POST-OPERATIVE PAIN MANAGEMENT IN NEONATAL PATIENTS AT THE KENYATTA NATIONAL HOSPITAL

DR. ROBERT M. MUGO

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STUDENT'S DECLARATION

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

Dr. Robert Murithi Mugo

Sign _____ Date _____

SUPERVISORS DECLARATION

This dissertation has been submitted with our approval as the university supervisors:

Dr. Peter Mwika

MBChB, MMED Paediatric Surgery (UON)

Department of Surgery, University of Nairobi.

Consultant Paediatric Surgeon, KNH

Sign_____ Date _____

Dr. Kihiko Kuria

MBChB (MOI), MMED Surgery (UON)

Department of Surgery, University of Nairobi.

Consultant Paediatric Surgeon, KNH

Sign_____ Date _____

LIST OF INVESTIGATORS/ CO-INVESTIGATORS

1. **Principal researcher**

Dr. Robert M. Mugo
Registrar, Paediatric Surgery
Department of Surgery
University of Nairobi.
P. O. BOX 67174- 00200 Nairobi.
Tel. 0738491953/ 0725491955
Email- robmugo@gmail.com

2. **Research supervisors**

Dr. Peter Mwika
MBChB, MMED Paediatric Surgery (UON)
Department of Surgery, University of Nairobi.
Consultant Paediatric Surgeon, KNH
P. O. BOX 19676- 00202 KNH, Nairobi
Email- mwikapeter@gmail.com

Dr. David Kihiko Kuria
MBChB (MOI), MMED Surgery (UON)
Department of Surgery, University of Nairobi.
Consultant Paediatric Surgeon, KNH
P. O. BOX 19676- 00202 KNH, Nairobi
Email- kihikodk@gmail.com

3. **Research assistants**

Dr. Leon Onkunya
Registrar, Paediatric Surgery
Department of Surgery
The University of Nairobi.
P. O. BOX 19676- 00202 KNH, Nairobi
Tel- 0720955652

4. **Biostatistician**

Stephen Nyaga
Email- skariuki70@gmail.com
Tel- 0737231022

DEDICATION

To my parents, Jamleck and Agnes Mugo for their encouragement and support throughout this undertaking.

To Beth, who cheered me on every step of the way.

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DEFINITION OF TERMS

Pain: An unpleasant somatic or visceral sensation due to actual or potential tissue damage.

Neonate: A child under 28 days of age.

Analgesia: Insensibility to pain without loss of consciousness.

Allodynia: Central nervous system sensitization to pain due to increased neuronal response.

Hyperalgesia: Increased sensitivity to pain.

Multimodal analgesia: A combination of analgesic drugs with different mechanisms of action.

Bimodal analgesia: A combination of two analgesic drugs with different mechanisms of action.

Trimodal analgesia: A combination of three analgesic drugs with different mechanisms of action.

ABBREVIATIONS

CNS	Central Nervous System
GA	General Anaesthesia
KNH	Kenyatta National Hospital
LA	Local Anaesthesia
NBU	New Born Unit
NICU	Newborn Intensive Care Unit
NSAIDS	Non- Steroidal Anti- Inflammatory Drugs
UON	University of Nairobi

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ABSTRACT

Background

Proper detection, assessment and management of post-operative pain in neonatal patients is vital to mitigate poor outcome. In our setting various analgesic modalities are routinely used to control pain in neonates post-operatively, hence there is need to objectively determine the most efficacious agents, which will ultimately be recommended with evidence basis. Currently, no data exists on the current practice of controlling pain after surgery in neonatal patients at Kenyatta National Hospital.

Study Objectives

The primary aim of this study was to assess postoperative pain management in neonatal patients within the first 24 hours of surgery at the Kenyatta National Hospital. To achieve this we scored the level of pain in neonatal patients following surgery, determined the modalities used in post-operative pain management and then correlated the modalities used and the level of pain following surgery.

Methods

This was a cross-sectional hospital based study set in Kenyatta National Hospital. The CRIES score was used to assess the level of post-operative pain. Neonates with a score of ≤ 3 had no pain; those with > 3 had pain while those with > 6 had severe pain. Data was collected on the various modalities used for pain control and classified as single agent, bimodal or trimodal regimens. The data was analysed using SPSS 21.0, (Chicago, Illinois) to determine any co-relation between the modalities used and the level of pain following surgery. Fisher's exact tests was used to test bivariate relationships, with results concluded as significant at a P value <0.05

Results

In this study, we enrolled eighty neonates. Thirty-one patients (39%) were pain free while 61% of patients had pain in the immediate postoperative period with only 5% having severe pain. The average pain score was 4 (SD= 1.1). The most efficacious regimen for pain control was trimodal analgesia with a combination of fentanyl, paracetamol and bupivacaine OR: 0.341 [0.108 – 1.081]. Bimodal analgesia with combinations including locoregional agents provided superior levels of pain control, specifically fentanyl and bupivacaine OR: 0.410 [0.141 – 1.192] and bupivacaine and paracetamol OR: 0.500 [0.192 – 1.299]. The least efficacious modality was a combination of fentanyl and paracetamol OR 0.635 [0.248 – 1.629]

Conclusion

Trimodal analgesia gave the best post-operative pain control, with analgesic combinations incorporating loco-regional agents providing superior levels of pain control.

Recommendations

Wider utilization of trimodal analgesic regimens incorporating loco-regional agents for post-operative pain control in neonatal patients.

Additionally, we encourage the adoption of non-pharmacologic analgesic techniques in neonates that can act as a very effective adjunct to pharmacological modalities.

CHAPTER ONE: INTRODUCTION

Pain is defined as an unpleasant somatic or visceral sensation due to actual or potential tissue damage. (1) It is imperative to manage post-operative pain since the physiologic stress response to pain is an important determinant of surgical outcome. Efforts to reduce the intensity, frequency and duration of pain are a vital part of postoperative management.

There is increasing scientific evidence that even neonates experience pain in response to stressful stimuli. The human fetus has a highly differentiated and functional sensory system by the second trimester.(2) (3) This disproves past misconceptions where it was thought that pain transmission in neonates uses immature and unmyelinated pathways that were incapable of transmitting painful stimuli to the brain.

Neonates respond to pain by manifesting changes in behavior such as facial grimace, hormonal responses such as increased catecholamine and cortisol secretion, and autonomic responses like increases in pulse rate and blood pressure. The tools used to assess pain in the neonate are based on these responses (4)

Interventions that attenuate neonatal pain improve postoperative clinical outcomes. It has been shown that post-operative infants who received an appropriate amount of anaesthesia/ analgesia compared to controls had reduced levels of stress hormones such as norepinephrine, epinephrine, and glucagon. Consequently, these neonates had lower postoperative morbidity such as developing septic complications, metabolic acidosis, coagulopathy and disseminated intravascular coagulation, and an overall lower mortality rate. (5)

It is therefore vital to first identify, properly assess, and appropriately manage pain in neonatal patients to mitigate its deleterious effects on the immediate and long-term outcomes of neonates in our care.

The Paediatric Surgical service at the Kenyatta National Hospital operates on many neonatal patients, and pain management is an important part of their post-operative care. Currently, no published data exists describing the current post-operative pain management practices for neonatal patients at Kenyatta National Hospital. This study therefore aims to elaborate on the current pain management practices for neonatal patients operated at KNH, as well as assessing their effectiveness in preventing postoperative pain.

CHAPTER TWO: LITERATURE REVIEW

2.1 Pain in the Neonate

Neonatal pain was previously categorised as follows: (6)

- Acute or physiological pain: This occurs following tissue injury or skin breaking procedures.
- Established pain: This occurs following a localized inflammatory condition, birth trauma, or after surgical procedures.
- Prolonged or chronic pain- This occurs in severe ongoing disease processes such as necrotising enterocolitis.

A new framework was developed to better characterize neonatal pain based on various parameters including the timing of the pain, the clinical character, effects of the painful stimulus and the response pattern in the neonate. This framework differentiates neonatal pain into several categories, i.e., acute episodic, acute recurrent, prolonged, persistent, and chronic pain. This novel classification also takes into account the presence or absence of primary or secondary hyperalgesia, i.e., increased sensitivity to pain, or allodynia, i.e., central nervous system sensitization to pain due to increased neuronal response to repetitive stimulation. (1)

2.2 Epidemiology

Neonates admitted to the hospital frequently experience many painful procedures. In Sub-Saharan Africa, the exact incidence of neonatal pain is not known. Research has shown that postoperative pain in neonates is severely undertreated in Africa (7). A study done by Kyololo et al. looking at the prevalence of procedural pain in neonatal units in Kenya recruited ninety-five preterm and term neonates and observed them for twenty-four hours. During the study period, there were four hundred and four painful procedures done on the neonates. The neonates who were on mechanical ventilators and those admitted in higher level neonatal units were found to have been subjected to more painful procedures compared to those cared for in lower level units. Unfortunately, none of the procedures had been done with any form of peri-procedural analgesia. (8)

A study done at KNH estimated that the prevalence of pain among younger children admitted in the general paediatric wards was 68.8% (9)

A large prospective study among 430 neonates admitted to French tertiary Newborn Intensive Care Units (NICUs) noted that over fourteen days, these neonates underwent a total of forty two thousand, four hundred and thirteen (42,413) painful procedures. Despite this, only in 20% of the procedures was any specific analgesic therapy provided. (10)

2.3 Pathophysiology of pain

The pain pathway is conceptualised as originating in the periphery, ascending through the spinal cord and relaying in the thalamus before being transmitted to the cerebral cortex. Peripheral nociceptors capable of sensing mechanical, chemical or thermal insults relay to Aδ and C nerve fibers. These neurons then enter the central nervous system through the dorsal horn of the spinal cord; here, they synapse with second-order neurons. These then ascend in a somatotopically-organised fashion as the spinothalamic tract to end at the thalamus. Here, they synapse with neurons that then project to the somatosensory cortex, thus enabling perception of pain in discrete parts of the body. The pain pathway, however, is more than a simple ascending circuit. It is a redundant intricate system that undergoes modulation at peripheral, spinal cord, brainstem, and cortical regions. (11)

Loeser developed a pain model that includes four components namely: nociception, pain, suffering, and pain behavior. (12) Nociception occurs when potential or actual tissue damage is detected by receptors connected to Aδ and C nerve fibers. This is the neural process of encoding noxious stimuli. Pain is then perceived when the signal from the peripheral nervous system reaches the central nervous system. Pain leads to suffering, which is a result of a physical or psychological threat to the integrity of the person. Pain behavior is the fourth component.

2.4 Pain in Neonates

Pain assessment and control in neonates has traditionally not been a priority in clinical management. This is due to several persistent misconceptions among medical practitioners, e.g.:

- Pain pathways in neonates are incompletely developed and hence cannot transmit stimuli efficiently to the brain.
- Only the cerebral cortex is capable of perceiving painful stimuli, and this needs fully mature connections from the thalamus.
- The infant has no psychological context to definitively identify any experience as painful, and this does not develop until two years of age. (13)

Health providers also fear that newborns are at higher risk from adverse effects of commonly prescribed analgesic agents and that the medications potentially have long-term neurodevelopmental and behavioural adverse effects. (14) Another common misconception is that verbal self-reporting by the patient is the gold standard when it comes to assessing an experience as subjective as pain.

A negative attitude by health workers towards opioid use in children was found to be one of the hindrances to adequate treatment of pain at a tertiary children's hospital based in Nairobi. In this study, they also found that other barriers to pain management were inadequate knowledge and skills among the staff, especially on the use of pain rating tools. In this study, only 50% of patients had pain assessment recorded. (15)

In a study done on the knowledge and attitudes of health workers regarding pain assessment and management in paediatric patients at Kenyatta National Hospital, it was found that there were significant deficiencies in knowledge regarding the principles and practice of pain management. Doctors in this study performed better than other cadres of healthcare workers who filled out the study questionnaire. (16) In contrast to this, a study done at Moi Teaching and Referral Hospital looking at the factors influencing postoperative pain management among neonates found that most of the doctors and nurses had adequate knowledge on how to assess postoperative pain in neonates. However, this was not uniform across everyone who participated in the study. Hence, the authors found that pain assessment and subsequent management depended on the knowledge base and

personal decision of the health worker. Lack of tools to assess for the presence of pain as well as the absence of readily available guidelines for post-operative pain management in the newborn unit were cited as one of the critical challenges faced by the healthcare workers. (17)

There is a lot of evidence that both preterm and term neonates experience pain and stress in response to injury. Studies have documented various neonatal reactions to painful stimuli, including autonomic response such as increases in blood pressure and pulse rate, hormonal such as increased cortisol and catecholamine secretion and behavioural responses such as facial grimacing and limb flexion. (18) (19) The various tools used for pain assessment in the neonate are based on these responses.

2.5 Consequences of Inadequately Treated Pain in the Neonate

Inadequately treated pain in the immediate post-operative period is associated with deleterious physiologic effects. Respiratory compromise can occur due to rapid shallow breathing, reduced alveolar expansion, and inadequate cough. This leads to decreased oxygen saturation, atelectasis, and retention of secretions, which leads to prolonged oxygen dependence and predisposes to respiratory tract infections. Sympathetic nervous system activation leads to tachycardia, elevated blood pressure, and changes in sleep patterns. Increased cortisol secretion in response to stress causes increased metabolic rate with rapid glucose utilization and breakdown of stored amino acids. Cortisol also depresses the immune system with an increased risk of infection and poor wound healing. The stress response to pain also impairs gastrointestinal motility, causing delayed gastric emptying and prolonged ileus. This causes delayed resumption and advancement of enteral feeds. (20)

Being exposed to nociception in the neonatal period has longer-term adverse effects on subsequent responses to pain and developmental outcomes. It has been shown that exposure to repeated painful stimuli during the neonatal period leads to the development of enhanced pain sensitivity or chronic pain syndromes later in life. For instance, in one study, infants who had repeated heel sticks in the period just after birth to assess for hypoglycemia had augmented pain responses during subsequent venipunctures compared to healthy infants not subjected to the same. (21) Infants exposed to pain as they were circumcised at birth were shown to experience more significant pain at immunization

six months later (22). It has also been shown that in adolescents who were born preterm there is higher somatic pain sensitivity compared to adolescents born at term. (23)

Clinical outcomes are improved by interventions that attenuate neonatal pain. In one study, it was shown that post-operative infants who received an appropriate amount of anaesthesia/analgesia compared to controls had reduced levels of stress hormones such as norepinephrine, epinephrine, glucagon, and cortisol. These infants had decreased morbidity in the postoperative period, i.e. septic complications, metabolic acidosis, coagulopathy such as disseminated intravascular coagulation and an overall lower mortality rate (24)

In long-term follow up, neonates exposed to pain-related stress have been shown to have an increased risk of adverse outcomes such as impaired cognitive development, altered cognitive processing, and disturbances in the hypothalamic-pituitary-adrenal axis. (25) (26)

Because of all the above reasons, it is vital to first identify, properly assess, and appropriately manage pain in neonatal patients in order to mitigate its deleterious effects on the immediate and longer-term outcomes of neonates in our care.

2.6 Neonatal pain assessment tools

A pre-requisite to optimal pain assessment and management in the neonate is to select a pain assessment tool that is sufficiently sensitive, accurate, and validated for clinical use. Neonates cannot self-report the presence of pain; hence, the assessment tools used in neonates rely on surrogate measures of physiological and behavioural changes after exposure to painful stimuli. Physiological assessments include alterations in heart rate, beat-to-beat heart rate variability, blood pressure, breathing pattern, respiratory rate, oxygen saturation, palmar sweating, skin colour, or pupillary size. Behavioural responses include facial expressions, crying patterns, hand and body movements, muscle tone, sleep pattern, and consolability. This cluster of findings is associated with acute and post-operative pain. (27) (28) (29)

Some of the various clinically validated tools used in the assessment of post-operative neonatal pain include the following:

1) CRIES score: This is a tool structured as a ten-point scale. It is an acronym of five behavioural and psychological variables that are associated with neonatal pain. C--Crying; R--Requires increased oxygen administration; I--Increased vital signs; E--Expression; S--Sleeplessness. It is validated for assessing postoperative pain. The CRIES tool is advantageous since it employs a mnemonic that is easy to remember. It also involves the measurement of just five variables that are coded on a scale from zero to two; hence, it is easy to apply. This is in contrast to other scales that need one to assess anything from seven to ten variables, which may be overwhelming for a busy healthcare professional in a crowded unit. CRIES score also does not necessitate manoeuvers that may agitate the neonate like invasive measurements of mean arterial pressure. The CRIES tool has been in use for over twenty years and has been validated against other commonly employed pain assessment tools. (27) (28) (30) It has been employed successfully to assess for postoperative pain in neonates in our environment in a study done at a tertiary institution in Kenya. (17)
2) PIPP-R- Premature Infant Pain Profile-Revised: The PIPP-R is a 7-item multidimensional measure of pain. The PIPP includes three behavioral (facial actions: brow bulge, eye squeeze, nasolabial furrow), two physiological (heart rate and oxygen saturation), and two contextual (gestational age and behavioral state) items. Each item is scored on a 4-point scale (0, 1, 2, 3), which reflects increasing changes in each variable from baseline values. The scores obtained for the seven items are summed for a total pain intensity score. The maximum attainable PIPP score is 21 for preterm neonates <28 weeks gestational age and 18 for full-term neonates. It is validated for procedural and post-operative pain. (31)
3) N-PASS- Neonatal Pain Agitation and Sedation Scale- The five indicators utilised in the N-PASS were chosen for their ease of assessment, their established validity and their ease of applicability in clinical settings: crying/irritability, behavior/state, facial expression, extremities/tone and vital signs (heart rate, respiratory rate, blood pressure and/or oxygen saturation). The pain assessment portion of the N-PASS is labeled ‘pain/agitation' as these are virtually indistinguishable clinically. It is validated for post-operative and procedural pain and can be used in mechanically ventilated patients. (32)
4) COMFORT scale: The COMFORT tool was developed to evaluate discomfort in paediatric patients admitted in the Intensive Care Unit. It has been validated in 0- to 3-year-old

paediatric post-operative patients. The COMFORT indicators include alertness, calmness, respiratory response, movement, mean arterial blood pressure (MAP), pulse, muscle tone, and facial expression. A low score is indicative of coma or sedation; moderate scores are indicative of no distress, and high scores are indicative of distress. (33)

These tools share similar weaknesses. For instance, they require evaluation of signs by subjective observers; hence, there may be some inter-observer variability.

Additionally, these tools often require bedside observations, mental calculation, and the real-time recording of three to ten parameters by the observer. Sometimes the person performing the painful procedure is also the one supposed to observe the neonate's pain response at the same time.

Pain assessment using these tools is limited in a subset of clinical settings and patients. For instance, critically ill or extremely pre-term neonates may demonstrate muted responses to painful stimuli. Some tools cannot assess patients who are on mechanical ventilators or patients who are neurologically impaired or receiving neuromuscular paralytic medications.

2.7 Prevention and treatment of neonatal pain.

Every clinical establishment that takes care of neonates should set up a program to ensure that neonates receive adequate pain control. It should include routine assessment of the infant to detect acute or prolonged pain, anticipate and address post-operative pain following surgery and monitor the responses to analgesics using validated assessment tools.

There are various techniques to achieve analgesia in neonates, including both pharmacologic and non-pharmacologic approaches. These are often used in combination.

2.8 Non- Pharmacologic Analgesia

Non-pharmacologic analgesic techniques effectively reduce pain and discomfort from routine care and minor procedures. They are more efficacious when combined. These include the following:

1. Breastfeeding/ breastmilk: Breastfeeding involves maternal proximity and skin-to-skin contact, which increases endorphin levels and oxytocin levels in the neonate. The sugars

and other nutrients in breastmilk also serve to divert the neonate from the painful procedure (34)

2. Non- nutritive suckling: Having the neonate suck on a pacifier can reduce pain-related distress in both preterm and term infants; however, it is less effective than breastfeeding or oral glucose. (35)
3. Swaddling or facilitated tucking: Gently flexing the infant's limbs stimulates proprioceptive and tactile pathways. In addition, it promotes behaviors like hand to mouth movements that soothe the neonate. (36)
4. Skin to skin contact: Kangaroo care with the neonate in the mother's bosom stimulates tactile pathways and has been shown to reduce neonatal pain responses. (37)

2.9 Pharmacologic Therapy

Pharmacologic therapy for neonatal pain control includes agents such as sucrose administered orally, local analgesics including topical anesthetics and systematic analgesia including paracetamol, non-steroidal analgesic agents, and opioids.

1. Oral sucrose: The mechanism of action is through the activation of opioid and non-opioid systems in the central nervous system. The efficacy of sweet tasting liquids as analgesics has been shown in systematic reviews of randomized controlled trials that included both term and preterm infants. Suggested dosing is 0.1 to 0.2 mL placed on the tongue or buccal surface (via oral syringe or pacifier) (38)
2. Local anaesthetic agents: This includes topical and injectable anaesthetic agents. The most widely used topical agent is a cream based mix of lidocaine and prilocaine. The most common side effect of this is irritation of the skin and transient methemoglobinemia related to the prilocaine component. The most widely used injectable agent is lidocaine. In neonates, combining lidocaine with epinephrine should be avoided to minimize the risk of tissue necrosis and tachyarrhythmias. Recommended dosages are as follows: for topical lidocaine 4% apply 2 g; for infiltration not to exceed 5 mg/kg/dose. Bupivacaine is used for regional blocks, at a peripheral infiltration concentration of 0.125 to 0.25% solution, not to exceed the maximum dose 2 mg/kg (39)

3. Acetaminophen systemic analgesia: The mechanism of action is to block pain impulse generation in peripheral nerves. It is postulated that it may also inhibit synthesis of prostaglandins in the brainstem and hypothalamus. It is administered via the oral, intravenous, or rectal route. Current evidence suggests that acetaminophen alone is ineffective in reducing acute severe pain in neonates. It, however, remains useful as an adjunct combined with opioid therapy or topical anesthetics to treat acute pain in neonates undergoing procedures. Dosing recommendations for this drug are 10 mg/kg/dose every 6 hours; maximum daily dose: 40 mg/kg/day if given IV. Oral dosing for term neonates <10 days: 10 to 15 mg/kg/dose every 6 hours; maximum daily dose: 60 mg/kg/day, oral dosing for term neonates ≥10 days: 10 to 15 mg/kg/dose, every 4 to 6 hours, not to exceed five doses in twenty four hours; maximum daily dose: 75 mg/kg/day. Rectal administration loading dose: 30 mg/kg; then 20 mg/kg/dose every 6 to 8 hours; do not exceed five doses in 24 hours; maximum daily dose: 75 mg/kg/day (40)
4. Non- Steroidal Anti-Inflammatory Agents (NSAIDS): These drugs are not routinely used in neonates because of their adverse effects in newborns, such as the increased risk of bleeding from gastric mucosal ulceration, inducing platelet functional disorders and decreasing glomerular filtration rate. (41)
5. Ketamine: This is an NMDA receptor antagonist. Ketamine provides effective analgesia, sedative and amnesic effects. Patients on ketamine maintain their respiratory drive. Ketamine has only minimal hemodynamic effects. Recommended dosing, as established in a subset of NICU neonates, is 1–2 mg/kg/dose. (42)
6. Opioids: These are agonists of opiate receptors; their analgesic effect is by inhibiting ascending pain pathways. Opioids remain the most effective analgesic option for patients of all ages in moderate or severe pain. However, they should be reserved for neonates undergoing invasive procedures or as post-operative analgesia because of adverse effects such as respiratory depression and sedation. Morphine: Dosing recommendations for intermittent administration IM, IV (preferred), Subcutaneously: Initial: 0.05 to 0.1 mg/kg/dose; usual frequency every 4 to 6 hours. Continuous IV infusion: Initial 0.01 mg/kg/hour (10 mcg/kg/hour); titrate carefully to effect; maximum: 0.03 mg/kg/hour (30 mcg/kg/hour). Oral morphine: 0.08 mg/kg/dose every 4 to 6 hours. Fentanyl intermittent dosing: Slow IV push: Initial: 1 to 2 mcg/kg/dose; may repeat every 2 to 4 hours, titrate

dose to effectiveness. Continuous IV infusion: Initial IV bolus slow IV push: 1 to 2 mcg/kg, then 0.5 to 1 mcg/kg/hour; titrate upward; usual range: 1 to 3 mcg/kg/hour (43)

The American Academy of Paediatrics recommends a stepwise approach to pain management in neonates, similar to the WHO pain ladder. (44)

- Step 1: Non-pharmacologic measures e.g. breastfeeding, sucking, skin to skin kangaroo care, and swaddling.
- Step 2: Topical anaesthetic agents such as lidocaine cream.
- Step 3: Acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDS)
- Step 4: Slow infusion of opioids
- Step 5: Infiltrating local anaesthetics subcutaneously or regional blocks
- Step 6: Deep sedation by combining opioids and sedative analgesics, or general anaesthesia

2.10 Study justification

The paediatric surgical service operates on many neonatal patients. Controlling pain after surgery is an important determinant of surgical outcomes. Currently, no data exists on the current practice of controlling pain after surgery in neonatal patients at Kenyatta National Hospital. The results of this study will form a baseline to show that pain in neonates can be assessed in a simple, objective, and reproducible way in our setting. Additionally, it can be used to form a protocol for post-operative pain management for neonates at Kenyatta National Hospital (KNH).

CHAPTER THREE: RESEARCH QUESTION AND STUDY OBJECTIVES

3.1 RESEARCH QUESTION

What is the current practice of post-operative pain management for neonatal patients at the Kenyatta National Hospital?

3.2: STUDY OBJECTIVES

Broad Objective

To assess postoperative pain management in neonatal patients within the first 24 hours of surgery at the Kenyatta National Hospital.

Specific Objectives

1) To score the level of pain in neonatal patients following surgery at Kenyatta National Hospital.
2) To determine the modalities used in post-operative pain management in neonatal patients undergoing surgery at Kenyatta National Hospital.
3) To correlate the modalities used and the level of pain following surgery in neonatal patients at Kenyatta National Hospital.

CHAPTER FOUR: RESEARCH METHODOLOGY

Study design

This was a cross-sectional study.

Study area

The study was conducted at the Kenyatta National Hospital. This is a national teaching and referral hospital, with two thousand-bed capacity. It serves as the teaching hospital for the University of Nairobi, College of Health Sciences for both the undergraduate and postgraduate programs. This study took place in the wards where neonatal paediatric surgical patients were admitted, namely the New Born Unit, the Paediatric Renal Unit, and the Paediatric Surgical ward. On average, about sixteen neonates were operated on each month.

Study population

All neonatal patients, from birth to twenty-eight days post-natal undergoing surgery at the Kenyatta National Hospital who met the inclusion criteria were recruited for the study.

Inclusion criteria

All patients from birth to twenty-eight days post-natal undergoing surgery by the paediatric surgical unit at the Kenyatta National Hospital whose parents or guardians provided written consent.

Exclusion criteria

- Any patient whose parents declined to consent for the study.
- Any preterm patient
- Any continuously sedated patient
- Any mechanically ventilated patient
- Any patient with an underlying neurologic disorder.
- Any patient managed by multiple specialized surgical services

Sampling technique

Consecutive non-random recruitment of patients who met the inclusion criteria until the desired sample size was reached.

Sample size

Sample size was calculated using the Fisher's formula:

$$n = \frac{Z^2 x\ P(1-P)}{d^2}$$

Where,

n = Desired sample size

Z = Value from standard normal distribution, this corresponds to the desired confidence level (Z=1.96 for 95% CI)

P = expected proportion of the attribute present in the population. This is arbitrarily estimated to be 50% as there is no data available on the prevalence of postoperative pain in neonates.

d = desired precision (0.05)

$$n_0 = \frac{1.96^2 x\ 0.5(1-0.5)}{0.05^2} = 384$$

Data collection was over a period of five months. In that time was expected there would be approximately 100 neonates operated on. The sample size after adjustment for finite populations less than 10,000 was:

$$nf = \frac{n_0}{1 + \frac{n_0 - 1}{N}} = \frac{380}{1 + \frac{380 - 1}{100}} = 79$$

Hence, a sample size of 79 patients was required for this study. During the course of the study, we managed to recruit 80 patients.

Consenting procedure

A consent form with a description of this study and its significance was administered to the parents/ guardians by the principal researcher or his research assistant. Only those patients whose parents/guardians willingly provided written consent were included in this study.

Data collection

Neonates who met the inclusion criteria and whose parents or guardians provided consent were recruited into the study. The following data was recorded:

1) Patient demographics - their age, weight, and gender.
2) Operative diagnosis and type of surgery performed.
3) Analgesic agents initiated intraoperatively
4) Analgesic agents continued in the first twenty four hours after surgery.

The anesthesiologist conducting the case or the surgical team prescribed analgesic agents for post-operative pain control. The investigator and research assistant had no role in influencing what analgesic agents were prescribed.

Pain assessment was done at time 0 (exit from the operating room), 3, 6, 12, and 24 hours postoperatively. This is because neonatal stress hormone elevation following surgery have been shown to return to baseline at twenty-four hours postoperatively under most circumstances, similar to the ebb phase of the metabolic response to trauma. The physiologic response to stress hormones is the basis of the measures used in neonatal pain assessment tools. (45,46) Prior research has demonstrated that there is closest co-relation in findings between the various neonatal pain assessment tools in the first twenty-four hours. (28) For reproducibility by other researchers who may wish to conduct a similar study using different pain assessment tools, we limited our assessments to a similar period.

Pain assessment was done using a scientifically validated scale, the CRIES scale. This is validated for post-operative pain assessment in neonates and is simple to use. The investigator and research assistant conducted the evaluation. All the information obtained was recorded in a standardised data sheet, which was coded and uploaded into a database. This database was password protected

to prevent unauthorised access or tampering. Furthermore, it was backed up on an external hard drive and online cloud-based storage to mitigate against data loss.

Quality Assurance

Strict quality control measures were put in place during the course of this study. The study instruments were pre-tested to assess and ensure the clarity of the questions. Only patients who met the inclusion criteria were enrolled in the study. The research assistant was trained in data collection methods and in the ethical handling of the study participants. The pain scoring system employed used vital signs and other clinical signs that are charted as part of routine care of the newborn. The principal investigator and research assistant held regular meetings to review and handle any emerging issues arising relevant to quality control during the study. The primary researcher verified each questionnaire to confirm that responses were filled correctly with no skipped questions.

Data analysis and presentation

The data was entered into a database, which was have data coding and quality control incorporated to limit inaccuracies. Afterwards, the data was exported to Statistical Package for Social Sciences software (SPSS 21.0 Chicago, Illinois), which was used for data analysis. Continuous variables such as age and weight were summarised using mean and standard deviation or median and interquartile range depending on the presence of outliers. Categorical variables such as gender and severity of pain were summarized as frequencies and percentages and presented in tables, pie charts, and histograms. Chi-square test and Fisher's exact test were used to ascertain association among clinical variables. A P-value of less than 0.05 was considered statistically significant based on two sided tests.

Dissemination plan of study findings

The findings of this study shall be presented at the departmental and college level, and as presentations at national and international scientific conferences. The results shall be submitted for publication in a peer-reviewed scientific journal.

Ethical considerations

This study began only after approval from the Department of Surgery at the University of Nairobi (UON) and the Ethics and Research Committee of the University of Nairobi/ Kenyatta National Hospital (Ref KNH-ERC/A/358; Appendix VI). The parents/ guardian of every patient included in the study was taken through the process of informed consent, with the option of declining to participate in the study at will clearly explained to them. The patients also had the option to withdraw from the study at any time with no consequence. The study was observational, with no direct intervention on the participants due to the study. However, the patients who were observed to be in pain during the study were brought to the attention of the relevant personnel for appropriate action. Confidentiality was upheld at all times, with the use of only inpatient numbers and detailed information only available to the researcher and authorized research assistant.

CHAPTER FIVE: RESULTS

5.1: Participant Characteristics

In this study, we enrolled eighty eligible neonates undergoing surgery over a period of five months from October 2019 to February 2020.

The patients' ages ranged from one day to twenty-eight days with a median age of seven days and a mean age of 8.98 ± 6.58 days. The age distribution is demonstrated in the chart below:

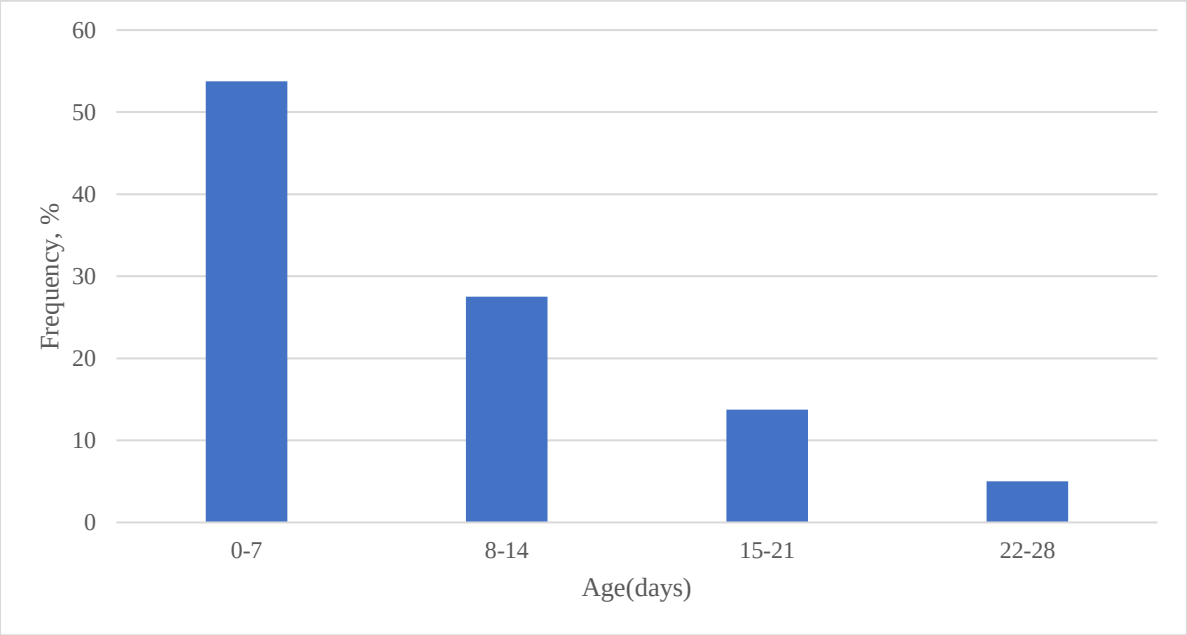

Figure 1: Age distribution of study participants.

The study participants were thirty-seven male patients (46.3%), and forty-three female patients (53.8%). This is demonstrated in figure 2 below:

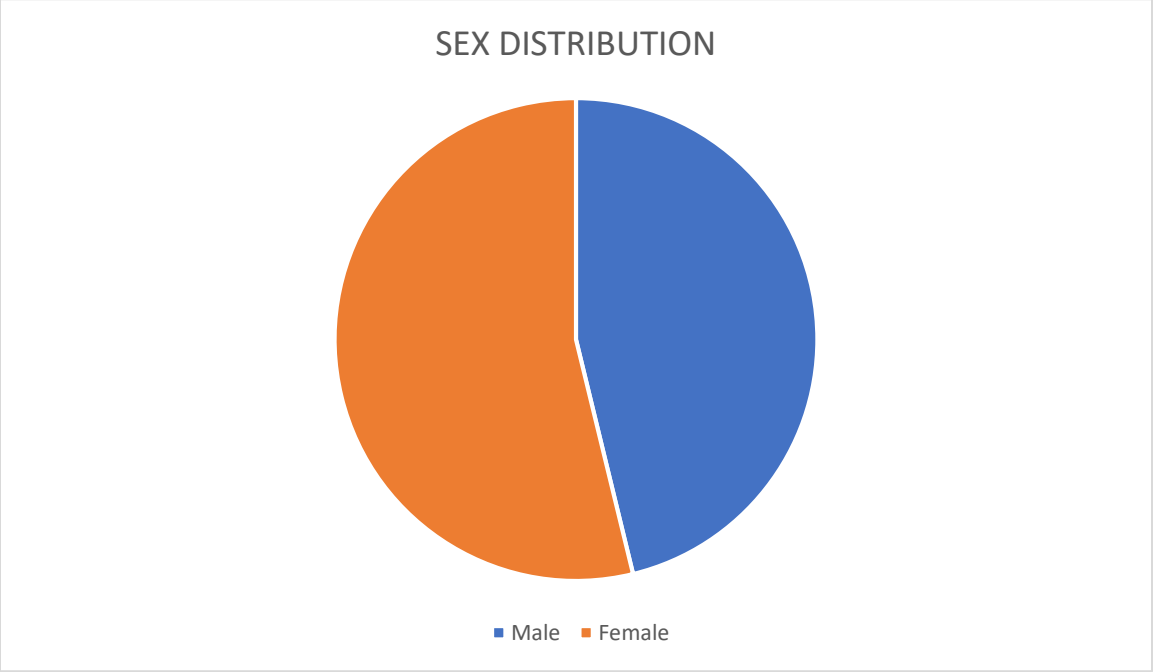

Figure 2: Sex distribution of study participants

The weights of the patients ranged from 2 to 4.5 kg, with a mean of 2.80±0.55 kg and median of 2.80kg, (IQR=2.40kg-3.00kg)

The pre-operative heart rate as taken before surgery ranged from 100bpm to 170bpm with a mean heart rate of 133 bpm ±14.7. This is represented in the figure below:

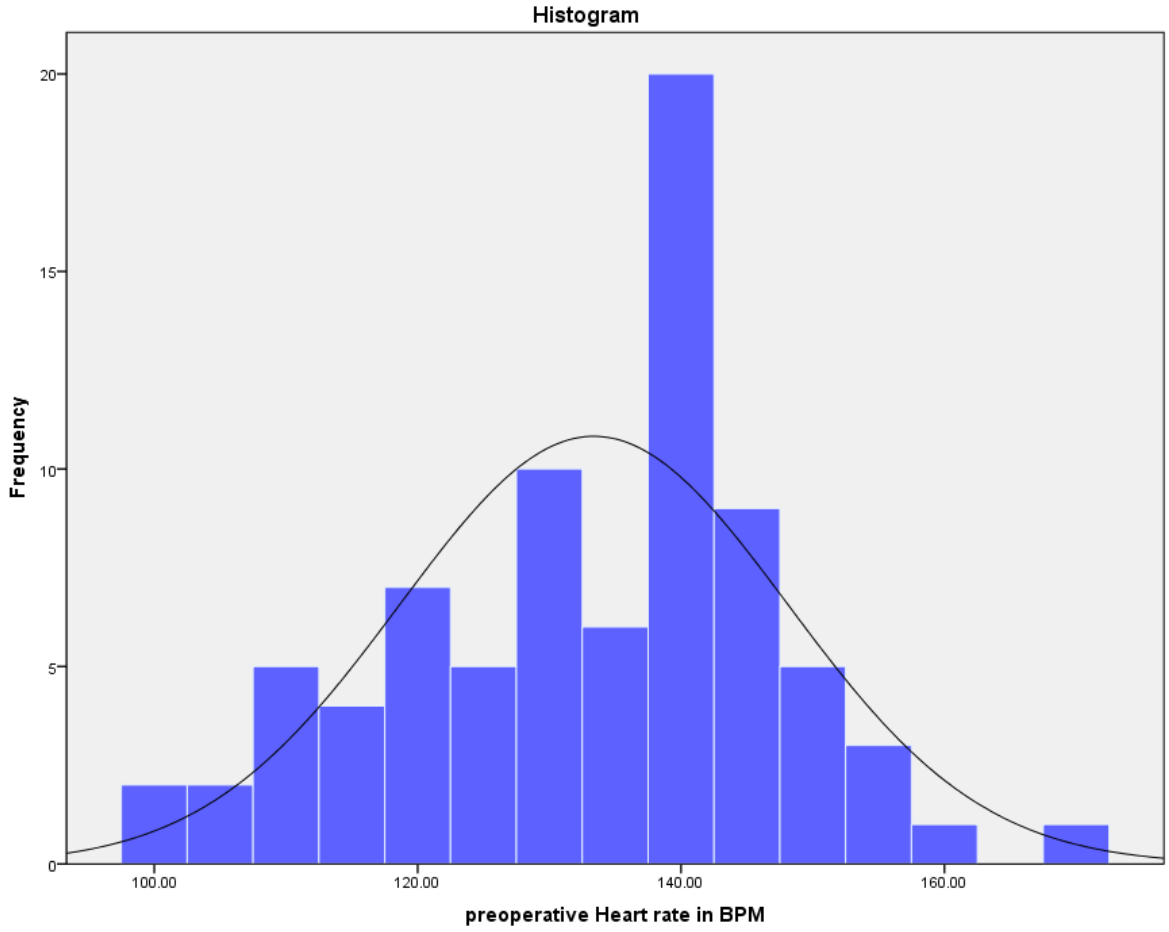

Figure 3: Histogram of pre-operative heart rate of study participants

Table 1: Operations carried out on study participants

OPERATIONS	Number (N=80)	Percentage
Laparotomy	50	63%
Mini-laparotomy	25	31%
Excision of mass	4	5%
Thoracotomy	1	1%

The neonates that met the inclusion criteria for the study had operative management as summarized in the table above. The commonest operation was laparotomy, followed by mini-laparotomy for peritoneal dialysis catheter insertion.

5.2 Post-operative pain scores

The CRIES score is a validated neonatal postoperative measurement tool, which we used to assess the level of pain following surgery. Pain assessment was done at time 0 (exit from the operating room), 3, 6, 12, and 24 hours postoperatively. For analysis, we used the score at a standard time of 6 hours after exit from the operating room. This timeframe allowed us to review the neonates before they received additional analgesic medication in the ward, either as scheduled or as a result of being assessed as having pain. Neonates with scores of 3 or less were categorized as having no pain while those with scores of above 3 were categorized as having pain in the immediate post-operative period. Neonates that had scores above 6 were categorized as having severe pain.

Of the patients assessed, thirty-one patients (39%) were pain free while 61% of patients had pain in the immediate postoperative period. Of the patients who had pain, only 5% had severe pain. No patient had a pain score above 7. The average pain score was 4 (SD= 1.1) The distribution of the pain scores is demonstrated in the chart below:

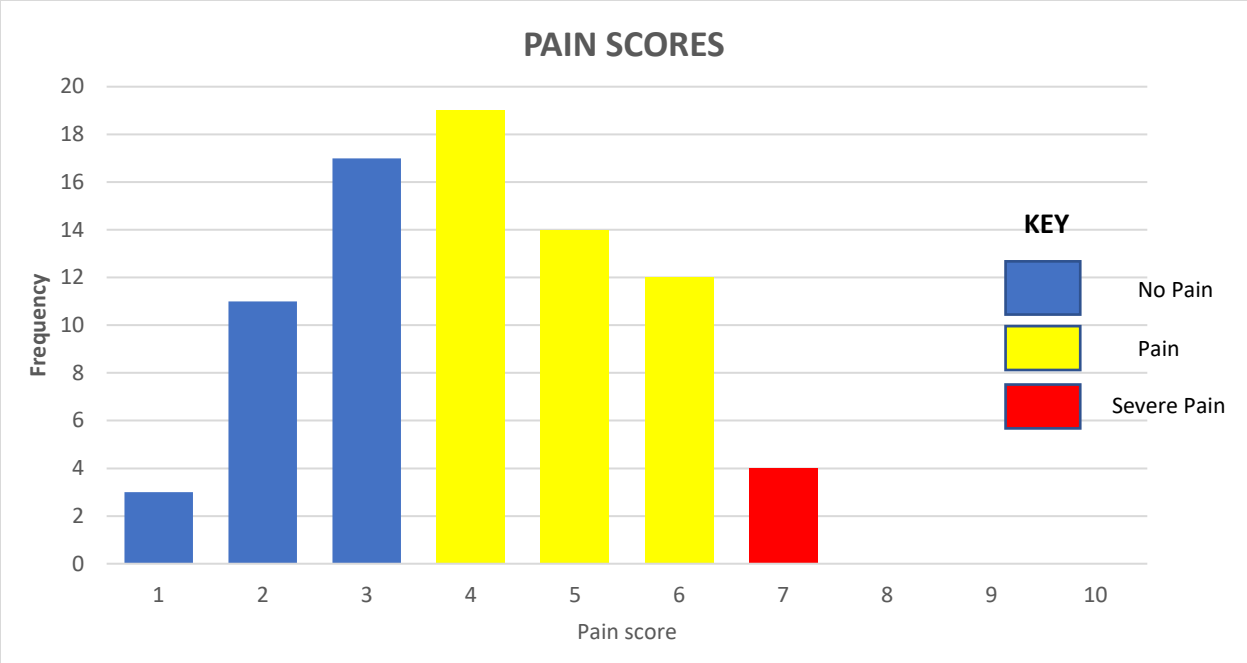

Figure 4: Post-operative pain scores

5.3 Modalities used in pain control

5.3.1: Pharmacologic management

Table 2: Analgesic modalities employed

Analgesic modalities		No of Patients	Percentage
Single agent (Bupivacaine)		5	6%
Bimodal:	Fentanyl + Paracetamol	49	61%
	Fentanyl + Bupivacaine	18	22%
	Bupivacaine+ Paracetamol	26	32%
Trimodal:	Fentanyl + Paracetamol + Bupivacaine	15	18%

The table above summarises the pre-emptive analgesic modalities employed.

Seventy-five patients (94%) had multimodal analgesia, with only 6% on a single agent. In all cases, the single agent was bupivacaine local anaesthesia infiltrated at the incision site, utilised during peritoneal dialysis catheter insertion.

Bimodal analgesia was defined as a combination of two analgesic drugs with different mechanisms of action. There were three combinations in this category with the most commonly employed being a combination of fentanyl and paracetamol (61%), followed by bupivacaine and paracetamol (32%).

Trimodal analgesia, defined as a combination of three analgesic drugs with different mechanisms of action, was employed in 18% of patients.

5.3.2: Non-pharmacologic management

Fifty-six patients (70%) had at least one non-pharmacological pain management modality.

Swaddling was the most common technique employed in fifty-four patients, (67.5%) followed by breast-feeding in thirty-six (45%). The frequency of non-pharmacologic pain management techniques employed is represented in the figure below:

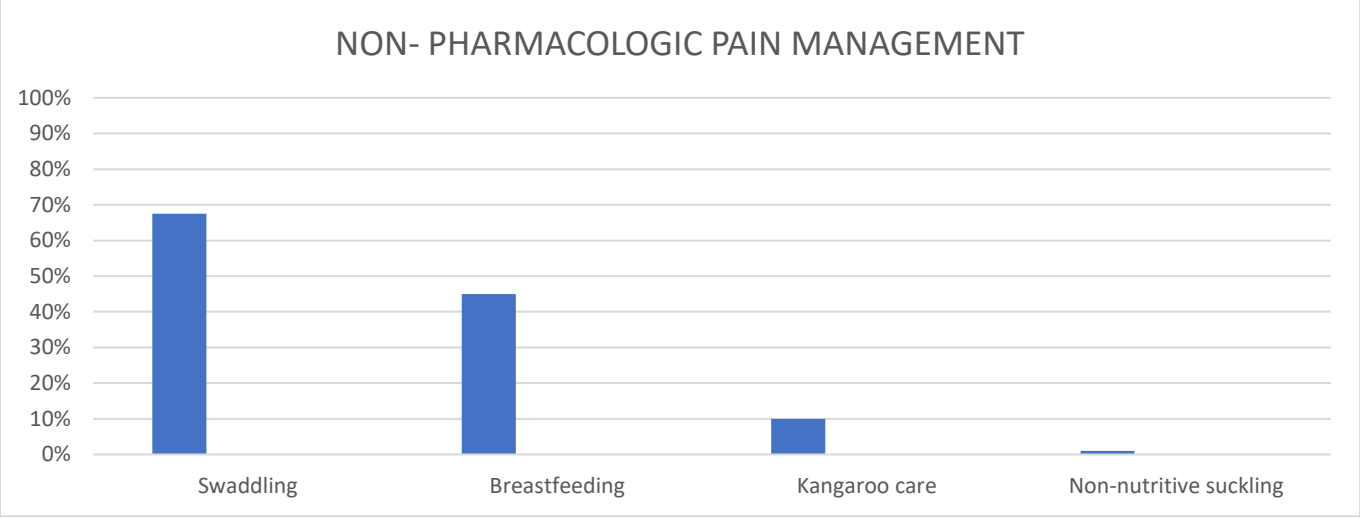

Figure 5: Non-pharmacologic pain management techniques employed.

5.4: Analysis of analgesic modalities and post-operative pain scores

Table 3: Analysis of multimodal analgesic modalities used and post-operative pain scores

	Modality		No pain	Pain	ODDS RATIO	P-value
Trimodal	Fentanyl+ Paracetamol+ Bupivacaine	Yes	9(60)	6(40)	0.341 [0.108 – 1.081]	**0.07**
		No	22(38.8)	43(66.2)		
Bimodal	Fentanyl + Bupivacaine	Yes	10(55.6)	8(44.4)	0.410 [0.141 – 1.192]	**0.10**
		No	21(33.9)	41(66.9)		
	Bupivacaine + Paracetamol	Yes	13(50)	13(50)	0.500 [0.192 – 1.299]	**0.15**
		No	18(33.3)	36(66.7)		
	Fentanyl + Paracetamol	Yes	21(42.9)	28(57.1)	0.635 [0.248 – 1.629]	**0.34**
		No	10(32.3)	21(67.7)		

We performed a logistic regression analysis to determine the most efficacious combination of analgesic regimen. Although not significant, trimodal analgesia provided the highest level of pain control. OR: 0.341 [0.108 – 1.081]. Additionally, bimodal combinations with locoregional agents appeared to be more efficacious in pain control. This association is shown in table 3 above and figure 6 below:

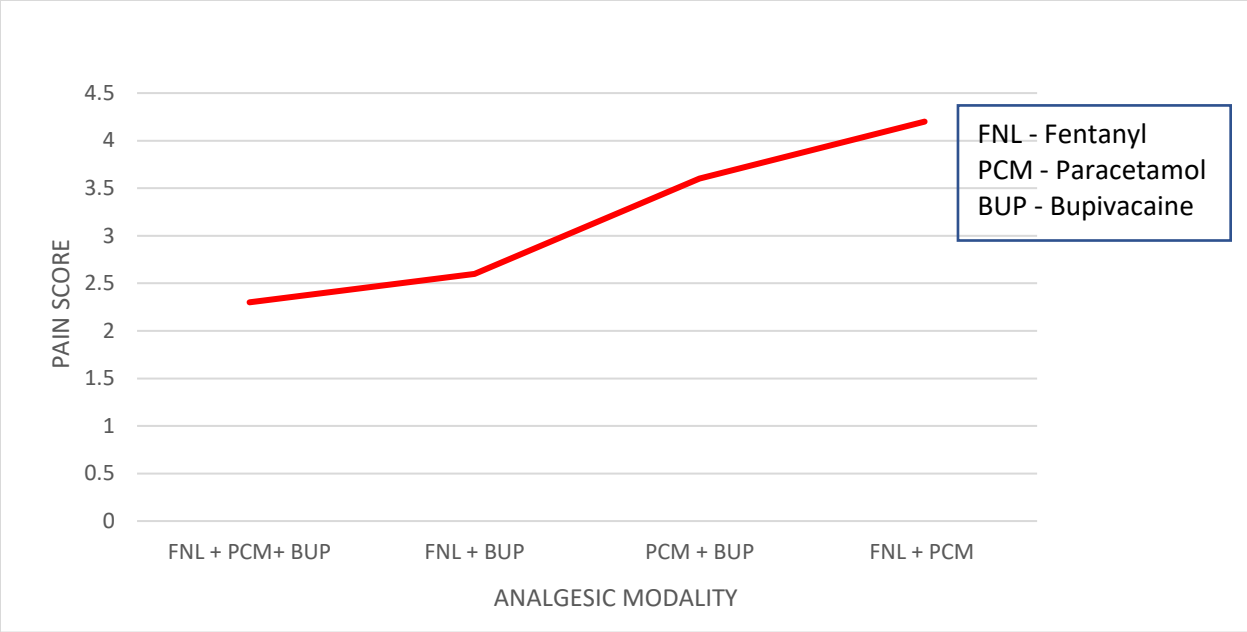

Figure 6: Association of analgesic modalities administered and post-operative pain scores

CHAPTER SIX: DISCUSSION

The main objective of this study was to assess post-operative pain management practices for neonatal patients. It is critical to accurately assess and manage post-operative pain since the physiologic stress response to pain is an important determinant of surgical outcome. To this end, we scored the level of pain in neonatal patients following surgery using a validated neonatal pain score, the CRIES score. We then determined the modalities used in post-operative pain management in neonatal patients undergoing surgery. Finally, we analysed the data to see whether there was a co-relation between the modalities used and the level of pain following surgery. In doing so, we determined that a majority of our patients had some degree of pain. Additionally, this study determined that trimodal analgesia appeared to be the most effective form of pain control and the inclusion of locoregional agents in multimodal analgesia provides superior levels of pain control. These study findings are further explored below:

Demographic and clinical characteristics:

The median age of our patients at surgery was seven days. This reflected the fact that these patients presented with life threatening congenital anomalies that needed timely operative management or had acquired conditions that needed operative intervention soon after birth as part of their management. In our series, a large number of patients had anorectal malformation, anterior abdominal wall defects, small bowel atresia and other conditions that necessitated laparotomy. The case mix therefore was a good representation of the neonatal pathologies commonly handled by paediatric surgeons. This compares well to a study done at Moi Teaching and Referral Hospital in Eldoret where the most common surgery done in neonates was for anorectal malformation followed by gastroschisis repair (47) as well as similar studies done in developed countries. (14), (28)

Pain assessment

This is the first study done to assess post-operative pain in neonatal patients at the Kenyatta National Hospital. A pre-requisite to optimal pain assessment and management in the neonate is to select a pain assessment tool that is sufficiently sensitive, accurate, and validated for clinical use. The CRIES tool has been in use for over twenty years and has been validated against other commonly employed pain assessment tools. It has also been employed successfully in our

environment to assess for postoperative pain in neonates. (17) The CRIES scale was easy to apply since it involved the measurement of just five variables coded on a scale from zero to two. The parameters assessed are key to its validity and include both physiologic measures such as vital signs and oxygen saturation as well as behavioral signs such crying and facial expressions. The CRIES score is objectively reliable despite a possibility of confounding from other stressors that may bias the score for example an underlying disease, hunger, fatigue, restraint, etc. in the neonate.

From this study, we found that 39% of patients were pain free for the duration of the assessment period. 61% of patients had some pain in the immediate postoperative period, but only 5% of all patients had severe pain on assessment. A similar study done by Martina et al regarding management practices of postoperative pain in neonates at Moi Teaching and Referral Hospital in Eldoret found that at 75% (51/68) of patients were assessed to have some or severe post-operative pain by the 24^{th} hour of assessment using the CRIES score. (47) In this study the average pain score was 4, which reflected the fact that a majority of our patients had some pain in the post-operative period. The fact that a significant number of neonates were found to be in pain in the immediate post-operative period is concerning, given all that is known about the deleterious effects uncontrolled pain has in the neonate in the immediate post-operative period and on longer term outcomes. (24)

Pharmacologic pain control:

Multimodal analgesia is defined as the use of a variety of analgesic medications that target different mechanisms of action in the peripheral and/or central nervous system. They have synergistic effects and more effective pain relief compared with single-modality interventions. The clinical practice guidelines from the American Pain Society give a strong recommendation based on high quality evidence that clinicians should offer multimodal therapy for the management of post-operative pain. (48) From our study, 94% of patients had multimodal analgesia.

Bimodal analgesia was defined as a combination of two analgesic drugs with different mechanisms of action. There were three combinations in this category, namely fentanyl and paracetamol, fentanyl and bupivacaine and bupivacaine and paracetamol. The most commonly employed was a combination of fentanyl and paracetamol (61%), followed by bupivacaine and

paracetamol (32%). This is in contrast to a study done by Mutungi et al looking at the analgesic medications used intra-operatively in children undergoing elective inguinal hernia repair at Kenyatta National Hospital that found that the most common analgesic agents used were a combination of paracetamol and loco regional analgesic agents. (49)

Trimodal analgesia was defined as a combination of three analgesic drugs with different mechanisms of action. It was employed in 18% of patients, who received a combination of fentanyl, paracetamol and bupivacaine.

None of the patients in our study received an NSAID for analgesia. These drugs have adverse side effects in neonates, related to increased rates of necrotising enterocolitis, acute kidney injury with decreased glomerular function, gastric mucosal ulceration leading to upper gastrointestinal bleeding and platelet dysfunction. For this reason, they are contraindicated in neonates. (41)

The mode of delivery of analgesic agents was intravenous in all cases for paracetamol and opioids. Local anaesthetic drugs were administered as regional blocks, i.e. caudal block in 22% and as infiltration at the incision site in 78%. Other options for delivering local anaesthetic drugs in neonates include specific nerve blocks e.g. ilioinguinal nerve block employed in inguinal hernia surgery. Another method is use of indwelling epidural catheters placed at the time of surgery, with the catheter tip level of placement varying depending on the dermatomal level of the procedure. This catheter may be used to infuse analgesic medication in the post-operative period. Local anesthesia delivered using a wound catheter at the surgical site placed under direct vision by the surgeon has been described for pain relief after median sternotomy in neonates. (50) In our setup, several challenges may have precluded the application of these techniques. Neonatal epidural or peripheral infusion catheters are not routinely available in this hospital.

Non-pharmacologic pain control

Non-pharmacologic pain control was employed in a majority of the patients in the study. The most commonly employed technique was swaddling followed by breastfeeding. Non-pharmacologic analgesic techniques effectively reduce pain and discomfort from routine care and minor surgical procedures. After major surgery, they act as an adjunct to pharmacologic analgesia. This effect is achieved by increasing the release of endogenous endorphins. (51) Of note is that despite its known beneficial effects, kangaroo care was employed in only 10%. This

may reflect the different nature of surgical neonates who might have drains, multiple intravenous drips and wound dressings that may be a barrier to kangaroo care.

Association of pain scores and analgesic medications:

Pre-emptive analgesia is a treatment modality initiated before the painful stimulus, and it plays an important role in pain management as it prevents activation and sensitization of peripheral and central pain pathways. Potentially, it is more effective than similar analgesic treatment started after surgery. Both animal studies and clinical studies in neonates have shown that pre-emptive analgesia in the neonatal period prevent both immediate and long term side effects of pain. (52)

The patients who received trimodal analgesia with bupivacaine, fentanyl and paracetamol were less likely to have pain in the immediate post-operative period compared to the other multimodal analgesic regimens employed which had two agents. This is to be expected since the drugs act synergistically targeting different levels in the pain pathway, with bupivacaine blocking impulse transmission from peripheral sensory nerves, fentanyl inhibiting transmission through the spinal tracts and paracetamol acts centrally on the hypothalamus and peripherally by preventing prostaglandin mediated sensitization of peripheral nerves.

On analyzing the bimodal analgesic regimens, we found that the only regimen in which a majority of patients was pain free in the post-operative period was a combination of fentanyl and bupivacaine. This highlights the central role loco-regional analgesic techniques have in neonatal pain control. There is abundant evidence in literature showing that the use of various loco-regional analgesic techniques is associated with sustained pain relief following the different procedures done in neonatal patients. It has been shown that epidural post-operative analgesia in infants undergoing major abdominal surgery results in significantly better modification of the neuroendocrine surgical stress response compared to postoperative intravenous morphine infusion. (52, 51).

Study limitations

The sample size was small and therefore not powered for sub group analysis, therefore conclusive statements on associations between pain scores and analgesic modalities can only be inferred on hypothetical basis. However, the results from this study can generate hypotheses for future larger prospective studies on this subject.

This study used a measurement tool that assessed physiological stress parameters. Although all pain is stressful, not all stresses are caused by pain. Physiological distress may have been due to an underlying disease, hunger, fatigue, restraint, etc. in the neonate.

For the purposes of the study, we assumed that the medication on the treatment sheet were given at the doses indicated.

Conclusion

This study demonstrates the current practices of post-operative pain management in neonatal patients at a tertiary hospital setting. The CRIES tool is a reliable and easy to use 10 point score through which we determined an average score of 4 in the immediate post-operative period. The most commonly employed mode of analgesia was multimodal analgesia. Notably, trimodal analgesia gave the best pain control. Furthermore, analgesic combinations that incorporate loco-regional agents are associated with superior levels of pain control.

Recommendations

For clinicians:

- The CRIES tool should be adopted in our setting as a standard, reproducible and validated tool for assessing post-operative pain in neonates.
- Trimodal analgesic regimens incorporating loco-regional agents for post-operative pain control in neonatal patients.

For caregivers:

- Education on the benefits of non-pharmacologic analgesic techniques in neonates that can act as a very effective adjunct to pharmacological modalities.

For policymakers:

- To encourage and fund more studies on neonatal pain management that will lead to development of an evidence based pain management protocol for neonatal patients.

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APPENDICES

Appendix I- CRIES Scale

DATE/TIME						
Crying - Characteristic cry of pain is high pitched. 0 – No cry or cry that is not high-pitched 1 - Cry high pitched but baby is easily consolable 2 - Cry high pitched but baby is inconsolable						
Requires O_2 for SaO_2 < 95% - Babies experiencing pain manifest decreased oxygenation. Consider other causes of hypoxemia, e.g., oversedation, atelectasis, pneumothorax) 0 – No oxygen required 1 – < 30% oxygen required 2 – > 30% oxygen required						
Increased vital signs (BP* and HR*) - Take BP last as this may awaken child making other assessments difficult **0** – Both HR and BP unchanged or less than baseline **1** – HR or BP increased but increase in < 20% of baseline **2** – HR or BP is increased > 20% over baseline.						
Expression - The facial expression most often associated with pain is a grimace. A grimace may be characterized by brow lowering, eyes squeezed shut, deepening naso-labial furrow, or open lips and mouth. **0** – No grimace present **1** – Grimace alone is present **2** – Grimace and non-cry vocalization grunt is present						
Sleepless - Scored based upon the infant's state during the hour preceding this recorded score. 0 – Child has been continuously asleep 1 – Child has awakened at frequent intervals **2** – Child has been awake constantly						
TOTAL SCORE						

A score of 4 and above is indicative that pain is present; a score above 6 is indicative of severe pain.

Appendix II- Data Collection Tool

DATA COLLECTION TOOL

PATIENT STUDY NO…….

GENDER	
AGE	
WEIGHT	
DATE OF SURGERY	
PRE-OPERATIVE HEART RATE	
SURGERY PERFORMED	
TIME SURGERY ENDED	

MEDICATIONS USED INTRAOPERATIVELY

CLASS	**DOSE PRESCRIBED**	**CORRECT DOSE Y/N**
OPIOID-MORPHINE • Intermittent dosing IM, IV, SubQ: Initial: 0.05 to 0.1 mg/kg/dose; usual frequency every 4 to 6 hours • Caudal block- 0.03- 0.1 mg/kg • Continuous IV infusion: Initial: 0.01 mg/kg/hour (10 mcg/kg/hour); titrate carefully to effect; maximum: 0.03 mg/kg/hour (30 mcg/kg/hour)		
OPIOID- FENTANYL • Intermittent doses: Slow IV push: Initial: 1 to 2 mcg/kg/dose; may repeat every 2 to 4 hours, titrate dose to effectiveness • Caudal block 0.25, 0.5 or 1mcg/kg • Continuous IV infusion: Initial IV bolus: Slow IV push: 1 to 2 mcg/kg, then 0.5 to 1 mcg/kg/hour; titrate upward; usual range: 1 to 3 mcg/kg/hour		
KETAMINE		

• IV: 0.5 to 2 mg/kg/dose		
LOCAL ANESTHESIA- LIDOCAINE • Infiltration not to exceed 5 mg/kg/dose		
LOCAL ANESTHESIA- BUPIVACAINE • Caudal block: Usual concentration ≤0.25% solution, dose range: 0.5 to 1.25 mL/kg; dose should not exceed 2.5 mg/kg. • Peripheral infiltration concentration 0.125 to 0.25% solution: not to exceed the maximum dose 2 mg/kg		
PARACETAMOL (IV) • 10 mg/kg/dose every 6 hours; maximum daily dose: 40 mg/kg/day		
PARACETAMOL (PR) • Loading dose: 30 mg/kg; then 20 mg/kg/dose every 6 to 8 hours; do not exceed 5 doses in 24 hours; maximum daily dose: 75 mg/kg/day		
NSAIDS –DICLOFENAC (Not recommended in neonates)		

MEDICATIONS PRESCRIBED POSTOPERATIVELY

CLASS	**DOSE, FREQUENCY**	**CORRECT DOSE Y/N**
OPIOID- IV MORPHINE • IM, IV (preferred), Sub Q: Initial: 0.05 to 0.1 mg/kg/dose; usual frequency every 4 to 6 hours • Continuous IV infusion: Initial: 0.01 mg/kg/hour (10 mcg/kg/hour); titrate carefully to effect; maximum: 0.03 mg/kg/hour (30 mcg/kg/hour)		
OPIOID- IV FENTANYL • Intermittent doses: Slow IV push: Initial: 1 to 2 mcg/kg/dose; may repeat every 2 to 4 hours, titrate dose to effectiveness • Continuous IV infusion: Initial IV bolus: Slow IV push: 1 to 2 mcg/kg, then 0.5 to 1 mcg/kg/hour; titrate upward; usual range: 1 to 3 mcg/kg/hour		
OPIOID- ORAL MORPHINE		

• 0.08 mg/kg/dose every 4 to 6 hours		
NSAID- IV DICLOFENAC (Not recommended for analgesia in neonates)		
NSAID- ORAL BRUFEN (Not recommended for analgesia in neonates)		
LOCAL ANESTHETIC- TOPICAL • Lidocaine 4% apply 2 g		
LOCAL ANESTHESIA- LIDOCAINE • Infiltration not to exceed 5 mg/kg/dose		
LOCAL ANESTHETIC- BUPIVACAINE • Peripheral infiltration concentration 0.125 to 0.25% solution: not to exceed the maximum dose 2 mg/kg		
PARACETAMOL (IV) • 10 mg/kg/dose every 6 hours; maximum daily dose: 40 mg/kg/day		
PARACETAMOL (Oral) • Term neonates <10 days: 10 to 15 mg/kg/dose every 6 hours; maximum daily dose: 60 mg/kg/day • Term neonates ≥10 days: 10 to 15 mg/kg/dose every 4 to 6 hours, do not exceed 5 doses in 24 hours; maximum daily dose: 75 mg/kg/day		
PARACETAMOL (PR) • Loading dose: 30 mg/kg; then 20 mg/kg/dose every 6 to 8 hours; do not exceed 5 doses in 24 hours; maximum daily dose: 75 mg/kg/day		
ORAL SUCROSE • Oral: 0.1 to 0.2 mL of 24% solution placed on the tongue or buccal surface (via oral syringe or pacifier)		

NON PHARMACOLOGIC ANALGESICS TECHNIQUES EMPLOYED

MODALITY	EMPLOYED WITHIN 24 HOURS POST-OP Y/N
BREASTFEEDING	
SKIN TO SKIN/ KANGAROO CARE	
SWADDLING	
NON-NUTRITIVE SUCKLING	

CRIES SCALE

	Date/ Time				
	0 hrs	3hrs	6hrs	12 hrs	24hrs
CRYING The characteristic cry of pain is high pitched. Score: **0.** If no cry or cry which is not high pitched **1.** If cry high pitched but the baby is easily consoled score 1 **2.** If cry is high pitched and baby is inconsolable score 2					
REQUIRES O2 FOR SAT > 95% Look for ***changes*** in oxygenation. Babies experiencing pain manifest decreases in oxygenation as measured by Oxygen saturation. Score: **0.** If no Oxygen is required **1.** If < 30% **O2** is required **2.** If > 30% is required					
INCREASED VITAL SIGNS Use baseline pre-op parameters from a non-stressed period. Multiply baseline HR x 0.2 then add this to baseline HR to determine the HR which is 20% over baseline. Score: **0.** If HR unchanged or less than baseline **1.** If HR is increased but increase is < 20% of baseline score **1** **2.** If HR is increased > 20% over baseline score **2**					
EXPRESSION The facial expression most often associated with pain is a grimace. This may be characterized by brow lowering, eyes squeezed shut, deepening of the naso-labial furrow, open lips and mouth. Score: **0.** If no grimace is present **1.** If grimace alone is present **2.** If grimace and non-cry vocalization grunt is present					

SLEEPLESS This parameter is scored based upon the infant's state during the hour preceding this observation. Score: **0.** If the child has been continuously asleep **1.** If he/she has awakened at frequent intervals **2.** If he/she has been awake constantly					
TOTAL SCORE					

A score of 4 and above is indicative that pain is present; a score above 6 is indicative of severe pain.

APPENDIX III: STUDY TIME FRAME

Table 3: Study Timeline

ACTIVITY	Apr 2019	May 2019	Jun 2019	Jul- Sept 2019	Oct 2019- Feb 2020	Mar 2020	Apr 2020	May 2020
Proposal development								
Ethical Approval								
Data Collection								
Data Analysis								
Dissertation Writing and presentation								

APPENDIX IV: STUDY BUDGET

Budget Item	Amount (Kshs)
Research fee for KNH-ERC	5,000
Statistician consultation fee	30,000
Stationery: (a) Printing (b) Photocopying (c) Binding (d) Pens	 30,000 15,000 30,000 1,000
Research assistant fee	20,000
Pulse Oximeters	20,000
Total	**151,000**
Miscellaneous 10% of total	15,100
Grand total	**166,100**

APPENDIX V: CONSENT FORM

English version

POST-OPERATIVE PAIN MANAGEMENT IN NEONATAL PATIENTS AT THE KENYATTA NATIONAL HOSPITAL

This Informed Consent form is for parents/ guardians with children participating in this study at Kenyatta National Hospital.

We are requesting these patients to participate in this research project, whose title is **"**Post-Operative Pain Management In Neonatal Patients At The Kenyatta National Hospital."

Principal Investigator: Dr. Robert M. Mugo

Institution: School of Medicine, Department of Surgery- University of Nairobi

Supervisors: Dr. Kuria, Dr. P. Mwika

This informed consent has three parts:

1. Information sheet (to share information about the research with you)

2. Certificate of Consent (for signatures if you agree to take part)

3. Statement by the researcher

You will be given a copy of the full informed consent form**.**

Part I: Information sheet

Introduction

My name is Dr. Robert M. Mugo, a postgraduate student at the University of Nairobi's School of Medicine. I am carrying out a study to determine post-operative pain management in neonatal patients at the Kenyatta National Hospital.

This will be determined by data collection by filling a questionnaire and patient examination.

Purpose of the research

Information obtained from this study will reveal to the doctors the post-operative pain management in neonatal patients at the Kenyatta National Hospital.

This study is also a requirement for any doctor who aspires to graduate from our college as a paediatric surgeon.

Voluntary Participation/Right to Decline or Withdraw

I extend an invitation to participate in this study. You will have the opportunity to ask questions before you decide on your child's enrollment into the study. You may seek clarification regarding any bit of the study from myself or my assistant(s) should any part be unclear. The decision to participate in this study will be entirely voluntary after you have comprehensively understood the details herein. By refusing to participate in the study, your child will not be denied medical care. Furthermore, you may stop participating at any time with no consequences whatsoever.

Confidentiality

If you agree to participate, you will be asked to provide personal information and other details related to your child's condition. All the information which you provide will be kept confidential, and no one but the researchers will access it. Your name or your child's name will not appear in any document. A number will identify the information about the participant, and only the researchers can relate the identification number to the said participant. The data will not be shared

with anyone else unless authorized by the Kenyatta National Hospital/University of Nairobi – Ethics and Research Committee (KNH/UoN-ERC).

Risks

Your child or kin's involvement in this research will be through clinical evaluation after surgery, and they will not expose themselves to any additional risks if you consent on their behalf to participate in this research. There is no additional treatment or procedure that your child will be subjected to because of this study, this study is simply to assess whether the child is in pain after surgery.

Cost and Compensation

There will be no extra cost incurred by you (or your kin) from participation in this study. There is also no compensation or any other inducement to participate in this study.

Sharing of information

Following authorization by the Kenyatta National Hospital/University of Nairobi – Ethics and Research Committee (KNH/UoN-ERC), which is a committee whose work is to make sure research participants are protected from harm, relevant medical information yielded from this study may be shared with fellow doctors through scientific seminars, workshops, and publications. Personal information will not be disclosed whatsoever.

Who to contact

This proposal has been reviewed and approved by the KNH/UoN-ERC, for the duration of one year. The responsibility of this committee is to make sure research participants are protected from harm. It was submitted to them through the Chairman of the Department of Surgery at the School of Medicine of the University of Nairobi with the approval of university supervisors. The contact information of these people is given below if you wish to contact any of them for whatever reason;

The Secretary, KNH/UoN-ERC
P.O. Box 20723 KNH,

Nairobi 00202

Tel 726300-9

Email: KNHplan@Ken.Healthnet.org

Principal researcher:

Dr. Robert M. Mugo

Resident, Department of Surgery, School of Medicine, University of Nairobi

P.O. Box 19676 KNH, Nairobi 00202

Mobile No. 0738491953

Research Assistant

Dr. Leon Onkunya

Resident, Department of Surgery, School of Medicine, University of Nairobi

P.O. Box 19676 KNH, Nairobi 00202

Mobile phone 0720955652

University of Nairobi research supervisors

Dr. Kihiko Kuria

Department of Surgery, School of Medicine, University of Nairobi

P.O. Box 19676 KNH, Nairobi 00202

Tel: 0202726300

Dr. Peter Mwika

Department of Surgery, School of Medicine, University of Nairobi

P.O. Box 19676 KNH, Nairobi 00202

Tel: 0202726300

Part II: Consent certificate by patient

I……..freely give consent for my child

(name) ……. to take part in the study conducted by Dr. Robert M. Mugo, the nature of which has been explained to me by him/ his research assistant. I have been informed and have understood that my child's participation is entirely voluntary and I understand that I am free to withdraw my consent at any time if I so wish and this will not in any way alter the care given to my child. The results of the study may directly be of benefit to my child or other patients and to the medical professionals in order to understand better the post-operative pain management in neonatal patients at the Kenyatta National Hospital.

Signature (Parent/Guardian) ……

Date (Day/Month/Year) ……

Statement by the witness if the participant is illiterate

I have witnessed the accurate reading of the consent form to the participant, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Name of witness……

Signature of witness……..

Date……

Left thumb

Part III: Statement by the researcher

I have accurately read out the information sheet to the participant, and to the best of my ability and made sure of the following:

- That the participant consent has been given voluntarily and free of duress.
- That all information given will be treated with confidentiality.
- That refusal to participate or withdrawal from the study will not in any way compromise the quality of care and treatment given to the patient.
- That the results of this study might be published to enhance the knowledge of the subject of research.
- That I have answered all the questions asked by the participant to the best of my ability and knowledge.
- That a copy of this Informed Consent Form has been provided to the participant.

Name of the researcher taking consent ……

Signature of the researcher taking the consent ……

Date ……Day/Month/Year

SWAHILI VERSION

FOMU YA MAKUBALIANO YA KUJIUNGA NA UTAFITI

Fomu hii ya makubaliano ni ya wale watoto ambao wanahudumiwa kwenye kliniki upasuaji wa watoto katika hospitali ya KNH na wamealikwa kujiunga na utafiti **"USIMAMIZI WA MAUMIVU YA BAADA YA UPASUAJI KATIKA WATOTO WACHANGA KATIKA HOSPITALI YA TAIFA YA KENYATTA"**

Mtafiti mkuu: Dkt. Robert M. Mugo

Kituo: Kitengo cha Upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi.

Fomu hii ya makubaliano ina sehemu tatu:

- Habari itakayo kusaidia kukata kauli
- Fomu ya makubaliano (utakapo weka sahihi)
- Ujumbe kutoka kwa mtafiti

Utapewa nakala ya fomu hii.

SEHEMU YA KWANZA: Ukurasa wa habari

Kitambulizi

Jina langu ni Dkt. Robert M. Mugo. Mimi ni daktari ninayesomea upasuaji katika Chuo Kikuu cha Nairobi. Ninafanya utafiti kwa anwani ya, **"USIMAMIZI WA MAUMIVU BAADA YA UPASUAJI KATIKA WATOTO WACHANGA KATIKA HOSPITALI YA TAIFA YA KENYATTA"**

Lengo kuu la utafiti.

Ujumbe utakaodhihirika kutokana na utafiti huu utasaidia madaktari kutadhimini usimamizi wa maumivu ya baada ya operesheni katika watoto wachanga baada ya upasuaji katika Hospitali ya Taifa ya Kenyatta. Utafiti huu utasidia katika matibabu ya watoto walio na shida hiyo.Utafiti huu pia ni mojawapo wa mahitaji ya kuhitimu kwa stashada ya upasuaji.

Ushiriki wa Hiari/Haki ya Kukataa

Ningependa kukualika ushiriki katika utafiti huu. Utapata nafasi ya kuuliza maswali kuhusu utafiti huu, aidha kutoka kwangu au kutoka kwa wasaidizi wangu. Baada ya kuelewa kabisa undani wa maelezo ya utafiti, ushiriki wako utakuwa wa hiari. Iwapo utaamua kutoshiriki katika utafiti, mtoto wako hatanyimwa matibabu. Isitoshe, ukishaamua kushiriki, ni haki yako kukataa kuendelea na ushiriki huo wakati wowote ule bila madhara yoyote.

Taadhima ya Siri

Ujumbe wote utakaotokana na utafiti huu utahifadhiwa kwa siri, na utatumika tu na wahusika wa utafiti kwa malengo ya utafiti pekee. Jina lako au la mtoto wako halitaorodheshwa popote katika utafiti huu; nambari spesheli itatumika katika utambulizi.

Utumizi wa Matokeo ya Utafiti

Nakala za matokeo ya utafiti huu zitahifadhiwa kwa siri katika maktaba ya Idara ya Upasuaji, Chuo Kikuu cha Nairobi. Kwa minajili ya kuendeleza ujuzi wa Sayansi ya Utabibu, huenda haja ya kuarifu matabibu wengine kuhusu utafiti huu itokee. Cha muhimu ni kwamba, ruhusa itaombwa kutoka kwa Afisi ya Maadili ya Utafiti inayosimamia utafiti katika Hospitali kuu ya Kenyatta na Chuo Kikuu cha Nairobi, kabla ya kutumia matokeo ya utafiti huu katika warsha za

Sayansi au kuyachapisha katika majarida ya Sayansi. Nyakati hizo, ujumbe wa kibinafsi hautafichuliwa kamwe.

Madhara

Utafiti huu hauna madhara yoyote kwa mtoto wako.

Gharama/Malipo

Hakuna gharama ya ziada wala malipo utakayopata kutokana na kushiriki kwako katika utafiti.

Anwani za Wahusika

Ikiwa uko na maswali ungependa kuuliza baadaye, unaweza kuwasiliana na:

Mtafiti Mkuu:

Dkt. Robert M. Mugo,

Kitengo cha Upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi,

SLP 19676 KNH, Nairobi 00202.

Simu: 0738491953.

Mtafiti Msaidizi

Dr. Leon Onkunya,
Kitengo cha Upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi,

SLP 19676 KNH, Nairobi 00202.

Simu: 0720955652

Wahadhiri wahusika:

Dkt. Kihiko Kuria
Idara ya Upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi,

SLP 19676 KNH, Nairobi 00202

Simu: 0202726300

Dkt. Peter Mwika
Idara ya Upasuaji, Shule ya Afya, Chuo Kikuu cha Nairobi,

SLP 19676 KNH, Nairobi 00202

Simu: 0202726300

Wahusika wa maslahi yako katika Utafiti:
Karani,
KNH/UoN-ERC
SLP 20723 KNH, Nairobi 00202
Simu: +254-020-2726300-9 Ext 44355
Barua pepe: KNHplan@Ken.Healthnet.org

SEHEMU YA PILI: Fomu ya makubaliano

Nimeelezewa utafiti huu kwa kina. NakubaIi kushiriki utafiti huu kwa hiari yangu. Nimepata wakati wa kuuliza maswali na nimeelewa kuwa iwapo nina maswali zaidi, ninaweza kumwuliza mtafiti mkuu au watafiti waliotajwa hapa juu.

Jina la Mshiriki_____

Sahihi ya mshiriki _____

Tarehe_____

Kwa wasioweza kusoma na kuandika:

Nimeshuhudia usomaji na maelezo ya utafiti huu kwa mshiriki. Mshiriki amepewa nafasi ya kuuliza maswali. Nathibitisha kuwa mshiriki alipeana ruhusa ya kushiriki bila ya kulazimishwa.

Jina la shahidi_____ Alama ya kidole cha mshiriki

Sahihi la shahidi_____

Tarehe _____

SEHEMU YA TATU: Ujumbe kutoka kwa mtafiti

Nimemsomea mshiriki ujumbe kiwango ninavyoweza na kuhakikisha kuwa mshiriki amefahamu yafuatayo:

- Kutoshiriki au kujitoa kwenye utafiti huu hautadhuru mtoto wake kupata matibabu.
- Ujumbe kuhusu majibu yake yatahifadhiwa kwa siri.
- Matokeo ya utafiti huu yanaweza chapishwa ili kuwezesha kuzuia na kutibu matatizo yanayosababishwa na uchungu baada ya upasuaji katika watoto wachanga.

Ninathibitisha kuwa mshiriki alipewa nafasi ya kuuliza maswali na yote yakajibiwa vilivyo. Ninahakikisha kuwa mshiriki alitoa ruhusa bila ya kulazimishwa.

Mshiriki amepewa nakala ya hii fomu ya makubaliano.

Jina la mtafiti _____

Sahihi ya Mtafiti _____

Tarehe_____

Appendix VI: UON/KNH ERC Approval certificate

KENYATTA NATIONAL HOSPITAL
APPROVED
30 SEP 2019
KNH/UoN-ERC
P. O. BOX 20723 - 00202 NAIROBI

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00202
Telegrams: varsity
Tel:(254-020) 2726300 Ext 44355

KNH-UON ERC
Email: uonknh_erc@uonbi.ac.ke
Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/358

30th September, 2019

Dr. Robert Murithi Mugo
Reg. No. H58/80819/2015
Dept. of Surgery
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Mugo

RESEARCH PROPOSAL: POST-OPERATIVE PAIN MANAGEMENT IN NEONATAL PATIENTS AT THE KENYATTA NATIONAL HOSPITAL (P479/06/2019)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and **approved** your above research proposal. The approval period is 30th September 2019 – 29th September 2020.

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. Clearance for export of biological specimens must be obtained from KNH- UoN ERC for each batch of shipment.
f. 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*).
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.

Protect to discover

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

Yours sincerely,

PROF. M. L. CHINDIA
SECRETARY, KNH-UoN ERC

c.c. The Principal, College of Health Sciences, UoN
The Director, CS, KNH
The Chairperson, KNH- UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine, UON
The Chair, Dept. of Surgery, UoN
Supervisors: Dr. Peter Mwika, Dept.of Surgery, UoN
Dr. Kihiko Kuria, Dept.of Surgery, UoN