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Caudal additives in children: a comparative evaluation of bupivacaine with ketamine vs bupivacaine with butorphanol

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Key points

The addition of preservative free ketamine and butorphanol to bupivacaine in caudal epidural space in children undergoing sub-umbilical surgery results in superior and prolonged analgesia with lesser requirement of rescue analgesics without any side effects with longest duration of analgesia achieved with butorphanol.

Abstract

Background

To compare the efficacy of caudal additives Ketamine (preservative free) and Butorphanol (preservative free) in pediatric age group undergoing infra umbilical surgery.

Methods

60 male children of ASA grade I, aged 4-10 years, <25 kilograms, were randomised to one of the two groups. Group BK received 0.75 ml/kg (0.25%) bupivacaine with ketamine 0.5mg/kg and Group BB received 0.75ml/kg (0.25%) bupivacaine with butorphanol 20 mcg/kg in caudal epidural anesthesia. Hemodynamic variables and respiratory rate were monitored in all patients. Sedation score, pain score and requirement of rescue analgesia were recorded at preset time intervals along with post-operative complications.

Results

Intra-operative hemodynamics, respiratory rate, SpO_2, $EtCO_2$ were maintained within normal limits in each group. Children were found to be more sedated in group BB till 2 hours post operatively as compared to group BK. There were no post operative complications in any of the groups. Mean duration of analgesia was longest in Group BB (19 hours) as compared to Group BK (14 hours). Minimum number of rescue analgesics were required in the BB group (1.12) as compared to group BK (1.76) in 24 hours postoperatively.

Conclusions

The addition of 0.5 mg/kg of preservative free ketamine and 20mcg/kg of butorphanol to bupivacaine in caudal epidural space results in superior analgesia with a longer period without any side effects with longest duration of analgesia achieved with butorphanol.

Keywords: pediatric surgery, caudal epidural anesthesia, butorphanol, ketamine, bupivacaine

Introduction

Caudal anesthesia is one of the most popular regional blocks in children. This technique is useful adjunct during operative and post-operative period to provide analgesia. [1,2] Caudal blocks are used worldwide to provide safe and effective perioperative analgesia for paediatric patients undergoing urological, lower abdominal, and lower limb surgery[3]. It has gained popularity[4] as this

regional technique is easy to learn[5], offers a high success rate[6], and has a low incidence of major adverse events, including dural puncture or intravascular injections[7].Also caudal epidural is useful as it attenuates the stress response of surgery and anesthesia in sub-umbilical surgeries[1,2].

Plain bupivacaine being an agent of shorter duration, different caudal additives have been coadministered with bupivacaine to prolong the duration of caudal epidural analgesia[8,9,10]. In our study we compared preservative free ketamine and butorphanol used as additives to bupivacaine for caudal epidural analgesia in children undergoing sub-umbilical surgery. Both preservative free ketamine and butorphanol used in our study were preservative free.

Methods

After approval from the hospital ethical committee, a study was conducted on 60 male children of ASA grade I, aged 4-10 years, <25 kilograms, scheduled for sub-umbilical elective surgery including inguinal and genito-urinary operations at department of anaesthesia & intensive care VMMC & Safdarjang Hospital, New Delhi. Careful pre-anesthetic examination was performed including neurological examination for any spinal deformities or limb abnormalities. A written informed consent was obtained from the parents of all children. Patients with airway problems, tonsillitis, upper respiratory tract infections, huge hernial sacs, allergies to local anesthetics, spinal deformities, local infection and bleeding tendencies were excluded from the study. After appropriate fasting all patients were pre medicated with syrup promethazine (0.5 mg/kg) body weight two hours prior to surgery. All procedures were carried out under general anesthesia in supine position.

Patients were shifted to operation theatre and all monitors were attached including SpO_2, noninvasive B.P., ECG. Basal parameters (pulse rate, blood pressure, respiratory rate, SpO_2) were recorded and anesthesia was induced with O_2/ N_2O (50:50%) with high concentration of Sevoflurane (3-4 MAC%) on spontaneous respiration (tidal volume breathing) using Ayre's T-piece circuit via face mask. Intravenous access made and Ringer's lactate as per fasting period, started simultaneously. Injection ranitidine 1mg/kg and injection ondansetron 0.1 mg/kg was added to the pediatric set in all patients. All patients were randomly allocated in two groups using table of random numbers:

Group BK (n=30) : 0.75ml/kg (0.25%) bupivacaine with preservative free ketamine 0.5 mg/kg.

Group BB (n=30): 0.75ml/kg (0.25%) bupivacaine with butorphanol 20mcg/kg.

Caudal block was given in the left lateral position. Cases with bloody tap were excluded from the study. Patients were then turned supine and an LMA (proseal / classic) of appropriate size was placed and secured. No analgesia was given during the operation.

All monitoring (pulse rate, blood pressure, respiratory rate, SpO_2, $EtCO_2$) was carried out every 10 minutes throughout the surgery. Anaesthesia was maintained on O_2 / N_2O (33:66%) with sevo flurane (1-2) MAC% on assisted respiration using Ayre's T-piece circuit with fresh gas flow of 2-3 times the minute volume. After the surgery was over LMA was removed after proper oxygenation and suctioning in an awake patient.

Postoperatively the patients were scored for pain and sedation along with monitoring of vitals (pulse rate, blood pressure, respiratory rate) by a blinded observer who was not aware about the group to which the patient belong. A modified objective pain score, given a maximum score of 10 (table 1) was used to assess pain over a 5-minute period. Given below in the table 2 are listed the demographic data of the patients. Sedation scoring was done according to the four point sedation scores (0 = eyes open spontaneously, 1 = eyes open on speech, 2 = eyes open when shaken, 3 = unarousable). Rescue analgesia (with syrup paracetamol 20 mg/kg) was given only on demand or when the pain score was ≥ 4. Total doses of rescue analgesic were noted for 24 hours. Patients were evaluated for any postoperative complications –pruritis, nausea, vomiting, urinary retention, local

hematomas and headache. Time of passing urine and ambulation (taken as independent sitting) was inquired and assessed at 8 hours postoperatively.

Variable	Score 0	Score 1	Score 2
Crying	None	Consolable	Not consolable
Movement	None	Restless	Thrashing
Agitation	Asleep/calm	Mild	Hysterical
Posture	Normal	Flexed	Holds injury site
Verbal	Asleep/No complaint	Complains but cannot localize	Complains and can localize

Table 1. Modified Objective Pain Score

Descriptive statistics i.e. mean and standard deviation have been used for continuous variables like age, weight, duration of surgery, duration of anaesthesia, heart rate, blood pressure (systolic, diastolic and mean), duration of post operative analgesia, total number of doses of rescue analgesic intake in 24 hours. Statistical methods used are ANOVA, followed by POST HOC test for comparison of the continuous variables. Frequency distributions and their percentage were applied for the categorical variables (pain score, sedation score). CHI SQUARE test was applied for the comparison of categorical data. P value <0.05 is taken as statistically significant.

Demographic Data	Group BB (n=30)	Group BK (n=30)	P Value
Age (in years): range and Mean ±SD	5-7 6.4±2.12	5-7 6.10±1.74	0.49
Weight (in kg): range and Mean ±SD	15-18 16.36±3.71	15-17 16.44±2.63	0.42
Heart Rate (beats/min): range and Mean ±SD	107-114 110.56±8.66	107-112 109.56±6.39	0.07
Systolic BP (mm of Hg): range and Mean ±SD	106-111 108.52±5.42	103-108 105.20±5.57	0.77
MAP(mm of Hg): range and Mean ±SD	74-80 76.73-7.36	74-81 77.60±7.94	0.27
Diastolic BP (mm of Hg): range and Mean ±SD	57-65 60.84±9.59	60-68 63.80±10.24	0.89
Duration of surgery (minutes): range and Mean ±SD	35-49 42.00±16.58	35-43 39.20±9.54	0.73
Duration of anaesthesia (minutes): range and Mean ±SD	55-69 62.00±16.58	55-63 59.20±9.54	0.73

Table 2. Patient demographics

Results

Demographic variables (table 2) were comparable in the two groups, including age, weight, basal heart rate and blood pressure (systolic, diastolic and mean), duration of surgery and the duration of anaesthesia with p>0.05. There was a symmetrical decrease in heart rate with time from basal to post induction to post caudal and up to 40 minutes in each group (Fig. 1) (p value<0.05). Mean Arterial Pressure showed a fall after induction of anesthesia, but was stable after the administration of caudal block (Fig. 2). Respiratory rate was maintained at 24-26 breaths per minute throughout the intra operative period and there was no respiratory depression, post operatively. Supplementary analgesia was not needed intra operatively in any of the groups after the effect of caudal block was established.

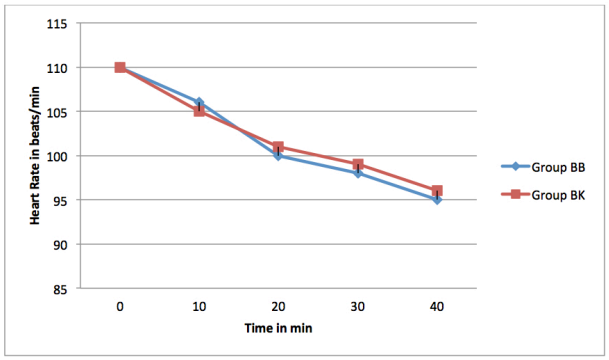

Fig 1. Intraoperative variation in Heart rate in the two groups.

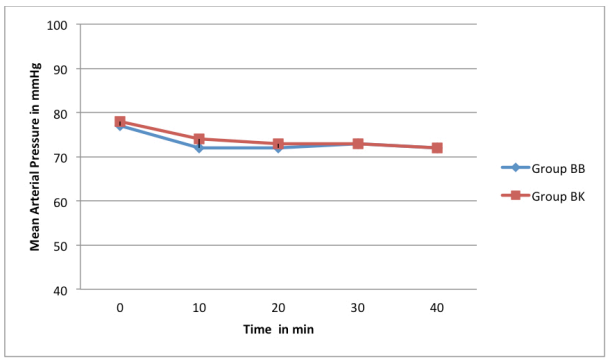

Fig 2. Intraoperative variation in Mean Arterial Pressure in the two groups.

There was some sedation seen in group BB, with 32% children remaining sedated (sedation score= 2) till half hour post operatively. Only 8% in group BB were sedated at 2 hour postoperatively with sedation score= 1 (p value=0.01). Pain score ≥4 was found in 8% children in group BK and only in 4% children in group BB at 12 hours post operatively. The pain scores were recorded at regular intervals post operatively as shown in Fig. 3.

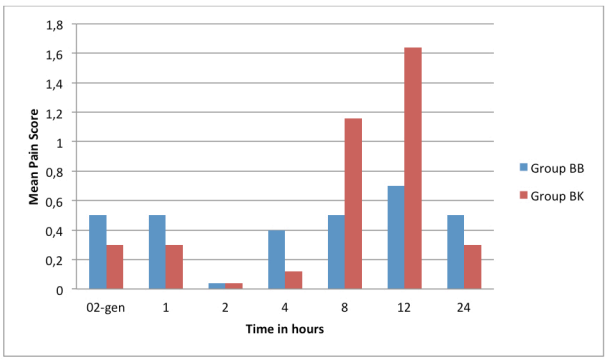

Fig. 3 Mean Pain Score in the Post operative period

The time to first rescue analgesic was 14.16 hours in group BK and 18.18 hours in group BB (P<0.05). Mean rescue analgesic requirement was 1.76 and 1.12 in groups BK and BB, respectively (P<0.05).

There were no post operative complications like nausea, vomiting, pruritis, urinary retention, respiratory depression, hypotension, headache, local hematoma and no motor blockade noted in any of the groups.

Mean time of passage of urine was comparable in both groups was 3.94 hours in group BK and 3.96 hours in group BB (p value=0.88) and time to ambulation in groups BK and BB were 2.97 hours and 3.96 hours, respectively (p=0.001).

Discussion

The present study results show that both preservative free ketamine (0.5 mg/kg) and butorphanol (20 mcg/kg) when added to bupivacaine (0.25%) in caudal epidural space prolong the duration of analgesia with a longer duration achieved with butorphanol.

Butorphanol is a totally synthetic compound of the nalorphine cyclazocine series. It is a mixed agonist – antagonist with intrinsic activity at receptors of the mu opioid type (morphine like). It is also an agonist at kappa opioid receptors. Its interactions with these receptors in the CNS apparently mediates most of its pharmacological effects, including analgesia. Butorphanol has an

analgesic action similar to that of morphine, with less respiratory depression, less nausea and vomiting, no undesirable psychomimetic effects and the provision of

Group	Group BB Mean±S.D.	Group BK Mean±S.D.	P value
Sedation score	0.30±0.32	0.04±0.58	0.001
Mean Pain score	0.44±0.63	0.55±0.58	0.001
Duration of analgesia (hours)	18.85±2.05	14.16±1.65	<0.05
Total no. of rescue analgesics	1.12±0.33	1.76±0.52	<0.05
Time to passage of urine (hours)	3.94±0.21	3.96±0.17	0.88
Time to ambulation (hours)	3.96±0.22	2.97± 0.16	0.001

Table 3. Sedation Score, Mean Pain score, Duration of Analgesia, Total no. of rescue analgesics, time to passage of urine, time to ambulation in the Postoperative Room in Different Groups.

perioperative amnesia.[11] Its high lipid solubility and high affinity for opioid receptors are additional factors that contribute to the paucity of side effects with its use.[12] High lipid solubility increases diffusion in the spinal cord and limits the amount of drugs remaining in the CSF, capable of reaching the brainstem where side effects are detected.[13] In a recent trial it has been demonstrated that there were less chances of complication or side effects with caudal analgesia as compared to parenteral use of analgesics or penile block in patients for circumcision.[14]

In a study conducted by Singh V, Knaujia A, et al in 2006 demonstrated that butorphanol 25 µg/kg added to caudally administered local anesthetics significantly increased the duration of postoperative analgesia in patients undergoing elective infraumblical surgery with a mean duration of analgesia being 14.5±3.5 hours (P value<0.001) without any significant side effects[15]. Similarly Lawhorn CD, et al (1997) in their study found that significantly fewer patients in the butorphanol group required rescue morphine sulfate in the postanesthesia care unit (p ≤0.001) and were much less likely to develop pruritis or nausea and vomiting or to require supplemental O_2 to maintain SpO_2 above 90%[16]. Bailey AG (1994)[17], William MS(1995)[18], and Lawhorn CD (1995)[19] all observed that addition of a narcotic agonist antagonist butorphanol in the epidural space virtually eliminated side effects of nausea, vomiting, pruritis, urinary retention or respiratory depression without causing undue sedation.

Ketamine, a derivative of phencyclidine, works at a number of different target sites which could explain this analgesic effect in the spinal cord. It is an antagonist at Nmethyl-D-aspartate (NMDA) receptors[20], which are found throughout the central nervous system, including the lumbar spinal cord, and play an important role in nociceptive processing.[21] Analgesic effects may also result from agonist activity at mu-opioid receptors[22] and interaction with voltage-sensitive sodium channels[23].

A. Schnabel et al (2011) conducted a meta-analysis of 13 Randomised Control Trials (published between 1991 and 2008) and found that there was a significantly longer time to first analgesic requirements in children receiving a caudal regional anaesthesia with ketamine in addition to local anaesthetics which indicates that adding ketamine to caudal local anaesthetics provides a prolonged and improved postoperative analgesia with few adverse effects compared with local anaesthetics with no major neuropathological events in the early postoperative follow-up (6–8 weeks after surgery) of four trials.[24]

The use of caudal ketamine may elicit concern about potential neurotoxicity. No major sequelae have been reported after the use of caudal ketamine 1% in human studies. Animal studies have demonstrated the safety of intrathecal ketamine 1% after a single dose[25-27] and after multiple doses.[28] One study has claimed to show a definite neurotoxic effect of ketamine 1%[29] but those same workers subsequently demonstrated that it was the preservative chlorbutanol administered intrathecally that caused neurotoxicity whereas ketamine without preservative did not.[20] A review on the neurotoxicity of intrathecally administered drugs concluded that intrathecal ketamine is safe if used without a preservative.[30]

Caudal additives ketamine (0.5 mg/kg) and butorphanol (20 mcg/kg) when added to bupivacaine (0.25%) prolong the duration of block without any side effects. Children were found to be more sedated in group BB till 2 hours post operatively with longest duration of analgesia in Butorphanol group.

Conclusions

We can now conclude that both preservative free ketamine and butorphanol are useful additives to bupivacaine in caudal block to prolong the duration and improve the quality of analgesia in paediatric infra umbilical surgery without any undue side effects. The haemodynamics are stable intra-operatively. There is no motor blockade and urinary retention with any of these additives. Duration of analgesia up to 20 hours has been achieved with butorphanol which is excellent for the pediatric population as no supplementation of analgesia is required for a long time and child can enjoy an active life.

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