 DOI: 10.18231/2394-4994.2017.0092

A study of the effect of caudal epidural neostigmine for post operative pain relief in children undergoing lower abdominal surgery

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Abstract

Introduction and Objective: Providing adequate pain relief has always been part of anaesthesiologist's role in the perioperative period beyond post anaesthesia care unit. Among the many adjuvants studied neostigmine was also found to be effective in acute post-operative and chronic pain. We have studied the analgesic efficacy of caudal bupivacaine with and without neostigmine in children.

Materials and Method: In this randomized double blind study, sixty children belonging to ASA I and II, aged 2-8 years undergoing lower abdominal surgeries were randomly allocated into two groups to receive a caudal injection of 0.25% bupivacaine alone or a mixture of 0.25% bupivacaine 0.5ml/kg with 2µg/kg neostigmine. Monitoring of scores for pain, postoperative nausea and vomiting was performed by an Anaesthesiologist blinded to the study allocations.

Results: Time to the first analgesic administration of syrup Paracetamol was longer ($P<0.05$) with mean duration of analgesia of 14.6 hrs in the bupivacaine-neostigmine than in the bupivacaine only group with a mean duration of 4.3 hrs. Side effect such as emesis was not significantly different between the two groups.

Conclusion: Caudal co-administration of bupivacaine with neostigmine produces significant prolongation of the duration of postoperative analgesia when compared to caudal bupivacaine alone.

Keywords: Bupivacaine, Caudal epidural, Neostigmine, Ramsay scale, Aldrete score

Introduction

Pain now has become the fifth vital sign and has become a critical focus of the patient management. Optimization of pain has a major role in improving the clinical outcome, felicitate early recovery, mobilization and return to daily living. Mismanaged pain relief can lead to physiologic complications, psychological distress, and personality changes in developing children, family disruption, interruption of hospital routine and prolongation of hospitalization with resultant increased costs. Many methods of reducing were used to avoid under treatment of pain in pediatric patients. Many adjuvants have been tried with bupivacaine like clonidine, morphine, and fentanyl etc.[(1)] Various methods have been tried to prolong the duration of regional analgesia with local Anaesthetic like placing a catheter and the use of an adjuvant. Caudal epidural block with bupivacaine is very effective until the immediate postoperative period.[(10-11)] Though accepted the presence of a catheter for postoperative pain relief has a potential risk of infection and the use of adjuvants like opioids, clonidine and ketamine has limitations due to the adverse effects such as Respiratory depression, sedation, nausea and vomiting.[(21)]

There has been various studies of neostigmine as an adjuvant along the local anaesthetic epidurally and it's been established as an analgesic in adults and children. Caudal neostigmine in a dosage of 2µg/kg with the local anaesthetic has been found to prolong analgesia. Neostigmine acts by inhibiting the breakdown of acetylcholine the endogenous neurotransmitter thereby producing analgesia when given with a central neuraxial route.[(1)] It has been theorized that the analgesic effect is mediated through spinal muscarinic receptors. In the pediatric patients a dose response study of caudal neostigmine has proved to be safe and effective[(7)] and also it has been observed that with neostigmine in the range of 20-50ug/kg a dose dependent analgesia is produced. In children undergoing genitourinary surgery caudal neostigmine 2ug/kg with bupivacaine 0.25% has an extended duration of post-operative analgesia up to 20 hrs, and thereby reduces the need for additional analgesics.

Aim

To study the effect of neostigmine on the duration of caudal block produced by 0.25% bupivacaine in a volume of 0.5ml/kg in children undergoing lower abdominal surgery.

Materials and Method

After the institutional ethical committee approval 60 children belonging to ASA I and II in the age group of 2 years to 8 years scheduled to undergo elective lower abdominal surgery at Raja Mirasudhar Hospital, Tanjavur Medical College between January and August 2007 were chosen for this study.

Children with local sepsis, bleeding diathesis, cardio respiratory diseases, preexisting neurological or spinal diseases and congenital anomaly of back were excluded. The parents were informed about the procedure and a written consent was obtained for postoperative

analgesia. All were kept nil oral for 6 hours and no premedication was prescribed.

In the operating room baseline cardio respiratory parameters such as pulse rate, systolic blood pressure, ECG, respiratory rate and (SpO_2) were recorded start of procedure until and monitored continuously until extubation. Intravenous line was secured after achieving adequate depth of anaesthesia by inhalation of halothane at increasing concentrations in N_2O and oxygen mixture. After intravenous access Thiopentone was used as the induction agent. Intubation was performed with an appropriate size uncuffed endotracheal tube. No opioids or benzodiazepines were used intraoperatively. Under controlled ventilation, muscle relaxation was maintained with required dose of atracurium calculated according to the weight of the child.

The children were randomly placed into two groups with 30 patients in each group

Group B: 0.25% bupivacaine alone

Group BN: 0.25% bupivacaine with 2µg/kg neostigmine

The children were placed in left lateral position with hips and knees flexed. The dosage of local anaesthetic was calculated according to the ARMITAGE formula.[6]

Under strict asepsis with a 22G hypodermic needle the sacrococcygeal membrane was penetrated, epidural space identified with loss of resistance and the calculated volume and dosage was injected into the caudal space after gentle aspiration to rule out any intrathecal and intravascular placement. The preparation of neostigmine used in this study was 0.5 mg/ml of ampoules which contained neostigmine methyl sulphate. General anaesthesia was maintained with a mixture of oxygen and nitrous oxide in 40% 60% along with halothane. 20 min after administering caudal block surgical incision was made during which time the patients were prepared and draped.

Adequate analgesic effect was defined as stability hemodynamically as indicated by absence of increase in heart rate and systolic rise of blood pressure for more than 15% when compared with basal values obtained just before surgical incision with the Minimum alveolar concentration of halothane at 1%. If there is a rise of systolic blood pressure for more than 15% then analgesia was considered inadequate and rescue analgesic with fentanyl at the dosage of 2µg/kg was given. Intraoperative fluid management was calculated using holiday and Segar formula. After the surgery the children were shifted to the recovery room for continuous observation and monitoring. Postoperative sedation score was done with RAMSAY scale every hour for first six hours and every 2 hours thereafter. The recovery was assessed by the Modified ALDRET Score. Later the children were transferred to the postoperative ward where respiratory rate, (SpO_2). Pulse rate and systolic blood pressure were continuously monitored.

Modified Alderete Score

Observation	Modified Alderete Criteria	Score
Activity	Able to move all 4 extremities voluntarily or on command	2
	Able to move 2 extremities voluntarily or on command	1
	Not able to move extremities voluntarily or on command	0
Respiration	Able to deep breathe and cough freely	2
	Dyspnea or limited breathing	1
	Apneic	0
Systolic Blood Pressure	$\pm$ 20 % of Pre-anesthetic level	2
	$\pm$ 20 – 50 % of Pre-anesthetic level	1
	$\pm$ 50% of Pre-anesthetic level	0
Consciousness	Fully awake	2
	Arousable	1
	Not responding	0
Oxygen saturation	Able to maintain O_2 saturation > 92% on room air	2
	Needs O_2 inhalation to maintain O_2 saturation > 90%	1
	O_2 saturation < 90% even with O_2 supplement	0

Objective pain Scale Score devised by Hannallah RS was used to assess the intensity of pain. Each parameter was awarded a score of 0-2 accordingly. The sum total of the awarded score was taken at each time interval. This measures pain as a physiological variable, blood pressure along with behavioral changes. This scoring is a sensitive and reliable tool in assessment of postoperative pain in children who are not able to verbally comment on their pain. This takes into account the systolic blood pressure, cry and it's response to love and care, movement, agitation and verbal evaluation as described by Hannallah RS.[4]

Objective Pain Scale

Observation	Criteria	Score
Systolic blood pressure	±10% of pre-op value >20% of pre-op value >30% of pre-op value	0 1 2
Crying	Not crying Crying but responds to TLC* Crying not responds to TLC*	0 1 2
Movement	None Restless Thrashing around	0 1 2
Agitation	Asleep or calm Mild agitation Hysterical	0 1 2
Verbalization of Pain	Asleep, States no pain Vague, Can't localize Localize pain	0 1 2

*TLC-Touch, Love and Care

Complications such as hypotension, urinary retention, nausea and vomiting were noted and managed accordingly. Paracetamol 10mg/kg was administered as rescue analgesia if pain is felt which was taken as objective pain scale value of 5. The duration of analgesia was calculated from the time of epidural injection to OPS score of 5. Respiratory depression was taken as a decrease of (SpO_2) of less than 93% or a decrease in respiratory rate of less than 10 /min.

Ramsay sedation score of V or VI was considered as excessive sedation and urinary retention was defined as inability to void urine for a period of at least 8 hours. The anaesthesiologists who performed the caudal block and monitoring of scores for pain, nausea and vomiting and sedation were not involved in the study.

Observation and Results

Sixty patients who were scheduled for elective lower abdominal surgery physical status ASA I and II were taken up for the study. They were randomly allocated into two groups of 30 patients each to receive caudal block.

Group BN received a mixture of Bupivacaine 0.25% and neostigmine at 2µg/kg, 20 minutes before surgery and Group Received 0.25% bupivacaine 20 minutes before surgery. All the patients were assessed by a blinded observer during the postoperative period.

The distribution of age in both groups ranged was between 2-8 years. In group B 66.7% are male and 33.3% are female and in group BN 73.3% are male and 26.7% are female. The sex distribution in both the group is also not much different. Hence there is no bias in the age and sex distribution. There is no statistical difference between the two groups.

Table 1: Type of Surgery

Surgical procedure	Group B	Group BN
Herniotomy	15	15
PV sac ligation	8	5
Hypospadias	7	10
Total	30	30

It can be noted that there is no bias in the type of surgical procedures as their distribution is quite similar (Table 1).

Duration of Analgesia: The duration of analgesia in group B (0.25% bupivacaine) ranged between 3 to 5 hours with a mean duration of 4.3 hours. In group BN (0.25% Bupivacaine + 2 µg/kg Neostigmine) the duration of analgesia ranged between 10 to16 hours and had a mean duration of 14.6 hours (Table II).

Table 2: Duration of Analgesia

Duration of Analgesia	Group B	Group BN
Range	3-5	10-16
Mean	4.3	14.6
Standard Deviation	0.75	1.52

It can be seen that in group BN the mean duration of analgesia was 14.6 hours, whereas in group B it was only about 4.3hours. The group BN had a longer duration of analgesia when compared with group B. This duration of analgesia is statistically significant as detected by using one sample T test. The probability value is less than 0.05 (P value <0.0005) and therefore is highly significant. There post-operative sedation score were not different between the groups in (P> 0.05).

Side effects

Nausea and Vomiting: One Patient in group B (3.3%) and two patients in group BN (6.6%) had nausea and vomiting and were managed with intravenous ondansetron 0.1mg/kg. There were no differences in the incidence of urinary retention between the two groups. Other side effects such as hypotension, respiratory depression or apnea were not seen in any child.

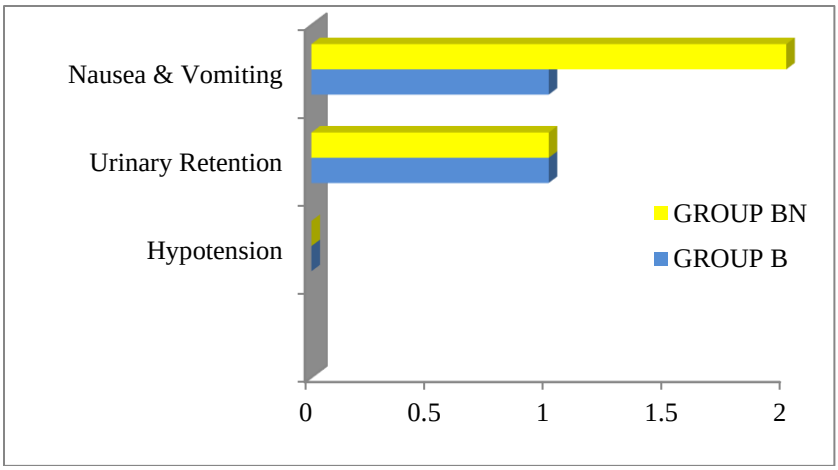

Fig. 1: Side effects

Table 3: Frequency Statistics

	Gp B Analgesia	Gp BN Analgesia	Wt Gp B	Wt Gp BN	Age Gp B	Age Gp BN
N	30	30	30	30	30	30
Missing	0	0	0	0	0	0
Mean	4.3	14.6	21.33	23.87	4.43	5
Median	4	15	24	26	4	5
Std. Deviation	0.75	1.52	5.79	4.76	1.85	1.6

Table 6: Duration of Analgesia

	N	Mean	Std. Deviation	Std. error mean
Gp BN Analgesia	30	14.6	1.52	0.28
Gp B Analgesia	30	4.3	0.75	0.14

Here the mean time in the BN group (14.6 hrs) is higher than the group B (4.3). When we take the mean value of B group as test value and compare it with BN group the difference in the mean observed is statistically significant ($p<0.0005$) with a 99% CI of 9.53 to 11.07.

Statistical Analysis: Microsoft office excel 2010 version was used for the data record. Measurement comparison was done with student t test and the nonparametric data done by chi-square test with IBM software SPSS15 statistics. Significance was considered if the P value is < 0.05.

Discussion

Postoperative pain is a universal concern and more so in the pediatric population. There has been numerous studies using various methods involving pharmacological or psychological or both. Various adjuncts were used to prolong postoperative analgesia that includes various pharmacologic agents which had been studied extensively. One such drug is neostigmine which was found to be effective in prolonging the duration of postoperative analgesia without any major adverse effects when administered in central neuraxial blocks.

Neuraxial neostigmine was found to produces analgesia in animal studies and later in human volunteers and it was found useful in patients with acute postoperative and chronic pain.[10,11,12,13] Neostigmine prevents the metabolism of acetylcholine by inhibiting the action of cholinesterase thereby producing analgesia Eisenach et al.[15] This increases the acetylcholine concentration in the CSF gives the analgesic effect which is effected by the M_1 spinalM_1 M_2supraspinal muscarinic receptors and nicotinic receptors.[15]

Krukowski et al[16] Studied the effect of various doses of intrathecal (10, 30 and 100µg) found a dose independent analgesia lasting for nearly ten hours in all the groups. Study done by Lauretti et al[17,18,19,20] patients undergoing knee surgery with addition of neostigmine 1, 2 0r 4 $\mu g/kg^{-1}$ and 25 µg - 75 µg in patients undergoing vaginal hysterectomy respectively made a similar inference of dose independent analgesia.

Batra YK, et al[21] demonstrated that neostigmine in doses of< 10 µg/kg or > 10 µg/kg neuraxially had no difference in the duration of analgesic effect and the lowest dose of 2 µg/kg have potentiated the analgesic effect of neuraxial local anaesthetic. This dose also has an advantage of reducing the potential gastrointestinal effects such as nausea and vomiting.

Our observation and results in our study confirmed the analgesic efficacy and also in providing a longer duration of analgesia with caudal neostigmine which is

similar to the outcome of Lauretti et al,[17,18,19,20] Batra YK, et al.[21]

Batra YK, et al[21] reported that the duration of analgesia lasted for nearly 10 -16 hours and in our study the mean duration of analgesia was 14.6 hours which correlates with our values. This value is statistically significant as probability value is less than <0.05.

In the present study the duration of analgesia in group B was 3 to 5 hours and in Group BN the duration ranged from 10-16 hours which was very similar and comparable to the results observed by Abdullatif et al[22] and also by Rudra et al.[23]

Abdullatif et al[22] in their study claimed that the duration of analgesia of caudal neostigmine alone as an analgesic is comparable to that of 0.25% caudal bupivacaine. Therefore the combination of both will have a synergistic effect in extending the duration of postoperative analgesia which correlates to the finding in this study.

Although the use of neuraxial neostigmine has been associated with gastrointestinal side effects such as nausea and vomiting, these were very minimal in our study due to the minimal effective dosage. Lauretti et al and Roelants et al[24] reported that the gastrointestinal adverse effects were negligible when neostigmine is given epidurally; Abdullatif et al found similar results and was statistically insignificant. They also inferred that the incidence of nausea and vomiting is independent of the dose of neostigmine epidurally and it should also be remembered that these adverse effects could also be attributed to bupivacaine.[25,26]

In the study group BN the nausea and vomiting incidence was 6.6% and this is similar to the study results of Rudra et al who reported the incidence at less than 20%.

Conclusion

Caudal epidural analgesia using a combination of 0.25% bupivacaine0.5ml/kg and neostigmine (2µg/kg) significantly prolonged the postoperative analgesia when compared to 0.25% bupivacaine alone in children undergoing lower abdominal surgical procedures without any significant increase in side effects.

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