DISSERTATION

UNIVERSITY OF NAIROBI

COLLEGE OF HEALTH SCIENCES.

EFFECTS OF FENTANYL ADMINISTERED FEW MINUTES BEFORE THE END OF SURGERY ON EMERGENCE DELIRIUM AMONG CHILDREN UNDERGOING ADENO-TONSILLECTOMY: A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED CLINICAL TRIAL.

A DISSERTATION SUBMITTED IN PART FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN ANESTHESIOLOGY OF UNIVERSITY OF NAIROBI.

DR. ELISHA KIPRONO KIRWA

2017

PRINCIPAL INVESTIGATOR;

DR. KIRWA ELISHA KIPRONO, MBCh.B.

Postgraduate student in Anaesthesiology and Critical Care Medicine (University of Nairobi).

Supervisors;

DR. MARK V. GACII, MBCh.B, M.MED (ANAESTHESIA).

Lecturer,

Department of Anaesthesia,

University of Nairobi.

DR. ALFRED OSOTI, MBCh.B, M.MED (OB GYN), MPH.

Lecturer.

Department of Obstetrics and Gynaecology.

University of Nairobi.

DR. EMMA MUTIO, MBCh.B, M.MED (ANAESTHESIA).

Paediatric anaesthesiologist.

Mbagathi District Hospital-Nairobi.

DECLARATION

I declare that this dissertation is my original work and has not been presented for the purpose of award of any degree or any other purposes in any institution.

Signature……Date……

…….

Dr. Kirwa Elisha Kiprono, MBCh.B. (Principal investigator)

Registration Number: H58/69263/2013.

Postgraduate student in Anaesthesiology and Critical Care Medicine

University of Nairobi.

This dissertation has been submitted for examination for master of medicine in anaesthesiology and critical care medicine with our approval as the university Supervisors.

Signature……Date……

Dr. Mark V. Gacii, MBCh.B, M.Med (Anaesthesia)

Lecturer,

Department of Anaesthesia

University of Nairobi.

Signature……..Date……

Dr. Alfred Osoti, MBCh.B, M.Med (Ob Gyn), MPH.

Lecturer.

Department of Obstetrics and Gynecology.

University of Nairobi.

Signature……Date……

……

Dr. Emma Mutio, MBCh.B, M.Med (Anaesthesia),

Paediatric anaesthesiologist.

Mbagathi District Hospital.

Nairobi.

DEDICATION

To my parents Mr. Kirwa Sitienei, late mum Martha Jepkemboi and step mum Pauline Sitienei for their guidance, inspiration, hard work and dedication during my education process.

To my dear wife Janet, sons Ryan and Regan for their endless support, friendship, love, motivation, understanding and endurance during my long absence from home during my postgraduate studies.

ACKNOWLEDGEMENTS

I wish to sincerely express my gratitude and acknowledge the following;

- My supervisors; Dr. Mark V. Gacii, Dr. Alfred Osoti, Dr. Emma Mutio, for their positive guidance and input during proposal development, data collection, analysis and presentation.

- Dr. Onchiri F. for his dedication and help during data management and analysis.

- Mr. Martin Njenga and colleagues for their assistance in data collection and adherence to study protocol.

- KNH department of anaesthesia for accepting my data protocol and allowing me conduct this study on their patients.

- My colleagues and friends for their overwhelming support and encouragement.

- KNH/UON Ethics and research committee for reviewing their positive inputs and approval of this study.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ED- Emergence delirium.

PAED scale- Paediatric Anaesthesia Emergence Delirium scale.

KNH- Kenyatta National Hospital.

ENT- Ear, Nose and Throat.

MRI- Magnetic Resonance Imaging.

U.O.N- University of Nairobi.

WHO- World Health Organization.

ERC- Ethics and Research Committee.

CDC- Centre's for Disease Control.

IV- Intravenous.

ug/kg- Micrograms per kilogram body weight.

mg/kg-Milligrams per kilogram body weight.

mcg/kg-Micrograms per kilogram body weight.

A_2- Alpha two.

SPSS-Statistical Package For the Social Sciences

GA-General Anaesthesia

ASA-American Society of Anaesthesiologist's physical status classification.

LIST OF TABLES

LIST OF FIGURES

OPERATIONAL DEFINITIONS

Emergence delirium(ED)-children scoring 3 or 4 after general anaesthesia reversal using Watcha scale will be interpreted to have ED.

Watcha scale-this is a simple scale for determining the presence of ED in clinical practice, it has a better specificity and sensitivity, it defines ED at a score of 3 and 4.

Sleep-altered state of consciousness easily aroused by external stimuli.

Calm-patient not showing nervousness, anger, emotions, violence or confrontational activity

Emergence from anaesthesia-in this study will be defined as when the patient displays facial grimacing, purposeful movements, regular breathing pattern and eye opening after anaesthesia

End of surgery-in this study will be defined as the time the mouth gag is removed.

.

ABSTRACT

Background; Modern volatile, insoluble inhalational anaesthetic agents used in surgery are associated with increased incidence of emergence delirium(ED) in children. Fentanyl prevents ED in high income settings where sevoflurane and desflurane are the predominant anaesthetics. However, in low income settings, halothane and isoflurane are the most frequently used anaesthetics; the effect of Fentanyl on reducing the incidence of ED has not been evaluated.

Objectives The study estimated the incidence of ED using watcha scale, the effectiveness and effects of fentanyl administered approximately ten minutes to end of surgery on the incidence of ED, among children undergoing adeno-tonsillectomy under halothane and isoflurane anaesthesia.

Methods A randomized double blind placebo controlled clinical trial, in which children aged between 1-12 years undergoing adeno-tonsillectomy under halothane and isoflurane anaesthesia at Kenyatta National Hospital were randomized to either Fentanyl at 1ug/kg or equivalent volume of normal saline in blocks. Fentanyl or normal saline was administered approximately ten minutes to the end of surgery. Children were observed for a period of 30 minutes after surgery in the recovery room. The main outcome was the proportion of children experiencing ED. We conducted intent to treat analysis and compared incidence of ED using logistic regression to obtain odds ratios.

Results: A total of 110 children were randomized, 50 % to Fentanyl and 50% to placebo. The mean age was 4.6 years for intervention and 4.1years for control. The leading type of surgery was adeno-tonsillectomy for both groups. The incidence of ED was significantly

lower among children randomized to Fentanyl (14.6%) compared to normal saline (47.3%), p<0.001. Fentanyl was associated with 81% reduction in the odds of emergence delirium (OR=0.19; 95% CI: 0.08- 0.48, p<0.001) in univariate analysis and in multivariate analysis after adjusting for the imbalances in the covariates (OR=0.18; 95% CI: 0.07-0.48; p<0.001). There were no statistical difference in the average time to full recovery between the patients randomized to receive fentanyl and those randomized to control (25.2 vs. 22.6; p=0.189) and majority of the patients in both arms; 96.4% in control and 94.6% in fentanyl group did not experience any immediate complications.

Conclusion: In resource constrained settings where halothane and isoflurane anaesthetics are most frequently used , Fentanyl given approximately ten minutes before the end of surgery significantly reduced the risk of ED among children (1-12 years) undergoing adeno-tonsillectomy without affecting the average time to full recovery and immediate complications.

Recommendation; Administration of fentanyl 1 mcg/kg towards the end of surgery in children undergoing adeno-tonsillectomy should be considered as a routine practice to prevent ED.

CHAPTER ONE

INTRODUCTION

Emergence delirium (ED) also known as emergence agitation is a common post-operative dissociative behaviour observed in children after undergoing general anaesthesia (GA) using modern highly potent inhalational anaesthetics such as Halothane, Isoflurane, Sevoflurane and Desflurane.

The aetiology of ED remains largely unknown and studies to determine its cause are ongoing. Theories postulated as contributing to development of ED include; Sudden emergence from general anaesthesia into a disordered state of consciousness or into an unfamiliar environment, Elevated postoperative pain, role of modern volatile anaesthetics having intrinsic properties that affect brain activity by interfering with the balance between neuronal synaptic inhibition and excitation in the central nervous system, causing ED and sensation of suffocation during ear nose and throat (ENT) surgical procedures.

The signs and symptoms associated with ED include irritability, non-cooperation and thrashing. The children become inconsolable or uncompromising, incoherent, experience paranoid ideation and unable to recognize and identify familiar and known objects or people.

This disorder is usually self-limiting lasting between 5-15 minutes; its effects are devastating and contribute to increased morbidity and mortality in the post-operative period.

The incidence of ED after Halothane, Isoflurane, Sevoflurane and Desflurane ranges from 10-80%, with a more frequent incidence in children. Its incidence varies according to the regions and current incidence in our region is unknown.

There are several risk factors which have been postulated to increase incidence of ED, these include; postoperative pain, use of short-acting volatile anaesthetics, rapid emergence from anaesthesia, preschool-aged children: 2-5, male gender, types of procedures: i.e. ENT, urologic, postoperative pain, personalities and child temperaments have all been associated with increased incidence of ED.

Assessment of presence and severity of ED is done using various scales including; Paediatric Anaesthesia Emergence Delirium (PAED), Watcha scale and Cravero scale (Table 1, 2, 3). These scales have their own advantages and weaknesses but the Watcha scale is the simplest to use in clinical practice and has better sensitivity and specificity.

Table 1. Watcha scale.

Behaviour	**Score**
Asleep	0
Calm	1
Crying, but can be consoled	2
Crying, but cannot be consoled	3
Agitated and thrashing around	4

The Watcha scale is a four-point scale as shown in Table 1.

The observer assesses the child's behaviour during recovery and gives a score as per the behaviour characteristics as shown in the table.

The Watcha scale defines ED at a level of 3 or 4 at any time during recovery from GA.

The Watcha scale has a higher correlation than Cravero with respect to the PAED scale.

Studies have shown that Watcha scale is a simpler tool to use in clinical practice and has a higher overall sensitivity and specificity than the other scales and for these reasons it will be used in this study. [1]

Table 2 Peadiatric anaesthesia emergence delirium scale.

Behaviour	Not at all	Just a little	Quite a bit	Very much	Extremely
Makes eye contact with caregiver	4	3	2	1	0
Actions are purposeful	4	3	2	1	0
Aware of surroundings	4	3	2	1	0
Restless	0	1	2	3	4
Inconsolable	0	1	2	3	4

The PEAD scale is validated scale for assessment of ED. [1]

The PAED scale has five items scored from 0 to 4 (with reverse scoring where applicable).

The scores are summed to obtain a total score with a range of 0–20.

The PAED scale is reported to have the advantage of being validated and better reflects the presence of ED rather than pain.

The PAED scale's first item, "The child makes eye contact with the caregiver," and third item, "The child is aware of his/her surroundings," reflects disturbances in the child's consciousness during an ED reaction.

The second item on the PAED scale, "The child's actions are purposeful," addresses changes in the child's cognition during an ED reaction.

The inclusion of items that reflect disturbances in consciousness and cognition may be pivotal in differentiating ED from pain.

The authors of the PAED scale have described a sensitivity of 64% and a specificity of 86% with a PAED score of >=10 [1].

The PAED scale is cumbersome and difficult to use in clinical practice. [1]

Table 3 Cravero scale.

Behaviour	Score
Obtunded with no response to stimulation	1
Asleep but responsive to movement or stimulation	2
Awake and responsive	3
Crying (for >3 min)	4
Thrashing behaviour that requires restraint	5

The Cravero scale shown in Table 3.

It is a five-point scale.

The observer assesses the child's behaviour and gives a score from 1-5.

The definition for ED in this scale is reached if level 4 or 5 was evident and present for at least 3 minutes.

The Cravero scale has the advantage of simplicity.

In summary Subjective assessment of ED is highly likely to score positive on all three scales although all three scales have their limitations, they appear to be reasonably reliable in detecting ED in clinical practice. The Watcha scale and the PAED scale when >12 give the highest sensitivity in detecting ED. [1]

Prevention is an important strategy in management of ED since its experience may increase the incidence of new-onset postoperative maladaptive behavioural changes such as general anxiety, night-time crying, enuresis, separation anxiety, and temper tantrums for up to 14 days after surgery.

Preventive measures which have been studied with varied results include the co-administration of Propofol, sedatives, opioids and α_2-adrenoreceptor agonists such as clonidine.

Treatments of ED include use of opioids, ketamine, Propofol and flumazenil, intravenous (I.V) Propofol (0.5 milligrams per kilogram/kg (mg/kg) or intravenous (I.V) Ketamine 0.25 mg/kg have both been used successfully in treating ED in children.

Fentanyl

Fentanyl is a potent synthetic opioid agonist; it is 100 times more potent than morphine. It is the most frequently used opioid in anaesthesia due to its good safety profile and high potency.

Fentanyl is highly lipid soluble hence crosses rapidly into biologic membranes and allows for fast onset of action and brief duration of action.

Indications and dosages; Fentanyl is used as analgesic of short duration during anaesthetic procedures at a dose of 50-150 micrograms per kilogramme (ug/kg), used as analgesic supplementation in regional and general anaesthesia at a dose of 12.5-25 ug/kg, used for administration with neuroleptic as anaesthetic premedication, for induction of anaesthesia and as an adjunct in maintenance of general and regional anaesthesia at a dose of 1.5-3 ug/kg.

Fentanyl is also indicated for management of chronic pain.

Lower sub-analgesic doses have been recommended for prevention of ED.

Mechanism of action; Fentanyl is a narcotic agonist which binds to opiate receptors in the central nervous system causing analgesia by increasing pain threshold, sedation and respiratory depression in a dose dependent manner.

Pharmacokinetics; Fentanyl can be administered via intravenous or intramuscular routes; it is compatible with most intravenous fluids including normal saline, ringers lactate, Hartman's solution and dextrose 5% solutions. It has bioavailability of 50%, has immediate onset of action (10 seconds) when given intravenously and 7-15 minutes when given in intra muscular route. The duration of action is 30 -60 minutes in intra venous route and 1-2 hours in intra muscular route. It is 80-85% protein bound and has a volume of distribution of 4-6 litres/kilogram. Its terminal elimination half-life is 3-6 hours.

Pharmacodynamics; Fentanyl is metabolised in live by cytochrome P3A4 enzymes and eliminated in urine (75%) and faeces (9%), it has elimination half-life of 2-4 hours.

Adverse effects; Fentanyl is generally a safe opioid, rare adverse effects occur in a dose dependent manner; these include nausea, vomiting, respiratory depression and easily reversed by opioid antagonist naloxone.

There are no recommended, specific or ideal treatments of ED but studies have shown some success with use of opioids, Clonidine, Dexmedetomidine, Propofol and Flumazenil. Propofol 0.5 mg/kg I.V or Ketamine 0.25 mg/kg I.V have both been used successfully in treating ED in children.

1.2 Justification.

Emergence delirium(ED) is a disturbing post-operative dissociative behaviour with a potential of causing life threatening complications and increasing morbidity and mortality after general anaesthesia (GA) using volatile anaesthetic agents. We routinely use these volatile anaesthetic agents during surgeries for induction and maintenance of anaesthesia. These agents are associated with increased risk in development of ED, for these reasons there is need to establish the incidence and severity of ED in our set up in order to be able to adequately prevent and treat it. This will improve the overall out come from general anaesthesia.

Several studies have shown a wide range of ED incidence (10-80%) and its risk factors across various regions in the world. There is no such local or regional data on ED although we frequently observe and manage ED in children who are recovering from GA, for this reason there is need to study ED in our set up and this study provides some insight into the local burden and incidence of ED in children undergoing surgery under general anaesthesia in KNH.

Most randomized trials done on emergence delirium(ED) have been done on use of Sevoflurane and few have been done on Isoflurane and halothane which we use routinely at KNH and other local and regional health centres. This study therefore helps anaesthesia care providers to understand the local burden of ED and assists in its prevention.

Fenmei Shi et al reviewed 16 randomised clinical trials on use of Fentanyl in1362 patients to prevent ED and found that no study could beat a high risk of bias for any of the criteria considered other short comings in these studies included inadequate blinding of participants and personnel, inadequacy in the blinding of the outcome measures, presence of incomplete outcome data, Random sequence generation was unclear in five trials and allocation concealment was unclear in 14 studies. This study aimed at eliminating these methodological flaws and find out the true incidence of ED and role of Fentanyl in preventing it in our local and regional centres. [2]

Failure to prevent, recognize and manage appropriately emergence delirium is disturbing and leads to delays in discharge from post anaesthetic care unit. The child may pull out drains, intravenous lines and surgical site dressings; this jeopardizes the safety of the child and others leading to increase in morbidity and mortality. The child with ED can inflict self-injury and cause increase in the surgical site bleeding, the child can also cause injury to the caregiver and other children in the recovery room. The affected child will also disturb other patients and the parents and decrease their satisfaction with treatment. Therefore preventing ED will help avoid all these problems and improve health care delivery to children undergoing surgery under GA, this study helps in doing so.

Occurrence of emergence delirium may lead to increased incidence of post-operative maladaptive behaviours including sleep disorders, separation anxiety and developmental regression and prevention is of paramount importance.

ED leads to increase in the cost of health care in that additional nursing help may be required and additional medications may be prescribed, therefore its prevention can greatly reduce the cost of health care.

This study will provides information on prevention of ED, if protective, use of fentanyl may help in reducing delays in discharge from recovery units; reduction on incidence of self-harm may reduce the morbidity and mortality in post-surgical children. There will also be improvement in the patient's safety and satisfaction in post anaesthesia period. The findings also help in providing information to stakeholders and anaesthetists in formulation of local policies and protocols of on prevention and management of emergence delirium.

Finally with ongoing use of more potent short acting inhalational agents, and ED being their distressing complication, there is need to define the best ways of preventing ED and this study provides important information on use of Fentanyl in preventing ED.

1.3 General Objective

To determine the incidence of ED and effects of fentanyl given approximately ten minutes to the end of surgery on emergence delirium in children undergoing adeno-tonsillectomy at Kenyatta National Hospital.

1.4 Specific Objectives

2. To determine the incidence of emergence delirium in children (1-12 years) undergoing adeno-tonsillectomy at Kenyatta National Hospital.
3. To determine whether Fentanyl prevents emergence delirium in children (1-12 years) undergoing adeno-tonsillectomy at Kenyatta National Hospital.
4. To evaluate whether Fentanyl prolongs emergence time from anaesthesia in children (1-12 years) undergoing adeno- tonsillectomy at Kenyatta National Hospital.

1.5 Hypothesis

Null Hypothesis: Fentanyl given approximately ten minutes to the end of surgery does not prevent occurrence of emergence delirium and does not alter (decrease or increase) emergence time in children undergoing adeno-tonsillectomy at Kenyatta National Hospital.

Alternative Hypothesis: Fentanyl given approximately ten minutes to the end of surgery prevents occurrence of emergence delirium and alters (increases/decreases) emergence time in children undergoing adeno-tonsillectomy at Kenyatta National Hospital.

CHAPTER TWO

2.1 LITERATURE REVIEW

Emergence delirium (ED) also known as emergence agitation is a common post-operative dissociative behaviour observed in children, it is a significant problem seen in children during recovery from general anaesthesia with a potential of causing harm and increasing morbidity and mortality.

The child becomes irritable, uncooperative, thrashing, inconsolable or uncompromising, and incoherent, the observations seen in this post-operative phenomenon include paranoid ideation and they are not able to recognize and identify familiar or known objects or people, this behaviour is reported as unusual and abnormal according to the parents or guardians of the children. [3]

Studies have shown increase in incidence of ED with the recent popularity and use of the newer highly potent inhalation agents, and numerous clinical studies have been published questioning the association of these anaesthetics with an increased incidence of emergence delirium. [3-6]

There are several risk factors which have been postulated to increase incidence of emergence delirium, these include; postoperative pain, use of short-acting volatile anaesthetics, rapid emergence from anaesthesia, pre-school children aged 2-5years, male

gender, types of procedures: i.e. ENT, urologic, postoperative pain, personalities and child temperaments have also been associated with increased incidence of ED. [7- 9]

There is historical increase in the incidence of ED correlating with the introduction of modern highly potent and short-acting inhalation anaesthetics, studies with patients undergoing MRI support the theory that there are intrinsic properties of inhalation anaesthetic that are primarily responsible for ED. [6]

The overall incidence of emergence delirium after Halothane, Isoflurane, Sevoflurane and Desflurane ranges from 10-80%. [7-13]

Bong C.L. & Ng, A, found the incidence in Asian children to be 10% which is less than reported in western world, this raises the question as to whether there is a racial or cultural association with ED. [13]

Smessaert A, Schehr CA, Artusio JFJ et al did an observational study in the immediate post-anaesthesia period and concluded that the incidence of emergence delirium in all postoperative patients is 5.3% with a more frequent incidence in children (12-13%). [14]

The main cause of ED remains largely unknown, sudden emergence from anaesthesia into a disordered state of consciousness or into an unfamiliar environment has been proposed as a cause of ED. However, the incidence of ED in patients receiving Propofol is markedly lower than those receiving Sevoflurane, despite the similar rapid emergence profile of both agents. [5, 16]

All inhalation anaesthetic agents, even Halothane increase the risk of ED, while shorter-acting agents increase the incidence further; there may be an underlying mechanism of action of inhalation anaesthetics triggering ED which has yet to be fully elucidated.

Volatile anaesthetic agents may affect brain activity by interfering with the balance between neuronal synaptic inhibition and excitation in the central nervous system hence causing ED. [8, 10, 32]

Elevated postoperative pain has been suggested to underlie ED. But given that ED is seen in patients undergoing MRI, pain cannot be the sole cause of ED. Occurrence of ED in patients undergoing MRI studies excludes pain as a confounding variable allowing for more controlled investigation of ED. [8, 5, 15]

Aono J, Ueda W, Mamiya K, et al. noted occurrence of emergence delirium in children after Sevoflurane anaesthesia despite effective regional blocks to prevent postoperative pain. These authors also demonstrated that ED occurred more frequently in preschool age children, 1 to 5 years of age, lasted 5-15 minutes in the recovery room and often resolved spontaneously. [7]

Eckenhoff JE, Kneale DH, Dripps RD and Bastron and Moyers found an increased incidence of ED in otorhinolaryngology procedures and speculated a "sense of suffocation" may contribute to ED in patients undergoing head and neck procedures though there is no enough data to support this theory. [15, 16]

Kain ZN, Mayes LC, O'Connor TZ et al studied predictors and outcomes in preoperative anxiety in children: and showed that children with no siblings, those who are impulsive, not enrolled in day care had a higher risk for developing negative behaviour changes such as separation anxiety, nightmares and bedwetting. [17]

Voepel-Lewis T, Malviya S, Prochaska G et al demonstrated that children with low adaptability and temperaments were at risk of sedation failures. [18]

Assessment of presence and severity of emergence delirium is done using various scales including; Paediatric Anaesthesia Emergence Delirium (PAED), Watcha and Cravero scales (Table 1, 2, 3). [1]

Bajwa SA, Costi D, Cyna AM compared these three scales in assessing the presence of emergence delirium and concluded that, the three scales correlated reasonably well with each other but have individual limitations in their potential to assess presence of emergence delirium. PAED score >12 appears to provide greater sensitivity and specificity than a PAED score > or=10. However the Watcha scale is a simpler tool to use in clinical practice and have a higher overall sensitivity and specificity than the other scales. The PAED scale has been validated but it could be difficult to use in a normal clinical setup, it is therefore much more practical to use a simpler scale than use PAED scale to assess the presence and severity of ED. [1, 5, 19]

For these reasons Watcha scale was used to assess the presence of emergence delirium in this study.

Prevention is important strategy in management of ED since its experience may increase the incidence of new-onset postoperative maladaptive behavioural changes such as general anxiety, night-time crying, enuresis, separation anxiety, and temper tantrums for up to 14 days after surgery. [10]

Pieters BJ, Penn E, Nicklaus P. et al randomized 42 patients undergoing adeno-tonsilectomy to maintenance with Propofol or Sevoflurane, ED was assessed using PAED scale. This study found out that the median PAED score in Propofol group was 14

compared to 17 in Sevoflurane group. Propofol group needed less pain medications and had low incidence post-operative nausea and vomiting (5.3% vs. 36.8%, $P < 0.05$). They concluded that Propofol does not influence agitation after adeno-tonsilectomy but associated with less post-operative nausea and less need for pain medications. [3]

Perioperative analgesia has been shown to be effective in preventing ED. Several analgesics have been studied for the prevention of ED including: Intravenous Fentanyl 1µg/kg, given 10 min before the end of a procedure, intravenous ketamine 0.25 mg/kg, given at the end of procedure, or as a premedication 6 mg/kg orally, and α_2-adrenoreceptor agonists such as clonidine caudally 1–3 µg/ kg; or intravenous 2–3 µg/kg and intravenous Dexmedetomidine 0.15–0.3 µg/kg, all these medications showed different efficacy in preventing ED in various regions. [3, 4, 5, 20-25]

Cho EJ, Yoon SZ, Cho JE et al compared 0.03mg/kg and 0.05mg/kg midazolam with a placebo in ninety (90) children aged between 1-13yrs undergoing strabismus surgery, the children were evaluated using PAED scale and concluded that midazolam 0.03mg/kg reduces the incidence of ED without delaying emergence time. [21]

Pattaravit N, Oofuwong M, Klaina S et al randomised 144 children undergoing elective surgery to receive fentanyl 1ug/kg and saline placebo at 1ml/10kg, they used Watcha scale to assess presence of emergence delirium. The study findings showed reduced incidence of ED in Fentanyl group compared to the placebo group [11/72 vs. 23/72] and

concluded that use of Fentanyl 1ug/kg reduced incidence of ED, and also reduced the need for rescue analgesia without affecting emergence time or increasing post-operative complications. [22]

Cravero J, Surgenor S, Whalen K. questioned whether inadequate pain management is the cause of ED in their study of Sevoflurane vs Halothane administration in patients undergoing MRI (no pain surgery) and found the incidence of ED in 33% in Sevoflurane treated patients versus 0% in halothane treated children. In the same study the patients undergoing MRI with Sevoflurane anaesthesia and given a dose of intravenous Fentanyl at 1 ug/kg, 10 minutes before discontinuation of the anaesthetics had an incidence of emergence agitation of 12% versus 56% in the placebo group. The discharge time was similar in both groups but whether Fentanyl caused a slower awakening time was not answered by this study. [25]

Uezono S, Goto T, Terui K, et al. Compared Propofol versus Sevoflurane anaesthetic techniques and noted a 38% incidence of ED with Sevoflurane versus 0% with Propofol. However, sevoflurane still provided a shorter PACU stay than Propofol in another study. [26]

Cohen IT, Hannallah RS, Hummer K et al found an incidence of 23.1% of patients with ED who received Sevoflurane versus 3.7% with propofol. [27]

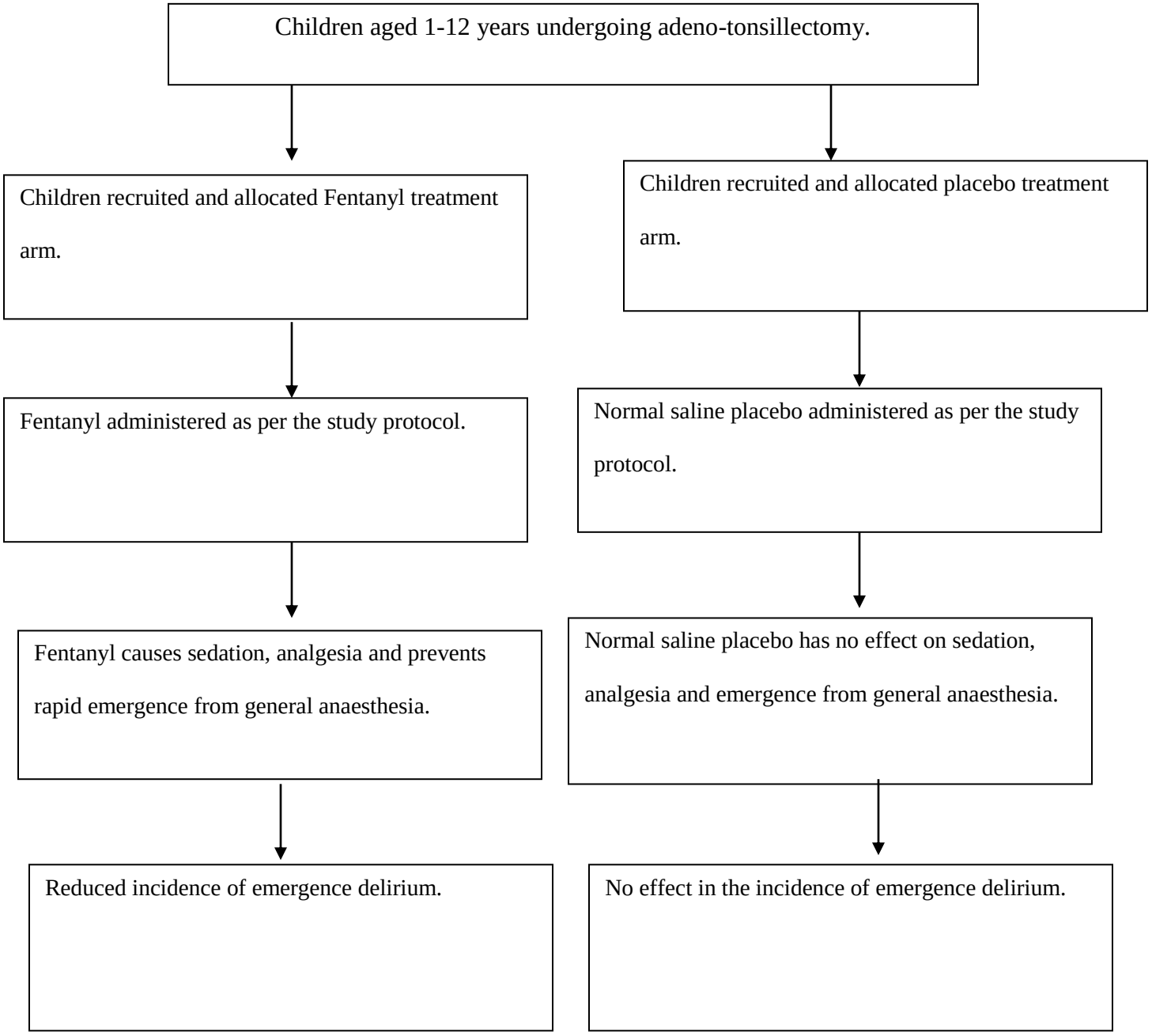
Bortone L, Bertolizio G, Engelhardt T et al compared intravenous Clonidine 2 mcg/kg, intravenous Fentanyl 2 mcg/kg or placebo (Intravenous saline) before sub-umbilical

surgery under Sevoflurane in ninety (90) children to determine the incidence of early negative post-operative behaviour and found out that Fentanyl and not Clonidine reduced the incidence of early negative post-operative behaviour and children in this group also had lower pain scores. [28]

Dahmani, S.et al did a meta-analysis of published studies on pharmacological prevention of ED,37 articles where reviewed,1695 patients in intervention groups and 1477 patients in control groups. This analysis showed that there is evidence that prophylactic treatment with Propofol, Fentanyl, Ketamine, A_2 receptor agonist-Clonidine and preoperative analgesia prevented occurrence of ED, Propofol [OR 0.21 (0.16, 0.28)], ketamine [OR 0.28 (0.13, 0.60)], A_2-adrenoceptors [OR 0.23 (0.17, 0.33)], Fentanyl [OR 0.31 (0.18, 0.56)], and perioperative analgesia [OR 0.15 (0.07, 0.34)].The analgesic properties of these drugs do not seem to have a role in this effect. [29]

Kim MS, Moon BE, Kim H et al did a prospective randomized control double blind study in 222 children to compare Propofol and Fentanyl given at the end of anaesthesia using PAED scale to assess for emergence agitation, this study showed that the Propofol group had lower PAED scores of 4.3 compared to 4.9 in Fentanyl group, Propofol group had lower incidence of post-operative nausea and vomiting. They concluded that low doses of Propofol and fentanyl reduced incidence of ED and Propofol was better due to low incidence of post-operative nausea and vomiting. [33]

Figure1. Theoretical frame work.



CHAPTER THREE

RESEARCH METHODOLOGY

3.1 Study Design.

This was a randomized placebo controlled double blind clinical trial involving children aged between 1-12 years who were undergoing adeno-tonsillectomy at the Kenyatta National Hospital. The intervention group received Fentanyl 1ug/kg while the placebo control group received normal saline equivalent to the volume of Fentanyl. The primary outcome was the incidence of ED as observed using Watcha scale and secondary outcomes were weather Fentanyl administered approximately ten minutes to the end of surgery helped prevent ED, delayed emergence from general anaesthesia and any immediate complications associated with fentanyl use.

All children who participated in the study were assessed for presence of ED using the Watcha emergence delirium scale due to its simplicity and high sensitivity and specificity.

We chose on a randomized placebo controlled clinical trial because there is currently no standard management of ED in our setting. Randomization provides evidence for use of the proposed medication (Fentanyl) and helps in developing standardized protocols for managing ED in our setting and beyond.

Blinding would eliminate bias and show efficacy or effectiveness; if the anaesthesiologists were given an option to know the medication everyone would administer the active ingredient. There was equipoise as the patient still received additional treatment if required. In addition there may have been patients who did not need medications to prevent ED so if we gave everyone medication it would have been unnecessary treatment. There was no risk of harm if the patient gets second dose of Fentanyl since there is no risk of overdose and the doses given in the study were still within the accepted therapeutic range.

We used the placebo in this study because currently there is no standard of care and the incidence rate in our setting is unknown, just like the treatment arm this did not prevent the patient from receiving additional care.

This was a simple randomized trial with short period of intervention to outcome and minimal risk since fentanyl is not a new medication and has excellent safety and efficacy profile. We were only trying to find out the efficacy and effectiveness in our setting. We had the expertise and the supervision necessary to carry out this simple randomized control trial through DSMB and ERC approval and no other supervisory requirements was required. We felt that this was the best study design in this setting to balance confounding and bias since an observational study wold not have answered our questions.

3.2 Study Site.

This research was carried out at the Kenyatta National Hospital ENT operating theatre between February and August 2016.

KNH is the largest referral and teaching hospital in Kenya. The clientele of the Kenyatta national hospital is national in outlook with both rural and urban catchments.

The bed capacity in the hospital is more than 1,800,it has 50 wards, 20 outpatient clinics, 24 operating theatres and accident and emergency department.

Approximately twenty [20] to thirty [30] adenoid-tonsillectomies are done weekly at Kenyatta national hospital and there is no standard practice in prevention of ED neither its incidence is known, hence the suitability of the site for this study.

In KNH ED is usually diagnosed in the observation room by the care givers and appropriate treatment is usually administered, there is no standard treatment given and care depends on caregivers experience with the medication at hand.

3.3 Study Population

The study population comprised all children undergoing elective adeno-tonsillectomy under general anaesthesia and meeting the inclusion criteria and whose guardians/parents gave an informed consent in Kenyatta national hospital.

3.4 Inclusion/exclusion criteria

3.4.1 Inclusion criteria

-American Society of Anaesthesiologists classes (ASA) 1 and 2 children.

ASA 1-Normal healthy child scheduled for adeno-tonsilectomy.

ASA 2-Child with mild systemic disease without functional limitations.

-Children aged 1 to 12 years.

-Children undergoing elective adeno-tonsilectomy.

-Those children whose parents/guardians gave a written informed consent.

3.4.2 Exclusion criteria.

The exclusion criteria was determined and assessed by taking a proper medical history and doing complete physical examination of the children on the day before surgery.

The exclusion criteria for this study included;

- Children with genetic syndromes.
- Children with psychological/neurological behavioural disorders.
- Children with allergies to Fentanyl.
- Children who had psychiatric disorders/ use of psychiatric medications.
- Use of sedative medications one hour prior to surgery.
- Children with developmental delay.
- Children who came in as day cases.
- Children who had airway problems not related to the surgery-sleep apnoea.
- Children less than 1 year and those above 13 years.

3.5 Sample size estimation

The main outcome of this study was the proportion of children who experienced ED after general anaesthesia.

The estimated rates of ED without treatment ranges from 10-80%. [30.]

We assumed ED rate of 25% in our setting.

We postulated that administering Fentanyl about 10 minutes before the end of surgery would reduce the incidence of ED to 5%.

Therefore for us to detect a 20% difference in the reduction of ED using Fentanyl versus placebo, we estimated the sample size using the formula by Donner A. [31]

$$n = \frac{2\left(z_{1-\alpha_{/2}}\sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta}\sqrt{p_c(1-p_c)+p_a(1-p_a)}\right)^2}{(p_c - p_a)^2}$$

Where we define p_c=5% and p_a=25% to be the proportions of children in the ED and placebo groups respectively.

and $\bar{p} = (p_C + p_a)/2$ ($z_{0.25}$ =1.960, and $z_{0.8}$ =0.842).

We needed to study a total of 108 children (49 per group) to achieve 80% power to detect the stated difference of 20% at a two-sided alpha=0.05 level of significance.

This study utilized 55 respondents in each group to provide for 10% attrition.

3.6 Sampling,

The sampling was done using consecutive sampling method of all the children admitted to undergo adeno-tonsillectomy and meeting the inclusion criteria at Kenyatta National Hospital.

The Sampling frame for this study represented the list of all the children scheduled for adeno-tonsillectomy during the study period.

3.7 Recruitment and randomization.

The study participants were recruited the night before surgery in the wards where the parent/caretaker or guardian was approached to obtain informed written consent. The study participants parents/caretaker or guardians received an explanation about the study after which a written informed consent was obtained.

Children coming as day cases for adeno-tonsillectomy were excluded from the study since we could not get enough time to determine their suitability and recruitment procedures.

Randomization was done using block randomization and computer generated numbers.

The statistician generated random numbers that corresponded to the study arm in the ratio of 1:1.and placed them in serially numbered opaque envelopes.

The statistician kept the records of the random numbers and serial numbers of the envelopes.

3.8 Description of intervention and study protocols.

The first research assistant who was a pharmacist in profession collected the serialized envelopes which contained the random numbers and study arms from the statistician, he then prepared the treatment in the morning of surgery as per the study arm in 1cc syringe noting the envelope serial number on the syringe and placed it back into the serialised envelope.

All medications were prepared under the recommended aseptic techniques as per the KNH set guidelines; the drugs were stored in the room temperature and administered via intra venous route as per the manufacturer's guidelines.

The second research assistant who was a post graduate student in anaesthesia attached to the Ear, Nose and Throat (ENT) theatre picked the prepared treatment and gave it to the anaesthesia provider who then administer the medication to the study participant and noted the serial number of the envelope on the accompanying questionnaire, this assistant and the anaesthesia provider were not able to know the treatment arm being administered hence minimizing bias.

Fentanyl is a drug that is readily available, stored in room temperature and no extra storage requirement; it is usually prepared for daily use by each and every anaesthesiologist. To ensure standardization we worked with a research assistant who was a trained pharmacist each morning to prepare adequate samples for the day as per the

number of recruited patients under strict aseptic techniques. Normal saline is safe intravenous fluid which is used at the same volume to flash IV if needed. These are not new drugs in the market and daily anaesthesia practice.

The researcher and his assistants had no control on the anaesthetist. They only sought compliance to the randomization by ensuring adherence to randomization arm of the study, ready supply of medications and clear documentation.

Patients participating in the study were not pre-medicated and other medications the child was using were noted and factored in during data analysis.

Anaesthesia was induced with either an inhaled technique consisting of nitrous oxide/oxygen (50%:50%) and halothane or intravenous Propofol at 2-5mg/kg.

The patients were given intravenous Atracurium during induction of anaesthesia at 0.5mg/kg to facilitate smooth endotracheal intubation.

All participants received standard antiemetics for prophylaxis against post-operative nausea and vomiting.

Ventilation was controlled and monitored using end tidal carbon dioxide maintained between 30-40mmHg.

Anaesthesia was maintained using Isoflurane, nitrous oxide and oxygen.

Standard monitoring of the patients during surgery included electrocardiogram (ECG), Non-invasive blood Pressure cuff, pulse oximeter, temperature, and end tidal gas measurements.

Those randomized to the intervention arm received intravenous Fentanyl at 1ug/kg approximately ten minutes before the end of surgery using 1ml syringe to improve on the accuracy of the dosing.

Those randomized to the placebo arm received intravenous normal saline at a volume equivalent to fentanyl dose of 1ug/kg approximately ten minutes before the end of surgery using 1ml syringe to improve on the accuracy of the dosing.

The induction agents, antiemetics, analgesics and any other medications administered during the course of surgery were recorded and analysed.

Analgesics administered during surgery varied slightly as per the anaesthesia provider.

The treatment was administered by the person administering general anaesthesia approximately ten minutes to the end of surgery which was determined by the time of removal of mouth gag.

The time of treatment administration and time of fully emergence from anaesthesia defined as when the patient displays facial grimacing, purposeful movements, regular breathing pattern and eye opening, was recorded and analysed.

The patients were moved to recovery room after full emergence from anaesthesia had been established and tracheal extubation done.

The principal investigator filled the research questionnaire at the recovery room and monitored for presence of ED in the first 20 minutes using Watcha scale.

Children who develop ED during the study were treated with Propofol (0.5 mg/kg IV) or Ketamine (0.25 mg/kg IV), and any complications arising from the trial or management of ED was managed as per the set protocols.

The research data was periodically analysed and results shared with the data safety and monitoring board for their independent review after which they made recommendations on whether the study should continue or stop basing on the effects of fentanyl.

3.8.1 Expected complications and management.

Fentanyl 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. Rare complications include respiratory depression and post-operative nausea and vomiting.

Respiratory depression would managed by assisted ventilation and administration of naloxone which immediately reverses it at a dose of 0.01mg per kilogram.

Post- operative nausea and vomiting was managed by standard administration of antiemetic prophylaxis and in case of vomiting in the recovery room which was rare; suctioning, positioning and administration of appropriate antiemetic was done.

3.9 Data management

3.9.1 Data collection

Pre-testing of study instrument was carried out to structure and modify the research instrument by clarifying grammar and language used so as to avoid bias and misinterpretations of the questions. The questionnaire was also pre-tested for consistency, timing, accuracy and reliability.

The study questionnaire was filled by the principal investigator or trained research assistant at the recovery room.

At the end of each study the filled questionnaire was cross checked for completeness and any missing entries corrected.

The exposure variables were Exposures to Fentanyl or Normal Saline while the outcomes variable were incidence of ED in each treatment arm, time to emergence, complications and the effects of fentanyl.

Other variables included the type of induction and analgesic agents used and other medications administered during surgery, previous medications used prior to surgery and additional potential confounders, socio-demographics, other medications used were also be analysed.

The reliability of the research findings were determined using Cronbach's alpha coefficient. The test splits all the answers to a given question into two section or groups then the scores obtained are summed up

3.9.2 Data analysis and presentation

All data collected in the study were sorted, coded and entered in a computer using SPSS version 22.

The data was cross checked against the data files for any inconsistencies and obvious data entry errors. The data entry and editing was done throughout the study process.

The incidence of ED from previous studies varies from 10-80%, as per our power analysis we would need a sample size of 49 children per group to achieve 80% power to detect the stated difference of 20% at a two-sided alpha=0.05 level of significance. This study utilized 55 respondents in each group to provide for 10% attrition. Demographic, clinical and laboratory characteristics were summarized and compared between study arms. Continuous variables were summarized using means and standard deviations and compared using the two-sample t-test if normality assumptions are met; otherwise they were summarized using medians and interquartile ranges and compared using nonparametric Wilcoxon rank sum test. Categorical variables were summarized using counts and proportions and compared between study groups using Pearson's chi-square tests or Fisher's exact tests as appropriate. To determine the effect of the intervention on ED we compared the incidence of children with ED between children randomized to the intervention and the control arms. Odds associating intervention with intervention were estimated using univariate and multivariate logistic regression models. Adjusted odds ratios (aORs) and their 95% confidence intervals (CIs) were computed.

Odds ratio with 95% CI was used to determine whether there is an association between fentanyl and occurrence of ED.

Kaplan Meier survival analysis was used to compare Time to emergence.

P values of <0.05 was considered statistically significant and 95% CI was used to show any significant associations if they did not include the null value.

The study finding will be presented using figures, tables, pie-charts and bar-graphs.

Conclusions and recommendations will be made based on the results.

3.9.3 Data Storage, Privacy/security and Archival

All data collected was kept locked and confidential at all times.

Electronic forms of data were protected with confidential passwords at all times.

Data was kept locked and only accessible to the investigator and data manager.

Data will be preserved until analysis, presentation and archival done.

3.10 Ethical considerations.

The parents or the guardians of the children undergoing adeno-tonsillectomy and meeting the study criteria were furnished with brief information concerning the research i.e. the research objectives, benefits and any adverse effects and a written informed consent signed by them.

The choice to participate in the research was completely voluntary

Every child, even after giving consent to participate, retained the right to opt out of the research at any time the parent/guardian feels like without repercussion against them

No monetary or other forms of tangible benefits were realized in appreciation for participation in the research as a respondent.

Every respondent was entitled to full information pertaining to the progress and findings of the research.

No extra cost was incurred by the parents or guardians during the study period.

All information obtained was strictly kept confidential and was only used for the purposes of the said research.

A respondent who consents to participate confirmed such consent by appending her signature or thumb print on the availed Consent Form.

Children who developed ED during the study were treated with Propofol (0.5 mg/kg IV) or midazolam (0.02 mg/kg IV).any other complications arising was managed as per the set protocols by the care givers at the observation rooms.

This clinical trial was registered at clinicaltrials.gov. (Trial number; NCT02753725).

This study was approved by the KNH/UON-Ethics and Research Committee prior to carrying out the study. (Reference P628/10/2015)

Children aged 7-12 and able to read and write signed the assent form appendix III.

There were no interests declared during this study.

This study was solely funded by the principal investigator.

3.11 Data Safety Monitoring Board.

The following members who have a lot of experience in clinical trials were approached to form independent data safety monitoring board.

1. Prof. James Kiarie-Ob gyn, epidemiologist, WHO.
2. Dr. Frankline Onchare-CDC epidemiologist, Statistician.
3. Dr. Andrew Muchukira-University of Washington-Epidemiologist.
4. Dr. George Osanjo; senior lecturer; department of pharmacology and pharmacognosy, college of health sciences, University of Nairobi.
5. Dr.Mark V. Gacii; MBCh.B, M.Med. Lecturer department of Anaesthesia; university of Nairobi.

This was an independent group of experts whose roles and responsibilities were to;

1. Advice ERC and the investigator and give independent recommendations on the study.
2. Periodically review and evaluate accumulated study data for participant safety, study conduct and progress.
3. Make recommendations to ERC concerning, continuation, modification of termination of the trial.

3.12 Study Findings Dissemination.

The findings of this study will be disseminated through; presentation to members of anaesthesia department of the 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

RESULTS

All 110 children recruited successfully completed the study.

The demographic and clinical characteristics of the study participants are presented in Table 1. Except for weight and use of tramadol analgesic, the distributions of the rest of the characteristics were statistically similar between the study arms. The effect of the intervention on ED persisted in the multivariate analysis that adjusted for the imbalances in the covariates.

The incidence of ED was significantly lower among children randomized to receive Fentanyl compared to those in the control (14.6% vs. 47.3%; $p<0.001$). The results of the regression analyses of the effect of the intervention are presented in table 2. In the univariate logistic regression, the intervention was associated with a statistically significant 81% reduced risk of Emergence delirium (OR=0.190; 95% CI: 0.076- 0.475, $p<0.001$). This effect of the intervention on ED persisted in the multivariate analysis that adjusted for the imbalances in the covariates observed in Table 1 (OR=0.184; 95% CI: 0.070-0.479; $p<0.001$).

Figure 2. Summary of Patients Flow.

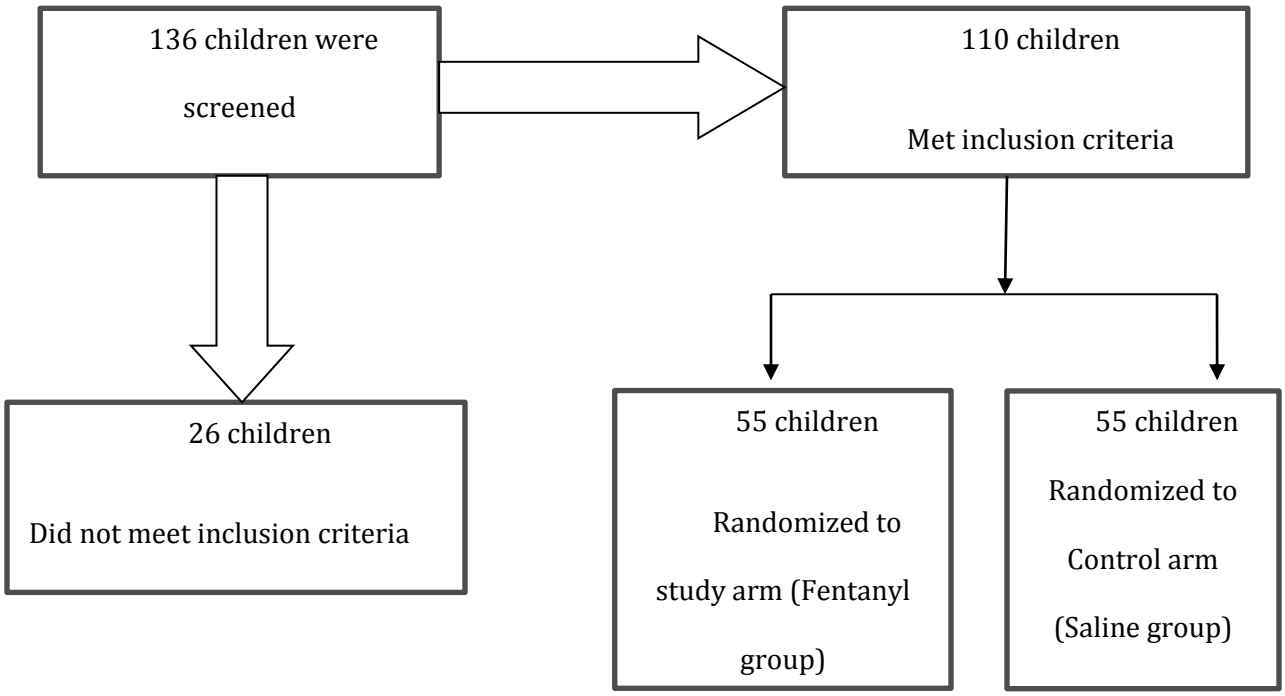
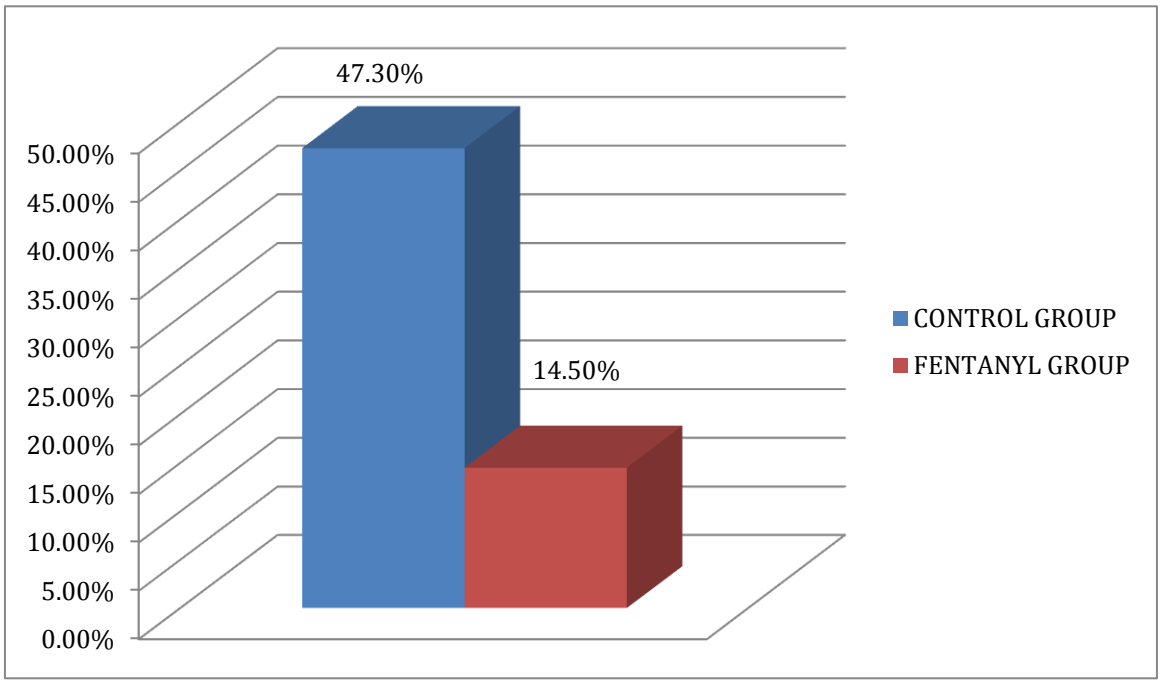


Table 4. Demographic and Clinical Characteristics of Study Participants.

Variable	Arm		p-value
	Control (n=55)	Fentanyl (n=55)	
Age (yrs.), mean (SD)	4.1 (2.3)	4.6 (2.2)	0.29
Gender			0.70
Female	25 (45%)	23 (42%)	
Male	30 (55%)	32 (58%)	
Weight (Kg), Mean (SD)	15.7 (5.7)	18.0 (5.3)	0.030
Type of surgery			0.240
Adenoidectomy	20 (36%)	12 (22%)	
Adeno-tonsillectomy	33 (60%)	40 (73%)	
Tonsillectomy	2 (4%)	3 (5%)	
Tramadol analgesic used?			0.033
No	28 (51%)	17 (31%)	
Yes	27 (49%)	38 (69%)	
Tramadol dose used[mg], Mean (SD)	25.4 (26.7)	19.8 (7.7)	0.23
Diclofenac analgesic used?			0.24
No	52 (95%)	55 (100%)	
Yes	3 (5%)	0 (0%)	
Fentanyl analgesic use?			0.40
No	2 (4%)	4 (7%)	
Yes	53 (96%)	51 (93%)	
Fentanyl dose used [mcg], Mean (SD)	15.4 (7.9)	16.7 (8.3)	0.43
Paracetamol analgesic used?			
Yes	55 (100%)	55 (100%)	
Paracetamol dose used[mg], mean (SD)	241.3 (101.9)	264.4 (125.2)	0.29

Figure 3 The Incidence of ED Per The Study Arm.



The incidence of ED was significantly lower among children randomized to receive Fentanyl compared to those in the control (14.6% vs. 47.3%; p<0.001).

Table 5. Effect of Fentanyl on Emergence delirium among children undergoing adenotonsillectomy.

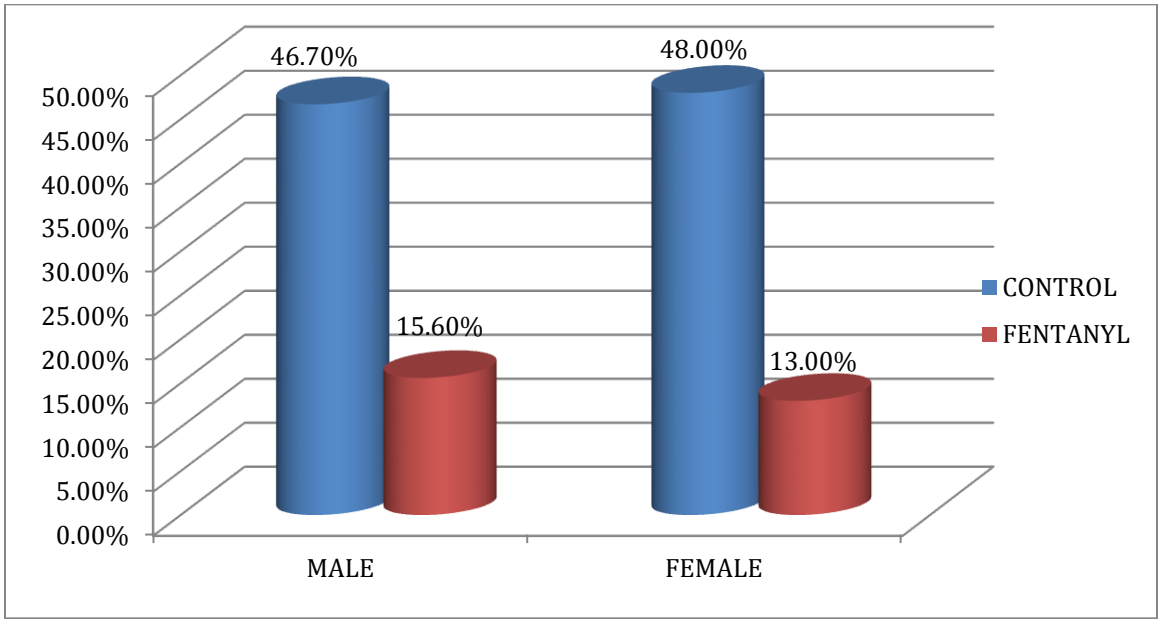
	Unadjusted Analysis			Adjusted Analysis		
	RR	**95% CI**	**p-value**	**RR**	**95% CI**	**p-value**
Study_Arm2						
Control*	1			1		
Fentanyl	0.190	(0.076- 0.475)	<0.001	0.184	(0.070-0.479)	<0.001
Sex						
Female*				1		
Male				0.998	(0.414-2.419)	0.999
Type of surgery						
Adenoidectomy or Tonsillectomy*				1		
Adeno-tonsillectomy				0.596	(0.235-1.514)	0.277
Age(yrs.)				0.891	(0.657-1.209)	0.460
Weight (Kg)				1.053	(0.933-1.189)	0.399

The effect of the intervention on ED persisted in the multivariate analysis that adjusted for the imbalances in the covariates observed in Table 1 (OR=0.184; 95% CI: 0.070-0.479; p<0.001).

Table 6. Sex as an interaction term on the effectiveness of Fentanyl on ED.

Covariate	OR	95% CI	p-value
Study_Arm2			
Control*	1		
Fentanyl	0.163	(0.038- 0.689)	0.014
Sex			
Female*	1		
Male	0.948	(0.327-2.744)	0.921
Fentanyl & Sex interaction	1.302		
Fentanyl & Male		(0.200-8.487)	0.782
* Baseline category			

Figure 4. Incidence of ED stratified by gender of children.



There was no evidence that the effect of fentanyl on ED was different between the male and females. The interaction term of intervention and gender was not significant; p=0.782

Table 7. Duration of emergence by study arm,

	Study arm		
Factor	Control (n=55)	Fentanyl (n=55)	p-value
Duration of emergence [Min], Mean (SD)	22.6 (9.3)	25.2 (10.6)	0.189

There were no statistically significant difference in the average time to full recovery between the patients randomized to receive fentanyl and those randomized to control (25.2 vs. 22.6; p=0.189).

Table 8. Complications experienced at recovery.

Factor	Control	Fentanyl	p-value
N	55	55	
Complications after reversal			0.50
Laryngospasms	2(4%)	2(4%)	
Post-operative nausea and vomiting	0(0%)	1(2%)	

Majority of the patients in both arms; 96.4% in control and 94.6% in fentanyl group did not have any complications

CHAPTER FIVE

5.0 DISCUSSION

This study found that there is increased incidence of ED in the control group compared to the fentanyl group 47.3% vs 14.6% ($p<0.001$) in children undergoing general anesthesia under halothane and isoflurane. Hanny M.Yassin, Maged L.Boules [34] found the incidence of 46.9% in control group and 12.5% in fentanyl group using pediatric anaesthesia emergence delirium scale (PAED scale) in children undergoing inguinal hernia repair under sevoflurane anesthesia, this correlates well with our findings, Welborn L.G, Hannallah R.S, and Norden J.M et al [10] described the incidence of ED ranges from 10-80% depending on the scale used and the type of surgery involved.

Studies have associated ED with use of sevoflurane but in our setting we mostly use halothane and isoflurane, this study showed that use of halothane and isoflurane is also associated with comparable increased incidence of ED, the aetiology of ED in children is still largely unknown, sevoflurane has been well studied in association with ED [2, 21, 22], this study shows that isoflurane and halothane play a role in development of ED and supports the theory that short acting, insoluble volatile inhalational agents play a role in development of ED [22]

ED has been observed in children undergoing painless procedures under inhalational agents and ideally immediate postoperative pain should be ruled out while determining

the presence of ED, in this study all children under going adeno-tonsillectomy, pain was adequately managed by use of multimodal analgesics that includes opioids, non-steroidal anti-inflammatory agents and paracetamol during surgery. Patients undergoing this kind of surgery usually experience moderate pain which is usually well controlled by two analgesics of different modes of action, therefore severe post-operative pain was not expected in this study [2, 22]

Fentanyl is short acting opioid analgesics whose effects in reducing the incidence of ED have been shown, this study found out that Use of fentanyl significantly reduced the incidence of ED in children undergoing adeno-tonsillectomy under halothane and isoflurane compared to the control group, fentanyl has been shown to prevent ED independent of its analgesic properties, this confirms the findings from studies of incidence of ED in sevoflurane anaesthesia [16, 23,] Cravero JP, Thyr B, Beach M [6] found out that use of 1microgram per kilogram of fentanyl ten minutes to stoppage of sevoflurane anaesthesia is effective in reducing ED from 56% to 12%. The univariate logistic regression of our study shows that the intervention was associated with a statistically significant 81% reduced risk of Emergence delirium (OR=0.190; 95% CI: 0.076- 0.475, $p<0.001$). This effect of the intervention on ED persisted in the multivariate analysis that adjusted for the imbalances in the covariates observed in Table 1 (OR=0.184; 95% CI: 0.070-0.479; $p<0.001$).

This study found out that there is no difference in emergence time from anaesthesia between the two treatment arms and confirms that fentanyl use prior to reversal from general anesthesia does not prolong the emergence time. Pattaravit N, Oofuwong M, Klaina S, et a [22] found that use of fentanyl to prevent ED does not alter the recovery or discharge times after general anesthesia

This study also looked at the immediate postoperative complications during reversal from general anaesthesia and recovery period in the recovery room and found out that there was no difference in terms of development of laryngospasms in the two groups, however the fentanyl group had an incident of immediate nausea and vomiting though not statistically significant, Kim MS, Moon BE Kim H et al [33] found increased incidence of postoperative nausea and vomiting with use of fentanyl to prevent ED, this is expected when using opioids due to their increased risk of causing postoperative nausea and vomiting, the use of standard antiemetic prophylaxis greatly reduced the occurrence of this complication, therefore use of antiemetic's while using fentanyl to prevent ED should be encouraged to prevent development of postoperative nausea and vomiting due to its associated increased risk.

This study also found out that there was no interaction between the gender and the incidence of ED, in the control group there was no statistical difference between development of ED in the female and the male gender (48% vs 46.7%) whereas the fentanyl group also showed no statistical difference in Incidence of ED between female

and the male gender (13% vs 15.6%). The fentanyl group had significantly lower incidence of ED in both gender, the males control group had higher incidence of ED than control group (46.7 % vs 15.6% $p<0.001$) while females had significantly lower incidence of ED in fentanyl group than the control group (48% vs 13% $p<0.001$), this indicates that the occurrence of ED is equal across male and females and gender doesn't play any role in its occurrence, it also indicates that the effect of intervention is effective across both gender.

The strengths of this study include being a double blind randomized clinical trial; double blinding prevents selection and observer bias. The study had a large sample size which reduced the variability. This study is the first of its kind in this setting and provides evidence of effectiveness of intervention.

However this study has a few limitations in that we never followed children past recovery room to determine whether there was any significant differences in the two groups thereafter in terms of late development of postoperative nausea and vomiting, secondly we never looked at children who might have had preoperative anxiety which has been shown to increase the incidence of ED since children on sedatives where excluded from the study thirdly this study only looked at the children undergoing adeno-tonsillectomy and studies have shown that the incidence of ED varies with the type of surgery, despite of all these limitations the significant difference in incidence of ED between the fentanyl group and control group(14.6% vs. 47.3%; $p<0.001$) and the fact that fentanyl

significantly reduced the incidence of ED by 81% confirmed to us that there is high incidence of ED in use of halothane and isoflurane and fentanyl given prior to the end of surgery prevent ED.

CHAPTER SIX

6.0 CONCLUSIONS, RECCOMENDATIONS AND STUDY LIMITATIONS.

6.1 Conclusion.

In conclusion we found that there is increased incidence of Emergence delirium in control group compared to fentanyl group (47.3% Vs14.6%) in children undergoing general anaesthesia under halothane and isoflurane, use of fentanyl significantly reduced the risk of incidence of emergence delirium by 81% with no statistically significant difference in the average time to full recovery (25.2 vs. 22.6; p=0.189) and occurrence of immediate complications in children (1-12 years) undergoing adeno-tonsillectomy at Kenyatta National Hospital.

6.2 Recommendations.

Due to the positive results of this study we recommend that;

1. Routine use of fentanyl be encouraged to prevent ED in children undergoing adeno-tonsilectomy.
2. Further studies be carried out on this topic to compare fentanyl with other drugs such as propofol or alpha 2 agonists e.g. clonidine in prevention of ED.

6.3 Study limitations and minimization.

During the surgery, different anaesthesia providers used different analgesics and might have affected the study findings but this was minimized by randomization and taken into account during data analysis.

The timing of ten minutes to the end of surgery might have varied from one surgeon to another due to the speed of operation, this was taken into account during data analysis and randomization could still be able to minimize this limitation.

We never looked at the interaction of ED with preoperative anxiety since the children who were on any sedatives where excluded in the study.

REFERENCE

1. Bajwa SA, Costi D, Cyna AM. A comparison of emergence delirium scales following general anesthesia in children. Paediatric Anaesthesia. 2010 Aug; 20(8):704-11.
2. Fenmei Shi, Ying Xiao, Wei Xiong, et al Effects of Fentanyl on Emergence Agitation in Children under Sevoflurane Anesthesia: Meta-Analysis of Randomized Controlled Trials. PLoS One. 2015; 10(8):PMC4537096.
3. Pieters BJ, Penn E, Nicklaus P, et al. Emergence delirium and postoperative pain in children undergoing adeno-tonsillectomy: a comparison of propofol vs. sevoflurane anesthesia. Paediatric Anaesthesia. 2010 Oct; 20(10):944-50.
4. Zhang C, Li J, Zhao D, et al. Prophylactic midazolam and clonidine for emergence from agitation in children after emergence from Sevoflurane anesthesia: a meta-analysis. Clin Ther. 2013 Oct; 35(10):1622-31.
5. Costi D, Ellwood J, Wallace A, et al. Transition to Propofol after sevoflurane anesthesia to prevent emergence agitation: a randomized controlled trial. Paediatric Anaesthesia. 2015 Jan; 25(5):517-23.
6. Cravero JP, Thyr B, Beach M, et al. The effects of intravenous fentanyl on agitation in pediatric patients. Anesthesiology. 2001; 95:A1222.

7. Aono J, Ueda W, Mamiya K, et al. Greater incidence of delirium during recovery from sevoflurane anaesthesia in preschool boys. Anesthesiology.1997; 87:1298-1300.

8. Cravero J, Surgenor S, Whalen K. Emergence agitation in paediatric patients after sevoflurane anaesthesia and no surgery: a comparison with halothane. Paediatric Anaesthesia. 2000; 10:419-424.

9. Gooden R, Tennant I, Brian J, et al, The incidence of emergence delirium and risk factors following sevoflurane use in pediatric patients for day case surgery, Kingston, Jamaica. J.bjane. 2013; 09.012.

10. Welborn LG, Hannallah RS, Norden JM, et al. Comparison of emergence and recovery characteristics of sevoflurane, desflurane, and halothane in pediatric ambulatory patients. Anesth Analg 1996; 83:917-920.

11. Sury MR, Black A, Hemington L, et al. A comparison of the recovery characteristics of sevoflurane and halothane in children. Anaesthesia. 1996; 51:543-546.

12. Lerman J, Davis PJ, Welborn LG, et al. Induction, recovery, and safety characteristics of sevoflurane in children undergoing ambulatory surgery: A comparison with halothane. Anaesthesiology. 1996; 84:1332-1340.

13. Bong, C.L. & Ng, A. Evaluation of emergence delirium in Asian children using the Pediatric Anesthesia Emergence Delirium scale. Pediatric Anesthesia. 2009; 19: 593-600.

14. Smessaert A, Schehr CA, Artusio JFJ. Observations in the immediate post-anaesthesia period. II. Mode of recovery. Br J Anaesthesia. 1960; 32:181-185.

15. Eckenhoff JE, Kneale DH, Dripps RD. The incidence and etiology of post-anesthetic excitement. Anesthesiology 1961; 22:667-673.

16. Bastron RD, Moyers J. Emergence delirium. JAMA 1967; 200:179.

17. Kain ZN, Mayes LC, O'Connor TZ, Cicchetti DV. Preoperative anxiety in children: predictors and outcomes. Arch Pediatr Adolesc Med. 1996; 150:1238-1245.

18. Voepel-Lewis T, Malviya S, Prochaska G, et al. Sedation failures in children undergoing MRI and CT: is temperament a factor? Paediatric Anaesthesia. 2000; 10:319-323.

19. Stamper MJ, Hawks SJ, Taicher BM, et al. Identifying pediatric emergence delirium by using the PAED Scale: a quality improvement project. AORN J. 2014 Apr; 99(4):480-94.

20. Ozcan A, Kaya AG, Ozcan N, et al. Effects of ketamine and midazolam on emergence agitation after sevoflurane anaesthesia in children receiving caudal block: a randomized trial. Braz J Anesthesiol. 2014 Nov-Dec; 64(6):377-81.

21. Cho EJ, Yoon SZ, Cho JE, et al. Comparison of the effects of 0.03 and 0.05 mg/kg midazolam with placebo on prevention of emergence agitation in children having strabismus surgery. Anesthesiology. 2014 Jun; 120(6):1354-61.

22. Pattaravit N, Oofuwong M, Klaina S, et al. Effect of intravenous fentanyl given prior to the end of surgery on emergence agitation in pediatric patients. J Med Assoc Thai. 2013 Dec; 96(12):1556-62.

23. Chen J, Li W, Hu X, et al. Emergence agitation after cataract surgery in children: a comparison of midazolam, Propofol and ketamine. Paediatric Anaesthesia. 2010 Sep; 20(9):873-9.

24. Breschan C, Platzer M, Jost R, et al Midazolam does not reduce emergencedelirium after sevoflurane anaesthesia in children. Paediatr Anaesthesia. 2007 Apr; 17(4):347-52.

25. Cravero JP, Thyr B, Beach M, et al. The effects of intravenous fentanyl on agitation in pediatric patients. Anesthesiology. 2001; 95:A1222.

26. Uezono S, Goto T, Terui K, et al. Emergence agitation after sevoflurane versus Propofol in paediatric patients. Anaesth Analg. 2000; 91:563-566.

27. Cohen IT, Hannallah RS, Hummer K. Emergence agitation following sevoflurane vs. Propofol anesthesia in young children. Anesth Analg 2000; 90:S354.

28. Bortone L, Bertolizio G, Engelhardt T, et al. The effect of Fentanyl and clonidine on early postoperative negative behavior in children: a double-blind placebo controlled trial. Paediatric Anaesthesia. 2014 Jun; 24(6):614-9.

29. Dahmani.S. I. Stany1, C. Brasher1, et al , pharmacological prevention of sevoflurane and desflurane related emergence agitation in children a meta-analysis of published studies. British Journal of Anaesthesia 2010; 104 (2): 216–23.

30. Singh, R., M. Kharbanda, N. Sood et al. Comparative evaluation of incidence of emergence agitation and post-operative recovery profile in paediatric patients after isoflurane, sevoflurane and desflurane anaesthesia. Indian J Anaesth. 2012 Apr; 56(2): 156-161.

31. Donner, A. Approaches to sample size estimation in the design of clinical trials-a review. Stat Med, 1984; 3(3): 199-214.

32. Hapfelmeier G, Schneck H, Kochs E. Sevoflurane potentiates and blocks GABA-induced currents through recombinant $alpha_1$ $beta_2$ $gamma_2$ $GABA_A$ receptors: Implications for an enhanced GABAergic transmission. Eur J Anaesthesiol. 2001; 18:377-383.

33. Kim MS, Moon BE, Kim H, Lee JR. Comparison of propofol and fentanyl administered at the end of anaesthesia for prevention of emergence agitation after sevoflurane anaesthesia in children. Br J Anaesth. 2013 Feb; 110(2):274-80.

34. Hany M. Yassin, Maged L.Boules comparative study between the effect of propofol an fentanyl on the incidence and severity of emergence agitation after sevoflurane anesthesia in paediatrics. Ain-Shams Journal of anesthesiology 2015, 08:529-534.

Appendix I: **Date** (DDMMYYYY) _____

RESEARCH QUESTIONAIRRE

TOPIC;EFFECT OF FENTANYL GIVEN APPROXIMATELY TEN MINUTES TO THE END OF SURGERY ON EMERGENCE DELIRIUM IN CHILDREN UNDERGOING ADENO-TONSILECTOMYAT KENYATTA NATIONAL HOSPITAL, A RANDOMIZED PLACEBO CONTROLLED CLINICAL TRIAL,

Serial No……

Part 1-Demographic Data, (indicate)

1. Date of Birth [DDMMYYYY]……. Weight……Kilograms
2. Gender; (Tick one) Female □

   Male □
3. Co-morbidities if any (list other medical conditions the child is suffering from)

   ……

   ……
4. Current medications and dosages if any (list the medications the child has been on dosage and

   duration)……

……

Part 2- Type of surgery. (Tick appropriately)

5. Adenoidectomy □

6. Tonsillectomy □

7. Adeno-tonsillectomy □

Part 3- Type of induction of anaesthesia,(Tick one)

8. inhalational □

9. Intravenous □

10. Drugs used (indicate the drugs used)

……

……

Part 4 Analgesics

11. Type of Analgesia given, (Tick and indicate the dosages given)

    i. Fentanyl □ Dose……

    ii. Tramadol □ Dose…….

    iii. Paracetamol □Dose …….

iv. Diclofenac □Dose……..

v. Others,(specify)……

Part 5 Level of ED observed in recovery room as per the Watcha scale, (Tick the child's behaviour as observed in the recovery room in the first 20min)

12. Watcha scale. Score is observed values defines ED at score 3 and 4

Behaviour	Score	
Asleep	0	□
Calm	1	□
Crying, but can be consoled	2	□
Crying, but cannot be consoled	3	□
Agitated and thrashing around	4	□

Part 6 Duration of emergence, (indicate)

13. Time treatment is given----------

14. Time fully awake ----------

15. Duration in minutes----------

Part 7 Complications.

16. Indicate the complications observed post reversal, management and outcome.

Part 8.Other medications used during surgery.

17. Indicate other medications used during surgery,

Appendix II:

CONSENT FOR PARTICIPATION

Consent explanation.

My name is Dr. Kirwa; I am doing my postgraduate study in anaesthesia at the University of Nairobi. As part of my course work I am required to perform clinical research and my study is on **EFFECT OF FENTANYL GIVEN APPROXIMATELY TEN MINUTES TO THE END OF SURGERY ON EMERGENCE DELIRIUM IN CHILDREN UNDERGOING ADENO-TONSILECTOMY IN KENYATTA NATIONAL HOSPITAL, A RANDOMIZED PLACEBO CONTROLLED CLINICAL TRIAL,**

The objectives of this study are to determine the incidence of emergence delirium and effect of fentanyl in its prevention,

The benefits of this study are to will also help doctors know the burden of emergence delirium and improve the care and safety of children undergoing surgery under general anaesthesia by using fentanyl to prevent emergence delirium.

To participate in this study is voluntary and no rewards or compensations will be awarded.

As the participant's parent/ guardian you will be expected to get explanation about the study and give informed written consent,

There are no risks involved in this study since the medications we are using are not new and are safe and available for use daily on patients undergoing surgery.

The adverse effects associated with Fentanyl are extremely rare, self resolving and easily managed by use of antagonist naloxone, they include confusion, hallucination, seizures, headache, nausea, vomiting, diarrhoea, dry mouth, dizziness, QT prolongation, ST elevation, bradycardia, pruritus, rash, muscle pains, hypoventilation, apnoea, dyspnoea, urinary retention and oliguria.

As the participant's parent/ guardian, you have a right with full information on the study out comes and free to withdraw the participant at any time before treatment is given.

With your consent, the child will be randomly selected and given treatment towards the end of the operation and the Childs response to surgery will be observed at the recovery room.

The expected follow up time for the participant is the first 20 minutes after emergence from general anaesthesia.

Thereafter, I will do statistical analysis on this information and publish it in a book that will be in the custody of the University of Nairobi. All information gathered will be treated with utmost confidentiality.

You need to know that the Childs participation in this study is voluntary

May I now take this opportunity to request you to ask any questions relating to this study?

If you accept to be part of this study please append your signature on the space provided

Any questions about the study may be forwarded to the KNH-ERC, Kenyatta National Hospital, P.O. BOX 20723, Nairobi, and Tel: 2726300-9.

Participants Consent/ Declaration Form Serial No……

Name …….

I am the parent/Guardian of the child undergoing tonsillectomy and or adenoidectomy, Dr. Kirwa has explained to me about the study and I understand that my/child's rights will be respected and confidentiality maintained.

I also understand that participation is voluntary.

I therefore consent that child be recruited into the study.

Parents'/Guardians Signature ……Or Thumb print ……Date

Witness…….....Signature……Date……

Investigators declaration

I declare that I have explained to the participant's parent/guardian about this study and have understood the purpose, objectives, benefits, risks and their rights of the study and have agreed to consent to participate in the study.

Name……Date…….Sign

For further information, issues or clarification you may contact:

Dr. Kirwa Elisha. Telephone number – 0722944535or

KNH/UON – Ethics & Research Committee. Telephone number – 2726300-9

Kiambatanisho II:

IDHINI YA KUSHIRIKI

Maelezo Kuhusu Idhini

Jina langu ni Dk.Kirwa, ninafanya utafiti wa shahada ya juu katika anaesthesia kwenye Chuo Kikuu chaNairobi.

Kama sehemu ya masomo yangu, nahitajika kufanya utafiti wa hospitalini juu ya **MADHARA YA FENTANYL INAYOTOLEWA TAKRIBAN DAKIKA KUMI KABLA YA KIKOMO YA UPASUAJI KWA MASUMBUKO (DELIRIUM) YA KUAMKA KATIKA WATOTO WANAOFANYIWA UPASUAJI WA ADENO-TONSILECTOMY KATIKA HOSPITALI YA RUFAA YA KITAIFA YA KENYATTA.**

Malengo ya utafiti huu ni kudhibitisha kiwango cha masumbuko (emergence delirium), na vile dawa ya fentanyl inaweza kusaidia kuthibitisha.

Utafiti huu itasaidia madaktari kuboresha huduma inayotolewa kwa wagonjwa kwa kuwapa matibabu ya kuzuia masumbuko huu,pia itaimarisha usalama ya watoto wanaofanyiwa upasuaji.

Kwa idhini yako, mtoto atachaguliwa kwa njia ya nasibu kushiriki na atapewa matibabu mwishoni mwa operesheni na mtoto atachunguzwa jinsi atakavyokabiliana na upasuaji katika chumba afueni.

Kusajiliwa kwa utafiti huu ni kwa hiari yako na hakuna mapato yeyote yatapeanwa.

Kama mzazi au mlezi wa mtoto utahitajika kuelewa juu ya utafiti na kutia sahihi kibalio ili mtoto asajiliwe kwa utafiti.

Hakuna hatari ya kushiriki katika utafiti huu tangu dawa tunatumia si mpya, salama na tunatumia mara kwa mara kwa wagonjwa wanaofanyiwa upasuaji.

Madhara yanayohusishwa na Fentanyl ni nadra sana, zinapona zenyewe na kwa urahisi kwa kutumia dawa ya naloxone, madhara hayo ni kuchanganyikiwa, kifafa, maumivu ya kichwa, kichefuchefu, kutapika, kuhara, kukauka kinywa, kizunguzungu, moyo kupika pole pole, kuwashwa kwa ngozi, maumivu ya misuli, kupumua pole pole, mkojo kutoka pole pole.

Baadaye, nitafanya uchambuzi wa takwimu na taarifa hii na kuchapisha habari katika kitabu ambacho kitakuwa chini ya mamlaka ya Chuo Kikuu cha Nairobi.Taarifa zote zilizokusanywa zitawekwa kwa usiri mkubwa.

Mtoto atafuatiliwa kwa muda wa takriban dakika ishirini baada ya kuamka kutoka upauaji.

Unahitaji kujua kwamba kushiriki kwa mtoto katika utafiti huu ni kwa hiari.

Naomba sasa nichukue fursa huu kukuomba uulize maswali yoyote yanayohusiana na utafiti huu.

Ikiwa umekubali kushiriki katika utafiti huu, tafadhali tia sahihi yako kwenye nafasi iliyotolewa.

Maswali yoyote kuhusu utafiti huu yanaweza kuelekezwa kwa KNH - ERC , Hospitali ya Kitaifa ya Rufaa ya Kenyatta, Sanduku la Posta 20723 , Nairobi, na Tel: 2726300-9 .

FOMU YA IDHINI

Nambari ya Usajili……

Jina …….

Mimi ni mzazi/mlezi wa mtoto anayefanyiwa upasuaji wa adeno-tonsilectomyidectomy, Dk.Kirwa amenielezea kuhusu utafiti yake na naelewa kwamba haki ya mtoto itaheshimiwa na usiri utaimirishwa.

Naelewa kwamba kushiriki kwa utafiti huu ni kwa hiari.

Kwa hivyo ninatoa idhini kwamba mtoto achaguliwe kushiriki katika utafiti huu.

Sahihi ya mzazi/mlezi..... Au Alama ya kidole.....Tarehe……..

Shahidi…….....Sahihi……Tarehe……
…

Kwa taarifa/habari zaidi, masuala au ufafanuzi zaidi unaweza kuwasiliana na:

Dk. Kirwa Elisha. Nambari ya simu - 0722944535 au

KNH / UON - Kitengo cha Maadili na Kamati ya Utafiti. Nambariyasimu - 2726300-9

Appendix III

ASSENT FORM FOR CHILDREN AGED 7-12YRS.

Study Title: EFFECT OF FENTANYL GIVEN APPROXIMATELY TEN MINUTES TO THE END OF SURGERY ON EMERGENCE DELIRIUM IN CHILDREN UNDERGOING ADENO-TONSILECTOMY IN KENYATTA NATIONAL HOSPITAL, A RANDOMIZED PLACEBO CONTROLLED CLINICAL TRIAL,

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

We are doing a research study about a medical condition that occurs after waking up from anaesthesia called emergence delirium. 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 medication during surgery and be observed for 20 minutes after waking up. The medication you will be given are harmless

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 description 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……..

Kiambatanisho III

IDHINI YA WATOTO WENYE UMRI YA MIAKA 7-12.

Jina langu ni Dk Kirwa ninafanya utafiti juu ya mada huu.

Mada ya Utafiti; MADHARA YA FENTANYL INAYOTOLEWA TAKRIBAN DAKIKA KUMI KABLA YA KIKOMO YA UPASUAJI KWA MASUMBUKO (DELIRIUM) YA KUAMKA KATIKA WATOTO WANAOFANYIWA UPASUAJI WA ADENO-TONSILECTOMY KATIKA HOSPITALI YA RUFAA YA KITAIFA YA KENYATTA.

Tunafanya utafiti kuhusu hali ya matibabu ambayo utokea baada ya kuamka kutoka anesthesia inaoitwa emergence delirium. Utafiti huu ni njia ya kujifunza zaidi na kuielewa hali hii.

Kama utaamua kwamba unataka kushiriki katika utafiti huu, wewe utapewa dawa wakati wa upasuaji na kutunzwa kwa muda wa dakika 20 baada ya kuamka. dawa hii haina madhara yeyote.

Nitakueleza taratibu, faida, hatari na 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, _____, nitashiriki katika utafiti huu.

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

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

KENYATTA NATIONAL HOSPITAL APPROVED 23 FEB 2016 KNH/UoN-ERC P.O. Box 20723-00202 NRB.

Ref: KNH-ERC/A/71

23rd February, 2016

Dr. Kirwa Kiprono Elisha
H58/69263/2013
Dept.of Anaesthesia
School of Medicine
College of Health Sciences
University of Nairobi

Dear Dr. Kirwa

Revised research proposal: Effects of Fentanyl given approximately ten minutes to the end of surgery on Emergence Delirium in children undergoing adeno-tonsilectomy at KNH, A randomized placebo controlled clinical trial (P628/10/2015)

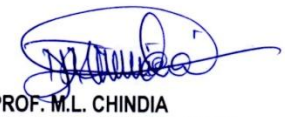
This is to inform you that the KNH- UoN Ethics & Research Committee (KNH-UoN ERC) has reviewed and **approved** your above proposal. The approval period is from 23rd February 2016 – 22nd February 2017.

This approval is subject to compliance with the following requirements:

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

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

Yours sincerely,



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

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director, CS, KNH
The Chair, KNH-UoN ERC
The Assistant Director, Health Information, KNH
The Dean, School of Medicine,UoN
The Chair, Dept.of Anaesthesia,UoN
Supervisors: Dr. Mark Gacii, Dr. Alfred Osoti, Dr. Emma Mutio

Turnitin Originality Report

FENTANYL ADMINISTERED FEW MINUTES BEFORE THE END OF SURGERY PREVENTS EMERGENCE DELIRIUM AMONG CHILDREN UNDERGOING ADENO-TONSILLECTOMY: A RANDOMIZED DOUBLE BLIND PLACEBO CONTROLLED CLINICAL TRIAL
by Elisha Kirwa

From Anaesthesia (Masters in Internal Medicine)

- Processed on 11-Sep-2017 14:38 EAT
- ID: 845431058
- Word Count: 10571

Similarity Index
11%
Similarity by Source

Internet Sources:
6%
Publications:
7%
Student Papers:
5%

sources:

1 1% match (Internet from 03-Dec-2016)
https://digital.library.adelaide.edu.au/dspace/handle/2440/60973

2 1% match (student papers from 04-Jun-2013)
Submitted to Strathmore University on 2013-06-04

3 1% match (student papers from 29-Apr-2013)
Submitted to UI, Springfield on 2013-04-29

4 1% match (Internet from 07-May-2010)
http://bja.oxfordjournals.org/cgi/content/full/104/2/216

5 < 1% match (publications)
Makkar, J. K., N. Bhatia, I. Bala, D. Dwivedi, and P. M. Singh. "A comparison of single dose dexmedetomidine with propofol for the prevention of emergence delirium after desflurane anaesthe in children", Anaesthesia, 2015.

6 < 1% match (student papers from 04-Jun-2015)
Submitted to Monash University on 2015-06-04

7 < 1% match (student papers from 03-Mar-2012)