LOW DOSE COMBINATION OF MORPHINE AND KETAMINE VERSUS STANDARD DOSE MORPHINE ALONE IN PAIN CONTROL DURING CHANGE OF DRESSING IN ADULT BURN PATIENTS. A PARALLEL GROUP, RANDOMIZED CONTROL TRIAL

THIS DISSERTATION IS SUBMITTED IN PART FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN ANAESTHESIOLOGY, UNIVERSITY OF NAIROBI

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DECLARATION

I declare that this dissertation does not incorporate, without acknowledgement, any material previously submitted for a degree or diploma in any university; and that to the best of my knowledge it does not contain any material previously published or written by another except where due reference has been made in the text.

The editorial assistance provided to me has in no way added to the substance of my dissertation which is the product of my own research endeavours.

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This dissertation has been submitted for the degree of Master of Medicine in Anaesthesiology with our approval as University supervisors.

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DEDICATION

To my beloved parents Naftali Mose and Jael Njoki who believed in my ability to become a medical doctor since my childhood and their invaluable support.

To my beloved wife Eunice and my daughter Kayla for their moral support and encouragement through this level of specialization in my medical career.

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LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CNS: Central Nervous System

FLACC: Face, Legs, Activity, Cry, Consolability

ICP: Intra-cranial Pressure

IM: Intramuscular

IOP: Intra-ocular Pressure

IV: Intravenous

KNH: Kenyatta National Hospital

mg/kg: Milligrams per kilogram

MTRH: Moi Teaching and Referral Hospital

NMDA: N-Methyl-D-Aspartate

NPO: Nil per oral

PCIN: Patient Controlled Intra Nasal

PI: Principal Investigator

TBSA: Total Burn Surface Area

UoN: University of Nairobi

VAS: Visual Analog Scale

VR: Virtual Reality

TABLE OF CONTENTS

ABSTRACT

Background: Burn injuries occur when the skin is exposed to excessive heat with resultant extensive tissue damage. A cardinal element in the management of burn injuries is the performance of change of dressing that normally results in excruciating pain. Health care providers thus have a responsibility to mitigate this pain using either pharmacological or non-pharmacological means.

Research objective and hypothesis: This study aimed to establish the effect of a combination of low dose morphine and ketamine compared to standard dose morphine alone on pain control during dressing change in adult burn patients. It hypothesized that the response to a combination of ketamine and morphine is clinically inferior to the response to morphine alone against an alternative that it is clinically non - inferior.

Methodology: This study was a Non-Inferiority Randomized Controlled Trial consisting of a total of 100 adult subjects randomized into two parallel groups. It was conducted at Kenyatta National Hospital Burns Unit and Ward 4D. Statistical Analysis involved fitting linear regression models, model building and verification of model assumptions in SAS 9.4 and R Studio version 3.1.1 (2014-07-10). Ethical clearance was obtained from Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee.

Results: A total of 100 subjects were enrolled into this study and randomized into the control and treatment arms. Comparison of pain scores between the control and treatment arms revealed pain control in the low dose ketamine/morphine combination was non inferior to standard dose morphine alone. In addition, the low dose ketamine/morphine combination experienced more adverse effects compared to the standard dose morphine alone group. However, most of the adverse effects were minor and could be easily mitigated.

1. INTRODUCTION

Burns occur when the skin is exposed to heat either from fire or hot liquids, high voltage electricity, corrosive chemicals, or radiation. Burns are further classified according to the severity of tissue damage: [14]

1. First degree burns: Affect only the epidermis causing pain and hyperemia.
2. Second degree burns: Involve both the epidermis and dermis causing pain, hyperemia and blisters that may ooze. Deep second degree burns may progress to third degree burns over the course of time.
3. Third degree burns: Involve both the epidermis and dermis and also damages the underlying muscles, and tendons. The burn site appears pale and charred. There is generally no pain in the area because the nerve endings are destroyed.
4. Fourth degree burns: Extend through the epidermis, dermis and subcutaneous fat into the underlying muscle and bone. Fourth degree burns are stiff and charred.

Pain is defined an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [2]. Burn injuries normally result in extensive tissue damage. The resultant pain that occurs is due to the stimulation of skin nociceptors. In addition, the injury will trigger an intense inflammatory response and the release of chemical mediators that lower the threshold for sensitization of the active nociceptors, a phenomenon called primary hyperalgesia. This will cause the wound to be very sensitive to both mechanical and chemical stimuli [14].

Repeated peripheral stimulation of nociceptive afferent fibres causes an increase in dorsal horn excitability. A major player in this increase in dorsal horn excitability is the N-methyl-D-Aspartate receptors. This leads to increased sensitivity in the surrounding unburned skin areas, a phenomenon called secondary hyperalgesia. An example is frequent dressing changes that can result in development of secondary hyperalgesia.

Burn pain is characteristically severe and has both an emotional and sensory component. Notably, burn pain evolves and changes over time making the experience different at any given time. This complex nature of burn pains has thus stirred a lot of interest in exploring different therapeutic interventions to optimize pain relief in burns patients. Pain from burns is not a single constant entity. It comprises of several components that together result in excruciating pain if not mitigated. These include:

1. Background or rest pain.
2. Breakthrough pain.
3. Psychogenic pain.
4. Procedural pain [18].

Background pain

Background/rest pain is a continuous throbbing or burning sensation present at rest. It is relatively constant and dull and its severity varies between different individuals. The treatment of choice is regular slow release analgesics to keep plasma drug concentrations steady.

Breakthrough pain

This is a transitory flare up of pain in the setting of background/rest pain. It can also be described as a pain that 'breaks through' the ceiling of pain relief provided by other analgesics. It is characteristically intermittent, has a short duration and has a rapid onset and offset. The optimal treatment for breakthrough pain is usually a strong, short-acting opioid medication that works quickly and lasts about as long as a breakthrough pain episode. Breakthrough pain medication is taken on an as-needed basis, as soon as symptoms are experienced.

Psychogenic pain

This is burn pain that occurs in the absence of any mechanical stimulation. It is mainly anticipatory and occurs due to prior poor pain control in the patient. Management of psychogenic pain is basically ensuring good pain control in a burn patient from the first contact. In instances where it has already set in, anti-depressants and distraction techniques help alleviate it.

Procedural pain

This is burn pain that occurs at the site of injury during therapeutic procedures like cleaning and removal of dressing, debridement, escharotomy and joint range of motion movements. It is characteristically excruciating and can continue for minutes to hours after the procedure is completed. Management of procedural pain is multi-pronged and includes:

1. Non pharmacological interventions; Relaxation techniques, meditation, imagery, massage, music, play activities.
2. Pharmacologic interventions

Pharmacological agents for managing procedural pain range from non-opioid analgesics, opioid analgesics, local anesthetics and may even involve procedural sedation.

Several studies have been carried out on modalities of procedural pain management. Studies involving use of ketamine explore it as an agent for procedural sedation in which it must be administered in the presence of a skilled anaesthesia provider and in anaesthetic doses [6]. No study has been done to assess the sub-anaesthetic doses of ketamine to ascertain whether the analgesic effect is adequate enough to defer the need to sedate patients. In addition, studies on the combination of morphine and ketamine have not fully evaluated the optimum dosing [9]. This study compared the pain control of a low dose combination of morphine and ketamine versus the standard dose of morphine alone. This in essence addressed the disparities in previous studies around pain control and ultimately optimized pain relief for burn patients during change of dressing.

1.1 Assessment of Pain

It is important that clinicians assess pain intensity to establish the severity of pain and the effectiveness of analgesia. This assessment should be done from the onset with subsequent reassessments.

The pain experienced by burn patients varies greatly from patient to patient [18]. This is the basis upon which treatment protocols stipulate starting doses of analgesics, and allow for adjustments to be made based on the individual pain assessment.

The picture based Wong Baker face scale is well suited in assessing pain in young children [20].The scale shows a series of faces from 0 to 10 and is descriptive of the child's facial expression.

Figure 1: Wong Baker face scale

For adults and children aged over seven, a visual analogue scale or a verbal numeric scale are excellent tools for assessing pain [19].

Figure 2: Visual analogue scale

In this study, the visual analogue scale was used in the assessment of procedural pain.

2. LITERATURE REVIEW

The excruciating nature of procedural pain in burns patients has triggered a lot of research on therapeutic modalities to mitigate this pain. This is necessitated by the fact that therapeutic procedures in burns patients are nonetheless 'compulsory' because they facilitate healing, prevent infection, diminish pain and avoid limitations in movement [21].

Given the severe nature of unmanaged procedural pain, studies have been done to get the perceptions of burns specialists on the importance of controlling pain during dressing change in burn patients. Dominic Upton et al [3] conducted a study to explore the views of burn specialists on the importance of reducing stress and pain during wound treatment. Burns specialists were invited to complete an online survey, consisting of 10 questions about pain and stress in their patients. The total respondents were 141 drawn from 39 countries. Overall, pain-free dressing was viewed as important by 47.5% of respondents whereas stress-free dressing by 40.8%. Nonetheless, in both cases, 11.3% did not view either to be important. Most respondents equally acknowledged that pain is linked with stress but disagreement levels ranged from 21.9% to 25.3%. Additionally, only 22.5% agreed that stress is related to wound healing. This can be summed up to mean most burn specialists recognized that pain can lead to stress and that it is important to reduce stress and pain at dressing changes. However, these results suggest a need for further research on perceptions about pain and stress, and how these perceptions can impact wound management practices [3].

The experience of procedural pain in burn patients would be the best yardstick to conceptualize its excruciating nature. Weinberg K et al [4] did a study on "Pain and anxiety with burn dressing changes: patient self-report" to demonstrate this. A total of 24 patients were recruited in this study. Pain scores were taken by the Visual analogue scale immediately before, immediately after and half an hour after change of dressing. The results indicated that pain and anxiety progressively increased with subsequent sessions of change of dressing. In addition, pain correlated with anxiety. Through the descriptive study, it was found that the pain score

immediately after dressing changes was greater than 3 on all study days. This finding indicates sub-optimal pain management in burn patients during dressing change and thus a need to further evaluate pain management regimes.

As indicated earlier, the modalities for mitigating burn procedural pain are both pharmacological and non-pharmacological. Both modalities are effective and are best instituted in tandem to optimize pain relief. To appreciate the importance of non-pharmacological therapies, Hoffman et al [5] explored the novel use of immersive virtual reality (VR) to distract patients from pain during physical therapy. At the burn care unit of a regional trauma center, twelve patients aged 19 to 47 years were recruited with an average of 21% total body surface area burned. Range of motion exercises of their injured extremity was done by an occupational therapist. Each patient spent 3 minutes of physical therapy with no distraction and 3 minutes of physical therapy in virtual reality. Visual analogue scale pain scores for each served as the dependent variables. All patients reported less pain when distracted with VR, and the magnitude of pain reduction by VR was statistically significant (e.g., time spent thinking about pain during physical therapy dropped from 60 to 14 mm on a 100-mm scale. These results indicated that VR can function as a strong pain reduction technique for adult burn patients during physical therapy and potentially for other painful procedures or pain populations.

Pharmacological therapies for procedural pain are varied. They range from non-opioid analgesics, opioid analgesics, local anesthetics and in some cases sedative drugs. This study was limited to two pharmacological agents; ketamine and morphine.

2.1 Ketamine

Ketamine is an arylcyclohexylamine that is structurally related to phencyclidine. It was first developed in 1962 and is used as an intravenous anesthetic induction agent [15], analgesic, sedative agent, in treatment of bronchospasms and as an antidepressant.

Modes of administration of ketamine include Intravenous, Intramuscular, Oral, Rectal, Topical and Intranasal. Parenteral analgesic dosage of ketamine is in the sub-anesthetic range and is typically 0.1-0.5mg/kg. Onset of action after intravenous administration is 30 seconds to 1 minute with duration of action of 10-20 minutes. However, full recovery from its effects may take 60-90 minutes.

Ketamine is extensively metabolized by hepatic microsomal cytochrome P450 enzymes and its primary metabolite, norketamine, has a potency of 30% of the parent compound. The metabolites of norketamine are excreted by the kidney as water-soluble hydroxylated and glucoronidated conjugates.

Ketamine produces its effects by acting as an antagonist at the NMDA receptors. Ketamine produces dose-dependent CNS depression leading to a so-called dissociative anesthetic state characterized by profound analgesia and amnesia, even though patients may be conscious and maintain protective reflexes. It is important to note that at analgesic doses the CNS effects of ketamine may not develop or if they do, they may not be as pronounced as in higher doses.

In addition, as a result of its NMDA-receptor blocking activity, ketamine should be highly effective in opioid-resistant chronic pain states. This as had been attributed to earlier is because tolerance to opioids is believed to be mediated through NMDA receptors. Another beneficial effect is that use of ketamine together with an opioid has an opioid-sparing effect hence decreasing the dose of opioid needed.

Ketamine is reported to have psychomimetic effects mainly hallucinations, nightmares, altered short-term memory and cognition during the early recovery period. The incidence of these

reactions is dose dependent and can be reduced by co-administration of benzodiazepines, barbiturates or propofol.

Other side effects of ketamine include elevation of blood pressure, increased airway secretions, purposeless limb movements, raised intracranial and intraocular pressure, nausea and vomiting and transient erythema. Ketamine is contraindicated in patients with high blood pressure, raised intracranial pressure and severe coronary artery disease [22].

San Francisco General Hospital has developed a protocol for the use of ketamine during dressing changes in burn patients [7] with a recommended intravenous dosing of 0.5-1mg/kg. This produces analgesia for 5-30 minutes. Precautionary measures undertaken include access to emergency equipment e.g. oxygen, suction and crash cart. In addition a Medical Doctor must be present during administration. Contraindications for ketamine administration for procedural pain in this protocol include: history of psychiatric illness, hypertension, myocardial infarct, elderly patients, increased ICP or IOP and patients with respiratory difficulties.

Most research involving ketamine explore it as an agent for procedural sedation. Ward CM et al [6] evaluated 10 adults (ages 24-74 years) who received ketamine as a part of their burn dressing change sedation. These patients were kept NPO for 4 hours prior to sedation. Ketamine was administered by an anesthesiologist. Their protocol consisted of an induction dose of ketamine 2mg/kg IV followed by ketamine 4mg/kg IM. Subsequent IM doses of ketamine were administered when the patient made purposeful movements or nystagmus reappeared. A final dose of ketamine 1mg/kg was administered at the end of the dressing change. Ketamine was found to provide adequate analgesia. A limitation of this research is that the sub-anesthetic doses of ketamine were not adequately assessed to ascertain whether the analgesic effect achieved was adequate to defer the need to sedate the patients

2.2 Morphine

Morphine is an opioid analgesic drug used in the treatment of both acute and chronic moderate to severe pain. It also has sedative properties in super analgesic doses. It was first isolated in 1804 by Friedrich Sertürner from the dried seedpods of *Papaver somniferum* and he subsequently began distributing it in 1817 [16].

It can be administered by intravenous, intramuscular, subcutaneous, oral, rectal, epidural and intra-thecal routes. Parenteral dosage for pain relief ranges from 0.01mg/kg to 0.2mg/kg. Oral dosage for pain relief is approximately 3 times the parenteral dosage. Epidural dosage is a tenth of the parenteral dose whereas intra-thecal dosage is a tenth of the epidural dosage. Onset of action is within 5 minutes when given via the parenteral route and 30 minutes when given orally. The peak effect is achieved within 10-40 minutes. Its duration of action is typically 3-4 hours.

Morphine is about 35% bound to plasma proteins. It undergoes extensive first pass metabolism resulting in a low bioavailability after oral administration. Metabolism is mainly in the liver to morphine-3-glucoronide, morphine-6-glucoronide and sulfate conjugates. Excretion is through the kidneys hence care should be taken in patients with renal failure.

Morphine acts as an agonist at the μ_1 and μ_2 opioid receptors throughout the body. Its effects include analgesia, sedation, miosis, depression of the cough reflex and drowsiness. Notable adverse effects include euphoria, dysphoria, respiratory depression, nausea and vomiting, histamine release manifested as pruritus, decreased visceral smooth muscle motility causing constipation and urinary retention

Morphine has an addiction potential. However, when used optimally for pain relief, this potential is reduced and thus shouldn't act as an impediment to its use in burns patients.

Finn J et al [8] sought to compare the analgesic efficacy and safety of PCIN fentanyl with oral morphine for procedural wound care in burns patients. A randomized double-blind placebo

controlled trial was conducted in the Burns Unit of a major teaching hospital in Perth, Australia. Patients requiring wound care procedures on two consecutive mornings were randomized to receive either PCIN fentanyl with oral placebo or oral morphine with intranasal placebo on 1 day, followed by the alternate active drug on the following day. Twenty six patients aged between 18 and 69 years with TBSA range 1-25% had pain scores assessed using a 10 point numeric scale at various time periods before, during and after the procedure. A mean total dose of 1.48 +/- 0.57 microgram/kg of PCIN fentanyl and 0.35 +/- 0.12 mg/kg of oral morphine was administered. No statistically significant difference was found between the scores recorded in both study arms. It was concluded that PCIN fentanyl is similar in efficacy and safety to oral morphine for relief of procedural pain.

Oral morphine takes 30-90 minutes to reach peak effect and hence should be administered at least 60 minutes before the dressing change. Oral morphine equally has a couple of drawbacks that limit its efficacy. These include its reduced and uncertain bioavailability (15%-50%), inability to give extra doses in response to severe pain during the procedure (delay for peak plasma concentration: 30-90 minutes) and its long post-procedural sedation [23].

Thus IV opioids may offer some advantages over oral opioids. The use of IV opioids for severe procedural pain does, however, have its drawbacks in that some patients may require such high doses of analgesia, that there is an increased risk of apnoea and loss of consciousness. This can be problematic during the first dressings of superficial burns, as patients may need to undergo extensive debridement of necrotic tissue. In these cases, to avoid subjecting the patient to pain, the option of adding low doses of ketamine is ideal. This is because the addition of ketamine will reduce the dose requirement of the opioid. In addition, ketamine will reduce the development of opioid tolerance through its blockage of NMDA receptors [22].

Beaudoin FL et al [9] carried out a study to determine the effectiveness of low-dose ketamine as an adjunct to morphine versus standard care with morphine alone for the treatment of acute moderate to severe pain among emergency department patients. This study was a double-blind,

randomized, placebo-controlled trial conducted at an emergency department over a 10-month period. Eligible patients were 18 to 65 years old with a pain score of at least 5 out of 10 on the numerical pain rating scale [NRS] and pain duration less than 7 days. It involved three study groups with 20 patients in each group: 1) morphine and normal saline placebo, 2) morphine and 0.15 mg/kg ketamine and 3) morphine and 0.3 mg/kg ketamine. Participants were assessed at 30, 60, and 120 minutes after study medication administration and received rescue analgesia as needed to target a 50% reduction in pain. The primary outcome measure was the summed pain-intensity (SPID) difference over 2 hours. The amount and timing of rescue opioid analgesia and occurance of adverse events was also measured.

Over the 2-hour post study medication administration period, the SPIDs were higher for the ketamine study groups than the control group. Rescue analgesia was received by: 35% in group 1, group 2 20% and group 3 20%. From the study it was concluded that low dose ketamine is a viable analgesic adjunct to morphine for the treatment of moderate to severe acute pain. Dosing of 0.3 mg/kg is possibly more effective than 0.15 mg/kg, but may be associated with minor adverse events.

The large catchment area of MTRH and its status as a National Teaching and referral hospital has resulted in numerous admissions of patients with burns. This in essence implies that numerous therapeutic procedures are done on every single day. Werunga et al [1] carried out a study in the burns ward of MTRH on the use of combined paracetamol and low dose ketamine in pain control during change of dressings in burn patients. Consenting patients were recruited to the study on admission. There was statistically significant change in the pain score on both FLACC and VAS (both $p<0.001$) after the introduction of low dose Ketamine with paracetamol. The conclusion from this study was that the use of oral paracetamol combined with the low dose intravenous Ketamine, is effective in controlling burn pains during change of dressings. It is a safe and cheap alternative, that can be applied in remote and resource limited medical facilities.

2.3 Problem statement

Change of dressing in burn patients is a very painful procedure. Health care workers have a responsibility to ensure that this procedure is as painless as possible to minimize patient suffering and hasten recovery. However, currently most burn patients undergo this procedure in excruciating pain since health care workers use their discretion to choose which analgesics to administer and at no standard dosing schedule. Using the standard dose morphine or the low dose combination of morphine and ketamine will optimize pain relief for adult burn patients undergoing change of dressing. This will in addition serve as reference data for health care workers and ultimately minimize patient suffering and hasten recovery.

3. JUSTIFICATION

Previously conducted studies have indicated from self-reports of patients that pain during therapeutic procedures is excruciating and there is need to further examine the way pain is managed during dressing changes.

In addition, clinical management of burn wounds requires frequent change of dressing. The control of stress and pain during this procedure has been shown to be beneficial in burn wound healing, reducing length of hospital stay, minimizing morbidity and mitigating development of psychological sequelae in burns patients.

Furthermore, the drugs that were used in this study are readily available in Kenyatta National Hospital and other hospitals across the country.

Additionally, the use of intravenous opioids especially morphine has been sub-optimal due to the fear of the adverse effects of opioid use. In this study, the addition of ketamine reduced the dose requirement of morphine. Also, ketamine has been reported to play a role in reducing the development of opioid tolerance through its blockage of NMDA receptors that have been implicated in the development of the same

This study compared two pharmacological methods of mitigating procedural pain with an intention of reducing the pain experienced by burns patients during change of dressing and proposing a protocol for procedural pain management.

4. OBJECTIVES

4.1 General objective

To compare the pain control of a combination of low dose morphine and ketamine versus standard morphine alone during change of dressing in adult burn patients

4.2 Specific objectives

I. To assess pain control with the use of standard dose morphine alone during dressing change.

II. To assess pain control with the use of a low dose combination of morphine and ketamine during dressing change.

III. To assess for adverse effects with use of standard dose morphine alone and the combination of low dose morphine and ketamine.

5. HYPOTHESES AND CONCEPTUAL FRAMEWORK

5.1 Null Hypothesis

The response to a combination of low dose morphine and ketamine for pain control during dressing change in adult burn patients is clinically inferior to the response to morphine alone.

5.2 Alternative hypothesis

The response to a combination of low dose morphine and ketamine for pain control during dressing change in adult burn patients is not clinically inferior to the response to morphine alone.

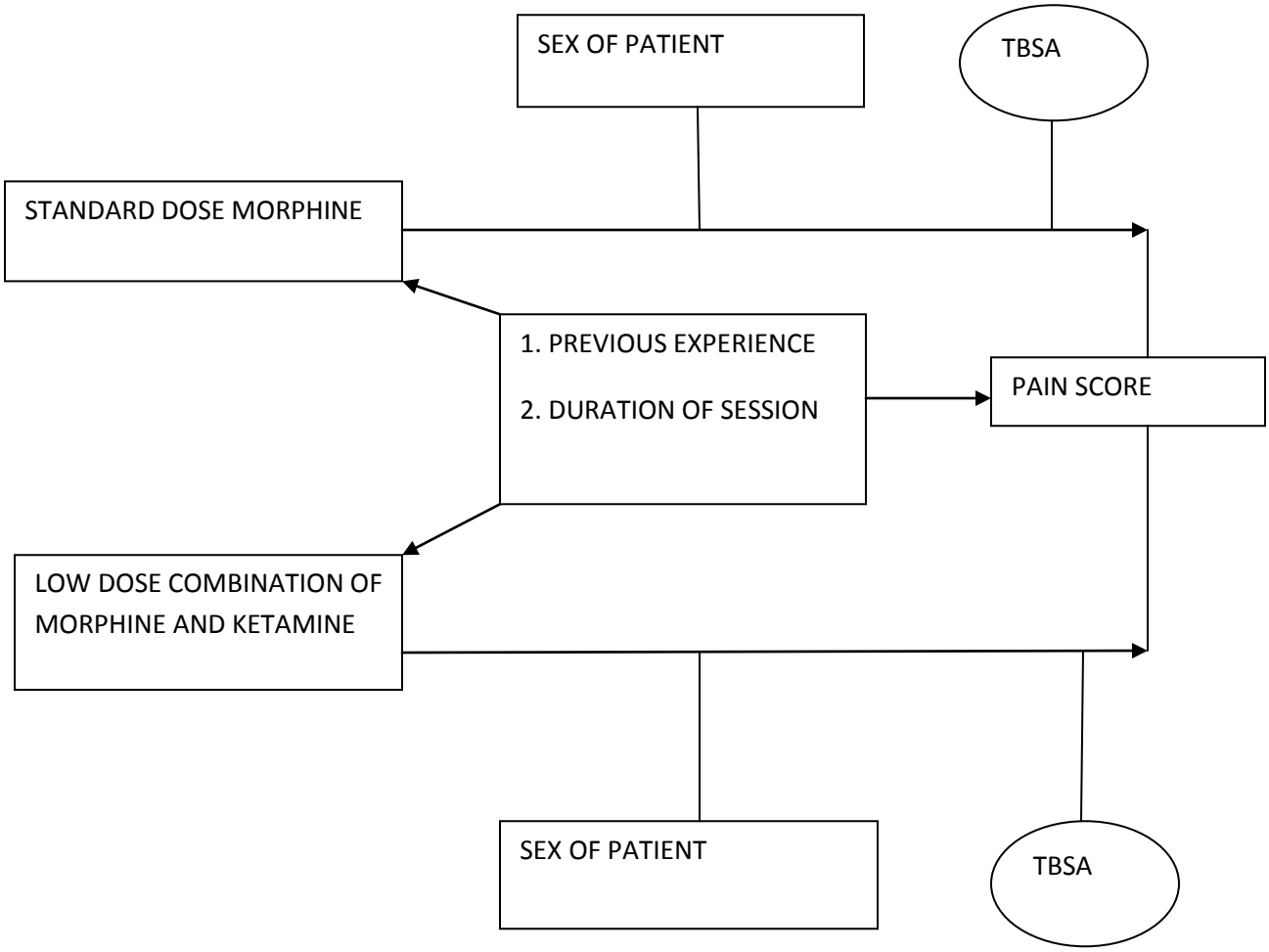
$$H_0: \mu_E - \mu_C \leq -\delta \quad versus \quad H_A: \mu_E - \mu_C > -\delta$$

Where μ_E and μ_C denote the means for experimental and control groups respectively while δ represents the clinically important margin [13].

5.3 Conceptual framework

The key dependent variable in this study was the pain score of the burn patients undergoing dressing change. The independent variables include the type of medication administered i.e. either morphine alone or the combination of low dose ketamine and morphine, sex of the patient, the total burn surface area and the time-span since the burn injury was sustained. Confounders include level of background pain control prior to dressing change, previous painful experience during change of dressing and the duration of the dressing change**.**

Figure 3: Diagrammatic presentation of the Conceptual Framework



6. METHODOLOGY

6.1 Study design, Site and Population

The study was a Parallel Group, Randomized Control Trial that was conducted at Kenyatta National Hospital Burns Unit and Ward 4D. The study population consisted of adult burn patients admitted in Kenyatta National Hospital Burns Unit and Ward 4D; and scheduled to have change of dressing.

6.2 Inclusion and exclusion criteria

The study included adult burns patients with first and second degree burns in Burns Unit and Ward 4D scheduled to have change of dressing who consented to participate in the study.

Pediatric burns patients and patients who failed to consent to participate in the study were excluded from the study. In addition, patients with third and fourth degree burns, psychiatric illnesses, hypertension, respiratory difficulties, history of cerebrovascular accidents and previous myocardial infarction were also excluded from the study.

6.3 Sample size

Taking into account the underlying latency in pain perception and the relatively large number of categories (10) in the discrete response, the scores were treated as a continuous variable [10]. In relation to this, ordinary linear regression model was used in the analysis because it assumes a normally distributed response and can also accommodate independent variables of both discrete and continuous nature [12].

Sample size computation was based on the equation below [13] using *R Studio version 3.1.1 (2014-07-10).*

$$N = 2\left[\frac{z_{1-\alpha} + z_{1-\beta}}{\delta_0}\right]s^2$$

Where:

N: denotes sample size for each study arm

α: denotes the type I error

β: denotes the type II error

δ: denotes the non-inferiority margin

s: denotes the standard deviation

A non-inferiority margin of 1 and standard deviation of 2 was used in the computation. Taking the control group as the reference category and a mean difference of 1 as the non-inferiority margin a total sample size of 100 on a 1:1 ratio of control to treatment group was required in order to obtain a statistical power of more than 0.8 at a two sided alpha significance level of 0.05.

$$N = 2\left[\frac{z_{(1-0.05)} + z_{(1-0.20)}}{1}\right]2^2 \approx 50$$

6.4 Sampling procedure

Recruitment and randomization

The study participants were recruited from the Kenyatta National Hospital Burns Unit and ward 4D on the evening prior to the change of dressing. All potential participants received verbal and written explanation on the purpose and procedure of the study from the principal investigator; and written informed consent sought. The patients who gave written informed consent were then enrolled into the study and assigned a study number from 1 to 100 sequentially whereby; the first participant recruited was allocated number 1 and the last 100.

Randomization was done using block randomization. Using computer software, the statistician generated random numbers ranging from 1 to 100 that were sequentially allocated to either the control or treatment arms in a 1:1 ratio. He then put them in serially numbered opaque envelopes. The statistician kept the records of the random numbers and serial numbers of the envelopes.

Informed consent

Informed consent was obtained by the Primary Investigator after a detailed explanation of the nature of the study, and any queries were addressed with the patient. In cases where an enrolled and consented patient withdrew consent, the next consecutively randomized patient was selected.

Blinding

This study was a double blind study. Both the principal investigator and the study participants were blind to their allocations.

Study drugs

The study drugs once procured were stored in the Dangerous Drugs Act (DDA) cabinet in burns unit and Ward 4D. This cabinet was under lock and key and was only accessible to the study assistant in the presence of the ward matron. The study assistant was responsible for preparation and administration of the study drugs. He was a higher national diploma student in anaesthesia with knowledge on drug preparation and basic resuscitation skills.

The control arm received **standard dose morphine; a dosage of 0.1 mg/kg**.

The treatment arm received the **low dose combination of morphine and ketamine; morphine at a dosage of 0.05 mg/kg and ketamine at a dosage of 0.25 mg/kg.**

6.5 Flow of events

The study assistant picked the serialized opaque envelopes corresponding to the numbers assigned to the study participants the previous night from the statistician on the morning of the change of dressing. These envelopes contained the allocated study arm.

Prior to commencement, the principal investigator assembled a self-inflating bag for ventilation, face masks, functional laryngoscopes, assorted endotracheal tubes, oxygen delivery system, intravenous fluids, and resuscitation tray with basic drugs needed for resuscitation and establishment of an advanced airway. A suction machine was made available for use in case it became necessary.

The principal investigator started by filling in part 2 of the data entry form. Subsequently, the study assistant opened the serialized envelope and prepared the drugs as directed by the arm allocated and administered them. He then completed part 1 of the data collection form and put it in the envelope and sealed it. The nurses immediately proceeded with the change of dressing after which the principal investigator filled in Part 3 of the data collection form immediately after completion of the change of dressing and 30 minutes later. He then attached the forms to

the respective sealed opaque envelope that was later handed over to the statistician for data entry and analysis.

6.6 Data management and analysis

Upon collection, data was entered and stored in an MS Excel work sheet on the same day in a coded form, awaiting analysis. All data entered was verified by the principal investigator. In case of missing data, the Principal Investigator (PI) conducted a follow up and tried to retrieve it from the patient's medical records.

Every precaution was taken to respect the privacy of the patients whose data was collected and analyzed in this study. However, in the course of monitoring data quality and adherence to the study protocol only the study supervisors were allowed to refer to the recruited patients' medical records. After analysis; the data was stored in soft copy. The hard copies are also under the custody of the PI for a period of 5 years from the completion of this study. A notice for destruction of the data will be given to the research committee and once approval is granted the data will be destroyed upon expiry of the 5 years.

Statistical analysis involved fitting of linear regression models, model building, verification of model assumptions of normality and homoscedaticity in *SAS 9.4* and *R Studio version 3.1.1(2014-07-10).*

6.7 Ethical consideration

Approval to carry out the study was sought and obtained from the KNH/UoN Ethics and Research Committee. Written informed consent was obtained from each participant. This study respected the right of the patients to decline participation. There was no additional cost or incentive for participating in this study.

There was no penalty for refusal to participate in this study, and the standard of care was the same for both study participants and non-participants. Appropriate measures to mitigate any

adverse events were put in place i.e. ambu-bag, oxygen delivery system, laryngoscopes, endotracheal tubes, face masks and resuscitation and intubating drugs.

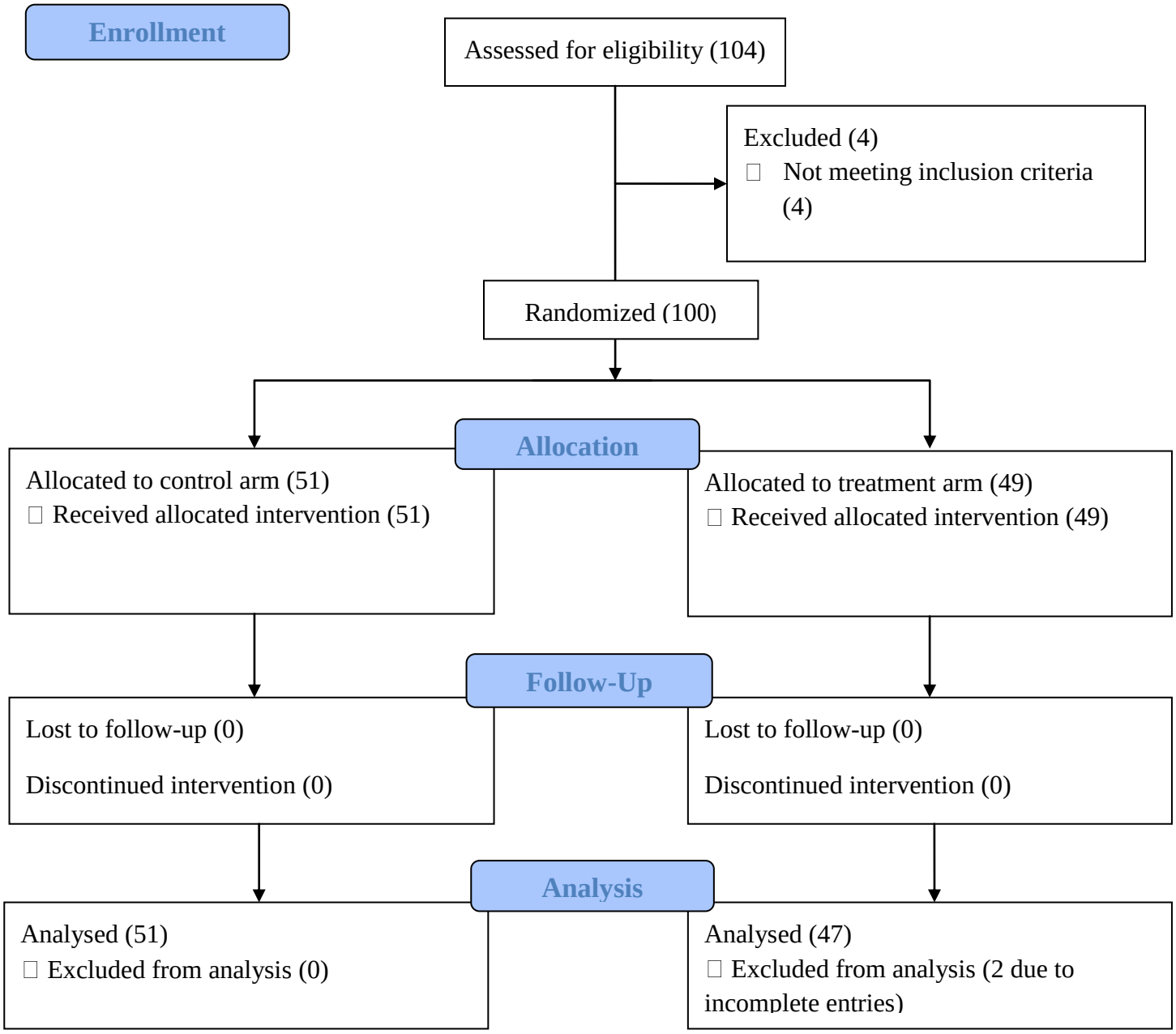
The information obtained from each participant was treated with utmost confidentiality. No individual staff member was victimized in view of the results obtained from the research. No study participant was denied rescue analgesia in cases where the pain experienced during the procedure was unbearable.

6.8 Study limitation

Drugs administered during the study were based on estimated weight since most of the patients were bed ridden and posed a challenge in measuring their exact weight.

7. RESULTS

Figure 4: Participant flow



7.1 Study period

Age eligible participants were recruited from September 2016 to March 2017 at the Kenyatta National Hospital Burns Unit and Ward 4D.

7.2 Dataset

The data consisted of measurements obtained from a total of 100 subjects from both the control and treatment groups. It had a total of 16 variables. The response variable was dressing pain score which was measured on an ordinal scale of 1 to 10.

7.3 Baseline demographics and clinical characteristics

Table 1:

	MORPHINE/ KETAMINE (N=47)	**MORPHINE (N=51)**	**P value**
Age (years)	29.83(8.90)	29.24(9.49)	0.7521
Sex (female)	14(29.79%)	22(43.14%)	0.1720
TBSA (%)	30.40(12.76)	30.22(13.69)	0.9466
Time since injury (days)	6.04(4.76)	9.05(8.01)	0.0276

Control group

Fifty-one subjects were randomized into the control group. Among them were 29 males and 22 females. The youngest and oldest subjects in this group were aged 17 and 72 years respectively; with the group's average age being 29 years. This average age is suggestive of a relatively young population with possible outlying older subject(s).

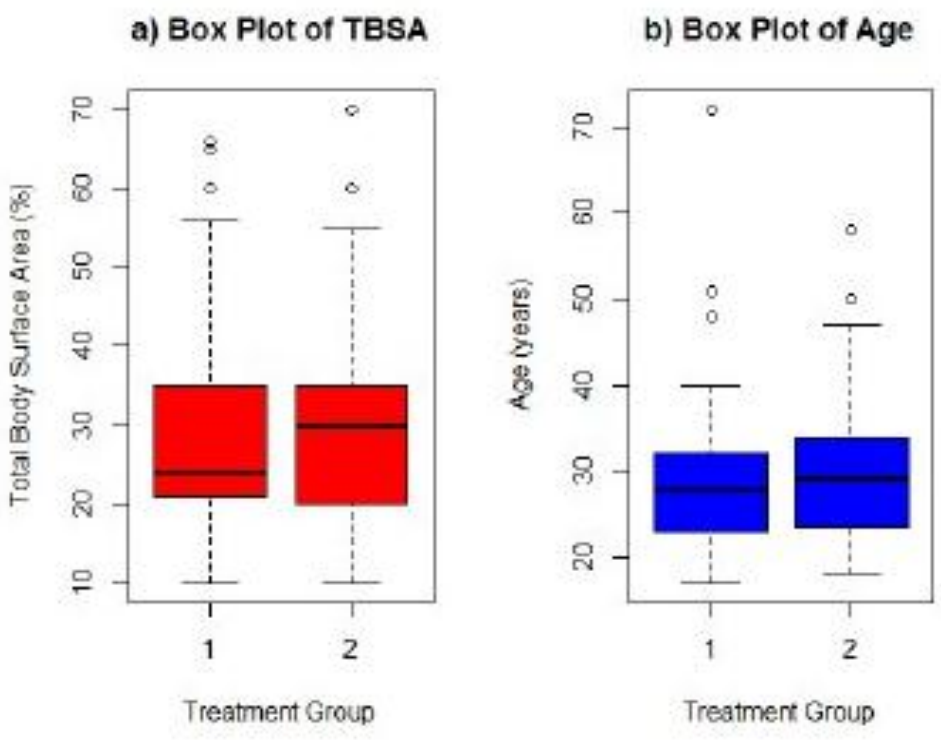
The subjects had 10% and 66% as the lowest and highest total burn surface area (TBSA). The average TBSA was 30.22%.

Treatment group

The treatment group had 33 males and 14 females hence a total of 47 subjects. Their age ranged from 18 to 58 years with an average of 29.8 years. Like in the control group, the average age is suggestive of a relatively young population.

The subjects had 10% and 70% as the lowest and highest total burn surface area respectively. The average TBSA was 30.4%.

Figure 5: Box plots for TBSA and Age

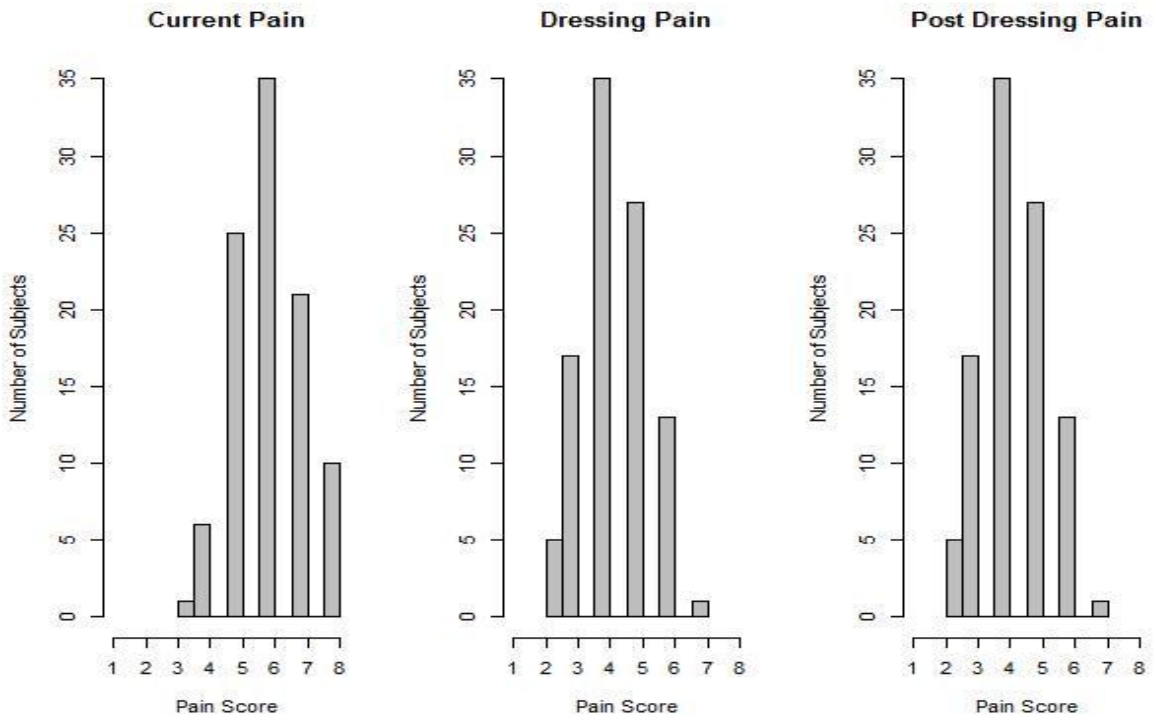


Key: Group 1: Morphine only, Group 2: Morphine/Ketamine

7.4 Outcomes

The primary outcome of interest was the pain score during the change of dressing in both the control and treatment arms. This is depicted in the histograms below. Most patients recorded a pain score of 6 when assessed before dressing. This was followed by pain scores of 5,7,8,4 and 3 in that order. During dressing most subjects recorded a pain score of 4. This was followed by pain scores of 5, 3, 6, 2 and 7 in that order. This shows a shift towards the left in the pain scores during dressing as compared to before dressing. The number of subjects who recorded a pain score of 2 and 3 also increased compared to that of pain before dressing. There was no noticeable difference between the histogram of dressing pain and that of pain 30 minutes after dressing. This is suggestive of the effect of the drugs administered still being felt 30 minutes after the change of dressing.

Figure 6: Histograms of outcome in both study groups

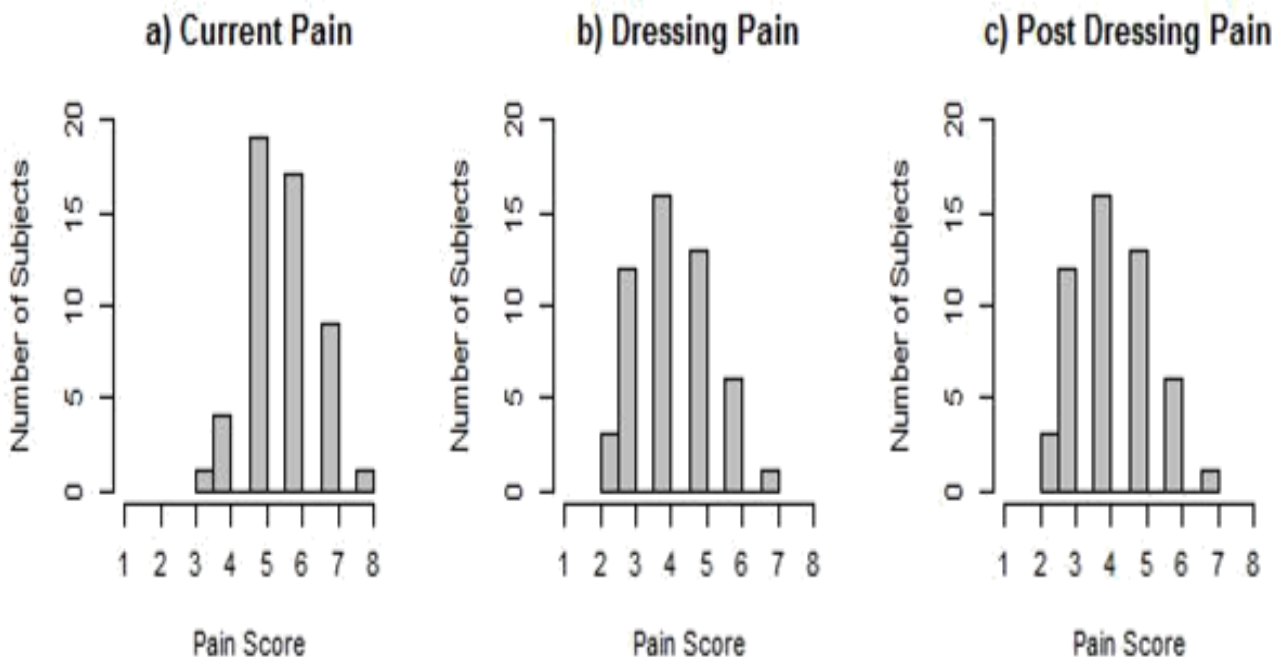


The exploratory data analysis is further broken down into the two study groups.

Control group

Exploration of pain scores within the control group revealed a similar pattern. Most subjects reported a pain score of 5 when assessed before dressing. This was followed by scores of 6, 7 and 4 in that order. Scores 3 and 8 were almost similar. When pain was assessed during dressing, most subjects reported a score of 4. This was followed by 5, 3, 6, 2 and 8 in that order. There was a notable shift of the histogram to the left which represents the effect of morphine only as an analgesic. When pain was assessed 30 minutes after dressing, there was no noticeable difference from the results obtained during dressing. This is suggestive of the effects of morphine still being felt 30 minutes after dressing. The histograms below summarize these observations.

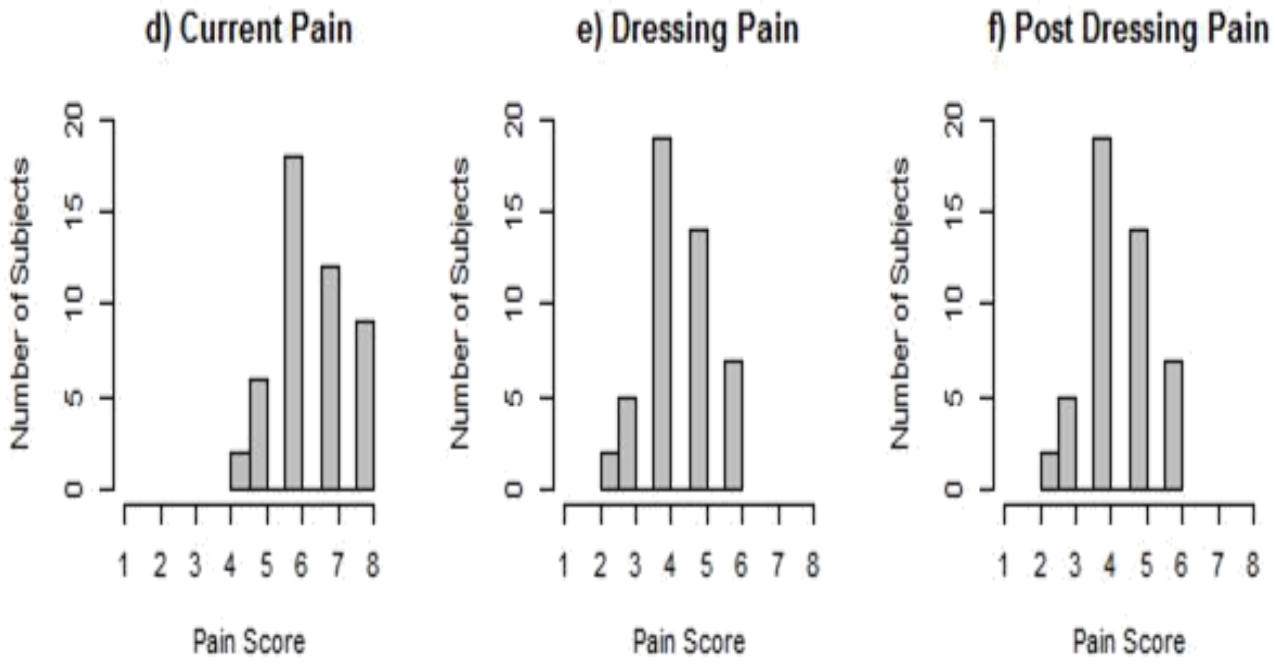
Figure 7: Histograms of outcome in Control group



Treatment group

Exploration of pain scores within the treatment group revealed a trend similar to the control group. There was, however, a greater shift of the histogram to the left. The lowest pain score reported reduced from 4 to 2 while the highest score reduced from 8 to 6 when pain was assessed before and during dressing. This suggests a greater effect of the morphine and ketamine combination in pain control. Like in the control group, there was no noticeable difference in the graph of pain assessed during dressing and 30 minutes after dressing. This likely indicates the effect of the morphine and ketamine combination was still being felt 30 minutes from the time of dressing. The histograms below summarize these observations.

Figure 8: Histograms of outcome in treatment group.



Another outcome of interest was adverse effects arising in either study arm. In total, out of the 98 subjects analyzed, 26 representing 26.5% got adverse effects attributable to the drugs administered.

Of the 51 subjects in the control group, only 10 (19.61%) experienced side effects associated with morphine. Of these 10 subjects, 9 (90%) had nausea with 1 (10%) having both nausea and euphoria.

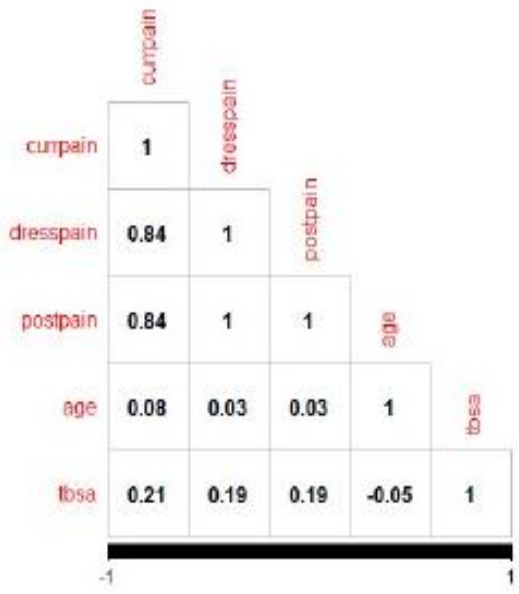
Of the 47 subjects in the treatment group, 16 (34.04%) experienced side effects associated with the morphine/ketamine combination. 25% experienced euphoria, 31.25% nausea and 43.75% hallucinations. This suggests that the combination may have greater side effects compared to morphine only.

Table 2: Adverse effects

	MORPHINE/KETAMINE 16(34.04%)	**MORPHINE 10(19.61%)**
NAUSEA	5(31.25%)	9(90%)
VOMITTING	0(0.00%)	0(0.00%)
PRURITUS	0(0.00%)	0(0.00%)
EUPHORIA	4(25%)	1(0.00%)
HALLUCINATIONS	7(43.75%)	0(0.00%)
RESPIRATORY DEPRESSION	0(0.0%)	0(0.00%)

A correlation plot was designed to show the correlation between different variables. It showed that the pain score during dressing was perfectly correlated (1) to the score 30 minutes after dressing. There was also a high positive correlation (0.84) between pain score before (currpain) and during dressing (dresspain). Subjects who experienced a lot of pain before dressing also experienced a lot of pain during dressing. This is depicted in figure 9 below;

Figure 9: Correlation plot



7.5 Analysis

Simple linear regression models were fitted against each response variable to assess their individual relations.

The final model consisted of the drug administered and pain before dressing as the main predictors of pain score during dressing. Age, sex, TBSA, rescue analgesic, time span since burn injury, side effect and pain 30 minutes after dressing were all insignificant hence they were dropped out of the model. The model had an AIC value of 172.1654.

Table 3: Parameter Estimates of the final model

	VALUE	STD. ERROR	t VALUE	p VALUE
Morphine/Ketamine	-2.0852	0.5162	-4.0397	0.0001
Current pain	3.5761	0.4517	7.9173	<0.0001
2/3	13.7553	2.0408	6.7401	<0.0001
3/4	17.4705	2.3227	7.5216	<0.0001
4/5	21.2738	2.6896	7.9096	<0.0001
5/6	25.0512	3.1204	8.0281	<0.0001
6/7	29.2505	3.5108	8.3316	<0.0001

In this study, Morphine only group was used as the reference. The coefficient (-2.0852) therefore, describes the effect of the ketamine/morphine combination on the perception of pain during dressing.

It measures the log odds of falling into or below any category of pain (during dressing) associated with a switch from ketamine/morphine combination to morphine only, while assuming that pain before dressing remains the same. Since the coefficient expresses a negative slope, there exists a tendency for the pain during dressing to increase as one switches from Ketamine/Morphine combination to Morphine only. This shows that the former exhibits a better pain control during dressing than the latter. This is, however, with an assumption that pain before dressing remains the same.

The coefficient (3.5761) of current pain expresses the effect of pain before dressing on the perception of pain during dressing. It measures the log odds of falling into or below any category of pain (during dressing) associated with a unit increase in pain score before dressing, while

assuming the treatment group does not change. The coefficient expresses a positive slope hence there exists a tendency for the pain during dressing to increase as the pain before dressing increases.

This confirms what was observed in the bivariate graphical exploration; that the perception of pain before dressing has an influence on the perception of pain during dressing. Subjects who record high pain scores before dressing are also likely to record high scores during dressing.

To aid in hypothesis testing, the values in table 3 which were expressed in the log-odds scale were exponentiated to the odds ratio scale and subsequently generating p values. This is seen in table 3 below.

Table 4: Parameter estimates of the final model in Odds ratio.

	VALUE	**STD. ERROR**	**t VALUE**	**p VALUE**
Morphine/Ketamine	0.1243	1.6756	-4.0397	0.0001
Current pain	3.57326	1.5709	7.9173	<0.0001

7.6 Discussion

The main objective of this study was to compare the pain control of a combination of low dose morphine and ketamine versus standard dose morphine alone during change of dressing in adult burn patients. The study drugs were administered to males and females, all eligible adults and a wide range of total burn surface areas; hence these results are largely applicable to the entirety of burn patients.

From the results and analysis above, there was a difference in the pain control of the low dose ketamine/morphine group compared to the standard dose morphine group i.e. the odds of getting a high pain score during change of dressing in adult burn patients when using standard dose morphine alone is high in comparison to the low dose combination of morphine and ketamine.

This replicates and extends the study by Beaudoin F.L et al [9]. Beaudoin F.L and his team carried out a study to determine the effectiveness of low dose ketamine as an adjunct to morphine versus standard care with morphine alone for the treatment of acute moderate to severe pain among emergency department patients. It involved three study groups with 20 patients each: 1) morphine 0.1mg/kg and normal saline placebo, 2) morphine 0.1mg/kg and 0.15 mg/kg ketamine and 3) morphine 0.1mg/kg and 0.3 mg/kg ketamine. The study results indicated there was greater pain relief for the ketamine/morphine study groups than the morphine only group. From the study it was concluded that low dose ketamine is a viable analgesic adjunct to morphine for the treatment of moderate to severe acute pain. Dosing of 0.3 mg/kg is possibly more effective than 0.15 mg/kg. This is closely comparable to the dose of ketamine used in our study; 0.25mg/kg.

In addition to assessing pain control, this study also aimed to assess for adverse effects with use of standard dose morphine alone and the low dose combination of morphine and ketamine. In this study 26.5% of the study participants experienced adverse effects of the study drugs. It's noteworthy that the adverse effects reported were minor and could be mitigated by commonly available antidotes to minimize the discomfort to patients i.e. administration of anti-emetics to prevent nausea and administration of benzodiazepines to prevent hallucinations. No study participant experienced any life threatening adverse effect.

The low dose morphine and ketamine group however had a higher percentage experiencing side effects (34.04%) as compared to the standard dose morphine alone group (19.06%). Among the patients in the ketamine/morphine group who experienced adverse effects, 68.5% experienced psychomimetic adverse effects i.e. hallucinations in 43.5% and euphoria in 25%. Comparatively only 10% in the morphine only group experienced euphoria. Thus, it's likely that most of the psychomimetic adverse effects experienced in the ketamine/morphine group could be attributable to ketamine. In addition, morphine is one of the drugs used to ameliorate the psychomimetic effects of ketamine. Since its administration in the combined morphine/ketamine group didn't quite reduce the psychomimetic adverse effects, it's possible the dose of morphine administered in the ketamine/morphine combination wasn't adequate enough to mitigate the said adverse effects.

In the study by Beaudoin F.L et al [9], a higher proportion (45%) of patients receiving the 0.3mg/kg ketamine and morphine experienced dizziness and light-headedness as compared to (10%) in the morphine only group. Of note is 5% of the 0.3mg/kg ketamine and morphine group experienced respiratory depression (oxygen saturation < 92%) but not necessitating supplemental oxygen. This is largely in conformity with this study since none of the adverse effects experienced was unbearable or life threatening.

Miller et al [17] also had slightly different results.45 subjects were enrolled in this study, Morphine 21 and low dose ketamine 24. From the results, there was no difference in percentage of patients with adverse effects with ketamine (0.3mg/kg) vs morphine (0.1mg/kg) (58% vs 57%). Nonetheless, there was no reported life threatening adverse effect.

The null hypothesis in this study stated that;"the response to a combination of low dose morphine and ketamine for pain control during dressing change in adult burn patients is clinically inferior to the response to morphine alone". From table 3, the p values for both morphine/ketamine combination and current pain are < 0.05 **hence the null hypothesis can be rejected**. The table further shows that the odds of getting a higher score for pain while using the low dose Ketamine/Morphine combination is lower than while using Morphine only.

An incidental finding in this study was the relationship between the pain score prior to dressing (currpain) and the pain score during the change of dressing. Collectively, both study groups had

a high number of patients with pain scores of 5 and 6 prior to the change of dressing. This in itself serves to show that there is poor background pain control in the patients in the burns unit. On further exploration, study participants who had high pain scores prior to the change of dressing equally had high pain scores during the change of dressing. This is elaborated on the correlation plot that depicted a very high positive correlation (0.84) between the pain prior to dressing and pain during change of dressing. This in essence implies that good background pain control contributes to good pain control during the change of dressing.

7.6 Conclusion

The results obtained after data analysis can thus be summarized as follows:

1. The pain control during dressing change with the use of the low dose combination of morphine and ketamine is non inferior to standard dose morphine alone.
2. The low dose morphine/ketamine combination has more adverse effects compared to morphine only. The adverse effects are however not life threatening and can be easily mitigated.
3. Subjects who record high pain scores before dressing are also likely to record high scores during dressing.

7.7 Recommendations

1. Healthcare providers should adopt multimodal analgesia to optimize pain relief of burns patients during change of dressing.
2. Healthcare providers should aim to adequately control background burn pain since patients with poor background pain control tend to experience a lot of pain during painful procedures.

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APPENDIX 1: BUDGET

ITEM	**UNIT COST**	**NUMBER NEEDED**	**TOTAL COST (KSH)**
Stationary	2500	6	15000
Drugs			50000
Flash disc	3000	1	3000
Research assistant	30000	1	30000
Statistician	40000	1	40000
TOTAL			**138000**

APPENDIX 2: EXPLANATION FORM

Name of Principal Investigator: Dr Manasseh Nyamari Mose.

Name of the institution: University of Nairobi.

Introduction

I am a Medical Doctor training for a postgraduate degree in Anaesthesiology at The University of Nairobi.

I am conducting a study to compare pain control during change of dressing using either standard dose morphine alone or a combination of low dose morphine and ketamine. As you read this form, there may be some words that you do not understand. Please do not hesitate to ask me to clarify as we go through the information and I will take time to explain.

Purpose of the research

Burns patient normally experience excruciating pain during change of dressing. The reason we are undertaking this study is compare drugs used to control pain during this painful procedure. Your care during this study will not be affected in any negative way if you agree to participate.

Type of research intervention

For this research you will receive either a single drug or a low dose combination of two drugs. The drugs used in this study are normally used for pain control.

Participant selection

You are being asked to participate as part of a group of burn patients who will need change of dressing.

Risks and discomforts

The drugs you will receive during this study will be administered in doses that are safe. However they may cause respiratory depression, nausea, vomiting, pruritus, euphoria and hallucinations. Should you still experience excessive pain despite administration of the study drugs, rescue analgesia will be provided.

Benefits

The knowledge obtained from this project will improve our understanding of the management of pain during change of dressing in burn patients.

Study outcome

If you are interested we could communicate the results of this study to you through electronic mail or post office mail.

Compensation

You will receive no compensation for participating in this study.

Confidentiality

Any information you provide during the study will be kept strictly confidential. Your full name will not appear on any study document and only staff participating in this study will have access to the information you provide.

Right to refuse or withdraw

Your participation in this research is entirely voluntary. You are free to choose whether or not you wish to participate. Your decision whether or not to participate will not affect you current or future relations with KNH or UoN.

You will suffer neither penalties nor loss of any benefit should you decided not to participate. If for any reason, you are not eligible for the study, or decide not to participate, you will receive normal care and standard treatment and medications. You are also free to withdraw from the study at any time should you wish to do so, for any reason

Your co-operation is appreciated.

Should you have any questions feel free to communicate with me concerning the study on the following address;

Dr Manasseh Nyamari Mose

Mobile telephone number: 0725248481

Email:nyamz.nm@gmail.com University of Nairobi

Dr Patrick Otieno Ragot Olang'

Mobile telephone number: 0722523116

Email:patrick.olang@uonbi.com University of Nairobi

KNH-UoN ERC

Email:uonknh_erc@uonbi.ac.ke

APPENDIX 3: CONSENT FORM

I. . . . . hereby consent to participate in this study, having been fully informed of the nature of the study by Dr Nyamari.

Signature .....

Date .....

I, Dr Nyamari confirm that I have fully explained to my patient what this research involves and hereby undersign.

Signature .....

Date .....

APPENDIX 4: EXPLANATION FORM TRANSLATED TO SWAHILI

Low dose combination of morphine and ketamine versus morphine alone in pain control during change of dressing in adult burn patients;parallel group,randomized control trial

Jina la Mtafiti Mkuu: Dkt. Manasseh Nyamari Mose
Jina la chuo: Chuo Kikuu cha Nairobi

Kitangulizi

Mimi ni daktari wa matibabu anayepitia mafunzo ya shahada la postgraduate katika masomo ya nusu kaputi (Anaesthesiology) katika chuo kikuu cha Nairobi.

Ninafanya utafiti unaolinganisha tofauti za kupunguza maumivu nyakati za kubadilishwa bendeji baina ya wagonjwa walio na majeraha ya kuchomeka kwa kutumia morphine au morphine na ketamine zikiwa kwa vipimo vya kadri. Unaposoma fomu hii, utakabiliana na maneno mengine yatakayokushinda kuelewa. Tafadhali usisite kuniomba nifafanue au kuniomba nitamatishe tunapopitia habari na nitachukua muda kukueleza.

Madhumuni ya utafiti

Wagonjwa walio na majeraha ya kuchomeka huhisi maumivu sana nyakati za kubadilishwa bendeji. Madhumuni yetu ya kufanya utafiti huu ni kulinganisha dawa zinazotumika kupunguza maumivu nyakati za kubadilishwa bendeji. Huduma yako haitaathiriwa wakati wa utafiti huu iwapo utakubali kushiriki.

Aina ya mradi wa utafati

Katika utafiti huu, utapokea dawa aina moja au mchanganyiko wa dawa aina mbili. Madawa yanayo tumika katika utafiti huu kwa kawaida hutumika kupunguza maumivu.

Uchaguzi wa washiriki

Unaombwa kushiriki kama mmoja katika wagonjwa wenye majeraha ya kuchomeka watakao badilishwa bendeji.

Athari na kero

Madawa ambayo utapokea katika utafiti huu yatakuwa katika kipimo kisichokuwa na athari. Hata hivyo, yanaweza kusababisha kushindwa kupumua, kuchafukwa na roho, kutapika, kujikuna au kujihisi mchangamfu kupita kiasi. Iwapo utahisi maumivu au kero wakati wa matibabu tutaumia kile kinachojulikana kama "dawa ya kuokoa" iliyothibitishwa kuweza kudhibiti maumivu.

Faida

Elimu itakayopatikana kupitia utafiti huu itaboresha ufahamu wetu wa namna bora ya kupunguza maumivu nyakati za kubadilishwa bendeji miongoni mwa wagonjwa wenye majeraha ya kuchomeka.

Matokeo ya utafiti

Iwapo utataka kujulishwa matokeo ya utafiti huu, tunaweza kukutumia matokeo haya kwa barua pepe au sanduku la posta.

Fidia

Hautapata fidia yoyote kwa ajili ya kushiriki katika utafiti huu.

Siri

Habari yoyote utakayopeana wakati wa utafiti itawekwa kama siri. Majina yako kamili hayatatokezea kwenye hati zozote za utafiti na ni wafanyikazi wanaoshiriki katika utafiti huu pekee watakaoweza kufikia habari utakayopeana.

Haki ya kukataa au kujiondoa

Kushiriki kwako katika utafiti huu ni kwa hiari. Uko huru kuamua iwapo unataka au hutaki kushiriki. Uamuzi wako kuhusu iwapo utashiriki au la hauta athiri uhusiano wa sasa na wa siku za usoni kati yako chuo kikuu cha Nairobi wala Hospitali ya Kitaifa ya Kenyatta.

Hauta athirika au kupata hasara yoyote ya faida iwapo utaamua kutoshiriki. Iwapo kwa sababu yoyote, haufai kujiunga na utafiti, au uamue kutoshiriki, utapokea huduma ya kawaida pamoja na matibabu na madawa za kawaida. Pia uko huru kujitoa kwenye utafiti wakati wowote iwapo utataka kwa sababu yoyote ile.

Ushirikiano wako unathaminiwa. Iwapo una maswali yoyote jisikie huru kuwasiliana nami kuhusu utafiti katika anwani ifuatayo,

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APPENDIX 5: FOMU YA IDHINI

Mimi. . . . . nakubali kushiriki katika utafiti huu, baada ya kuelezewa kamili madhumuni ya utafiti huu na Dkt. Nyamari

Sahihi .....

Tarehe .....

Mimi, Dkt. Nyamari nadhibitisha ya kwamba nimemuelezea mgonjwa huyu kamili madhumuni ya utafiti huu

Sahihi .....

Tarehe .....

APPENDIX 6: DATA COLLECTION TOOL

Part 1

IP Number…….

Age……

Sex…….

TBSA……

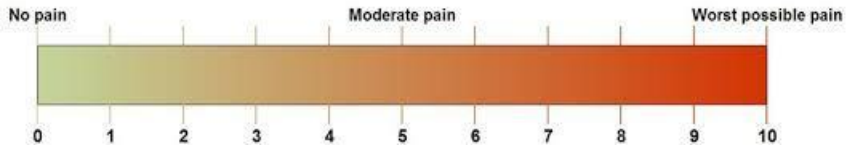
Time span since burn injury……..

I.V drug administered……..

Dosage……..

Part 2

1. Please rate how much pain you have right now using the scale below.



2. What medications are you receiving for pain?

   ……

3. How long ago was the medication for pain administered?

   ……...

4. During the past 24hrs, which of the following have been affected by your pain?

General activity……..

Mood……..

Sleep……...

Walking ability……...

Relations with other people……

Part 3

1. Please rate how much pain you experienced during the session of change of dressing on the scale below.

2. Did you experience any of the following:

Nausea……

Vomiting……..

Pruritus…….

Euphoria……..

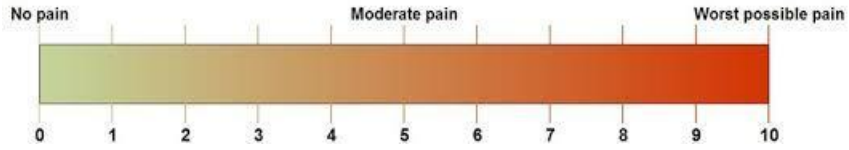
Hallucinations…….

Difficulty in breathing……

3. Was any rescue analgesia given? If yes indicate which one and at what dosage.

……

4. Please rate how much pain you have right now on the scale below (30 minutes after change of dressing)



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Ref: KNH-ERC/A/217

21st June, 2016

Dr. Manasseh Nyamari Mose
Dept. of Anaesthesia
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Nyamari

REVISED RESEARCH PROPOSAL- LOW DOSE COMBINATION O FMORPHINE AND KETAMINE VERSUS STANDARD DOSE MORPHINE ALONE IN PAIN CONTROL DURING CHANGE OF DRESSING IN ADULT BURN PATIENTS: A PARALLEL GROUP: RANDOMIZED CONTROL TRIAL (P154/02/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval period is from 21st June 2016 – 20th June 2017.

This approval is subject to compliance with the following requirements:

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

For more details consult the KNH- UoN ERC website **http://www.erc.uonbi.ac.ke**

LOW DOSE COMBINATION OF MORPHINE AND KETAMINE VERSUS STANDARD DOSE MORPHINE ALONE IN PAIN CONTROL DURING CHANGE OF DRESSING IN ADULT BURN PATIENTS. A PARALLEL GROUP, RANDOMIZED CONTROL TRIAL

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