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SCHOOL OF MEDICINE

DEPARTMENT OF ANAESTHESIA AND CRITICAL CARE

KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.

(#NCT03407404)

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A DISSERTATION SUBMITTED IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE-ANAESTHESIOLOGY AND CRITICAL CARE- MAKERERE UNIVERSITY.

DECLARATION

I, Namata Christine, hereby declare that the work presented in this dissertation has not been presented for any other degree in any University.

The opinions expressed herein are mine unless otherwise stated and where such has been the case-references have been documented.

Signed.... Dr. Namata Christine ....

Date.....22/10/2019.....

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DEDICATION

This book is dedicated to health care providers conducting clinical research in resource limited settings. There are numerous hurdles, and it is inspiring that they soldier on to do quality research in spite of all these.

I am grateful for organizations like THRIVE whose support eases the difficulty somewhat in the conduction of such studies.

I also dedicate this book to my late Aunties; Ms. Rose-Marie Connie Nabatanzi and Ms. Immaculate Nalweyiso who passed away during the course of this study. You will dearly be missed but we are glad for the time we spent with you.

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ACRONYMS AND ABBREVIATIONS

AIDS: Acquired Immuno-Deficiency Syndrome

APACHE: Acute Physiology Age and Chronic Health Evaluation

CAM-ICU: Confusion Assessment Method for the Intensive Care Unit

HIV: Human Immunodeficiency Virus

ICP-intracranial pressure

ICU: Intensive Care Unit

IHK: International Hospital Kampala

LMIC-low and middle-income countries

LOS- length of stay

MEWS-Modified Early Warning Score

MLS/HR- millilitres per hour

MRRH-Mbarara Regional Referral Hospital

MNRH-Mulago National Referral Hospital

NHL-Nakasero Hospital Limited

PI- Principal Investigator

RASS- Richmond Agitation Sedation Score

SCCM-Society of Critical Care Medicine

SD- Standard Deviation

SOMREC-School of Medicine Research and Ethics Committee

UBOS-Uganda Bureau Of statistics

UHI-Uganda Heart Institute

vs-versus

DEFINITIONS

Critical illness: refers to any acute life-threatening systemic illness, involving acute derangements in physiology with >1 significant organ dysfunction requiring support, with or without need for mechanical ventilation.

Sedation refers to use of pharmacologic means to blunt a patients' response to external stimuli.

Delirium refers to an acute fluctuating course in mental status, characterised by inattention with disorganised thinking or altered level of consciousness.

Analgesia refers to use of pharmacological agents to relieve pain without loss of consciousness**.**

Analgo-sedation refers to the practice of ensuring adequate pain relief prior to use of drugs to reduce one's reactivity to stimuli.

ABSTRACT

Introduction: Critically ill patients experience pain, discomfort and anxiety, which require sedation to facilitate life-saving procedures such as mechanical ventilation. Ketamine poses an attractive and readily available alternative for continuous analgo-sedation of critically ill patients to usual care of opioids. It may provide better clinical outcomes in terms of incidence of delirium, incidence of hypotension requiring vasopressor support and duration of mechanical ventilation compared to Morphine in combination with Midazolam.

Objective: The aim of this study was to compare duration of mechanical ventilation, incidence of delirium and use of vasopressor therapy among patients on continuous sedation with Ketamine-Midazolam with those under Morphine-Midazolam in intensive care units in Uganda.

Methodology: We conducted a prospective, double-blinded, superiority, multicenter randomized control trial. Critically ill patients above 12 years of age requiring continuous sedation for at least 24 hours in the ICU were screened, and those meeting selection criteria were enrolled into the study. Participants were consecutively randomized to receive either Ketamine-Midazolam or Morphine-Midazolam using a block sequence technique. Blinding was done at patient/next of kin level as well as investigator/data collector level. Enrolled subjects were followed up for incidence of delirium, duration of mechanical ventilation and vasopressor requirements for 14 days or until discharge/death. Patient demographics, admission diagnosis, co-morbidities and related data were collected and results analyzed.

Results: At study termination due to futility, 124 patients were enrolled from the 6 intensive care units involved in the study; 60 patients were randomized to Morphine-Midazolam group and 64 to Ketamine-Midazolam. There was no statistically significant difference between the Morphine-Midazolam group and Ketamine-Midazolam group in terms of duration of mechanical ventilation, incidence of delirium and incidence of vasopressor therapy by days 3, 7 or 14 of follow up. However, trends towards increased delirium incidence in the Ketamine group by day 3 (12.5% vs 22.2%, 0.199) and increased vasopressor use in the Ketamine-Midazolam were noted by day 7 of follow up (7.1% vs 18.8%, 0.187).The ICU length of stay(9.3±8.2 vs 9.1±7.2, 0.892) daily intravenous fluid therapy, and mortality rates(43.6% vs 46.3%, 0.768) were comparable between the two treatment arms.

Conclusion: This study shows that Ketamine-Midazolam is not superior to Morphine-Midazolam for continuous patient sedation in the intensive care unit as far duration of mechanical ventilation, incidence of delirium and incidence of vasopressor therapy are

concerned. The study also affirms the safety of ketamine use for analgo-sedation without increase in incidence of adverse events, ICU length of stay or mortality rate.

CHAPTER ONE: INTRODUCTION

BACKGROUND

Critical illness involves numerous physiological and psychological stresses, which is why patients may require sedation to facilitate necessary but uncomfortable interventions such as mechanical ventilation. They also commonly have pain resulting from interventions or the primary illness, so analgesia must be provided. (Shapiro et al., 1995) (Adhikari, Fowler, Bhagwanjee, & Rubenfeld, 2010; Barr et al., 2013)

Opioids are the mainstay of analgesia with or without sedation in the critically ill, for whom absence of pain or discomfort is a major goal. (Shapiro et al., 1995){Robinette, 2018 #2375} (Robinette, Weant, Hassig, Smith, & Field, 2018)The most commonly used opioids are morphine and fentanyl, other potent synthetic opioids being alternatives. Non-opioid drugs such as midazolam are also widely used due to availability and familiarity, but the recommended sedatives by the SCCM for long term sedation of critically ill patients are propofol and dexmedetomidine. (Barr et al., 2013) However, all have drawbacks as regards to slow onset and offset, adverse effects, withdrawal syndromes and toxic accumulation. (Aurélie Bourgoin et al., 2003; Umunna, Tekwani, Barounis, Kettaneh, & Kulstad, 2015) (Shapiro et al., 1995)

Ketamine has a wide range of applications, and its use extends beyond the field of anesthesia and emergency department into intensive care. It is being used more in low doses as an adjunct to sedation with other drugs such as midazolam.(Kurdi, Theerth, & Deva, 2014) (Kurdi et al., 2014) Using sedative drugs in combination helps mitigates occurrence of dose-dependent side/adverse effects of the single agents. (Benken & Goncharenko, 2016; Kurdi et al., 2014; Patanwala, Martin, & Erstad, 2015)

Ketamine provides combined sedation and analgesia, with favorable effects on hemodynamics and airway tone. (Kurdi et al., 2014) It was found to reduce inotropic support and exert anti-inflammatory effect in patients with cardiovascular instability secondary to sepsis. (Yoon SH *, 2012) (Taniguchi & Yamamoto, 2005). This study therefore set out to compare duration of mechanical ventilation, incidence of delirium and incidence of hypotension among patients sedated with ketamine-midazolam against those sedated with morphine-midazolam.

PROBLEM STATEMENT

Usual care for continuous patient sedation in most Ugandan ICUs involves use of opioids and benzodiazepines, depending on availability and affordability of the drugs for continuous

sedation. These have been found to be associated with increasing incidence of hypotension(opioids), respiratory depression, delirium, withdrawal syndromes and prolonged mechanical ventilation (Hughes, McGrane, & Pandharipande, 2012; Kurdi et al., 2014)

Ketamine on the other hand is readily available with sedative and analgesic properties among other favorable properties, which may be of benefit to our critically ill patient population. However, is not commonly used due to earlier concerns about its safety in critically ill patients, which have been disproven by studies done in high and middle-income countries. These studies showed ketamine use for continuous sedation to be as good as use of other conventional sedatives with no increased incidence of adverse events. (Miller, Jamin, & Elamin, 2011; Umunna et al., 2015).

This study aimed to determine whether using a combination of ketamine with midazolam for continuous sedation led to better early outcomes in terms of duration of mechanical ventilation, incidence of delirium and incidence of hypotension compared to morphine with midazolam for critically ill patients in a low-income country setting like ours.

JUSTIFICATION

Ketamine is relatively cheap with a large therapeutic window and is more readily available compared to other drugs commonly used for continuous sedation of patients in the ICU. (SM Green, Clem, & Rothrock, 1996). Given its minimal cardiorespiratory depression, immune modulating effects, analgesia and other aforementioned favorable effects, ketamine may make a better alternative for sedation and analgesia of our critically ill patients. (Bourgoin, Albanèse et al. 2003, Parashchanka, Schelfout et al. 2014, Mazzeffi, Johnson et al. 2015)

Use of ketamine for sedation and analgesia for our critically ill could help improve patient outcomes as regards incidence of hypotension, incidence of delirium and duration of mechanical ventilation.

GENERAL OBJECTIVE

1. To compare clinical outcomes among patients continuously sedated with ketamine-midazolam against those under morphine-midazolam in intensive care units in Uganda.

SPECIFIC OBJECTIVES

i. To compare duration of mechanical ventilation among patients sedated with ketamine-midazolam versus morphine-midazolam.

Null hypothesis (H0); There is no difference in duration of mechanical ventilation among patients sedated with ketamine midazolam compared with morphine midazolam.

Alternative hypothesis (HA); The duration of mechanical ventilation will be 4 hours less in patients under continuous sedation with ketamine-midazolam vs those under morphine-midazolam.

ii. To compare incidence of hypotension necessitating vasopressor support among patients under ketamine-midazolam versus morphine-midazolam.

H0; There is no difference in vasopressor requirements among patients sedated with ketamine-midazolam compared with morphine-midazolam.

HA; The incidence of hypotension requiring vasopressor support would be 5% less in the ketamine-midazolam group versus those in the morphine-midazolam group.

iii. To compare incidence of delirium among patients under ketamine-midazolam versus morphine- midazolam.

H0; There is no difference in incidence of delirium among patients sedated with ketamine-midazolam compared with morphine-midazolam.

HA; The incidence of delirium would be 15% less in the ketamine-midazolam group than in the morphine-midazolam group of patients.

RESEARCH QUESTION

Does Ketamine-Midazolam provide better clinical outcomes than Morphine-Midazolam when used for continuous sedation of critically ill patients in intensive care units in Uganda?

CHAPTER TWO: LITERATURE REVIEW

There is increasing need for critical care services in Uganda's health care system given increase in non-communicable diseases, prevalence of infections and increase in trauma victims coupled with the gradual increase in population (38.7 million) (UBOS 1989, 2015) (Kwizera, Dünser, & Nakibuuka, 2012) However, unlimited growth of critical care is hindered by high costs, as expensive resources are involved. (Kwizera, Dunser et al.2012)

The specialty of critical care therefore needs to find solutions to this challenge, one of which would be finding therapeutic interventions that are sustainable in various health care systems. (Adhikari et al., 2010; Dünser, Baelani, & Ganbold, 2006) Uganda; like other LMICs, has a substantial burden of critical illness with limited capacity to provide adequate care for the critically ill from a study by Kwizera et al in 2012. (Kwizera et al., 2012)

Critical care illness and sedation

According to the 2013 ICU Pain-Agitation-Delirium (PAD) guidelines, it is important to maintain light levels of sedation, but also ensure comfort in critically ill patients as that has been shown to improve clinical outcomes. (Barr et al., 2013). However, continuous sedation of patients in the ICU has generally been shown to increase the duration of mechanical ventilation (by 3.2 days, p=0.0191), ICU length of stay (by 9.7 days, p=0.0316), and incidence of delirium in a study by Hershwz et al, Ogundele et al.

Monitoring levels of sedation with various assessment models available is therefore important. The Richmond Agitation Sedation Score is a validated subjective clinical assessment method that is widely used, with good inter-rater reliability. A RASS score of 0 to -2 is recommended to avoid complications associated with deep sedation e.g. increased length of stay in the ICU and prolonged mechanical ventilation. (Barr et al., 2013; Hughes et al., 2012)

Sedation options, recommendations and usual care

There are various pharmacologic options for patient sedation, choice limited by availability, cost and patient characteristics. These include propofol, benzodiazepines e.g. midazolam, opioids e.g. morphine and fentanyl, alpha 2 agonists like dexmedetomidine, ketamine and thiopental. (Barr et al., 2013) (Hughes et al., 2012; Shapiro et al., 1995)

The most commonly used opioids for analgesia and sedation are morphine and fentanyl, preference varying between countries, ICUs and individuals. Morphine may cause histamine release and respiratory depression, especially in newborns, patients with cognitive deficits, hemodynamically unstable and those with history of apnea and respiratory disease. Other

disadvantages include, constipation, pruritus, development of opioid tolerance in some patients, and its metabolism plus excretion being affected by organ dysfunction (liver and kidney). (Sakata, 2010; Shapiro et al., 1995)

Midazolam is a fast-acting benzodiazepine, with a short duration of action after single bolus. It is more titratable, but prolonged administration results in accumulation especially in obese patients, hypoalbuminemia and renal failure patients. It can also cause hypotension at doses above 25mg/hr. Other unwanted effects include development of tolerance and tendency to cause delirium. (Hughes et al., 2012; Sakata, 2010)

About Ketamine

Ketamine is a phencyclidine derivative; a colorless clear fluid, commonly supplied in 50mg/ml ampoules. It's a racemic mixture, with S and R isomers. There is a purely S-enantiomer formulation (Esketamine), which is more potent, more expensive and causes less salivation than the racemic mixture commonly used in our resource limited settings.

Ketamine is a unique anesthetic agent, because it provides amnesia and analgesia in addition to hypnosis and sedation. It generally has short onset of action and relatively long duration of action, with an elimination half-life of 2-4hrs. It increases cardiac output even in patients with poor ventricular function. Though mechanisms to that effect are still controversial, studies suggest direct positive inotropic effect contrary to general teaching of direct myocardial depression.

It has favorable effects on cardiovascular system through central sympathetic nervous system stimulation, inhibition of catecholamine re-uptake for the CVS. A study by Johnstone showed that ketamine was a direct myocardial stimulant whose effects could be blocked using verapamil (Kurdi et al., 2014). (Johnstone, 1976), (Gelissen et al., 1996; Mazzeffi, Johnson, & Paciullo, 2015)

Ketamine also has immune modulating effects to endotoxemia (inhibits TNF alpha, IL-6 and IL-1), and reduces elevation in C-reactive protein levels, which may be of additional benefit in septic and trauma patients (Ho et al., 2013; Hudetz et al., 2009; Taniguchi & Yamamoto, 2005) who constitute majority of the bulk of critically ill patients in our ICUs. (Kwizera et al., 2012) It also has respiratory advantages as it causes bronchodilation, preserves pharyngeal and laryngeal reflexes and improves pulmonary perfusion (Strayer and Nelson 2008, (Kurdi et al., 2014)

Earlier anesthesiologists recommended use of ketamine with a benzodiazepine and anticholinergic to reduce occurrence of emergence delirium and increased airway secretions

that was associated with ketamine. However, recent studies show no benefit from use of a benzodiazepine for prophylaxis, and there was no increased incidence of respiratory issues or clinically important airway secretions when an anticholinergic was omitted. (Steven Green, Andolfatto, & Krauss, 2015), (Reuben J Strayer, 2008)

Ketamine use for continuous sedation in the ICU

A systematic review study done by Strayer et al in 2007 showed that Ketamine has been reported to be efficacious and safe in provision of continuous sedation for procedures or mechanical ventilation. Emergence reactions which are among the most feared were reported to occur in 10 to 20% of adult patients, easily reversed and prevented by conventional treatments plus environmental optimization. (Miller et al., 2011; Reuben J Strayer, 2008) (Adhikari et al., 2010)

In a retrospective study done by Umunna et al on patients who received continuous infusions of ketamine for sedation, average infusion rate was 2.0 +/-0.98mg/kg/hr. starting dose at 0.5mg/kg/hr. (and titrated to effect). The frequency of adverse events in those patients did not differ significantly from that in those sedated with other agents.

Miller et al did a systematic review that showed various reports of reduced vasopressor requirements, better MAPs and reduced fluid requirements in hypotensive patients under ketamine infusions. (Miller et al., 2011; Umunna et al., 2015) Ketamine given at induction of general anesthesia in low doses has been shown to reduce incidence of postoperative delirium in patients undergoing cardiac surgery with cardiopulmonary bypass. (Deiner & Silverstein, 2009; Hudetz et al., 2009) It is also widely used in prehospital settings in the treatment of excited delirium syndrome. (Ho et al., 2013)

Established side effects include a fairly predictable tachycardia, which may be detrimental in patients with stenotic valvular disease and coronary artery disease. It's also been known to cause increased incidence of emergence reactions and has potential for negative psychotropic effects e.g. unpleasant dreams. (Mazzeffi et al., 2015; Shapiro et al., 1995) These can be prevented by pretreatment or administration with a benzodiazepine.

Ketamine, with its various favorable physiological effects is one of the proposed alternative drugs to use for sedation and analgesia. The others include remifentanil, dexmedetomidine and fospropofol which are relatively more expensive and not readily available in Ugandan health facilities. (Benken & Goncharenko, 2016; Mohrien, Jones, MacDermott, & Murphy, 2014)

Effects on vasopressor requirements, ICP, LOS

Study done by Bourgoin et al on severe head injury patients found comparable effects on ICP between patients treated with ketamine-midazolam to those under sufentanil-midazolam. It also showed, along with other studies, reduced fluid requirements by almost half (429 +/- 405 mL compared with 992 +/- 703 mL, *p* _ .02), and reduced vasopressor requirements (p-value =.15). The difference in average cost of sedation per day per patient between the ketamine – midazolam and sufentanil-midazolam were not significant however. (Aurélie Bourgoin et al., 2003; Miller et al., 2011; Umunna et al., 2015)

There was paucity of data regarding use of ketamine for continuous sedation in critical care units in resource limited settings. The studies available had all been done in developed countries despite the implications being potentially favorable for this setting.

CHAPTER THREE: RESEARCH METHODS

Study design

The study was a double-blinded, multi-center, parallel group superiority randomized clinical trial. The study was registered under the clinical trial domain, www.clinicaltrials.gov(#NCT03407404) and with the Uganda National Council for Science and Technology (HS76ES).

Study setting and sites

This study was conducted in 6 intensive care units, including 2 government, 1 private-not-for-profit, and 3 private hospitals in Uganda. The government hospitals included Mulago National Referral Hospital and Mbarara Regional Referral Hospital, found in Kampala and Mbarara districts respectively.

The private hospital intensive care units included those in International Hospital Kampala, Nakasero Hospital Limited, Case Medical Clinic and Mengo Hospital; all in Kampala. Initially, Uganda Heart Institute had been approved as a study site but had to be withdrawn due to very low number of patients that met study criteria. Nsambya hospital declined participation in the study, while Nakasero hospital suspended the study within four months of administrative approval due to concerns about safety that were never validated.

The mode of operation of the intensive care units was a mixture of open and closed units generally. All were mixed ICUs, admitting both medical and surgical patients as well as catering for both adults and children.

Target population

This study targeted critically ill patients admitted to the selected intensive care units.

Study population

Critically ill patients in need of continuous sedation in intensive care units.

Selection criteria

Inclusion criteria; patients admitted to the intensive care unit with the following characteristics;

1. Age >12years of age.
2. Anticipated need for sedation for >24hours.

Excluded all eligible patients with;

1. Hypertensive crisis i.e. sustained SBP >200mmHg/DBP>110mmHg.
2. Refractory Status epilepticus.
3. Ischemic heart disease and severe LV dysfunction.
4. Persistent tachyarrhythmias.

5. History of mental illness.

6. Hypersensitivity to ketamine, morphine or midazolam(known).

7. Tetanus –due to the muscle rigidity that may be worsened by ketamine.

Randomization

Patients admitted to any of the selected ICUs and meeting the selection criteria (and who had consented) were enrolled in to the study. Participants were randomized using a balanced eight-block sequence generated from a random table, in a 1:1 ratio, to ketamine-midazolam or to control (morphine-midazolam) group. Random blocks of 6 to 10 were generated, and in each block a random sequence for the participant intervention group was generated. Drugs were pre-mixed by a pharmacist and labelled either A or B, with A for Morphine-Midazolam and B for Ketamine-Midazolam.

Blinding

Blinding was done at patient/NOK level and investigator level (data collectors) to minimize bias. At recruitment of a participant, the principal investigator retrieved the next available envelope indicating the treatment arm code from a block of envelopes and the drug mixture was availed to the intensivist/nurse in charge for sedation to start. The premixed drugs were labelled and kept in the fridges of each of the participating ICUs for easy accessibility, up to a maximum of 4 weeks after which any unused drugs were removed and replaced by fresh syringes.

Allocation concealment

The sequence was concealed from all participants by inserting it into opaque, sequentially arranged and sealed envelopes by a statistician (independent of the analysis team). The coded intervention group allocations were placed in brown envelopes that were then given to the principal investigator. The information regarding the definition of the codes was kept by the pharmacist mixing the drugs until a participant developed an adverse reaction presumed to be secondary to the study mixture. In such events, the pharmacist unblinded the DSMB and the principal investigator.

Drug Preparation and Use.

The syringes containing the assigned drug combination were prepared by a pharmacist in identical syringes to provide a uniform volume of 50mls.

The drugs were diluted to similar volumes that would result in equipotent drug solutions on a microgram per kilogram per minute basis: a syringe of 50 mL containing 35 mg of midazolam, and 900mg of ketamine for the Ketamine group or 54mg of morphine in the control group.

Depending on sedation targets, a 2ml bolus followed by 2ml/hr. infusion rate was recommended for light sedation targets (+1 to -2 RASS) and 4ml bolus followed by 4ml/hr. infusion rate for heavy sedation targets. The study drug solution would then be titrated to desired effect (RASS) by the medical team on ground for each patient.

Study participants received the rest of care as dictated by the attending intensivist/physician with no interference from the study team. The attending physician decided when to stop or adjust the sedative mixture rate, and all other decisions concerning the patient's treatment.

Participant follow up.

Study participants were reviewed daily by a research assistant/data collector for assessments of presence of delirium, duration of mechanical ventilation, use of vasopressors, and level of sedation among others. One to two ICU nurses were employed as research assistants/data collectors in each of their respective units to allow easy follow up of patients. Follow up period was 14 days, or until discharge from ICU or death (whichever came first).

Only patients on mechanical ventilation were recruited to ensure controlled ventilation given potential effect of the drugs used in the study on respiratory function.

Study Outcomes

Primary outcomes include;

1. Duration of mechanical ventilation in hours from the start of the intervention.
2. Incidence of hypotension necessitating vasopressors, defined as failure to achieve a mean arterial pressure of 60mmHg despite adequate fluid resuscitation.
3. Incidence of delirium, defined as acute fluctuating course in mental status, characterized by inattention and disordered thinking (assessed by the CAM-ICU score)

Secondary outcomes

4. Average intravenous fluid requirements per day in liters.
5. Length of stay in the ICU, from admission to discharge/death.
6. Mortality rate.

Sample size

1. Duration of mechanical ventilation, continuous response

$N = f(\alpha, \beta) \times 2\sigma^2 / d^2$

Standard deviation (sigma) =10, N=sample size estimate, standard error I (alpha) = 0.05

Type II error (beta) = 0.2, effect size (d) =4 hours.

N= 7.9 x 2 x10x10/4x4

N= 98.75

The sample size required to detect a difference of 4 hours in duration of mechanical ventilation between the 2 treatment groups was 99 people.

2. Incidence of hypotension requiring vasoactive drug therapy

Using Pocock's formula for dichotomous responses still, and Bourgoin et al's study results;

$$N=\frac{p1\ (1-p1) + p2\ (1-p2)}{(P2-p1)\ ^2}\ f\ (\alpha, \beta)$$

P1=0.30, p2=0.15, alpha=0.05, beta=0.2

$$N=\frac{0.3x0.7 + 0.15x0.85}{0.15x0.15}\ x7.9$$

$$N=\frac{0.21 + 0.1275}{0.0225}\ x7.9$$

N=118.5

Hence estimated sample size for the incidence of hypotension is 119.

3. Dichotomous response: incidence of delirium.

Using Ogundele and Yende plus (Kwizera et al., 2015) studies, and using Pocock's formula and table for f (α, β);

General incidence of delirium in our ICU patients, P1=0.51

Proposed benefit of ketamine use for sedation reducing it to a p2=0.35

Level of significance, alpha=0.05

Power of the study=80% (beta=0.2)

$$n =\frac{p1\ (1-p1) + p2\ (1-p2)}{(p2-p1)\ ^2}\ f\ (\alpha, \beta)$$

P1=0.51, p2=0.35, alpha=0.05, beta=80%

$$N=\frac{0.51(1-0.51) + 0.35(1-0.35)}{(0.51-0.35)\ ^2}\ x7.9$$

$$N=\frac{0.51x\ 0.49 + 0.35x0.65}{0.16^2}\ x\ 7.9$$

$$N=\frac{0.2499 + 0.2275}{0.0256}\ x7.9$$

N= 147.32

Allowing for 10% lost to follow up;

N=148/1-0.1

N= 164.4

Hence the estimated sample size for the incidence of delirium was 165 people.

We therefore set out with a sample size of 165 for this study, with a 12-month projection for study completion. However, due to multiple challenges at various study sites the study recruited 124 patients (complete CRFs) in 18 months of enrollment.

Distribution in the study sites

52 patients were recruited from Mulago, 37 from International Hospital Kampala and 17 patients from Nakasero hospital. 8 patients were recruited from Case Hospital, 9 patients from Mbarara hospital and 1 patient from Mengo hospital.

DATA MANAGEMENT

Data collection

The Principle Investigator got a research assistant in charge for each site, and was responsible for availing the study drug mixtures at each site. The research assistants were also trained in using the attached assessment tools by the Principle Investigator before data collection started. The Principle Investigator was contacted by research assistants about patients being enrolled so as to check the pre-prepared block envelopes and provide the next study code for that particular participant.

The research assistant monitored the site for possible participants, screened patients and got consent/assent from eligible participants or their next of kin. For all patients who were incapable of making decisions at the time of enrollment, their guardians or next of kin were engaged in the consenting process.

Data was collected using pretested questionnaires by the research assistants. Filled in and completed questionnaires were forwarded to the principal investigator, and errors were corrected before data entry in to an Epidata 3.1.5 based tool and subsequent storage.

Quality control

Research assistants, attending physicians and patient/next of kin were blinded as to which group patients were assigned through maintenance of undefined codes throughout the study.

Research assistants were trained on how to assess and ask questions regarding symptoms, and it was ensured that they would be conversant with making the relevant clinical scores and filling the questionnaire appropriately prior to enrollment.

Data was re-checked for completeness by the principal investigator prior to entry.

Drug mixtures were pre-mixed and coded by a pharmacist, then availed to research assistants. The number of study mixture syringes provided to each research assistant per participant/time would vary depending on patient flow through the unit and their sedation requirements. Used syringes and infusion lines were discarded along with other patient medical waste following each unit's protocol for waste management.

Data analysis

Data was exported and analyzed using STATA software version 12. An independent statistician for the analysis process conducted the interim analyses using the Haybittle Peto method with a p value of 0.001 after 30%, 50%, 63% and 75% of the sample size had been recruited and follow up completed.

Univariate analysis was used to summarize basic characteristics of participants expressed as categorical and continuous variables. Continuous variables were expressed as means and standard deviations, while categorical data was expressed as frequencies with their respective percentages. Linear regression and logistic regression were used to analyze outcomes, as well as multivariate analysis to detect associations. We used analysis of variance when variances were homogeneous and the Kruskal-Wallis test when variances were heterogeneous. The results of the study were reported following the 2015 CONSORT guidelines.

Data Safety and Monitoring Board.

A Data Safety Management Board comprised of an anesthesiologist, intensive care physician, a statistician and a pharmacist. The board advised, monitored and gave guidance as regards patient safety during the course of the study. Three interval analyses were done; at 30%, 50%, and 63% study completion, and a final analysis at 75% completion. The board included Dr. Jane Nakibuuka (Intensivist), Dr. Peter Agaba (Anesthesiologist), Ms. Birabwa Catherine (Pharmacist) and Dr. Mukisa John (Statistician).

Adverse event monitoring

Patients were assessed for adverse events; a serious adverse event being defined as an experience that results in any of the following outcomes:

1. Death occurring within 1 hour of receiving the study drug in the absence of other causes.

2. Life-threatening experience (one that puts a patient at immediate risk of death at the time of the event), such as malignant arrhythmias, anaphylactic reactions and others attributed to the drug mixture used.

When a serious adverse event occurred, standard Advanced Cardiac Life Support and other relevant resuscitative protocols were instituted as required. The Data Safety Management Board were notified as soon as possible, and a written report was submitted to the School of Medicine Research and Ethics Committee (Institutional Review Board) within a period of 14 days. In addition, reporting guidelines of the Uganda National Council of Science and Technology were followed.

A patient that developed a serious adverse event was not withdrawn from the study, rather the study solution was stopped and the patient followed up for other outcomes. Data pertaining to such a patient was incorporated for analysis using intention-to-treat technique.

Development of significant hypersensitivity to any of the study drugs was to lead to withdrawal from the study and further management would involve other sedatives as prescribed by the attending physician. Patients who developed significant persistent tachy-arrhythmias, severe respiratory depression, or persistent opioid related muscle rigidity also required a treatment change.

Hypotension that is unresponsive to fluid boluses was treated with available vasoactive agents e.g. norepinephrine or epinephrine to a target MAP of 65mmHg or higher as required. Increased airway secretions treated with anticholinergic agents as prescribed by the attending physician and led to treatment changes for some cases.

Study Termination.

Due to equivocal findings at interim analyses done at 30%, 50%, 63% and 75%, the study was terminated due to futility following discussion with the DSMB and approval from the Institutional Review Board.

Data dissemination

Upon completion of the study and acceptance of the research findings by the research and ethics committee, a copy of the study results was provided to:

1. Critical Care teams involved in the study.
2. Hospitals involved in the study.
3. Makerere University's School of Graduate Studies, Sir Albert Cook Library
4. Department of Anaesthesia and Critical Care

The study was also submitted to peer reviewed journals for publication.

ETHICAL CONSIDERATIONS

Approval was received from Department of Anaesthesia and the Makerere University School of Medicine Research and Ethics Committee (SOMREC), as well as participating hospital administrations to involve their ICU patients in the study.

We also received permission from the Uganda National Council for Science and Technology to conduct this research study.

Informed Consent was received from adult patients' next of kin. We received assent for participants under 18 years of age, and received consent from their guardians when they were unable to make decisions at the time.

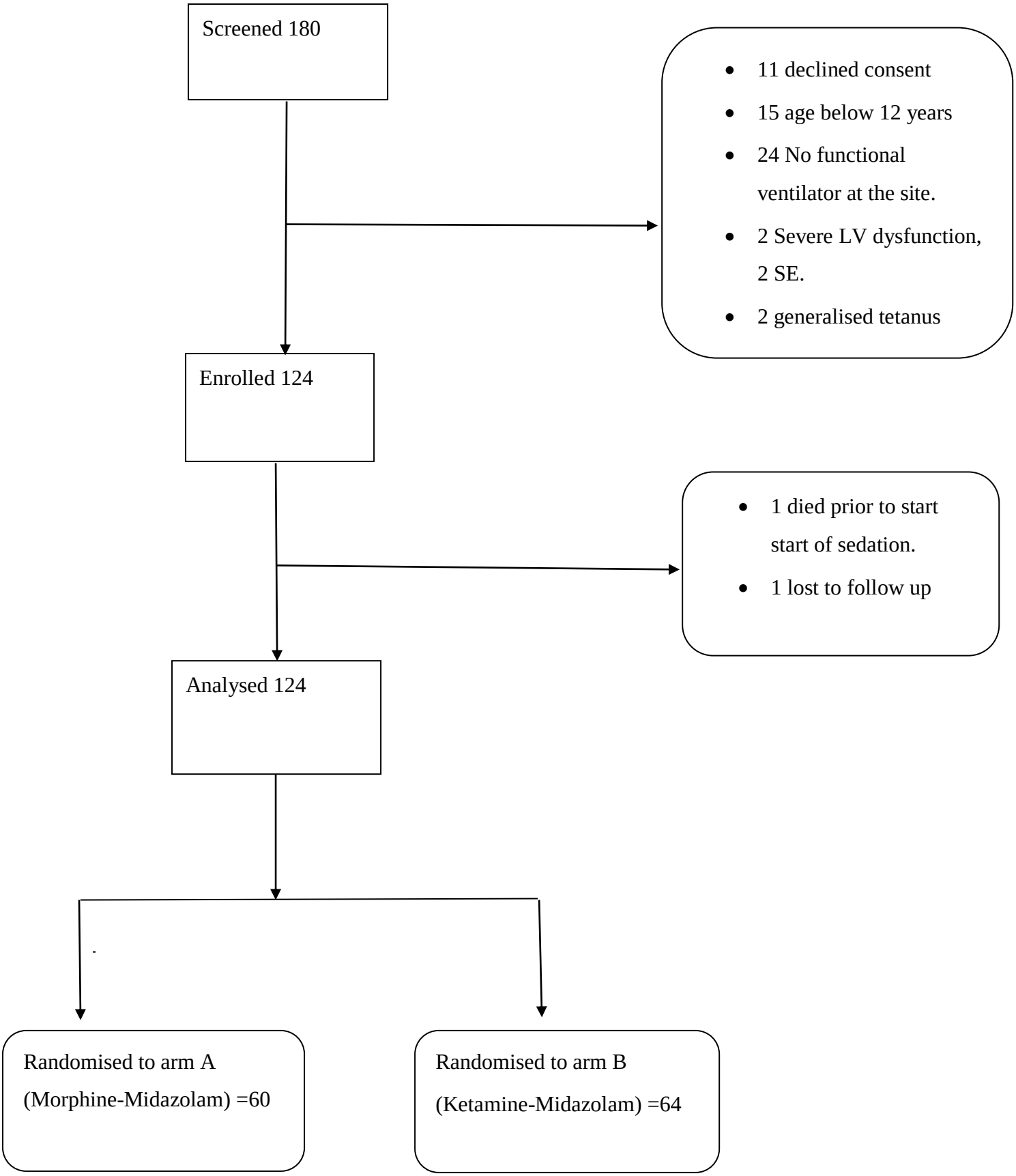
LIMITATIONS

Physician blinding as regards individual patient's treatment arm may have been partial given some characteristic physiological responses of patients to certain drugs like ketamine. This was overcome by extending the blinding to data collectors' and statistician's level to further minimize bias.

Some patients died for reasons related to their primary illnesses less than 24hrs after recruitment into the study. Data from these patients was analyzed using the intention-to-treat analysis as well.

There are other factors unrelated to sedative that affect duration of mechanical ventilation, ICU length of stay, incidence of delirium, incidence of hypotension and ICU mortality. Randomization of study subjects was done to mitigate these sources of confounding as well as multivariate analytic techniques.

Figure 1: Patient flow through the study.



CHAPTER FOUR: STUDY RESULTS

Recruitment of participants started November 2017, and this analysis was done for patients recruited and followed up till June 2019. Of the 165 patients proposed as total sample size, 124 (75.15%) had been recruited and followed up when the study was terminated due to futility based on interim analysis findings.

Baseline characteristics.

The two groups were comparable as regards to demographic factors and baseline characteristics such as time in ICU prior to enrollment into the study and admission source.

Table 1: Patient characteristics and distribution in the study sites.

Variable	N(percentage)or Mean+/-SD		p value
	Group 1 (N=60)	**Group 2 (N=64)**	
Study site			
Mulago	22 (36.7)	30 (46.9)	0.419
Nakasero	11 (18.3)	6 (9.4)	
IHK	19 (31.7)	18 (28.1)	
Others*	8 (13.3)	10 (15.6)	
Sex			
Male	38 (63.3)	41 (64.1)	0.933
Female	22 (36.7)	23 (35.9)	
Age	41.5 ± 17.9	45.3 ± 18.9	0.248
Time in ICU before study	0.69 ± 2.60	0.97 ± 2.5	0.572
Source before admission			
Accident and emergency	28 (46.7)	23 (35.9)	0.383
Ward	14 (23.3)	20 (31.3)	
Operating theatre	15 (25.0)	14 (21.9)	
Transfer from another**	3 (5.0)	7 (10.9)	

**Transfer from another ICU, * other intensive care units in the study including Case hospital, Mbarara hospital and Mengo Hospital.

Table 1 shows the distribution of participants among the sites as well as some baseline characteristics of study participants.

More than 65% of participants were recruited from International Hospital Kampala and Mulago National Referral Hospital intensive care units combined in each arm, the rest coming from other study sites involved as shown above. More than 35% of admissions came

in from the Accident and Emergency with less than 11% coming in as transfers from other intensive care units in each arm.

Table *2:* Prognostic factors at admission into the ICU and recruitment into the study.

	N(percentage) or Mean ±SD		
Variables	Group 1(N=60)	Group 2(64)	p value
Reason for admission			
Respiratory support	50(50.5)	53(50.0)	0.178
Neurocritical care	30(30.3)	32(30.2)	
Cardiovascular support	15(15.3)	13(12.2)	
Others*	4(4.0)	8(7.5)	
MEWS			
0-3	5(8.5)	7(10.9)	0.667
4-6	16(27.1)	15(23.4)	
7-9	28(47.5)	26(40.6)	
10-12	8(13.6)	14(21.9)	
13-15	2 (3.4)	1(1.6)	
16-18	0 (0)	1(1.6)	
Comorbidity			
HIV	11(18.3)	8(12.5)	0.367
Diabetes	4(6.7)	6(9.4)	0.580
Hypertension	14(23.3)	16(25.0)	0.829
Mental health	1(1.7)	0(0.0)	0.300
Others**	6(16.7)	9(23.1)	0.560

Key; * include post cardiac arrest care, postoperative monitoring, pain management and hemodialysis.

** include Malignancy, Sickle Cell disease, Chronic Obstructive Pulmonary Disease, Chronic Kidney Disease, Asthma, Systemic Lupus Erythematosus, Malnutrition and Obstructive sleep apnea.

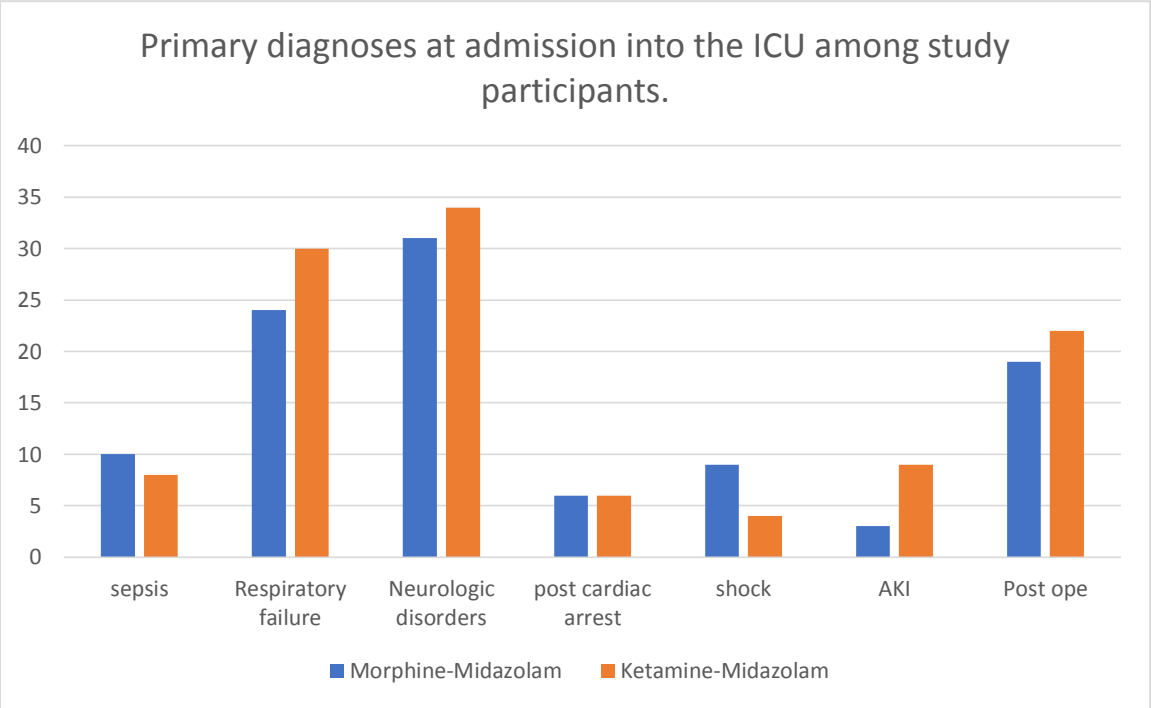
Group 1=Morphine-Midazolam, Group 2 =Ketamine-Midazolam

MEWS-Modified Early Warning Sign score; maximum score of 18, minimum of 0.

Prognostic factors included reason for admission to the ICU, diagnosis at admission, Modified Early Warning Sign and known co-morbidities at admission. There was no significant statistical difference in these factors between the two treatment arms as shown above.

The Ketamine-Midazolam group had more patients with documented acute kidney injury than the morphine-midazolam group, while the Morphine-Midazolam group had more patients in shock at admission. Other organ dysfunctions and primary diagnoses were comparably distributed between the two treatment arms as shown in the bar graph below.

Figure 2: Bar graph showing diagnoses at admission in to the ICU.



Participants had multiple organ dysfunctions, requiring support for more than one organ system as shown in the bar graph above. Respiratory failure and neurological disorders were the most common diagnoses among participants at admission into the intensive care unit.

Duration of mechanical ventilation, incidence of delirium and vasopressor requirements.

There was no statistically significant difference in duration of mechanical ventilation, incidence of delirium or incidence of delirium between the two study groups as shown in table 3. However, the Morphine-Midazolam group had higher mean arterial pressures recorded as worst vitals compared to the Ketamine-Midazolam group despite comparable incidence of vasopressor therapy throughout the follow up period.

Table 3:Composite data by days 3, 7 and 14 of follow up

Variable	N(percentage) or Mean±SD		p value
	Group 1	**Group 2**	
By day 3			
Mechanical ventilation/24hrs	20.5±5.0	21.3±4.4	0.375
Total IV fluids/24hrs	1.84±1.67	1.83±1.55	0.956
Presence of delirium	6(12.5)	12(22.2)	0.199
Average sedative infusion rate	2.06±1.25	2.22±1.44	0.573
Need for vasopressors	14(29.2)	13(24.1)	0.561
Need for additional sedatives	5(10.4)	7(13.0)	0.690
Worst vitals recorded			
Mean arterial pressure	103.2±20.2	94.8±21.1	0.295
SPO2	92.8±5.67	92.4±6.93	0.799
Respiratory rate	26.9±7.0	27.3±10.6	0.870
By day 7			
Mechanical ventilation time	20.8±4.2	20.8±4.3	0.988
Total IV fluid/24hrs	1.21±0.78	1.31±1.28	0.700
Presence of delirium	2(7.1)	4(12.5)	0.490
Average sedative infusion	1.07±0.81	1.37±1.37	0.329
Need for vasopressors	2(7.1)	6(18.8)	0.187
Need for additional sedatives	1(3.6)	4(12.5)	0.212
Worst vitals/24hrs			
Mean arterial pressures	100.8±14.9		87.6±16.1
0.173			
SPO2	93.2±4.87	92.4±5.0	0.560
Respiratory rate	27.2±7.5	25.1±5.5	0.396
By day 14			
Mechanical ventilation time	16.9±7.1	20.6±5.1	0.102
Total fluids/24hrs	0.87±0.74	0.94±1.0	0.840
Presence of delirium	0(0)	1(6.7)	0.294
Average sedative infusion	0.53±0.39	0.63±0.61	0.600
Need for vasopressors	0(0)	2(13.3)	0.131
Need for additional sedatives	1(6.25)	0(0)	0.325
Worst vitals/24hrs			
Mean arterial pressure	103.1±18.1	80.3±8.0	0.297
SPO2	94.8±2.17	94.0±3.50	0.546
Respiratory rate	27.4±6.3	25.7±2.3	0.614

Group 1=Morphine-Midazolam, Group 2=Ketamine-Midazolam

Study mixture administration and need for additional sedatives

The Ketamine-Midazolam group generally needed slightly higher infusion rates of the drug mixture, however that was no statistically significant throughout the follow up period. There is a slight trend towards more use additional sedatives in the Ketamine-Midazolam group by day 7 of follow up, 3.6% vs 12.5%, p=0.212.

Drug safety profile, Mortality rates and ICU length of stay.

Table 4:Mortality rates, ICU length of stay and adverse events in each study arm.

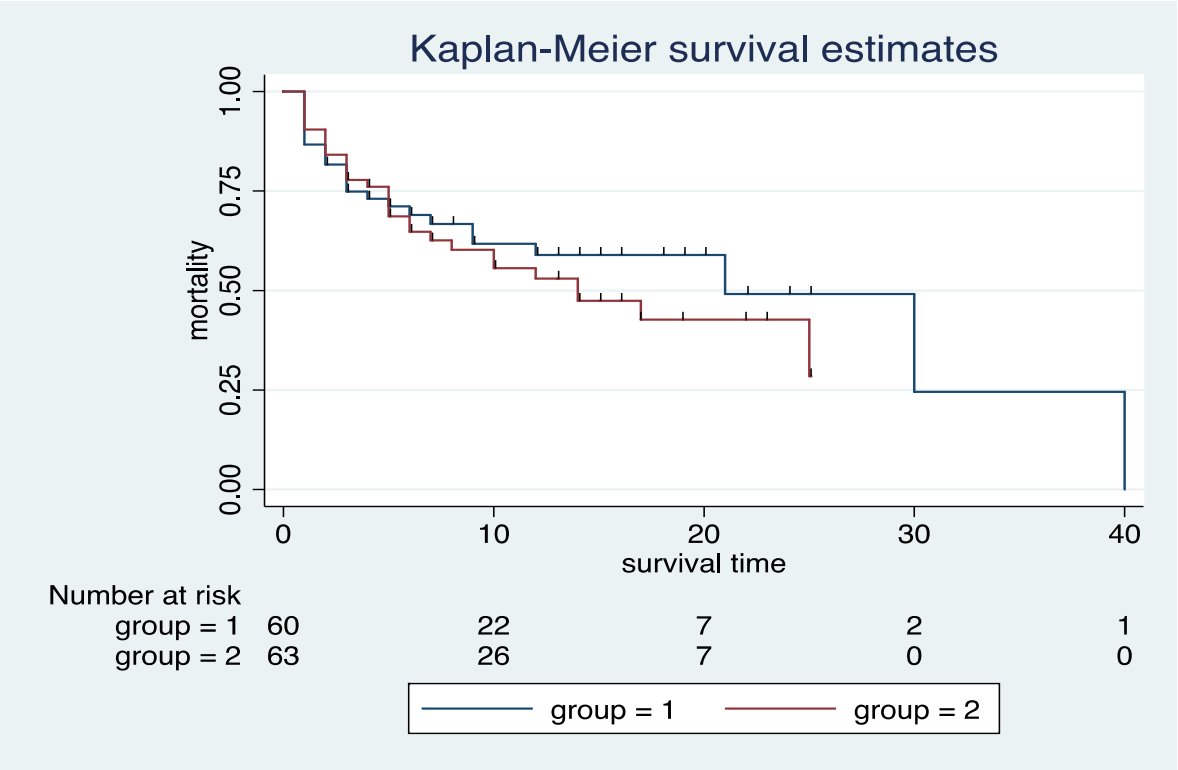
Variable	Group 1(N=60)	Group 2(N=64)	NNH/NNT	OR	p value
Mortality	24(43.6)	25(46.3)		0.91(0.42-1.9)	0
.768					
ICU length of stay	9.3±8.2	9.1±7.2			0.892
Adverse events					
Persistent arrythmias	2(3.5)	0(0)	29		0.243
Excessive salivation	5(8.6)	3(4.9)	27	3.9(0.61-11.56)	0.472
Agitation	0(0)	1(1.6)			63
0.327					
Constipation	1(1.7)	0(0)			59
0.303					
Hypotension	2 (3.5)	0(0)			29
0.243					
Respiratory depression	1(1.7)	0(0)	59		0.303
Excessive sedation	0(0)	1(1.6)	63		0.327

Group 1= Morphine-Midazolam, Group 2=Ketamine-Midazolam

Table 5 above shows there was no statistically significant difference in mortality rates or length of stay in the ICU between Midazolam-Morphine group and the Midazolam-Ketamine group.

The Midazolam- Morphine group reported more life-threatening adverse events including respiratory depression, persistent arrythmias and significant hypotension compared to the Ketamine-Midazolam group. However, the incidence of individual adverse events was not statistically significant between the two treatment arms.

Figure 3:Kaplan-Meier survival curve for the two treatment arms from recruitment to discharge from the intensive care unit.



Group 1=Morphine-Midazolam, Group 2=Ketamine-Midazolam.

IV fluid requirements, Mortality rate and Length of stay in the intensive care unit.

There were no significant differences in length of stay in the intensive care unit between the two groups, averaging out at 9.3±8.2 days in the Morphine-Midazolam group and 9.1±7.2 in the Ketamine-Midazolam group (p-0.892). Similarly, the Mortality rates were comparable between the two study groups at 43.6% in the Morphine-Midazolam group and 46.3% in the Ketamine-Midazolam group (p=0.768). The use of intravenous fluids was comparable, with p-values >0.7 throughout the follow up period.

CHAPTER FIVE: DISCUSSION

The use of ketamine for continuous sedation in the intensive care unit has been of considerable interest in the past decade or so, with the Society of Critical Care Medicine recommending it as an adjunctive sedative when needed in the PAD guidelines (Barr et al., 2013) (Devlin et al., 2018). Ketamine's dissociative effects and its effects on cerebral blood flow raised concerns about increased intracranial pressure, delirium and adverse events among ICU patients, prompting various studies to address these questions. (A. Bourgoin et al., 2003; Miller et al., 2011; Umunna et al., 2015; Whitman, Rhodes, Tellor, & Hampton, 2015) Most of these studies were of retrospective design or case reports, and the RCTs were not powered enough to address some of the concerns. However, they had positive reports of reduced inotropic support, better MAPs, airway tone and anti-inflammatory effects with Ketamine's use for sedation.(Elamin, Huges, & Drew, 2007; Kurdi et al., 2014; Whitman et al., 2015) This study therefore assessed superiority of Ketamine as an adjunct to Midazolam over Morphine-Midazolam for prolonged sedation (≥24hrs) in regards to duration of mechanical ventilation, vasopressor use and incidence of delirium.

There were no differences in baseline patient characteristics and prognostic factors such as age, gender, time in the intensive care unit prior to enrollment, modified early warning score and primary diagnoses between the two groups. More than 60% of patients were male in both treatment arms, and the ages were comparable at 41.5±17.9 vs 45.3±18.9, p=0.248. This study population is older than that used in the (A. Bourgoin et al., 2003) study, but younger than that in retrospective studies on ketamine use for adjunctive sedation in medical ICU patients. (Umunna et al., 2015) (Shurtleff, Radosevich, & Patanwala, 2018) (Patanwala et al., 2015)

In this study, the MEWS score was used as a marker of disease severity. This was due to multiple challenges in getting laboratory results and arterial blood gases which made use of, such as the APACHE II or SOFA score impractical in our setting. There was no significant statistical difference in MEWS scores between the two treatment arms. (Gardner-Thorpe, Love, Wrightson, Walsh, & Keeling, 2006) (Fullerton, Price, Silvey, Brace, & Perkins, 2012).

Similarly, patients were well randomized in terms of primary diagnoses/organ dysfunctions between the treatment arms. The Ketamine-Midazolam group had more patients with documented acute kidney injury, and the Morphine-Midazolam group got more patients with

documented shock at admission. However, there was no statistical difference of significance between the groups in terms of participants' primary diagnoses and co-morbidities.

Our findings show that Ketamine-Midazolam is not superior to Morphine-Midazolam for continuous sedation of critically ill patients in terms of duration of mechanical ventilation as initially reported(A. Bourgoin et al., 2003). There was no significant statistical difference between duration of mechanical ventilation in hours between the two treatment arms on both individual days and at composite data analysis by days 3, 7 or 14. Instead, we noted a trend towards longer duration of mechanical ventilation at comparison of composite data by day 14 in the Ketamine group (p=0.102). This is in agreement with findings from recent studies that compared ketamine to non-ketamine based sedation, which found less ventilator-free days with ketamine sedation (Reese, Sullivan, Boyer, & Mount, 2018; Shurtleff et al., 2018)

The incidence of hypotension requiring vasopressor use was not statistically significant between the two groups by day 3, day 7 and day 14. However, there were more patients on vasopressor therapy in the Ketamine group by day 7 and day 14. In addition, there was a consistent trend towards higher mean arterial pressures in the Morphine group, more pronounced by day 7 and day 14 of follow up (p=0.173 and 0.297).This is in contrast with findings from prior studies that showed trends to better mean arterial pressures and reduced vasopressor use with ketamine sedation (Reese et al., 2018) (A. Bourgoin et al., 2003) (Whitman et al., 2015). This could be explained theoretically by exhaustion of sympathetic mechanisms in critically ill patients, unmasking the myocardial depressant effects of ketamine with prolonged infusions. However, we cannot attribute these trends solely to Ketamine as we did not perform multivariate analysis for hypotension given the fact that the difference in incidence of hypotension between the two groups was not statistically significant.

There was no significant statistical difference in incidence of delirium between the Ketamine-Midazolam group compared to the Morphine-midazolam group at composite data analysis. This agrees with more recent studies done to determine effects of ketamine use for analgo-sedation on incidence and duration of delirium (Robinette et al., 2018) (Shurtleff et al., 2018). However, there were trends towards increased incidence of delirium in the Ketamine group by day 3 (12.5% vs 22.2%, p=0.199), but this became comparable to the Morphine group by day 7 (p=0.49). This could be related to more patients with acute kidney injury at admission being randomized into the Ketamine-Midazolam group, which studies have demonstrated to be an individual risk factor for delirium. (Bihorac & Hobson, 2017; Siew et al., 2017)

The use of Midazolam in both study groups may have altered differences on individual effects of Ketamine or Morphine on the duration of mechanical ventilation, incidence of delirium and length of stay in the intensive care unit according recent guidelines that recommend non-benzodiazepine-based sedatives. (Devlin et al., 2018) (Barr et al., 2013). (Benken & Goncharenko, 2016).

The trend towards lower intravenous fluid requirement for the Ketamine group noted in (A. Bourgoin et al., 2003)'s study was not reproduced in this study, possibly due to a larger sample size (124 versus 25) This could be also be related to the varied pathologies among participants in this study, some of which necessitate large volume fluid resuscitation as opposed to traumatic brain injury alone. (Aurélie Bourgoin et al., 2003)

The sedative infusion rates used were comparable, with no significant statistical difference in need for additional sedatives and need for additional analgesia between the two groups at composite data analysis. This is in agreement with prior findings affirming Ketamine's effectiveness for prolonged sedation in the intensive care unit. (Aurélie Bourgoin et al., 2003; M. et al., 2018; Umunna et al., 2015)

The length of stay in the intensive care unit was comparable between the two treatment groups. Similarly, there was no significant statistical difference in mortality between the two study groups., which is in line with what prior studies on ketamine sedation in the intensive care unit have found. (A. Bourgoin et al., 2003) (Reese et al., 2018; Robinette et al., 2018)However, both mortality rates and length of stay in the ICU were significantly longer in our study compared to earlier findings from observational studies among critically ill patients in our setting(Ttendo et al., 2016; W Dünser, M Towey, Amito, & Mer, 2016). This may be explained by the fact that our study criteria selected for considerably sicker patients given the requirement for prolonged sedation.

This study found the adverse event rate in the Ketamine-Midazolam group (5/64, 7.8%) to be lower than that in the Morphine-Midazolam group (9/60, 15%). The individual adverse events reported in the Ketamine-Midazolam group included excessive sedation (1/64), excessive salivation (3/64) and 1/64 with drug-related agitation. Life-threatening adverse events were more common in the Morphine-Midazolam group, and included persistent hypotension (2/60), respiratory depression (1/60) and persistent arrhythmias (2/60). These led to cessation of the study solutions for each patient and resuscitative measures in each case were initiated as needed. However, there was no statistically significant difference in

incidence of particular adverse events between the two treatment arms, just as reported by prior studies. (Umunna et al., 2015).

CONCLUSION

In conclusion, study results suggest that Ketamine-Midazolam use for prolonged analgo-sedation is not superior to Morphine-Midazolam in terms of duration of mechanical ventilation, incidence of hypotension necessitating vasopressor use or incidence of delirium. The study reaffirms the safety of ketamine use for prolonged sedation of patients in the intensive care unit, in view of reduced incidence of serious adverse events. However, there are slight trends towards increased duration of mechanical ventilation, incidence of delirium and vasopressor use among patients on Ketamine-Midazolam compared to Morphine-Midazolam.

RECOMMENDATION

Prospective studies comparing Ketamine use (without Midazolam) with conventional sedatives would be helpful in further addressing the question of its individual effect on duration of mechanical ventilation and incidence of delirium among critically ill patients.

REFERENCES

Adhikari, N. K., Fowler, R. A., Bhagwanjee, S., & Rubenfeld, G. D. (2010). Critical care and the global burden of critical illness in adults. *The Lancet, 376*(9749), 1339-1346.

Barr, J., Fraser, G. L., Puntillo, K., Ely, E. W., Gelinas, C., & Dasta, J. F. (2013). Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med, 41*. doi:10.1097/CCM.0b013e3182783b72

Benken, S. T., & Goncharenko, A. (2016). The Future of Intensive Care Unit Sedation A Report of Continuous Infusion Ketamine as an Alternative Sedative Agent. *Journal of pharmacy practice*, 0897190016646293.

Bihorac, A., & Hobson, C. (2017). Kidney and Brain, an Unbroken Chain: American Thoracic Society.

Bourgoin, A., Albanese, J., Wereszczynski, N., Charbit, M., Vialet, R., & Martin, C. (2003). Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. *Crit Care Med, 31*. doi:10.1097/01.ccm.0000044505.24727.16

Bourgoin, A., Albanèse, J., Wereszczynski, N., Charbit, M., Vialet, R., & Martin, C. (2003). Safety of sedation with ketamine in severe head injury patients: comparison with sufentanil. *Critical care medicine, 31*(3), 711-717.

Deiner, S., & Silverstein, J. H. (2009). Postoperative delirium and cognitive dysfunction. *BJA: British Journal of Anaesthesia, 103*(suppl_1), i41-i46. doi:10.1093/bja/aep291

Devlin, J. W., Skrobik, Y., Gélinas, C., Needham, D. M., Slooter, A. J., Pandharipande, P. P., . . . Rochwerg, B. (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical care medicine, 46*(9), e825-e873.

Dünser, M. W., Baelani, I., & Ganbold, L. (2006). A review and analysis of intensive care medicine in the least developed countries. *Critical care medicine, 34*(4), 1234-1242.

Elamin, E. M., Huges, L. F., & Drew, D. (2007). IS ketamine the right sedative for mechanically ventilated patients? *Chest, 132*(4_MeetingAbstracts), 574-574. doi:10.1378/chest.132.4_MeetingAbstracts.574

Fullerton, J. N., Price, C. L., Silvey, N. E., Brace, S. J., & Perkins, G. D. (2012). Is the Modified Early Warning Score (MEWS) superior to clinician judgement in detecting critical illness in the pre-hospital environment? *Resuscitation, 83*(5), 557-562.

Gardner-Thorpe, J., Love, N., Wrightson, J., Walsh, S., & Keeling, N. (2006). The value of Modified Early Warning Score (MEWS) in surgical in-patients: a prospective observational study. *The Annals of The Royal College of Surgeons of England, 88*(6), 571-575.

Gelissen, H. P., Epema, A. H., Henning, R. H., Krijnen, H. J., Hennis, P. J., & Den Hertog, A. (1996). Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle. *Anesthesiology: The Journal of the American Society of Anesthesiologists, 84*(2), 397-403.

Green, S., Andolfatto, G., & Krauss, B. (2015). Ketofol for procedural sedation revisited: pro and con. *Annals of emergency medicine, 65*(5), 489-491.

Green, S., Clem, K., & Rothrock, S. (1996). Ketamine safety profile in the developing world: survey of practitioners. *Academic emergency medicine: official journal of the Society for Academic Emergency Medicine, 3*(6), 598-604.

Ho, J. D., Smith, S. W., Nystrom, P. C., Dawes, D. M., Orozco, B. S., Cole, J. B., & Heegaard, W. G. (2013). Successful Management of Excited Delirium Syndrome with Prehospital Ketamine: Two Case Examples. *Prehospital Emergency Care, 17*(2), 274-279. doi:10.3109/10903127.2012.729129

Hudetz, J. A., Patterson, K. M., Iqbal, Z., Gandhi, S. D., Byrne, A. J., Hudetz, A. G., . . . Pagel, P. S. (2009). Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. *Journal of cardiothoracic and vascular anesthesia, 23*(5), 651-657.

Hughes, C. G., McGrane, S., & Pandharipande, P. P. (2012). Sedation in the intensive care setting. *Clinical Pharmacology : Advances and Applications, 4*, 53-63. doi:10.2147/CPAA.S26582

Johnstone, M. (1976). The cardiovascular effects of ketamine in man. *Anaesthesia, 31*(7), 873-882.

Kurdi, M., Theerth, K., & Deva, R. (2014). Ketamine: Current applications in anesthesia, pain, and critical care. *Anesthesia: Essays and Researches, 8*(3), 283-290. doi:10.4103/0259-1162.143110

Kwizera, A., Dünser, M., & Nakibuuka, J. (2012). National intensive care unit bed capacity and ICU patient characteristics in a low income country. *BMC research notes, 5*(1), 475.

Kwizera, A., Nakibuuka, J., Ssemogerere, L., Sendikadiwa, C., Obua, D., Kizito, S., . . . Nakasujja, N. (2015). Incidence and Risk Factors for Delirium among Mechanically Ventilated Patients in an African Intensive Care Setting: An Observational Multicenter Study. *Critical care research and practice, 2015*.

M., G. L., M., R. R., William, B., Marshall, B., Katherine, C., J., M. B., & Ian, B. (2018). Ketamine Infusion for Adjunct Sedation in Mechanically Ventilated Adults. *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 38*(2), 181-188. doi:doi:10.1002/phar.2065

Mazzeffi, M., Johnson, K., & Paciullo, C. (2015). Ketamine in adult cardiac surgery and the cardiac surgery Intensive Care Unit: An evidence-based clinical review. *Annals of cardiac anaesthesia, 18*(2), 202.

Miller, A., Jamin, C., & Elamin, E. (2011). Continuous intravenous infusion of ketamine for maintenance sedation. *Minerva Anestesiol, 77*(8), 812-820.

Mohrien, K. M., Jones, G. M., MacDermott, J. R., & Murphy, C. V. (2014). Remifentanil, ketamine, and fospropofol: a review of alterative continuous infusion agents for sedation in the critically ill. *Critical care nursing quarterly, 37*(2), 137-151.

Patanwala, A. E., Martin, J. R., & Erstad, B. L. (2015). Ketamine for Analgosedation in the Intensive Care Unit. *Journal of Intensive Care Medicine*, 0885066615620592. doi:10.1177/0885066615620592

Reese, J. M., Sullivan, V. F., Boyer, N. L., & Mount, C. A. (2018). A Non-Comparative Prospective Pilot Study of Ketamine for Sedation in Adult Septic Shock. *Military Medicine, 183*(11-12), e409-e413. doi:10.1093/milmed/usy121

Reuben J Strayer, L. S. N. (2008). Adverse events associated with ketamine for procedural sedation in adults. *The American Journal of Emergency Medicine, 26*(26), 985–1028. doi:10.1016/j.ajem.2007.12.005

Robinette, E., Weant, K., Hassig, T., Smith, R., & Field, L. (2018). 927: Effects Of Ketamine On Sedation And Delirium In Mechanically Ventilated Adults. *Critical care medicine, 46*(1), 447.

Sakata, R. K. (2010). Analgesia and sedation in intensive care unit. *Revista brasileira de anestesiologia, 60*(6), 653-658.

Shapiro, B. A., Warren, J., Egol, A. B., Greenbaum, D. M., Jacobi, J., Nasraway, S. A., . . . Stone, J. R. (1995). Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. *Critical care medicine, 23*(9), 1596-1600.

Shurtleff, V., Radosevich, J. J., & Patanwala, A. E. (2018). Comparison of Ketamine- Versus Nonketamine-Based Sedation on Delirium and Coma in the Intensive Care Unit. *Journal of Intensive Care Medicine*, 0885066618767619. doi:10.1177/0885066618767619

Siew, E. D., Fissell, W. H., Tripp, C. M., Blume, J. D., Wilson, M. D., Clark, A. J., . . . Girard, T. D. (2017). Acute Kidney Injury as a Risk Factor for Delirium and Coma during Critical Illness. *American journal of respiratory and critical care medicine, 195*(12), 1597-1607. doi:10.1164/rccm.201603-0476OC

Taniguchi, T., & Yamamoto, K. (2005). Anti-inflammatory effects of intravenous anesthetics on endotoxemia. *Mini reviews in medicinal chemistry, 5*(3), 241-245.

Ttendo, S. S., Was, A., Preston, M. A., Munyarugero, E., Kerry, V. B., & Firth, P. G. (2016). Retrospective Descriptive Study of an Intensive Care Unit at a Ugandan Regional Referral Hospital. *World Journal of Surgery, 40*(12), 2847-2856. doi:10.1007/s00268-016-3644-5

Umunna, B.-P., Tekwani, K., Barounis, D., Kettaneh, N., & Kulstad, E. (2015). Ketamine for continuous sedation of mechanically ventilated patients. *Journal of emergencies, trauma, and shock, 8*(1), 11.

W Dünser, M., M Towey, R., Amito, J., & Mer, M. (2016). Intensive care medicine in rural sub-Saharan Africa. *Anaesthesia, 72*. doi:10.1111/anae.13710

Whitman, C., Rhodes, H., Tellor, B., & Hampton, N. (2015). Continuous infusion ketamine for adjunctive sedation in medical intensive care unit patients: a case series. *Enliven: J Anesthesiol Crit Care Med, 2*(5), 1-5.

APPENDICES

APPENDIX I: STUDY COLLECTION TOOL.

1. Study number……
2. Study site: …….
3. Study group; A or B……
4. Date of admission……
5. Sex; Male/Female……
6. Age in years…….
7. Time in ICU before enrollment into the study……
8. What is/are the reasons for admission to the ICU?

   ……
   ……
   ……
   ……
9. Admission diagnoses

   ……
   ……
   ……
   ……
10. Where was the patient prior to admission?
    a) Accident and Emergency
    b) Ward
    c) Operating theatre

d) Transfer from another ICU

e)

11. MEWS score at admission (check appendix IV) …… ……

12. Co-morbidities;

a) HIV
b) Diabetes mellitus
c) Substance abuse
d) Hypertension
e) Mental illness
f) Malnutrition
g) Others (mention)……

13. Daily assessment/measurement records.

parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Mechanical ventilation hours/day														
Total intravenous fluid received in liters/24hrs														
Presence of Delirium (check appendix III) (yes/no)														
Average sedative infusion rate(mls/hr.)														

Need for vasopressor support; Y-yes OR N- no														
Need for additional sedative agent? (Y-yes or N-no)														
RASS at assessment (appendix II)														
Need for additional analgesic (yes or no)														
Time of day at assessment; D-day, N-night														
Worst vitals in 24 hours. (MAP, SPO2, RR, GCS)														

14. Was the patient discharged alive prior to end of 14 days? If yes,

    Date of discharge……
    …

    OR

    Date of death……

15. Where there any adverse effects necessitating treatment or study drug termination?

i. Persistent tachyarrhythmias (e.g. atrial fibrillation, SVTs, atrial flutter)
ii. Excessive salivation
iii. Drug related agitation
iv. Nausea and vomiting
v. Constipation

    Others (mention) ……..

16. If yes, what adverse events were attributed to the drug mixture?

Mixture A

……

……

……

……

……

……

…

Mixture B

……

……

……

……

……

…

……

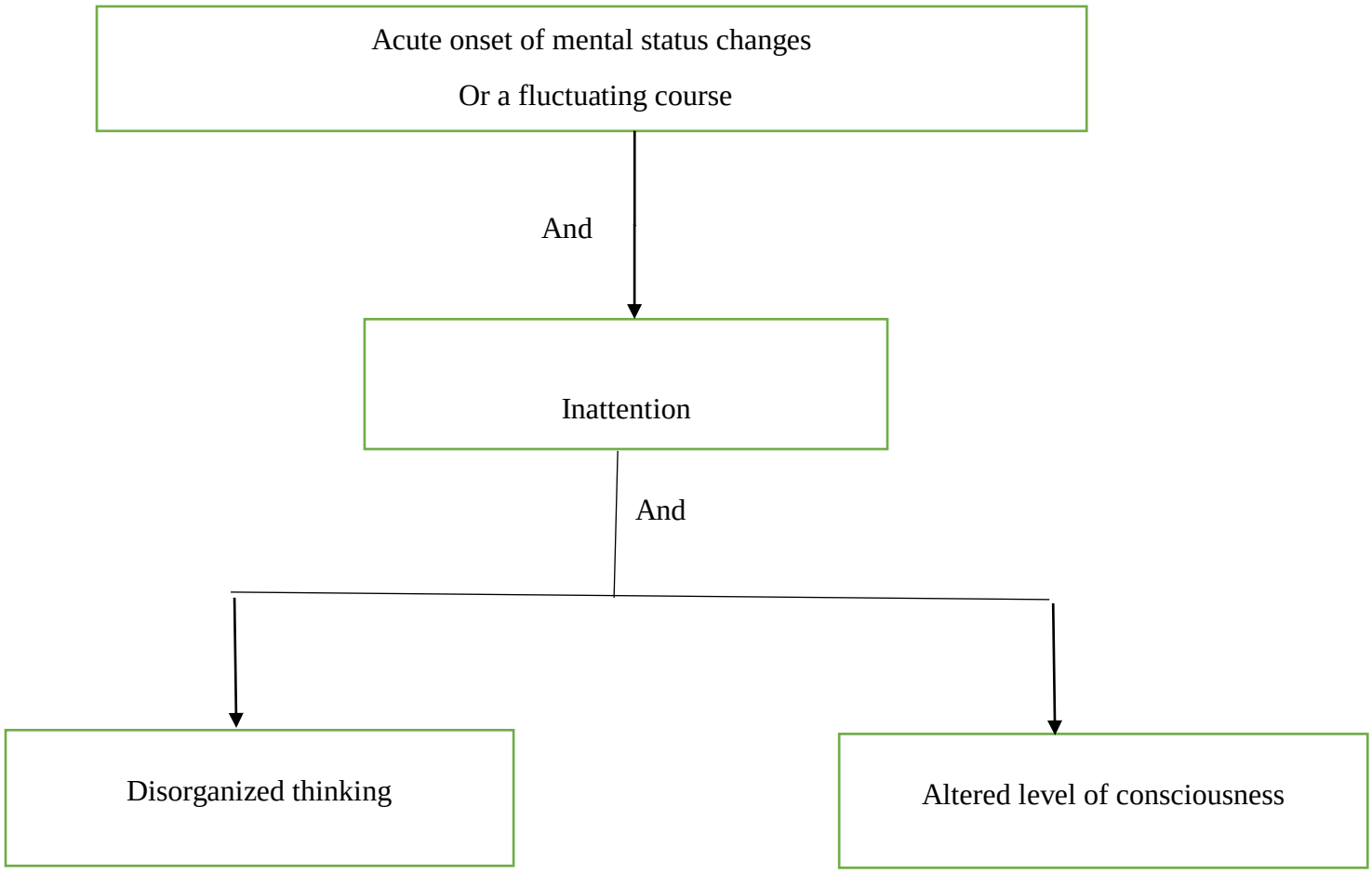
…

17. Treatment switched to……..

APPENDIX II: RICHMOND AGITATION-SEDATION SCORE

SCORE	**DESCRIPTION OF PATIENT'S MENTAL STATE**
+4	Combative, violent, immediate danger to staff
+3	Pulls or removes tube(s) or catheter(s); aggressive
+2	Frequent non-purposeful movement; fights ventilator
+1	Anxious, apprehensive, but movements not aggressive or vigorous
0	Alert and calm
-1	Not fully alert but has sustained (>10 sec) awakening (eye opening/ contact) to voice
-2	Drowsy; briefly (>10 sec) awakens to voice or physical stimulation
-3	Movement or eye opening (but no eye contact) to voice
-4	No response to voice, but movement or eye opening to physical stimulation
-5	No response to voice or physical Stimulation

APPENDIX III: CONFUSION ASSESSMENT METHOD-INTENSIVE CARE UNIT (CAM-ICU)



APPENDIX IV: THE MODIFIED EARLY WARNING SIGN SCORE

Score	**3**	**2**	**1**	**0**	**1**	**2**	**3**
Respiratory rate (min^{-1})		≤ 8		9–14	15–20	21–29	> 29
Heart rate (min^{-1})		≤ 40	41–50	51–100	101–110	111–129	> 129
Systolic BP (mmHg)	≤ 70	71–80	81–100	101–199		≥ 200	
Urine output (ml/kg/h)	Nil	< 0.5					
Temperature (°C)		≤ 35	35.1–36	36.1–38	38.1–38.5	≥ 38.6	
Neurological				Alert	Reacting to voice	Reacting to pain	Unresponsive

APPENDIX IX: TIME FRAME

ACTIVITY	MAY-JUL 2016	AUG –OCT 2016	NOV-DEC 2016	JAN –MAY 2017	JUN-DEC 2017	JAN –JUN 2019
Proposal writing, consultation of statistician	X	X				
Literature review	X	X	X			
Department presentations			X			
Assembling material				X	X	
Data collection					X	X
Data analysis					X	X
Report writing					X	X
Submit letter of intent to school of graduate studies						X

APPENDIX V: LETTER OF CONSENT

TITLE: KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.

Principal investigator: Dr Namata Christine

+256 772079499

chremma13@gmail.com

Institute: Makerere University College of Health Sciences, School of Medicine, Department of Anaesthesia

Introduction: My name is Dr Namata Christine. I am a medical doctor pursuing a master's degree in Anaesthesia and Critical care. I am carrying out a study on the **SUPERIORITY OF KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS SEDATION OF PATIENTS IN UGANDAN ICUs,** under supervision of lecturers with training in this field of health care attached to Makerere University.

Purpose of the study: The purpose of the study is to obtain information regarding the proposed superiority of ketamine-midazolam compared to use of morphine-midazolam for continuous sedation of critically ill patients in Ugandan intensive care units. This information will be help guide choice of sedative drugs for various patients in the intensive care unit. It will also provide baseline information for future studies involving critically ill patients in Uganda, as well as add to existing knowledge about various uses of ketamine.

Procedures: The patient's demographics including age, sex, address, reason for admission among other information will be collected at the time of admission to any of the intensive care units involved in the study. Upon recruitment, a participant will be randomised to receive either ketamine-midazolam or morphine-midazolam intravenously for the purpose of continuous sedation as prescribed by the attending physician.

This study will involve 165 participants, who will be followed up daily for the period of 14 days, or until discharge for information regarding duration of mechanical ventilation, incidence of delirium, vasopressor and fluid requirements as markers of treatment outcomes.

Possible risks and benefits: I understand that there may be risks associated with either interventions, including allergic reactions, hemodynamic disturbances, increased risk of delirium and others which are unforeseeable at the start. The investigators shall follow the recommended guidelines for initiation and maintenance of an adequate level of sedation for

each patient, enforced by the attending physician in the intensive care unit. Treatment of any side effects or adverse events attributed to drugs used in the study will be provided at no cost for the participant or their next of kin.

There is no direct financial or other benefit or cost for the participant from the study. This study is partially sponsored by Thrive Masters' Research Fellowship.

Results from this study will be communicated to both study participants and the public, and will help clinicians draw up recommendations regarding choice of sedatives for patients in the intensive care unit in our resource limited setting. Any new information that comes up during the study period will be communicated to the study participants or their next of kin by research assistants at subsequent daily visits by the research assistants.

Confidentiality: The information provided to me will be confidential. No body except research assistant and the principal investigator will have access to the information. A study number known to me and the study personnel will be used instead of my names. However, the data may be made accessible to the Ethics review committee and may be published in a journal or elsewhere without giving the participants' names or disclosing their identity.

My rights as a research volunteer: This form gives you information that will be discussed with you. Once you understand the study and agree to participate, you will be asked to sign this consent form. You understand that your participation in this study is entirely voluntary and you may decide to withdraw from the study at any time. If you decide to stop your participation at any time, all you would need to do is inform the research assistant that follows you up or the attending physician and your decision shall be respected. Such a decision will not affect your medical care or possible participation in future research studies in any way.

Ethical Issues:

This study has been approved by the School of Medicine Ethics and Research Committee. If you have any further questions concerning ethical issues in the conduct of this study, you may contact the School of Medicine and Ethics Committee Chairman (Assoc. Prof. Ponsiano Ocama 0772421190).

Volunteer's Consent

STATEMENT OF CONSENT

I _____ have been asked to participate in a research study entitled: **KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.**

The study has been explained to me, as have its risks and benefits. I understand that by signing this consent I accept on my/my patient's behalf to participate as a volunteer in the study and that I don't waive any of my legal rights, neither do I accept liability for anything.

I am appending my signature/thumbprint as my indication of consent to participate in the study.

_____ _____

(Signature/ thumbprint of participant or guardian) (Date)

Name of witness; _____

_____ _____

(Signature of witness) (Date)

Name of research assistant _____

_____ _____

(Signature of research assistant) (Date)

APPENDIX VI: ASSENT FORM 12 TO 14YRS

Introduction: My name is Dr Namata Christine. I am a medical doctor pursuing a master's degree in Anaesthesia and Critical care at Makerere University College of Health Sciences. I am carrying out a study on the proposed superiority of **KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS SEDATION OF PATIENTS IN UGANDAN ICUs,** under supervision of lecturers with training in this field of health care attached to Makerere University.

We are carrying out a study to find out whether changing one medication in the sedation of very ill patients like yourself who are admitted in the intensive care unit will improve your recovery or not. We are asking you to participate in this study, along with other patients because we do not know whether children your age would benefit more from one of the treatments compared to the others we commonly use for sedation. The study will involve 165 patients in total.

Participation does not require you to do any extra work, you will get the same treatment as the other patients that you will need but with one switch in the drugs used for intravenous sedation. This medication will be prescribed by the attending physician whenever they think the patient needs it, as with all the rest of treatments the participant will be receiving.

One person on the study team will check on you daily to see how you are progressing and you can talk to them about any concerns. For example, if you need support with breathing, we shall check to see how long you need that support for. We may also need to discuss a few things concerning your progress with the doctor in charge of your treatment.

You can ask questions about this study at any time during your participation, and any new information that arises during the course of the study will be communicated to you at the daily visits. You can address any concerns that arise after recruitment to whoever will be coming to check on you daily or the doctor attending to you. If you decide to stop your participation at any time, aall you would need to do is inform the research assistant that follows you up or the attending physician and your decision shall be respected. Your treatment shall continue as required by your attending doctor.

Whatever information we collect about you will be kept confidential, between you and the study team plus your guardian if you allow it. Study results will be communicated through public forums such as medical journals.

Any dangerous unforeseen reactions to any of the treatments used in the study will be noted, treatment immediately stopped and any additional medicines given free of charge to make sure you are safe and comfortable throughout the study.

This study is partially sponsored by Thrive Masters Research Fellowship.

If you have any further questions or concerns, please contact the lead investigator at any time; Dr Christine Namata. Her cell number is 0772079499. For any ethical concerns please contact the School of Medicine and Ethics Committee Chairman (Assoc. Prof. Ponsiano Ocama 0772421190), as the study has been approved by the above committee.

Name of participant or next of kin…….

Your

signature……

Date…….

Names of person obtaining consent…….

Signature…….

Date……..

Name of witness……

Signature……..

Date……..

APPENDIX VII: ASSENT FORM: 15 TO 17YRS

STUDY TITLE: KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.

Principal investigator: Dr Namata Christine

+256 772079499

chremma13@gmail.com

Institute: Makerere University College of Health Sciences, School of Medicine, Department of Anaesthesia

Introduction: My name is Dr Namata Christine. I am a medical doctor pursuing a master's degree in Anaesthesia and Critical care. I am carrying out a study on the proposed superiority of **KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS SEDATION OF PATIENTS IN UGANDAN ICUs,** under supervision by lecturers and specialists in this field attached under Makerere University.

Purpose of the study: The purpose of the study is to get information regarding the proposed superiority of ketamine-midazolam (one sedative option) compared to use of morphine-midazolam (alternative sedation option) for continuous sedation of critically ill patients in Ugandan intensive care units. This information will be help guide choice of sedative drugs for other patients in the intensive care unit in our setting. It will also provide baseline information for other studies in the future involving critically ill patients in Uganda.

Procedures: The participant's information including age, sex, address, reason for admission to the intensive care unit, among other information will be collected at the time of admission to any of the units involved in the study.

Participants will receive either ketamine-midazolam or morphine-midazolam as long as continuous sedation is prescribed by the attending physician. They will be followed up daily for information regarding duration of respiratory support, incidence of delirium, and requirement for hemodynamic support as markers of treatment outcomes. The study is to involve 165 participants in total.

Possible risks and benefits: There are some unforeseeable risks associated with either treatment option, including allergic reactions, body function disturbances, increased risk of episodes of confusion and others. The investigators shall follow the recommended guidelines for initiation and maintenance of an adequate level of sedation for each patient, and any disturbances shall be noted and solutions sought immediately free of financial cost.

Treatment of any side effects will also be provided at no cost for the participant or their family.

This study is partially sponsored by Thrive Masters' Research Fellowship. However, there is no direct financial or other benefit to the participant. Results will be provided to participants/next of kin and health workers through public forums like medical journals.

This will help doctors draw up recommendations regarding choice of sedatives for patients in the intensive care unit in our resource limited setting.

Confidentiality: The information provided to me will be kept confidential. No body except the principal investigator and study team will have access to the information. A study number known to me and the study personnel will be used instead of the name. However, the data may be made accessible to the Ethics review committee and may be published in a journal or elsewhere without giving the participants' names or disclosing their identity.

My rights as a study volunteer: This form gives you information that will be discussed with you. Once you understand the study and agree to participate, you will be asked to sign this form. You should understand that your participation in this study is entirely voluntary and you may decide to withdraw from the study at any time. All you would need to do is inform the research assistant that follows up or the attending physician, and your decision shall be respected. Such a decision will not affect your treatment or possible participation in future research studies in any way.

Ethical Issues: If you have any further questions concerning ethical issues in the conduct of this study, you may contact the School of Medicine and Ethics Committee Chairman (Assoc. Prof. Ponsiano Ocama 0772421190)

Volunteer's Consent

STATEMENT OF CONSENT

I _____ have been asked to participate in a research study entitled: **KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.**

The study has been explained to me as have its risks and benefits. I understand that by signing this consent I accept on my/my patient's behalf to participate as a volunteer in the study and that I don't waive any of my legal rights, neither do I accept liability for anything.

I am appending my signature/thumbprint as my indication of consent to participate in the study.

(Signature/ thumbprint of participant or guardian) (Date)

Name of witness

(Signature of witness) (Date)

Name of research assistant

Signature

Date

APPENDIX VIII: TRANSLATED CONSENT FORMS

EKIWANDIIKO KYOKUKKIRIZA OKWETABA MU KUNOONYEREZA. OMUTWE GWOKUNOONYEREZA: "EDDAGALA LYA 'KETAMINE-MIDAZOLAM KILUNGI OKUSINGA ELYA MORPHINE-MIDAZOLAM' KULWOKUSANYALAZA ABALWADDE MU BUSENGE BW'ABAYI."

Akulira okunoonyereza: Musawo Namata Christine

+256 772079499, chremma13@gmail.com

Etendekero: Makerere University College of Health Sciences, School of Medicine, Department of Anesthesia

Enyanjula: Erinya lyange nze Musawo Namata Christine. Ndi musawo era nsoma digili eyokubili mu byokulabilira abalwadde wamu nokubasilisa nga bagenda okulongoosebwa. Nkola okunoonyereza ku **"EDDAGALA LYA 'KETAMINE-MIDAZOLAM KILUNGI OKUSINGA ELYA MORPHINE-MIDAZOLAM' KULWOKUSANYALAZA ABALWADDE MU BUSENGE BW'ABAYI."** Nga ndabirirwa abasawo abakenkefu mu kujanjaba abalwadde abayi wano e Makerere.

Omugaso gwokunoonyereza: Omugaso gwokunoonyereza kwekufuna obubaka obukwata ku ddagala lya 'Ketamine-Midazolam kilungi okusinga elya morphine-midazolam' kulwokusanyalaza abalwadde mu busenge bw'abayi mu Uganda." Obubaka buno bujja kuyamba okulagilira eddagala elyokusirisa ettuufu kulw'abalwadde abalala mu bisenge byabayi mu kitundu kyaffe. Era bujja kuwa obubaka obutandikirwako eri okunoonyereza okulala mu biseera byomumaaso ebilimu abalwadde abayi mu Uganda. Okunoonyereza kuno kugenda kutunulira abalwadde 165 wonna wamu.

Emitendera

Ebikwata ku mulwadde omuli emyaka, obutonde, gyabeera, ensonga yokuweebwa ekitanda, wamu n'obubaka obulala bujja kukunganyizibwa mu kaseera kokuweebwa ekitanda mu kasenge konna akali mu kunoonyereza.

Abalwadde abanetaba mu kunoonyereza kuno basuubilwa okuwera 165 wonna, era nga buli omu kubbo ajja kujjanjabwa nga omusawo omukulu mu busenge buno obwa bayi bwanaba asazeewo. Enjawulo ejja kuva mu ddgala eri nakozesebwa oku kkakanya oba okwebasa omulwadde, ketamine-midazolam oba morphine-midazolam. Buli eyetaba mu kunoonyereza kuno ajja kulabibwa buli lunaku kulw'obubaka obukwata ku bbanga ly'okuyambibwako okussa, embeera y'okutabuka omutwe, wamu n'obwetaabu bw'okuyamba ku ntambula yomusaayi ng'ebilaga ebiva mu kujanjaba.

Akatyabaga wamu n'ebyokuganyurwa ebiyinza okuvaamu: Nkitegeera nti waliwo akatyabaga akali mu kubuuza ebibuuzo omuli embeera ya 'Allergy', okutaatanganya enkola yomubili, okweyongera kwakatyabaga k'okuwunga n'ebilala. Abanoonyereza bajja kugobera endagiliro ezilagibwa kulwokutandika wamu nokukuuma eddaala essaamusaamu ely'okusanyalaza mu buli mulwadde.

Tewali kuganyurwa kwabuliwo kulwokwetabamu kwonna okuva mu kunoonyereza. Okujanjaba ebiva mu kunoonyereza ebibi kujja kuweebwa ku bwerere eri eyetabyemu, era nga kuyambibwako ekitongole kya ThRIVE Masters Research Fellowship.

Ebinaava mu kunoonyereza kuno bijja kuyamba abasawo okufuna okulagila okukwata ku kusalawo ku kisanyalaza ekituufu eri abalwadde abali mu busenge bwabayi mu mbeera yaffe eyebikozesebwa ebitono.

Okukuuma ebyama: Obubaka obunampeebwa bujja kukuumibwa nga bwakyama. Tewali muntu yenna okujjako akulira okunoonyereza yajja okufuna ku bubaka. Namba yokunoonyereza emanyidwa nze wamu nali ku kunoonyereza yejja okukozesebwa mukifo kyerinya. Wabula obubaka bujja kufunibwako akakiiko akakwasisa empisa mu kunoonyereza era biyinza okufulumizibwa mu bitabo oba awalala wonna ng'amanyago oba ebikukwatako tebilagidwa.

Eddembe lyange ngeyetabye mu kunoonyereza: Ekiwandiiko kino kikuwa obubaka obujja okwogerwako wamu nawe. Bwotegeera okunoonyereza era nokkiriza okwetabamu, ojja kusabibwa okuteeka omukono ku kiwandiiko ky'okukkiriza kino. Olina okukimanya nti okwetabakwo mu kunoonyereza kuno kwa kyeyagalire era oyinza okuvaamu akadde konna. Okusalawo okwo tekujja kukosa nzijanjabayo oba okwetaba mu kunoonyereza okwomumaaso mu ngeri yonna.

Ebyempisa:

Bwoba olina ebibuuzo ebilala ebikwata ku nsonga z'empisa mu kukola okunoonyereza, oyinza okutuukirira sentebe wakakiiko akakwasisa empisa mu kunoonyereza mu somero ly'ebyeddagala akayitibwa 'School of Medicine Research Ethics Committee' sabakenkufu Ponsiano Ocama, ku ssimu 0772421190.

OLUNYIRIRI LWOKUKKIRIZA

Nze…….. nsabidwa okwetaba mu kunoonyereza okutuumidwa **"EDDAGALA LYA 'KETAMINE-MIDAZOLAM KILUNGI OKUSINGA ELYA MORPHINE-MIDAZOLAM' KULWOKUSANYALAZA ABALWADDE MU BUSENGE BW'ABAYI."**

Okunoonyereza kunyinyonyodwa wamu nakatyabaga n'emiganyulo. Ntegeera nti okuteeka omukono ku kiwandiiko kino nzikiriza kulw'omulwadde wange okwetaba mu kunoonyereza era nti sikugira ddembe lyange lyabwebanje, oba okweteekako omusango kulwensonga yonna.

Nteeka omukono gwange oba ekinkumu ng'ekilaga nti nzikirizza okwetaba mu kunoonyereza.

Omukono/ekinkumu kyeyetabyemu oba omukuza……..

Enaku zomwezi……..

Amanya g'abaddewo……

Omukono gw'abaddewo……

Enaku zomwezi……..

Amanya g'anonyereza……..

Omukono gwe……

Ennaku zomwezi……..

EKIWANDIIKO KYABAANA ABALI WAKATI WEMYAKA 15-17

EKYOKUKKIRIZA OKWETABA MU KUNOONYEREZA

OMUTWE GWOKUNOONYEREZA: "EDDAGALA LYA 'KETAMINE-MIDAZOLAM KILUNGI OKUSINGA ELYA MORPHINE-MIDAZOLAM' KULWOKUSANYALAZA ABALWADDE MU BUSENGE BW'ABAYI."

Etendekero: Makerere University College of Health Sciences, School of Medicine, Department of Anesthesia.

Enyanjula: Erinya lyange nze Musawo Namata Christine. Ndi musawo era nsoma digili eyokubili mu byokulabilira abalwadde wamu nokubasilisa nga bagenda okulongoosebwa. Nkola okunoonyereza ku **"EDDAGALA LYA 'KETAMINE-MIDAZOLAM KILUNGI OKUSINGA ELYA MORPHINE-MIDAZOLAM' KULWOKUSANYALAZA ABALWADDE MU BUSENGE BW'ABAYI."**

Omugaso gwokunoonyereza: Omugaso gwokunoonyereza kwekufuna obubaka obukwata ku ddagala lya 'Ketamine-Midazolam kilungi okusinga elya morphine-midazolam' kulwokusanyalaza abalwadde mu busenge bw'abayi mu Uganda." Obubaka buno bujja kuyamba okulagilira eddagala elyokusirisa ettuufu kulw'abalwadde abalala mu bisenge byabayi mu kitundu kyaffe. Era bujja kuwa obubaka obutandikirwako eri okunoonyereza okulala mu biseera byomumaaso ebilimu abalwadde abayi mu Uganda. Okunoonyereza kuno kugenda kutunulira abalwadde 165 wonna wamu.

Emitendera

Obubaka bweyetabyemu omuli emyaka, obutonde, gyabeera, ensonga yokuweebwa ekitanda mu kasenge kabayi, wamu n'obubaka obulala bujja kukunganyizibwa mu kaseera kokuweebwa ekitanda mu kasenge konna akali mu kunoonyereza.

Abeetebyemu bajja kulabibwa buli lunaku kulw'obubaka obukwata ku bbanga ly'okuyambibwako okussa, embeera y'okutabuka omutwe, wamu n'obwetaabu bw'okuyamba ku ntambula yomusaayi ng'ebilaga ebiva mu kujanjaba.

Akatyabaga wamu n'ebyokuganyurwa ebiyinza okuvaamu: Waliwo akatyabaga akekuusa ku kika kyenzijanjaba, omuli embeera ya 'Allergy', okutaatanganya enkola yomubili, okweyongera kwakatyabaga kokuwunga n'ebilala. Abanoonyereza bajja kugobera endagiliro ezilagibwa kulwokutandika wamu nokukuuma eddaala essaamusaamu ely'okusanyalaza mu buli mulwadde, era ebilala ebitawaanya bijja kulabibwa era embeera ezigonjoola zijja kunoonyezebwa.

Tewali kuganyurwa kwabuliwo kulwokwetabamu kwonna okuva mu kunoonyereza. Okujanjaba ebiva mu kunoonyereza ebibi kujja kuweebwa ku bwerere eri eyetabyemu oba enganda. Okunoonyereza kuno kuyambibwako Thrive Masters Research Fellowship.

Ebinaava mu kunoonyereza kuno bijja kuyamba abasawo okufuna okulagila okukwata ku kusalawo ku kisanyalaza ekituufu eri abalwadde abali mu busenge bwabayi mu mbeera yaffe eyebikozesebwa ebitono.

Okukuuma ebyama: Obubaka obunampeebwa bujja kukuumibwa nga bwakyama. Tewali muntu yenna okujjako akulira okunoonyereza era ekibinja ekinoonyereza kekijja okufuna ku bubaka. Namba yokunoonyereza emanyidwa nze wamu nali ku kunoonyereza yejja okukozesebwa mukifo kyerinya. Wabula obubaka bujja kufunibwako akakiiko akakwasisa empisa mu kunoonyereza era biyinza okufulumizibwa mu bitabo oba awalala wonna ng'amanyago oba ebikukwatako tebilagidwa.

Eddembe lyange ngeyetabye mu kunoonyereza: Ekiwandiiko kino kikuwa obubaka obujja okwogerwako wamu nawe. Bwotegeera okunoonyereza era nokkiriza okwetabamu, ojja kusabibwa okuteeka omukono ku kiwandiiko ky'okukkiriza kino. Olina okukimanya nti okwetabakwo mu kunoonyereza kuno kwa kyeyagalire era oyinza okuvaamu akadde konna. Okusalawo okwo tekujja kukosa nzijanjabayo oba okwetaba mu kunoonyereza okwomumaaso mu ngeri yonna.

Ebyempisa:

Bwoba olina ebibuuzo ebilala ebikwata ku nsonga z'empisa mu kukola okunoonyereza, oyinza okutuukirira sentebe wakakiiko akakwasisa empisa mu kunoonyereza mu somero ly'ebyeddagala akayitibwa 'School of Medicine Research Ethics Committee' sabakenkufu Ponsiano Ocama, ku ssimu 0772421190.

OLUNYIRIRI LWOKUKKIRIZA

Nze…….. nsabidwa okwetaba mu kunoonyereza okutuumidwa "……..."

Okunoonyereza kunyinyonyodwa wamu nakatyabaga n'emiganyulo. Ntegeera nti okuteeka omukono ku kiwandiiko kino nzikiriza kulw'omulwadde wange okwetaba mu kunoonyereza era nti sikugira ddembe lyange lyabwebanje, oba okweteekako omusango kulwensonga yonna.

Nteeka omukono gwange oba ekinkumu ng'ekilaga nti nzikirizza okwetaba mu kunoonyereza.

……

Omukono/ekinkumu kyeyetabyemu oba omukuza……..

Enaku zomwezi……..

Amanya g'abaddewo……

Omukono gw'abaddewo……

Enaku zomwezi……..

Amanya g'anonyereza……..

Omukono gwe……

Ennaku zomwezi……..

EKIWANDIIKO KYABAANA ABALI WAKATI WEMYAKA 12-14

EKYOKUKKIRIZA OKWETABA MU KUNOONYEREZA

Enyanjula. Erinya lyange nze musawo Namata Christine. Ndi musawo era nsoma digili eyokubiri mu kulabilila abalwadde wamu nokusilisa abalwadde abagenda okulongoosebwa. Nkola okunoonyereza ku "**EDDAGALA LYA 'KETAMINE-MIDAZOLAM KILUNGI OKUSINGA ELYA MORPHINE-MIDAZOLAM' KULWOKUSANYALAZA ABALWADDE MU BUSENGE BW'ABAYI."**

Tukola okunoonyereza okuzuula oba okukyusa ekika ekimu ekyeddagala mu kujanjaba abalwadde abayi nga gwe abaweebwa ebitanda mu kasenge kabayi kiyinza okwongera ku kuwonakwo. Okunoonyereza kuno kugenda kutunulira abalwadde 165 wonna wamu.

Tukusaba okwetaba mu kunoonyereza kuno kubanga tetumanyi oba abaana abemyakagyo bandiganyurwa enyo mu nzijanjaba ezimu okugerageranyizibwa n'endala gyetutela okukozesa

Okwetabamu tekukwetaagisa kukola mulimu mulala, ojja kufuna obujanjabi bwebumu ng'abalwadde abalala bw'onoofuna naye okukyusa kweddagala kumu kujja kozesebwa.

Omuntu omu ku kibinja ekinoonyereza ajja kukukeberako buli lunaku okulaba engeri gyolimu era oyinza okwogerako nabo ku nsonga zonna. Okugeza, bwoba wetaaga obuyambi okussa, tujja kukebera tulabe bbangaki lyewetaaga obuyambi obwo. Era tuyinza okwetaaga okwogerako n'omusawo akwasaganya ebyokukujanjaba ku ngeri gyolimu.

Oyinza okubuuza ebibuuzo ebikwata ku kunoonyereza kuno akadde konna mu kwetabaamukwo. Oyinza okutuukirira yenna anaba ajja okukukeberako buli lunaku oba omusawo akujanjaba. Bwosalawo okukomya okwetabamukwo akadde konna, oyinza okutubuulira era tujja kukolanga bwoyagala nga tewali buzibu bwonna. Obujanjabibwo bujja kugenda mumaaso nga bwekyetaagibwa omusawo wo akujanjaba.

Tewali kuganyurwa kwabuliwo kulwokwetabamu kwonna okuva mu kunoonyereza. Okujanjaba ebiva mu kunoonyereza ebibi kujja kuweebwa ku bwerere eri eyetabyemu oba enganda. Okunoonyereza kuno kuyambibwako Thrive Masters Research Fellowship.

Obubaka bwonna bwetunaakunganya obukukwatako bujja kukuumibwa mu kyama, wakatiwo n'ekibinja ekinoonyereza wamu n'omukuzawo bwoba okikkirizza.

Ebinaava mu bujanjabi ebyobulabe ebikozesebwa mu kunoonyereza bijja kwekaanyizibwa, obujanjabi bukomezebwe bunnambiro era eddagala eddala liweebwe okukakasa nti oli bulungi akadde konna.

Bwoba olinayo ebibuuzo ebilala, bambi tuukilila akulira okunoonyereza akadde konna , musawo Christine Namata. Essimuye eli 0772079499. Ku nsonga zonna ezekuusa ku mpisa mu kunoonyereza, tuukirira sentebe wakakiiko akavunaanyizibwa ku byempisa wamu nokunoonyereza akayitibwa 'School of Medicine Research Ethics Committee', sabakenkufu Ponsiano Ocama ku ssimu 0772421190

Omukono gwo…….

Ennaku zomwezi……

Amanya g'abaddewo……

Omukono gw'abaddewo……

Enaku zomwezi……..

Amanya g'anonyereza……..

Omukono gwe……

Ennaku zomwezi……..

APPENDIX V: RUNYANKOLE CONSENT FORMS.

EBALUHA YOKUSHABA OLUSYA.

OMUTWE; KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.

(OMIBAZI KETAMINE-MIDAZOLAM NNESINGA MORPHINE-MIDAZOLAM OMU KKU BYAMISA ABARWEIRE OMUBUSHENGYE BWA ABARWEIRE MUNONGA OMURI UGANDA)

OMUCHONDOZI OMUKULU. DR NAMATA CHRISTINE.

+256772079499

Chremma13@gmail.com

Itendekyero. Makerere University College of Health Sciences, School of Medicine, Department of Anaesthesia

Okwanjura.

Izinna ndi Dr Namata Christine. Ndi omushahoo wa abantu kandi ndi kushoma Masters degree mu Anaesthesia and Critical care. Ndi kuchondoza ha **SUPERIORITY OF KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS SEDATION OF PATIENTS IN UGANDAN ICUs, ahansi yobureberezi** bwa abashomesa abashaho baine obukugu mmu mwanya gwa anaesthesia (abashaho abaku shanyaraza omukushemeza) abakukora Makerere University.

Omugasho gwo kuchondoza. Omugasho gwo kuchondoza oku nokuboona amagezi agakwasire ahamani gga emibazi ketamine nna midazolam wageraganisa nnano okukoresa emibazi morphine nna midazolam omukubyamisa abarweire abarikubi munonga omu intensive care units zza Uganda. Amagezi agga nigaza ku yamba omu abashaho omu ku torana omubazi ogwo kukozesa ahabarweire abo. Kandi nni kiza kuha amagezi agarayambe omumishomo yanyensya ahabarweire abarikubi omu Uganda nanokwongera migasho ya omubazi gwa ketamine.

Engederwaho. Ebikukwata aha barweire ka emyaka, oburugo, eshonga eyokumuha ekitanda nna yaba ari omukazi nari omushaija nane ebindi, amagezi agga negaza kurundanwa aha kwijja kwomurwire kumuha ekitanda.

Bamara kumutamu omu kuchodoza omurweire nniba mutoranna kubonna emibazi ketamine-midazolam neinga morphine –midazolam zirikurabira omumisi kwendaggu abyame okurugirira aha ekyomushaho arasharemu.

Okukyodonza oku nikuza kwetagga abarweire kikuki kanga na batano. Nibaza kukuratirwa buriezoba kumara esande eibiri nninga ahubarasiburwe kwenda kumanya obwire obubamazire ahakwoma ekyokwisya yaba yatungireho akahugye, yaba ayetagire amaize nane emibazi yokurinda pressure kka ekyokureberaho omubujjajjabi.

Ebizibu nane ebirungi ebikubasa kurugamu.

Oyinne kwetegereza ggu hariho ebizibu kubasa kubaho ahabwokukozesa emibazi eggi koku gira efuumbi, pressure kuteganisibwa, okugira akahujje nane ebindi ebitakumawya ahakutandika. Abakyondozi nibaza kukuratira ebihandiko aha kutandika ananoku gumizamu okubyamisa abarweire koku omushaho arasharemu. Obujjanjabi bwe ebizibu nibuza kuhebwa ahabwabusha.

Tihariho kushsurwa ninga okugobba kwenna okirimu omukweshumba omukukyodoza oku.

Okushoma oku niku shagikwa Thrive Masters Research Fellowship.

Ebirarugye omukukyondoza oku nibiza kugambirwa abarweire hamwe nabantu abandi haza beyambe abashaho kukora ebihandiko ebirayambe omuku sharamu emibaziki eziriku koragye omukubyamisa abarweire omumarwariro agateine ebikozeso ebirikumara. Ebibyonna nibiza kuba nibigambirwa abarweire narishe abanyabuzare buri obu omushaho arabarebe.

Ebihama.

Burikimwe eki muraganbire abashaho nikiguma kiri ekihama. Tihariho odijjo omuntuwenna kwihaho omukyodozi omukuru nana abayambi beye arabimanye. Enyugutta erikumawya omukyodozi nneza kukoresebwa omumwanya gwa ezinna.konka Ethics review committee nnezza kubanebimanya kandi ebirarugemu nibizza kuhandikwa omumpapura zzobushaho konka nabwe amazina ggabarweire tigaramaywe,

Obugabebwawe komurweire.

Ekihandiko eki nekyereka ekyokwetagga kumamya. Kubaramare kukushobororera okikiriza kweshumba omurushomo, noshabwa kuta omukono aharupapura oru, oyetegereze ngu okweshumbamu kwawe omukukyodoza oku nahabwokweyendera kandi norugamu ahuwayendera. Wakunda kurugamu omukukyondoza oku, nogabira abakyodozi nana abashaho abakukureberera lero okusharamu kwawe nikuza kukuratirwa, okusharamu oku tikurachumbagizze obujjanjabi nari kweshumba omukukyodoza okundi.

Ebikwatereine nemigyenzo.

Okukyondoza oku kutungire orusya kurugga aha eishomero eryo obushaho ethics and research committee. Wabba oyine ebibuzo ebindi ahabikwateriene nane emichwe

nemitwarize eyokuchondoza, nobasa to hikirira eishomero eryo obushaho nana ethics and research committee chairman. (Associate professor Ponsiano Ocama 0772421190).

Volunteer's Consent

Ekihandiko ekyokwikiriza.

Nashabwa kweshumba omukukyondoza okwesirwe; **KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.**

Okukyondoza kwashobororwa hamwe nane ebirungi nari obuzibu oburimu. nayetegereza ggu kutekaho omukono nikimanyisa ggu nayikiriza, nari nayikiriza ahabwomurwire wangye kko owayehayo mukukyodoza kandi tina hayo obugabe bwangye ninga kwikiriza okufferwa nari ebizibu byonna.

Nataho omukono nari ekikumu kwereka ggu nayikiriza kuza mukukyondoza oku.

……..……

……

(Omukono ninga ekiikumu kyangye / omunyabuzare) (Ebiro ebyokwezi)

Ezina eryo omujjurizi; …….

…….. ……..

…….

(Omukono gwo omujjurizi) (Ebiro ebyokwezi)

Ezinna eryomukyodonzi.....

……..

(Omukono gwomukyodozi) (Ebiro ebyokwezi)

APPENDIX VI: ASSENT FORM 12 TO 14YRS

Ebaruha eyorusya eyaba emyaka 12 kuhika 14

Okwanjura.

Izinna ndi Dr Namata Christine. Ndi omushahoo wa abantu kandi ndi kushoma masters degree mu Anaesthesia and Critical care. Ndi kuchondoza ha SUPERIORITY OF KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS SEDATION OF PATIENTS IN UGANDAN ICUs,

(OMIBAZI KETAMINE-MIDAZOLAM NNESINGA MORPHINE-MIDAZOLAM OMU KKU BYAMISA ABARWEIRE OMUBUSHENGYE BWA ABARWEIRE MUNONGA OMURI UGANDA)

Ahansi yobureberezi bwa abashomesa abashaho baine obukugu mmu mwanya gwa anaesthesia (abashaho abaku shanyaraza omukushemeza) abakukora Makerere University.

Turikukyodoza yabba kuhindura omubazi ggumwe aha ezibarikukozesa omukubyamisa abarweire kiewe abari ahakitanda omu intensive care unit nikiyamba omukukira shuba ninga. Nitukushaba oyeshumbe omukushoma oku nana abarweire abandi ahabwokuba titurikumanya yabba abana aha myaka yawe nibagayirwamu omukukozesa omubazi ggumwe nari ogundi omuri eyiturikukozesa kubyamisa abarweire. Okukyodoza oku nikuza kubamu abarweire eigana nkaga na batanno.

Okwejjunbamu tikurakuhe emirimo eyindi kandi noza kuboona obujjanjjabi kabandi kureka omubazi gumwe niguzza kuhindurwa. Omubazzi niguzza kuhandikwa omushaho wawe yyasharamu ggu nogwetagga nanne emibazi eyindi eyi orabe nno ntungga.

Omukyondozi omwe naza kubba naku shura buri eizoba kureba koku ori kandi nobasa kumugambire ekirikukuteganiesa kyona. Ekyokureberaho, wannoyetenga kuyambwa omukwiesya nnitukyebera ebihaha byawe kureba nokwetanga kumara obwireki. Nituba kandi nitwetagga kugamba nana abashaho bawe aha mpidahinduka zzona wori ahamibazzi.

Nobasa kubuza ebibuzo ahabikwatireinne nano okukyodoza oku obwire bwonna kandi ebirarugyemu omumushomo oggu nibiza kuku gganbirwa buri eizoba. Woyinna ekirikuteganaisa nobasa kukigambira omushaho arayijje kuku kyeberaho. Washaramu ku rugamu omumushomo oggu, oyetagissa kugambira omukyondozi arikukufaho ninga omushaho wawe kandi okusharaho kwawe nikuza kukuratirwa. Obujjanjabi nibugumizamu koku omushahowawe ari kusharamu.

Burikintu ki barajjure ninga eki oratugambire nikiza kubba kiri ekihama kikumanwya abakyodozi hamwe na abanyabuzare wakikunda. Ebirarugyemu omukukyondoza nibiza kurangwa omu baruha zza obushaho.

Omubazi gwakukora kubi nikiza kuhandikwa lero omubazi kurekyerwe aho kandi emibazi eyindi eyaretagisse neza kubba eyabusha kurebeka ggu origye omumumwanya gwokukyondoza.

Okukyondoza oku nikushagikwa Thrive Masters Research Fellowship.

Waba oyinne ebibuzzonari ekirikuteganaisa, hikirira omukyondozi omukuru eshaha yonna; omushaho doctor Christine Namata. Esimu 0772079499. Woo yinne ekirikukuteganisa ahamitwarizze nari emichwe hikirira eishomero eryo obushaho nana Ethics Committee Chairman (Assoc. Prof. Ponsiano Ocama 0772421190), habwokushanga ggu nibo bahire orusya gwoku kyondoza oku.

Eizinna eryo omurweire ninga……..
omunyabuzare.....

Omukonno gwawe.....

Eizoba eryo kwezi.....

Eizina eryo omukyondozi.....

Omukonno.....
.....

Eizoba eryo
kwezi.....

Eizina eyro omujjurizi.....

Omukonno ogwo omujjurizi.....

Eizoba eryo kwezi.....

ASSENT FORM: 15 TO 17YRS

Ebaruha eyokushaba orusya ahabwe emyaka 15 kuhika 17

Omutwe ogw'okukyondoza:

KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.

(OMIBAZI KETAMINE-MIDAZOLAM NNESINGA MORPHINE-MIDAZOLAM OMU KKU BYAMISA ABARWEIRE OMUBUSHENGYE BWA ABARWEIRE MUNONGA OMURI UGANDA)

Omukyodozi omukuru: Dr Namata Christine

+256 772079499

chremma13@gmail.com

Eitendekyero: Makerere University College of Health Sciences, School of Medicine, Department of Anaesthesia

Okwanjura.

Izinna ndi Dr Namata Christine. Ndi omushahoo wa abantu kandi ndi kushoma Master's degree mu Anaesthesia and Critical care. Ndi kuchondoza ha **SUPERIORITY OF KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS SEDATION OF PATIENTS IN UGANDAN ICUs,**

(OMIBAZI KETAMINE-MIDAZOLAM NNESINGA MORPHINE-MIDAZOLAM OMU KKU BYAMISA ABARWEIRE OMUBUSHENGYE BWA ABARWEIRE MUNONGA OMURI UGANDA)

Ahansi yobureberezi bwa abashomesa abashaho baine obukugu mmu mwanya gwa anaesthesia (abashaho abaku shanyaraza omukushemeza) abakukora Makerere University.

Omugasho gwo kuchondoza. Omugasho gwo kuchondoza oku nokuboona amagezi agakwasire ahamani gga emibazi Ketamine nna Midazolam wagerageranisa nnano okukoresa emibazi morphine nna midazolam omukubyamisa abarweire abarikubi munonga omu Intensive Care Units zza Uganda. Amagezi agga nigaza ku yamba omu abashaho omu ku torana omubazi ogwo kukozesa ahabarweire abo. Kandi nni kiza kuha amagezi agarayambe omumishomo yanyensya ahabarweire abarikubi omu Uganda nanokwongera migasho ya omubazi gwa ketamine.

Engederwaho. Ebikukwata aha barweire ka emyaka, oburugo, eshonga eyokumuha ekitanda nna yaba ari omukazi nari omushaija nane ebindi, amagezi agga negaza kurundanwa aha kwijja kwomurwire kumuha ekitanda.

Bamara kumutamu omu kuchodoza omurweire nniba mutoranna kubonna emibazi ketamine-midazolam neinga morphine –midazolam zirikurabira omumisi kwendaggu abyame okurugirira aha ekyomushaho arasharemu.

Okukyodonza oku nikuza kwetagga abarweire kikuki kanga na batano. Nibaza kukuratirwa buriezoba kumara esande eibiri nninga ahubarasiburwe kwenda kumanya obwire obubamazire ahakwoma ekyokwisya yaba yatungireho akahugye, yaba ayetagire amaize nane emibazi yokurinda pressure kka ekyokureberaho omubujjajjabi.

Ebizibu nane ebirungi ebikubasa kurugamu.

Oyinne kwetegereza ggu hariho ebizibu kubasa kubaho ahabwokukozesa emibazi eggi koku gira efuumbi, pressure kuteganisibwa, okugira akahujje nane ebindi ebitakumawya ahakutandika. Abakyondozi nibaza kukuratira ebihandiko aha kutandika ananoku gumizamu okubyamisa abarweire koku omushaho arasharemu. Obujjanjabi bwe ebizibu nibuza kuhebwa ahabwabusha.

Tihariho kushsurwa ninga okugobba kwenna okirimu omukweshumba omukukyodoza oku.

Okushoma oku niku shagikwa Thrive Masters Research Fellowship.

Ebirarugye omukukyondoza oku nibiza kugambirwa abarweire hamwe nabantu abandi haza beyambe abashaho kukora ebihandiko ebirayambe omuku sharamu emibaziki eziriku koragye omukubyamisa abarweire omumarwariro agateine ebikozeso ebirikumara. Ebibyonna nibiza kuba nibigambirwa abarweire narishe abanyabuzare buri obu omushaho arabarebe.

Ebihama.

Burikimwe eki muraganbire abashaho nikiguma kiri ekihama. Tihariho odijjo omuntuwenna kwihaho omukyodozi omukuru nana abayambi beye arabimanye. Enyugutta erikumawya omukyodozi nneza kukoresebwa omumwanya gwa ezinna.konka Ethics review committee nnezza kubanebimanya kandi ebirarugemu nibizza kuhandikwa omumpapura zzobushaho konka nabwe amazina ggabarweire tigaramaywe.

Obugabebwawe komurweire.

Ekihandiko eki nekyereka ekyokwetagga kumamya. Kubaramare kukushobororera okikiriza kweshumba omurushomo, noshabwa kuta omukono aharupapura oru, oyetegereze ngu okweshumbamu kwawe omukukyodoza oku nahabwokweyendera kandi norugamu

ahuwayendera. Wakunda kurugamu omukukyondoza oku, nogabira abakyodozi nana abashaho abakukureberera lero okusharamu kwawe nikuza kukuratirwa, okusharamu oku tikurachumbagizze obujjanjabi nari kweshumba omukukyodoza okundi.

Ebikwatereine nemigyenzo.

Okukyondoza oku kutungire orusya kurugga aha eishomero eryo obushaho ethics and research committee. Wabba oyine ebibuzo ebindi ahabikwateriene nane emichwe nemitwarize eyokuchondoza, nobasa to hikirira eishomero eryo obushaho nana ethics and research committee chairman. (Associate professor Ponsiano Ocama 0772421190).

Volunteer's Consent

Ekihandiko ekyokwikiriza.

Nashabwa kweshumba omukukyondoza okwesirwe; **KETAMINE-MIDAZOLAM VERSUS MORPHINE-MIDAZOLAM FOR CONTINOUS PATIENT SEDATION IN INTENSIVE CARE UNITS IN UGANDA. A RANDOMISED CONTROLLED TRIAL.**

Okukyondoza kwashobororwa hamwe nane ebirungi nari obuzibu oburimu nayetegereza ggu kutekaho omukono nikimanyisa ggu nayikiriza, nari nayikiriza ahabwomurwire wangye kko owayehayo mukukyodoza kandi tina hayo obugabe bwangye ninga kwikiriza okufferwa nari ebizibu byonna.

Nataho omukono nari ekikumu kwereka ggu nayikiriza kuza mukukyondoza oku.

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(Omukono ninga ekiikumu kyangye / omunyabuzare) (Ebiro ebyokwezi)

Ezina eryo omujjurizi; …….

…… ……..

(Omukono gwo omujjurizi) (Ebiro ebyokwezi)

Ezinna eryomukyodonzi.....

(Omukono gwomukyodozi) (Ebiro ebyokwezi)