A PROSPECTIVE RANDOMISED CONTROLLED STUDY COMPARING INTRA-OPERATIVE AND POST-OPERATIVE ANALGESIC EFFICACY OF CLONIDINE WITH BUPIVACAINE FOR CAUDAL BLOCK IN PAEDIATRIC SURGICAL PROCEDURES AT KENYATTA NATIONAL HOSPITAL.

A DISSERTATION SUBMITTED IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE (ANAESTHESIA) OF THE UNIVERSITY OF NAIROBI.

BY

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DECLARATION

This dissertation is my original work and has not to my knowledge been presented for a degree progamme in any other University.

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DEDICATION

To my wife Flora, my son Owen Ayora, and daughters Zillah Moraa, Lavender Nyanduko and Bilhah Nyaboke, who patiently bore the pain of my reduced attention in the course of the study. Their support, love and understanding made it possible for me to concentrate on my postgraduate studies to eventual completion.

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CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ABBREVIATIONS

AA	Adrenoreceptor Agonist.
ANOVA	Analysis of variance.
ASA	American Society of Anaesthesiologists.
α	Alpha.
β	Beta.
BP	Blood Pressure.
CSF	Cerebrospinal fluid.
DIC	Disseminated intravascular coagulation.
EC	Effective concentration.
ECG	Electrocardiogram.
ERC	Ethical and research Committee.
HOCM	Hypertrophic obstructive cardiomyopathy.
HR	Heart Rate.
ICP	Intracranial pressure.
INR	International Normalizing Ratio.
ITP	Intermittent thrombocytopaenic purpura.
KNH	Kenyatta National Hospital.
MAP	Mean arterial pressure.
mCHEOPS	modified Children Hospital of Eastern Ontario Pain Scale.
O_2	Oxygen.
spO_2	Saturation of oxygen.
VAS	Visual Analogue Scale.

SUMMARY

Caudal analgesia is the most popular and commonly used regional block in paediatric surgery. It continues to offer a safe and effective intra and post - operative analgesia for many surgical procedures in the region of the umbilicus and below. The use of local anaesthetics in combination with opioids has been demonstrated to improve caudal analgesia in children but has also been associated with side effects such as nausea and vomiting, pruritus, urinary retention, and potentially life threatening respiratory depression. Clonidine, an alpha$_2$ agonist has been used effectively for the treatment of acute and chronic pain. It has been shown to provide analgesia of variable efficacy and duration and to potentiate postoperative analgesia when used in combination with local anaesthetics or opioids via extradural and intradural routes. Furthermore, it lacks side effects that are associated with the use of systemic and spinal opioids but does demonstrate adverse effects including sedation, hypotension, and bradycardia.

This study was designed to compare the analgesic efficacy and incidences of side effects of clonidine with bupivacaine. It was a prospective randomized controlled study, which was carried out at Kenyatta National Hospital (KNH) over a period of two months. The study subjects were the paediatric patients aged two months to thirteen years scheduled for elective surgery. Statistical analysis was performed using chi square test for nominal data. Continuous data was compared using Kruskal-wallis one-way analysis of variance (ANOVA). $P<0.05$ was considered significant.

Sixty patients aged 2 months to 13 years were randomly allocated to three equal groups to receive 0.25% bupivacaine 1ml kg^{-1} body weight (group B), clonidine 2μ kg^{-1} body weight (group C) and 0.125% bupivacaine 1ml kg^{-1}

body weight combined with clonidine 1μ kg^{-1} body weight (group BC). The median time for duration of analgesia was 5.18 hours for group B, 6.17 hours for group C and 8.03 hours for group BC ($P<0.001$). There was a significant difference in the incidence of side effects between the three groups. The median time to first micturition and ambulation was significantly higher in group B as compared to groups C and BC ($P<0.001$). The incidence of sedation was higher in groups BC and C as compared to group B. This resulted partly from the longer duration of analgesia provided by clonidine and the clonidine bupivacaine mixture as well as the sedative effect of clonidine. It was concluded that the analgesic efficacy of clonidine is better than bupivacaine and that a combination of clonidine and bupivacaine in lowered dosages improves the efficacy of caudal analgesia in children with reduced incidences of side effects.

INTRODUCTION

Regional anaesthesia and nerve blocks are now widely used in children, mostly in conjunction with general anaesthesia. They provide part of anaesthesia and significantly improve comfort in the post-operative period.

Caudal block is one of the epidural techniques used for procedures in the region of the umbilicus and below. It has gained widespread popularity in paediatric analgesia with the advantages of reducing the requirement of inhalational anaesthetics, ease of application and providing effective intra- and post-operative analgesia.

Several studies previously done confirmed the efficacy of caudal analgesia for intra and post-operative pain relief. It is a technique particularly applicable to children undergoing urologic procedures. Several drugs and local anaesthetic agents have been used giving effective post-operative analgesia comparable to that produced by oral and parenteral agents.

The purpose of this study therefore was to compare the efficacy of clonidine with bupivacaine for caudal block in providing intra and post-operative pain relief and to document the incidences of side effects.

LITERATURE REVIEW

Caudal blockade is part of the regional anaesthetic techniques in which sensorimotor nerve activity is temporarily pharmacologically blocked to give an anaesthetised field. This technique requires good background knowledge of topographical anatomy and drugs used. The drugs used produce their effects by interfering with electrical activity of the nervous system. The most commonly used drugs are local anaesthetic agents.

Caudal epidural blockade was first introduced by Cathelin in 1901. It consists of a single injection of an anaesthetic agent administered to the sacral hiatus[1]. The ease of performance and reliability makes it the most common of all blocks performed in children. If well carried out, it combines the advantage of simplicity with a high success rate and has successfully been used for pelvic, orthopaedic and lower abdominal and urological surgery with or without light sedation according to the patients age and wishes [2].

The block is achieved by injecting local anaesthetic agents or other pharmacologic agents into the epidural space through the sacral hiatus. The sacral hiatus is situated 1-2cm above the gluteal crease, superior to the coccyx and between the prominent sacral cornuae. It can be located by drawing an equilateral triangle of which the two superior angles overlie the posterior superior iliac spines and the third angle overlies the sacral hiatus [3].

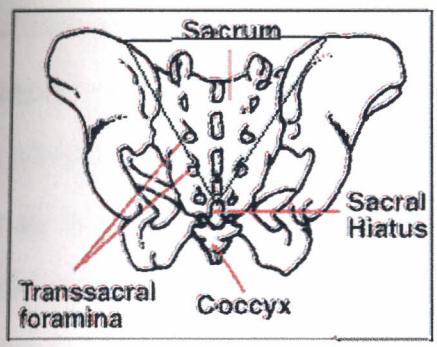

Figure 1.The sacral hiatus.

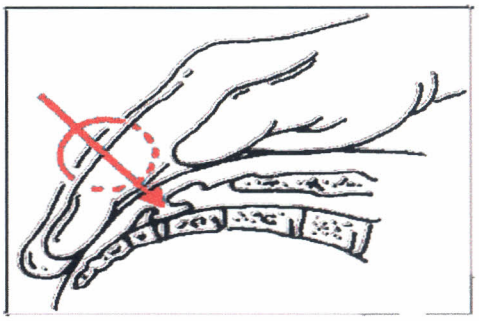

Figure 2. Locating the sacral hiatus by palpating the coccyx.

The sacral hiatus and the

Superior iliac spines form an

Equilateral triangle pointing inferiorly.

The sacral hiatus is large in the newborn, increased in size by yet to fuse, lowermost sacral arches. Induction of anaesthesia is done, an intravenous access is secured and the patient is then placed in the left lateral position. The lumbar sacral area is cleaned with an antiseptic solution and draped. The sacral hiatus is located as shown in figures 1 and 2 above. Under sterile condition, a needle is advanced at an angle of approximately 60^0 to the coronal plane through the apex of the sacrococcygeal membrane where loss of resistance is felt most easily. The needle may be lowered to an angle of 10^0 - 20^0 and advanced only 3-4mm, feeling the lack of resistance with advancement.

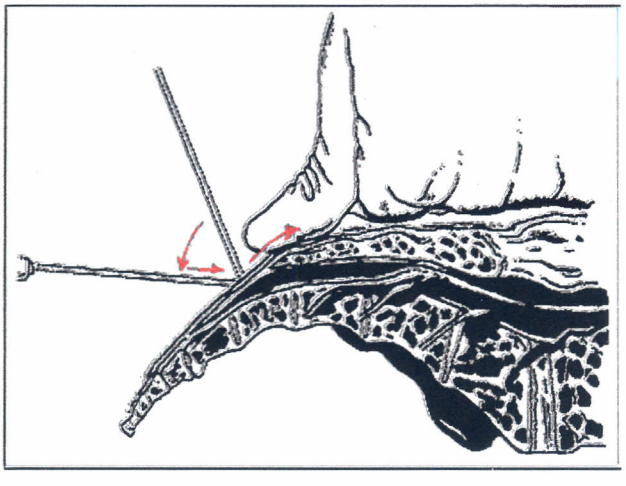

Figure 3. Accessing the sacral hiatus. The needle is advanced at an angle of approximately 60° then lowered to 10^0 - 20^0.

Alternatively, as the apex of the sacrococcygeal membrane overlies the deepest part of the space, injection can be made directly as the tip of the bevel is wholly in the space after infancy. Loss of resistance with injection of saline or air is not used during this manouvre. If blood or more rarely cerebrospinal fluid (CSF) appears in the hub of the needle during placement or after gentle aspiration, the needle is removed completely and the procedure repeated. With repeated aspiration of blood or CSF, this approach to epidural space is abandoned. Dalens and Hasnaoui noted a 1% failure rate in children less than seven years compared to a 14.5% failure rate in older children [4]. After successful needle positioning, the syringe is attached and aspiration is done to confirm the needle has not dislodged into a vessel. The drug is then injected slowly, monitoring the pulse for any changes in rate or rhythm. During the injection, aspiration is done again to ensure that the needle has not dislodged into a vessel.

The type of needle used depends on the operator preference. The most commonly used is 21-23 French gauge intramuscular needle. The larger bore allows blood or CSF to be detected more readily. But Dalens and Mansoor support the use of a special 23-gauge short beveled needle to decrease the chance of vessel puncture [4]. Others prefer the use of 22-gauge in plastic cannula with removal of the stylette on perforation of the sacroccoygeal membrane and advancing only the blunter plastic cannula, lessening the risk of intravascular perforation. Toxicity has been reported using various accepted techniques [5, 6, 7].

Caudal block can be used for all surgical procedures below the umbilicus. Being a major neuroaxial procedure, it is ideal for major perineal and penoscrotal operations. In one series, operations for inguinal hernia, undescended testis, circumcision and hydrocoele formed 85% of the total

indications.[4] However, consideration should always be given to alternative local anaesthetic techniques (e.g. penile block for circumcision, ilioinguinal/iliohypogastric block or wound infiltration for inguinal hernia).

A successful caudal block provides excellent analgesia for inguinal herniorrhaphy but at the expense of a large dose of local anaesthetic (e.g. bupivacaine 2-2.5 mg/kg) pushed from a sacral to a low thoracic level (T_{10}). The nerve supply to the operative site (T_{12}, L_1) are the last blocked and the first to regress. Splinter, Bass and Komocar noted a similar analgesia comparing caudal and ilioinguinal-iliohypogastric block combined with subcutaneous injection into the wound. Both groups had a low incidence of inadequate block (4-10%) when assessed in the recovery period.[8]

Continuous caudal techniques using catheters are often used in small infants, as the technique is easier to perform in this age group than older children and adults; 19-gauge (needle) epidural kits are suitable for this technique without using loss of resistance to define the epidural space. Maintenance of sterility has always been an issue with the use of caudal catheters but Kost-Byerly and colleagues did not find an increased risk of infection comparing lumbar with caudal catheters in the short term (less than five days).[9]

CONTRAINDICATIONS OF CAUDAL ANAESTHESIA

Infection near the site of the needle insertion: Caudal epidural anesthesia should not be used if there is an active infection at the site of injection either at the skin surface or below. This includes active cellulitis, pilonidal/ perirectal abscess, and meningitis. Even in the absence of localized infection, the caudal region has a higher bacterial count than the lumbar epidural space. Insertion of the epidural needle through an area of skin infection may introduce pathogenic

bacteria into the epidural space, leading to serious complications such as meningitis or epidural abscess.

Coagulopathy or anti coagulation: Insertion of an epidural needle or catheter into the epidural space may cause traumatic bleeding into the epidural space. Clotting abnormalities may lead to the development of a large haematoma leading to spinal cord compression. Bleeding abnormalities are an absolute contraindication to caudal epidural anaesthesia. These abnormalities can be due to disorders of coagulation factor activity (such as Hemophilia, ITP, tumors, or DIC from sepsis) or from the administration of anticoagulants such as heparin or warfarin. If there are any questions about the coagulation status, the anesthetist should perform a bleeding time test and confirm that the bleeding time is normal. Bleeding time is a simple laboratory procedure that can be done at the bedside and gives results within five minutes. Another laboratory test to consider is INR. This is a more sophisticated test and may not be available at all hospitals.[3]

Congenital anatomic anomalies of the spinal cord or vertebral bodies: In cases of Spina Bifida, caudal epidural anaesthesia should not be attempted as the spinal cord may be tethered within the spinal canal. Scoliosis is not an absolute contraindication to caudal epidural anaesthesia though scoliosis may make caudal epidural anesthesia technically more difficult to achieve.[3]

Raised intracranial pressure: Accidental dural puncture in a patient with raised ICP may lead to brainstem herniation (coning).

Pre-existing neurological disorders, such as multiple sclerosis, may be a contraindication, because any new neurological symptoms may be ascribed to the epidural.

Fixed cardiac output states: These are probably relative rather than absolute. This includes aortic stenosis, hypertrophic obstructive cardiomyopathy (HOCM), mitral stenosis and complete heart block. Patients with these cardiovascular abnormalities are unable to increase their cardiac output in response to the peripheral vasodilatation caused by caudal blockade, and may develop profound circulatory collapse which is very difficult to treat.[3]

Patient or parent refusal

COMPLICATIONS OF CAUDAL ANAESTHESIA.

The commonest problems are failure of the block and pain on injection and each bears, or should bear a reciprocal relationship to experience and manipulative ability. Those who achieve high competence in hiatal identification are those most likely to perform injection with minimal trauma because each is a function of manual dexterity. Pain is best eluded by use of fine needles and by accurate identification of the hiatus in order to avoid multiple skin puncture. 22-gauge and 23-gauge needles are adequate for most patients. Use of subcutaneous infiltration to avoid pain during injection is usually unnecessary and tends to obscure landmarks.[10]

Infection is frequently listed among the complications of caudal blockade but it is rarely encountered in clinical practice. The background fear of infection dates from the early use of indwelling needles and catheters for prolonged blockade, and often to their misplacement. This complication is totally avoidable if needle insertion takes place within the boundaries of the sacrum, and maintenance of sterility.[10]

Intraosseus injection sometimes occurs especially when the wrong technique and force are used. A wafer-thin, brittle layer of cortex that is easily damaged covers the cancellous mass of sacral bone. This occurs especially when the needle is inserted in the direction of the anterior sacral wall. It results in failure of block and high serum levels of the drug. This complication is best avoided by needle insertion in the line of the sacral canal, which in its lower third follows the curve of the posterior sacral wall.

Intravenous injection occurs as a result of penetration of an epidural vein by the needle. This is easily detected as blood flows freely from the needle hub. In such a case the needle must be withdrawn and the procedure repeated. Repeated aspiration following each needle movement or each re-injection through indwelling catheters is a useful guard against intravenous injection. Before injecting the chosen dose of drug, it is preferable to inject a small test dose of the drug to eliminate the possibility of the needle or catheter being in a vein.[13] The amount of drug used as a test dose and the time allowed must be adequate to show the effects of incorrect placement. Thus in an adult, 4-5mls of drug injected into subarachnoid space and left for 5 min will give an easily detected spinal block whereas 2mls left for 2minutes might well not do so. If the needle or catheter is lying within a vein, even 5ml may be insufficient to cause systemic effects unless epinephrine (0.1 mg i.e. 0.1ml of 1:1000 solution) is added and the heart rate and arterial pressure are measured before and after injection. It is important that if a test dose is used, a negative result should not be taken as absolute proof of correct placement. Care must still be taken while injecting the main dose.[11]

Intrathecal injection with caudal blockade can occur if the needle insertion goes beyond the lower level of S_2 (marked by a line joining the dimples over posterior superior iliac spines). This can cause dural puncture, which will be

diagnosed by cerebrospinal fluid escaping from the needle. Dural puncture is technique dependent and its incidence has been quoted within a range of 0 - 1.2%.[11]

Misplaced injections occur most frequently into the subcutaneous tissue overlying the lower third of the sacrum. This is readily diagnosed by the appearance or feel of an injection tumour. Other common areas for misplaced injection are lateral to the coccyx and sacrococcygeal junction. Injection deep to the sacrococcygeal ligament is less common and results in a rapid increase in resistance to injection which serves as a warning. If the catheter has been incorrectly inserted and does not lie within the spinal canal, then no nerve block will result from the injection of the drug. This possibility must be entertained if there is no evidence of a nerve block within 15-20min.

Breakages of needles and catheters though rare have been reported. Usual precautions pertain in avoiding needle breakage; in particular needles should never be inserted to the level of the hub. Also catheters should never be pulled back through needles lest they shear off.

Hypotension results from widespread sympathetic blockade, which causes a reduction in peripheral resistance due to vasodilatation. Hypotension may also be contributed to by hypovolaemia or caval occlusion both of which require a degree of vasoconstriction to maintain a normal arterial pressure. Ephedrine, a vasopressor with both α and β – receptor activity, is useful in treating hypotension resulting from sympathetic blockade. It will increase the heart rate and the arterial pressure.[11]

Acute generalized toxic reactions can occur because epidural block often requires large amounts of local anaesthetic. If by accident an excessive amount

of local anesthetic is injected into the subarachnoid space, a high or total spinal anaesthetic will ensue. This will involve widespread paralysis with respiratory arrest, severe hypotension and if there is substantial cranial spread, unconsciousness. All these appear within a few minutes of the injection. Management of total spinal includes artificial ventilation and vasopressor support of the circulation.[11]

Neurological complication includes motor paralysis, which occurs within the operative area in which case muscle paralysis is usually beneficial. However, in epidural anaesthesia paralysis of the lower limbs may be a problem as some patients or patients parents are disturbed by it, especially if the block is prolonged, resulting in delayed ambulation.[4, 8, 11] Reassurance of the patient is essential and the use of lower concentration of drug will usually allow more active movement of the lower limbs. Urinary retention can occur as a result of parasympathetic motor block of the spinal segments s_2, s_3, and s_4 and sympathetic sensory nerve block to the bladder which enter spinal cord via $T_{11} - L_2$.[12] Patients will not be aware of their distending bladder and as such, they must be observed both in regard to urinary output and palpable bladder. Catheterization is often required although it carries the risk of urinary infection. Prophylactic antibiotics will prevent infection becoming established.[11]

LOCAL ANAESTHETIC AGENTS

Drugs available as local anaesthetic agents have a common molecular structure and a similar mode of action. All commonly used local anaesthetic agents have a three-part structure; aromatic ring, intermediate chain and an amino group. The intermediate chain contains either an ester or an amide linkage. As such they are conveniently divided into esters and amides.[11]

They differ to a greater or lesser extent in regard to potency, onset time or latency, duration of effect and toxicity. Examples of ester local anaesthetic agents include procaine, chloroprocaine, tetracaine, cocaine, benzocaine and amethocaine. The ester linkage is relatively unstable, and ester local anaesthetics are broken down by hydrolysis both in solution and, following injection, in the plasma by pseudocholinesterase. They are relatively non-toxic and their duration of effect is brief. Tetracaine is an exception in that it is long acting and quite toxic.[11]

Amide local anaesthetic agents include lidocaine, prilocaine, mepivacaine, etidocaine, bupivacaine, ropivacaine and dibucaine. The amide linkage is much more stable than an ester and the drugs in solution withstand heat sterilization and changes in pH. They are not broken down in plasma and they are metabolized by the liver. Little or no drug is excreted unchanged.[11]

Local anaesthetic agents, opioids, α_2 adrenoceptor agonists, ketamine, or a combination of any one of the latter three agents with local anaesthetic agents can be used to provide analgesia during and after operation.[13,14]
Spinal opioids are not recommended for day case surgery due to risk of delayed respiratory depression.[14]

BUPIVACAINE

Bupivacaine has been the most common agent used for caudal block. It is an amide local anaesthetic agent with a structure similar to lidocaine except that the entire amine-containing group is butyl piperidine.

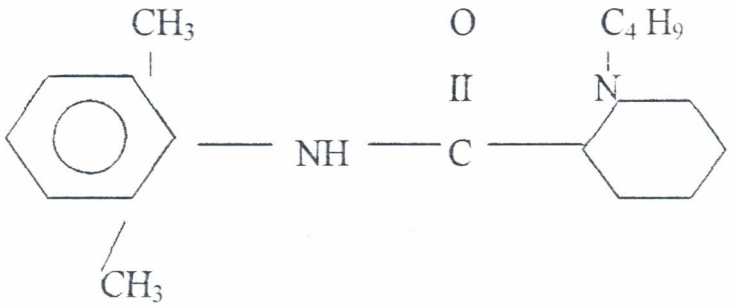

Figure 4. Structure of bupivacaine

It is a potent agent capable of producing prolonged anaesthesia. Its long duration of action plus its tendency to provide more sensory than motor block has made it a popular drug for providing prolonged analgesia intra-operatively and post-operatively. It is used for nerve blocks with exception of intravenous regional anaesthesia. It is particularly suitable for continuous epidural analgesia in labour and is also of value for single dose epidural injections for surgery and spinal anaesthesia.[15]

Bupivacaine is rapidly absorbed from the site of injection but the rate of absorption is dependent on the vascularity of the site and the presence or absence of a vasoconstrictor in the solution.[15] The onset time of bupivacaine is about 5-8 minutes, which is higher than most other local anaesthesic agents.[11] This is due to its relatively high pka value of 8.1 compared to for example lidocaine's 7.7 with an onset time of 2-4 minutes.[11] Pka of a compound determines how much is ionized and how much is unionized when injected into the body. The higher the pka, the less of the ionized base form is present at the body pH. As only unionized drug can penetrate nerve membranes, the pka will affect the speed of onset of the drugs.

Bupivacaine has a partition coefficient of 27.5 and protein binding of 95.6%. It is mainly bound to α_1 acid glycoprotein.[15] These physicochemical properties make it favorable with regard to its potency, duration of effect and toxicity. Its high protein binding determines the duration of effect, presumably because highly bound drugs stay in the lipoprotein of nerve membranes longer[11]. It has the longest duration of action, 3-6 hours. Lipid solubility is the main determinant of potency. Bupivacaine has a high lipid/ water partition coefficient, which makes it more potent than most other local anaesthetic agents. The degree of motor block increases with increase in concentration and at the highest concentration of 0.75%, it may outlast the sensory block.[15] It has a long elimination half life of 2-7 hours, accompanied by a low plasma clearance of 0.58 l/min. This tends to increase the systemic toxicity. Most of the drug is metabolized in the liver and only 4-10% appears unchanged in urine.[15]

Cardio-toxicity is its main toxicity profile. Inadvertent intravascular administration of large doses causes severe ventricular arrhythmias and myocardial depression. Bupivacaine rapidly blocks cardiac sodium channels during systole, and dissociates very slowly during diastole leaving a significant fraction of sodium channels blocked at the end of diastole. Block by bupivacaine is cumulative and substantially more than would be predicted by its local anaesthestic potency. A portion of the cardiac toxicity of bupivacaine may be mediated centrally as direct injection of small quantities of bupivacaine into the medulla can produce malignant ventricular arrhythmias. This cardiac toxicity is difficult to treat and its severity is enhanced in the presence of acidosis, hypercarbia and hypoxaemia, which become inevitable during resuscitation.[10]

In children, high concentrations of local anaesthetics are unnecessary and potentially toxic. Wolf and colleagues demonstrated that for caudal block for the most simple procedures (inguinal hernia, orchidopexy, hypospadias) in children aged 6 months-10years, 0.125% bupivacaine with epinephrine 1in 200 000 (5μg/1ml) provided adequate analgesia and minimal motor block.[16]

Addition of epinephrine, clonidine and opioids to bupivacaine has been found to increase the duration of intra and post-operative analgesia of epidural blocks by up to 25% in adults. In contrast, a much larger increase in duration of post-operative analgesia has been noted in children less than 5 years of age undergoing penoscrotal operations compared with plain solutions of bupivacaine.[17] This increase in duration was not supported by Fisher, Shaffner and Yaster, who concluded that the addition of epinephrine may be useful marker of intravascular injection and to reduce peak plasma concentrations of local anaesthetics, but does not significantly prolong analgesia.[18]

THE α_2 AGONISTS AND ANAESTHESIA

Alpha$_2$ – adrenergic mechanisms of analgesia have been exploited for more than 100 years. Cocaine, the first spinal anesthetic, produces analgesia primarily by its local anesthetic action but also inhibits re-uptake of nor-epinephrine. Spinal cocaine produces analgesia, in part, by enhancing noradrenergic stimulation of α_2 –adrenoreceptors.[19]

Near the turn of the century epinephrine was shown to produce spinal analgesia in animals, an effect now recognized to be secondary to α_2 - adrenoreceptor stimulation.[20,21] Nearly 60 years ago, spinal epinephrine alone

was shown to produce clinically useful analgesia although it is most commonly combined with local anaesthetics for this purpose.[22]

Veterinarians have used α_2 -adrenoreceptor agonists (α_2 -AAs) (Xylazine, detomidine and medetomidine) for many years for regional analgesia, but experience with these agents in humans dates back only slightly more than twenty years. In 1984, Tamsen and Gordh after testing for neurotoxicity in animals injected a parenteral preparation of α_2 - adrenoreceptor agonists, clonidine epidurally in two patients with chronic pain.[23,24] Since then a complete toxicological assessment in animals have suggested that clonidine is safe for intraspinal use.[25,26,27,28]

The α_2-adrenoreceptors mediate a wide range of physiologic and pharmacologic activities including sedation, analgesia and haemodynamic effects. Two adrenergic agonists, clonidine and dexmedetomidine, have been studied and approved for use as sedatives and/or analgesics. Clonidine, the first α_2-adrenoreceptor agonist is available in an intravenous formulation. An expanding body of literature describes the use of these α_2-AAs in the perioperative and critical care settings where they provide sedation and analgesia without respiratory depression.[24,31,32,33,34,35,36,37]

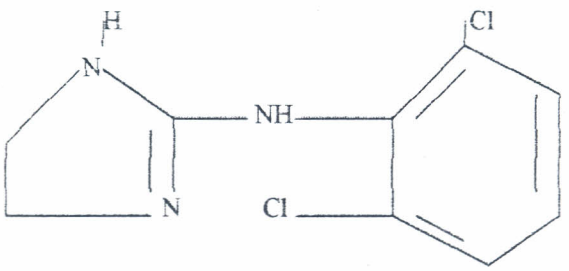

Figure5. Structure of Clonidine.

Clonidine was initially synthesized in the early 1960s. Preliminary studies yielded evidence of cardiovascular effects and the first indication for clonidine

was as an antihypertensive agent. It is currently indicated for treatment of hypertension (in both oral and transdermal formulations) and for cancer pain in combination with opioids (in an injectable epidural formulation).[29,30]

In addition to these indicated uses, α_2-adrenoreceptor agonists have been studied in other applications. These include their use as premedication for surgery, as an adjuvant to anesthesia during surgery, and in some patients with compromised airways as a main anesthetic agent, and in post-operative critical care setting, among other uses. The use of α_2-adrenoreceptor agonists in these applications is related to their analgesic and sedative effects.[24,32,33] The quality of sedation with α_2-adrenoreceptor agonists is unique among sedative agents in that patients administered dexmedetomidine, for instance, can be aroused despite significant sedation. Once the stimulus is removed, the patient returns to a sleeplike state. This state has been called "conscious sedation".[31,37,38]

In invitro studies, α_2 -adrenoceptors produce clinical effects after binding to α_2 adrenergic receptors, of which there are three subtypes (α_{2A}, α_{2B}, and α_{2C}). These receptor subtypes are distributed ubiquitously, and each may be uniquely responsible for some but not all, of the actions of the α_2 agonists.[39,40]

All the subtypes produce cellular action by signaling through a G-protein. G-proteins couple to effector mechanisms, which, appear to differ depending on the receptor subtype (and possibly the location of the receptor). For example, the α_{2A} adrenoreceptor subtype seems to couple in an inhibitory fashion to the L-type calcium channel in the locus ceruleus, whereas, in the vasculature the α_{2B} adrenoreceptor subtype couples in an excitatory manner to the same effector mechanism.[31]

However, the mechanisms by which α_2-adrenoreceptor agonists produce analgesia are not completely understood. Pain signals may be modified by α_2-adrenoreceptor activities at a number of sites in the central and peripheral nervous systems. α_2-adrenoceptors are located on the primary afferent terminals, on neurones within lamina 2 and 3 of the dorsal horn of the spinal cord, the area where substantia gelatinosa exists and in several brainstem nuclei, all of which are associated with analgesia.[41] Evidence from animal studies supports analgesic activity of α_2-adrenoreceptor agonists acting at all three sites; peripherally, in the spinal cord and in the brain.[31] However the exact influence of each remains unknown.

Analgesia via modulation of spinal α_2-adrenoceptors has been demonstrated with α_2-adrenoreceptor agonists in both animals and humans.[31] In one clinical study for example, a small dose of clonidine administered intrathecally after minor surgery produced durable analgesia, whereas analgesia induced by epidural or intramuscular administration of similar doses of clonidine was not different from that produced by placebo.[32,33] The α_2-adrenoreceptor agonists may modulate pain signals both directly and indirectly in the spinal cord. Descending noradrenergic pathways, such as those originating in the locus ceruleus are known to regulate nociception. The release of norepinephrine by descending noradrenergic fibers can affect the transmission of pain signals directly as well as through the stimulation of acetylcholine release. Studies in animal models suggest that analgesia attributable to α_2- adrenoreceptor agonists is at least in part mediated by cholinergic activation in the spinal cord.[42,43]

The α_2-adrenoreceptor agonists have also been known to stimulate α_2 adrenoreceptors directly within the spinal cord. Stimulation of adrenoreceptors in the substantia gelatinosa of the dorsal horn of the spinal cord results in the

inhibition of nociceptive neurons that are activated by peripheral A-Δ and A-c fibers, as well as inhibiting the release of substance P.[44]

Pharmacokinetic and pharmacodynamic analysis supports a spinal site of action of clonidine in humans. After epidural administration in volunteers and patients, clonidine is rapidly absorbed with peak concentrations in arterial blood within 10 minutes and in venous blood within 30-45 minutes. Elimination half-life of clonidine is between 9 and 12 hours with approximately 50 % metabolized in the liver, whereas the rest is excreted unchanged in the urine. Elimination from blood is slow compared with the relatively brief duration of analgesia after epidural clonidine administration. In contrast to blood, there is a strong correlation between clonidine concentration in CSF and analgesia after epidural clonidine administration. Clonidine is lipid soluble and is therefore rapidly and extensively absorbed into the spinal CSF compartment after epidural administration, with concentrations peaking 30-60 minutes after injection. This coincides closely with attainment of near-maximal analgesia. There is close correlation between lumbar CSF clonidine concentration and analgesia to noxious stimulus to the lower extremity, with a concentration of 130ng/ml producing 95% efficacy (EC_{95}) [31]

Other clinical effects of α_2-adrenoreceptor agonists are sedation and haemodynamic alterations. The mechanisms underlying these effects are understood to varying degrees. Sedation associated with α_2-adrenoreceptor agonists appears to be mediated in large part through activation of α_2 adrenoreceptors in the locus ceruleus nucleus of the brainstem.[45] This nucleus is associated with a number of physiologic processes, including the regulation of sleep and wakefulness. It is also the site of origin for the descending medullospinal noradrenergic pathway which is centrally involved in nociceptive neurotransmission.[45,46] The locus ceruleus also contains one of the

highest densities of α_2 adrenoreceptors anywhere in the body.[47] Evidence from several sources attributes the sedative effects of α_2-adrenoreceptor agonists to the inhibition of "activator" neurons in this nucleus.[48,49]

Haemodynamic effects of α_2-adrenoreceptor agonists result from peripheral and central mechanisms. α_2-adrenoreceptor agonists can produce either hypotension or hypertension. Vascular adrenoreceptors also contribute to the haemodynamic response to α_2-adrenoreceptor agonists. Vascular smooth muscles have α_{2B} adrenoreceptors, which mediate vasoconstriction. This has been shown to be responsible for the increase in blood pressure following an infusion of a bolus of dexmedetomidine, a recently discovered α_2-adrenoreceptor agonists.[50,51] A study by Talke et al showed that this drug induced dose dependent vasoconstriction and increases in blood pressure in anaesthetised patients in whom sympatholytic effects were eliminated by general anaesthesia.[52] Higher doses of α_2-adrenoreceptor agonists predominantly cause hypertension, mainly via activation of α_{2B} adrenoreceptors located on the smooth muscle cells in resistance vessels. Blood vessels especially larger vessels contain both postsynaptic α_1- and α_2-adrenoreceptors.[53] α_2-adrenoreceptor agonists may also react with α_1-adrenoreceptors, contributing to vascular response. This response may be especially prominent with clonidine, which has a lower specificity for α_2-adrenoreceptors compared to dexmedetomidine.[31,54]

Counteracting this vasoconstrictive activity are sympatholysis, i,e ability to block the sympathetic arm of autonomic nervous system, which is mediated by the α_{2A}-adrenergic receptor subtype.[40] This results in reduced norepinephrine release. At lower doses the predominant action of α_2-adrenoreceptor agonists is sympatholysis. In the central nervous system, activation of α_2-adrenoreceptors leads to reduction in sympathetic outflow and an increase in cardiac vagal

activity.[55] These central effects are mediated by α_{2A}-adrenoreceptors.[56] Activation of presynaptic α_2-adrenoreceptors on sympathetic terminals results in reduced norepinephrine release.[57] This reduction in norepinephrine release and stimulation of central α_2 adrenoreceptors is associated with reductions in blood pressure and heart rate to below baseline values.[45]

Although clinical trials have demonstrated that epidural clonidine has an analgesic effect and reduces the need for other analgesic agents in patients, epidural clonidine is not an anxiolytic.[31] It therefore has no significant sedative effects. α_2-adrenoreceptor agonists do not have any notable adverse effects on respiration.[31,34,35,36] Other agents commonly employed for epidural analgesia in combination with general anaesthesia for example, opioids, can cause respiratory depression complicating spontaneous respiration following extubation after reversal from anaesthesia. α_2-adrenoreceptor agonists also do not potentiate the effects of respiratory depression associated with opioids.[58,59] The relative lack of respiratory depression is an important advantage in anaesthesia.

Adverse effects most frequently associated with epidural clonidine include hypotension, postural hypotension, bradycardia, rebound hypertension, dry mouth, nausea, confusion, dizziness, somnolence and fever.[30] Hypotension is the adverse effect most commonly requiring treatment. Generally intravenous fluids and ephedrine are effective.[30]

AIMS AND OBJECTIVES

BROAD OBJECTIVE:

To compare intra-operative and postoperative analgesic efficacy of clonidine with bupivacaine for caudal blockade in paediatric surgical procedures.

SPECIFIC OBJECTIVES:

1. To compare the caudal block analgesic efficacy of clonidine with bupivacaine in providing intra and post-operative pain relief.

2. To assess the incidences of side effects with caudal block for both clonidine and bupivacaine.

3. To assess the analgesic efficacy and side effects when clonidine is combined with bupivacaine in lowered dosages.

STUDY JUSTIFICATION

The practice of regional anaesthetic techniques is of low level in this country. Caudal block technique is used widely in children in many other parts of the world and many advances have been made. The technique is simple, safe and does not require any complicated equipments. It offers excellent analgesia with minimal side effects when performed properly. The pharmacological agents available for use locally are limited. Many studies have been done comparing the various pharmacologic agents in other parts of the world but none has been done locally. Studies have demonstrated that clonidine is safe for use in caudal block and provides potent and prolonged analgesia. Sedation, haemodynamic changes and side effects resulting from systemic absorption are not deleterious as compared to the toxicity resulting from systemic absorption of the commonly used local anaesthetic agent, bupivacaine. This study was therefore to establish how the results compare with those carried out elsewhere and form a basis for recommendation for use of clonidine as a sole agent, or in combination with bupivacaine for caudal analgesia in paediatric surgery.

METHODOLOGY OF THE STUDY

Study Site

The study was carried out at Kenyatta National Hospital (KNH) in the paediatric surgical ward and the main theatre.

Study Population

The study population was the paediatric surgical patients aged between two months and thirteen years, scheduled for elective surgery. The operations were the procedures in the region of the umbilicus and below.

Study Design

This was a prospective randomized controlled study.

Sample Size:

The number of patients required for the study was calculated from the statistical formula:[60]

$$n = \frac{Z^2_{1-\alpha/2}\{P_1(1-P_1) + P_2(1-P_2)\}}{d^2}$$

(Source: Day SJ, Graham DF. Sample size and power for comparing two or more treatment groups in clinical trials. *Br Med J* 1989 sep 9-299(6700);663-5.)

Where;

Z = Standard error of the mean corresponding to 95% confidence level (one tailed)

$Z_{1-\alpha/2}$ = 1.645

P_1 = Percentage of success (bupivacaine group)

P_2 = Percentage of success (clonidine group)

d = Absolute precision

The number of patients therefore required, using 5% level of significance with 90% power for bupivacaine group and 90% power for clonidine group to within 10 points, a minimum sample of 20 patients per group is required; therefore a total of 60 patients were enlisted for the study.

PATIENT SELECTION.

Inclusion Criteria:

1. American Society of Anaesthesiology (ASA) Class I and II.
2. Inpatients with post-operative stay for duration of 24 hours or more.
3. Elective surgical cases (age 1month - 14 years).
4. Surgery from the region of the umbilicus and below.
5. Surgical procedures lasting less than four hours.
6. Signed informed consent to participate in the study.

Exclusion Criteria:

1. ASA Class III or greater.
2. Contraindications to caudal anaesthesia as outlined in the literature review. This was evaluated during the preanaesthetic assessment of the patients.
3. Emergency surgical procedures.
4. Day case surgeries (less than 24 hours post-operative hospital stay).
5. Allergies to the study drugs or previous reaction to the study drug as obtained from the allergic history and examination during the preanaesthetic assessment of the patients. Recruited patients with negative history of allergy who may end up reacting to the study drugs shall be appropriately managed for any allergic reactions but discontinued from the study.
6. Surgical procedures lasting more than four hours.
7. Declined consent to participate in the study.

ETHICAL CONSIDERATIONS

1. Procedures detailed in the study are safe and have been used elsewhere and pose no danger to the subjects.

2. The study was done after a written parental informed consent was obtained.

3. The consultant paediatric anaesthesiologist on duty in charge of the list performed the caudal block procedure. The investigator recruited the patients, performed a thorough preanaesthetic assessment, counseled the patients, obtained informed written consent and informed the consultant on duty.

4. Patients' confidentiality and information was maintained.

5. Approval for this study was obtained from the KNH Ethical and Research Committee (ERC) before the study was undertaken.

perioperatively and vagolysis especially in children in relation to their high vagal tone. Vital signs namely pulse rate, blood pressure, respiratory rate and temperature was taken and recorded in the ward, and rechecked at the receiving area of the main theatre. The patients were then taken into the operating theatre and placed to lie on the operating table. Monitoring equipment including ECG electrodes, automatic blood pressure cuff and temperature recording probe were attached to the patients and a record made.

All the patients were scheduled to receive general anaesthesia combined with caudal extradural block. A sensory block up to T_{10} was sufficient for the surgical procedure. Anaesthesia was induced by facemask with halothane 0.5-3% and 50% oxygen in nitrous oxide for smaller children, before an intravenous access was obtained. For older children, induction was facilitated by sodium thiopentone at a dose of 4-7mg/kg intravenously after preoxygenation for 3-5 minutes. In all patients, tracheal intubation was facilitated by intravenous suxamethonium at a dose of 1mg/kg. Anaesthesia was maintained with halothane 1-2%, and 50% oxygen in nitrous oxide. All the patients were on spontaneous respiration.

Caudal anaesthesia was performed in the left lateral position with a 21 or 22-gauge needle and one of the three different mixtures described above was randomly administered on a weight related basis into the caudal space.
The heart rate (HR) and mean arterial blood pressure (MAP) were recorded after induction but before caudal anaesthesia and then every 5 minutes after caudal anaesthesia. During surgery, adequate analgesia was monitored using haemodynamic stability. This was indicated by the absence of an increase in mean arterial pressure (MAP) or heart rate of more than 25% compared to baseline values obtained just before the surgical incision with halothane maintained at approximately 1-2%. A 15% increase in heart rate or mean

arterial pressure within 15 minutes of skin incision was considered failure of caudal anaesthesia.

If more than 45minutes after skin incision, heart rate or mean arterial pressure increased by more than 15%, analgesia was considered inadequate and the patient was to receive a rescue opioid during the operation. Fentanyl 1µg/kg or pethidine 1mg/kg was to be administered intravenously as the rescue opioid. The need for rescue opioid was considered as the 1st end point of the study and subsequent data obtained from these patients not considered.

Fluid therapy was standardized during surgery. The patients received half strength darrows solution according to the weight and the number of hours starved. The following times were recorded; time from caudal block to skin incision, time from caudal block to end of surgery and time from discontinuing the volatile anaesthetic to tracheal extubation.

At the end of surgery, halothane and nitrous oxide was discontinued and the patient ventilated with 100% oxygen. The pharynx was cleared of secretions/debris and the trachea extubated after return of protective reflexes. Extubated patients were given 100% oxygen by mask until it was safe to move them to the recovery ward where an observation of vital signs was made. Analgesia, sedation, haemodynamic state, and side effects were monitored in the recovery room and ward until six hours after surgery. In children who did not receive opioids during operation, analgesia was evaluated every 30 minutes by modified Children Hospital of Eastern Ontario Pain Scale (mCHEOPS)[61] (for children less than 5 years), or Visual Analogue Scale (VAS)[62] (for children older than 5 years). If mCHEOPS score was 6 or greater than 6 or VAS was greater than 40mm, a conventional analgesic was administered as per treatment chart ordered by the ward registrar who had been briefed on the study protocol. Times to administration of analgesic were

recorded. The time from caudal block to the first post-operative analgesia requirement was the endpoint. Global assessment of the duration of effective analgesia was performed by comparing the time from caudal block to administration of the first analgesic (either during surgery or after surgery).

For protocol and operative purpose, bradycardia and hypotension were defined as a 20% decrease in heart rate and mean arterial pressure compared with the initial values taken before administration of caudal blockade. This was treated if they were symptomatic with fluids initially and drugs if there was no response to fluid therapy. The drugs used were atropine 0.01mg/kg for bradycardia and ephedrine 0.5-5mg intravenously.

Sedation was assessed every 30 minutes using a three point sedation score; 0-Awake, 1-drowsy, or 2-Asleep. MAP and HR were recorded every 30 minutes. Oximetry was monitored continuously and oxygen desaturation was defined as spO_2, < 94%. Ambulation and urinary retention were assessed on arrival in the ward.

Patient data were analyzed using Kruskal-wallis one-way analysis of variance (ANOVA) and chi-square test. Time to the first supplementary analgesic, time to first micturition and time to first ambulation were compared using ANOVA followed by the Log rank test. Nominal data were analyzed using the chi-square test. Results were expressed as median. $P<0.05$ was considered significant.

RESULTS

The study groups were compared with respect to age, weight, ASA status, duration of surgical procedure, recovery time, side effects and duration of analgesia. The number of patients undergoing different types of operations is shown in table II.

Patient and clinical data:

A total of sixty patients were studied, twenty in each group (Table I). Age distribution for the three groups was in the range of 2 months to 13years with a median age of 2.5years in group B, 2.33years in group C and 1.79years in group BC. The median weight for group B was 11.5kg (range 4.7 – 2.5kg), 11.3kg (range 4.4 – 16kg) for group C and 10.35kg (range 4.4 – 16kg) for group BC. There was no statistically significant difference in the age and weight distribution (P=0.13).

ASA status of all the patients was I & II. The distribution is as shown on the table II. The median time for duration of surgery was 34 minutes (Range 17-137) for group B, 40 minutes (Range 12-110 minutes) for group C and 33.5 minutes (Range 16-47 minutes) for group BC. This was not statistically significant (P=0.06).

	Group B	Group C	Group BC
Number of subjects	20	20	20
Age (years)	2.5 (0.17-9.42)	2.33 (0.42-14)	1.79 (0.17-4.5)
Weight (kg)	11.5 (4.7-25)	11.3 (6.2-41)	10.35 (4.4-16)
ASA Status (No. (%))	ASA I 20(100)	ASA I 16(80) ASA II 4(20)	ASA I 19(95) ASA II 1(5)
Duration of surgery (mins)	34 (17-137)	40 (12-110)	33.5 (16-47)
Recovery time (mins)	5 (3-17)	7 (4-15)	5 (2-10)

Table I. Patient and clinical data (Median, (range)).

Type of operation	Number of Patients		
	Group B	Group C	Group BC
Hydrocoelectomy	3	2	2
Herniotomy	9	6	9
Orchidopexy/Release of chordee	4	3	4
Rectal Biopsy/Myotomy	1	4	1
Posterior Sagital Ano Rectal Plasty (PSARP)	0	2	0
Urethroplasty	2	1	2
Hypospadia repair	1	0	2
Vaginoplasty/Exision of labial mass	0	2	0
TOTAL	20	20	20

Table II. Number of patients undergoing different types of operations.

All children were sufficiently awake within 17 minutes of switching off anaesthetic gases and were taken to the recovery room on supplemental oxygen by mask at 5 liters per minute. The recovery time for all the three groups was comparable ranging from 3-17 minutes with a median time of 5

minutes for group B, 7 minutes for group C and 5 minutes for group BC. There was no significant difference in these recovery times (P=0.104).

Haemodynamic Changes: *(Table III)*

Times from caudal block to when the maximal decrease in MAP and HR for the various groups were noted and recorded in Table III below. Intraoperatively, the maximal decrease occurred long after the surgical procedure was over. This was because from the induction of anaesthesia to starting of surgery, it took time to prepare the patient for the caudal block and the surgical procedure. A minimum of 15 minutes was also allowed for the caudal block to take effect before the surgical incision was made. This prolonged the duration of anaesthesia.

Compared to the baseline values recorded before caudal blockade, the median maximal magnitude of decrease in MAP and HR for group B was 8mmHg (11.9%) and 22.5beats min^{-1} (15.57%) during the intra-op period. In the post-op period, the median maximal magnitude of decrease in MAP and HR for group B was 8.5mmhg (12.4%) and 8beats min^{-1} (6.4%) respectively.

The intra-operative median maximal decrease in MAP and HR was 9mmHg (13.85%) and 26beats min^{-1} (16.67%) for group C and 7.5 mmHg (11.63%) and 4.5beats min^{-1} (3.18%) for group BC. The changes were not significantly different in all the three groups and non required therapeutic interventions.

	Group B	Group C	Group BC
Heart Rate (beat min^{-1})			
Baseline HR (beat min^{-1})	144.5	156	141.5
Lowest HR recorded	122	130	137
Maximal decrease magnitude median, (%))	22.5 (15.57)	26 (16.67)	4.5 (3.18)
Time(mins) after caudal block	50	40	60
MAP mmHg			
Baseline MAP mmHg	67	65	64.5
Lowest recorded MAP	58	56	57
Maximal decrease magnitude (Median, (%))	8 (11.9)	9 (13.85)	7.5 (11.63)
Time(mins) after caudal block	60	35	40

Table III. Haemodynamic Data: Intra-operative HR beat min^{-1} and MAP mmHg (median).

Timings for increase in MAP and HR were not recorded as patients who showed an increase in MAP and HR of more than 15% of the baseline values recorded before caudal block administration were given rescue opioid and discontinued from the study. This was however not observed.

Postoperative MAP and HR monitoring was routinely done incase of any delayed absorption and sympathetic blockade, although this was not expected. None was reported.

The graphs in figures 6, 7, 8 and 9 show the intra-operative and post-operative trends in MAP and HR.

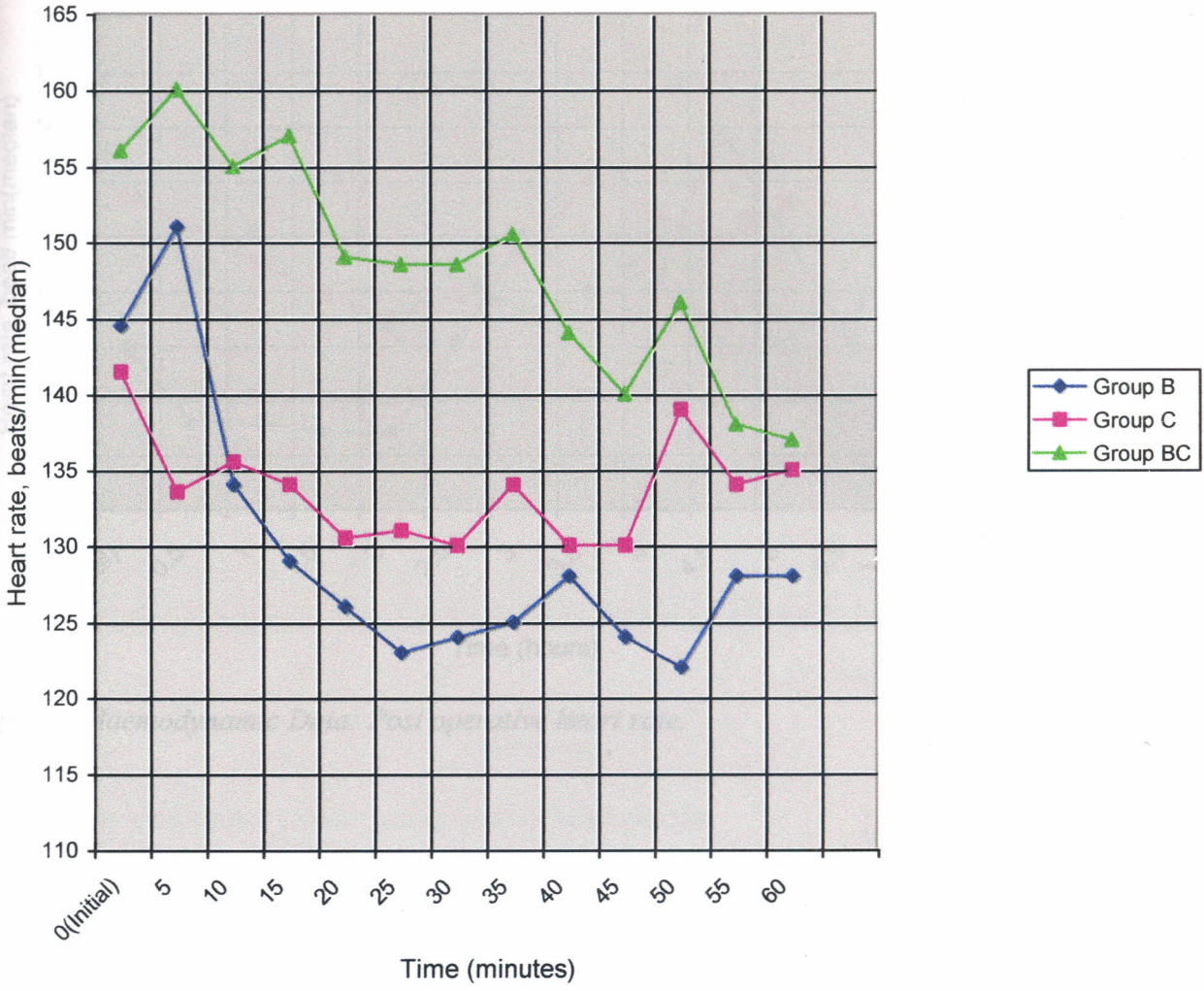

Figure 6. Haemodynamic Data: Intra-operative heart rate.

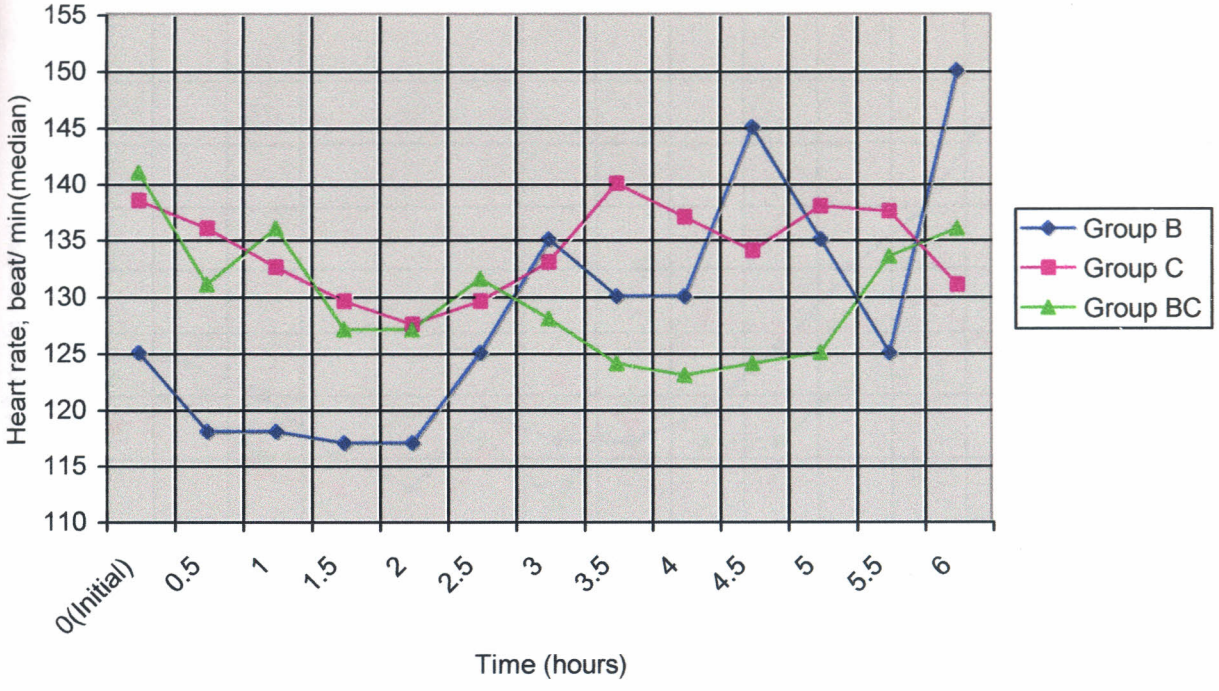

Figure 7. Haemodynamic Data: Post operative heart rate.

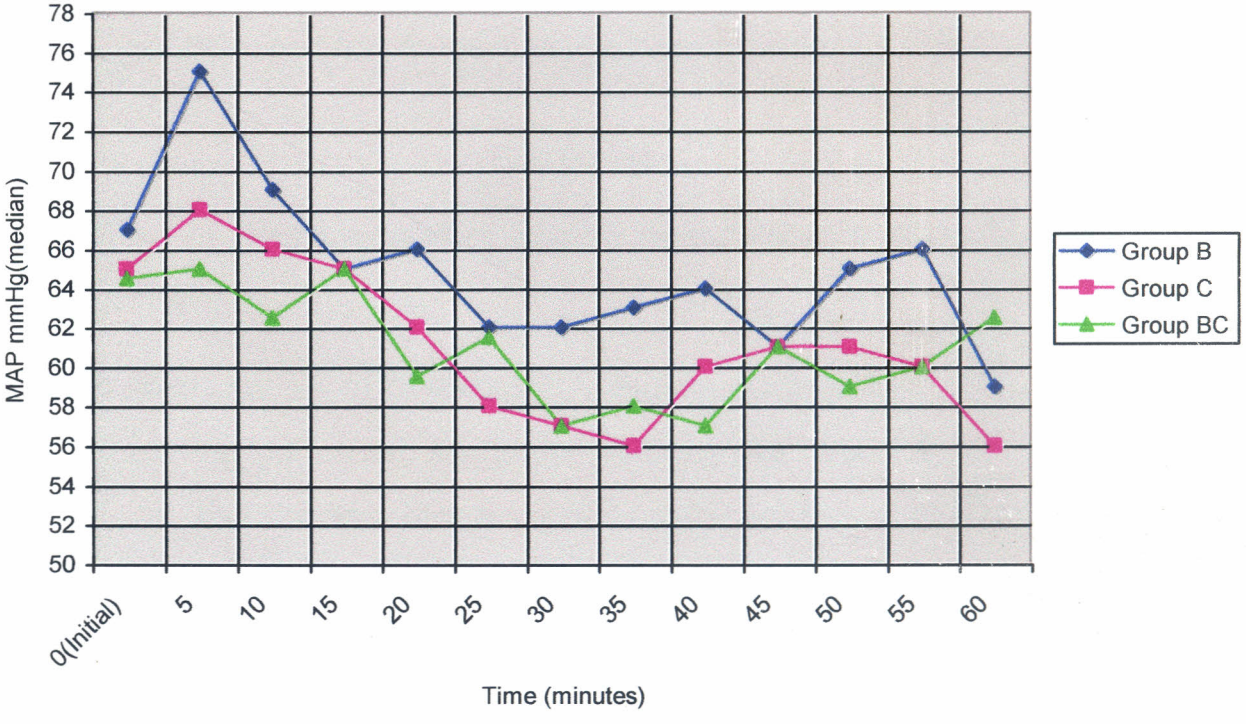

Figure 8. Haemodynamic Data: Intra operative MAP mmHg.

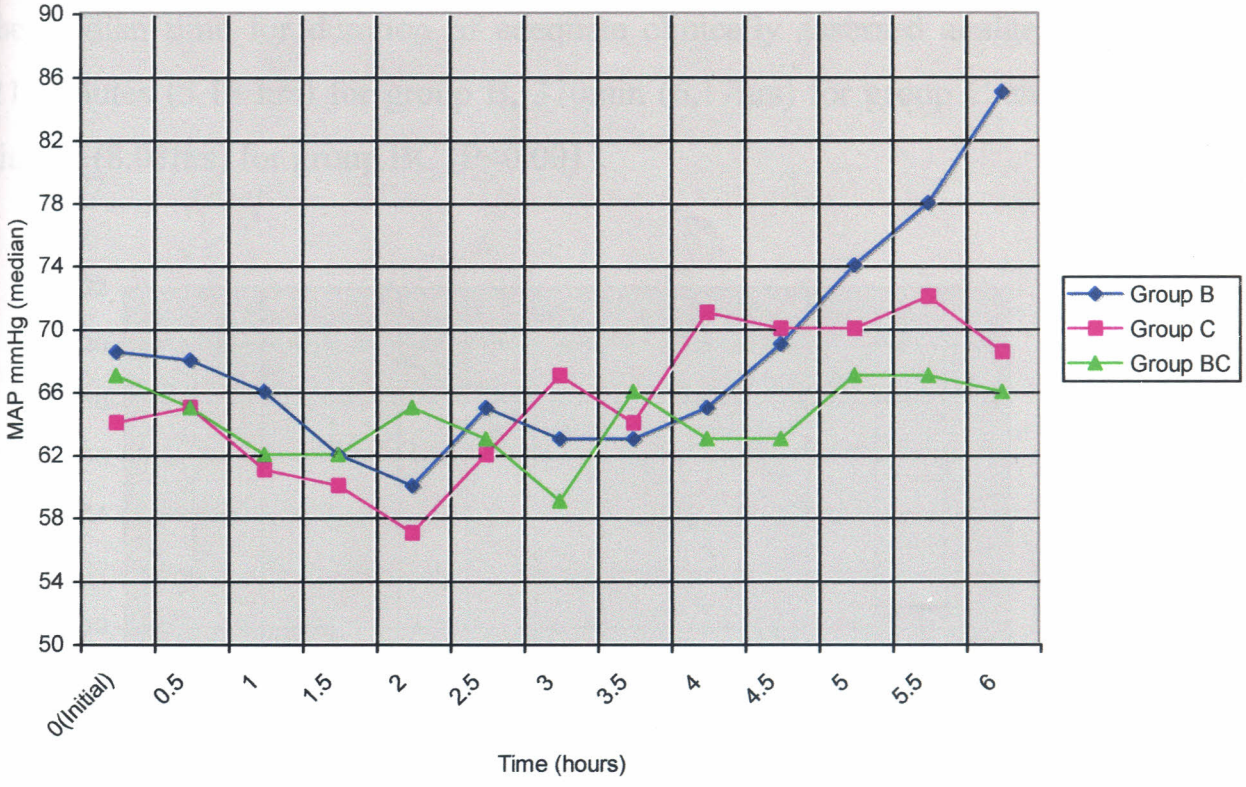

Figure 9. Haemodynamic Data: Post-operative MAP mmHg.

Analgesia:

The median time for duration of adequate clinically assessed analgesia was 311 minutes (5.18 hrs) for group B, 370min (6.17hrs) for group C and 482.5 minutes (8.03hrs) for group BC ($P<0.001$).

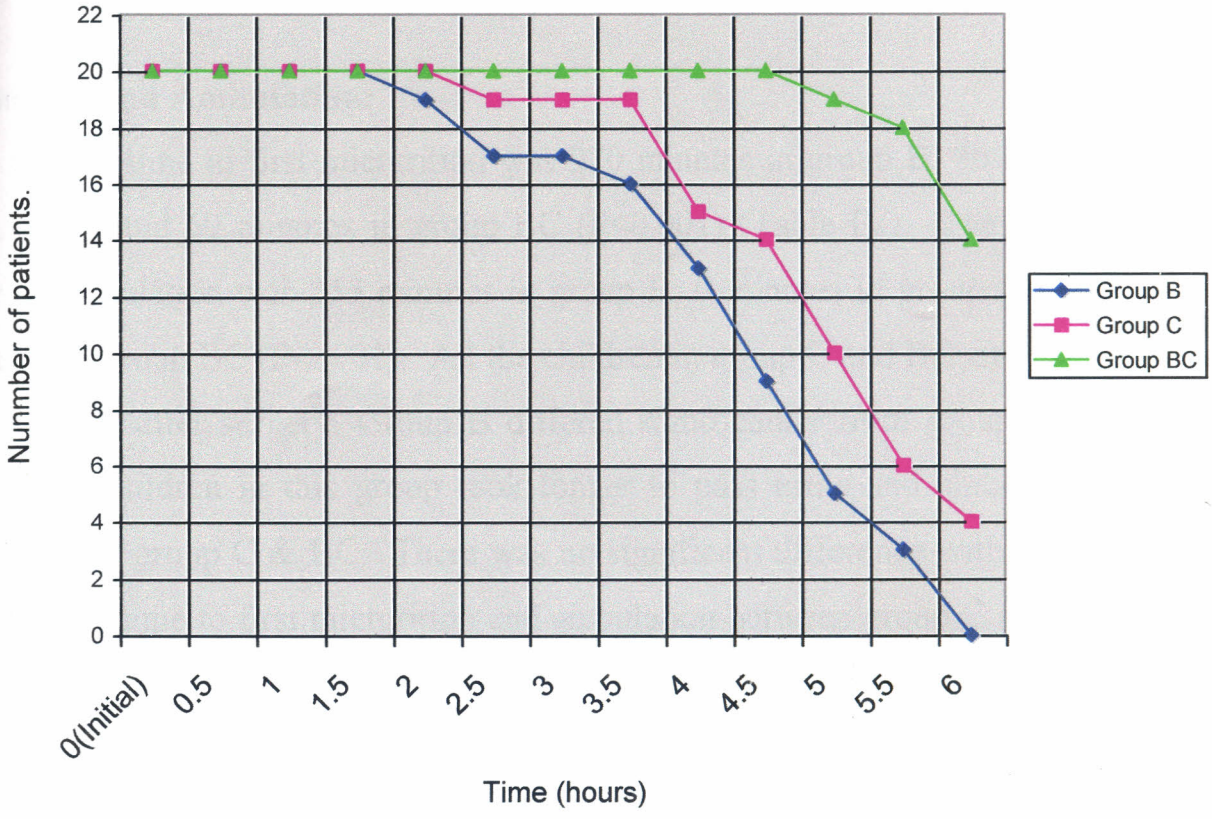

Figure 10. No. of patients maintaining adequate caudal analgesia without the need for additional analgesic.

Figure 10 shows the no. of patients who maintained adequate caudal analgesia without requiring additional analgesic. During the first 1.5 hrs after the operation, all the children had adequate caudal analgesia in all the three groups. Subsequently the number of patients with adequate analgesia in group B declined much more rapidly than those in group C and BC, and by the sixth hour post operatively all the patients in group B required an additional analgesic. A rapid decline in the number of patients maintaining adequate caudal analgesia was noted from 3.5hours postoperative in group C. By the

sixth hour only 20% of the patients in group C maintained adequate caudal analgesia, unlike 70% in group BC. Analgesia was not given to any child in group BC in the first 4 ½ hours after the operation. The difference in postoperative analgesia requirements between the three groups was statistically significant by between one and three hours (P<0.001).

Urination and Ambulation:

The median time to first micturition was 270 minutes in group B, 30 minutes in group C and 60 minutes in group BC (P<0.001) (Table IV). The median time to ambulation was 255 minutes in group B, 0 minutes in group C and 0 minutes in group BC (P< .001). All the children in group C and BC ambulated immediately after surgery. Group B differed significantly from group C and BC. The children in this group took longer to pass urine and ambulate as compared to group C & BC. There was no significant difference with respect to the onset time to first micturition and ambulation between group C and BC. However no child had urinary retention requiring catheterization in all the three groups.

Table IV. Time to first micturition and ambulation, (median (range))

Variable	Study Group			P-Value
	Group B (n=20) Median	Group C (n=20) Median	Group BC (n=20) Median	
Time to first micturition after caudal block.	270 (90-360)	30 (0-240)	60 (0-150)	< 0.001
Time to first ambulation after caudal block.	255 (120-360)	0 (0-60)	0 (0-60)	< 0.001

Sedation:

The incidence of sedation was noted to be higher in group BC and C as compared to group B. More patients were awake in group B as compared to both group C and BC (Table V). This was due to the sedative effect of clonidine.

None of the children had an spO_2 of less than 94% throughout the post operative period. The sedation scores and observed spO_2 recorded at the stated intervals after surgery are shown in table v.

Interval after surgery(hrs)	Group B			Group C			Group BC		
	Score			Score			Score		
	1	2	spO_2	1	2	spO_2	1	2	spO_2
0(Immediate post-op)	18(90)	0	98.5	12(60)	5 (25)	99	17 (85)	1 (5)	99
0.5	1 (5)	1 (5)	99	1 (5)	16 (80)	98	3 (15)	10 (50)	99
1.0	1 (5)	0	99	0	18 (90)	98	0	14 (70)	99
1.5	0	3 (15)	99	0	9 (45)	97	0	14 (70)	99
2.0	0	4 (20)	99	2 (10)	10 (50)	98	0	6 (30)	100
2.5	0	4(21.1)	99	0	15 (75)	98	2 (10)	3 (15)	99
3.0	0	3(17.6)	99	0	16 (84.2)	99	2 (10)	8 (40)	98
3.5	0	0	99	0	4 (21.1)	99	0	14 (70)	98
4.0	0	1 (6.3)	98.5	0	2 (10.5)	99	1 (5)	11 (55)	98
4.5	0	0	99	0	6 (40)	98	0	3 (15)	99
5.0	0	0	98	0	3 (21.4)	98	0	4 (20)	99
5.5	0	0	98	0	0	96	0	6 (31.6)	99
6.0	0	0	96	0	0	97	0	1 (5.3)	99

Table V. Post-operative sedation score (No. (%)) and spO_2 (median)

DISCUSSION

Most paediatric surgical procedures below the umbilicus cause much intra and post-operative pain, which may give rise to restlessness, agitation and crying. This may cause the child to manipulate the operation site and interfere with the outcome of surgery, sometimes causing more pain to the child and stress to the parent/guardian. Caudal blocks using bupivacaine has been seen to provide pain relief intra and post operatively. In this study, analgesic efficacy and incidences of side effects of clonidine was compared with bupivacaine.

A total of sixty patients aged 2 months to 13 years were studied. They were randomly allocated to three equal groups to receive caudal block of 0.25% bupivacaine 1ml kg^{-1}, clonidine 2μ kg^{-1}, and 0.125% bupivacaine 1 ml kg^{-1} combined with clonidine 1μ kg^{-1}. Their weights ranged from 10.35kg to 11.5kg. There was no statistical difference in their age and weight distribution. All the patients were of ASA I and II status and the type of operations included procedures below the umbilicus.

The median duration of surgery was 34 minutes for the group that received caudal bupivacaine, 40 minutes for the group that received caudal clonidine and 33.5 minutes for the group that received clonidine-bupivacaine combination. The recovery time for all the three groups ranged from 3 to 17 minutes with a median range 5, 7 and 5 minutes respectively. There was no statistically significant difference.

Haemodynamic changes monitored intraoperatively did not show any hypotension or bradycardia significant enough to require therapeutic intervention. There were no cases of inadequate or failure of caudal block observed. Postoperative haemodynamic monitoring was routinely done and no

cases of postoperative hypotension or bradycardia resulting from delayed absorption and sympathetic blockade were observed.

The median time for the duration of analgesia was 5.18 hours for the group that received caudal bupivacaine, 6.17 hours for the group that received caudal clonidine and 8.03 hours for the group that received clonidine-bupivacaine combination. This was statistically significant ($p<0.001$).

There was significant difference in the incidence of side effects between the three groups. The median time to first micturition and ambulation was significantly higher in the group that received caudal bupivacaine as compared to the groups that received caudal clonidine and clonidine-bupivacaine combination ($p<0.001$).

The incidence of sedation was higher in the clonidine and clonidine-bupivacaine group as compared to the bupivacaine group. This resulted partly from the sedative effect of clonidine and the prolonged analgesia provided by clonidine made the children more comfortable and were able to sleep. Although no oxygen desaturation was observed post operatively, central respiratory depression resulting from clonidine could not be adequately assessed as this was beyond the scope of this study. However, on the basis of spO_2 monitoring by pulse oximetry, there were no cases of hypoxia observed post operatively.

These findings showed that for caudal blockade addition of clonidine 1µg/kg to bupivacaine 0.125% 1ml/kg offered a significantly longer duration of post-operative analgesia compared with that provided by bupivacaine and clonidine alone, without an increase in the incidence of side effects. Postoperative analgesia provided by clonidine alone was also significantly higher than that

offered by plain bupivacaine. These findings compare to similar ones from previous studies[63,64] in which a mixture of 0.25% bupivacaine 1mg/kg and clonidine 2μ/kg produced a longer duration of caudal analgesia in children than bupivacaine alone (9.8 vs. 5.2 hrs respectively).

Neuroaxial administration of clonidine directly inhibits sympathetic preganglionic neurones in the spinal cord with resulting hypotension and bradycardia. The observed decrease in MAP & HR among the three groups was not significant. Results from previous haemodynamic studies derived from intra-operative[64] and early post-operative period [65] in adults suggest a MAP and HR decrease within 15-30 minutes after epidural injection. The degree of clonidine-induced hypotension is related to the spinal site of injection. Thoracic epidural administration of clonidine closer to the origin of sympathetic neurones causes a more pronounced MAP decrease than lumbar clonidine administration [66,67,68]. Thus a more distal caudal site of injection might favour a minimal moderate haemodynamic response to clonidine. This could explain the findings in this study also coupled with the fact that the low dose of clonidine used was not sufficient to induce marked sympatholysis. However haemodynamic effects of extradural clonidine are less pronounced in children than in adults and may depend on doses administered[64,73,74].

Neuroaxial blockade prolongs motor blockade of local anaesthetics [69] and can delay recovery of bladder function. All the patients in the group that received caudal clonidine and clonidine-bupivacaine combination could move their legs immediately after surgery. Ambulation was significantly delayed in patients who received bupivacaine, a local anaesthetic agent. Sympathetic outflow to the urinary tract promotes an increase in urethral resistance and depresses detrussor contraction favouring urinary retention. Bladder function was significantly delayed in patients who received caudal bupivacaine whereas

those who received caudal clonidine and clonidine-bupivacaine combination did not have a significant delay. The low dose of bupivacaine in the mixture was not sufficient to cause prolonged motor blockade and delay bladder function. Spinal administration of clonidine results in less difficulties in micturition. A study by M Gentili et al[70] showed that low dose caudal clonidine, through supraspinal and spinal (on preganglionic sympathetic neurons) routes facilitates micturition. Peripheral α_2 adrenergic receptors are documented in the bladder wall especially at the level of the trigone. Stimulation of these receptors peripherally induces contraction of the smooth muscle fibres of the internal sphincter tone and therefore increases urethral resistances impairing voiding. Gentili M, et al, in their study showed that a low dose of clonidine has no peripheral effects and that acting via supraspinal and spinal routes, it stimulates bladder motility by depressing sympathetic outflow to the bladder, hence facilitating micturition.

Dose dependent sedation usually accompanies the use of clonidine for regional anaesthesia and likely reflects systemic absorption and vascular redistribution to higher centers [31,71]. Sedative effects have been reported after extradural clonidine in adults [72] and to a lesser extent in children [64,65]. In this study extubation times did not differ in all the three groups. Postoperative respiratory depression could not be adequately assessed as this was beyond the scope of this study. There were higher incidences of postoperative sedation in children who received caudal clonidine and clonidine-bupivacaine combination as compared to those who received caudal bupivacaine. It was noticed that most of the patients were asleep but easily aroused provided they were comfortable, and they became restless or awake only when they were in pain and required analgesia. The greater analgesic effect of clonidine alone or in combination with bupivacaine might be mistaken for sedation and vice versa. No

observation on oxygen desaturation was made as an effect of sedation as all children maintained spO_2 above 94% breathing room air.

Hence it cannot be concluded reliably that the higher incidence of sedation was caused entirely by the sedative effect of clonidine. However, because sedation made the children look more comfortable it was actually appreciated by the parents and ward staff and may not be regarded as an adverse side effect given that it had no effect on oxygen saturation.

CONCLUSIONS AND RECOMMENDATIONS.

- This study has demonstrated that for caudal blockade clonidine is more potent than plain bupivacaine in providing intra-operative and post-operative analgesia without an increase in the incidence of side effects. Clonidine can therefore be reliably used as a sole agent in caudal block procedures below the umbilicus in paediatric surgery.

- Caudal block procedure is cheap and easy to perform in children and offers excellent analgesia. It should be popularized as an alternative to general anaesthesia where caudal block is indicated in paediatric surgery.

- Addition of clonidine to bupivacaine prolongs the duration of analgesia without affecting ambulation and urination as side effects. This is due to the use of lowered dosages, which are not enough to cause side effects but offer excellent analgesia.

- Use of clonidine alone or as an additive to bupivacaine is much cheaper and safer than bupivacaine alone.

- Lack of deleterious haemodynamic and respiratory side effects resulting from systemic absorption in the use of clonidine alone or in combination with bupivacaine combined with excellent analgesia it offers outweighs the use of bupivacaine alone.

APPENDIX 1.

PATIENT DATA RECORD SHEET

Date.....

Name of patient (initials) .....

IP number..... Ward.....

Age of patient ------Yrs -----Months

Sex..... Male / Female

Diagnosis .....

ASA Status .....

Weight .....Kilograms

Operation .....

Premedication IM Atropine .....mg

PREOPERATIVE VITAL SIGNS:

HR ...../min RR...../min BP.....mmHg SaO_2.....% Temp..... °C

INDUCTION:

Inhalational / Intravenous Time.....

HR ...../min BP.....mmHg SaO_2.....% Temp..... °C

Caudal block - time given.....

Group: B/C/BC

INTRAOPERATIVE MONITORING (see table below)

Surgery starting time (skin incision).....

Surgery ending time.....

Duration of operation.....mins

Rescue Opioid(fentanyl/pethidine).....µg/mg Time given.....

Reversal time (time volatile anaesthetics discontinued) .....

Time trachea extubated.....

INTRAOPERATIVE MONITORING

TIME	HR /min	MAP mmHg	SPO_2 %	TEMP ^0C

POST-OPERATIVE MONITORING:

	PAIN SCORE-VAS / mCHEOPS	SEDATION	URINATION	AMBULATION	MAP mmHg	HR	SPO_2	OTHER (SPECIFY)
IMMEDIATELY *POST-OP* Time.....								
½ hr post-op								
1 hr post-op								
1½ hrs post-op								
2 hrs post-op								
2½ hrs post-op								
3 hrs post-op								
3½ hrs post-op								
4 hrs post-op								
4½ hrs post-op								
5 hrs post-op								
5½ hrs post-op								
6 hrs post-op								

Time first analgesic required.....

APPENDIX 2

Modified CHILDREN HOSPITAL OF EASTERN ONTARIO PAIN SCALE (mCHEOPS).

SCORE	0	1	2
CRY	NO CRY	CRYING	SCREAM
FACIAL	SMILING	COMPOSED	GRIMACE
VERBAL	POSITIVE	NONE OR OTHER COMPLAINT	PAIN COMPLAINT
TORSO	NEUTRAL	SHIFTING, TENSE, UPRIGHT	RESTRAINED
LEGS	NEUTRAL	KICK, SQUIRM, DRAWN UP	RESTRAINED

(Source: McGrath PJ, Johnson G, Goodman JT, Schillinger J, Dunn J, Chapman J. CHEOPS: A behavioral scale for rating postoperative pain in children. In: Fields HL, Dubner R, Cervero F, eds. *Advances in Pain Research and Therapy: Proseedings of the 4th World Congress of Pain, vol* 9. New York: Ravens Press, 1985; 395-402.)

Maximum Total score 10. A Score of 6 and above requires an additional analgesic.

PAIN VISUAL ANALOGUE SCALE:

(Source: Myles PS, Troedel S, Boquest M, Reeves M: The Pain Visual Analogue Scale: Is It Linear or Nonlinear? REGIONAL ANAESTHESIA AND PAIN MANAGEMENT: *Anesth Anal* 1999; 89: 1517)

0 1 2 3 4 5 6 7 8 9 10cm

No Pain | Mild pain | Moderate pain | Severe pain | Very severe Pain | Worst possible pain

A score of 4cm and above requires an additional analgesic.

APPENDIX 3a.

AMERICAN SOCIETY OF ANAESTHESIOLOGISTS SCORE (ASA-SCORE).

The score is used to estimate the anaesthesia risk.

ASA	Class	Physical Status
I.	Normal healthy patient.	
II.	Patient with mild systemic disease.	
III.	Patient with systemic disease severe enough to limit activity but not incapacitating.	
IV.	Patient with severe systemic disease that is a constant threat to life.	
V.	Moribund patient not expected to survive 24 hours with or without surgery.	
EMERGENCY	Emergency operation appends symbol E	

(SOURCE: Richard W. Ashburton UK. ASA AND CEPOD SCORING: *Update in An aesthesia*. Issue 14(2002), Article 5)

APPENDIX 3b.

THREE POINT SEDATION SCORE.(SOURCE: Constant I. Gall O.Chauvin M et al: Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of analgesia. Br. J. Anaesth 1998; 80: 294-298.)

0 – AWAKE
1 – DROWSY
2 –ASLEEP .

APPENDIX 4

CONSENT INFORMATION

This consists of information given to parent of the patient prior to their signing the consent form, and briefly outlines relevant details of the study, expectations of the study in relation to the patient, and obligations of the patients and of the investigator.

The Study

This study examines the caudal analgesic efficacy of clonidine compared with bupivacaine in paediadric patients undergoing surgical procedures under caudal anaesthesia.

Confidentiality

The medical records relating to the case are the property of Kenyatta National Hospital and the information they contain is protected to ensure patients confidentiality. Confidentiality will be assured by referring to the patients in terms of inpatient number and initials. The patient's name will not be used during data processing. The patient data record sheet will be in safekeeping with the investigator after it has been completed by either the investigator or research assistant. The patient data record sheet will be used as reference by the investigator during the process of data compilation and processing. The information may be published but the patient's name will not be known. The records may be accessed by the University of Nairobi for quality assurance.

Participation in the Study

The decision to participate in the study will be voluntary and not obtained by coercion. No guarantee is given to the patients and/or guardians that consent to participate in the study ensure a favorable outcome of the surgery. Refusal to

participate in the study will not affect the availability and outcome of the medical treatment.

Procedures

The study does not involve additional procedures apart from those normally employed during paediatric surgery under caudal block. It will not involve drawing of blood. The risks of bleeding, infection, and pain are related to the caudal block procedure and the surgery itself, and not to the study process.

Liability

No complications from the study are envisaged apart from those related to the caudal block procedure. As such, no compensation is expected by the patient and/or guardians in the event of complications related to the caudal block procedure or the surgical procedure.

APPENDIX 5

CONSENT FORM

Name: Patient _____ **Age** _____

Parent/Guardian: _____ **Age** _____

I do hereby consent to the release of medical records information of my child named above for research involving a study on Caudal Analgesic efficacy of Clonidine Compared with Bupivacaine for paediatric surgical procedures, as explained to me by Dr Kennedy O. Momanyi, having fully understood what the study will entail, as outlined in the foregoing consent information. I have all the information I desire, and my questions have been answered satisfactorily.

I have been assured that information concerning my child will be kept safely and treated with a high degree of confidentiality by the investigators. My signature below acknowledges that I have understood and agreed to the foregoing.

Signed (Patient/Guardian): _____

Witness: Name _____

Signed _____

Date: _____

I _____ have adequately informed the patient and/or guardian _____ of the risks and benefits related to this study.

Signed (Physician): _____

Witness: Name: _____

Signed: _____

Date: _____

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Ref: KNH-ERC/01/2952 **Date: 25th August 2005**

Dr. Kennedy 0. Momanyi
Dept. of Surgery
Faculty of Medicine
University of Nairobi

Dear Dr. Momanyi

RESEARCH PROPOSAL: "A PROSPECTIVE RANDOMISED CONTROLLED STUDY COMPARING INTRA-OPERATIVE AND POST-OPERATIVE ANALGESIC EFFICACY OF CLONIDINE WITH BUPIVACAINE FOR CAUDAL BLOCK IN PAEDIATRIC SURGICAL PROCEDURES AT K.N.H" (P53/4/2005)

This is to inform you that Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** revised version of your above cited research proposal for the period 25th August 2005 to 24th August 2006. You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely,

Prof. A. N. GUANTAI
SECRETARY -KNH-ERC

c.c: Prof. K. M Bhatt, Chairperson, and KNH-ERC
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