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Caudal Ropivacaine and Neostigmine in Pediatric Surgery

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Background: **Neostigmine has been added to local anesthetics for different nerve blocks. This study was conducted to evaluate effects of neostigmine when added to ropivacaine for caudal anesthesia.**

Methods: **We studied children, aged 1–5 yr, undergoing inguinal hernia and hypospadias surgery. After standard induction of anesthesia, Group I received 0.2% ropivacaine 0.5 ml/kg and Group II received 0.2% ropivacaine 0.5 ml/kg with 2 μg/kg neostigmine *via* the caudal route. Heart rate, mean arterial pressure, and pulse oximetry were recorded before induction, after induction, and then every 10 min after caudal anesthesia. Hemodynamic, Toddler-Preschooler Postoperative Pain Scale pain score, and sedation score values were recorded 30 min after extubation and at hours 2, 4, 6, 12, and 24. A pain score greater than 3/10 resulted in administration of rectal paracetamol.**

Results: **There were no differences between the groups in demographic and hemodynamic data, duration of surgery and anesthesia, time to extubation, or sedation scores. The pain scores were significantly lower in Group II at 6 and 12 h ($P < 0.05$). Time to first analgesic requirement was statistically prolonged in Group II (19.2 ± 5.5h) when compared with Group I (7.1 ± 5.7 h) ($P < 0.05$). Total analgesic consumption was statistically larger in Group I (174 ± 96 mg) when compared with Group II (80 ± 85.5 mg) ($P < 0.05$). The incidence of vomiting (3 patients in Group II and 1 patient in Group I) was not statistically significantly different.**

Conclusions: **The authors found that a single caudal injection of neostigmine when added to ropivacaine offers an advantage over ropivacaine alone for postoperative pain relief in children undergoing genitourinary surgery.**

The most common regional procedure used for treating children is the caudal approach to the extradural space. It combines the advantages of a fairly simple technique with a high success rate.[1,2] The caudal block can be used as an adjunct to general anesthesia or administered at the completion of surgery to provide postoperative analgesia. Single injection may have only a relatively short duration of action[3]; placement of a catheter into the extradural space either at the caudal or lumbar region adds a risk of infection and tends to prevent early mobilization.[4] Attempts to overcome these problems by combining local anesthetic agents with other drugs such as adrenaline, clonidine, ketamine, or various opioids have met with different degrees of success[3,5,6,7] in prolonging the pain-free period.

Neostigmine is a drug that has been used to antagonize muscle relaxants. Intrathecal administration of neostigmine in animals and humans causes analgesia by inhibiting the breakdown of acetylcholine in the spinal cord.[8,9] Acetylcholine has been shown to induce analgesia by increasing cyclic guanosine 3′,5′ = monophosphate (GMP) by generating nitric oxide.[10] Intrathecal neostigmine also enhances the onset of tetracaine and provides postoperative analgesia.[11] Spinal neostigmine results in significant dose-dependent nausea and is not responsive to standard antiemetics.[12] Epidural neostigmine (1, 2, or 4 μg/kg) in lidocaine produces a dose-independent analgesic effect in adult patients and a reduction in postoperative rescue analgesic consumption without increasing the incidence of adverse effects.[13] Epidural neostigmine in bupivacaine provides longer duration of analgesia than does bupivacaine alone after abdominal hysterectomy.[14] Epidural neostigmine results in prolonged analgesia when compared with peripheral application after knee surgery.[15] The objective of this study was to evaluate analgesia and side effects of caudal neostigmine coadministered with ropivacaine for pediatric genitourinary surgery.

Materials and Methods

After obtaining Institutional Ethics Committee approval (Trakya University, Edirne, Turkey), and written informed consent from the parents of the patients, ASA I, 44 children, aged 1–6 yr, undergoing elective surgery of inguinal hernia or hypospadias were included in study. The study design was randomized and double blind; patients were randomly allocated according to a computer-generated randomization. Exclusion criteria consisted of local infection in the patient's caudal region, bleeding diathesis, aspirin ingestion during the previous week, preexisting neurologic or obvious spinal diseases, and congenital anomaly of the lower back as determined by physical examination.

Children were premedicated 45 min before surgery with midazolam 0.4 mg/kg rectally. Heart rate (HR) mean arterial pressure (MAP), and peripheral oxygen saturation (Spo_2) were recorded. Anesthesia was induced by facemask with sevoflurane and 60% nitrous oxide in oxygen. After placing an intravenous cannula, the trachea was intubated with atracurium 0.5 mg/kg and mechanically ventilated. Anesthesia was maintained by sevoflurane. After induction of anesthesia, patients were turned to the left lateral position and an Epican® Paed (Braun, Melsungen, Germany) caudal needle was

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inserted into the sacral hiatus to produce caudal anesthesia. The study used a double-blind methodology with random allocation to the two groups by a computer-generated list. Study solutions were prepared by an anesthesiologist not involved in the patients' care by using standardized written instructions for study drug preparation. Group I (n = 22) received 0.2% ropivacaine 0.5 ml/kg, and Group II (n = 22) received 0.2% ropivacaine 0.5 ml/kg with 2 μg/kg neostigmine *via* the caudal route. Association of saline is not necessary because the methodology is based on a final caudal volume, which is similar to the groups.

Heart rate, MAP, and Spo_2 were recorded before induction, after induction, and then every 10 min after caudal anesthesia. During surgery, adequate analgesia was defined by hemodynamic stability, as indicated by the absence of an increase in MAP or HR of more than 15% compared with baseline values obtained just before the surgical incision, with sevoflurane concentration maintained at less than 0.6 MAC and less than 1.5%. An increase in HR or MAP within 15 min of skin incision indicated failure of caudal anesthesia. If more than a 15% increase occurred, analgesia was considered inadequate and children received a rescue opioid during surgery (alfentanil 10 μg/ kg) Fluid therapy was standardized during and after surgery. During surgery, children received lactated Ringer's solution 6 ml · kg^{-1} · h^{-1} whereas 5% dextrose with electrolytes was given at a rate of 4 ml · kg^{-1} · h^{-1} in the postoperative period. Intraoperative decreases in MAP and HR more than 30% from baseline values were defined as severe hypotension or bradycardia, respectively, and were treated by a rapid infusion of fluids or, if unsuccessful, the use of ephedrine, or atropine. Time from discontinuing the volatile anesthetic to tracheal extubation was recorded.

MAP, HR, and Spo_2 values were recorded 30 min after extubation and at hours 2, 4, 6, 12, and 24. Motor block was assessed on awakening using a modified Bromage scale that consisted of 4 points: 0, full motor strength (flexion of knees and feet); 1, flexion of knees; 2, little movement of feet only; 3, no movement of knees or feet.[16] For young children who could not move their lower extremities on command we stimulated their feet and legs. A TPPPS pain score (Toddler-Preschooler Postoperative Pain Scale) modified to give a maximum score of 10 was used for postoperative pain evaluation.[3] Sedation score (0 = eyes open spontaneously, 1 = eyes open to speech, 2 = eyes open when shaken, 3 = unrousable) were also measured postoperatively. Assessment of postoperative pain and sedation scale were measured 30 min after extubation and at hours 2, 4, 6, 12, and 24. A pain score greater than 3/10 resulted in the administration of 20 mg/kg rectal paracetamol. The duration of postoperative analgesia was defined as the time between caudal drug injection and the first rectal paracetamol administration. If no rectal paracetamol was necessary within 24 h, the duration of analgesia was counted as 24 h. All measurements were recorded by the same anesthesiology resident who did not know which medication was administered. The same person performed measurements for all patients. The amount of supplementary analgesic required by each child in a 24 h period, total analgesic consumption during the study period, and any local or systemic complications were recorded.

Table 1. Patients and Clinical Data

	Group I (n = 22)	Group II (n = 22)
Age, yr	3.9 ± 1.5	3.5 ± 1.6
Height, cm	96 ± 10	98 ± 13
Weight, kg	18.5 ± 4.4	18.2 ± 2,5
Duration of surgery, min	55.5 ± 20.2	60 ± 17.5
Duration of general anesthesia, min	65 ± 22	71 ± 20
Time of extubation, min	9.3 ± 2	9.1 ± 2.2
Type of surgery inguinal hernia/ hypospadius	16/6	17/5

Data shown as mean ± SD. There were no differences between the groups.

Statistical Analysis

Demographic data, duration of surgery and anesthesia, and time to extubation were analyzed for independent samples using the *t* test. Pain scores and sedation scores in groups were analyzed using Friedman Repeated Measures Analysis of Variance on Ranks test between groups by Mann–Whitney U test. MAP, HR, and Spo_2 values were analyzed using the Mann–Whitney U test. Total analgesic consumption and first analgesic requirement time were analyzed using the Mann–Whitney U test. The amount of supplementary analgesic required by each child in a 24 h period was analyzed using the Mann–Whitney U test. The incidence of complications was analyzed using the Fisher exact test. According to a power analysis for VAS scores in patients, we calculated that 20 patients in each group would be required to demonstrate a (maximum difference = 0.93, SD = 1.0) between groups ($\alpha = 0.05$, $\beta = 0.2$). Unless otherwise specified, data are given as arithmetic mean and SD (mean ± SD). A *P* value of less than 0.05 was considered statistically significant.

Results

Data from the 44 children included in the study were analyzed (22 children in each group). There were no differences between the group members in weight, height, age, duration of surgery, duration of general anesthesia, or time to extubation ($P > 0.05$) (table 1). There were no differences between group members in MAP and HR during the study. Severe hypotension or bradycardia was not observed in any patient. Spo_2 (> 96%) was always within the clinically acceptable

Table 2. Postoperative Pain Scores

Pain Scores	Group I	Group II
At 30 min	1 (0–3)	1 (0–2)
At 2 hr	1 (0–3)	1 (0–2)
At 4 hr	2 (0–4)	1 (0–4)
At 6 hr	3 (0–6)	1 (0–4)*
At 12 hr	3 (0–6)	1 (0–3)*
At 24 hr	1 (0–2)	1 (0–2)

Pain scores are expressed as median (range in parentheses). n = 22 in each group.

*$P < 0.05$ when compared with group I.

range. There were no differences between the groups in alfentanil requirements ($P > 0.05$).

There were no significant differences between the groups in postoperative sedation scores ($P > 0.05$). The pain scores were significantly lower in Group II at 6 and 12 hr, when compared with Group I ($P < 0.05$) (table 2). No motor block was seen in either group on awakening and throughout the study period.

The first analgesic requirement time was statistically prolonged in Group II (19.2 ± 5.5 h) when compared with Group I (7.1 ± 5.7 h) ($P < 0.05$). Total analgesic consumption was statistically higher in Group I (174 ± 96 mg) when compared with Group II (80 ± 85.5 mg) ($P < 0.05$). Paracetamol was given to six children once and one child twice in Group II, while 13 children were given paracetamol once and 5 children twice in Group I ($P < 0.05$). Fifteen children in Group II and 4 children in Group I required no additional pain medication during the first 24 h study period, which was statistically significant ($P < 0.05$).

The incidence of vomiting (3 patients in Group II and 1 patient in Group I) was not statistically significantly different. No other side effects were seen.

Discussion

The addition of neostigmine to ropivacaine prolonged the period of analgesia from 7.1 h to 19.2 h, while decreasing the postoperative consumption of paracetamol. Pain scores were found to be lower in the neostigmine group at 6 and 12 h.

Intrathecal neostigmine produces analgesia in animals, volunteers, and patients, inhibiting the breakdown of the central neurotransmitter acetylcholine as a result.[8,17,18,19] Spinal muscarinic receptors are believed to play a role in the analgesic properties of spinal neostigmine. Studies have shown muscarinic binding in the substantia gelatinosa, and to a lesser extent, in the laminae III and V of the dorsal horn of the spinal cord, coincident with opioid and adrenergic sites.[20] The analgesic action of systemic anticholinesterase drugs such as physostigmine is believed to be a result of indirect stimulation of spinal muscarinic M1 receptors and supraspinal muscarinic M1 and M2 and nicotinic cholinergic receptors.[8,21]

In clinical studies Nakayama *et al.*[14] found 10 μg/kg epidural neostigmine combined with bupivacaine provides a longer duration of analgesia than epidural bupivacaine after abdominal hysterectomy. Lauretti *et al.*[13] found epidural neostigmine (1, 2, or 4 μg/kg) in lidocaine produced a dose-independent analgesic effect and a reduction in postoperative rescue analgesic consumption without increasing the incidence of adverse effects.

In a preliminary study that we conducted we were unable to determine the difference with the addition of 1 μg/kg neostigmine to bupivacaine.[22] We commented that the dose of neostigmine we used may have been insufficient. The drug was changed to ropivacaine, and the dosage of neostigmine was changed to 2 μg/kg. Ropivacaine is more advantageous for children when compared with other local anesthetics, because of its specificity to sensory C fibers, producing less motor block.[23]

The duration of caudal analgesia was longer in our study in the control group when compared with other studies using ropivacaine.[16] This may be because of the evaluation score or the cultural differences in exterminating pain.

Neostigmine causes unwanted muscarinic effects such as arrhythmia, bradycardia, bronchospasm, increased bronchial secretions and salivation, increased motility of intestines,[24] and increased incidence of nausea-vomiting.[25] Preclinical toxicity screening studies of intrathecal neostigmine were done long ago, however they were associated with nausea and vomiting, subjective leg weakness, spontaneous micturition and defecation, spontaneous ejaculation, hallucinations, and increased blood pressure and heart rate.[19] In our study, neostigmine did not induce significant side-effects but it is conceivable that the limited number of patients and the low dose of neostigmine used rule out a specific conclusion. In our study, the amount of vomiting encountered was not enough to be associated with neostigmine.

We conclude that a single caudal injection of neostigmine (2 μg/kg) added to ropivacaine offers an advantage over ropivacaine alone for postoperative pain relief in children undergoing genitourinary surgery, without increasing the incidence of adverse effects.

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