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A comparative study of caudal block with bupivacaine or preservative free ketamine for herniorrhaphy in children

Stanley Ikenna Ilo[1], Marcellinus Anosike Erondu[1], Longinus Ndubuisi Ebirim[2*]
[1] Department of Anaesthesia, Federal Medical Centre, Umuahia, Abia State, Nigeria
[2] Department of Anaesthesiology, University of Port Harcourt Teaching Hospital, Port Harcourt, Rivers State, Nigeria

Abstract
Background: Use of Local anaesthetics for caudal block in children may be associated with limited duration of action, systemic toxicity and motor block. This may be mitigated with use of a low dose of S-ketamine which has good analgesic effect in the caudal route.
Objective: To compare the analgesic efficacy of bupivacaine and preservative free S (+)- ketamine when used for caudal block in children.
Methods: Seventy, six children aged 2-7 years of ASA class I or II scheduled for inguinal herniorrhaphy were recruited into this prospective double blinded study. They were randomly allocated into two groups B and K of thirty, eight each. Children in Group B received caudal Bupivacaine 0.25% (1ml/kg) while those in Group K received caudal S –Ketamine 1mg/kg.
The outcomes assessed included duration of analgesia, mean pain scores, mean time to ambulation in the post-operative period and incidence of side effects such as sedation, shivering and vomiting.
Results: The mean duration of analgesia was significantly prolonged in the ketamine group compared to the bupivacaine group (p=0.0000). Mean post-operative pain score was comparable between bupivacaine and ketamine groups. Average Sedation score was not significantly different between the two groups. The mean time to first ambulation without support was significantly shorter in the ketamine group than in the bupivacaine group (p=0.001).
Conclusion: Caudal S (+) ketamine (1mg/kg) is superior to (0.25%) bupivacaine 1ml/kg in the duration of analgesia for herniorrhaphy in children.

Keywords: caudal block, S-ketamine, bupivacaine, children, analgesia

Introduction

Caudal block is a technique in which a local anaesthetic agent is injected into the epidural space through the sacral hiatus to provide regional block of sacral and lower lumbar nerve roots for anaesthesia and analgesia in various clinical settings. Regional block (spinal, epidural, and peripheral nerve block) can be used as adjuvant to general anaesthesia [1]. Caudal block was first described in 1933 and has become one of the most accepted regional anaesthetic techniques [2].

Pain is the most frequent complication following paediatric surgery [3]. Caudal analgesia is used worldwide to provide safe and effective perioperative analgesia for paediatric patients undergoing urological, lower abdominal and lower limb surgeries [4, 5] It has a low incidence of major adverse events[6]. However, adverse effects particularly related to systemic toxicity of the local anaesthetic agent may be observed. Agents to be used for caudal block must be effective, long lasting and safe [6]. The most commonly used local anaesthetic agent is bupivacaine, because it is readily available, has long duration of action and its effects are very well known [7] The main disadvantages of caudal anaesthesia with local anaesthetic agents are the limited duration of postoperative analgesia, motor block, and the potential for systemic drug toxicity [8]. A number of adjuvants (opioids and non-opioids) such as clonidine, fentanyl, ketamine, midazolam, and neostigmine reduce the incidence of side effects [9]. Clonidine and ketamine have been demonstrated to increase significantly the duration of caudal block, ketamine can however be used as a sole agent [4]. When administered via the caudal route, ketamine produces its effects by blocking N-Methyl D-aspartate (NMDA) receptors in the spinal cord; it has pharmacologic similarities with common local anaesthetics [2]. Ketamine occurs as a mixture of two enantiomers the-R, the-S and both provide excellent analgesia as caudal agents. The R-ketamine is not recommended for epidural and spinal route because of neurotoxicity of the preservative agent that is contained in all commercially available ketamine preparations [10]. The S-ketamine, one of the enantiomers of ketamine does not have preservative and is used for caudal administration.

The goal of post-operative pain relief is to reduce or eliminate pain with minimum side-effects. Effective pain relief will help to achieve a smooth postoperative period and an early discharge of patients from hospital [11].

This study therefore, compared the effectiveness of 0.25% bupivacaine (1ml/kg) and ketamine (1mg/kg), administered by the caudal route in achieving quality intra and post-operative analgesia in paediatric patients.

Patients and Methods

This randomized, double-blinded, prospective study was carried out at the Federal Medical Centre (FMC) Umuahia from September 2017 to November 2018.The patients were admitted a day before surgery for proper review and were monitored at least 24 hours postoperatively. The study population was drawn from patients aged between 2 and 7 years of American Society of Anesthesiologists (ASA) physical status I or II, scheduled for inguinal herniorrhaphy under caudal anaesthesia.

Excluded from the study were patients whose parents/guardians refused to give consent, those who had any contraindication to the use of bupivacaine or ketamine.

Sample size calculation[12] showed that a minimum of 68 participants were required for the study. Allowing for 10% loss to protocol violation (attrition), a total of 76 patients, approximately 38 per group were entered for the study. Patients in group B received caudal bupivacaine 0.25% (1ml/kg). Those in group K received caudal ketamine 1mg/kg (1ml/kg).

Ethical clearance was obtained from the institutional Health Research Ethics committee and eligible patients were identified during the preoperative evaluation. The study was explained to the parents or guardians in a language they understood. Written consent was obtained from them. The patients were clinically assessed and fitness for the study verified.

Fasting guidelines (six hours for solid food, 4 hours for formula feed, and 2 hours for clear fluid) was communicated to the parent or guardian and ward nurse. The ward and post- anaesthesia care unit (PACU) nurses were educated on the modified objective pain scale (OPS) to be used after the surgery. The selected patients were randomized into two groups, B and K, 38 per group. Anaesthesia for the selected patients was conducted by the lead researcher.

Patient Randomization

Seventy, six equal-sized square pieces of paper were cut. Thirty, eight of them were labeled B and the remaining Thirty, eight labeled K. Each of these labeled pieces of paper was placed in a sealed opaque envelope. The seventy, six opaque envelopes were placed inside a bag and thoroughly mixed up. For each of the patients the theatre pharmacist blindly picked one of the opaque envelopes, the content of which guided him on which solution that was prepared. Patients and their parents/guardians were also blinded to randomization as well.

Preparation of Study Drugs and Premedication

The study solution was prepared outside the induction room by the theatre pharmacist. The syringes containing the study drugs were serially labeled by the theatre pharmacist. The theatre pharmacist alone knew the group to which each patient was assigned for the duration of the study. All the patients were premedicated with IV midazolam 0.05mg/kg after securing intravenous access 5 minutes before induction.

Anaesthesia

Monitors were attached to obtain baseline vital signs. The monitors included precordial stethoscope, pulse oximeter, non-invasive blood pressure cuff, electrocardiography (ECG), and a temperature probe (nasopharyngeal) inserted after induction of Anaesthesia, using a multi-parameter monitor Mindray DPM4(PM-8000)

All patients were preoxygenated with 100% oxygen and induction was with intravenous propofol 2.5mg/kg mixed with plain 1% lidocaine 0.25mg/kg. Laryngeal mask airway (LMA) of appropriate size was inserted. After correct placement was confirmed, the patient was placed in the left lateral position and caudal block was administered.

Insitution of Caudal Block

Caudal blocks were carried out under strict asepsis by the lead researcher. Skin preparations were done using chlorhexidine and 70% methylated spirit; sterile drape was placed over sacral hiatus. Surgical hand washing, gloving and gowning were done by the Anaesthetist before performing the block. The landmark includes the sacral hiatus and the posterior superior iliac spines which form an equilateral triangle that points inferiorly. The sacral hiatus was located by first palpating the coccyx, then sliding the palpating finger cephalad until a depression in the skin was felt. The site was infiltrated with 1-2 ml of 1% lidocaine and a 23 gauge hypodermic needle was directed at about 45° to the skin. The needle was inserted till a "click" was felt signifying the piercing of the sacro-coccygeal ligament. The needle then was carefully directed in a cephalad direction to about an angle of 30 ° with the skin approaching the long axis of the spinal canal. The needle advanced about 2-3mm to ensure the entire bevel was within the sacral canal. Aspiration was done to rule out dural puncture or intravascular placement. Following a negative aspiration, with a hand positioned over the sacrum to detect any tissue swelling resulting from malposition of the needle either subperiosteally or along the dorsal surface of the sacrum, the definitive dose (of the already prepared caudal solution) was administered over 60- 90 seconds. The needle was withdrawn following injection and an occlusive dressing applied. Adequacy of the blockade was determined by monitoring the haemodynamic parameters (pulse rate, blood pressure) once surgery was continued. Increase of

15 % [10], from the baseline of heart rate and mean arterial pressure was assumed to signify inadequate block. Such a patient was to be excluded from the study and intramuscular pentazocine 0.5mg/kg administered for analgesia to continue the surgery. Surgery commenced 15 minutes after the caudal block, no additional analgesic was administered to the patients, and hypnosis was maintained with a hypnotic dose of propofol 3.5mg/kg/hour through an infusion pump. Oxygen was delivered with a Mapleson F (Jackson Rees Modification of Arye's T-piece) or Bain circuit (coaxial of Mapleson D) according to patient's weight. Fluid maintenance was with intravenous 4.3% dextrose in 0.18% saline 10ml/kg/hr.[10]The on-going losses were added to the hourly fluid maintenance.

Intraoperative Management

The patients were routinely monitored with a precordial stethoscope, pulse oximeter, non-invasive blood pressure cuff, electrocardiography (ECG), and a temperature probe, using a multi-parameter monitor (Mindray DPM4(PM-8000). Vital signs (S_pO_2, heart rate, blood pressure) were recorded at 5 minutes interval. If the heart rate or blood pressure became lower than 30% of the baseline, atropine 0.01mg/kg or ephedrine 0.2mg/kg respectively was to be administered. At the end of the surgery, administration of propofol was discontinued and the LMA removed when the patient was awake; each patient was then transferred to the post-anaesthesia care unit (PACU) where monitoring was continued.

In the postoperative observation period, all assessments and recordings of parameters were made by staff nurses, previously instructed, who were blinded to randomization of the patients. Leaflets containing OPS were placed in both the PACU and the paediatric surgery ward. This was intended to aid the quality of pain score assessment both in the ward and PACU.

In the PACU, vital signs (heart rate, blood pressure, respiratory rate) were recorded and postoperative pain was assessed using OPS and at 30- minute intervals for the first 2 hours. Intramuscular pentazocine (0.5mg/kg) was administered by the ward/ recovery room nurse when OPS became > 4 (OPS 0 - 10). Presence of side effects like nausea and vomiting, urinary retention and shivering were noted. Patients were discharged from the PACU to the ward by a senior anaesthetist.

Postoperative Pain Assessement and Management

Monitoring of vital signs and pain assessments were continued in the paediatric surgery ward. Pain was assessed hourly for 4 hours, 2 hourly for 8 hours and then every 4 hours until 24 hours after caudal block using the OPS. Intramuscular pentazocine 0.5mg/kg was administered by the ward nurse if the OPS > 4. Duration of analgesia was taken as the time from caudal block to administration of 1st dose of supplementary analgesia. Residual motor block in the lower extremity was assessed using a modified Bromage scale (0 =no residual motor block, 1 =inability to raise extended legs, 2 = inability to flex knee, 3 =inability to flex ankle). Postoperative sedation was assessed using a 4-point scale (0 = eyes open spontaneously, 1 = eyes open to speech, 2 = eyes open when shaken and 3= unarousable), less than 1hour and 4 hours later.

Side-effects, especially odd behaviour, shivering, urinary retention, nausea and vomiting were recorded. Each patient was accompanied by a parent or guardian. Parents were asked to inform the nurses about unusual behaviour or distress unlikely to be related to pain. The end point of this study was taken as when pain score was more than 4 or 24 hours after surgery.

All the data collected in the study were analyzed using statistical package for social sciences (SPSS) version 20. The results were presented in tables, graphs and charts. Numerical data was expressed as mean ± standard deviation and comparison between the groups was done using independent sample t-test. Paired t-test was used for intragroup analysis. Categorical data was expressed as frequencies and compared using chi-square test. Statistical significance was assumed if $p < 0.05$.

Results

A total of 76 patients completed the study, 38 in each group. They were categorized into two groups: group B received caudal Bupivacaine 0.25% and group K, received caudal ketamine 1mg/kg. There was no significant difference in the demographic data and clinical characteristics (Table I). All the patients belonged to ASA I physical status.

There was no significant difference in baseline vital signs (pulse rate, mean arterial blood pressures, peripheral oxygen saturation). The average MAP was 68.9 ± 7.7 mmHg for bupivacaine group and 70.0 ± 7.0 mmHg for ketamine group with p-value of 0.54. The mean pulse rate was similar in both groups 99.3 ± 12.6 b/m for bupivacaine group while 99.7 ± 12.7 b/m for ketamine group p= 0.384. The oxygen saturation was also similar with mean values of 98.9 ± 0.9 % for bupivacaine group and 98.2 ± 0.7 % for ketamine group p= 0.086.

Table II, Shows that there was a significant difference in the mean duration of analgesia between ketamine group and bupivacaine group p = 0.0001.

The mean pain scores are as shown in fig 1. The mean pain scores were lower in ketamine group at all times during the study period, however no statistically significant difference was found.The intra-operative pulse rate and MAP were not significantly different in the two groups, p>0.05. The post-operative pulse rate and MAP were also not significantly different in the two groups, p>0.05The mean sedation score for the bupivacaine group at 30 minutes was 1.3 ±0.4, whereas in the ketamine group it was 1.6±0.6, p =0.69. All the patients had sedation score of zero after 60 minutes. Five (13.2%) versus four (10.5 %) patients had shivering in bupivacaine group and ketamine group respectively p=1.000. Four children vomited in this study three of them were in the bupivacaine group (7.9%) one in ketamine group, p=0.185. Nystagmus was observed in three patients in the ketamine group non in the bupivacaine group. All (100%) of the children in the ketamine group were able to ambulate in less than one hour after surgery. However, 24 (63.2%) children in bupivacaine group ambulated without support in less than one hour as shown in table III. The mean time of ambulation was 65.6±12.6 minutes for bupivacaine group and 29.2±8.0 minutes in ketamine group, p= 0.001.

Tables and Figures

Table 1: Comparison of demographic data and clinical characteristics

Parameter	Bupivacaine group Mean ±SD	Ketamine Group Mean ±SD	T	p-value
Age (years)	3.2±0.9	3.0±1.0	0.9	0.39
Sex (F/M)	2/36	3/35		0.23
Height (cm)	99.7±6.2	96.2±7.8	2.20	0.31
Weight (Kg)	14.6±1.2	14.2±1.5	1.37	0.18
Duration of surgery(min)	23.7±3.2	23.9±3.1	-0.24	0.81

Table 2: Duration of analgesia

Parameter	Bupivacaine Mean ±SD	Ketamine Mean ±SD	T	p-value
Duration of analgesia(min)	417.5±20.1	649.1±29.3	-5.3	0.00001*

* p value is statistically significant.

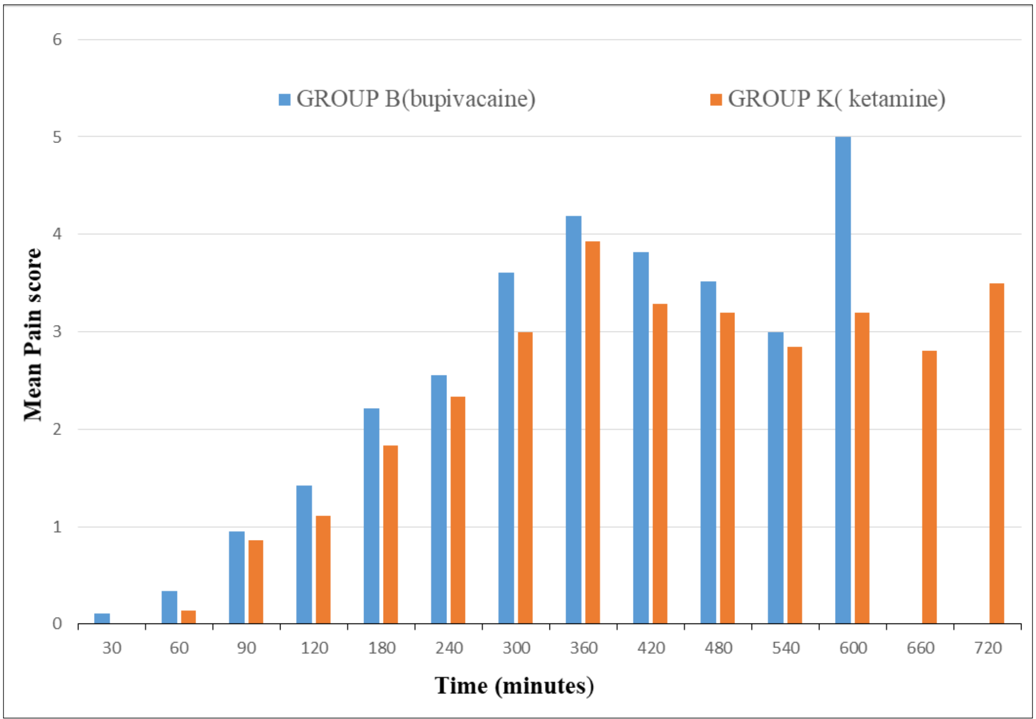

Fig 1: Comparison of Mean pain score.

Table 3: Comparison of Time of ambulation/micturition

Parameter	Bupivacaine Mean ±SD	Ketamine Mean ±SD	T	p-value
Ambulation	65.6±12.6	29.2±8.0	1.27	0.001*
Micturition	223.0±24.8ᶲ	149.5±31.5⁺	1.583	0.002

*p<0.05
ᶲ n=21
⁺ n= 22

Discussion

This study has shown that caudally administered S-ketamine as a sole agent provided analgesia of more prolonged duration than when bupivacaine was used. Both groups showed comparable post-operative pain scores. All the children in ketamine group were able to ambulate within 60 minutes of the end of surgery. The incidences of side effects were comparable among the groups.

This study demonstrated that analgesia provided by caudal block was satisfactory as no patient was excluded from the study because of poor block. This finding is similar to that of other researchers where high success rates following caudal block in children were observed [7, 13, 14] The finding in this study correlates with the findings of other studies where no additional analgesics were administered to patients intraoperatively.[10,13]Nafiu and co-workers,[14] and also Marhofer *et al*,[10] used haemodynamics changes of less than 15 % from the baseline obtained fifteen minutes after performing caudal block to adjudge the block adequate. The present study also showed adequate intraoperative analgesia in the two groups. There was no significant variation in the MAP and HR between the two groups p >0.05.

There were no significant increases in mean pulse rate and MAP following caudal S (+) ketamine administration. The haemodynamic response of ketamine group was comparable with that of the bupivacaine group in this study, this was similar to the observations made by a previous study [13] and this suggests that the analgesic effect of caudal ketamine is likely mediated largely through a central pathway [7]. Hanaoka *et al* [15] suggested that N methyl D aspartate (NMDA) receptor in the spinal cord could be the mode of action of caudally administered S (+) ketamine. Marhofer and co-workers [10], in their study concluded that caudally administered ketamine in children is minimally absorbed into the systemic circulation. In contrast Odes *et al* [6] reported a significant increase in the systolic blood pressure in ketamine group at the 5th min of the operation (p<0.05). Odes *et al*[6] also demonstrated significantly higher diastolic blood pressure in ketamine group as compared to the other group at the surgical incision point and at the 5th, 15th and 45th min of the operation (p<0.05). Patients in their study were intubated with cuffed endotracheal tube (associated with increased haemodynamic response), this may affect comparison of the results obtained from their study with result of other studies where LMA's were used.

There was a significant difference in the mean duration of analgesia observed in the ketamine group compared to bupivacaine group 649.1 minutes vs 417.5 minutes respectively p<0.001. Similar findings of statistically significant longer mean duration of action in ketamine group were noted in other studies.[6,9] Other workers, using ketamine as adjuvant to local anaesthetics have demonstrated a statistically significant increase in the duration of action as compared to local anaesthetics alone.[2] Nafiu and colleagues in their study observed a significant difference in the mean duration between ketamine group (0.5mg/kg S-Ketamine) and bupivacaine(0.125%) [14]. The mean duration of action was 8 hours for ketamine. It was 4 hours for bupivacaine p <0.005. The concentration of agent used in the study by Nafiu and colleagues [14], was lower than that of index study, yet the study established that S-ketamine was superior to bupivacaine in the duration of action. With increase in the concentration of ketamine (1 mg/kg) in the index study the mean duration of action was more (649 minutes equivalent of 10.8 hours) than 8 hours found in the work of Nafiu and colleagues (ketamine 0.5mg/kg). This infers that increasing the dose of ketamine to 1mg/kg will increase the duration of action of S-ketamine. Warner and Kunkel demonstrated that children of younger age have increased duration of action following caudal block [16]. They thought that the age-related anatomic differences may be responsible for longer duration in younger children. The reason for the difference in duration of action in relation to age could be more cephalad sensory block of the volume of anaesthetic injected in younger as compared with older children.

Both groups showed good postoperative analgesia in terms of pain scores. The average pain scores were lower in the ketamine group as compared to the bupivacaine group at all times of the study. However, there was no statistically significant difference in mean pain score. This finding in the index study is in keeping with that of another study which observed that pain score at each time interval was lower in the ketamine group [14].

The post-operative sedation scores did not differ significantly between the bupivacaine and the ketamine groups (P>0.05), although the mean sedation score was less in bupivacaine group as compared to ketamine group. After one hour in the recovery room, all the patients were fully awake. This finding is in keeping with the report of other workers who found insignificant difference in the mean sedation score with ketamine.[2] Semple and colleagues, demonstrated that there was no significant difference in the mean sedation score among three doses of caudal S- ketamine 0.25mg/kg, 0.5mg/kg and 1mg/kg.[2] Siddiqui *et al* [4], observed that the sedation score did not differ significantly between the bupivacaine and the ketamine groups during the first 2 hours of recovery. In their study, patients who had received caudal bupivacaine were more awake with less sedation score as compared with the other 2 groups but the difference was not statistically significant (P>0.05) [4]. Sedation score obtained in the index study is not in keeping with that of another study that observed statistically significant difference in the sedation scores [3]. Ahuja and co-workers [3], observed a significant difference in sedation score in less than 30 minutes of arrival in the recovery room in ketamine group as compared to the bupivacaine group. However, they found no significant variation in the sedation score after 30 minutes in the recovery room.

The current study demonstrated that patients in the ketamine group were able to ambulate without support earlier than those in bupivacaine group, with a mean time of 65.6 ± 12.6 for Bupivacaine group while it was 29.2 ± 8.0 for Ketamine group. (p < 0.001) Resumption of motor function which is estimated from the time of ambulation or onset of micturition is dependent on dose of local anaesthetics [4]. In the study by Semple and colleagues [2], using similar concentration of local anaesthetics (0.25% Bupivacaine) but different concentration of ketamine (0.25mg/kg, 0.5mg/kg, and 1mg/kg) they found that there was no difference in the incidence of motor block [2]. This finding shows that motor blockade is an inherent characteristic of local anaesthetic agents.

The mean time to micturition was found to be significantly longer in the bupivacaine group as compared to ketamine group in the index study. Longer time to micturition in bupivacaine group was observed in another study [5] During caudal block, urinary retention is produced as a result of sympathectomy and the resultant unopposed action of the parasympathetic nervous system. Nafiu and colleagues [14] reported that more patients in bupivacaine (0125%) group had delayed micturition as compared with S(+)-ketamine

Nystagmus was observed in 3 patients (7.9%) of ketamine group in the present study. Association of use of ketamine with nystagmus has been observed by other workers[2] Siddiqui *et al*[4] reported that there was a dose relationship between nystagmus and ketamine, the incidence of nystagmus was greater in high dose ketamine group, 20 % versus 5% in 1mg/kg and 0.5mg/kg ketamine groups respectively.

The incidence of vomiting observed in the current study was not significant among the two groups, however the incidence was higher in the bupivacaine group compared to ketamine group(7.9% vs 2.6% respectively) p=0.185. This trend was similar with the observations made by Nafiu and co-workers [14], who found that vomiting occurred in three (15%) patients in the bupivacaine group, two (9%) patients in the ketamine group and three (15%) patients in the bupivacaine-ketamine group (p=0.94). Semple and colleagues [2], also found that there was no significant difference in the incidence of vomiting between the groups with five, six and one in groups' bupivacaine-ketamine (0.25mg/kg), bupivacaine-ketamine (0.5mg/kg) and, bupivacaine-ketamine (1mg/kg) respectively. Naguib *et al* [17] observed that the incidence of vomiting was 25 %, and 13 % in the bupivacaine and ketamine groups respectively. On the other hand, Passariello and co-workers [8] observed that no patient had post-operative nausea and vomiting in ketamine and ketamine-clonidine groups. This finding stresses the point that caudal ketamine could be protective against peri-operative nausea and vomiting. Bupivacaine causes sympathetic block leading to reduction in the blood pressure and hypo perfusion of the chemoreceptor trigger zone, predisposing the patients in the local anaesthetic group to have higher incidence of nausea and vomiting.

Conclusion

This study has shown that caudal S (+)-Ketamine (1mg/kg) provided longer duration of post-operative analgesia when compared to Bupivacaine (0.25%) in children having herniorrhapy. Both groups had equipotent intraoperative analgesia and post-operative analgesia. Ketamine group had minimal affectation of postoperative motor function.

An important limitation of this study is that time of micturition was difficult to obtain as parents/guardians could not give accurate time of micturition in most of the children, hence this was not analysed.

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