EFFECTIVE DOSE OF RECTAL ACETAMINOPHEN FOR IMMEDIATE POSTOPERATIVE PAIN RELIEF IN PAEDIATRIC DAY-CASE INGUINAL SURGERY

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MAY 2007.
DECLARATION

I hereby declare that this work is original. It has not been presented for any publication or examination or fellowship award.

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CERTIFICATION

We certify that this study was carried out by Dr. I.A SOTANNDE of the Department of Anaesthesia, University College Hospital, Ibadan, Nigeria.

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DEDICATION

This work is dedicated to ALMIGHTY GOD for making this residency programme a reality.

My wife, Adeola and my children, Fawaz and Faizat, for their love and patience throughout the residency programme.
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SUMMARY

Postoperative pain is a major problem in paediatric day-case surgical procedures worldwide. The side effects of opioid analgesics and non-steroidal anti-inflammatory drugs in paediatric surgical patients have limited their use. The recent withdrawal of dipyrone from Nigeria drug formulary has made the search for an alternative drug that can be used perioperatively in paediatric day-case surgical procedures of paramount importance.

The aim of this study was to determine the effective dose of rectal acetaminophen for immediate postoperative pain relief in paediatric day-case inguinal surgery. The study was a randomized double blind trial of one hundred and five paediatric patients between the ages of one and seven years who had day-case inguinal surgical procedures. Patients were randomized to receive a single dose of either approximately 20, 40 or 60mg/kg of rectal acetaminophen after induction of general anaesthesia. General anaesthesia was induced and maintained with inhaled halothane, nitrous oxide and oxygen. Opioids and local anaesthetics were not used.

Postoperative pain was evaluated every ten minutes in recovery room by the use of Children’s Hospital of Eastern Ontario Behavioural Pain Scale (CHEOPS). The need for rescue analgesic, I.V Pentazocine 0.1mg/kg was decided by the researcher who was unaware of the dose of rectal acetaminophen administered. The parents were interviewed by phone after 24hrs regarding the quality of pain relief, nausea and vomiting. Postoperative analgesic at home was oral Paracetamol (10 -15 mg/kg) every 6 hours.
In the recovery room, pain scores were significantly lower in the 40- and 60mg/kg rectal acetaminophen groups compared with 20mg/kg group. Rectal acetaminophen had a clear dose-dependent analgesic effect in children, post day-case inguinal surgical procedures, with significance reached with 40 and 60mg/kg dose.

The need for rescue analgesic at home during the first 24hrs after surgery was also significantly less in 40 and 60mg/kg groups compared with 20mg/kg group. None of the one hundred and five patients studied vomited in recovery room. However, two (5.7%) patients in 20mg/kg group vomited at home while none in 40 and 60mg/kg group had emetic complication.

In conclusion, a single dose of 40 or 60mg/kg of rectal acetaminophen has a clear dose-dependent analgesic effect in children undergoing day-case inguinal surgical procedures.
CHAPTER ONE

INTRODUCTION

Recent advances in anaesthetic and surgical techniques along with escalating health care costs, have resulted in ever increasing number of surgical procedures being performed on a day-case basis world wide.

Paediatric day-case surgery was first described by James Nicoll\textsuperscript{1} in 1909 who performed 8,988 outpatient surgical procedures at Glasgow Royal Hospital for sick children over a period of ten years. In 1966, Ralph Waters opened the first outpatient anaesthesia clinic in Sioux City, Iowa.\textsuperscript{2} Since then paediatric ambulatory surgery has continued to grow and now about 50\%-60\% of paediatric surgical procedures are performed as outpatients in most of the western countries like USA and U.K.

The major priorities for successful paediatric day-case surgery are proper patient selection, prevention of common postoperative complications and the management of the acute pain that accompanies surgery.

Acute postoperative pain is a complex physiologic reaction to tissue injury, visceral distention, or disease. It is a manifestation of autonomic, psychological and behavioral responses that result in an unpleasant, unwanted sensory and emotional experience.\textsuperscript{3}

After an injury, there is liberation of algogenic substances such as potassium and hydrogen ions, lactic acid, serotonin, bradykinin, histamine, and the prostaglandins. These sensitize and excite nociceptors and act as mediators of inflammation.\textsuperscript{3}

The precursor of prostaglandins is arachidonic acid which is formed from cell membrane phospholipid via the action of the enzyme Phospholipase A\textsubscript{2}. The formed
arachidonic acid is then acted upon by cyclooxygenase enzyme to produce prostaglandins, thromboxane, prostacyclins and free radicals.

Aspirin, acetaminophen and the non steroidal anti-inflammatory drugs (NSAID) are the principal non opioid analgesics used to treat minor to moderate acute postoperative pain. They have a common mechanism of action, they cause inhibition of prostaglandin – mediated amplification of chemical and mechanical irritants on the sensory pathways. Whereas sensitization or intensification of painful stimuli is mediated by the prostaglandins, which also lower the threshold for further activation of the nociceptors, the prostaglandins alone directly evoke little painful response.

NSAID modulate prostaglandin synthesis through inhibition of the action of the enzyme cyclooxygenase, which is one of the first steps in the conversion of arachidonic acid into prostaglandins.

Prostaglandins are produced in the peripheral tissues and central nervous system. Although mediation of the peripheral inflammatory response is an important component of pain modulation by non steroidal anti-inflammatory drugs, inhibition of central mechanism of hyperalgesia is the other significant component.

Acetaminophen is a cyclooxygenase inhibitor with potent antipyretic and analgesic properties. It is equipotent to aspirin in inhibiting prostaglandin synthesis in the central nervous system but much less potent in inhibiting prostaglandin synthesis at peripheral sites.

Postoperative pain is a major problem in paediatric day-case surgery. The experience of unrelieved postoperative pain is the most important single cause of long lasting postoperative temper tantrum, and untoward behavioural changes in children. Unrelieved postoperative pain not only decreases the patient’s functional capacity but
is also associated with longer postoperative hospital stay and higher incidence of unanticipated readmission. Postoperative pain also predisposes to postoperative nausea and vomiting which is another cause of unanticipated readmission. The potential cost saving of outpatient surgery may be negated by unanticipated hospital admission for poorly treated pain. Therefore, overall anaesthetic plan must include provision for adequate pain relief.

Opioid analgesics are the gold standard in the management of severe post operative pain. However by its very definition, day-case procedures should not require such major analgesics.

Non-steroidal anti-inflammatory drugs such as Ibuprofen, Ketorolac and diclofenac are effective analgesics for mild to moderate pain. Lack of respiratory depression, sedation and nausea and vomiting are some of their advantages. However their use in paediatric patients has been limited by side effects such as gastric irritation, diarrhoea, renal impairment, decreased platelet function and impaired coagulation etc. Also the use of these agents is not recommended in children below one year of age due to possibility of immature renal function and hepatic metabolism.

**Acetaminophen (Paracetamol)** is the most commonly used analgesic and antipyretic worldwide. This is because it is cheap, safe and efficacious in neonates as well as in older children. It was first synthesized by Harmon Northrop Morse in 1873, via the reduction of p-nitrophenol with tin in glacial acetic acid to acetanilide. In 1899, paracetamol was found to be a metabolite of acetanilide. This discovery was largely ignored at this time. In 1948, Brodie and Axelrod linked the use of acetanilide with methaemoglobinaemia and found that the analgesic effect of acetanilide was due to its active metabolite paracetamol.
Acetaminophen is manufactured in large quantities from phenol, which is nitrated to give a mixture of the ortho- and para-nitrotoluene. The O-isomer is removed by steam distillation and p-nitro group reduced to a p-amino group. This is then acetylated to give paracetamol. Its chemical formula is $C_8H_9NO_2$, molecular weight of 151.17, melting point is 169°C, density is 1.263g/cm$^3$, solubility in water is 1.4/100ml at 20°C and is also soluble in ethanol.

Acetaminophen is a simple analgesic and antipyretic agent. It is a weak prostaglandin inhibitor in peripheral tissues and possesses no significant anti-inflammatory effect. Optimal use of acetaminophen is effective in the management of mild to moderate postoperative pain and it can be administered orally, rectally or intravenously.\textsuperscript{11} It is more commonly ingested orally but the intravenous formulation is now available in many European countries and in Nigeria. The rectal preparation is very useful in the day case setting compared to the oral route because the patient remains fasted and the unpleasant taste of the oral elixir is avoided. In the febrile and vomiting child the rectal route is also practical. The rectal route is however unpleasant to many patients as it is considered invasive of privacy. Furthermore the conscious patient may expel the suppository.

The rectal absorption is slower and more variable than the oral.\textsuperscript{12} The relative bioavailability of paracetamol suppositories is 80% that of the oral formulation.\textsuperscript{13} Most of the time physicians use doses of acetaminophen that are much too low, especially with rectal administration in children with resultant poor analgesia.\textsuperscript{11} The pharmacokinetics of rectally administered acetaminophen are unique and deserve consideration for clinical application, however identical doses for oral and rectal acetaminophen administration typically 10-15mg/kg every four to six hours are
recommended.\textsuperscript{14} It is well known that absorption from the rectal route is slow and often erratic. Several factors may account for the reduced bioavailability of rectal acetaminophen and these include the placement of the suppository, the degree of lipophilicity of the vehicle and the pH within the rectum. The erratic absorption pattern frequently results in serum acetaminophen concentrations that fail to reach the target for antipyresis or analgesia of 10-20µg/ml.\textsuperscript{15}

In order to overcome the problem of slow absorption, several investigators have studied the effects of higher doses of rectal acetaminophen in children,\textsuperscript{16-20} and about 40mg/Kg body weight dose was found to be equivalent to 10-15mg/kg oral dose and provided adequate analgesia for minor surgery. The slower rate of absorption may not provide adequate analgesia during and immediately after short procedures but it could provide a prolonged analgesic effect during recovery from anaesthesia.

If these higher doses were given every six hours there were fears of possible toxicity from drug accumulation.\textsuperscript{21} Hahn and colleagues reported that the lower dose of rectal acetaminophen every 6 hours, for 5 days did not cause toxic serum concentrations and no evidence of drug accumulation.\textsuperscript{22}

Studies using single, varying doses of rectal acetaminophen in paediatric day-case surgical procedures are few. The appropriate dose in the Nigerian setting is unknown. The use of rectal acetaminophen makes the practice of day-case surgical procedures more acceptable in paediatric setting. Unavailability of local studies on this subject coupled with the recent ban placed on dipyrrone stimulated the interest in this prospective study.

This study was set to determine the effective dose of rectal acetaminophen for immediate postoperative pain relief in paediatric day-case inguinal surgical
procedures. The outcome of this study may be used to improve the practice of paediatric day-case pain management in this institution and other health institutions in Nigeria and other developing countries.
AIM AND OBJECTIVES

**General objective**

This is to determine the effective dose of rectal acetaminophen for immediate postoperative pain relief in paediatric day-case inguinal surgical procedures.

**Specific objectives**

a. To determine the analgesic efficacy of different doses of rectal acetaminophen in the management of postoperative pain in paediatric day-case inguinal surgical procedures.

b. To examine potential adverse effects of the doses of rectal acetaminophen.

**SIGNIFICANCE OF THE STUDY**

1. To determine the effective analgesic dose of rectal acetaminophen in paediatric day-case inguinal surgery.

2. This study is particularly relevant in this environment with the withdrawal of dipyrone from the Nigerian drug formulary.
CHAPTER TWO

LITERATURE REVIEW

The numbers of paediatric surgical procedures that are performed as day-cases have greatly increased in recent times. In general, children make excellent candidates for day-case surgical procedures as they are usually healthy, free of systemic diseases and typically require straightforward, minor or intermediate surgical procedures. More than 60% of paediatric surgery in the United States of America are performed as day-cases. In the United Kingdom, the Royal College of Surgeons and the National Health Service Executive have estimated that 50% of all elective surgical procedures, especially in children can be performed on day-case basis.

The shift towards day-case surgery in paediatrics is as a result of advantages it has over in-patient care. These include minimal parental separation, less psychological upset, uninterrupted feeding schedule, less risk of nosocomial infection, convenience on the part of the parents, improved patient satisfaction and reduced cost of hospitalization. Behavioural problems, disrupted sleeping patterns, nocturnal enuresis are common in patients on admission and are avoided by day-case surgical care.

Consistent provision of high quality paediatrics day surgical care is challenging. The criteria for judging the quality of the day-care service are minimal postoperative morbidity, low re-admission rates and high parental and child satisfaction. Proper selection criteria, appropriate anaesthesia, adequate postoperative analgesia, adequate control of other postoperative symptoms and clear communication with parents are factors which ensure successful outcome.
Patient Selection for Ambulatory Surgery

The major concern is to determine which patients are appropriate for day-case surgery. The physical status of the patient according to American Society of Anesthesiologist's physical status classification, type of surgery, duration of surgery, special anaesthetic or postoperative consideration, and the attitudes of the parents are taken into consideration in selecting patients for ambulatory surgery.

In the past, paediatric day-case surgery was limited to brief surgical procedures in healthy children with American Society of Anesthesiologist's physical status 1 or II. Nowadays, children with controlled medical illnesses are also being accepted for day-case surgical procedures.\textsuperscript{27}

Exclusion criteria include inadequately controlled systemic disease such as upper respiratory tract infection, sickle cell disease, epilepsy, bronchial asthma and history of significant sleep apnoea. Major intra-thoracic, intra-abdominal or intracranial procedures and extremely painful procedures where postoperative pain is unlikely to be relieved by simple oral analgesics are also excluded.

Age is not a contraindication to day-case surgical procedures with few exceptions; neonates and ex-premature infants (<52 – 60 weeks post conceptual age) are not suitable candidates for outpatient surgery because of the risk of postoperative apnoea.\textsuperscript{28, 29}

Discharge criteria

In paediatric day-case surgery, rapid recovery, early post-operative ambulation, adequate analgesia and absence of postoperative complications are the major objectives.
Time tested objective recovery scores such as the Steward\textsuperscript{30} and Aldrete\textsuperscript{31} scores are used for assessing children before discharge. Marshall and Chung\textsuperscript{32} (Appendix I) used quantitative scoring system which take into consideration immediate postoperative complications to assess children before discharge. Later on Patel et al\textsuperscript{33} suggested fast-track eligibility criteria for children. The state of consciousness appropriate to the developmental level, normal respiratory pattern, stable haemodynamics, absence of nausea and vomiting, must be ensured before discharge. The parent or a responsible adult who will accompany the child home and stay with the child overnight must be ensured before discharge.\textsuperscript{34} Written instructions concerning analgesic use and a list of signs that might herald a complication should be read, explained and handed over to the person accompanying the child. It is mandatory that parents are able to communicate with and return to the hospital if needed.\textsuperscript{35}

**Factors Affecting Postoperative Pain**

Parkhouse et al\textsuperscript{36} stated that the site of operation was the single most important factor affecting the severity of postoperative pain. Yaeger\textsuperscript{37} found an association between upper abdominal surgery and severe postoperative pain.

Famewo\textsuperscript{38} in a prospective study of 200 patients in Ibadan found surgery of anorectal region to be most painful. Pain following surgeries in the lower abdomen, head and neck are less severe.

Other factors affecting postoperative pain according to Rawal\textsuperscript{39} include.

1. The physiologic and psychologic make up of the patient.
2. The perioperative anaesthetic management.
3. The patient’s preparation for surgery both pharmacological and psychological.

4. The site, nature and duration of procedure

5. The occurrence of postoperative complications.

6. The quality of post-operative care.

**Pathophysiological consequences of unrelieved Postoperative pain**

Perioperative pain is a potent trigger for the stress response and it activates the autonomic nervous system.\(^ {40}\) Moderate to severe postoperative pain, regardless of site can adversely affect nearly every organ function,\(^ {41,42} \) and attenuation of postoperative pain may decrease postoperative morbidity and mortality.

**Neuroendocrine system**

Unrelieved postoperative pain and surgical stress elicit a consistent and well-defined metabolic response, involving release of neuroendocrine hormones and cytokines that leads to a myriad of detrimental effects.\(^ {43} \) In addition to the rise in catabolically active hormones such as catecholamines, cortisol, angiotensin II, and antidiuretic hormones, unrelieved postoperative pain causes an increase in the levels of adrenocorticotropic hormones, growth hormone and glucagon and also a lower level of anabolic hormones, such as testosterone and insulin.\(^ {44} \) The end results is that the patient develops a negative postoperative nitrogen balance.

Local release of cytokine such as interleukin – 2, interleukin – 6, and tumor necrosis factor may contribute to abnormal physiologic response such as alterations in heart rate, temperature, blood pressure and ventilation.\(^ {45} \)
Catecholamines also sensitize peripheral nociceptive endings, which serve to propagate more intense pain and may contribute to vicious pain-catecholamine release-pain cycle.\(^{46}\) The magnitude of these neuroendocrine and cytokine responses is related to the severity of tissue injury and correlates with outcome after injury.\(^{47}\)

**Cardiovascular system**

Effects of unrelieved postoperative pain on the cardiovascular system are initiated by the release of catecholamines from sympathetic nerve endings and the adrenal medulla, of aldosterone and cortisol from the adrenal cortex, and of antidiuretic hormone from the hypothalamus, and by activation of the rennin-angiotensin system. These hormones have direct effect on the myocardium and vasculature, and they augment salt and water retention, which places a greater burden on the cardiovascular system. The sympathoadrenal release of catecholamine and the effects of angiotensin II include tachycardia, hypertension, enhanced myocardial irritability, increased systemic vascular resistance, increased cardiac output, increased myocardial oxygen demand and myocardial ischaemia.\(^{48}\) In neonates such increases in heart rate has been employed in pain assessment.\(^{49}\)

**Respiratory system**

Respiratory effects of unrelieved postoperative pain include decreased total lung compliance, hypoventilation, inability to cough adequately, increase in total body oxygen consumption, and development of postoperative pulmonary complications.\(^{50}\) These respiratory effects of pain lead to significant reduction in functional residual capacity ranging from 25% to 50% of preoperative values.\(^{51}\) These sequelae are
especially significant in patients with preexisting pulmonary disease, upper abdominal and thoracic incisions, advanced age or obesity.

**Gastrointestinal System**

Studies have shown that unrelieved postoperative pain may cause reflex inhibition of gastrointestinal function. This promotes postoperative ileus, which contributes to postoperative nausea, vomiting, and discomfort and delays resumption of an enteral diet.

**Haematologic effects**

Hematologic effects of unrelieved postoperative pain include stress related alterations in blood viscosity, platelet function, fibrinolysis and coagulation pathways. These stress mediated effects include increase in platelet adhesiveness, reduced fibrinolysis and hypercoagulability.

**Genitourinary systems**

An increase in sympathetic activity in response to pain causes reflex inhibition of most visceral smooth muscles, including urinary bladder tone. This results in urinary retention with subsequent urinary tract infections.

**Immune system**

The pain-related stress response suppresses both cellular and humoral immune function and results in lymphopenia, leukocytosis, and depression of the reticuloendothelial system. Studies have shown that cortisol and epinephrine infusions
decrease neutrophil chemotaxis\textsuperscript{59} These effects can lower resistance to pathogens and may be key factors in the development of perioperative infectious complications.

**Central Nervous systems**

Pain causes anxiety, fear, sleep disturbance and fatigue.\textsuperscript{56} Kotiniemi and colleagues followed up 551 children after day-case surgical procedures and they concluded that the experience of unrelieved postoperative pain is the most important single cause of long lasting postoperative temper tantrum, and untoward behavioural changes in children.\textsuperscript{7}

**PAIN ASSESSMENT IN PAEDIATRIC PATIENT**

Pain assessment is important for effective management of pain. In the paediatric age group, pain assessment must be practical to perform and must track both the pain experience of the child and efficacy of analgesic intervention over time. The assessment tool has to be appropriate for the child’s stage of development. Pain assessment must not be carried out in isolation on just one occasion. Assessment must be linked to appropriate interventions, with the aim of ensuring the child experiences no pain or only mild pain.

Pain assessment is most accurate when the child can tell the staff about their pain. Many children may not ask for pain relief either because they do not want to disturb the doctor or because the remedy itself is unpleasant e.g. intramuscular injection.
One major problem of pain assessment in paediatric age group is the inability of the less than 3 year-old patients to self report their pain. Behavioural and physiological values are then relied on. These can be misinterpreted as they can be affected by symptoms and signs other than pain.

**Neonates**

Pain assessment in the neonate is usually carried out using behavioural and physiological values. These are interpreted together to judge if the baby is in distress and needs analgesic intervention. Reassessment is necessary to know the effectiveness of the analgesic intervention. If there is no improvement, then either the intervention is not adequate or the responses may not have been caused by pain in the first place.

A variety of assessment tools have been developed and validated for neonates. These include observation of facial expression, body position and movement, crying, arterial pressure, heart rate, skin colour, oxygen saturation, ventilatory frequency and sleeplessness.\(^49\) However these can be affected by non painful stimuli. A more clinically useful assessment is a dynamic one, where improvement in behavioural and physiological changes is sought in response to comforting, analgesia, or sedation.\(^60,61\)

**Infants and children up to 3 years.**

Assessment of pain in this age group is based on behavioural and physiological response to comfort and analgesic therapy like in neonates. The exhibited behaviour may be more vigorous with an “all or none” type of response. Sometimes the response is more precise (e.g. grabbing at the operation site).\(^62\) Objective pain scale (OPS),
Children aged 3 – 7 yrs

This group of patients can differentiate the presence or absence of pain and locate pain. They can also express the intensity of pain in the form of nil, mild, moderate and severe. The Faces scale or Oucher scale can be used in this age group. Visual or coloured analogue scales can be used by children from the age of 5 years.62

Older Children and Adolescents (7yrs)

Like adult, older children can usually use visual analogue or colour analogue scales and can self report pain intensity, location and quality.62

Children’s Hospital of Eastern Ontario Behavioural Pain Scale (CHEOPS)63 (Appendix III)

This pain assessment tool is commonly used to measure acute post-operative pain in children. It was developed for use in the age group one to seven years.64

The use of Children’s Hospital of Eastern Ontario behavioral Pain Scale circumvent the potential difficulties with communicating pain inherent in any paediatric self-reporting scales.64

This pain assessment tool assigns a numerical value to six behavior patterns. These are: cry facial expression, verbalization, body posture, leg movement and attempts to touch the wound.65
Each behavioural indicator is scored with 1 or 2 except cry, facial expression and verbalization.

Cry is scored using 1, 2 or 3. Facial expression and verbalization are scored using 0, 1 or 2 (Appendix III). Children should be observed for one minute in order to fully assess each indicator. The score ranges from the lowest of 4 to the highest of 13.

A score of ≤6 is taken to be a reflection of satisfactory pain control, and a score of ≥ 9 is taken as an indicator of severe pain and treatment failure.

**PAIN MANAGEMENT IN PAEDIATRIC DAY-CASE SURGERY**

Postoperative pain relief is the right of the patient and it is an obligation that must be performed by the anaesthetist. It is the responsibility of the doctor to provide analgesia and not the responsibility of the child to request for pain relief. Simple techniques such as ilioinguinal/iliohypogastric nerves block, or caudal block can be very useful for common day-case inguinal surgical procedures. Kushimo and colleagues found that children that had direct local infiltration of surgical wounds with bupivacaine had prolonged analgesia during the postoperative period (as evidenced by longer mean time to first postoperative analgesic requirement) compared to the control group.

**Caudal block** is a common regional technique used in paediatric day-case surgery to provide analgesia for perineal or inguinal surgery. It is easy to perform and the sympathetic effects on the circulatory system are rare. It is usually instituted after the patient has been put under general anaesthesia but before the commencement of the surgical procedure. Weakness of the lower limbs associated with caudal block may delay the discharge of the patient. This has limited its use in paediatric day-case
surgery although the weakness of the lower limb can be minimized by using a dilute local anaesthetic solution such as 0.125% bupivacaine.\textsuperscript{69}

Another useful adjunct in the management of pain in paediatric day-case surgical procedures is the non-pharmacologic method. The most important of these is minimal separation from parents, and methods such as, cuddling, stroking and distraction are also useful. Of late, breast feeding has been found efficacious for procedural pain.\textsuperscript{70}

The role of opioids in paediatric day case surgery is controversial because of their well known side effects especially nausea and vomiting and respiratory depression. At equi-analgesic doses, the emetic effects of all opioids appear to be similar.\textsuperscript{71} In children, postoperative nausea and vomiting increases even after a single dose of morphine.\textsuperscript{72} There is evidence that avoidance of opioids virtually abolishes the postoperative complaints of nausea and vomiting that delay oral intake of fluids after surgery.\textsuperscript{71}

**Non steroidal anti inflammatory drugs (NSAIDS)** such as Ibuprofen, Ketorolac and diclofenac are effective analgesics for mild to moderate postoperative pain. These drugs act at peripheral sites of injuries by inhibiting prostaglandin synthesis and blocking activation of primary afferent nerve fibres. Lack of respiratory depression, sedation, emetic side effects and their opioid sparing effect are some of their advantages. However their use in paediatric patients has been limited by side effects such as gastric irritation, diarrhoea, renal impairment, decreased platelet function and impaired coagulation etc. A study has shown an increased incidence of wound haematoma in children given diclofenac.\textsuperscript{73} Increased post tonsillectomy bleed is another source of concern when NSAID, particularly ketorolac\textsuperscript{74} is used for
adenotonsillectomy in children. Also the use of these agents is not recommended in children below one year of age due to possibility of immature renal function and hepatic metabolism.

**Multimodal approach** to postoperative pain management, utilizing combinations of NSAIDs/paracetamol, systemic opioids, and regional nerve blocks has been advocated in children.\(^{75}\) This is because total or optimal pain relief allowing normal function can not be achieved by a single drug or method without major strain on equipment and surveillance system or without significant side effects.\(^{40}\) The rational for this strategy is achievement of sufficient analgesia due to additive or synergistic effects between different analgesics, with concomitant reduction of side effects, due to resulting lower doses of analgesics and differences in side-effect profiles. So far only few analgesic literatures on postoperative pain have considered multimodal pain therapy, most of which are on adult patients whereas there are numerous studies on the conventional unimodal treatment.

**Acetaminophen (Paracetamol)** is the most commonly used analgesic and antipyretic worldwide. This is because it is cheap, safe and efficacious in neonates as well as in the older children.\(^9\) It was first synthesized by Harmon Northrop Morse in 1873, via the reduction of p-nitro phenol with tin in glacial acetic acid to acetanilide. In 1899, paracetamol was found to be a metabolite of acetanilide. This discovery was largely ignored at this time. In 1948, Brodie and Axelrod\(^{10}\) linked the use of acetanilide with methaemoglobinaemia and found that the analgesic effect of acetanilide was due to its active metabolite paracetamol.

Acetaminophen is manufactured in large quantities from phenol, which is nitrated to give a mixture of the ortho-and para-nitrotoluene. The O-isomer is removed
by steam distillation and p-nitro group reduced to a p-amino group. This is then acetylated to give paracetamol. Its chemical formula is C₈H₉NO₂, molecular weight of 151.17, melting point is 169°C, density is 1.263g/cm³, solubility in water is 1.4/100ml at 20°C and is also soluble in ethanol.

The drug became more popular in paediatric age group after the reported association between Reye’s syndrome and aspirin in 1980s. In 1990, Styrt et al found that the analgesic and antipyretic effects of paracetamol are equivalent to that of aspirin although paracetamol differs in that it lacks anti-inflammatory properties. The drug is an effective antipyretic at plasma concentrations of 0.066 – 0.130 mmol/L (10-20µg/ml) and it is assumed that analgesia occurs in a similar range.

Paracetamol is a weak acid with a high Pka, and in the alkaline medium of the duodenum, it is non-ionized and rapidly absorbed. It has a high lipid solubility and low protein binding. The hepatic extraction ratio is less than 0.3.

Paracetamol has long been assumed to have similar mechanism of action to aspirin because of the similarity in their structures. It acts by reducing production of prostaglandins which are involved in the pain and fever processes by inhibiting the cyclooxygenase enzyme. However paracetamol has no appreciable anti-inflammatory action, no effect on blood clotting and no detrimental effects on the stomach lining. Boutaud et al in 2002 found that paracetamol indirectly block cyclooxygenase enzyme and that this blockage is ineffective in the presence of peroxides. This explains why paracetamol is effective in the central nervous system and in endothelial cells but not in platelets and immune cells which have high levels of peroxides.
The dose of paracetamol that is commonly administered is 10-15mg/kg four hourly orally and 15-20mg/kg four hourly rectally. The effectiveness of paracetamol is often underestimated, it has a dose related potency for postoperative pain in paediatric surgery. A study of 10mg/kg oral paracetamol has shown it to be no more effective as an analgesic than placebo after myringotomy or for the relief of symptoms of tonsillitis and pharyngitis. Oral paracetamol 15mg/kg given to unanaesthetised neonates undergoing circumcision did not ameliorate either intraoperative or immediate postoperative pain. Adequate analgesia in children undergoing tonsillectomy has been described using preoperative oral paracetamol in a dose of 40mg/kg.

The analgesic effect of a larger dose of rectal acetaminophen has been studied only in few reports; Anderson et al found 40mg/kg of rectal acetaminophen to be less effective than the same dose orally. However Korpela et al found in their study of 120 paediatric patients that a single dose of 40mg/kg or 60mg/kg of rectal
acetaminophen had a clear morphine-sparing effect in day-case paediatric surgical procedures.

In 1995, Montgomery and colleagues evaluated the pharmacokinetics of 45mg/kg dose of rectal acetaminophen in ten children. Based on their results the authors suggested that a 45mg/kg rectal acetaminophen dose was roughly equivalent to a 10-15mg/kg oral dose. The results of Montgomery’s group were subsequently reproduced by Birmingham and colleagues in a dose-ranging study. Birmingham and colleagues conducted a trial of rectal acetaminophen in twenty eight children (ages 2-12 years) undergoing orthopaedic surgery using a single dose of 10, 20, or 30mg/kg of rectal acetaminophen. The authors found that most patients did not achieve peak or sustained serum acetaminophen values in the 10 - 20µg/ml serum concentration range. They concluded that a rectal acetaminophen dose of 40mg/kg would likely be needed to provide adequate serum acetaminophen concentration in the perioperative setting. Hansen and coworkers observed similar results in a study of seventeen infants given rectal acetaminophen 25mg/kg during induction of anaesthesia. The maximum serum acetaminophen concentration (10.9±5.1µg/ml) was considered by the authors to be sub therapeutic. Rusy et al demonstrated low or even undetectable serum paracetamol concentrations in the first 40 minutes after surgery, when rectal paracetamol 30-35mg/kg had been administered intraoperatively. Mather et al demonstrated a need to supplement rectal paracetamol 20mg/kg with a non-steroidal anti-inflammatory agent to achieve satisfactory analgesia after tonsillectomy.

Metabolism of paracetamol occurs mainly in the liver, where most of it is converted to inactive compounds by conjugation with sulphate and glucuronide, and then excreted by the kidneys. Only a small portion is metabolized via the hepatic
cytochrome p-450 enzyme system. The toxic effects of paracetamol are due to a minor highly reactive alkylating metabolite (N-acetyl-P-benzo-quinone imine), not paracetamol itself or any of the major metabolites. Hepatic toxicity is reported with plasma concentrations above 0.8mmol/L after acute poisoning. Overdosage results in increased production of highly reactive alkylating metabolite by the hepatic cytochrome P-450 dependent mixed function oxidase enzyme system. This metabolite binds to intracellular hepatic macromolecule to produce cell necrosis and damage. Toxicity is increased in patients with induction of the cytochrome P-450 enzyme system, specifically cyp 2E1, through drugs such as rifampicin, Phenobarbital, isoniazid, phenytoin, carbamazepin and alcohol, or patients with low glutathione reserves as a product of genetic variation, HIV positive patients, malnutrition and alcohol-related or other liver disease. Paracetamol toxicity can also cause acute renal failure and chronic exposure to paracetamol has been linked to chronic renal failure. This is due to tubular necrosis caused by the highly toxic metabolite N-acetyl P-benzoquinone imine.

Penna and Buchanan reported seven deaths and eleven cases of hepatotoxicity associated with paracetamol poisoning in children. Mortality due to hepatotoxicity was associated with doses greater than 300mg/kg/day for one to six days. Current guidelines recommend that doses should not exceed 90 mg/kg/day.
CHAPTER THREE
RESEARCH DESIGN

3.1 PATIENT SELECTION

Study population

The study population were paediatric patients between the ages of one and seven (1-7) years scheduled to undergo elective day-case inguinal surgical procedures. The patients were randomly divided into three (3) groups: group 1, 2 and 3 to receive rectal paracetamol of 20, 40 and 60mg/kg body weight respectively.

Study location

The study was carried out in the operating theatre and the recovery room of the University College Hospital, Ibadan.

Sample size

Based upon previous work \(^{11,17,82}\) a sample size of thirty patients per group was needed for this study. However, to allow for dropouts, thirty-five patients per group were studied. Thus, the total sample size for this study was one hundred and five (105).

Inclusion criteria

One hundred and five paediatric patients between the ages of one and seven years with ASA physical status I or II, whose parents have means of communication (telephone), booked for elective day-case inguinal surgical procedures such as herniotomy, ligation of patent processus vaginalis, orchidopexy and hydrocoeleectomy were included in the study.
Exclusion criteria

These include patients with liver disease or allergy to acetaminophen, any clinical state which might prevent the evaluation of postoperative pain, concomitant medication which might interact with the study drug e.g. NSAIDS and other analgesics.

3.2 SAMPLING PROCEDURE

Patients were randomly divided into three groups. An assistant was allowed, on behalf of the patient, to pick from sealed envelopes that contains three coded papers: Groups 1, 2, and 3. Groups 1, 2, and 3 patients received approximately 20-, 40- and 60-mg/kg of rectal acetaminophen respectively, after the induction of general anaesthesia before the skin incision. The research drug was administered by the attending anaesthetist. Both the researcher and the recovery room nurse were unaware of the dosage of rectal acetaminophen that the patient had.

3.3 METHODOLOGY

Approval for the study was obtained from University College Hospital Ibadan cum University of Ibadan ethical review committee. One hundred and five paediatric patients, aged one to seven years, booked for elective day–case inguinal surgical procedures were included in the study. The patients and their parents were seen in surgical outpatient department a few days before the day of surgery. A detailed explanation of the consent form was given to the parents after which they gave written consent. Routine pre-anaesthetic assessment of the patients for fitness for surgery and anaesthesia was done. None of the patients was premedicated with any form of analgesic agent.
On the morning of surgery, in the theatre, all patients were weighed and randomized into one of three groups to receive a single dose of approximately 20, 40, or 60mg/kg of rectal acetaminophen after induction of general anaesthesia. Phardol suppositories with NAFDAC REG. NO. 01304 (produced by Pharma Deko PLC, Agbara Industrial Estate, Agbara Ogun State) were used. Combinations of the four commercially available doses (60, 125, 250 and 500mg) were used to deliver an amount of drug as close as possible to the calculated dose.

All patients fasted for at least two hours to clear liquid and six hours to solid foods according to the instructions given to their parents in the surgical outpatient clinic. The patients were transferred to the operating room after certifying them fit for day-case surgery.

Drugs and equipment were made ready in each case. Monitoring was done with a multi-channel automated monitor. Non-invasive blood pressure, heart rate, arterial oxygen saturation and respiration were monitored. Respiratory rate was monitored by counting thoracic excursions in 60 seconds.

Anaesthesia was induced with halothane, nitrous oxide and oxygen. Intravenous access was gained with size 20G or 22G cannula. This was followed by intravenous infusion of 4.3% dextrose in 0.18 saline, the volume of which depended on the calculated deficit and maintenance requirement of the child. The estimated preoperative fluid deficit is the product of number of hours of fasting and hourly maintenance fluid requirement of the child. The hourly maintenance fluid requirement of the child was calculated using the formula $4 - 2 - 1$, i.e. 4ml/kg for the first 10kg, 2ml/kg for the second 10kg and 1ml/kg for the subsequent kg. Intravenous atropine at 0.02mg/kg was given. Following the induction of general anaesthesia, an amount
close to the calculated dose (as much as possible) of acetaminophen was administered rectally (depending on the group the patient belonged to) by the attending anaesthetist who did not take part in the management of the patient in the recovery room.

Anaesthesia was maintained with 1-2% concentration of halothane and 50% of nitrous oxide in oxygen, and patients were allowed to breathe spontaneously through face mask or laryngeal mask airway using Jackson Rees modification of Ayre’s T-piece.

The cardiovascular and respiratory variables i.e. the blood pressure, pulse rate, respiratory rate and arterial oxygen saturation were monitored every 5 minutes till the end of procedure. No other analgesic was given.

At the end of the surgery, halothane and nitrous oxide were discontinued. The patients were allowed to breathe 100% oxygen for three to five minutes and thereafter transferred to the recovery room for monitoring of vital signs and pain assessment. The patients were handed over to the recovery room nurse who was unaware of the dose of rectal acetaminophen the child had. Vital signs were recorded every 10 minutes in recovery room. Pain assessment was done by the researcher using Children’s Hospital of Eastern Ontario behavioral Pain Scale (CHEOPS) (Appendix III). No pain was defined as CHEOPS score of ≤6, mild pain as CHEOPS score of 7, moderate pain as CHEOPS score of 8 and severe pain as CHEOPS score of ≥9 as validated by Suraseranivongse et al.66

Rescue pain medication in the recovery room was intravenous pentazocine 0.1mg/kg and the decision to give pentazocine was made by the researcher depending on the pain score.
The patients were monitored in the recovery room for two hours. They were discharged home when they were alert, cooperative with normal motor activity, pain free and without nausea and vomiting. Rescue pain medication at home was oral paracetamol 15mg/kg, 6hourly.

The parents were interviewed by phone after 24hours for postoperative pain, nausea and vomiting or any other untoward events.

3.4 Data Collection

Data collected were age, sex, weight, indication for surgery, heart rate, oxygen saturation, blood pressure, respiratory rate and pain score. This was done with the aid of data collection form which was designed for the study. (Appendix II and III).

3.5 Statistical Analysis

The data collected were analyzed using SPSS versions 11.0. Results are presented in tables and figures and expressed as mean (±SD) and counts. Data was edited and statistical association was determined using the chi-square($X^2$) test for categorical variables and the ANOVA and t-test for continuous variables. A p-value of less than 0.05 was considered significant.
CHAPTER FOUR

RESULTS

A total of one hundred and five (105) healthy paediatric patients with American Society of Anesthesiologist’s classification (ASA) 1 and II who had day-case inguinal surgical procedures were studied. They were randomized into three different groups. Thirty-five patients in each group received a single dose of either approximately 20-, 40- or 60-mg/kg of rectal acetaminophen after induction of anaesthesia.

Demographic Characteristics, ASA Status and Surgical Procedures of the Patients.

One hundred and three boys, (34 in 20mg/kg group, 34 in 40mg/kg group, 35 in 60mg/kg group) and two girls were studied. (Table 1). The male preponderance is due to the fact that inguinal surgical procedures are more common in males than females. The ages and body weights of the patients studied were comparable. (Table 1). Twenty-five patients in 20mg/kg group, 23 in 40mg/kg group and 27 in 60mg/kg group were ASA 1 while the others were ASA II.

Table 1 also showed that 20 patients in 20mg/kg group, 18 in 40mg/kg group and 22 in 60mg/kg group had herniotomy. This constituted the largest proportion of the patients studied. Five patients in 20mg/kg group, 10 in 40mg/kg group and 7 in 60mg/kg group had ligation of patent processus vaginalis. Two patients in 20mg/kg group, 2 in 40mg/kg group and 1 in 60 mg/kg group had orchidopexy. Eight patients in 20mg/kg group, 5 in 40mg/kg group and 5 in 60mg/kg group had groin exploration.
Operative Conditions.

The mean duration of surgery for 20-, 40-, and 60-mg/kg groups were 38.97 min (SD±8.62), 42.03 min (SD±9.11), 40.89 min (SD±8.69) respectively. (Table 2). The mean time of administration of the drug to the end of surgery for 20-, 40- and 60-mg/kg group were 43.69 min (SD±7.98), 44 min (SD±9.12) and 42.6 min (SD±7.49) respectively. Table 2 also shows that the mean time from the administration of the research drug to the time of admission into recovery room for 20-, 40-and 60-mg/kg group were 51.8 min (SD±8.61), 53.6 min (SD±9.61) and 53.17 min (SD±7.73) respectively. The three groups were comparable in terms of duration of surgery, time of administration of the research drug to the end of surgery and time of administration of the research drug to the time of admission into the recovery room.

Intraoperative Vital Signs

Intraoperative mean arterial pressure

During the one hour of intraoperative monitoring period there were no statistically significant difference in mean arterial pressure in the 40-and 60mg/kg groups compared with 20mg/kg group (p>0.05), with the exception of the tenth minute when the mean arterial pressure was significantly higher. (p=0.01). Figure1.

Intraoperative mean heart rate

There was initial increase in the mean heart rate in all the three groups during the intraoperative monitoring period. By the fifteenth minute of the intra operative period, a decrease trend was observed which persisted until the end of the procedure. Both the initial increase and later decrease in mean heart rate were not statistically
significantly different in 40 – and 60mg/kg groups compared with 20mg/kg group (p>0.05) figure 2.

**Intraoperative mean respiratory rate**

Figure 3 showed an initial decrease in the mean respiratory rate in the first five minute of intraoperative period after which it started increasing and reached peak by the tenth minute. It later showed a downward trend which persisted until the end of the procedure. This trend was observed in all the three groups studied and did not reach statistical significance at any time (p>0.05).

**Intraoperative mean arterial oxygen saturation of haemoglobin**

Figure 4 showed that the intraoperative mean arterial oxygen saturation of haemoglobin ranged between 99% and 99.6%. This was observed in all the three groups.

Pain Severity and Pain Score On Children Hospital Of Eastern Ontario Pain Scale (CHEOPS) In Recovery Room

During the two hours period in the recovery room, pain scores were significantly lower in the 40- and 60mg/kg groups compared with 20mg/kg group (Table 4) and the lower pain scores observed persisted for the duration of stay in the recovery room. Table 3 and Figure 6 shows that 10, (28.6%) patients who received 20mg/kg rectal acetaminophen experienced severe pain in the recovery room, while none of the patients who received 40 or 60mg/kg of rectal acetaminophen experienced severe pain throughout their stay in recovery room. Severe pain is defined as CHEOPS score ≥ 9

**Rescue Analgesic in the Recovery Room**

Eighteen (51.4%) patients in 20mg/kg group received rescue analgesic, I.V pentazocine 0.1mg/kg, in the recovery room and 7 (20%) of them had at least two doses of pentazocine (Table 3).
Nine (25.7%) of children in 40mg/kg group received 0.1mg/kg of intravenous pentazocine in the recovery room. None of them required more than single dose throughout the two hour period of their stay in recovery room. (Table 3).

Table 3 also showed that 6 (17.1%) children in 60mg/kg group required i.v pentazotone 0.1mg/kg in the recovery room, and also none of them had more than one dose. There is a good relationship between the dose of acetaminophen and percentage of children who did not require rescue analgesic, i.v pentazocine in the recovery room (Fig 6).

**Time to First Analgesic Requirement in the Recovery room.**

The mean time to first postoperative analgesic requirement in the recovery room in 20; 40 and 60mg/kg groups were 60.4 min (S.D ±6.21), 64.33 min (S.D± 7.85) and 66.5 min (S.D± 9.14) respectively. (Table 2). The three groups were statistically comparable. (p<0.05).

**Analgesia at Home**

Twenty (57.1%) children in 20mg/kg group received oral Paracetamol at home within the first twenty four hours after surgery, as against 10 (28.6%) in 40mg/kg groups and 4 (11.4%) in 60mg/kg group (Table 3).

**Postoperative Nausea and Vomiting**
None of the 105 children studied vomited in the recovery room. However, 2 patients (5.7%) in the 20 mg/kg rectal acetaminophen group vomited at home during the first 24 hours, while none of the children in the 40- or 60 mg/kg group had emetic complication at home (Table 3).

**Vital Signs in the Recovery Room**

**Mean Arterial Pressure**

During the two hours stay in recovery room, the mean arterial pressure were statistically significantly lower in the 40- and 60-mg/kg groups compared with the 20mg/kg group (p<0.05), with the exception of the first 10 minutes when p >0.05 (Figure 7).

**Mean heart Rate**

Figure 8 shows that there was sustained lowering of mean heart rate in all the three groups during the period of their stay in recovery room. The reduction in the heart rate was more in the 40- and 60-mg/kg group compared with the 20mg/kg group but did not reach statistical significance all of the time.

**Mean respiratory Rate**

The mean respiratory rates were statistically significantly lower in the 40- and 60-mg/kg group when compared with the 20mg/kg group (P<0.05) throughout the two hours period in recovery room. (Figure 9).
# TABLE 1

DEMOGRAPHIC CHARACTERISTICS, ASA STATUS ANDSURGICAL PROCEDURES OF THE PATIENT

(Results are presented as mean, ± S.D).

<table>
<thead>
<tr>
<th>Acetaminophen mg/kg</th>
<th>20mg/kg</th>
<th>40mg/kg</th>
<th>60mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>4.15±1.49</td>
<td>4.67±1.49</td>
<td>3.81±1.55</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>15.47±3.83</td>
<td>14.82±3.31</td>
<td>15.51±3.47</td>
</tr>
<tr>
<td>Sex(male/female)</td>
<td>34/1</td>
<td>34/1</td>
<td>35/0</td>
</tr>
<tr>
<td>ASA1/11</td>
<td>25/10</td>
<td>23/12</td>
<td>27/8</td>
</tr>
<tr>
<td>Herniotomy</td>
<td>20</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Ligation of PPV</td>
<td>5</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Orchidopexy</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Groin Exploration</td>
<td>8</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

ASA - American Society of Anesthesiologists

PPV - Patent Processus Vaginalis

SD - Standard Deviation
TABLE 2

OPERATIVE CONDITIONS

Results are presented as mean ± S.D.

<table>
<thead>
<tr>
<th>Acetaminophen mg/kg</th>
<th>20mg</th>
<th>40mg</th>
<th>60mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (mins)</td>
<td>38.97 ± 8.62</td>
<td>42.03 ± 9.11</td>
<td>40.89 ± 8.69</td>
</tr>
<tr>
<td>Time of administration of drug to end of surgery (mins)</td>
<td>43.69 ± 7.98</td>
<td>44 ± 9.12</td>
<td>42.6 ± 7.49</td>
</tr>
<tr>
<td>Time of administration of drug to time of admission into recovery room (mins)</td>
<td>51.8 ± 8.61</td>
<td>53.6 ± 9.61</td>
<td>53.17 ± 7.73</td>
</tr>
<tr>
<td>Time to first analgesic requirement in the recovery room. (mins)</td>
<td>60.4 ± 6.21</td>
<td>64.33 ± 7.85</td>
<td>66.5 ± 9.14</td>
</tr>
</tbody>
</table>
# TABLE 3

**INCIDENCE OF SEVERE PAIN, ITS TREATMENT, AND POSTOPERATIVE NAUSEA AND VOMITING IN THE STUDY GROUPS.**

<table>
<thead>
<tr>
<th>Acetaminophen mg/kg</th>
<th>20mg/kg</th>
<th>40mg/kg</th>
<th>60mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
</tr>
<tr>
<td>Children who had severe pain in the recovery room.</td>
<td>10</td>
<td>28.6</td>
<td>0</td>
</tr>
<tr>
<td>Children who had pentazocine in the recovery room.</td>
<td>18</td>
<td>51.4</td>
<td>9</td>
</tr>
<tr>
<td>At least two doses of pentazocine</td>
<td>7</td>
<td>20.0</td>
<td>0</td>
</tr>
<tr>
<td>Children who received p/c/m at home within 24 hours.</td>
<td>20</td>
<td>57.1</td>
<td>10</td>
</tr>
<tr>
<td>PONV</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>in recovery room</td>
<td>2</td>
<td>5.7</td>
<td>0</td>
</tr>
<tr>
<td>by 24 hours</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

PONV - Postoperative Nausea and Vomiting
P/c/m - Paracetamol
No – Number
% - Percentage
TABLE 4
CHEOPS PAIN RATING OF DIFFERENT DOSES OF RECTAL ACETAMINOPHEN IN RECOVERY ROOM (mean score±S.D)

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>CHEOPS - SCORE</th>
<th>CHEOPS - SCORE</th>
<th>CHEOPS - SCORE</th>
<th>CHEOPS - SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20mg/kg</td>
<td>40mg/kg</td>
<td>60mg/kg</td>
<td>p-value</td>
</tr>
<tr>
<td>10min</td>
<td>9.03±1.89</td>
<td>7.46±0.741</td>
<td>7.34±0.68</td>
<td>0.000</td>
</tr>
<tr>
<td>20min</td>
<td>8.89±1.84</td>
<td>7.40±0.77</td>
<td>7.23±0.73</td>
<td>0.000</td>
</tr>
<tr>
<td>30min</td>
<td>8.03±1.18</td>
<td>7.06±0.80</td>
<td>7.00±0.69</td>
<td>0.000</td>
</tr>
<tr>
<td>40min</td>
<td>7.71±0.93</td>
<td>7.00±0.77</td>
<td>6.89±0.76</td>
<td>0.000</td>
</tr>
<tr>
<td>50min</td>
<td>7.46±1.04</td>
<td>6.77±0.43</td>
<td>6.74±0.61</td>
<td>0.000</td>
</tr>
<tr>
<td>60min</td>
<td>7.27±0.95</td>
<td>6.63±0.49</td>
<td>6.54±0.51</td>
<td>0.000</td>
</tr>
<tr>
<td>70min</td>
<td>7.56±0.78</td>
<td>6.54±0.51</td>
<td>6.51±0.51</td>
<td>0.000</td>
</tr>
<tr>
<td>80min</td>
<td>6.94±0.80</td>
<td>6.57±0.50</td>
<td>6.46±0.51</td>
<td>0.004</td>
</tr>
<tr>
<td>90min</td>
<td>6.83±0.82</td>
<td>6.57±0.50</td>
<td>6.28±0.62</td>
<td>0.004</td>
</tr>
<tr>
<td>100min</td>
<td>6.60±0.50</td>
<td>6.29±0.46</td>
<td>6.14±0.65</td>
<td>0.002</td>
</tr>
<tr>
<td>110min</td>
<td>6.66±0.48</td>
<td>6.09±0.45</td>
<td>5.89±0.63</td>
<td>0.000</td>
</tr>
<tr>
<td>120min</td>
<td>6.63±0.49</td>
<td>6.00±0.59</td>
<td>5.71±0.62</td>
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</table>

CHEOPS – Children’s Hospital of Eastern Ontario Pain Scale.
Figure 1

Intraoperative mean arterial pressure in the 20; 40 and 60mg/kg groups.
Figure 2

Intraoperative mean heart rate in the 20; 40 and 60mg/kg groups.

Mean heart rate.

20mg/kg
40mg/kg
60mg/kg

Figure 3
**Intraoperative mean respiratory rate in the 20;40 and 60 mg/kg groups.**

- **Figure 4**
Intraoperative mean arterial oxygen saturation of haemoglobin in 20; 40 and 60mg/kg groups.

![Graph showing mean arterial oxygen saturation over time for 20mg/kg, 40mg/kg, and 60mg/kg groups.](image)

FIGURE 5

INCIDENCE OF PAIN
Figure 6

Rectal acetaminophen dose and children spared pentazocine analgesic in the recovery room.
FIGURE 7

Mean arterial pressure in recovery room in the 20; 40 and 60 mg/kg groups.
Mean heart rate response over 2 hours in recovery room in the 20; 40 and 60mg/kg groups.
Mean respiratory rate over 2 hours in recovery room in the 20; 40 and 60mg/kg groups.
CHAPTER FIVE

DISCUSSION

The results of this study have demonstrated that rectal acetaminophen has a clear dose-dependent postoperative analgesic effect in children, after day-case inguinal surgical procedures with significance reached with a 40- or 60-mg/kg dose. This result follows the pattern of results that had been reported in the previous studies.11, 16, 17, 19.

The dose of acetaminophen that is commonly administered is 10-15mg/kg four hourly orally and rectally. The rectal dose should be higher because of slow and erratic absorption of acetaminophen suppository.12 Several factors may account for this variability including the placement of the suppository, the degree of lipophilicity of the vehicle, and the pH within the rectum.

In 1995, Montgomery et al. evaluated the pharmacokinetics of high-dose rectal acetaminophen in ten children (average age 3.4±0.5 years).16 A single 650mg suppository, providing a dose of approximately 45mg/kg was administered immediately after induction of anaesthesia. Serum samples were collected over a period of four hours in the first five patients, but extended to seven hours in the remaining patients after a prolonged absorption phase was identified. The average maximum serum concentration for the ten children was 13.3±5.9µg/ml. The time to reach maximum concentration occurred at 198±70 minutes. Based on their results, the authors suggested that a 45mg/kg rectal acetaminophen dose was roughly equivalent to a 10- 15mg/kg oral dose.16
The results of Montgomery’s group were subsequently reproduced in a dose-ranging study. Birmingham and colleagues in Children’s Memorial Hospital in Chicago conducted a trial of rectal acetaminophen in twenty-eight children (ages 2 to 12 years) undergoing orthopedic surgery. Patients were randomized to receive a single dose of 10-, 20- or 30-mg/kg of rectal acetaminophen after induction of anaesthesia. Serum sampling was performed over a 24-hour period and the results were analyzed. Pharmacokinetic analysis showed considerable patient variability and wide differences in dissolution rate. In those patients who received the two larger (325 and 650 mg) suppositories, the average time to complete dissolution was 3 hours. Only the 30 mg/kg dose produced serum concentration within the predetermined target range of 10-20 µg/ml, with an average maximum concentration of 14.2±5.1 µg/ml. Though the study was not designed to evaluate analgesic efficacy of acetaminophen, the author went ahead to conclude that the rectal acetaminophen dose of 40 mg/kg would likely be needed to provide adequate serum acetaminophen concentrations for analgesia in the perioperative setting. The findings of Anderson et al. was in support of the use of single high dose of rectal acetaminophen when they reported a maximum serum concentration of 17.2 µg/ml following a rectal dose of 40 mg/kg.

Plasma concentration of acetaminophen required for analgesic has not been defined but the accepted therapeutic plasma concentration range for an antipyretic effect is 10-20 µg/ml. The elevation of the mean arterial pressure, mean heart rate and mean
respiratory rate between the 5th and 15th minutes of intraoperative period in all the three groups studied suggests inadequate analgesia. This period corresponds to onset of surgery. (Figures 1, 2 and 3). The sustained lowering of the intraoperative mean vital signs after the initial increase could not be taken as being due to adequate analgesia because a study had demonstrated low or undetectable serum paracetamol concentration in the first 40 minutes after rectal administration of 30 – 35mg/kg of paracetamol,83 but may be due to deepening the level of anaesthesia with halothane. The peak plasma concentration of acetaminophen after rectal administration is usually achieved between 120 and 180 mins.16,17,19 This is much longer than after oral administration which is usually between 30 and 60 minutes.78,92 Thus in this study there was a decrease of pain intensity already within the first 10 minutes in recovery room i.e. within the first one hour after administration of 40-or 60-mg/kg of rectal acetaminophen (Table 4).

The results obtained from this study also showed good relationship between the dose of acetaminophen and the percentage of children who did not require rescue analgesic, i.v pentazocine in the recovery room. Nine (25.7%) patients in 40mg/kg group and 6 (17.1%) children in 60mg/kg group had rescue analgesic i.v. pentazocine 0.1mg/kg in recovery room and none of them needed more than one dose as opposed to 18 (51.4%) patients in 20mg/kg group and 7 (20%) of them having at least two doses. This shows that analgesia is superior at the higher doses with fewer requirements for opioid analgesia. This finding is similar to that of Korpela and colleagues,11 in the conclusion of their study of 120
paediatric patient, that a single dose of 40- or 60-mg/kg of rectal acetaminophen had a clear morphine-sparing effect in day-case paediatric surgical procedures.

It is worth mentioning that as much as seventeen (48.6%) patients in 20mg/kg rectal acetaminophen group did not require rescue analgesic in the recovery room. This may be because of the erratic absorption of rectal acetaminophen or may be because their parents were allowed to stay with them in the recovery room as soon as they woke up from the effect of anaesthesia. Minimal separation from the parents has long been recognized as the most important non-pharmacologic method of pain management.\textsuperscript{93,94} Other non-pharmacologic methods of pain management include reassurance, cuddling, stroking and distraction. Most of these were also employed in the recovery room by the parents thereby reinforcing analgesia.

Only four (11.4%) patients in 60mg/kg group and ten (28.6%) patients in 40mg/kg group received oral paracetamol at home within the first 24-hours postoperatively as opposed to twenty (57.1%) patients in 20mg/kg group. These relatively high doses reduced the total requirement of postoperative pain medication in twenty-four hours. This indicates that a single effective dose of acetaminophen seems to have long-lasting effect beyond the pharmacokinetic profile. Fifteen (42.9%) patients in 20mg/kg rectal acetaminophen group did not require oral paracetamol at home within 24-hours. Thirteen (13) of this fifteen (15) were among those that received rescue analgesic I.V pentazocine 0.1mg/kg in the recovery room, with seven (7) of them receiving two (2) doses each. The remaining two (2) children did not receive either pentazocine in the recovery
room nor oral paracetamol at home. More analgesic requirement would have been expected in view of the short duration of action of pentazocine in this group of patients. Non administration of analgesic may be because the patients were at home playing with other siblings causing distraction from the pain, also the other forms of non-pharmacologic method of pain management were employed at home. A study has shown parents to withhold analgesics from children.95

The time to first analgesic requirement in the recovery room were comparable in the three groups. (Table 2). One would have expected the relatively higher doses of rectal acetaminophen that showed superior analgesia to have significantly longer time to first analgesic requirement in the recovery room. The comparable time to first analgesic requirement obtained in the three groups may be as a result of the erratic absorption of rectal acetaminophen. Also some patients had their first postoperative analgesic medication at home as against in the recovery room.

None of the one hundred and five children studied vomited in recovery room, however two (5.7%) in 20mg/kg group vomited at home within the first twenty-four hours, while none in 40-or 60-mg/kg group had emetic complication. One of the two patients that vomited had orchidopexy and the other one had inguinal herniotomy. Some surgical procedures have been particularly identified with vomiting in children. These include squint surgery, tonsillectomy, adenoidectomy, orchidopexy and hernia repair.96 The number of patients that had emetic symptom in this study is low compared to 12.2% reported by Amanor-Boadu and Soyannwo.97 This difference may be because they followed
up the patients for five days as against 24-hours in this study. Also only 19 (30.6%) of 62 patients they studied had analgesic, dipyrone, intraoperatively, others did not have any form of intraoperative analgesia and it is a well known fact that postoperative pain predisposes to postoperative nausea and vomiting.\textsuperscript{8} This may account for their higher figure.
CONCLUSIONS

1. The results of this study have demonstrated that rectal acetaminophen has a clear dose-dependent postoperative analgesic effect in children undergoing day-case inguinal surgical procedures, with significance reached with 40- or 60-mg/kg dose.

2. Single effective dose of rectal acetaminophen have long lasting effect beyond the pharmacokinetic profile.

3. The incidence of nausea and vomiting is by far reduced when a single high dose rectal acetaminophen is administered.

LIMITATION

There are some limitations associated with this study. Firstly the postoperative pain assessment was done for a period of two hours in the recovery room. Extension of the pain assessment to their homes after discharge could have yielded a better result. Also inability to measure the serum level of rectal acetaminophen prevented the determination of the dose and rate of acetaminophen absorption. Serum level would have determined if 10 – 20μg/ml acetaminophen value currently accepted to provide analgesia was attained in the groups. The time to first postoperative analgesic requirement was limited to the recovery room, meanwhile some patients had their first postoperative analgesic medication at home. Extension of the time to first postoperative analgesic requirement to include their homes could have yielded a better result.
RECOMMENDATION

From this study 40-60mg/kg dose of rectal acetaminophen should be considered in day case paediatric surgical procedures for postoperative analgesia. This is particularly important especially in the perioperative setting when there is restriction of oral intake, and there is possibility of gastric dysfunction.
REFERENCES


59. **Davis JM, Albert JD, Tracy KJ.** Increased neutrophil mobilization and decreased chemotaxis during cortisol and epinephrine infusion. J Trauma 1991; 31: 725 – 730.


82. **Anderson BJ.** What we don’t know about paracetamol in children. Paediatric Anaesthesia 1998; 8: 451-460.


## APPENDIX I

**MODIFIED POST ANAESTHESIA DISCHARGE SCORING SYSTEM (PADSS)** - MARSHALL AND CHUNG

<table>
<thead>
<tr>
<th>Vital signs (stable/consistent with age and pre operative baseline)</th>
<th>Score</th>
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<tr>
<td>BP and Pulse within 20% of pre operative baseline</td>
<td>2</td>
</tr>
<tr>
<td>BP and Pulse 20%-40% of pre operative baseline</td>
<td>1</td>
</tr>
<tr>
<td>BP and Pulse &gt;40% of pre operative baseline</td>
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<table>
<thead>
<tr>
<th>Activity Level (Ambulation at pre operative level)</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Steady gait, no dizziness</td>
<td>2</td>
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<tr>
<td>Requires assistance</td>
<td>1</td>
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<tr>
<td>Unable to ambulate</td>
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<table>
<thead>
<tr>
<th>Nausea and vomiting</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>Minimal: Treated with PO medication</td>
<td>2</td>
</tr>
<tr>
<td>Moderate: Treated with IM medication</td>
<td>1</td>
</tr>
<tr>
<td>Continues after repeated treatment</td>
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<table>
<thead>
<tr>
<th>Pain</th>
<th>Score</th>
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<tr>
<td>Acceptable to patient; controlled with post operative medications</td>
<td>2</td>
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<tr>
<td>No</td>
<td>1</td>
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<table>
<thead>
<tr>
<th>Surgical bleeding</th>
<th>Score</th>
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<tr>
<td>Minimal: No dressing change required</td>
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<tr>
<td>Moderate: Up to two dressing changes required</td>
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</tr>
<tr>
<td>Severe: More than three dressing change required</td>
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Maximum score = 10 Score > 9 required for discharge
APPENDIX II

EFFECTIVE DOSE OF RECTAL ACETAMINOPHEN FOR IMMEDIATE POSTOPERATIVE PAIN RELIEF IN PAEDIATRIC DAY-CASE INGUINAL SURGERY

DATA COLLECTION FORM

1. Serial Number in Study
2. Hospital Number
3. Age
4. Weight
5. Sex
6. ASA classification
7. Date
8. Surgical Procedure
9. Duration of Procedure
10. Anaesthetic technique
11. Time of Administration of study drug
12. End of Surgery
13. Time of admission into recovery room
14. Rescue analgesic in the recovery room (Pentazocine) and time
15. Post-operative Complications.

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<tr>
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<th>Recovery room</th>
<th>At home</th>
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<tbody>
<tr>
<td>Nausea</td>
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<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td></td>
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<tr>
<td>Others</td>
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VITAL SIGNS

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<tr>
<td></td>
<td></td>
<td>10m</td>
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<td>Heart Rate</td>
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<tr>
<td></td>
<td>Lowest</td>
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<tr>
<td>B.P</td>
<td>Highest</td>
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<td></td>
<td>Lowest</td>
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<tr>
<td>R.R</td>
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<td>Lowest</td>
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<tr>
<td>Sa0₂</td>
<td>Highest</td>
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<td></td>
<td>Lowest</td>
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<tr>
<td>Pain Score</td>
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## Children’s Hospital of Eastern Ontario Behavioural Pain Scale (CHEOPS)

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<th>80</th>
<th>90</th>
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<th>120</th>
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<tbody>
<tr>
<td>1. No Cry</td>
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<tr>
<td>2. Moaning, Crying</td>
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<td>3. Screaming</td>
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<td>0. Smiling</td>
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<td>0. Positive</td>
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<td>1. Calm or neutral</td>
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<tr>
<td>2. Change Position, become agitated or rigid, restless</td>
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<tr>
<td>2. Kick, Drawn-up, restrained</td>
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<th>100</th>
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<tbody>
<tr>
<td>1. Doesn’t advance the hand to the site of operation</td>
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<td></td>
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<tr>
<td>2. Advances the hand or touches / grips the site of operation</td>
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<th>90</th>
<th>100</th>
<th>110</th>
<th>120</th>
</tr>
</thead>
</table>
APPENDIX IV

ETHICAL CONSIDERATIONS

1. STATEMENT OF CONFIDENTIALITY

Patient participation in the clinical research is confidential. Only the investigator will have access to the patient’s identity and to information that can be associated with his/her identity. In case of publication of this research, no personal identifying information will be disclosed.

2. STATEMENT OF TRANSLATION TO LOCAL LANGUAGE

The content of the consent form will be translated to patient’s own language for better understanding, and if there is language barrier, an interpreter will be used for this purpose.

3. BENEFICENCE TO PARTICIPANTS

The patients will not be required to pay for the rectal acetaminophen. This drug will be provided by the investigator. The result of the study will be useful in the perioperative pain management in paediatric day-case inguinal surgery.

4. NON MALEFICIENCE TO PARTICIPANTS

The study will not expose the patient to any drug that has not been used safely in the past.

5. VOLUNTARY PARTICIPATION

The choice to participate in this study shall be voluntary; the parents have the right to withdraw at any stage of the study. This will not affect the patient’s statutory rights as a patient.
UI/UCH INSTITUTIONAL REVIEW COMMITTEE

CERTIFICATION LETTER

Principal Investigator: Dr. A. I. Sotannde
IRC Protocol No: UI/IRC/05/0108
Protocol Title: DETERMINATION OF EFFECTIVE DOSE OF RECTAL ACETAMINOPHEN IN PAEDIATRIC DAY-CASE INGUINAL SURGERY.

STATUS: APPROVED

The UI/UCH Institutional Review Committee has reviewed your protocol titled: “Determination of Effective Dose of Rectal Acetaminophen in Paediatric Day-case Inguinal Surgery.”

This study sets out to determine the effective dose of rectal acetaminophen in paediatric day-case inguinal surgery. The outcome of the study would help to improve the management of postoperative pain in paediatric day-case inguinal surgery.

THE RESEARCH PROTOCOL DESCRIBED ABOVE HAS BEEN REVIEWED BY THE UI/UCH IRC WITH THE RESULTS AS INDICATED.

international Regulations require that any severe drug reactions and unexpected adverse occurrence to subjects during the conduct of this research be reported to the UI/UCH IRC Secretariat promptly. Any changes to this protocol must be submitted for review to the UI/UCH IRC.
APPENDIX V

PATIENT INFORMED CONSENT

Dear Parent,

My name is Dr. Sotannnde Adeshola Isiaq. I am a staff of the Department of Anaesthesia, UCH, Ibadan. Your child is being asked to participate in a clinical research study.

This consent form gives you information about the study. Once you understand the study, you will be asked to sign this form if you wish your child to participate. The research study being proposed is determination of effective dose of paracetamol suppository in relieving pain following children groin surgery.

PURPOSE OF THE STUDY

The purpose of this study is to determine the dose of paracetamol suppository that will be adequate for pain management in children during surgical operation of the groin. This study is necessary because of the recent withdrawal of analgin, (a drug that is commonly used for this type of procedures) from Nigerian market.

DESCRIPTION OF THE RESEARCH PROCEDURE

Your child will have the surgery under general anaesthesia. The research drug will be administered into the rectum of your child after the induction of anaesthesia.

Your child will be allocated by chance into any of the three groups. Group 1 will receive 20mg/kg of rectal acetaminophen, group 2 will receive 40mg/kg of rectal acetaminophen and group 3 will receive 60mg/kg of rectal acetaminophen.
Your child will be transferred to the recovery room at the end of the surgery where monitoring of blood pressure, heart rate, percentage of oxygen in blood, respiratory rate and pain assessment will be continued. In case of significant pain in the recovery room, your child will be given a rescue pain reliever, I.V Pentazocine 0.1mg/kg.

Participation in this research is voluntary. All information obtained from you and the result shall be confidentially treated. In the event of publication of this research, no personal identifying information will be disclosed.

Taking part in this study will not expose your child to any added risk and there will be no additional charges to you for taking part in this study.

You are free to refuse to take part in this study. You have the right to withdraw at any time if you choose to. Your withdrawal will not in anyway affect the right of your child to receive full and already established management protocol.

The University College Hospital/ University of Ibadan ethical review committee, located at room T10 on the 2nd floor of Biode Building, Institute for Advanced Medical Research & Training( IMRAT), College of Medicine, University of Ibadan, Tel:234-2-241-2170, 234-2-241-0088 ext.3594, which is responsible for making sure that research with patients is appropriate, has reviewed this study.

If you have any question or need further clarification about the conduct of this study, contact, Dr. I. A. Sotannnde, Department of Anaesthesia, University College Hospital, Ibadan. 08034871194 or 08053302269. Email address: sotanndesola@yahoo.co.com
CONSENT

I have read this consent form and the research study has been explained to me satisfactorily.

I hereby give my consent for my child to participate in the study titled above; I am also informed of my right to discontinue my child’s participation at any time, and that this will not in anyway affect the right of my child to receive full and already established management plan.

Participant

.............................................. ..... Signature/ thumb print Date

Investigator

.............................................. ..... Signature Date