CAUDAL ANALGESIA IN PAEDIATRICS: COMPARISON BETWEEN BUPIVACAINE ALONE AND IN COMBINATION WITH KETAMINE FOR POSTOPERATIVE ANALGESIA IN GVMC, VELLORE

Iswaran Chandra Thendralarasu[1], Rajamani Jayadharmarajan Balamurugan[2]

[1]Assistant Professor, Department of Anaesthesiology, Government Vellore Medical College Hospital, Adukkamparai, Vellore.
[2]Senior Assistant Professor, Department of Anaesthesiology, Government Vellore Medical College Hospital, Adukkamparai, Vellore.

ABSTRACT

BACKGROUND

Caudal block is a common technique for paediatric analgesia, but with the disadvantage of short duration of action of bupivacaine after single injection. Caudal ketamine could offer significant analgesic benefits. We compared the analgesic effects and side effects of ketamine added to bupivacaine in paediatric patients undergoing lower abdominal surgeries.

MATERIALS AND METHODS

One hundred patients (1 yr. to 10 yrs.) were randomly assigned into two groups in a double-blinded manner. After halothane in oxygen general anaesthesia, each patient received either a single caudal dose of bupivacaine 0.25% (1 mL/kg) with normal saline or bupivacaine 0.25% with ketamine 0.5 mg/kg. Haemodynamic variables, pain score, sedation score, use of analgesics and side-effects were assessed during the first 24 h.

RESULTS

Addition of ketamine to caudal bupivacaine significantly prolonged the duration of analgesia than the use of bupivacaine alone. There is a statistically significant difference between bupivacaine alone and in combination with ketamine with regards to the analgesia time ($p < 0.001$). No significant difference was observed in incidence of haemodynamic changes or side-effects.

CONCLUSION

Addition of ketamine to caudal bupivacaine significantly prolonged analgesia in children undergoing lower abdominal surgeries.

KEYWORDS

Caudal, Analgesia, Bupivacaine, Ketamine.

HOW TO CITE THIS ARTICLE: Thendralarasu IC, Balamurugan RJ. Caudal analgesia in paediatrics: comparison between bupivacaine alone and in combination with ketamine for postoperative analgesia in GVMC, Vellore. J. Evolution Med. Dent. Sci. 2016;5(102):7478-7483, DOI: 10.14260/jemds/2016/1693

BACKGROUND

Regional anaesthetic techniques have gained considerable popularity for use with paediatric patients. The primary advantage of regional supplementation are lowering general anaesthetic requirements intraoperatively and providing good postoperative pain relief.

Caudal anaesthesia is the most frequently used regional technique in children, accounting for almost 50% of all regional techniques. Many anaesthetic agents have been used for caudal analgesia in paediatric patients with lignocaine and bupivacaine being most common. But a single caudal injection provides analgesia only for the duration of action of the local anaesthetic. Most of the children undergoing subumbilical operations require further analgesia during the postoperative period, which influenced many authors[1,2,3] to search for means to prolong the duration[4,5,6,7] of caudal analgesia. The addition of opioids to the local anaesthetic mixture is known to prolong the duration of caudal analgesia, but the possibility of respiratory depression along with itching, vomiting and postoperative retention of urine has limited the use of such mixtures.[7]

Ketamine binds to a subset of glutamate receptors stimulated by the agonist N-methyl D-aspartate (NMDA)[8] and thus exerts its analgesic action. These receptors are found throughout the central nervous system including the lumbar spinal cord. Ketamine has a potent analgesic action when used in subdissociative doses. Moreover, it does not cause respiratory depression and therefore seems to be a suitable drug for pain relief.

Aim of the Study

The aim of the study is to compare the duration of postoperative analgesia, to evaluate postoperative sedation, to compare the haemodynamic effects and incidence of side-effects of ketamine and their combination with bupivacaine

MATERIALS AND METHODS

After approval from the Institutional Ethics Committee, the present study was conducted in 100 paediatric patients of either sex belonging to ASA Grade I or II in the age group 1 to 10 years scheduled for elective lower abdominal, orthopaedic and genitourinary surgery at Government Vellore Medical College Hospital, Vellore.

Detailed history and preoperative assessment was carried out a day before operation. A detailed general as well as systemic examination was done to rule out any major systemic illness. Routine investigations like haemoglobin and

Financial or Other, Competing Interest: None.
Submission 16-11-2016, Peer Review 09-12-2016,
Acceptance 16-12-2016, Published 22-12-2016.
Corresponding Author:
Dr. Iswaran Chandra Thendralarasu,
Assistant Professor,
Department of Anaesthesiology,
Government Vellore Medical College Hospital,
Adukkamparai, Vellore-632011.
E-mail: ictarasu@yahoo.co.in
DOI: 10.14260/jemds/2016/1693

urine analysis for albumin and sugar were carried out. Patients with drug allergy, skin infections at the site of block, abnormalities of sacrum, active central nervous system diseases, history of disorders of blood clotting, those on anticoagulation therapy and patients with cardiovascular, respiratory, hepatic and renal diseases were excluded from the study. Informed written consent was taken from parents. We conducted a prospective, randomised, double blind study. The patients were randomly allocated in two groups of fifty patients each using random number tables. The children belonging to each group received the following drugs[9,10,11]:

Group 1	Inj. Bupivacaine 0.25% + Inj. 0.9% normal saline	1 mL/kg
Group 2	Inj. Bupivacaine 0.25% + Inj. Ketamine 0.5 mg/kg	1 mL/kg

An anaesthesiology resident not involved in the study prepared the study solution.

Ketamine used in our study was a preservative free preparation containing S (+) and R (-) enantiomers[12] in equal amounts available in 50 mg/mL ampoules.

All the patients fasted for 6 hours before surgery. In the preoperative room, pulse rate and blood pressure were recorded. All the patients were premedicated with glycopyrrolate 0.008 mg/kg intravenously fifteen minutes before surgery.

After shifting the patient to the operation theatre, pulse oximetry and non-invasive blood pressure monitors were attached and pulse rate and mean arterial pressure measured for baseline readings.

After preoxygenation for 3 minutes, patients were induced with sodium thiopentone (2.5%) 4 to 6 mg/kg with succinylcholine 1.5 to 2 mg/kg intravenously. Anaesthesia was maintained with nitrous oxide 70% and oxygen 30% along with halothane 0.5 - 1% and injection vecuronium bromide as muscle relaxant.

Then the anaesthetised patients were placed in lateral decubitus position with hip and knee in 90^0 flexion. The skin disinfection was done with betadine solution. Sacral hiatus identified by palpating both posterior superior iliac spines and sacral cornu. After sacral hiatus was identified, the index and middle finger of the palpating hand were placed on the sacral cornu and the 23-G hypodermic needle was inserted at an angle of 45^0 to the sacrum. While advancing the needle, a decrease in the resistance to needle insertion was appreciated as the needle entered the caudal epidural space.[13] The needle was advanced until bone (i.e. dorsal aspect of the ventral plate of the sacrum) was contacted and then slightly withdrawn and the needle was redirected so that the angle of insertion relative to the skin surface was further reduced. In male patients, this angle was almost parallel to the coronal plane; in female patients, a slightly steeper angle (15^0) was necessary. The needle was advanced approximately 1 to 2 cm into the caudal space.[14]

After confirming no return of cerebrospinal fluid or blood, either spontaneously or with gentle aspiration, the study drug solution appropriate for the group was injected.

The children were then turned supine. Skin incision followed 10 - 15 minutes after caudal injection.

Intraoperatively, measurement of vital signs like pulse rate, mean arterial pressure was done and oxygen saturation was measured.

After completion of surgery, residual neuromuscular block was reversed with neostigmine 0.05 mg/kg and glycopyrrolate 0.008 mg/kg intravenously. Trachea was extubated and the patients were transferred to the recovery room and observed for two hours. Pulse rate, mean arterial pressure, respiratory rate and oxygen saturation were recorded at regular intervals.

The duration of caudal analgesia was defined from the time of caudal injection to the time of the first analgesic supplementation. Respiratory depression was defined as a respiratory rate of < 10 breaths/minute.

Patients were assessed for pain with Hannallah's[15] objective pain score. Motor block assessed with Bromage's motor scale and sedation assessed with Four Point sedation score.

These scores were assessed at 1, 2, 3, 4, 5, 6, 8, 10, 12, 18 and 24 hours postoperatively.

Observation	Criteria	Points
Blood Pressure	± 10% preoperative	0
	> 20% preoperative	1
	> 30% preoperative	2
Crying	Not Crying	0
	Crying, but responds to Tender Loving Care (TLC)	1
	Crying and does not respond to TLC	2
Movement	None	0
	Restless	1
	Thrashing	2
Agitation	Patient asleep or calm	0
	Mild	1
	Hysterical	2
Posture	No special posture	0
	Flexing legs and thighs	1
	Holding scrotum/groin or operated site	2
Complaint of pain (> 5 years)	Asleep or states no pain	0
	Cannot localise	1
	Can localise	2
Hannallah's Objective Pain Score		

If the total score is ≥ 5 in < 5 years old child or if total pain score is ≥ 7 in ≥ 5 years old child, then analgesia was supplemented with injection paracetamol 5 mg/kg intravenously. The time at which analgesic was first received and total number of analgesic doses required in the first 24 hours after operation were noted.

Grade 0	Eyes open spontaneous
Grade 1	Eyes open to speech
Grade 2	Eyes open when shaken
Grade 3	Unarousable
Four Point Sedation Score	

Grade 0	No paralysis
Grade 1	Inability to raise extended leg
Grade 2	Inability to flex knee
Grade 3	Inability to flex ankle
Bromage Motor Score	

Side effects like nausea, vomiting, pruritus, flushing, urinary retention, respiratory depression and hallucinations were noted.

Statistical Analysis

All data are presented as mean (SD) except where specified. Data were analysed using ANOVA for repeat measurements. Continuous variables were analysed using student's t-test. The paired t-test was used for comparisons within the groups and the unpaired t-test for intergroup comparisons. Probability values < 0.05 were considered significant.

RESULTS

The present study was carried out on 100 paediatric patients of either sex between ages of 1 and 10 years, belonging to ASA Grade I and II scheduled for lower abdominal, genitourinary and lower limb orthopaedic surgery at Government Vellore Medical College Hospital, Vellore.

Detailed history and preoperative assessment was carried out a day before operation. Informed written consent was obtained from parents. Patients were randomly divided into two groups of twenty patients each for caudal block. Children received the following drugs.[11]

Group 1	Inj. Bupivacaine 0.25% + Inj. 0.9% normal saline	1 mL/kg
Group 2	Inj. Bupivacaine 0.25% + Inj. Ketamine 0.5 mg/kg	1 mL/kg

The children's age, weight, duration of surgery involved in each group are as shown in Table 1.

	Bupivacaine Gr (Group 1) (n = 50)	**Bupivacaine-Ketamine Gr (Group 2) (n = 50)**
Age (Yrs.)	4.7 (2.15)	4.9 (2.4)
Weight (Kg)	14.15 (3.92)	13.9 (3.5)
Duration of Surgery (Min.)	62 (29.48)	54.5 (19.72)

Table 1. Patient's Data and Duration of Surgery [Mean (Standard Deviation)]

The below table shows the percentage of various surgeries performed in each group. Majority of patients were operated for congenital herniotomy (66%).

Surgery	**Gr 1**		**Gr 2**		**Total**
	n = 50		**n = 50**		
	No.	**%**	**No.**	**%**	**%**
Herniotomy	36	72	30	60	66
Hypospadias	4	8	5	10	9
Cystolithotomy	1	2	2	4	3
Orchiopexy	5	10	4	8	9
CTEV	1	2	3	6	4
Circumcision	2	4	4	8	6
Split Skin Graft	1	2	2	4	3

Table 2. Types of Surgery

	Gr 1	**Gr 2**
	n = 50	**n = 50**
Mean	4.6	10.3
S.D.	0.88	1.71

Table 3. Total Duration of Analgesia (Hours)

The above table shows the total duration of analgesia in both groups.

A statistically highly significant prolongation in the duration of analgesia was observed in Group 2, when compared with Group 1 ($p < 0.01$).

The mean duration of analgesia was 4.6±0.88 hours in Group 1, 10.3±1.71 hours in Group 2.

No. of Injection	**Gr 1 (n = 50)**		**Gr 2 (n = 50)**	
	No.	**%**	**No.**	**%**
0	0	0	0	0
1	0	0	0	0
2	0	0	38	75
3	3	5	8	15
4	27	55	4	10
5	20	40	0	0
Mean	4.35		2.35	
S.D.	0.58		0.67	

Table 4. Postoperative Analgesic Consumption in 24 hrs.

Postoperatively, injection paracetamol 5 mg/kg intravenously was given if pain score was more than 5 (if child's age was < 5 years) and pain score more than 7 (if child's age was ≥ 5 years).

In Group 1, 5% of patients required 3 injections, 55% of patients required 4 injections and 40% of patients required 5 injections in the first 24 hours postoperatively.

In Group 2, 75% of patients required 2 injections, 15% of patients required 3 injections and 10% of patients required 4 injections in the first 24 hours postoperatively.

The mean number of analgesic doses required in 24 hours was 4.35 ± 0.58 in Group 1 and 2.35 ± 0.67 in Group 2.

We found a statistically significant difference in the total number of analgesic supplements in 24 hours in Group 2 when compared to Group 1 ($p < 0.01$).

Side Effects	**Gr 1 (n = 50)**		**Gr 2 (n = 50)**	
	No.	%	No.	%
Nausea	5	10	3	6
Vomiting	3	6	5	10
Hallucination	0	0	5	10

Table 5. Percentage Occurrence of Complications in Both Groups

Nausea occurred in 10% of patients in Group 1 and 6% of patients in Group 2, Group 3 and Group 4.

Vomiting occurred in 6% of patients in Group 1 and 10% of patients in Group 2.

Hallucination occurred in 10% of patients of Group 2.

None of the patients had pruritus, flushing, respiratory depression or urinary retention in both the groups.

DISCUSSION

Caudal analgesia offers an excellent pain relief to children in the postoperative period. Prevention of pain is always much

easier than cure. Not providing adequate pain relief may lead to serious psychological upset in children. Early postoperative pain relief hastens the recovery and minimises hospital stay.[16,17] For outpatient surgery, agents which provide minimal side effects is essential.

Ketamine is an anaesthetic and analgesic chemically related to phencyclidine, has structure similar to that of bupivacaine and has local anaesthetic effect. It acts on NMDA[8,18,19] receptors in substantia gelatinosa of spinal cord synergistic effect of epidurally administered ketamine with bupivacaine[11] increases the duration of analgesia.

This study was undertaken to evaluate the efficacy of ketamine added to bupivacaine in caudal block to provide postoperative analgesia in paediatric patients.

Heart rate is an easy and generally valid measure of short, sharp pain. Heart rate initially decreases and then increases in response to short, sharp pain. Vagal tone and heart rate variability have been used as indices of pain and distress. Heart rate was not substantially elevated during postoperative pain in older children. Ill and premature babies have less predictable responses.

In our study, there were no significant differences in pulse rate and mean arterial pressure among the two groups at various intervals for the first 24 hours postoperatively ($p > 0.05$).

The following Studies are Consistent with our Study

Kumar et al[20] compared the efficacy of ketamine and midazolam as additives to bupivacaine in caudal analgesia and found no differences in heart rate and mean arterial pressure among the groups. None of the patients showed bradycardia.

Marhofer et al[21] compared S(+) ketamine of 0.5 mg/kg and 1.0 mg/kg with caudal bupivacaine 0.25% and found no significant changes in heart rate or mean arterial blood pressure during the intraoperative period in any group.

As the most serious side effects of opioids is respiratory depression when used as adjuvants to bupivacaine in caudal analgesia it has led to the search for non-opioid additives like adrenaline, clonidine, ketamine and midazolam for prolongation of duration of analgesia without respiratory depression unlike opioids.

In our study, there was no significant difference in the mean respiratory rate and mean oxygen saturation among the two groups measured at different time intervals for the first 24 hours postoperatively ($p > 0.05$).

The following Studies are Consistent with our Study

Naguib et al compared midazolam with caudal bupivacaine and found that no child had a recorded respiratory rate of less than 12 breaths per minute.

AK Pan[20,22] et al found no significant changes in the mean respiratory rate and oxygen saturation in all the groups.

Kumar[20] et al conducted the study where the oxygen saturation was always within the clinically acceptable range ($p > 0.05$).

Marhofer[21] et al found no respiratory depression in their study and SpO2 values during and after surgery did not differ between the groups.

In our study, all patients were premedicated with injection glycopyrrolate because of its antisialagogue property and its least effect on haemodynamic parameters. No preoperative and intraoperative sedatives or analgesics were given to any patient. All patients were induced with standard general anaesthesia with sodium thiopentone and succinylcholine with tracheal intubation and controlled ventilation. They were maintained with O_2, N_2O, halothane and vecuronium bromide. Immediately after induction with general anaesthesia, patients were given left lateral position for caudal injection. Surgery was started after caudal injection was given.

The following Studies used General Anaesthesia and then Caudal Injection before Surgery like our Study

AK Pan et al,[20,22] Cook et al,[5] P. Kumar et al.[20]

The following studies used General Anaesthesia, but Caudal Injection was given after Surgery which was in Contrast to our Study[23,24]

Naguib et al,[25,26] Shahriari Ali et al.[27]

In our study, caudal block was given before surgery, as it provides intraoperative and postoperative analgesia to the patient. So, there was no need of providing analgesics during intraoperative period. Further, supplementation of intraoperative analgesics or sedatives parenterally would interfere with postoperative pain assessment and sedation scores measured for assessing the efficacy of caudal block.

In our study, assessment of pain was done using Hannallah's Objective Pain Score at different time intervals postoperatively for up to 24 hours. By these pain score observations, the mean duration of analgesia was calculated.

The mean duration of postoperative analgesia was 4.6 ± 0.88 hours in Group 1 (Bupivacaine alone), 10.3 ± 1.71 hours in Group 3 (Bupivacaine - ketamine), so the mean duration of postoperative analgesia was statistically highly significant in Group 2 as compared to Group 1 ($p < 0.01$).

Ketamine used in our study was a mixture of both enantiomers [S(+) and R(-)] in equal amounts) available in preservative free form. Ketamine exerts its effect by binding non-competitively to a subset of glutamate receptors stimulated by the excitatory amide N-methyl-D-aspartate (NMDA), blockade of which leads to a decrease in the activation of dorsal horn neurons. These receptors are located throughout the CNS as well as in the substantia gelatinosa of spinal cord and play an important role in central pain processing and in neural plasticity in the spinal cord.

While NMDA receptor block appear to be the primary mechanism of action, ketamine also binds to opioid receptors with a preference to μ receptors. However, the affinity of ketamine for these receptors is a tenth of that for NMDA receptors and the analgesic effect of ketamine is not reversed by naloxone. Blockade of nor-epinephrine and serotonin receptors may also be involved in the antinociceptive actions of ketamine.

CONCLUSION

The double blind study was undertaken to evaluate the efficacy of ketamine co-administered with bupivacaine in caudal block for providing postoperative analgesia in paediatric patients.

The study was conducted in 100 paediatric patients of either sex, between the age group of 1 and 10 years belonging to ASA Grade I and II scheduled for elective lower abdominal, orthopaedic and genitourinary surgery at Government Vellore Medical College Hospital, Vellore.

Detailed history and preoperative assessment was carried out a day before operation. Informed written consent was obtained from parents. Patients were randomly divided into two groups of twenty patients each for caudal block. Children received the following drugs.

Group 1	Inj. Bupivacaine 0.25% + Inj. 0.9% normal saline	1 mL/kg
Group 2	Inj. Bupivacaine 0.25% + Inj. Ketamine 0.5 mg/kg	1 mL/kg

In the preoperative room, pulse and mean arterial pressure were recorded. All the patients were premedicated with glycopyrrolate 0.008 mg/kg intravenously fifteen minutes before surgery. After shifting the patients to operation theatre, pulse rate and blood pressure were recorded. Standard general anaesthesia was given by induction with sodium thiopentone 4 – 6 mg/kg intravenous and succinylcholine 1.5 - 2.0 mg/kg intravenous for facilitating tracheal intubation. They were maintained with O_2, N_2O, halothane, vecuronium bromide and intermittent positive pressure ventilation. Patients were then placed in lateral decubitus position and caudal block was given with 23 gauge hypodermic needle, according to their randomly allocated groups. Patients were turned supine and time of caudal block was noted. Pulse, mean arterial pressure and oxygen saturation were monitored intraoperatively. Surgery was begun after caudal block was given. At the end of surgery, anaesthetic agents were withheld and residual neuromuscular blockage was reversed. Postoperatively, pulse rate, mean arterial pressure, respiratory rate, oxygen saturation, pain score, sedation score and motor block were monitored up to 24 hours.

The age and weight of the patients and the duration of surgery were comparable between the two groups. There was no significant difference in the pulse rate, mean arterial pressure, respiratory rate and oxygen saturation at different time intervals between the two groups ($p > 0.05$).

Motor block was assessed with Bromage motor scale. The mean duration of motor block was 1.2 ± 0.41 hours in Group 1, 1.15±0.36 hours in Group 2. There was no significant difference in the duration of motor block among the four groups ($p > 0.05$).

Sedation was assessed with Four Point Sedation score. No significant difference among the two groups.

Pain was evaluated by Hannallah's objective pain score. Mean pain scores were higher in Group 1 as compared to Group 2 ($p < 0.01$). Mean pain score of more than 5 occurred at about 4 hours postoperatively in Group 1. Mean pain score of more than 5 occurred at about 10 hours postoperatively in Group 2. The mean duration of analgesia was 4.6 ± 0.88 hours in Group 1, 10.3 ± 1.71 hours in Group 2. We found a statistically highly significant prolongation of duration of analgesia in Group 2 as compared to Group 1 ($p < 0.01$).

Analgesic was supplemented when the pain score was more than 5 (Age < 5 years) and more than 7 (Age ≥ 5 years). The number of doses of analgesic (Injection paracetamol 5 mg/kg intravenous) required in 24 hours was noted. The mean number of doses required in 24 hours was 4.35 ± 0.58 in Group 1 and 2.35 ± 0.67 in Group 2. The analgesic requirements were significantly higher in Group 1 ($p < 0.01$) as compared to Group 2.

Side effects like nausea occurred in 10% of patients in Group 1 and 5% of patients in Group 2. Incidence of vomiting occurred in 5% of patients in both Groups 1 and 2. Hallucinations were experienced by 10% of patients in Group 2 only.

We thus conclude that the single shot caudal bupivacaine 0.25% prolongs the duration of postoperative analgesia for about 4 hours, whereas the addition of ketamine to it provides longest duration of postoperative analgesia for about 10 hours, while maintaining haemodynamic stability without prolonging the motor blockage producing minimal comparable side effects.

The postoperative analgesic requirement in the first 24 hours is also reduced, leaving the child calm, quiet, comfortable, minimally sedated and easily arousable in the immediate postoperative period.

REFERENCES

1. Akbas M, Titiz TA, Ertugrul F, et al. Comparison of the effect of ketamine added to bupivacaine and ropivacaine, on stress hormone levels and the duration of caudal analgesia. Acta Anaesthesiol Scandinavica 2005;49(10):1520-6.
2. Alemenrader N, Passariello M, D'Amico G, et al. Caudal additives for postoperative pain management in children: S(+)-ketamine and neostigmine. Paediatric anesth 2005;15(2):143-7.
3. Bano F, Haider S, Sultan ST. Comparison of caudal bupivacaine and bupivacaine-midazolam for peri and postoperative analgesia in children. J Coll Physicians Surg Pak 2004;14(2):65-8.
4. Constant I, Gall O, Gouyet L, et al. Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of surgical analgesia after single shot caudal block in children. British Journal of Anaesthesia 1998;80(3):294-8.
5. Cook B, Grubb DJ, Aldridge LA, et al. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal analgesia produced by bupivacaine in children. British Journal of Anaesthesia 1995;75(6):698-701.
6. de Beer DA, Thomas ML. Caudal additives in children-solutions or problems. British Journal of Anaesthesia 2003;90(4):487-98.
7. Gulec S, Buyukkidan B, Oral N, et al. Comparison of caudal bupivacaine, bupivacaine-morphine and bupivacaine-midazolam mixtures for postoperative analgesia in children. European Journal of Anaesthesiology 1998;15(2):161-5.
8. Nishiyama T, Gyermek L, Lee C, et al. Synergistic analgesic effects of intrathecal midazolam and NMDA or AMPA receptor antagonists in rats. Canadian Journal of Anaesthesia 2001;48(3):288-94.
9. Ecoffey C, Desparmet J, Maury M, et al. Bupivacaine in children: Pharmacokinetics following caudal anaesthesia. Anesthesiology 1985;63(4):447-8.
10. Malviya S, Fear DW, Roy WL, et al. Adequacy of caudal analgesia in children after penoscrotal and inguinal surgery using 0.5 or 1.0ml/kg bupivacaine 0.125%. Canadian Journal of Anaesthesia 1992;39(5 pt 1):449-53.
11. Nafiu OO, Kalawole IK, Salam RA, et al. Comparison of caudal ketamine with or without bupivacaine in pediatric subumbilical surgery. Journal of the National Medical Association 2007;99(6):670-3.

12. Martindale SJ, Dix P, Stoddart PA. Double blind randomized controlled trial of caudal versus intravenous S(+)-ketamine for supplementation of caudal analgesia in children. British Journal of Anesthesia 2004;92(3):344-7.
13. Atkinson RS, Rushman GB, Davies NJH. Extradural blocks. Lee's synopsis of anaesthesia. 11th edn. Butterworth-Heinemann 1993:719-36.
14. Miller RD. Acute postoperative pain; chronic pain; local anaesthetics; spinal, epidural and caudal anaesthesia; Intravenous nonopioidanesthetics. Anesthesia textbook. 6th edn. Churchill Livingstone 2005:334-350, 573-603, 1673-1674, 2729-2762, 2763-2777.
15. Hannallah RS, Broadman LM, Belman AB, et al. Comparison of caudal and ilioinguinal/ iliohypogastric nerve blocks for control of post-orchiopexy pain in pediatric ambulatory surgery. Anaesthesiology 1987;66(6):832-4.
16. Mahajan R, Batra YK, Grover VK, et al. A comparative study of caudal bupivacaine and midazolam-bupivacaine mixture for postoperative analgesia in children undergoing genitourinary surgery. Int Journal of Clinical Pharmacology 2001;39(3):116-20.
17. Malinovsky JM, Cozian A, Lepage JY, et al. Ketamine and midazolam neurotoxicity in the rabbit. Anesthesiology 1991;75(1):91-7.
18. Hirasaki NT, Odaka Y, Konishi H, et al. Epidural midazolam with saline-optimal dose for postoperative pain. Masui 1992;41(1):49-54.
19. Nishiyama T, Odaka Y, Hirasaki A, et al. Epidural midazolam for treatment of postoperative pain. Masui 1991;40(9):1353-8.
20. Kumar P, Rudra A, Pan AK, et al. Caudal additives in paediatrics: a comparison among midazolam, ketamine and neostigmine coadministered with bupivacaine. Anesth Analg 2005;101(1):69-73.
21. Marhofer P, Krenn CG, Plochl W, et al. S(+)-ketamine for caudal block in paediatrics anesthesia. British Journal of Anesthesia 2000;84(3):341-5.
22. Pan AK, Rudra A. Caudal analgesia in paediatrics: comparison between bupivacaine alone and in combination with ketamine, midazolam and ketamine-midazolam. J Anaesth Clin Pharmacol 2005;21(4):401-5.
23. Panjabi N, Prakash S, gupta P, et al. Efficacy of three doses of ketamine with bupivacaine for caudal analgesia in pediatric inguinal herniotomy. American Society of Regional Anesthesia and Pain Medicine 2004;29(1):28-31.
24. Schoeffler P, Auroy P, Bazin JE, et al. Subarachnoid midazolam: histologic study in rats and report of its effect on chronic pain in humans. Reg Anesth 1991;16(6):329-32.
25. Naguib M, el Gammal M, Elhattab YS, et al. Midazolam for caudal analgesia in children: comparison with caudal bupivacaine. Canadian Journal of Anaesthesia 1995;42(9):758-64.
26. Naguib M, Sharif A, Seraj M, et al. Ketamine for caudal analgesia in children: comparison with caudal bupivacine. British Journal of Anaesthesia 1991;67(5):559-64.
27. Shahriari A, Maryam K. Comparison of midazolam with lidocaine and fentanyl for caudal analgesia in children. J Med Sci 2007;7(4):660-4.