Original Research Article

Dose response of caudal neostigmine for postoperative analgesia in paediatric inguinal hernia repair: a prospective randomized double blinded study

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Abstract

Objective: This study was designed to evaluate the analgesic efficacy, duration of analgesia, and side effects of three different doses of caudal neostigmine used with bupivacaine in unilateral inguinal hernia repair. **Design:** This is a prospective randomized double blinded study. **Setting:** This study was carried out over one year at a single tertiary care centre.**Participants:** Eighty children, ASA I, between 2 years and 7 years, undergoing elective unilateral inguinal hernia repair were recruited for this study. **Intervention**: The 80 subjects were randomly allocated to 4 groups(n=20) to receive the following drugs by caudal route at 1ml.kg^{-1}: Group B – 0.25% plain bupivacaine; Group BN2 – 0.25% plain bupivacaine with neostigmine 2 µg•kg^{-1}; Group BN3 – 0.25% plain bupivacaine with neostigmine 3 µg•kg^{-1} and Group BN4 – 0.25% plain bupivacaine with neostigmine 4 µg•kg^{-1}.Postoperative pain was assessed for 24 h using AIIMS pain score. The time taken for first administration of rescue analgesia and the total amount of analgesic consumed was studied. The following adverse effects were documented: hemodynamics, PONV, sedation, prolongation of motor block or delay in micturition. **Observation and main results:** The neostigmine bupivacaine groups showed a statistically significant prolongation in the time taken to first administration of rescue analgesia: (6.10±1.55 h) in Group B, (15.70 ± 1.81 h) in Group BN2, (15.85±3.44 h) hours in Group BN3, (16.45±1.15 h) in Group BN4; p<0.01). From the 4th postoperative hour, the average pain score in group I 0.7(0.8) was statistically higher than group II (0.05), III (0.1) IV (0.15) p<0.01. Total number of doses of rescue analgesia in group B (1.95±0.69) was more than in group BN2 (1.20±0.41), BN3(1.15±0.37), BN4(1.10±0.31) , and this was statistically significant (p<0.01) (table 2). There was no statistically significant difference in time to first administration of rescue analgesia and also in the total analgesic consumption between groups BN2, BN3 and BN4 (p>0.05).Adverse effects were not different between the four groups.**Conclusion**: Caudal neostigmine (2, 3 and 4 µ.kg^{-1}) with bupivacaine 0.25% administered at 1ml.kg^{-1} body weight produces a dose independent prolongation of analgesic effect (16 h) in children as compared to those receiving caudal bupivacaine alone (6 h) and a reduction in number of postoperative rescue analgesia without increasing the incidence of adverse effects

Keywords*:* neostigmine,caudal block, postoperative analgesia, paediatric analgesia, regional anesthesia.

Introduction

The first twenty four hours following surgery are often the most painful part of the post-operative period[1]. Any prolongation of the pain relief from a single injection caudal block has the potential to translate into clinically significant positive impact in this period[2,3]. Adjuvants are added to local anesthetic solutions with the goal of extending the quality and duration of post-operative pain without causing serious side effects or complications[4]. Non-opioid adjuvants have been investigated to overcome the disturbing side effects of opioids which include vomiting, pruritus, urinary retention, sedation and potential for respiratory depression mandating prolonged supervision[5]. Prior studies have evaluated neostigmine as a caudal adjuvant in various subumbilical procedures[6].

Neostigmine, an anticholinesterase inhibitor, causes the accumulation of acetylcholine in the spinal cord. Inhibition of afferent pain impulses to lamina IIIand V of the dorsal horn through stimulation of the spinal muscarinic M1 and M2 receptors has been proposed as the mechanism of neuraxial analgesia[7].The reported effective caudal dose[8-14].has ranged from 1.5 µg.kg^{-1} to 6µg.kg^{-1}.The dose response relationship of caudal neostigmine is not clear. The incidence of side effects, particularly postoperative nausea and vomiting (PONV), have raised questions on the suitability of neostigmine as a caudal adjuvant in pediatric practice[15].This randomized double blinded study was conducted to determine if increasing doses of neostigmine produced prolongation of caudal analgesia when combined with bupivacaine in children aged between 2 years to 7 years undergoing elective unilateral inguinal hernia repair. Any increase in side effects was also noted as a secondary outcome.

Conduct of the study

Patient selection-After obtaining Institutional Ethics Committee approval and written informed consent from the parents or legal guardian of the patients, this study was conducted over one year at a single tertiary care centre, Sree AvitomThirunal Hospital, aligned to Government Medical College, Thiruvananthapuram. Eighty ASA class I children between 2 years to 7 years, and weighing 10Kg-20 Kg, who were scheduled for elective unilateral inguinal herniotomy were recruited for the study in a double- blind, randomized, prospective manner. Exclusion criteria included guardian refusal, class other than ASA I, and any contraindication to caudal block.

Anesthesia -No premedication was prescribed to any child. An intravenous line was established after inhalational induction with sevoflurane in stepwise incremental doses up to 6% via a Jackson Rees breathing circuit withoxygen and nitrous oxide. The airway was established using a laryngeal mask airway (LMA). Anesthesia was maintained with 66% nitrous oxide in oxygen and sevoflurane. Standard monitors including electrocardiography, non-invasive

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arterial pressure, pulse oximetry, end tidal carbon dioxide, and gas analyser were applied during induction and maintenance of anaesthesia.Spontaneous breathing was maintained during surgery. After completion of surgery, the LMA was removed, and the child was sent to a post-anaesthetic care unit so long as there was no intraoperative compromise in airway or haemodynamic instability.

Intervention -An anesthesiologist not involved in patient care prepared the study solutions by following standard written instructions. Patients were allocated randomly to one of four groups (n = 20) by a computer generated randomization scheme to receive the following drugs by the caudal route;Group B – 0.25% plain bupivacaine 1.0mL•kg^{-1}; Group BN2– 0.25% plain bupivacaine 1.0mL•kg^{-1} with neostigmine 2 µg•kg^{-1}; Group BN3 – 0.25% plain bupivacaine 1.0 mL•kg^{-1} with neostigmine 3 µg•kg^{-1} and Group BN4 – 0.25% plain bupivacaine 1.0mL•kg^{-1} with neostigmine 4 µg•kg^{-1}. Caudal block was administered by an investigator who was blinded to the caudal drug composition.After induction of anesthesia, patients were turned to the left lateral position. Caudal block was performed using a 23-gauge short-bevel needle under aseptic conditions. Surgical intervention was allowed 15 minutes after the caudal injection. No intraoperative sedatives or opioids were administered.

Assessment-Heart rate (HR), mean arterial blood pressure (MAP), respiratory rate (RR) and peripheral oxygen saturation (Spo2) were recorded before the anesthesia induction and every 5 minutes after the administration of caudal anesthesia. An increase in HR or MAP by >15% of pre-incision baseline values within 15 minutes of skin incision indicated failure of caudal anesthesia and the child received a rescue opioid (fentanyl; 2 µg.kg^{-1}).Subjects who required rescue opioid were excluded from the study. During surgery, children received lactated Ringer's solution at 6 mL • kg^{-1} • h^{-1}. An intraoperative decrease of MAP or HR by >30% was defined as hypotension or bradycardia, respectively, and was treated by fluid bolus, ephedrine, or atropine, as necessary.Assessment of postoperative pain was performed by an observer who was blinded to the randomization, and was made at 1, 2, 4, 8, 12 and 24 hours after caudal block. The same observer performedthe assessment in all subjects.Pain in the postoperative period was assessed by using All India Institute of Medical Sciences (AIIMS) pain discomfort scale[16,17].The scale uses five criteria: respiratory rate, heart rate, discomfort, cry and pain at site of operation. Each criterion scores from 0 to 2 to give a possible total score of 0–10 (see Table 1).Duration of analgesia was defined as the time interval from placement of caudal block to first demand for supplemental analgesia. Supplementary analgesia was given using oral paracetamol 15mg.kg^{-1} to patients who had an AIIMS pain score equal to or more than 4 at any time postoperatively during the first 24 hours. The total number of doses of postoperative analgesic in 24 hours was noted. Sedation score (opens eye spontaneously-0, opens eye to speech-1, opens eye when shaken-2, unarousable-3), time to limb movement and time to first micturition after caudal block was noted.PONV in the first 24 hours was documented. Subjects with one or more episodes of nausea or vomiting received intravenous ondansetron at 0.1 mg.kg^{-1}.

Statistical interpretation -A sample size of 20 patients in each group was determined with a target to detect a prolongation of postoperative analgesia by 200 minutes compared with placebo, with a power of 0.88 and a significance level (α) of 0.05[9,18].Data were analyzed using statistical package for the social sciences (SPSS) version 22.0 (IBM, Chicago, Illinois, USA). Numerical variables were presented as mean and standard deviation (mean ± SD) and categorical variables were presented as number (proportion,%). One-way ANOVA was used for between-group comparisons of numerical variables, if its assumptions were fulfilled, otherwise for non-parametric, the Kruskal– Wallis test was used. χ2-testwas used for between group comparisons of categorical variables. Kaplan Meier survival curves were drawn with the time to first analgesic administration in the postoperative period being considered as the event and log rank analysis performed for comparison between the groups. Data were considered significant when probability value was less than 0.05 ($p<0.05$).

Results

Eighty children were recruited in this study.The caudal blocks were successful in all patients. The four groups were similar with respect to age, weight and duration of surgery (Table 2). The intraoperative SpO2, heart rate and blood pressure were within the physiological range and were comparable in the four groups ($p>0.05$). There was no bradycardia, hypotension or desaturation in any of the subjects throughout the study period.

Analgesic efficacy and duration-Kaplan Meier survival curves were drawn for the time to first analgesic administration in the postoperative period (figure 1). The study period concluded at 24 hours. The neostigmine bupivacaine groups showed a statistically significant prolongation in the time taken to first administration of rescue analgesia:(6.10±1.55 h) in Group B, (15.70 ± 1.81 h) in Group BN2, (15.85±3.44 h) hours in Group BN3, (16.45±1.15 h) in Group BN4; $p<0.01$). Figure 2 presents pain scores during the 24 h postoperative period. The pain scores from the 4 h postoperative mark were significantly lower in the neostigmine groups. There was no statistically significant difference between group BN2, BN3 and BN4. Total number of doses of rescue analgesia in group B (1.95±0.69) was more than in group BN2(1.20±0.41), BN3(1.15±0.37), BN4(1.10±0.31) , and this was statistically significant ($p<0.01$) (table 3).There was no statistically significant difference in time to first administration of rescue analgesia and also in the total analgesic consumption between groups BN2,BN3 and BN4 ($p>0.05$). The number of patients who required more than one dose of rescue analgesia was more in group B (17/20,85%) when compared to group BN2(1/20,5%) BN3 (3/20,15%), BN4(3/20,15%), $p<0.01$.

Adverse effects -The adverse effects noted in the first 24 hours were sedation scores, time taken for first leg movement, time taken to first pass of urine, PONV and pruritus (Table 4). Sedation scores at 1,2,4,8,12 and 24 hours was comparable in all four groups with none of the patients having sedation score of>1 at any time ($p>0.05$) (figure 3). There was no statistically significant difference in the time taken for first leg movement after surgery in all study groups (98.25min in group B, 100min in group BN2, ,102.5min in group BN3 and 101.50 min in group BN4; $p>0.05$). Time taken for micturition after caudal block was not statistically significant (4.43 hours in group B, 4.18hrs in group BN2, 4.50hrs in group BN3 and 4.35 hours in groupBN4; $p>0.05$). No child required bladder catheterization.Vomiting occurred in 3 children in group B , four in group BN2, three in Group BN3 and four in group BN4 ($p>0.05$). Overall incidence of vomiting was 17.5% and was not significantly different between the groups($p<0.05$). None of the patients in our study had more than one episode of vomiting. Only a single dose of rescue ondansetron was needed in all cases with PONV. PONV in our study had no effect on oral intake or discharge from hospital.None of the patients reported pruritus.

Table 1:AIIMS pain score

Parameters	Criteria	Points
Respiratory rate	+ <20% of preoperative baseline	0
	+20-50% of preoperative baseline	1
	+ >50% of preoperative baseline	2

Heart rate	+10% of preoperative baseline +20% of preoperative baseline + 30% of preoperative baseline	0 1 2
Discomfort	Calm Restless Agitated	0 1 2
Crying	No cry or cry responding to water, food or parental presence Cry responding to tender loving care Cry not responding to tender loving care	0 1 2
Pain at site of operation	No pain States pain vaguely Can localise pain	0 1 2

Table 2: Patient characteristics and intraoperative data. Data represented as mean (SD). There were no differences between groups (p> 0.05).

	Group B	Group BN2	Group BN3	Group BN4
Age (in years)	4.7 (1.7)	4.4 (1.4)	4.5 (1.6)	4.3 (1.4)
Weight (in kilograms)	13.6 (2.4)	14.4 (2.5)	15.3 (3.1)	15 (1.5)
Duration of surgery (in minutes)	18.5 (2.6)	19.5 (3.2)	19.5 (3.2)	19.1 (1.6)
Heart rate (beats/minute)	102.9 (7.2)	105.8 (5.9)	100 (9.7)	100.9 (5)
Systolic blood pressure (mm Hg)	85.9 (7.5)	86.8 (7.3)	88.3 (10.2)	85.2 (8.1)
Diastolic blood pressure (mm Hg)	62.8 (4)	62 (5.2)	60.5 (6)	59.5 (2.2)
Respiratory rate (breaths/minute)	20.2 (2.3)	19.3 (1.8)	19.1 (1.9)	19 (1.4)
Pulse oximetry (SpO2 %)	98.3 (0.5)	98.6 (0.5)	98.6 (0.5)	98.2 (2)

Table 3: Analgesic consumption in the first postoperative 24 hours. * data expressed as mean (SD), + data expressed as numbers (proportion,%).

Parameter	B	BN2	BN3	BN4
Time to first dose of oral analgesic in hours*	6.10(1.55)	15.70(1.81)	15.85(3.44)	16.45(1.15)
Number of rescue analgesic administrations for postoperative 24 hours*	1.95 (0.69)	1.20 (0.41)	1.15 (0.37)	1.10 (0.31)
Number of patients who required more than 1 dose of rescue analgesic+	17 (85%)	1 (5%)	3 (15%)	3 (15%)

Table 4:Postoperative adverse events.

Postoperative events	B	BN2	BN3	BN4
Time to first leg movement (in hours)	1.63	1.67	1.71	1.69
Time to micturition (in hours)	4.43	4.18	4.50	4.35
PONV {in numbers (proportion,%)}	3 (15%)	4 (20%)	3 (15%)	4 (20%)

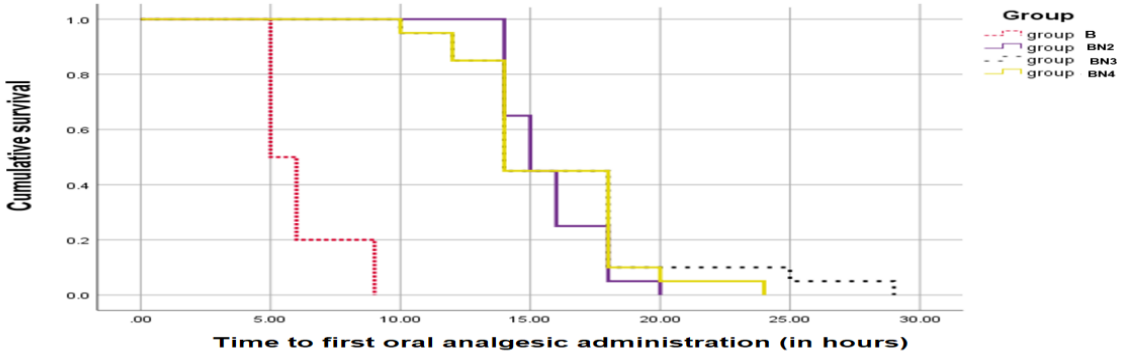

Fig 1: Kaplan Meier survival curves for time to first analgesic administration.

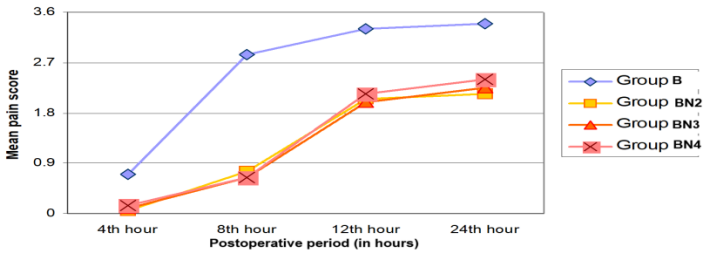

Fig 2:AIIMS pain scores (mean) in the first 24 h postoperative.

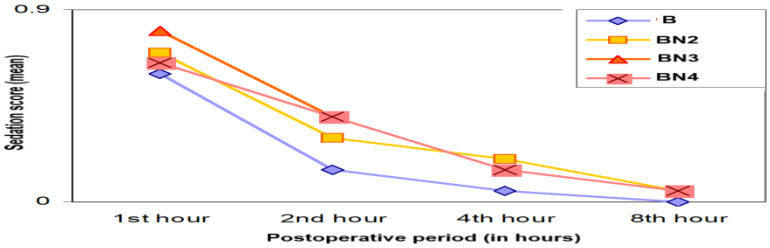

Fig 3:Mean sedation scores in the first 24 h postoperative.

Discussion

This study has supported findings from prior studies and confirmed the postoperative analgesic efficacy of caudal neostigmine when co administered as an adjuvant with bupivacaine in children. Caudal neostigmine combined with bupivacaine prolonged the duration of caudal analgesia (16 h) when compared to 0.25% plain bupivacaine alone (6.10±1.55 h). Significantly fewer doses of analgesics were required over the first 24 hours in the bupivacaine-neostigmine groups when compared with the bupivacaine only group. This was comparable to that reported previously[8-12].The study also demonstrated a dose independent analgesic effect of 2, 3 and 4 $\mu.kg^{-1}$ of caudal neostigmine with plain bupivacaine 0.25% administered at $1.0ml.kg^{-1}$ for postoperative analgesia in children undergoing unilateral inguinal herniotomy without any significant increase in side effects.Various investigators have reported a similar dose independent effect of caudal neostigmine in terms of prolongation of postoperative pain relief when compared to caudal bupivacaine alone[10-12].As proposed by Mahajan et al,[11] it may be possible that caudal bupivacaine potentiates the analgesic effect of neostigmine, thereby rendering additive doses of neostigmine ineffective. Alternately, the lowest dose of neostigmine may have maximally potentiated the analgesic effect of caudal bupivacaine, making higher doses of caudal neostigmine no more effective. Abdulatif et al[8] first reported the prolongation of postoperative analgesia with caudal neostigmine 2 $\mu.kg^{-1}$ combined with 0.25 bupivacaine at $1ml.kg^{-1}$(22.8 h) when compared to bupivacaine alone (5.2 h) in boys undergoing hypospadias surgery. Kumar et al[9] in their study conducted in 80 boys between 5 to 10 years who underwent unilateral inguinal herniotomy, demonstrated a prolongation of caudal analgesia (19.6 h) in patients receiving caudal neostigmine at 2 µ.kg-1 combined with bupivacaine at $1ml.kg^{-1}$ when compared to bupivacaine alone (7.6 h). Batra et al[10] demonstrated that increasing doses of caudal neostigmine (10,20,30, 40 and 50 $\mu.kg^{-1}$) without bupivacaine prolongs the duration of postoperative analgesia.Mahajan et al[11] studied the analgesic efficacy of three doses of caudal neostigmine (2,3 and 4 $\mu g.kg^{-1}$)co administered with bupivacaine at $0.5ml.kg^{-1}$when compared to 0.25% bupivacaine alone for hypospadias surgery in 2 to 8year olds. Their results showed that patients who received bupivacaine and neostigmine had a significantly longer time period to administration of first analgesic [17h] than the bupivacaine group [5 h] This is comparable with the findings reported in our study. Bhardwaj et al[13] reported that the addition of neostigmine did not significantly prolong the action of caudal bupivacaine in their study on the analgesic efficacy of three doses of caudal neostigmine (2,3 and 4 $\mu g.kg^{-1}$) co administered with bupivacaine in hypospadias surgery. The mean duration of action of caudal bupivacaine in their study [9 (3) h] was much longer than that reported in other studies. Bhardwaj et al used higher dose of bupivacaine $0.75ml.kg^{-1}$. The study was conducted in wide range of subjects between 1 to 10 years old. Two pain scores were used:objective pain score (1 to 5 years)and numerical rating score (6-12yrs). Memis et al[14] did not demonstrate a prolongation of analgesia with caudal neostigmine co-administered with bupivacaine at $1\mu g.kg^{-1}$ The duration of postoperative analgesia was reported as 15hours in both groups. The longer duration of caudal bupivacaine alone {Bhardwaj (9 h), Memis (15 h)} when compared to other studies[8,9,12] could have occurred if the pain score was insufficient to discriminate for mild pain[14,16].Time taken to first void after caudal block was not assessed in the prior studies[11-13]as all patients following hypospadias repair required post operative bladder cathererisation. There was no statistically significant difference in the time taken to first void between the four groups in our study: 4.43 hours in group I , 4.18hrs in group II, 4.50hrs in group III and 4.35 hours in group IV; ($p>0.05$). This is comparable to previously reported studies in caudal analgesia[19]. No child required bladder catheterization. Pruritus was not reported in any patient.In the present study, the number of patients who experienced vomiting was also comparable in the four groups. Vomiting occurred in 3 children in group , four in group II, three in Group III and four in group IV ($p>0.05$). Overall incidence of vomiting was 17.5% and was not significantly different ($p<0.05$). This is in agreement with other studies[9-12].Nausea is difficult to assess in children less than 5 years[20].Risk for PONV in children is multifactorial. Kranke et al[21] reported an overall incidence of PONV at 20.2% (106/524) in pediatric patients in the first 24 hours of non-strabismus surgery. Engelman et al[6] in their meta-analysis demonstrated the odds ratio (OR) for PONV with neostigmine threshold to be more than clonidine but less than tramadol. The number of episodes of vomiting and doses of rescue antiemetic administration were not reported in majority of the studies[9-12]. Abdulalif et al[8] reported a PONV incidence of 20 % (5/20).All cases responded to a single dose of ondansetron. None of the patients in our study had more than one episode of vomiting. Only a single dose of rescue ondansetron was needed in all cases with PONV.

There was no effect on oral intake or discharge from hospital. The duration of procedure in our study, surgical duration was less than 30 minutes and no intraoperative opioids were used to avoid contribution to PONV. Time taken to first leg movement in our study was comparable in all four groups. This corroborates with the findings in other studies[9-14].Neostigmine with methylparaben and propylparaben as preservatives has been safely administered in humans[23].Kumar et al[9] did not find any adverse neurological effect with caudal neostigmine in a two-month outpatient evaluation after surgery. A larger population with longer follow period up could shed additional light in this area[24].We included only elective, unilateral inguinal herniotomy in our study to avoid variability in the nature and duration of pain associated with different infraumbilical procedures[9,25].Since the spread of analgesia is unpredictable and failure rate is higher in children older than 7 years,[25,26] children belonging to 2 to 7 years age group alone were included in this study. Appropiate pain scores are crucial in determining analgesic efficacy[24,27,28]. A single pain score was used throughout our study. The AIIMS discomfort scale for assessment of pain provides used in this study is a clinically relevant scoring system and has been validated for use in children[14]. It provides allowance for thirst and hunger and includes physiological changes such as heart rate and respiration, which can be measured without causing discomfort to the patient[15].All observations were performed by a single observer to eliminate any inter- observer variability. There was no intraoperative opioid administration. Thus, we can assume that the difference in pain relief reflects the effectiveness of the caudal neostigmine[9].

Future directions

POV with neostigmine can be answered by further studies taking into consideration the POVOC scores of the patient and efficacy of prophylactic antiemetics[6].

Conclusion

Caudal neostigmine (2, 3 and 4 $\mu.kg^{-1}$) with bupivacaine 0.25% administered at $1ml.kg^{-1}$ body weight produces a dose independent prolongation of analgesic effect (16 h) in children as compared to those receiving caudal bupivacaine alone (6 h) and a reduction in number of postoperative rescue analgesia without increasing the incidence of adverse effects like PONV, sedation, prolongation of motor block or delay in micturition.

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