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Two different doses of caudal neostigmine co-administered with levobupivacaine produces analgesia in children

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Summary

Background: This study was aimed to evaluate the analgesic efficacy, duration of analgesia, and side effects of two different doses of caudal neostigmine used with levobupivacaine in children.

Methods: Sixty boys, between 5 months and 5 years, undergoing genito-urinary surgery were allocated randomly to one of three groups (n = 20 each). Group I patients received caudal 0.25% levobupivacaine (1 ml·kg^{-1}) alone. Groups II and III patients received neostigmine (2 and 4 μg·kg^{-1} respectively) together with levobupivacaine used in the same dose as Group I. Pain scores were assessed using Children's and Infant's Postoperative Pain Scale (CHIPPS) at 15th (t_1) min after arrival to postanesthetic care unit, and 1st (t_2), 2nd (t_3), 3rd (t_4), 4th (t_5), 8th (t_6), 16th (t_7), and 24th (t_8) hour postoperatively. Duration of analgesia, amount of additional analgesic (paracetamol), score of motor blockade and complications were recorded for 24 h postoperatively, and compared between groups.

Results: CHIPPS scores were higher during t_2, t_3, t_6, t_7 and t_8 periods, duration of analgesia was shorter, and total analgesic consumption was higher in Group I compare to neostigmine groups ($P < 0.05$). Duration of postoperative analgesia and total analgesic consumption were similar in Groups II and III ($P > 0.05$). Adverse effects were not different between three groups.

Conclusions: Caudal neostigmine in doses of 2 and 4 μg·kg^{-1} with levobupivacaine extends the duration of analgesia without increasing the incidence of adverse effects, and 2 μg·kg^{-1} seems to be the optimal dose, as higher dose has no further advantages.

Keywords: levobupivacaine; neostigmine; caudal block; postoperative analgesia

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Introduction

Postoperative pain still remains undertreated in most of the pediatric patients despite the progression in analgesic techniques and new technologies, and it may take long duration of time especially after genitourinary surgery. Caudal analgesia is the most popular regional anesthesia technique in pediatric population, and reported to provide efficient and adequate analgesia postoperatively (1,2). However, the single-shot caudal injection provides short duration of analgesia (3). Placement of a catheter into caudal space carries a risk of infection, and subsequently may delay mobilization (4). Many drugs (ketamine, clonidine, midazolam and opioids) have been co-administered up to now with caudal local anesthetics to maximize and extend the duration of analgesia (5–9). Neostigmine also was coadministered for caudal analgesia with bupivacaine (9–11) or ropivacaine (12) in children, and reported to provide prolonged analgesia without any adverse effects. In other two studies with a similar design in pediatric patients caudal neostigmine co-administered with bupivacaine did not change the analgesic efficacy compared with bupivacaine used alone (13,14). However, there is no study in the literature investigating the effects of caudal neostigmine when used together with caudal levobupivacaine in children. The objective of this study was to evaluate analgesic efficacy, duration of analgesia, and side effects of caudal neostigmine in two different doses (2 or 4 $\mu g \cdot kg^{-1}$) co-administered with levobupivacaine in pediatric patients scheduled for genitourinary surgery.

Methods

After obtaining Institutional Ethics Committee approval and written informed consent from the parents of the patients, 60 ASA class I children between 5 months and 5 years of age, who were scheduled for inguinal hernia or/and hypospadias or orchidopexy were enrolled for the study between May 1, 2006, and December 1, 2007, in a double-blind, randomized, prospective manner. Exclusion criteria consisted of local infection in the patient's caudal region, bleeding diathesis, aspirin ingestion during the previous week, pre-existing neurological or obvious spinal disease and congenital anomaly of the lower back as determined by physical examination.

All patients received a standard anesthetic protocol including premedication with oral midazolam 0.5 $mg \cdot kg^{-1}$ 20–30 min preoperatively. The patients were randomly allocated to one of the three groups by a computer-generated list. We delivered either only caudal 0.25% plain levobupivacaine 1 $ml \cdot kg^{-1}$ (Group I) or 0.25% plain levobupivacaine 1 $ml \cdot kg^{-1}$ with neostigmine (Neostigmine, Adeka Inc., Samsun, Turkey) 2 $\mu g \cdot kg^{-1}$ (Groups II) or 0.25% plain levobupivacaine 1 $ml \cdot kg^{-1}$ with neostigmine 4 $\mu g \cdot kg^{-1}$ (Group III). Propofol in the dose of 3 $mg \cdot kg^{-1}$ was given intravenously if the patient had intravenous line. An intravenous line was established in the other patients after inhalational induction with sevoflurane in stepwise incremental doses up to 6% via mask within 70% nitrous oxide in 30% oxygen. Infusion of Ringer's lactate at a rate of 10 $ml \cdot kg^{-1} \cdot h^{-1}$ was started in both groups after induction. Patients were turned to the left lateral position as soon as getting anesthesia deep enough after, and an Epican-Paed caudal needle (Epican Braun, Melsungen, Germany) was inserted into the sacral hiatus under aseptic conditions. Later on, anesthesia was maintained with 2 $mg \cdot kg^{-1} \cdot h^{-1}$ intravenous propofol infusion allowing the child to breathe spontaneously and oxygen was delivered (3 $l \cdot min^{-1}$) via simple face mask. Additional bolus doses of propofol was injected intravenously (0.5 $mg.kg^{-1}$) as needed. Heart rate (HR), mean arterial pressure (MAP), oxygen saturation (SpO_2), and respiratory rate (RR) were recorded before induction, after induction but before caudal anesthesia, and then every 5 min after caudal anesthesia. Postoperatively all children were observed in Postoperative Care Unit (PACU) for 2 h. As the patient was sedated and not deeply anesthetized we were able to evaluate onset time and level of caudal analgesia by pinching the skin which was carried out by a nonblinded observer. Patient moving from pinching was regarded as a positive response, i.e. caudal analgesia was not yet effective at that level.

Severity of postoperative pain was evaluated by blinded anesthesiologist using Children's and Infant's Postoperative Pain Scale (CHIPPS) (15) at 15th minute (t_1), 1st (t_2), 2nd (t_3), 3rd (t_4), 4th (t_5), 8th (t_6), 16th (t_7), and 24th hour (t_8) postoperatively. It includes five items. The five individual scores are

added together to produce a score that ranges from 5 (no pain) to 15 (severe pain). When pain scoring reached more than 10 points, the children received paracetamol (20 $mg{\cdot}kg^{-1}$) rectally. Pain scoring was accompanied by scoring of the level of sedation by the same blinded anesthesiologist. (Awake; 4 points, drowsy; 3, sleeps rousable; 2, sleeps not rousable; 1). Children stayed in the hospital for at least 24 h after the operation. The duration of postoperative analgesia was determined by noting the time from caudal injection to the time of first paracetamol as well as the time at which postoperative pain scoring exceeded 10 points. The total amount of paracetamol administered was also documented. HR, RR, MAP and SpO_2 were registered during the first 2 h after the operation.

Motor blockade scoring was performed at 15th min (t_1), 1st (t_2), 2st (t_3), 3rd (t_4), and 4th (t_5) hour postoperatively using the Bromage scale by the same blinded anesthesiologist and consisted of four points: 0; full motor strength (flexion of knees and feet), 1; flexion of knees, 2; little movement of feet only, 3; no movements of knees of feet (16). In young children who would not move their lower extremities on command, feet and legs were stimulated.

All adverse effects, including postoperative nausea and vomiting (PONV), hypotension, constipation, arrhythmia, and allergic reactions were recorded. The incidence of PONV was assessed for the first 24 h, and at various time intervals (0–2 , 2–6 , 6–24 h) by using Numeric Rank Score (NRS) (0: No nausea and no vomiting, 1: Nausea but no vomiting, 2: One episode of vomiting, 3: Two or ±2 episodes of vomiting) (17). No prophylactic agents were given to any case for nausea-vomiting, but 0.15 $mg{\cdot}kg^{-1}$ metochlopramide i.v. was given to cases with NRS values more than or equal to one in the postoperative period.

Statistical analysis

Data were analyzed using SPSS software program, version 13.0, for Windows (SPSS Inc., Chicago, IL). Data are expressed as mean ± SD or SEM. Normality was tested by performing a Shapiro-Wilk test. One way ANOVA was used for the statistical analysis as appropriate, and *post hoc* comparisons were carried out by Tukey's test. The ANOVA test was used for multiple comparisons of repeated measures. Pair wise comparisons were performed with the least significant difference test. Kaplan–Meier survival curves were drawn with the duration of postoperative analgesia being considered as the event and log-rank analysis performed for comparison between the groups. Values of $P < 0.05$ were considered statistically significant. Power analysis of duration of analgesia was performed using Epi info 2002. Power analyses for CHIPPS and Bromage; in one-way ANOVA study, sample sizes of 20, 20, and 20 are obtained from the three groups whose means are to be compared. The total sample of 60 subjects achieves 100% power to detect differences among the means vs the alternative of equal means using an *F*-test.

Results

Demographic and surgical data, and adverse reactions of all participants were similar in all groups ($P > 0.05$) (Table 1). There were no differences between group members in MAP and HR during the study. SpO_2 was always within the clinically acceptable range (>95%). There were no differences between the groups in propofol requirements ($P > 0.05$). All postoperative CHIPPS values in Group I were higher than those of both neostigmine groups, and these differences were statically significant in t_2, t_3, t_6, t_7 and t_8 periods ($P < 0.05$) (Table 2).

Kaplan–Meier survival curves for the duration of postoperative analgesia are shown in Figure 1. Duration of postoperative analgesia in Group I (302.00 ± 23.17 min) was significantly shorter than the other two groups (II: 909.80 ± 118.74 min; III: 1188.00 ± 102.23 min; $P < 0.05$). Total amount of analgesic (paracetamol) consumption was significantly higher in Group I (15.13 ± 2.19 $mg{\cdot}kg^{-1}$) than in the groups receiving caudal neostigmine (II : 8.02 ± 2.26 $mg{\cdot}kg^{-1}$ and III : 7.00 ± 3.00 $mg{\cdot}kg^{-1}$; $P < 0.05$). Additional analgesic drug was needed 16 times by 15 different patients in Group I, eight times by eight cases in Group II, and seven times by five cases in Group III. Groups II and III were comparable with regards to duration of postoperative analgesia and total analgesic consumption (Table 3). Bromage score was found to be higher in Group III during t_1 and t_4 compare to Group I, and during t_3 and t_4 compare to Group II ($P < 0.05$) (Figure 2). PONV has not been observed in any patient in

	Group I, n = *20*	*Group II*, n = *20*	*Group III*, n = *20*
Age (year)	1.41 ± 1.21	1.90 ± 1.39	2.23 ± 1.76
Weight (kg)	10.70 ± 3.01	11.18 ± 4.18	12.53 ± 4.87
Block onset time (min)	8.55 ± 3.20	9.40 ± 4.49	11.25 ± 3.92
Operation time (min)	42.25 ± 21.40	49.35 ± 28.12	53.50 ± 28.94
Inguinal hernia (*n*)	9	10	8
Hypospadias (*n*)	3	2	3
Orchidopexy (*n*)	8	8	9
Hypotension (*n*)	0	0	0
Constipation (*n*)	0	0	0
Arrythmia (*n*)	0	0	0
Allergic reaction (*n*)	0	0	0
NRS 1/2/3 (*n*)	0/0/0	0/0/0	0/2/1

Table 1 Demographic characteristics, surgical procedure and adverse effects in groups (mean ± SD)

SD, standart deviation; NRS, numeric rank score; 0: No nausea and no vomiting, 1: Nausea but no vomiting; 2: one episode of vomiting; 3: two or ±2 episodes of vomiting.

Table 2
CHIPPS and sedation scores for the study groups (mean ± SEM)

Time of assessment postoperatively	*Group I*, n = *20*		*Group II*, n = *20*		*Group III*, n = *20*	
	CHIPPS	*Sedation*	*CHIPPS*	*Sedation*	*CHIPPS*	*Sedation*
15 min	7.05 ± 0.34	2.50 ± 0.51	5.85 ± 0.28**	2.45 ± 0.51	6.80 ± 0.37	2.40 ± 0.50
1 h	8.10 ± 0.52*	2.61 ± 0.51	6.05 ± 0.32**	2.55 ± 0.51	6.60 ± 0.24	2.55 ± 0.51
2 h	7.75 ± 0.38*	3.50 ± 0.61	6.30 ± 0.40**	3.35 ± 0.67	6.35 ± 0.20	3.30 ± 0.66
3 h	6.55 ± 0.28	3.70 ± 0.47	6.05 ± 0.37	3.55 ± 0.51	6.30 ± 0.25	3.40 ± 0.60
4 h	6.50 ± 0.33	3.80 ± 0.41	6.05 ± 0.32	3.70 ± 0.47	6.30 ± 0.38	3.65 ± 0.59
8 h	7.05 ± 0.35*	3.85 ± 0.37	5.40 ± 0.11**	3.80 ± 0.41	5.80 ± 0.35	3.75 ± 0.55
16 h	6.00 ± 0.23*	3.85 ± 0.37	5.20 ± 0.09**	3.80 ± 0.41	5.10 ± 0.68	3.85 ± 0.37
24 h	5.55 ± 0.18*	3.97 ± 0.21	5.10 ± 0.07**	3.95 ± 0.22	5.05 ± 0.05	3.95 ± 0.22

SEM, standart error mean.
*$P < 0.05$ compared with Group III; **$P < 0.05$ compared with Group I.

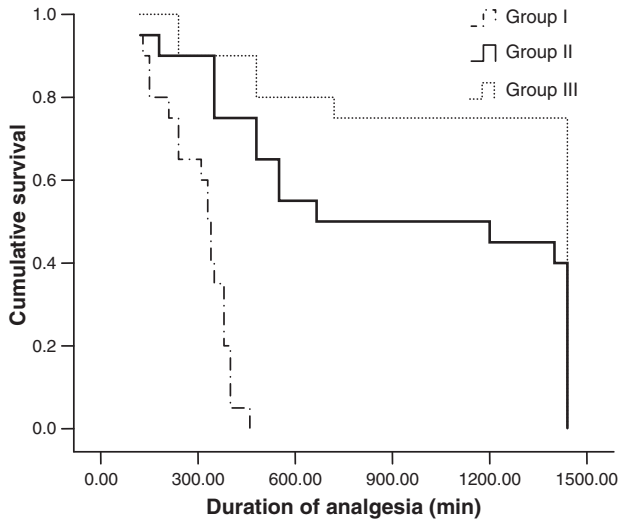

Figure 1
Kaplan–Meier survival curves for the duration of postoperative analgesia for groups.

Group I and II, but it is experienced by three patients (15%) in Group III. This difference was not statistically significant between groups ($P > 0.05$). There was no statistically significant difference in occurrence of other side effects (hypotension, constipation, arrhythmia allergic reaction) between groups (Table 1).

Discussion

The main finding of this study is that co-administration of neostigmine caudally together with levobupivacaine produces analgesia in two different doses, 2 $\mu g \cdot kg^{-1}$ and 4 $\mu g \cdot kg^{-1}$. Previously neostigmine have been used for caudal analgesia with bupivacaine and ropivacaine, but the first time in the literature its effect when used with levobupivacaine approved by this study. Neuraxial administration of

Table 3
Postop analgesia time and amount of total analgesic for groups (mean ± SEM)

Variable	*Group I*, n = *20*	*Group II*, n = *20*	*Group III*, n = *20*
Analgesia duration (min)	302.00 ± 23.17	909.80 ± 118.74*	1188.00 ± 102.23*
T_1 paracetamol, mg·kg^{-1} (no. children, criterions)	5.82 ± 2.04 (6, 6)	1.91 ± 1.32 (2, 2)	2.00 ± 1.38 (2, 2)
T_2 paracetamol, mg·kg^{-1} (no. children, criterions)	9.31 ± 2.18 (10, 10)	6.11 ± 2.14 (6, 6)	5.00 ± 1.99 (5, 5)
Total paracetamol, mg·kg^{-1} (no. children, criterions)	15.13 ± 2.19 (15, 16)	8.02 ± 2.26* (8, 8)	7.00 ± 3.00* (5, 7)
Propofol add, mg	11.75 ± 2.72	8.50 ± 2.46	7.75 ± 1.90

SEM, standart error mean; T_1, Postop 0–4 h; T_2, Postop 4–24 h.
*$P < 0.05$ compared with Group I.

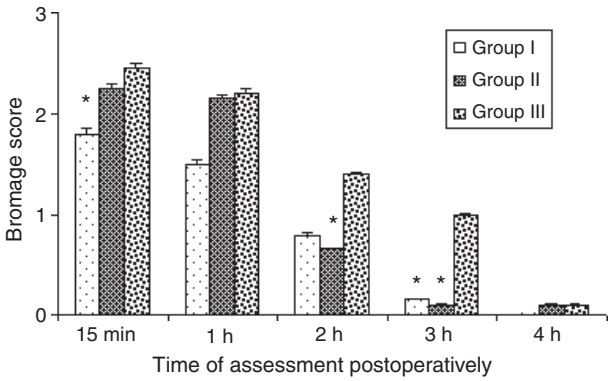

Figure 2
Postoperative motor block scores following caudal anesthesia. Bromage: 0: full motor strength (flexion of knees and feet); 1: flexion of knees; 2: little movement of feet only; 3: no movements of knees of feet. *$P < 0.05$ compare to Group III.

neostigmine also was reported to produce analgesia in both acute postoperative and chronic pain (18–22). The mechanism by which neostigmine produces such effect is speculated to be via acetylcholine. It inhibits the breakdown of the endogenous spinal neurotransmitter acetylcholine which causes the concentration of acetylcholine to be increased in cerebrospinal fluid, and it produces analgesia (23,24). This antinociception has been shown to be blocked by the intrathecal administration of a muscarinic antagonist in animals (19–25). Spinal muscarinic M1 receptors, supraspinal muscarinic M1 and M2, and nicotinic cholinergic receptors are thought to be the mediators of this analgesic effect (19,25). We did not investigate the mechanism of analgesia in this study, but we observed an adequate and longer duration of analgesia postoperatively with neostigmine when co-administered with levobupivacaine.

Caudal neostigmine has been used alone by some investigators, and found to be effective and safe in paediatric patients. Batra *et al.* (26) reported the effective dose of neostigmine between 20 and 50 μg·kg^{-1} in their dose-dependent analgesia study, but the incidence of PONV was high (20–60%). Contradictory to this high dose of neostigmine Abdulatif *et al.* (11) used much more smaller dose, 2 μg·kg^{-1}, and found it to produce enough postoperative analgesia, but the duration of analgesia was 3–4 h. Higher incidence of PONV in higher doses, and the short duration of analgesia in lower doses have contributed significantly to the importance of the co-administration of neostigmine with local anesthetics. However, although co-administration of neostigmine with local anesthetics has been demonstrated by some authors to extend the duration of analgesia postoperatively with minimal incidence of adverse effects (9–12), some others claim that addition of neostigmine did not change the duration of analgesia (13,14). Mahajan *et al.* (10) studied three different doses of caudal neostigmine (2, 3, and 4 μg·kg^{-1}), and observed that duration of analgesia was extended in all doses. Bhardwaj *et al.* (14) used similar doses of neostigmine (2, 3, 4 μg·kg^{-1}) co-administered with bupivacaine with similar design, but reported the duration of analgesias has not been extended. Memiş *et al.* (13) used 1 μg·kg^{-1} neostigmine with bupivacaine, and also reported no change in duration of analgesia. The difference between Memiş *et al.* (13) and other investigators may be associated with the lower dose of neostigmine that they used. The difference between Mahajan *et al.* (10) and Bhardwaj *et al.* (14) was speculated to be related to the lower volume of caudal bupivacaine Mahajan *et al.* used (0.75 ml·kg^{-1} vs 0.5 ml·kg^{-1}). However, we used higher volume (1 ml·kg^{-1}) and found longer duration of analgesia. This contraversy may be more cleared by new studies with larger series of patients in the future.

PONV was reported to occur up to 30% after the caudal use of neostigmine in some previous studies (26,27). The higher rate among these studies may be attributed to higher doses (10–30 $\mu g \cdot kg^{-1}$) of neostigmine. The rate of PONV in the previous studies performed with similar neostigmine doses as we used in our study was between 13%–15% (9,10,12). However, Abdulatif *et al.* (11) used also similar dose of neostigmine (2 $\mu g \cdot kg^{-1}$), but reported the rate of PONV between 25–30%. The rate of PONV observed in our study was comparable to that of neostigmine free group. This lower rate of PONV observed in neostigmine group may be associated with the relatively lower dose we used as well as to the method of the study; we did not intubate the patients, we did not use opioids and nitrous oxide, and propofol we used in the study may have had protected the occurrence of PONV after operation. In our study neostigmine did not induce significant other side-effects such as arrhythmia, hypotension. Another possible side effect of neostigmine is urinary retention (20). However, we did not record the first voiding time, which is a shortness of the study. This was because of the lack of standardization at this point because of the presence of urinary catheter in some patients, such as those having hypospadias operations, during the postoperative period. Transient motor weakness may also be seen with very high doses of intrathecal neostigmine (20). However, caudal neostigmine was not found to be associated with any neurological sign, and rapid mobilization was reported to be possible in all patients after caudal application of this drug (10). In our study Bromage scale has come to normal in almost all patients at the end of 4th hour. Most of neostigmine contain methyl- and propylparabens as preservatives of which intrathecal administration was reported not to be associated any neurological side effects (28,29). However, neostigmine that used in our study did not include any preservative agent.

Despite all studies Lönnqvist speculated that caudal neostigmine had increased the incidence of PONV and had not increased the duration of analgesia, and concluded that co-administration of neostigmine had no superiority to local anesthetics when used alone (30). However, as Almanrader *et al.* (31) and Mahajan *et al.* (32) have mentioned previously, by doing such conclusion Lönnqvist analyzed only two studies (11,27), sample sizes of which are quite small. Similar to the other investigators, we suggest the use of neostigmine together with levobupivacaine as it increased the duration of analgesia and does not affect the occurence of other side effects.

As a result, we conclude that caudal neostigmine with levobupivacaine produces longer duration of analgesia in two different doses (2 and 4 $\mu g \cdot kg^{-1}$) in children as compared with those receiving caudal levobupivacaine alone, and a reduction in postoperative rescue analgesic consumption without increasing the incidence of adverse effects, especially PONV. The dose of 2 $\mu g \cdot kg^{-1}$ seems to be the optimal dose for caudal administration, and higher doses seems to have no further advantages.

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