Caudal bupivacaine-neostigmine for perioperative analgesia in pediatric patients undergoing infraumbilical surgeries: A prospective, randomized, double blind, controlled study

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Citation

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Abstract

Background: Perioperative pain is of great concern for the anesthesiologist in pediatric patients. As presurgical caudal analgesia attenuates the stress response to anesthesia and surgery, we co-administered neostigmine with bupivacaine to prolong the duration of single shot caudal block. Objective: To compare the efficacy of caudal bupivacaine with or without neostigmine for perioperative analgesia in children undergoing infraumbilical surgery. Study design: A randomized, double-blinded, controlled, prospective study. Methods: 90 children, aged 2-10 years of ASA class I or II of either sex were randomly allocated into three groups (n=30) to receive a caudal injection of either 0.25% bupivacaine 1ml/kg or with 2 g/kg or 5 g/kg neostigmine, after induction of general anesthesia. Results: All children were hemodynamically stable intra and postoperatively. The caudal bupivacaine/neostigmine mixture resulted in superior analgesia compared with bupivacaine alone. Recovery to first rescue analgesic times were (mean ± SD), 6.05±2.04 h, 11.5±3.42h, and 16.86 ± 4.92 h in the bupivacaine alone, bupivacaine neostigmine 2 g/kg and bupivacaine neostigmine 5 g/kg groups, respectively (p<.05). In addition, patients in plain bupivacaine group received more doses of paracetamol than in the bupivacaine/neostigmine groups to maintain adequate analgesia in the first 24 postoperative h. Postoperative nausea and vomiting occurred in 6.7%, 16.7% and 33.3% patients in caudal bupivacaine, bupivacaine 2 g/kg neostigmine and bupivacaine 5 g/kg neostigmine groups, respectively (p<.05). Conclusion: Co-administration of caudal neostigmine with bupivacaine significantly extends the duration of postoperative analgesia with reduced need for supplementary analgesics.

INTRODUCTION

Pain induces a metabolic, neuro-endocrinal and cardio-respiratory response, which has a negative impact on morbidity and mortality i.e. outcome of the surgery. Despite an understanding of importance of adequate analgesia in adults, the treatment has frequently been only a secondary consideration in pediatric pain. Fortunately, recent studies have completely changed the approach to pediatric pain.

Caudal blockade is the most popular regional anaesthetic technique used in children. Recently it has been demonstrated that pre-surgical caudal analgesia attenuates the stress response of anaesthesia and surgery and decreases postoperative narcotic use [1] . Bupivacaine is a local anaesthetic most commonly administered in caudal anaesthesia for intraoperative and postoperative analgesia for perineal and lower abdominal surgeries [2] . Single shot "Kiddie caudal" with bupivacaine alone has short duration of action (4 - 8 hrs) [3,4] , and placement of catheter into the extradural space add to the risk of infection and tend to prevent early mobilisation [5] .

Attempts to overcome these problems many of drugs including epinephrine [3] , morphine [6] clonidine [7] , ketamine [8] midazolam [8] , tramadol [9] , fentanyl [10] , butorphanol [11] and neostigmine [8,12,13,14] have been co-administered with caudal bupivacaine to maximize and extend the duration of analgesia. Each of the above mentioned drug has its disadvantages too like caudal morphine may be associated with delayed respiratory depression [15] . Caudal clonidine and midazolam have been associated with prolonged sedation [7,8] . Behavioral side effects are reported with the use of caudal

ketamine [16] and increased incidence of postoperative nausea and vomiting associated with caudal tramadol and neostigmine. [917]

In past, neostigmine has been co-administered with local anesthetics in caudal analgesia in pediatric patients undergoing genitourinary / urological surgeries [1417] . Till date, there has been no study of its use in pediatric lower abdominal surgeries. Therefore, this double blinded, prospective, randomized, controlled study was designed to compare the effect of caudal neostigmine (2µg/kg or 5µg/kg) with bupivacaine on perioperative analgesia and associated side effects, in paediatric patients undergoing lower abdominal surgeries.

MATERIAL AND METHODS

After obtaining approval from the ethics committee of the University, an informed written parental consent was obtained. Ninety children aged 2-10 years, belonging to ASA physical status I or II of either sex, with ±20% of ideal body weight, undergoing lower abdominal surgeries of 1 to 2 hours duration, were selected for this study.

The exclusion criteria were; contraindication to caudal block, history of hypersensitivity reaction to any of the study medications, bleeding diasthesis, analgesic ingestion in the preceding week and preexisting neurological or spinal diseases.

A peripheral line was secured using 50% N_2O in oxygen and halothane given by mask. Intravenous atropine 0.01 mg/kg was given to each child. General anesthesia was induced with sodium pentathol 4-6 mg/kg followed by succinylcholine 1.5 mg/kg to facilitate endotracheal intubation. The anaesthesia was maintained using 60% N_2O in oxygen, 0.5-1% halothane and intravenous vecuronium bromide as non- depolarising muscle relaxant on Ayre's T piece or Pediatric Bain's circuit. No intraoperative intravenous sedation or analgesic was administered to any of the child and halothane was adjusted to maintain heart rate at ± 20% of baseline pre-induction value.

Caudal block was performed with patient in left lateral position using 23 gauge, short beveled needle under sterile conditions. The patients were randomly assigned into one of the three groups by using a computer generated table of random numbers.

Group I: Patient received 1 ml/kg of 0.25% caudal bupivacaine alone.

Group II: Patient received 1 ml/kg of 0.25% caudal bupivacaine in combination with 2µg/kg neostigmine.

Group III: Patients received 1 ml/kg of 0.25% caudal bupivacaine in combination with 5µg/kg neostigmine.

Surgery was allowed to begin after 15 minutes of the caudal injection. Parameters observed were: heart rate, arterial pressure and SpO_2 at baseline (before induction), after induction (before caudal block) and after caudal block and then every 10 minutes till completion of the surgery. After the completion of operation, the time between discontinuing anesthesia to spontaneous eye opening was also recorded (recovery time).

In the recovery room when the child became awake, the investigator unaware of the caudal analgesic treatment recorded the ventilatory frequency, arterial blood pressure, and heart rate at 2, 4, 6, 12, 24 hours, post-operatively. Post-operative pain was assessed using "Modified Objective Pain Score (MOPS)"(Table-I) [6] and rescue analgesia in the form of oral paracetamol (20mg/kg) was given at a score >4. Side effects/complications were also recorded.

Figure 1

Table 1: Modified Objective Pain Score (MOPS)

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

Mean age, weight, pain scores and time to rescue analgesia in each group were compared with each other using one-way analysis of variance (ANOVA) with post hoc comparisons using the Bonferroni multiple range test. The Pearson chi-square test with Fisher's exact test were used to compare the sex ratio, ASA class and the incidence of use of post-operative urinary catheters and complication in the three groups.

The study was designed to detect a minimum of 20%

difference in the requirement of rescue analgesia in the study groups to provide 95% power for two-tail t test at the level of 5% significance. A minimum sample size of 20 patients was determined in each group. To allow increased variability in effect size, 30 children were included in each group.

RESULTS

All the groups were comparable regarding patient characteristics (age, sex, weight, ASA class, duration of surgery and recovery times (Table-2).

Figure 2

Table 2 :Patient Characteristics

Groups	I	II	III
Age (in years)	5.12±1.12	5.42±1.34	5.28±1.42
Sex (M:F)	21:9	22:8	20:10
Weight (in kg)	16±4.59	15.9±4.24	16.6±5.42
ASA Class (I:II)	11:19	12:18	10:20
Duration of surgery (in min)	110±15.10	117±17.82	115±19.42
Recovery time (in min)	5.5±1.3	6.0±1.0	5.7±1.5

Data is being presented as mean ± SD or ratio.

Intraoperative hemodynamic variables (heart rate, blood pressure and oxygen saturation) were also comparable among the three groups (data not shown). None of the children required treatment for hypotension or bradycardia during surgery. All children were sufficiently awake when transferred to the recovery room breathing room air.

Caudal administration of bupivacaine with the addition of neostigmine resulted in superior analgesia compared with the plain bupivacaine group. Recovery to first analgesic times was 6.05±2.04 h, 11.5±3.42 h and 16.86±4.92 h, respectively in the plain bupivacaine, bupivacaine with 2µg neostigmine and bupivacaine with 5µg neostigmine groups ($p<0.05$) (Table-3).

Figure 3

Table 3: Duration of Analgesia (in Hours)

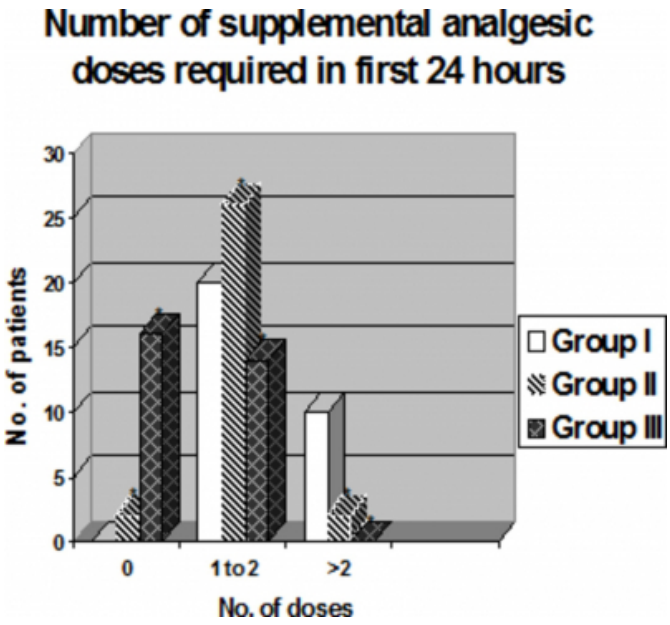
Groups	I	II	III
n	30	30	30
Mean	6.05	11.05*	16.86*
S.D.	2.04	3.42	4.92

*P<0.05 (among all the groups)

In addition, significantly more patients in plain bupivacaine group received rescue analgesia in the form of oral paracetamol syrup than in the bupivacaine-neostigmine groups to maintain adequate analgesia in the first 24 postoperative hours ($p<0.05$) (Figure 1).

Figure 4

Figure 1



* P <0.05 (Among all the three groups)

We found no significant difference in post-operative sedation scores (data not shown). No difference was observed regarding urinary retention requiring catheterization among the three groups. Times to first standing were not measured but we did not observe significant motor block and all children moved their legs spontaneously when leaving the recovery room 6 hr after caudal injection.

Vomiting occurred in recovery room in 2 (6.7%), 5 (16.7%) and 10 (33.3%) patients in the caudal bupivacaine, bupivacaine 2µg neostigmine and bupivacaine 5µg

neostigmine groups, respectively. This difference was statistically significant between plain bupivacaine and bupivacaine 5µg neostigmine group ($p<0.05$). Postoperative vomiting was not severe or repeated and was effectively managed with a single dose of I.V Ondensetron 0.1 mg/kg. Oral intake and discharge from hospital were not delayed. There were no instances of post-operative sedation, hypotension, bradycardia or pruritus, in any of the groups.

DISCUSSION

Caudal epidural anesthesia is commonly used in pediatric practice for treatment of pain following surgical procedure. Wide acceptance of caudal block is due to technical simplicity, reliability, safety and rapid performance in large series of infants and children [18]. Single shot caudal block is commonly used but this may have relatively short duration of action. We have used two doses of neostigmine (2µg /kg and 5µg/kg) in combination with bupivacaine to extend the duration of analgesia. The present study demonstrated that caudal neostigmine 5µg/kg in combination with 0.25% caudal bupivacaine markedly prolong post-operative analgesia and reduce the need for rescue analgesia in children undergoing lower abdominal surgeries.

The analgesic effect of caudal neostigmine observed in present study may be attributed either to the direct action at spinal cord level after transdural diffusion to CSF or a peripheral anti-nociceptive effect at surgical site after systemic absorption. Intrathecal neostigmine causes analgesic effect in human by exhibiting break down of acetylcholine (Ach) in dorsal horn of spinal cord [19]. Spinal muscarinic receptors are believed to be involved in the analgesic property of spinal neostigmine [20]. Studies also support the hypothesis of a peripheral anti-nociceptive effect of neostigmine [21].

Caudal anaesthesia in combination with general anaesthesia is used widely for many surgical procedures in children. Unintentional I.V. administration of local anaesthetics, resulting in severe cardiovascular and central nervous system complications, has been described in literature [22]. A potential advantage of subarchanoid neostigmine is that it may counteract local anaesthetic and clonidine-induced hypotension and tends to increase the respiratory rate [2324]. The addition of neostigmine has been demonstrated to effectively counteract the inhibitory effect of spinal bupivacaine on the sympathetic nerve activity [25]. The effectiveness of the small doses of caudal neostigmine (2 µg/kg & 5µg/kg) used in the present study suggests a spinal rather than a peripheral mechanism of action. The perioperative hemodynamic stability observed with the use of caudal neostigmine/bupivacaine mixture in the present study supports this view. The favorable hemodynamic and respiratory profile of neuroaxial neostigmine makes this drug an attractive alternative to the currently used epidural anti-nociceptive drugs.

Neostigmine preparation used in the present study included methyl and propylparabens as preservatives. Two investigations have confirmed that chronically administered intrathecal neostigmine containing methyl and propylparabens is not associated with any behavioral, chemical or histopathological evidence of neurotoxicity [2627]. Our study has no long term follow-up of the patients, so we can not comment on this aspect but none of the patient complained of any problem related to neurotoxicity in the doses (2µg/kg or 5µg/kg), we have used.

Caudal epidural neostigmine with or without local anesthetics has been used in many studies to extend the duration of analgesia in pediatric patients. Single caudal injection of 1 µg/kg neostigmine mixed with bupivacaine offers no advantage over bupivacaine alone for postoperative pain relief in children [12]. Caudal neostigmine 2 µg/kg diluted to normal saline (1 ml/kg) provided postoperative analgesia comparable to caudal bupivacaine alone and co-administration of two drugs was associated with extended postoperative analgesia and reduced need for supplemental analgesia in a previous study [14]. In the view of above two studies we have compared of 2µg/kg and 5µg/kg neostigmine with bupivacaine and we found that both the doses have significantly extended the duration of postoperative analgesia and reduced the need of rescue analgesia. It was previously noticed that caudal neostigmine provides a dose dependent analgesia [17] but in contrast, in a recent study, caudal neostigmine (2, 3 and 4 µg/kg) with bupivacaine produced a dose independent analgesic effect (approx. 16 -17 hrs) in children as compared to bupivacaine alone (approx. 5 hrs) and a reduction in postoperative rescue analgesic consumption without increasing the incidence of adverse effects [14]. Our study demonstrates a dose dependent analgesic effect of caudal neostigmine.

Despite its proven analgesic effectiveness neuraxial neostigmine is not yet a widely accepted analgesic modality in clinical practice and continue to be an off-label indication. This is mainly because of frequent nausea and vomiting [28].

In a previous dose response study of intrathecal neostigmine in a dose range of 6.25 - 50µg showed a relatively frequent incidence of nausea (33 - 67%) and vomiting (17-50%) [29]. Caudal epidural neostigmine in pediatric patients in previous studies showed significant postoperative nausea and vomiting in a dose of 2µg/kg [1214] but in a recent study co-administration of neostigmine upto 4 µg /kg did not show any increase in side effects. However, a previous dose response study of caudal neostigmine for postoperative analgesia in pediatric patients showed significant incidence of nausea and vomiting with doses exceeding 30µg/kg [17]. In our study, vomiting occurred in recovery room in 2 (6.7%), 5(16.7%) and 10 (33.3%) patients in caudal bupivacaine 0.25% alone and mixed with 2µg/kg neostigmine and 5µg/kg neostigmine, respectively. The incidence was found significantly higher with 5µg/kg neostigmine when compared to plain bupivacaine. In view of the various conflicting results till date regarding benefits versus side effects of different doses of caudal neostigmine, we recommend further clinical research to identify the minimally effective caudal neostigmine dose that should have analgesic efficacy but minimal or no side effects in pediatric patients undergoing lower abdominal surgeries.

In summary, co-administration of neostigmine with bupivacaine prolonged the duration of surgical analgesia after a single shot caudal injection, thus allowing single shot caudal anaesthesia to be recommended for surgery lasting more than 4 hours. This could be a safe and cheap alternative to extradural/caudal catheter placement for surgical procedures of intermediate duration. It provides excellent perioperative hemodynamic stability. Indeed, clinically significant undesirable side effects such as nausea and vomiting were observed in children who received 5µg/kg neostigmine. Therefore, neostigmine may be the drug of choice to prolong the duration of caudal analgesia provided by a single injection in children with due prophylactic to its side effect (nausea and vomiting).

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