A comparative study on the effectiveness and safety of 0.5mg/kg and 0.75mg/kg body weight of oral Midazolam as premedication to allay anxiety in children undergoing tonsillectomy and/or adenoidectomy at KNH

A Dissertation in part Fulfillment of the Requirement for the Award of the Degree of Master of Medicine in Anaesthesiology, University of Nairobi

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September 20th 2017©

DECLARATION

This dissertation is my original work and has not been submitted for the award of a degree in any university to the best of my knowledge

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DEDICATION

To my parents, my children and my dear wife Rahma

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TABLE OF CONTENTS

DECLARATION ..... **ii**

DEDICATION ..... **iii**

ACKNOWLEDGEMENT ..... **iv**

TABLE OF CONTENTS ..... **v**

LIST OF FIGURES ..... **vii**

LIST OF TABLES ..... **viii**

LIST OF ABBREVIATIONS ..... **ix**

OPERATIONAL DEFINITIONS ..... **x**

ABSTRACT ..... **xi**

CHAPTER ONE: INTRODUCTION **1**

1.0 Introduction 1
1.1 Background Information 1
1.2 Problem Statement 2
1.3 Research Questions 2
1.4 Research Objectives 3
1.5 Justification 4
1.6 Study Limitations 4
1.7 Study Assumptions 5

CHAPTER TWO: LITERATURE REVIEW **6**

2.0 Introduction 6
2.1 Preoperative anxiety 6
2.2 Risk Factor for Preoperative Anxiety 7
2.3 Preoperative Anxiety Scales 8
2.4 Prevention of Preoperative Anxiety 9
2.5 Premedication in children 9
2.6 Pharmacology of Midazolam 11
2.7 Emergency Delirium 12

CHAPTER THREE: RESEARCH METHODOLOGY **14**

3.0 Introduction 14
3.1 Research Design 14
3.2 Variables 15
3.3 Study Area 15
3.4 Target Population 15
3.5 Exclusion and inclusion criteria 16
3.6 Sample Size Determination and Sampling Procedure 17
3.7 Research Instrument and Data Collection Procedure 19

3.8 Data Analysis 22
3.9 Logistical & Ethical Considerations 23
3.10 Study Findings Dissemination 23
CHAPTER FOUR: FINDINGS 24
4.0 Introduction 24
4.1 Characteristics of Participants 24
4.2 Effectiveness and Safety of 0.5mg/kg and 0.75mg/kg of Oral Midazolam 25
4.3 Comparison in Effectiveness and Safety of 0.5mg/kg versus 0.75mg/kg of Oral Midazolam 31
CHAPTER FIVE: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS 33
5.1 Discussion 33
5.2 Conclusion 36
5.3 Recommendation 36
5.4 Limitation 37
REFERENCES 38
APPENDICES 42
Appendix 1: Data Capture Form 42
Appendix 2: Consent 44
Appendix 3: Assent Form for Children Aged 6-10 Years 48
Appendix 4: Ethical Approval 50
Appendix 5: Study Registration Certificate 51
Appendix 6: Turnitin Originality Report 52

LIST OF FIGURES

Figure 1: Modified-Yale Preoperative Anxiety Scale 8
Figure 2: Number of children undergoing tonsilectomy and/or adenoidectomy at KNH 16
Figure 3: Reaction to Parent Separation between Treatment Arms.....26
Figure 4: Time between Treatment Administration and Parent Separation 27
Figure 5: Mask Acceptance between Treatment Arms.....28
Figure 6: Time from End of Surgery to Extubation.....30
Figure 7: Requiring Supplementary Oxygen between Treatment Arms 31

LIST OF TABLES

Table 1: University of Michigan sedation scale (UMSS).....9
Table 2: Characteristics of Participants 24
Table 3: Changes in Vital Signs.....25
Table 4: Preoperative Sedation Scores 29
Table 5: Post-anaesthesia Sedation Scores 29
Table 6: Effectiveness and Safety of 0.5mg/kg versus 0.75mg/kg of Oral Midazolam 32

LIST OF ABBREVIATIONS

ASA American Society of Anesthesiologists

BWT Body weight

ECG Electrocardiogram

ENT Ear Nose and Throat

Kg Kilogram

KNH Kenyatta National Hospital

Mg Milligram

mYPAS Modified Yale Preoperative Anxiety Scale

OSA Obstructive Sleep Apnoea

PACU Post Anaesthesia Care Unit

RCT Randomized Clinical Trial

UMSS University of Michigan Sedation Scale

OPERATIONAL DEFINITIONS

Easy and comfortable parental separation denotes a child who is quit, unafraid and cooperative or asleep when separated from his or her parent

Uncomfortable parental separation denotes a child who cries consolably or inconsolably or complains when separated from his or her parent

Fair mask acceptance denotes a child who accepts a facemask albeit crying or complaining

Good mask acceptance denotes a child who accepts a facemask easily without crying or complaining

Poor mask acceptance refers to a child who attempt to pull off the mask if not restrained

Desaturation is defined as SPO_2 less than 92% in room air as measured by a pulse oxymeter

Bradycardia is defined as a fall in heart rate greater than 20% from the baseline

Hypotension is defined as a fall blood pressure greater than 20% from the baseline

ABSTRACT

Preoperative anxiety is a manifestations of psychological distress in children undergoing surgery and is found to be most prominent during anaesthesia induction(1) Oral Midazolam is a commonly used premedication drug to allay anxiety in children; the doses recommended in some of the literature indicate a range of 0.25mg/kg to 1.0mg/kg(2). In Kenyatta National Hospital a dose of 0.5mg/kg is used, however a number of studies suggest that the 0.5 mg/kg dose is not effective in 14 to 20% of the children(2,3). There are conflicting reports by previous studies on the different dose of oral midazolam used as premedication to allay anxiety in children undergoing surgery(4–6).

Objective*:* To compare the effectiveness and safety of 0.5mg/kg of oral Midazolam and 0.75mg/kg of oral Midazolam among children undergoing tonsillectomy and/or adenoidectomy in Kenyatta National Hospital.

Research Methodology: This was a prospective randomized controlled double-blinded trial in which children undergoing tonsillectomy and or adenoidectomy at KNH were randomized into two treatment groups, i.e. 0.5mg/kg Midazolam group and 0.75mg/kg Midazolam group. The dependent variables were the ease of parental separation, mask acceptance sedation scores, duration of reversal, and change from baseline vitals. The study utilized 80 children (40 0.75mg/kg group and 40 0.5mg/kg group). Systematic random sampling was applied on rolling basis. The study participants who fitted the inclusion criteria were recruited and randomized via block. All the data collected in the study were sorted, coded and entered in a computer using STATA version 14. Chi-square test and Odds ratio was used to measure the difference in incidences of children who achieved desired sedation between the treatments groups. Mann Whitney U test was used to assess the difference in parental separation scores, mask acceptance scores, Difference in time from end of surgery to extubation between the treatment groups and vital signs between the treatment groups.

Findings: Incidents of inconsolable cry after parental separation was nearly similar (8% versus 10%). Over twice as many participants in 0.5mg/kg arm (22.5%) were preoperatively anxious as compared to the 0.75mg/kg (10%), however, both arms registered similar levels (2.5%) of deep preoperative sedation. Although not statistically significant, more participants in the 0.75mg/kg arm (75%) achieved good mask acceptance as compared to 0.5mg/kg arm (63%).

Conclusion: Both the 0.5mg/kg dose of oral midazolam and 0.75mg/kg dose of oral Midazolam given to children to allay anxiety were found to be equally effective and safe

CHAPTER ONE: INTRODUCTION

1.0 Introduction

This chapter presents the background of the study, problem statement, research objectives and hypotheses, study justification, study assumptions and operational definitions.

1.1 Background Information

Preoperative anxiety, emergence delirium, and postoperative behaviour changes are all manifestations of psychological distress in children undergoing surgery. Preoperative anxiety is most prominent during anaesthesia induction(1). The chief risk factors for postoperative behaviour problems are young age, prior negative experience with hospitals or medical care, postoperative pain, parental anxiety, and certain personality traits of the child(1). Various strategies have been suggested to reduce the child's distress - which include preoperative preparation, premedication, and parental presence during anaesthesia induction among others. Midazolam has been shown to be an effective preoperative medication for reducing anxiety(1).

Oral Midazolam is a commonly used premedication drug to allay anxiety in children; the doses recommended in some of the literature indicate a range of 0.25mg/kg to 1.0mg/kg(2). In Kenyatta National Hospital a dose of 0.5mg/kg is used. However, a number of studies suggest that the 0.5 mg/kg dose is not effective in 14 to 20% of the children(2,3). There are conflicting reports by previous studies on the different dose of oral midazolam used as premedication to allay anxiety in children undergoing surgery. For example; while McMillan CO, Spahr-Schopfer IA, Sikich N et al reports no added advantage, but more side effects for both 0.75mg/kg and 1.0mg/kg doses compared to the 0.5mg/kg dose(4), Sheta and Alsarheed, 2009 and later Somri M, Parisinos CA, Kharouba J et al 2012 reported the superiority of 0.75 mg/kg dose(5,6).

In fact Coté CJ, Cohen IT, Suresh S et al, in their study - a comparison of three doses of a commercially prepared oral Midazolam (0.25, 0.5 & 1.0mg/kg up to a maximum of 20mg) revealed minimal effect on respiration and oxygen saturation even when given at doses as high as 1.0mg/kg orally (maximum 20mg) (7). They also showed no relationship between midazolam dose and duration of post-anaesthesia care unit stay(7). This study therefore aims to assess the effectiveness and safety of these different doses of Midazolam.

1.2 Problem Statement

Preoperative anxiety causes suffering in children prior to surgical procedures and has negative impact on their post-operative recovery(8–10). Anaesthesia induction has been identified as the most stressful event during the entire preoperative period(11). This therefore has called for a search for ways of alleviating anxiety. While non-pharmacological methods have been used, unfortunately a percentage of paediatric patients cannot be successfully managed solely with this method. Midazolam with its rapid onset and relatively short duration of action has proved to be useful in this regard(5). Its optimal oral dose is however, controversial. Doses ranging from 0.25mg/kg to 1.0mg/kg have been studied elsewhere with various results(4,5,7). However, there are no such studies done in Kenya.

1.3 Research Questions

1. What is the effectiveness and safety of 0.5mg/kg of oral Midazolam among children undergoing tonsillectomy and/or adenoidectomy in Kenyatta National Hospital
2. What is the effectiveness and safety of 0.75mg/kg of oral Midazolam among children undergoing tonsillectomy and/or adenoidectomy in Kenyatta National Hospital

3. How does the effectiveness and safety of 0.5mg/kg of oral Midazolam and 0.75mg/kg of oral Midazolam compare among children undergoing tonsillectomy and/or adenoidectomy in Kenyatta National Hospital

1.4 Research Objectives

The general objective for this study was to determine whether an oral dose of 0.75mg/kg of Midazolam is safe and more effective in allaying anxiety than an oral dose of 0.5mg/kg of Midazolam among children undergoing tonsillectomy and/or adenoidectomy at Kenyatta National Hospital

1.4.1 Specific Objectives

The study is guided by the following specific objectives:

1. To determine the effectiveness and safety of 0.5mg/kg of oral Midazolam among children undergoing tonsillectomy and/or adenoidectomy at Kenyatta National Hospital
2. To determine the effectiveness and safety of 0.75mg/kg of oral Midazolam among children undergoing tonsillectomy and/or adenoidectomy at Kenyatta National Hospital
3. To compare the effectiveness and safety of 0.5mg/kg of oral Midazolam and 0.75mg/kg of oral Midazolam among children undergoing tonsillectomy and/or adenoidectomy at Kenyatta National Hospital

1.4.2 Research Hypotheses

Null: The dose of 0.75mg/kg of oral Midazolam is equally effective and safe as that of 0.5mg/kg of oral Midazolam.

Alternative hypotheses: The dose of 0.75mg/kg oral midazolam is more effective than 0.5mg/kg of oral Midazolam and is equally safe.

1.5 Justification

Oral midazolam is a commonly used premedication to allay anxiety in children; the doses recommended in some of the literatures indicate a range of 0.25mg/kg to 1.0mg/kg(2). At Kenyatta National Hospital a dose of 0.5mg/kg is used. However, a number of studies suggest that the 0.5 mg/kg dose is not effective in 14 to 20% of the children(2,3).

Previous studies on different doses suggests conflicting result with McMillan et al reporting no added advantage, but more side effects for both 0.75mg/kg and 1.0mg/kg doses(4) compared to the 0.5mg/kg dose, while Sheta et al (2009) and later Somri et al (2012) reported the superiority of 0.75 mg/kg dose than 0.5 mg/kg dose and with lesser side effects than the 1mg/kg dose(5,6). While these studies were done elsewhere in the world, there is no such study done in Kenya. This study therefore aims to assess the effectiveness and safety of these different doses of Midazolam.

1.6 Study Limitations

- Inability to control the surgery starting time leading to poor timing of premedication.
- Inability to control duration of surgery leading to poor timing of premedication for the next case.

1.7 Study Assumptions

Study assumes that standard anaesthesia technique will be applied to all, using inhalational induction and intubation, muscle relaxation, maintenance with isoflurane and non-invasive monitoring.

CHAPTER TWO: LITERATURE REVIEW

2.0 Introduction

This section review literature in relation to the study objectives.

2.1 Preoperative anxiety

The impact of preoperative anxiety in children cannot be underestimated by the anaesthesiologist since it causes suffering in many children prior to their surgical experience, and has a negative impact on their postoperative recovery. Surgery in a child is a very significant and remarkable event for the entire family. But, unlike other remarkable events such as a vacation or a game drive, it has an element of threat because of fear of the unknown(8). It is therefore not unusual to find the fact that - approximately 40-60% of children experience anxiety regarding an impending surgical operation(12). Preoperative anxiety has been associated with a myriad of negative behaviour such as agitation, crying, spontaneous urination, and the need for physical restraint during anaesthetic induction. Preoperative anxiety has also been associated with the display of a number of maladaptive behaviour post-surgery, including postoperative pain, sleeping disturbances, parent-child conflict, and separation anxiety(9).

In determining whether children who are extremely anxious during induction of anaesthesia are more at risk of developing postoperative negative behavioural changes compared with children who appeared calm during the induction process, Kain ZN Wang SM, Mayes LC et al found that children who are anxious during the induction of anaesthesia have an increased likelihood of developing postoperative negative behavioural changes(10) . Anaesthesia induction has been identified as the most stressful event during the entire preoperative

period(11). An adverse neuro-endocrine response with deleterious effect in the immediate postoperative period, and future post-traumatic stress disorder has been associated with preoperative anxiety(13). It is therefore paramount to allay anxiety in these children in order to prevent these adverse effects.

2.2 Risk Factor for Preoperative Anxiety

The major risk factors for preoperative anxiety in children were classified in to child, parental and preoperative environmental factors.

The child factors include: age, temperament, previous medical encounters and attachment style and quality of parent-child relationship. Children between one to five years are at risk of preoperative anxiety while shy, inhibited children and those with high IQ with poor social adaptive abilities are more prone to anxiety, as poorly attended infant may develop poor copping skills in new settings and negative memories of previous hospital experiences can last in to adolescence(8). The children of anxious parents who use avoidant coping mechanisms and of divorced or separated parents are more anxious. The predictors of increased parental anxiety include; gender of the parent (i.e. mothers are more anxious), parents of infants, parents of children who have been through repeated hospitalizations and baseline temperament of the child(14).

Preoperative environmental factors include: hospitalization, anaesthetic technique, personnel and stimuli. Pertaining to the anaesthetic technique, children who underwent intravenous induction were more anxious (46%) compared to those induced with inhalational technique (10%)(15). Children are less anxious and illustrate increased compliance during induction when exposed to a single care-provider in a dimmed, quiet operating room with background music(16). The personnel factor is shown by the fact that the attending anaesthesiologists

who practice in paediatric settings are better than mothers in predicting the anxiety of children during induction of anaesthesia.(17)

2.3 Preoperative Anxiety Scales

Measures in assessing preoperative anxiety include the “Gold Standard”, "State-Trait-Anxiety Inventory for Children (STAIC)", which is best used with children over the age of 5 years but lacks practicability. The modified-Yale Preoperative Anxiety Scale (m-YPAS) has become the measurement tool of choice for assessing preoperative anxiety figure below(18).

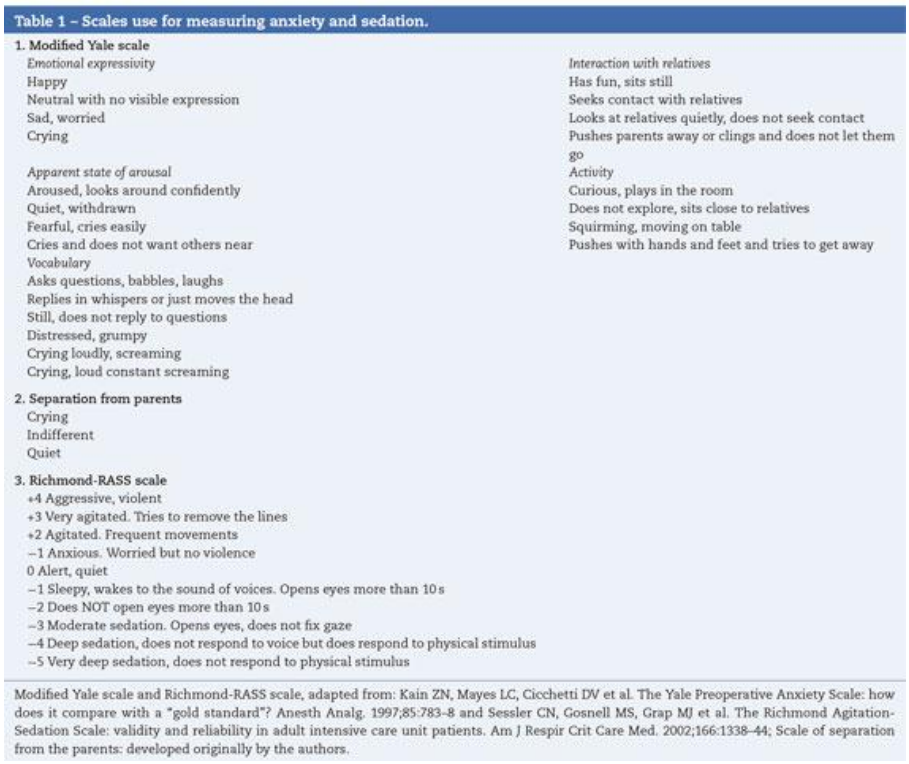

Table 1 – Scales use for measuring anxiety and sedation.

1. Modified Yale scale

Emotional expressivity
Happy
Neutral with no visible expression
Sad, worried
Crying

Apparent state of arousal
Aroused, looks around confidently
Quiet, withdrawn
Fearful, cries easily
Cries and does not want others near

Vocabulary
Asks questions, babbles, laughs
Replies in whispers or just moves the head
Still, does not reply to questions
Distressed, grumpy
Crying loudly, screaming
Crying, loud constant screaming

Interaction with relatives
Has fun, sits still
Seeks contact with relatives
Looks at relatives quietly, does not seek contact
Pushes parents away or clings and does not let them go

Activity
Curious, plays in the room
Does not explore, sits close to relatives
Squirming, moving on table
Pushes with hands and feet and tries to get away

2. Separation from parents
Crying
Indifferent
Quiet

3. Richmond-RASS scale
+4 Aggressive, violent
+3 Very agitated. Tries to remove the lines
+2 Agitated. Frequent movements
−1 Anxious. Worried but no violence
0 Alert, quiet
−1 Sleepy, wakes to the sound of voices. Opens eyes more than 10 s
−2 Does NOT open eyes more than 10 s
−3 Moderate sedation. Opens eyes, does not fix gaze
−4 Deep sedation, does not respond to voice but does respond to physical stimulus
−5 Very deep sedation, does not respond to physical stimulus

Modified Yale scale and Richmond-RASS scale, adapted from: Kain ZN, Mayes LC, Cicchetti DV et al. The Yale Preoperative Anxiety Scale: how does it compare with a "gold standard"? Anesth Analg. 1997;85:783–8 and Sessler CN, Gosnell MS, Grap MJ et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166:1338–44; Scale of separation from the parents: developed originally by the authors.

Figure 1: Modified-Yale Preoperative Anxiety Scale

However this study will use a 5 point sedation scale based on the University of Michigan sedation scale (UMSS) which is a simple, reliable and valid tool that facilitates rapid assessment of the depth of sedation in children(5,19).

Table 1: University of Michigan sedation scale (UMSS)

Awake, oriented & calm	1
Mildly sedated; may appear tired/sleepy, responds to verbal conversation and or sound	2
Moderately sedated; somnolent/sleeping; easily roused with light tactile stimulation or simple verbal command - "conscious sedation"	3
Deep sedation; deep sleep, arousable only with deep or significant physical stimulation	4
Unrousable	5

2.4 Prevention of Preoperative Anxiety

The techniques to care or avert childhood preoperative anxiety and perhaps reduce the progression of unhelpful behaviour post-surgery include; non pharmacological methods like parental presence during anaesthetic induction, behavioural preparation programs, music therapy, and acupuncture as well as pharmacological methods such as sedative premedication(9) which is the focus of this study. It is generally agreed that most children who are undergoing medical procedures and who are fearful and uncooperative can be managed with these non-pharmacological techniques. Unfortunately, some percentage of paediatric patients cannot be successfully managed solely with these techniques necessitating pharmacologic sedation(5).

2.5 Premedication in children

Sedation before surgery is an effective method that is widely used in young children for decreasing anxiety(2). The primary goals of premedication in children are to facilitate an anxiety-free separation from the parents and smooth induction of anaesthesia. Other effects that may be achieved by pharmacologic preparation of the patient include amnesia, anxiolysis, prevention of physiologic stress, and analgesia. In addition, children who are sedated before coming to the operating room may have fewer stress-related behavioural changes in the immediate postoperative time compared with those who are not sedated(2).

The pharmacological techniques employed are diverse and include benzodiazepines, alpha$_2$ agonist, Ketamine and opioids all with diverse routes of administration(2). However, this study will focus on oral midazolam – a short acting benzodiazepine. Premedication is best given by an oral route in children as children often exhibit an exaggerated psychological response to a needle, and it is easier to distribute a medication orally than to use nasal or rectal routes(20,21). Although rapid absorption and avoidance of first-pass hepatic metabolism of medications are advantages of the intranasal route, a major disadvantage in children is the cry on administration as it transiently irritates the nasal passages(2,22). Kogan A, Katz J, Efrat R, Eidelman LA who compared the effect of four routes of administration of midazolam revealed that the nasal route had significant irritation as 75% of the children in this group cried after drug administration(22). Above eighty five percent of all preoperative sedation in the United States is executed using midazolam(2).

Midazolam has swift and quick onset as well as predictable effect without causing cardiopulmonary depression. Its effect peaks approximately 30 minutes lasting an hour or more after administration in a dose of 0.5 to 0.75mg/kg(7) but about 14% of children may not respond to a midazolam dose of 0.5mg/kg(3). Higher doses of midazolam, 0.75mg/kg may be more appropriate in the non-responders. This agent with children undergoing ultra- short procedure less than 30 minutes may delay hospital discharge(23). Midazolam has been shown to be superior to parental presence in diminishing peri-operative stress for patients and families(2).

2.6 Pharmacology of Midazolam

Midazolam is water soluble in its acid formulation but is highly lipid soluble in vivo (24). It is an imidazobenzodiazepine with relatively rapid onset of action and high metabolic clearance when compared with other benzodiazepines. It produces reliable hypnosis, amnesia, and anti-anxiety effects when administered orally, intramuscularly, or intravenously. The uses of midazolam in the peri-operative setting include premedication, anaesthesia induction and maintenance, and sedation for diagnostic and therapeutic procedures. Midazolam is preferable to diazepam in many clinical situations because of its rapid, non-painful induction and lack of venous irritation(24).

Once administered, midazolam is absorbed and transported to its site of action by the blood plasma where it is extensively bound. It is metabolized to alpha hydroxyl-midazolam and conjugated to glucuronic acid into an inactive metabolite which is excreted in urine. Peak serum concentrations of midazolam is reached at different times in children depending on the route of administration(25) with the Intramuscular, rectal and oral route routes peaking at 15 and 30 and 53 min respectively(25). The volume of distribution is 1-2.5L/kg in healthy individuals but is increased in the obese due to the higher distribution of midazolam to peripheral adipose tissues (24). It is rapidly excreted with a half-life of about 2 hours(26)

Alzahrani AM & Weyne AH(27) in their review of the use of oral Midazom sedation in paediatric dentistry indicated that midazolam has a short elimination half-life of 1.5-3.0 hours and Plasma clearance of 5.8-9.0 ml/min/kg in healthy individuals though decreased in the elderly. They further suggested that about 90% of an orally administered dose of midazolam is excreted within 24 hours

Midazolam has virtually no any serious side effect if given in recommended oral dose; however, hypoventilation and hypoxaemia are found to be the major risks associated with high dose midazolam. Alzahrani AM & Weyne (27) in their review, showed that there are reports of respiratory depression in adult but fewer in children. However, these side effects are tenable to treatment with flumazenil an imidazobenzodiazepine derivative that antagonises the action of benzodiazepines like midazolam on the central nervous system. The safety of midazolam sedation is therefore significantly improved by the availability of flumazenil(27). Other side effect include paradoxical reaction such as restlessness, behavioural changes and hiccups and ketamine has been demonstrated to be an effective treatment for this undesirable effect(28).

2.7 Emergency Delirium

Emergency delirium is a 'dissociated state of consciousness in which a child is inconsolable, irritable, uncompromising and uncooperative typically thrashing, crying or incoherent'(29).

It has an incidence which may be as high as 80% but generally ranges from 10 to 50% (29).

A number of factors have been associated with this phenomenon including age, surgery type –such as ophthalmology and otorhinolaryngology procedures, use of sevoflurane, isoflurane, or sevoflurane/isoflurane, and short time to awakening(30).

Inadequate pain management before emergence has also been incriminated. Davis, P J

Greenberg, JA Gendelman, M and Fertal, K showed a decrease in the incidence of emergence delirium following ketorolac administration during myringotomy with either sevoflurane or halothane anaesthesia(31). Pain may not, however, be the only culprit as other studies revealed the occurrence of emergence delirium in children undergoing non painful

procedures such as magnetic resonance imaging(32) or even those with adequate regional postoperative pain control under sevoflurane anaesthesia(33).

Preoperative anxiety has been suggested as a cause of emergence delirium(34) and premedication with Midazolam was shown to reduce its occurrence(35,36). However, it is important to note the benzodiazepines including Midazolam are associated with paradoxical reaction but is tenable to ketamine(28) and flumazenil(37).

Adequate analgesia, premedication to allay anxiety, and provision of a quiet and stress free environment will go a long way in reducing emergence delirium, and when it occurs, especially with the risk of self injury, pharmacological intervention such as use of Propofol, Dexmedetomidine or Opioids is essential(29,38).

CHAPTER THREE: RESEARCH METHODOLOGY

3.0 Introduction

This chapter deals with the research design and methodology employed in the study. It also outlines the location of the study, target population, sample size, sampling technique, data collection and analysis methods.

3.1 Research Design

This is a prospective randomized controlled double blinded trial in which children undergoing tonsillectomy and or adenoidectomy at KNH satellite Ear Nose and Throat theatre will be randomized into two treatment groups. A double-blind RCT is a randomized trial in which two groups of individuals involved in the trial do not know the identity of the intervention that is given to each participant(39). The double-blind randomized controlled trial (RCT) is accepted by medicine as objective scientific methodology that, when ideally performed, produces knowledge untainted by bias(40). Once investigators ensure that allocation of participants to the study groups is random (to call the study an RCT), they can design the study using strategies to match the characteristics of the interventions they want to study(39). One treatment group received 0.5mg/kg oral Midazolam while the other treatment group received 0.75mg/kg oral Midazolam at least 30 minutes before induction.

The outcome which is, sedation scores, mask acceptance scores, anxiety scores, demographic characteristics, time taken to parental separation, time taken from end of surgery to extubation and vital signs among children undergoing tonsillectomy and or adenoidectomy were assessed case wise.

3.2 Variables

The independent variables were treatment groups i.e. 0.5mg/kg group and 0.75mg/kg group. The dependent variables were sedation scores, mask acceptance scores, parental separation score, demographic characteristics, time taken to parental separation, time taken from end of surgery to extubation and vital signs.

3.3 Study Area

The study was conducted at KNH satellite Ear Nose and throat theatre and the post Anaesthesia Care Unit. KNH is the largest referral and teaching hospital in Kenya with bed capacity of 2000 beds (41). KNH has 50 wards, 22 out-patient clinics, 24 theatres (16 specialized) and Accident & Emergency Department. Adenotonsillectomy is one of the most common elective otolaryngopharingologic operations at KNH Ear Nose and Throat/Head and Neck (ENT/HN) surgical units(42).

3.4 Target Population

Children undergoing tonsillectomy and/or adenoidectomy in Kenyatta National Hospital who meet the criteria for inclusion were the target population. As shown in the figure below there was a steady increase annually on the number of children undergoing tonsillectomy and/or adenoidectomy at KNH. Using the linear forecast, there were 669 such cases (approximate monthly average of 56 cases) at KNH during the year 2015.

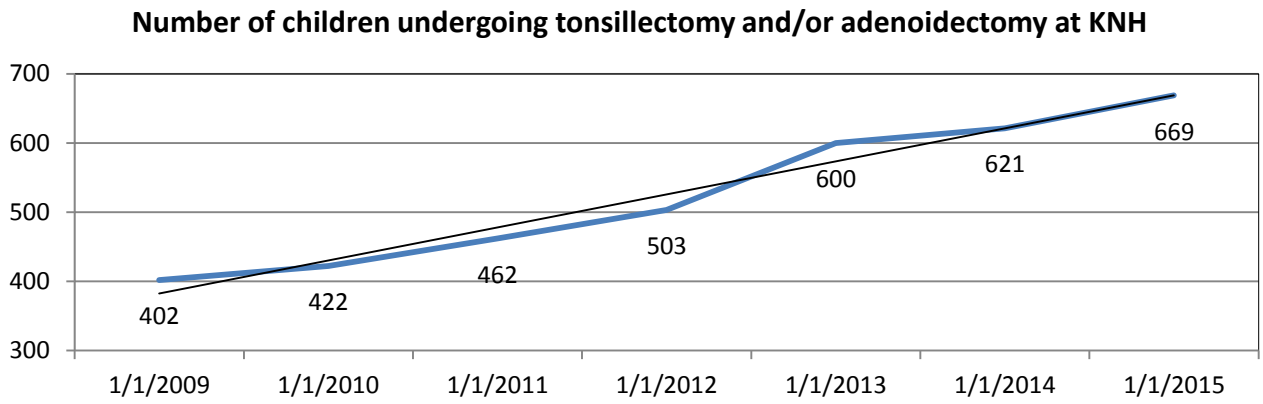

Figure 2: Number of children undergoing tonsillectomy and/or adenoidectomy at KNH

3.5 Exclusion and inclusion criteria

3.5.1 Inclusion Criteria

Children between the ages of 2 to 10 years undergoing elective adenotonsillectomy at KNH

Children whose parents/guardian give consent to participate in the study

Children with ASA class 1 and 2

3.5.2 Exclusion Criteria

Children with ASA class 3 and above

Children with OSA (who demonstrate daytime somnolence and interrupted sleep)

Children below the age of 2 years and above 10 years

Children undergoing emergency surgery

Syndromic children and children on sedative or anticonvulsants

Children with hemodynamic or respiratory instability

Children whose parents do not give consent to participate in the study

3.6 Sample Size Determination and Sampling Procedure

3.6.1 Sample Size Determination

According to Sheta and Alsarheed 2009, 80% of the children who received 0.75mg/kg and 65% of the children who received 0.5mg/kg had desirable sedation (oriented or calm or drowsy but responding to verbal commands)(5). Therefore transforming and applying the sample size calculation as proposed by Sakpal 2010(43) when comparing two proportions for non-inferiority clinical trials, the initial sample size per group will be given by the formula:

$$n_0 = \frac{\left(p_1(1-p_1) + p_2(1-p_2)\right) \times (Z_\beta + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

n = sample size required in each group,

p_1 = proportion of 0.75mg/kg group subjects achieving desirable sedation (80%)

p_2 = proportion of 0.5mg/kg group subjects achieving desirable sedation (65%)

p_1-p_2 = clinically significant difference

Z_β Represents the desired power (0.84 for 80% adopted for this study)

$Z_{\alpha/2}$ Represents the desired level of statistical significance (1.96 for 95% adopted for this study)

$$n_0 = \frac{\left(0.8(1-0.8) + 0.65(1-0.65)\right) \times (0.84 + 1.96)^2}{(0.8 - 0.65)^2} = 135.02 \approx 135 \; per \; group$$

Thus an initial sample of 270 children, undergoing tonsillectomy and/or adenoidectomy in Kenyatta National Hospital were involved but there were 112 (monthly average of 56 for 2

months) such Children during the study period, therefore applying the finite population correction factor, the final minimal sample size was given by:

$$n = \frac{n_0}{1+\frac{n_0-1}{N}} = \frac{270}{1+\frac{270-1}{112}} = 79.4 \approx 79$$

The final minimal sample size was 80 (to ensure equal number of controls and treatment groups) children (40 0.75mg/kg group and 40 0.5mg/kg group) undergoing tonsillectomy and or adenoidectomy at KNH. However the study was to utilize 88 children (44 0.75mg/kg group and 44 0.5mg/kg group) inclusive of 10% attrition for non-response and respondents lost on follow up.

3.6.2 Sampling Procedure

The researcher kept a consecutive list of all children undergoing tonsillectomy and/or adenoidectomy in Kenyatta National Hospital throughout the study period. Prior to the surgery day the researcher obtained the list of children scheduled to undergo tonsillectomy and/or adenoidectomy in Kenyatta National Hospital the next day. This list consecutively encompassed the study sampling frame from which the sample was drawn. Systematic random sampling was applied on rolling basis to randomly sample study participants from the study sampling frame where every second child scheduled to undergo tonsillectomy and/or adenoidectomy in Kenyatta National Hospital and whose parent/guardian consented to the study was recruited..

3.7 Research Instrument and Data Collection Procedure

3.7.1 Research Instrument

Research data consisting of treatment group, sedation scores, mask acceptance scores, parental separation score, demographic characteristics, time taken to parental separation, time taken from end of surgery to extubation and vital signs was collected via a questionnaire administered by the researcher.

3.7.2 Data Collection Procedure

Written informed consent was obtained from participants' parent/guardian during the preoperative visit by the principal investigator

Children who met the inclusion criteria were then randomly assigned in to one of two groups using sealed envelope technique.

One group received 0.5mg/kg and the other 0.75mg/kg injectable Midazolam mixed with double volume of apple juice orally at least half an hour before separation from parents. Midazolam is used for oral sedation in paediatric population. Unfortunately, it is not available as paediatric oral formulation for children in Kenya. However the parental formulation of midazolam has been shown to be chemically stable when diluted in flavoured syrups for oral use(44). Earlier studies have also used injectable midazolam prepared for oral use , in fact sheta and Alsarheed have mixed injectable midazolam with clear apple juice in their study for oral use(5)

Blinding Process

The researcher prepared and administered the drug as per the child's assigned group but observations on the child (blinded i.e. does not know which treatment he/she received) was

made by a trained research assistant (blinded i.e. does not know which treatment the recipient was assigned).

Role of providers in the study

The anaesthesiologist was informed of the study and was requested to use a standard anaesthetic protocol for all the participants.

The PACU nurse was trained on the 5 point sedation score by the principal investigator and requested to record the vital signs (blood pressure, heart rate, respiratory rate temperature and oxygen saturation) and sedation score using the data collection form provided,

Preoperative Receiving Area

The baseline vital signs were recorded and a prepared injectable Midazolam mixed with double volume of apple juice was administered orally at least 30 minutes before separation from parents. The patient's acceptance of the medication and reaction to separation from parent was also assessed in the preoperative receiving area.

Acceptance of the medication was defined as swallowing without spitting immediately

The reaction to separation from parents was graded as inconsolable cry, complaining, quiet but awake, or sleepy

Operating Room

The ease of mask acceptance graded as poor, fair, good, and excellent was assessed as well as level of sedation using a 5 point sedation scale in the operating room. The time taken from end of surgery to extubation was recorded.

PACU

At PACU vital signs, sedation score and the need to supplement oxygen to maintain Spo2 >92% was recorded.

Post Exposure Monitoring

All participants were monitored with ECG pulse-oxymeter and non-invasive blood pressure machine both in the operating room and PACU. Sedation depth was assessed post exposure both pre and post operatively

3.7.3 Randomization

Selection bias was minimized by using standardized criteria for enrolling patient into the two groups while observer/interviewer bias was minimized by blinding. A recall bias was unlikely as the study was prospective where events were recorded as they occurred. The study participants were randomized via block randomization so as to reduce bias and achieve balance in allocating participants to the treatment arms(45). Within each block, however the order of patients was random(46). This study utilized blocks of size 4 with allocation ratio of 1 (0.75mg/kg): 1 (0.5mg/kg). Within each block patients were assigned random numbers generated by a scientific calculator and the random number assigned was used to order the patients within the block. Since there were 6 different ways of assigning treatments in blocks, the blocks received a treatment method by lottery using a balanced 6-faced dice with each face representing a treatment plan. For each block, the researcher threw a dice and the face that appeared was used as the treatment plan for the block.

3.7.4 Expected Complications and Safety Mechanisms

Midazolam is a safe drug for use in anaesthesia; the side effects and complications are rare and short lived due to its short duration of action. It has virtually no serious side effect if given in recommended oral dose; however, hypoventilation and hypoxaemia were found to

be the major risks associated with high dose midazolam. Alzahrani AM & Weyne (27) in their review, showed that there are reports of respiratory depression in adult but fewer in children.

These effects were easily be managed by assisted ventilation, oxygen administration and administration of flumazenil 0.01mg/kg body weight over 15 seconds. The safety of midazolam sedation is therefore significantly improved by the availability of flumazenil(27). Participants were monitored closely for respiratory depression and desaturation by monitoring respiratory rate and oxygen saturation among other vital sign. Facilities for airway management, oxygen, and flumazenil were available to all participants throughout the study.

3.8 Data Analysis

All data collected in the study were sorted, coded and entered in a computer using STATA version 14. Data was crossed checked for any inconsistencies and obvious data entry errors. The filled questionnaires were kept under lock and key. Soft copy of the data set was secured and protected by password. Chi-square test and Odds ratio were used to measure the difference in incidences of children who achieved desired sedation between the treatments groups. Mann Whitney U test/t-test was used to assess the difference in vital signs, mask acceptance scores and parental separation score between the treatment groups. Difference in time taken from end of surgery to extubation between the treatment groups was assessed using Mann Whitney U test/t-test. P values of <0.05 was considered statistically significant and 95% CI was used to show any significant associations. The study finding was presented using figures, tables, and bar-graphs.

3.9 Logistical & Ethical Considerations

Approval from KNH/UON Ethics and Research committee and a written study explanation to each parent/guardian was provided and an informed consent obtained. The participants had the right to decline and withdraw with the assurance of no penalty for refusal to participate. The same standard of care was provided to both participants and non-participants. Confidentiality reigned supreme with respect to information gathered from each participant and there was no additional cost or incentive for participating in the study. The assent of children who are six years and above was also sought

3.10 Study Findings Dissemination

The findings of this study was disseminated through; presentation to members of the department of Anaesthesia - University of Nairobi, manuscripts, presentation in conferences organised by Kenya society of anaesthesiologists (KSA), feedback to the theatre team and a report to UON/KNH ERC

CHAPTER FOUR: FINDINGS

4.0 Introduction

This study was conducted between 27th September2016 and 4th April 2017with a sample of 80 children aged between 2 to 10 years who were randomized in to two treatment arms of equal size (40 children in each arm). The study had 100% completion rate with no loss to follow up. Pre and post operative parental separation, scores mask acceptance scores and sedation scores were compared.

4.1 Characteristics of Participants

Majority (63.8%) of the participant were children below the age of 5 years with an average age of 4 years. Female participants composed 41% while 59% were male participants. On average the participants weighed 16.1 kg, however, nearly half weighed between 16 to 20 kg. Most (79%) of the participants were undergoing Adenotonsillectomy while 21% were undergoing Adenoidectomy. All participants were ASA class 1. There was no significant variation in characteristics of participants between treatment arms as shown in Table 2. All participants swallowed the drug without spitting.

Table 2: Characteristics of Participants

		Treatment group		**Odds ratio (95% CI)**	**P-value**
		0.5mg/kg	**0.75mg/kg**		
Age in years	2 – 4.9	25(62.5%)	26(65%)	1.0(0.6-1.7)	0.889
	5 - 10	15(37.5%)	14(35%)	1.1(0.5-2.2)	0.853
Average age (years)		4.1(±0.2)	4.1(±0.3)	-0.231£	0.817
Gender	Male	22(55%)	25(63%)	0.9(0.5-1.6)	0.662
	Female	18(45%)	15(38%)	1.2(0.6-2.4)	0.602
Weight in kilograms	<= 15	20(50%)	20(50%)	1.1(0.6-2.0)	0.873
	16 – 20	17(43%)	13(32%)	1.4(0.7-3.0)	0.356
	> 20	3(8%)	7(18%)	0.4(0.1-1.7)	0.220
Average weight (kgs)		15.8(±0.6)	16.5(±0.8)	0.458£	0.647
Procedure	Adenoidectomy	9(23%)	8(20%)	1.1(0.4-2.9)	0.808
	Adenotonsillectomy	31(78%)	32(80%)	1.0(0.6-1.6)	0.900
£ Mann Whitney Z value					

4.2 Effectiveness and Safety of 0.5mg/kg and 0.75mg/kg of Oral Midazolam

4.2.1 Vital Signs

There was marginal decrease in systolic pressure in both treatment arms before mask placement but increased in PACU, however there was no significant difference in these changes of systolic blood pressure among the treatment arms. An increase in heart and respiratory rate in both treatment arms was also noted; however there was no significant difference in percentage changes in both heart and respiratory rate between the treatment arms. Respiratory rate among participants of the 0.5mg/kg arm in the immediate post-operative period was significantly lower as compared to participants of the 0.5mg/kg arm. A slight increase in the SPO2 was noted before mask placement with decreased in PACU but both treatments arms had similar SPO2 effects. The result therefore suggests no significant differences in vital signs changes between the treatment arms as shown in Table 3 below.

Table 3: Changes in Vital Signs

	Baseline			Preoperative			PACU		
Vital sign	A[£]	B*	P-value[§]	A[£]	B*	P-value[§]	A[£]	B*	P-value[§]
Mean systolic BP	100	102	0.337	99	99	0.711	102	102	0.856
Mean diastolic BP	45	45	0.996	45	44	0.267	46	45	0.839
Mean heart rate	113	117	0.444	131	129	0.762	129	134	0.238
Mean respiratory rate	23	25	0.312	26	28	0.843	25	28	0.043
SPO2	97	97	0.530	100	100	0.986	93	93	0.745
A[£] - 0.5mg/kg arm; B[*] - 0.75mg/kg arm; P-value[§] - Mann Whitney U test									

4.2.2 Parental Separation

As shown in Figure 3, more participants in the 0.5mg/kg arm had higher incidents of inconsolable cry as compared to the participants in 0.75mg/kg arm (10% versus 8% respectively). Both arms realized comparable percentage (77% of 0.5mg/kg arm versus 78% of 0.75mg/kg arm) of participants who were quite, unafraid and cooperative. It is apparent that there was no significant difference in reaction to parent separation among treatment groups (Chi-square test: χ^2 = 0.2375, df = 2, p-value = 0.888).

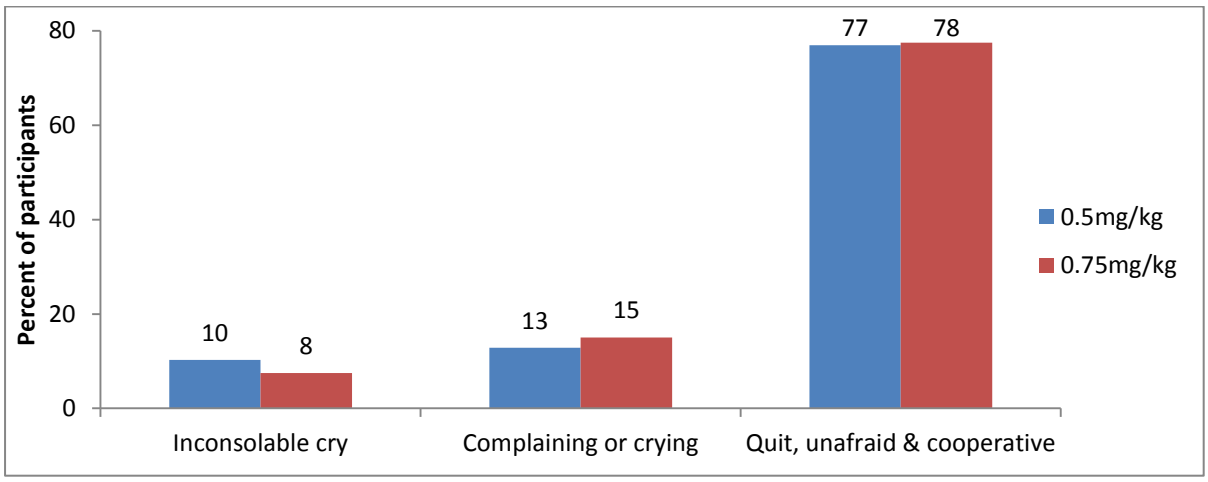

Figure 3: Reaction to Parent Separation between Treatment Arms

4.2.3 Time to Parental Separation

Results indicate that participants in both treatment arms had nearly equal time-lapse from swallowing midazolam to parental separation (72 minutes for 0.5mg/kg arm versus 72.5 minutes for 0.75mg/kg arm). This reveals no statistically significant difference between the treatment arms in terms of time-lapse from drug swallowing to parental separation (Mann Whitney U test: z = 0.877, p = 0.3807).

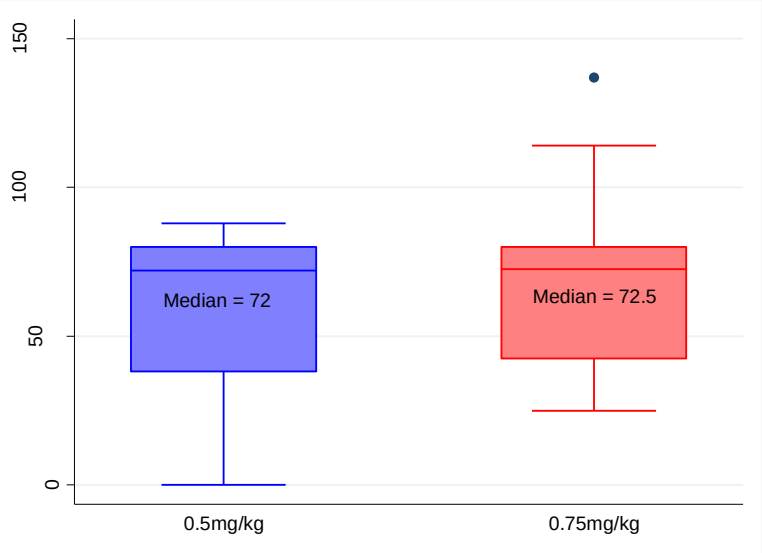

Figure 4: Time between Treatment Administration and Parent Separation

4.2.4 Mask Acceptance

In most children accepted the application of facemask without crying (75% in 0.75mg/kg arm versus 63% in 0.5mg/kg arm). The incidents of poor mask acceptance was higher in 0.5mg/kg arm as compared to 0.75mg/kg arm (20% & 8% respectively). However there was no significant difference in mask acceptance between the treatment arms (Chi-square test: χ^2 = 2.7273, df = 2, p-value = 0.256).

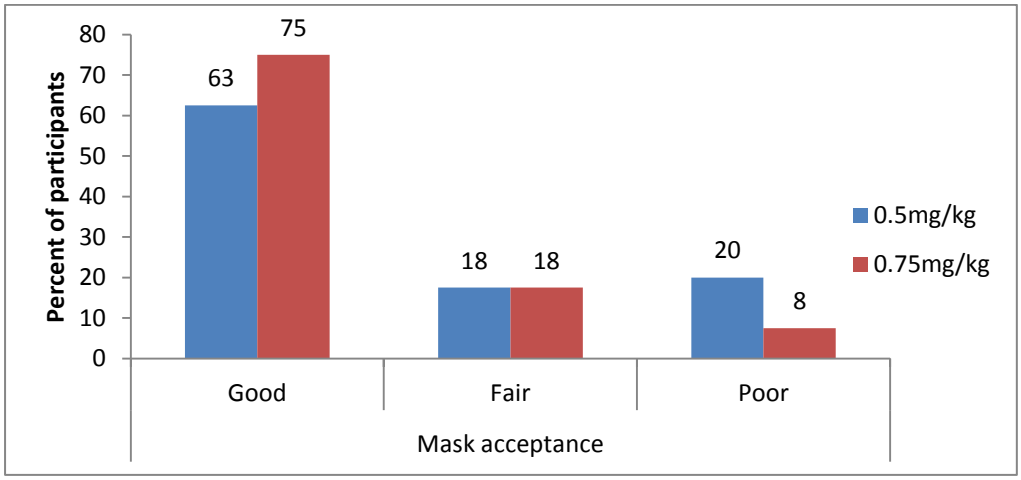

Figure 5: Mask Acceptance between Treatment Arms

4.2.5 Preoperative Sedation Scores

In preoperative time, over twice as many participants in the 0.5mg/kg were anxious as compared to 0.75mg/kg (22.5% in 0.5mg/kg arm versus 10% in 0.75mg/kg arm). Preoperatively, incidents of non-response to verbal or painful stimuli were similar in both treatment arms. In general there was no significant variation in preoperative sedation scores between the treatment arms.

Table 4: Preoperative Sedation Scores

	0.5mg/kg	**0.75mg/kg**	**OR (95% CI)**	**P-value**
Anxious	22.5%	10%	2.3(0.7-7.3)	0.177
Oriented , calm	55%	65%	0.8(0.5-1.5)	0.564
Drowsy but responds to verbal command	20%	22.5%	0.9(0.3-2.3)	0.808
Not responding to verbal command but responds to painful stimuli	2.5%	2.5%	1.0(0.1-16.0)	>0.999

4.2.6 Post-anaesthesia Sedation Scores

During post-operative phase, more participants in the 0.75mg/kg arm were anxious as compared to participants in the 0.5mg/kg arm (17.5% in 0.5mg/kg arm versus 22.5% in 0.75mg/kg arm). Similarly during post-operative phase, incidents of non-response to verbal or painful stimuli were nearly similar in both treatment arms. In general, there was no significant variation in post-anaesthesia sedation scores between the treatment arms.

Table 5: Post-anaesthesia Sedation Scores

	0.5mg/kg	**0.75mg/kg**	**OR (95% CI)**	**P-value**
Anxious	17.5%	22.5%	0.8(0.3-2.1)	0.618
Oriented , calm	5%	7.5%	0.7(0.1-4.0)	0.657
Drowsy but responds to verbal command	45%	40%	1.1(0.6-2.2)	0.732
Not responding to verbal command but responds to painful stimuli	25%	25%	1.0(0.4-2.4)	>0.999
Not responding to painful stimuli	7.5%	5%	1.5(0.3-9.0)	0.657

4.2.7 Time from End of Surgery to Extubation

Results indicated that participants in both treatment arms took similar time from end surgery to extubation (15 minutes each) showing no significant difference between the two treatment arms (Mann Whitney U test: z = 1.365, p = 0.1724).

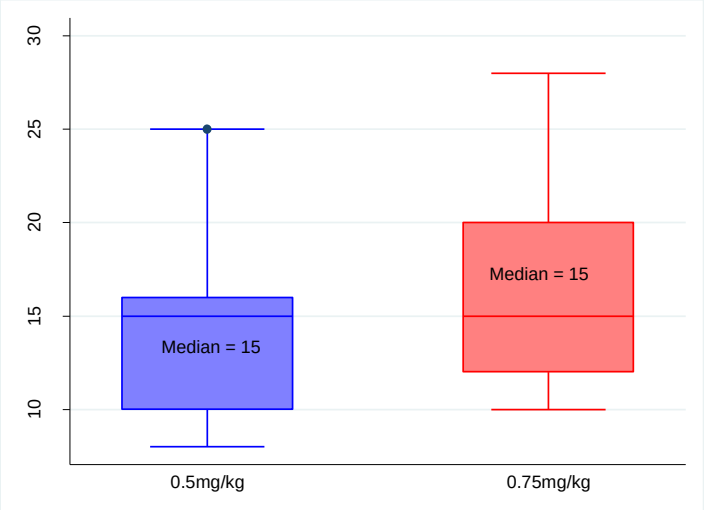

Figure 6: Time from End of Surgery to Extubation

4.2.8 Requiring Supplementary Oxygen

In general, 41.3% of participants required oxygen supplementation to maintain saturation above 92%. Although not significantly different (Odds ratio = 1.68, p-value = 0.258), more participants in the 0.5mg/kg arm (48%) required oxygen supplementation as compared to 0.75mg/kg arm (35%) in order to maintain oxygen saturation above 92%.

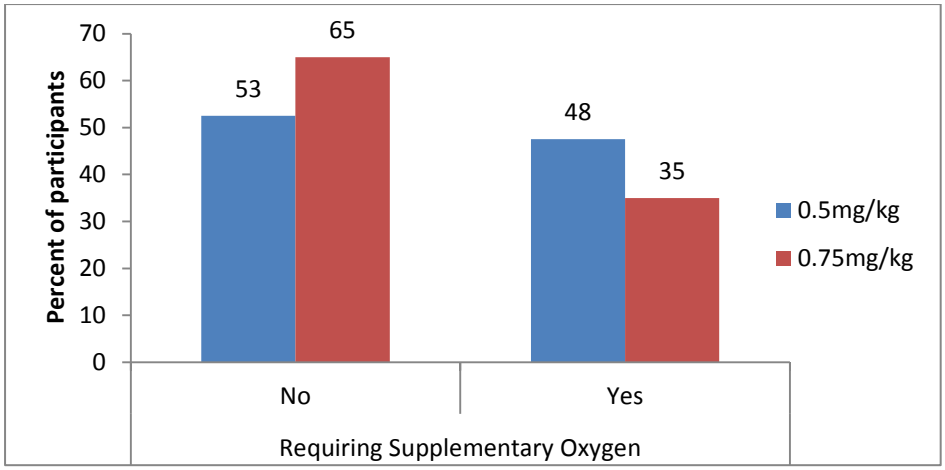

Figure 7: Requiring Supplementary Oxygen between Treatment Arms

4.3 Comparison in Effectiveness and Safety of 0.5mg/kg versus 0.75mg/kg of Oral Midazolam

Effectiveness of each treatment arm was assessed based on parental separation, sedation scores (Preoperative and post-operative anaesthesia), changes in vital signs (systolic blood pressure and heart rate), and the requirement for oxygen supplementation to maintain saturation greater than 92%. A dose was deemed effective if the participant was quit, unafraid and cooperative during parental separation, accepted mask placement with no crying, oriented and calm or drowsy but responds to verbal command or responded to painful stimuli during preoperative stage. A dose was deemed unsafe on occurrence of hypotension systolic blood pressure less than 20% of baseline at OR, heart rate fell by more than 20% of baseline at OR, and requirement for oxygen supplementation to maintain saturation greater than 92%. Although more participants in the 0.75mg/kg arm registered a drop in heart rate (40% versus 27.5%; P-value 0.235) and respiratory rate (40% versus 30%; P-value 0.349 than the 0,5mg/kg arm), there was no statistically significant difference in prevalence of side effects between the treatment arms. Effectiveness of both arms was also found to be similar. Adjusting for age of participants has very minimal changes in effectiveness and safety of both treatment arms. It is therefore apparent that this study reveals the oral dose of 0.75mg/kg

midazolam was equally effective and safe as the dose 0.5mg/kg when given to children between the ages of 2-9 years undergoing tonsillectomy and or adenoidectomy in Kenyatta National Hospital. We notice that the study fails to reject with the null hypothesis stated as "the dose of 0.75mg/kg of oral Midazolam is equally effective and safe as that of 0.5mg/kg".

Table 6: Effectiveness and Safety of 0.5mg/kg versus 0.75mg/kg of Oral Midazolam

		Treatment arm		**Unadjusted OR**		**Age adjusted OR**	
		A[£]	B[*]	OR (95% CI)	P-value	OR (95% CI)	P-value
Reaction to parental separation	Inconsolable cry	8%	10%	0.8(0.2-3.4)	0.706	0.8(0.2-3.7)	0.726
	Complaining or crying	15%	13%	1.2(0.4-3.9)	0.763	1.2(0.3-4.4)	0.758
	Quit, unafraid & cooperative	78%	77%	1.0(0.6-1.7)	0.898	1.1(0.4-3.2)	0.802
Preoperative sedation score	Anxiety	22.5%	10%	2.3(0.7-7.3)	0.177	2.7(0.7-9.7)	0.129
	Desirable	75%	87.5%	0.9(0.5-1.4)	0.536	0.4(0.1-1.4)	0.143
	Deep sedation	2.5%	2.5%	1.0(0.1-16.0)	>0.999	1.0(0.1-17.6)	0.977
Mask acceptance	Good	63%	75%	0.8(0.5-1.4)	0.501	0.5(0.2-1.4)	0.217
	Fair	18%	18%	1.0(0.4-2.9)	>0.999	1.0(0.3-3.2)	0.986
	Poor	20%	8%	2.7(0.7-10.1)	0.147	3.1(0.8-12.9)	0.112
Hypotension		5%	5%	1.0(0.1-7.5)	>0.999	1.0(0.1-7.4)	0.988
Drop in heart rate > 20%		40%	27.5%	1.8(0.7-4.5)	0.239	1.8(0.7-4.5)	0.235
Drop in respiratory rate > 20%		40%	30%	1.6(0.6-3.9)	0.350	1.6(0.6-3.9)	0.349
Requiring supplementary oxygen in post-anaesthesia period		47.5%	35%	1.7(0.7-4.1)	0.258	1.7(0.7-4.2)	0.267
Desirable post anaesthesia sedation		67.5%	70%	0.9(0.4-2.3)	0.809	1.1(0.4-2.7)	0.873
A[£] - 0. 5mg/kg arm; B[*] - 0.75mg/kg arm; OR – Odds ratio							

CHAPTER FIVE: DISCUSSION, CONCLUSIONS AND RECOMMENDATIONS

5.1 Discussion

5.1.1 Introduction

Preoperative anxiety, emergence delirium, and postoperative behavior changes are all manifestations of psychological distress in children undergoing surgery. Preoperative anxiety is most prominent during anaesthesia induction(1)

Preoperative anxiety causes suffering in children prior to surgical procedures and has negative impact in their post-operative recovery(8–10). Anaesthesia induction has been identified as the most stressful event during the entire preoperative period(11). This therefore has called for a search for ways of alleviating anxiety.

While non pharmacological methods have been used, unfortunately a percentage of paediatric patients cannot be successfully managed solely with this method. Midazolam with its rapid onset and relatively short duration of action has proved to be useful in this regard(5). It is shown to give more predictable and effective sedation than oral diazepam. Patel and Meakin revealed superior anxiolysis in oral midazolam than a combination of diazepam with droperidol or trimeprazine(47). However the optimal oral dose of midazolam is controversial. Doses ranging from 0.25mg/kg to 1.0mg/kg have been studied elsewhere with various results(4,5,7).

Commercially prepared oral midazolam is not available in Kenya and many other countries. We therefore used injectable formulation of midazolam mixed with a double volume of apple juice as an oral preparation of midazolam. The parental formulation of midazolam has been shown to be chemically stable when diluted in flavoured syrups for oral use(44). In fact

Brosius and Bannister found that intravenous Midazolam preparation mixed with syrpalta syrup yields more reliable sedation and higher plasma level than an equivalent dose of the commercially formulated oral preparation(48). It is also shown that small volume (3ml/kg) of apple juice given orally preoperatively decreases gastric volume hence decreases the risk of aspiration(49)

5.11. Effectiveness and Safety of Midazolam in allaying anxiety

We found that the orally administered intravenous preparation of midazolam dose of 0.75mg/kg was equally effective and safe when compared with a dose of 0.5mg/kg as a premedication to allay anxiety in children. The result of this study contradicts the finding of Somri M, Parisinos CA, Kharouba J et al(6) that the dose of 0.75mg/kg had a higher sedation score than 0.5mg/kg but agrees with Vaskle P, Pal R, and Arora KK(50) who found comparable sedation score in both doses of 0.5mg/kg and 0.75mg/kg. It is important to note that Somri M, Parisinos CA, Kharouba J et al did not assess for parental separation and acceptance of face mask since there study did not involve general anaesthesia, they assessed for level of sedation, cooperative behaviour and procedure completion rates during dental procedures.

McMillan CO, Spahr-Schopfer IA et al in their study of premedication of children with oral midazolam compared the dose of 0.5, 0.75 and 1mg/kg and reported that although, sedation and anxiolysis did not differ among the three midazolam groups, the 0.75 and 1mg/kg dose had higher side effect profile observed(4). Even though our findings agree with McMillan et al with respect to sedation and anxiolysis, our study reveals similar safety profile in the dose of 0.5 and 0.75mg/kg as assessed by a fall in vital signs of 20% from baseline, desaturation and undesirable deep sedation score and concurs with Vaskle P, Pal R, and Arora KK(50)

5.1.2 Conflict among studies a function of heterogeneity

While several studies agree with our findings in terms of face mask acceptance, reaction to parental separation and sedation score(4,7,50), quite a number of studies also differed from our results(5,6,51). The disagreement in the study findings is expected because of the heterogeneity of the studies with respect to patient characteristics, drug formulation, sedation scale used, and time between premedication and parental separation. For example, while we utilized a five point sedation scale based on the University of Michigan sedation scale (UMSS), Somri M, Parisinos CA, Kharouba J et al used Wisconsin sedation scale, grade 1–6 and had a different patient characteristics(6). While sheta SA, and Alsarheed M(5) and vaskle P, Pal R, and Arora KK (50) had set the time between premedication and parental separation at 30 minutes, we were unable to do so, because the time and the duration of surgery was unpredictable in our study.

5.1.3 Does younger age call for a higher dose of Midazolam?

Age is an important variable in predicting preoperative anxiety with children between the ages of 1-5years exhibiting a higher risk factor(8). Kain ZN, MacLaren J, McClain BC et al in their study Effects of age and emotionality on the effectiveness of midazolam administered preoperatively to children noted that 14.1% of the children given 0.5mg/kg of oral midazolam did not respond. They also noted that the non-responders were younger (4.2 +/- 2.3 vs. 5.9 +/- 2.0 yr), more anxious preoperatively, and higher in emotionality as compared with responders(3). In our study, although we did not asses for effect of age and emotionality on effectiveness of oral midazolam, we noted that Adjusting for age of participants has very minimal changes in effectiveness and safety of both treatment arms of the midazolam. However, Fraone et al, in their study of the effect of orally administered midazolam on

children of three age groups during restorative dental care, revealed no clinically significant difference among the age groups(52)

5.1.4 Recovery profile

The recovery profile in our study was similar between the two arms of treatment. It took similar time from end surgery to extubation (15 minutes each on the average) with no significant difference in time taken from end surgery to extubation (Mann Whitney U test: z = 1.365, p = 0.1724). Similarly the post anaesthesia sedation score between the treatment arms was not statistically significant. A number of studies agree with this finding(5,50,51)

5.2 Conclusion

We, therefore, conclude from our findings that a dose of 0.75mg/kg of orally given injectable Midazolam to children undergoing adenoidectomy and or tonsillectomy is equally effective and safe as a dose of 0.5mg/kg of orally administered injectable Midazolam.

5.3 Recommendation

I. Most studies used specific paediatric surgical population for example; children accessing paediatric dental care or neuro-surgical (5,6,51,52). This study also concentrated on children undergoing tonsillectomy and or adenoidectomy a specific surgical population. We, therefore recommend a bigger study involving children undergoing other general surgical procedures

II. We notice the conflicting reports on the dose of oral midazolam as premedication in children to alley anxiety(4–7,50,51). The decision on the dose and use of oral midazolam in KNH is practitioner dependant. We therefore recommend the

formulation of a protocol on the use of midazolam as premedication to allay anxiety in children.

III. Our study suggests a range of 0.5 to 0.75mg/kg body weight of oral midazolam as premedication to allay anxiety in children.

5.4 Limitation

It was difficult to control the surgery starting time and this led to poor timing of premedication.

The duration of surgery was unpredictable and varied leading to poor timing of premedication for the next case.

These two factors made it impossible to fix the time from premedication to parental separation as 30 minutes

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APPENDICES

Appendix 1: Data Capture Form

1. Serial Number..... Date.....
2. Patient initial.....
3. Age in years.....
4. Sex.....
5. Weight in Kilograms.....
6. ASA Class.....
7. Procedure.....
8. Patient Random Number.....
9. Baseline Preoperative vital signs

Blood pressure	
Heart Rate	
Respiratory Rate	
SpO_2	

10. Time of giving treatment.....

11. Drug acceptance (Please tick on the relevant box)

Accept(swallow without spitting)	1
Does not accept(spits immediately)	2

12. Time of parental separation.....
13. Reaction to parental separation (Please tick on the relevant box)

Inconsolable cry	1
Complaining or crying but consolable	2
Quit, unafraid &cooperative or asleep	3

14. Preoperative sedation score at OR (Please tick on the relevant box)

Anxious	1
Oriented , calm	2
Drowsy but responds to verbal command	3
Not responding to verbal command but responds to painful stimuli	4
Not responding to painful stimuli	5

15. Vital signs in the OR before mask placement

Blood pressure	
Heart Rate	
Respiratory Rate	
SpO_2	

16. Mask acceptance score (Please tick on the relevant box)

Good (Accepts mask with no crying)	1
Fair (Accepts mask with crying)	2
Poor (Attempt to pull off the mask if not restrained)	3

17. Duration of surgery.....
18. Time from End of surgery to extubation in minutes.....
19. Post anaesthesia sedation score (Please tick on the relevant box)

Anxious	1
Oriented , calm	2
Drowsy but responds to verbal command	3
Not responding to verbal command but responds to painful stimuli	4
Not responding to painful stimuli	5

20. Post operative vital signs

Blood pressure	
Heart Rate	
Respiratory Rate	
SpO_2	

21. Does the child require supplemental O_2 to maintain SpO2 above 92%? (tick the appropriate)

Yes ☐

No ☐

Appendix 2: Consent

The principal investigator: Dr Billow M Ali

Institution: University of Nairobi

Sponsor: Self

Proposal:

A comparative study on the effectiveness and safety of 0.5mg/kg and 0.75mg/kg body weight of oral Midazolam as premedication to allay anxiety in children undergoing tonsillectomy and/or adenoidectomy at KNH

Consent for Parent/Guardian

Written Explanation

My Names are Dr Billow M Ali and I am pursuing a post-graduate degree in Anaesthesia and Critical Care.

I am conducting a study to compare the effectiveness and safety of different doses (0.5 and 0.75 Mg/Kg Body weight) of oral Midazolam – a short acting sedative drug used as premedication to allay anxiety in children.

Preoperative anxiety has been associated with a number of negative behaviours such as agitation, crying, spontaneous urination, and the need for physical restraint during anaesthetic induction as well as maladaptive behaviours post-surgery, including postoperative pain, sleeping disturbances, parent-child conflict, separation anxiety and even post traumatic stress disorder.

Doses ranging from 0.25 to 1 Mg/Kg Body weight have been used but the optimum dose has not been determined. Various studies done elsewhere in the world have shown varying results but no such study has been done in Kenya. I therefore invite you to participate in this study.

The study will go a long way in improving our patient management and preventing maladaptive behaviour after surgery. There is no monetary gain in participating in this study. The drug used for the purpose of this study is catered for by the investigator and therefore there is no extra cost involved in participating in this study

The study will involve placing the participants in to two groups which are selected by chance, as if by tossing a coin. One group will be given a dose of 0.5 Mg/kg body weight of intravenous midazolam mixed with pineapple juice orally at least half an hour before induction of anaesthesia. The other group will be given 0.75 Mg/kg body weight of intravenous midazolam mixed with pineapple juice orally at least half an hour before induction of anaesthesia.

The risk associated in participating in this study is minimal and manageable. Since the drug used in the study is a sedative like most drugs used during anaesthesia, it may cause a deep sleep and respiratory depression in some people. This effect of the drug can be easily reversed with an antidote which available. The doctors attending to your child are well equipped in managing this problem.

Your participation in this study is entirely voluntary. Whether you participate or not all the services you receive in this hospital will continue and nothing will change. You will not be given any money or gifts to participate in this study. There may not be any benefit to you, but your participation will help us find an answer to the research question and therefore help us improve the management of our patients. If you change your mind, you can withdraw from participating at any time even if you agreed to participate earlier.

Information collected about your child during the study will not be identified by your name but by a number known only to the researcher and will not be shared with or given to anyone.

If there is anything you are concerned about or is bothering you about the study please do not hesitate to ask me at any time. You can reach me on cell-phone number 0720881300.

This study will be conducted with the approval of KNH-UoN ERC You can also direct any concerns or questions about this study to the KNH-Uon ERC, Kenyatta National Hospital, P.O. BOX 20723, Nairobi, and Tel: 2726300-9.

Thank you.

Consent Form for Participants

I have read the foregoing information or it has been read to me. I have had the opportunity to ask questions about it and the questions I asked have been answered to my satisfaction. I consent voluntarily for my child to participate in the study and i understand that i have the right to withdraw from the study at anytime without in anyway affecting my medical care

Parent/Guardian name.....

Parent/Guardian signature..... Date.....

Resercher’s signature..... Date.....

Maelezo ya kibali ya mshiriki

Jina langu ni daktari Billow M. Ali. Mimi ni mwanafunzi katika chuo kikuu cha Nairobi. Nina somea masomo ya udaktari

Ninafanya utafiti wa kubainisha utendaji kazi na usalama wa dozi tofauti ya dawa inayoitwa midazolam ambayo ni dawa ya kuleta utulivu inatumiwa kabla ya upasuwaji.

Hofi kwa mgonjwa kabla kufanyiwa upasuwaji imehusishwa na madhara kama vile kuhisi kero, kulia, kutokwa na mkojo na pia kulazimu utumiaje wa nguvu ili mgonjwa atulie wakati wa kupewa dawa ya ganzi. Pia madhara ya baada ya upasuaji kama vile uchungu, shida ya usingizi, shida katika uhusiano baina mzazi na mtoto, hofi ya kuwachwa kwa mtoto pekee yake na pia hofi kuendelea baada ya kupata mshtuko.

Dozi ya hii dawa imetumika ya kiasi 0.25 paka 1 Mg kwa kilo, lakini dozi mwafaka kabisa haija angaziwa. Utafiti umefanya sehemu nyingi duniani na kupatikana matokeo tofauti lakini Kenya utafiti kama huu bado hauja fanya. Kwa sababu hii nakuomba ujumuike kwa huu utafiti.

Utafiti huu utasaidia pakubwa kuboresha utowaji huduma kwa wagonjwa na kuzuia madhara baada ya upasuaji. Utafiti huu hauto kugharimu pesa zozote na pia hautopewa marupurupu yeyote.

Utafiti huu utafanywa kwa njia ya kuwagawanya wahusika katika vikundi viwili kwa njia ya bahati na sibu. Kikundi cha kwanza watapewa dose ya 0.5mg kwa kilo ya dawa inayo itwa midazolam ambayo imechanganywa na juisi ya nanasi ambayo atapewa kwa mda wa dakika 30 kabla kupewa dawa ya ganzi.

Kujijumuisha katika huu utafiti hauto kuletea madhara, na kama kutakuwa nayo ni madhara madogo na ambayo yanazuilika. Hii ni kwa ajili hii dawa ni kama dawa zengine zinazotumika kuleta ganzi. Inaweza kusababisha usingizi mzito na kudidimia kwa kupumuwa kwa watu wengine. Hizi athari ambayo zinaweza kutokea zinatibika na dawa ambayo inapatikana kwa urahisi. Madaktari ambao watahudumia mtoto wako wame jiandaa vyema kutatua shida kama hii pindi itapotokea.

Kujumuishwa kwako kwa utafiti huu ni kwa hiari yako. Uamuzi wako kujijumuisha au kutojijumuisha kwa huu utafiti hauto athiri matibabu yako kwa vyovyote vile. Hautopewa marupurupu yeyote. Kujijuumisha kwako kwa huu utafiti utasaidia ku boresha huduma ya afya. Uki baadilisha mawazo yako, unaweza kujitoa wakati wowote hata kama ulishakubali hapo mbeleni.

Mambo yote ambayo yatahusika na mtoto wako kama vile jina na ugonjwa wake hautojulikana na mtu mwengine na itabakia siri.

Kama una maswali yeyote ama ungependa maelezo zaidi niulize wakati wowote. Unaweza kunipata kwa namba 0720881300.

Hii utafiti itafanywa kwa idhini ya kamati ya utafiti ya KNH-UoN ERC na kwa hivyo kama una maswali yeyote unaweza elekeza kwa hiyo kamati kupitia sanduku la posta 20723, Nairobi, au nambari ya simu 2726300-9

Asante sana.

Kibali cha mshiriki

Nimesoma/nimesomewa maelezo ya utafiti. Nimepewa fursa ya kuuliza maswali na nimejibiwa kikamilifu. Nimekubali kwa hiari yangu kushiriki kwa utafiti huu. Nina elewa kwamba niko na haki ya kujitoa kwa utafiti huu wakati wowote bila kupoteza haki yangu ya matibabu.

Jina la mshiriki_____

Sahihi ya mshiriki_____Tarehe_____

Sahihi ya mtafii_____ Tarehe_____

Appendix 3: Assent Form for Children Aged 6-10 Years

Study Title: A comparative study on the effectiveness and safety of 0.5mg/kg and 0.75mg/kg body weight of oral Midazolam as premedication to allay anxiety in children undergoing tonsillectomy and/or adenoidectomy at KNH

My name is Dr. Billow and I am doing a research on above topic.

We are doing a research study about the effectiveness of different doses of a drug called midazolam in making you less fearful and anxious before undergoing your operation. A research study is a way to learn more about people. If you decide that you want to be part of this study, you will be given the drug called midazolam mixed with clear pineapple juice 30 minutes before surgery and be observed for the effects. The medication you will be given is harmless since it is the same ones commonly used during anaesthesia

I will explain to you the procedures, benefits, risks and your role as a participant in this study

The benefits you will get as a participant in this study be descriptive but no tangible benefits and participating in this study is voluntary

When we are finished with this study we will write a report about what was learned. This report will not include your name or that you were in the study.

You do not have to be in this study if you do not want to be. If you decide to stop after we begin, that's okay too. Your parents will know about the study too.

If you decide you want to be in this study, please sign your name.

I, _____, want to be in this research study.

Sign your name here---------- Date……..

IDHINI YA WATOTO WENYE UMRI YA MIAKA 6-10.

Jina langu ni daktari Billow M. Ali. Mimi ni mwanafunzi katika chuo kikuu cha Nairobi. Nina somea masomo ya udaktari

Ninafanya utafiti wa kubainisha utendaji kazi na usalama wa dozi tofauti ya dawa inayoitwa midazolam ambayo ni dawa ya kuleta utulivu inatumiwa kabla ya upasuwaji

Kama utaamua kwamba unataka kushiriki katika utafiti huu, wewe utapewa dawa inayoitwa Midazolamdakika 30 kabla upasuaji na kisha kuchuguzwa hali ya utulivu wako. kwa muda. Dawa hii haina madhara vile kwasababu inatumika kwaida wakati wa upasuaji.

Nitakueleza taratibu, faida, hatari na jukumu lako kama mshiriki wa utafiti huu

Utapata faida ya maelezo kama mshiriki wa utafiti, lakini hautapata faida zozote zitakazoonekana.

Tutakapomaliza utafiti huu, tutaandika ripoti kuhusu tulichojifunza. Ripoti hii haitakuwa na jina lako au kuonyesha kwamba ulikuwa mshiriki.

Kushiriki ni kwa hiari na wazazi wako watajua juu ya utafiti huu.

Kama umeamua kushiriki katika utafiti huu,tafadhali tia sahihi.

Mimi, _____, nataka kushiriki katika utafiti huu.

Sahihi yako hapa ---------- Tarehe.....

Appendix 4: Ethical Approval

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

KENYATTA NATIONAL HOSPITAL APPROVED 29 AUG 2016 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

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/339

29th August, 2016

Dr. Mohamed Ali Billow
Reg. No.H58/69676/2013
Dept.of Anaesthesia
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Billow

Revised Research Proposal: "A comparative study on the Effectiveness and Safety of 0.5mg/kg and 0.75mg/kg body weight of Oral Midazolam as premedication to allay anxiety in Children undergoing Tonsillectomy and/or Adenoidectomy at Kenyatta National Hospital" (P456/06/2016)

This is to inform you that the KNH- UoN Ethics & Research Committee (KNH- UoN ERC) has reviewed and approved your above revised proposal. The approval period is from 29th August 2016 – 28th August 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.

"Protect to discover"

Appendix 5: Study Registration Certificate

KENYATTA NATIONAL HOSPITAL
P.O. Box 20723-00202 Nairobi

Tel.: 2726300/2726450/2726565
Research & Programs: Ext. 44705
Fax: 2725272
Email: knhresearch@gmail.com

Study Registration Certificate

1. Name of the Principal Investigator/Researcher
   DR MOHAMED ALI BILLOW
2. Email address: billema@yahoo.com Tel No. 0720881306
3. Contact person (if different from PI).....
4. Email address: ..... Tel No. .....
5. Study Title
   A COMPARATIVE STUDY ON THE EFFECTIVENESS & SAFETY OF 0.5mg/kg BODY WEIGHT OF ORAL MIDAZOLAM AS PREMEDICATION TO ALLAY ANXIETY IN CHILDREN UNDERGOING TONSILLO & OR ADENOIDECTOMY AT KENYATTA NATIONAL HOSPITAL
6. Department where the study will be conducted .....
   (Please attach copy of Abstract) ENT SATELITE THEATRE
7. Endorsed by Research Coordinator of the Department where the study will be conducted.
   Name: ..... Signature ..... Date .....
8. Endorsed by Head of Department where study will be conducted.
   Name: Dr. H.O. OKERE Signature ..... Date 08-06-2017
9. KNH UoN Ethics Research Committee approved study number P456/06/2016
   (Please attach copy of ERC approval)
10. I DR MOHAMED ALI BILLOW commit to submit a report of my study findings to the Department where the study will be conducted and to the Department of Research and Programs.
    Signature..... Date 8/6/17
11. Study Registration number (Dept/Number/Year) ENT/A/2017
    (To be completed by Research and Programs Department)
12. Research and Program Stamp .....

All studies conducted at Kenyatta National Hospital **must** be registered with the Department of Research and Programs and investigators **must commit** to share results with the hospital.

08 JUN 2017 DEP. OF ANAESTHESIA & THEATRE P.O. BOX 20723-00202, NAIROBI

KENYATTA NATIONAL HOSPITAL H.O.D. RESEARCH & PROGRAMS 14 JUN 2017 P.O. Box 20723 NAIROBI

Version 2: August, 2014

Appendix 6: Turnitin Originality Report

A comparative study on the effectiveness and safety of 0.5mg/kg and 0.75mg/kg body weight of oral Midazolam as premedication to allay anxiety in children undergoing tonsillectomy and/or adenoidectomy by Mohammed Billow

From Anaesthesia (Masters in Medicine)

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