FIT / NOT FIT FOR ENROLLMENT**

Name of Investigator ……

Signature of Investigator ……

APPENDIX II: Data Collection Sheet

Study Number.....

Date of Surgery

Study Arm A

B

A. Patient information

1) Inpatient number
   ……

2) Age (yrs)
   ……

3) Sex: **M** **F**

4) Weight (kg)
   ……

B. Pre-operative Data

1) Duration of Injury (Days)
   ……

2) Fracture Pattern (AO / OTA)
   A **B** **C**

3) Preoperative Hemoglobin (g/dl)
   ……

4) Platelet Count
   ……

5) aPTT
   ……

6) PT-INR
   ……

C. Procedure Data

1) Type of Anaesthesia
   GA **Regional**

2) Time：Start of Surgery
   ……..

3) Time：End of Surgery
   ……

4) Duration of Surgery (hrs)
   ……

5) Nailing Approach
   Ante grade / Retrograde

6) Whole Blood Units Transfused
   ……

7) Adverse Event/s **Y** **N** (Describe Event/s)

……....

.....

D. Postoperative Data

1) Whole Blood Units Transfused

2) 72hr Post-operative Hemoglobin (g/dl)

…… ……

3) aPTT

…… ……

…… ……

4) PT-INR

…… ……

Peri-operative Blood Loss (g/dl)

= Pre-opHb – (Post-opHb + Blood Units)

= ……. - (……..…..+ …….……)

= ……. (g/dl)

Intraoperative and Post-operative Adverse Events and complications

Pre / Intraoperative Period				Comments
DVT / TEE	Nausea Vomiting Diarhoea	Anaphylaxis Dermatitis	Hypotension	
Others				
Day 1				Comments
DVT / TEE	Nausea Vomiting Diarhoea	Anaphylaxis Dermatitis	Hypotension	
Others				
Day 2				Comments
DVT / TEE	Nausea Vomiting Diarhoea	Anaphylaxis Dermatitis	Hypotension	

Others				
Day 3				Comments
DVT / TEE	Nausea Vomiting Diarhoea	Anaphylaxis Dermatitis	Hypotension Dizziness	
Others				
Day 3-14				Comments
DVT / TEE	Nausea Vomiting Diarhoea	Anaphylaxis Dermatitis	Hypotension Dizziness	
Others				

APPENDIX III: Transfusion Guidelines for patient's participating in "EFFECTIVENESS OF PREOPERATIVE INTRAVENOUS TRANEXEMIC ACID ON REDUCTION OF PERIOPERATIVE BLOOD LOSS IN OPEN INTRAMEDULLARY NAIL FIXATION OF FEMORAL SHAFT FRACTURES IN MULAGO" **Study**

Category 1	**Circle**	**Transfusion Criteria**
Intraoperative Hemoglobin Concentration of< 7g/dl	**YES / NO**	Transfuse with **1** Unit of**WB** or **PRBC** if **1** Criteria in category 1 is met
Category 2		
Intraoperative Hemoglobin Concentration of< 10g/dl	**YES / NO**	Transfuse with **1** Unit of**WB** or **PRBC** if **1** criteria in Category **2** is met together with **3** criteria in Category **3**
Category 3		
Severe bleeding at the surgical site and soiling of surgical drapes and mops	**YES / NO**	Transfuse with **1** Unit of**WB** or **PRBC** if ≥ **4** criteria in Category **3** are met
Tachycardia	**YES / NO**	
Oxygen Saturation < 90%	**YES / NO**	
Hypotension	**YES / NO**	
Severe pallor of the Mucous Membranes	**YES / NO**	
Decreasing Levels of Consciousness	**YES / NO**	
Dyspnoea	**YES / NO**	
Angina	**YES / NO**	
Severe active bleeding from surgical site soiling of wound dressings with blood	**YES / NO**	

Re-transfusion: Reassess patient using above guidelines before next transfusion.

KEY

WB – Whole Blood

PRBC – Packed Red Blood Cells

APPENDIX IV: Consent Form (English Version)

EFFECTIVENESS OF PREOPERATIVE INTRAVENOUS TRANEXEMIC ACID ON REPUCTION OF PERIOPERATIVE BLOOD LOSS IN OPEN INTRAMEDULLARY NAIL FIXATION OF FEMORAL SHAFT FRACTURES IN MULAGO

Investigator: Dr Kabazzi Kaweesa Paul, Department of Orthopaedics Makerere University, Tel:+256701047424, email: kabazzip@gmail.com

Introduction:

I am conducting a study to assess the efficectiveness of intravenous Tranexemic Acid in reduction of perioperative blood loss in open intramedullary nail fixation of femoral shaft fractures Mulago Hospital. Tranexemic acid is a drug used to prevent and reduce blood loss. As a result of major blood loss, patients become severly anaemic increasing risk of post operative complications and sometimes may blood transfusions. Resources blood tranfusion are scarce and transfusions can result in complications. This will increase costs for treatment,lengthening hospital stay and sometimes even death.

Purpose:

This study will help Orthopaedic surgeons at Mulago hospital to formulate evidence based method of preventing major perioperative blood loss. This, will inturn help to improve measures of preventing major perioperative blood loss in patients ungergoing femoral shaft fracture surgery.

Procedure:

A data collection form will be filled with your information. Blood Samples will be safely drawn from you before and after Surgery. You will be recieve Tranexemic Acid at 15mg/kg. This will be done by the principal investigator or research assistant after you have consented to participate in the study.

Risk of study

There is no identified risk associated with you being a participant of this study

Benefits

There is no direct benefits with you being a participant of this study, however knowledge that will be obtained from study will help to improve care of patients.

Confidentiality

Information related to you will be treated with strict confidence as provided by law. Your identity will be coded and will not be associated with any published results.

Cost of being a participant

You will incur no cost to participate in this study.

Compensation/Reimbursement for participation in the study:

There will be no any compensation/reimbursement to a participant but from this study many patients will benefit in future since the study will set the basis of development of protocal of Prevention if major perioperative blood loss in Femoral Shaft fracture surgery.

Incase of Serious Adverse Events the principal investigator together with the study team will ensure the you / participant gets timely and adequate intervention within the resources of the Hospital till full recovery.

Rights of Participant

Participation in this study is voluntary. Participant is at liberty to exit the study at any point in time. Refusal to participate in the study shall not have any effect on your care and management in Mulago National Referral Hospital nor your relations with Makerere University College of Health Sciences.

Question about the study

If you have any question about the study you may contact one of the following:

Dr Kabazzi Kaweesa Paul	**Principar investigator**	**0701047424**
Dr Sekimpi Patrick	**Supervisor**	**0772470060**
Dr Kironde Edward	**Supervisor**	**0772517273**

In case you have queries or questions in regard to your personal rights, you may contact the Chairman of Ethics Committee:

Assoc. Prof Ponsiano Ocama
Chairperson School of Medicine Research and Ethics Committtee (SOMREC)
P.O Box 7072, Kampala.
Mobile number: 0772421190

STATEMENT OF CONSENT

.....has described to me what is going to be done, the risks, the benefits involved and my rights regarding this study. I understand that my decision to participate in this study will not alter my usual medical care.In the use of information my identity will be concealed. I am aware that I may withdraw at any time.I undrestand that by signing this form, I do not waive any of my legal rights but merely indicate that I have been informed about the research study in which I am voluntarily agreeng to participate. A copy of this form will be provided to me.

Name	Signature of participant	Date
.....	.....	.....
Name	Signature of Interviewer	Date
.....	.....	.....
Name	Signature of Witness	Date
.....	.....	.....