

# Neostigmine does not prolong the duration of analgesia produced by caudal bupivacaine in children undergoing urethroplasty

Bhardwaj N, Yaddanapudi S, Ghai B, Wig J

Department of Anaesthesia and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh - 160 012, India

## Correspondence:

Neerja Bhardwaj  
E-mail: neerja.bhardwaj@gmail.com

Received : 12-04-07  
Review completed : 11-05-07  
Accepted : 21-06-07  
PubMed ID : ????

J Postgrad Med 2007;53:161-5

## ABSTRACT

**Context:** Neostigmine extends the duration of analgesia produced by caudal bupivacaine in children. **Aims:** To study the effect of different doses of caudal neostigmine on the duration of postoperative analgesia. **Settings and Design:** A randomized, double-blind study was conducted in 120 boys aged 1-12 years undergoing urethroplasty under combined general and caudal anesthesia. **Materials and Methods:** Children were administered 1.875 mg/kg bupivacaine alone (Group B), or with 2, 3 or 4  $\mu$ g/kg of neostigmine (groups BN<sub>2</sub>, BN<sub>3</sub> or BN<sub>4</sub> respectively) as caudal drug (0.75 ml/kg). Children with a pain score of 4 or more (OPS and NRS) postoperatively were administered rescue analgesic. Time to first analgesic and the number of analgesic doses administered in the 24h were recorded. **Statistical Analysis:** Parametric data were analyzed using ANOVA. Kaplan-Meier survival curves for the time to first analgesic administration were plotted and compared using log rank analysis. Chi-square test was used to analyze the incidence data. **Results:** The median [IQR] time to first analgesic in Group B (540 [240-1441] min) was similar to that in Groups BN<sub>2</sub> (450 [240-720]), BN<sub>3</sub> (600 [360-1020]) and BN<sub>4</sub> (990 [420-1441]). Significantly more patients in Groups B (9 [34.6%]) and BN<sub>4</sub> (13 [44.8%]) required no supplemental analgesic for 24h than those in Groups BN<sub>2</sub> and BN<sub>3</sub> (4 [13.8%] and 4 [13.3%]). The number of analgesic doses required in 24h in the four groups was similar. **Conclusion:** Addition of neostigmine to 1.875 mg/kg of caudal bupivacaine did not prolong the analgesia following urethroplasty in children.

**KEY WORDS:** Analgesia, bupivacaine, caudal, genitourinary, neostigmine, pediatric, postoperative

Caudal epidural block (CEB) with bupivacaine is commonly used for intraoperative and postoperative analgesia in children.<sup>[1]</sup> However, it provides short duration of analgesia.<sup>[2]</sup> Various adjuvants added to caudal bupivacaine successfully prolong the analgesic effect but may be associated with troublesome side-effects.<sup>[3-6]</sup> Neostigmine is also efficacious in this respect<sup>[9-11]</sup> but the effect of different doses of neostigmine on the duration of analgesia and side-effects is not well established. We studied the effect of three doses of neostigmine in combination with caudal bupivacaine on the time to first analgesic and the amount of analgesic required in 24h in children undergoing urethroplasty.

## Materials and Methods

A randomized, double-blind study was conducted in 120 American Society of Anesthesiologists physical status I boys of age 1-12 years undergoing elective urethroplasty for hypospadias. The study was approved by the Institute Ethics Committee. A written informed consent was obtained from the parents of the children. Patients with bleeding diathesis, preexisting neurological or spinal disease or a history of allergic reaction to local anesthetics were excluded from the study.

The children fasted for 6h after milk and for 2h after clear fluids. They were premedicated with 0.5 mg. kg<sup>-1</sup> of midazolam orally about 30 min before surgery. Anesthesia was induced with halothane in oxygen using a facemask or with a sleep dose of intravenous thiopentone based on the child's preference by one of the authors. The airway was maintained with either a tracheal tube (TT) or a laryngeal mask airway (LMA) depending on the expected duration of surgery (LMA for procedures lasting for less than 1h and TT for longer procedures). Patients with tracheal tube received atracurium and were mechanically ventilated, whereas those with LMA breathed spontaneously. Anesthesia was maintained with 70% nitrous oxide in oxygen and halothane. Intraoperative monitoring consisted of ECG, heart rate, noninvasive blood pressure (NIBP), oxygen saturation (SpO<sub>2</sub>) and end-tidal carbon dioxide (ETCO<sub>2</sub>).

After induction of anesthesia, CEB was administered in lateral position using a 23-G needle and the test drug administered. Simple randomization into four equal groups was done by one of the authors (NB) using Research Randomizer. The patients in the four groups received 0.75 ml/kg of caudal drug as follows: group B - 1.875 mg/kg of bupivacaine alone, groups BN<sub>2</sub>, BN<sub>3</sub> and BN<sub>4</sub> - 2, 3 and 4  $\mu$ g/kg of neostigmine respectively

in addition to the same amount of bupivacaine. The caudal drug was prepared by one of the investigators, and the parents of the patients and the anesthetist who administered the caudal drug and carried out the postoperative observations were blinded. The surgical procedure was started at least 10 min after the caudal injection. In case of failed caudal block (increase in heart rate or systolic blood pressure by more than 15% of the baseline on skin incision), 0.1 mg/kg of morphine was administered as rescue analgesic. Intravenous fluids were administered at a rate of 6 ml/kg/hour intraoperatively and 4 ml/kg/hour postoperatively. The patients received 0.45% saline in 5% dextrose up to 1h of surgery followed by normal saline for the duration of surgery and for the postoperative period. The neuromuscular blockade whenever used was reversed at the end of the procedure with neostigmine 0.05 mg/kg and 0.025 mg/kg atropine. The LMA or tracheal tube was removed and the child was transferred to the recovery room.

The children were monitored every 30 min for 4h postoperatively in the post-anesthesia care unit by an anesthetist and then every hour up to 24h in the ward by a nurse or an anesthetist for pain, sedation, vomiting, and muscarinic adverse effects such as diarrhea, increased salivation and bronchial secretions. Pain was assessed using objective pain score (OPS - blood pressure, crying, agitation, movement, posture and localization of pain scored from 0-2 to give a possible total score of 0-12) in children less than five years of age.<sup>[12]</sup> In older children an 11-point (0-10) verbal numerical rating scale (NRS) with 0 indicating no pain and 10 indicating maximum pain that can be imagined was used.<sup>[13]</sup> A pain score of 4 or more was treated with 15 mg/kg of oral paracetamol. The time interval between the administration of the caudal drug and the first administration of postoperative analgesic was recorded. The total number of analgesic doses administered in the 24 postoperative hours was also recorded. Sedation was assessed using the following sedation score - opens eyes spontaneously-0, opens eyes to speech-1, opens eyes when shaken-2, unarousable-3.<sup>[14]</sup> Patients received intravenous ondansetron 0.15 mg/kg in case of two or more episodes of vomiting.

We assumed a difference in duration of analgesia of 4h to be clinically relevant. The sample size calculated to detect this difference (with a within group standard deviation of 5h) on the basis of an error of 0.05 and  $\beta$  error of 0.8, was 26. Thirty patients were enrolled in each group to adjust for exclusion of patients.

Parametric data were analyzed using ANOVA. 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. Chi-square test was used to analyze the number of patients requiring analgesics and those with side-effects. A *P* value < 0.05 was considered significant.

### Results

Of the 120 children included in the study, 115 received CEB. The block could not be performed in five children due to calcified sacrococcygeal ligament. CEB was effective in all the 115 patients who received the block and the data from these patients was analyzed. There were 27 children in Group B, 29 each in Group BN<sub>2</sub> and BN<sub>4</sub> and 30 children in Group BN<sub>3</sub>.

The four groups were similar with respect to age, weight, duration of anesthesia, type of anesthetic induction technique (inhalational or intravenous) and the technique of airway control (LMA or tracheal tube) [Table 1]. The intraoperative heart rate and blood pressure were comparable in the four groups. We used OPS for children below five years of age and NRS for older children. The percentages of children below five years were 63, 58.6, 60 and 48.3% in Groups B, BN<sub>2</sub>, BN<sub>3</sub> and BN<sub>4</sub> respectively and were comparable in the four groups.

Kaplan Meier survival curves for the time to first analgesic administration in the postoperative period are shown in Figure 1. The study period concluded at 24h. Data from the patients who did not receive any analgesic during the study period formed the censored data. The median time to first analgesic in Group B was

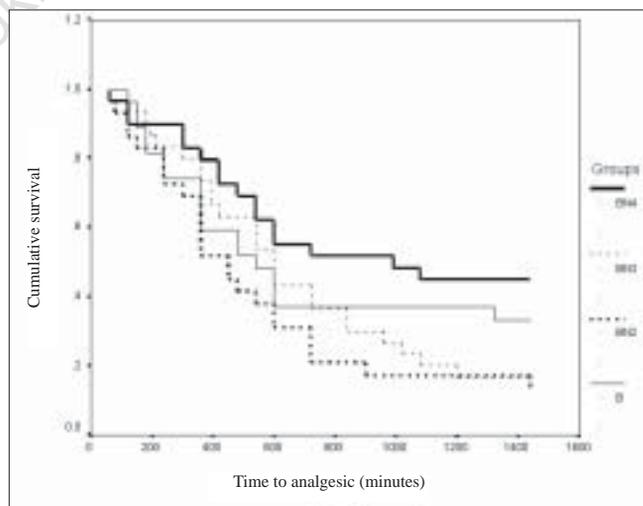


Figure 1: Kaplan meier survival curves for the time to first analgesic administration

Table 1: Demographic data

	Group B (n=27)	Group BN <sub>2</sub> (n=29)	Group BN <sub>3</sub> (n=30)	Group BN <sub>4</sub> (n=29)
Age (years)*	4.5 ± 2.1	5.1 ± 2.9	4.5 ± 2.3	5.2 ± 2.4
Weight (Kg)*	15.3 ± 4.6	16.6 ± 4.7	14.9 ± 3.8	15.9 ± 4.3
Duration of anesthesia (minutes)*	69.3 ± 23.3	67.4 ± 21.2	59.5 ± 21.6	64.1 ± 20.1
Inhalational induction of anesthesia†	23 (85.2)	19 (65.5)	25 (83.3)	24 (82.8)
LMA used for airway control†	23 (85.2)	22 (75.9)	24 (80.0)	20 (69.0)

\*Data expressed as mean ± SD, †Data expressed as number (%) of patients

comparable to that in Groups BN<sub>2</sub>, BN<sub>3</sub> and BN<sub>4</sub>. However, it was significantly longer in Group BN<sub>4</sub> than in Groups BN<sub>2</sub> ( $P=0.008$ ) and BN<sub>3</sub> ( $P=0.031$ ) [Table 2]. Significantly more patients in Groups B (34.6%) and BN<sub>4</sub> (44.8%) required no supplemental analgesic for 24h than those in groups BN<sub>2</sub> (13.8%) and BN<sub>3</sub> (13.3%). The number of analgesic doses required in 24h were, however, similar in the four groups [Table 2].

The incidence of sedation and vomiting were analyzed separately in patients with different techniques of airway control (LMA or TT). Similar number of patients were sedated (sedation score > 1) in the four groups in patients with LMA as well as in those with TT [Table 3]. The number of patients who experienced vomiting was also comparable in the four groups in patients with both the techniques of airway control. The overall incidence of postoperative vomiting in this study was 22.6%. The percentage of patients who received rescue antiemetic was 18.5, 10.3, 23.3 and 13.8 in Groups B, BN<sub>2</sub>, BN<sub>3</sub> and BN<sub>4</sub> respectively and was not significantly different.

Other side-effects observed during the study were increased oropharyngeal secretions (one patient in Group BN<sub>2</sub> and two in Group BN<sub>4</sub>), laryngospasm (two patients in Group B), pruritis (one patient in group BN<sub>3</sub>), diarrhea (three patients in Group BN<sub>4</sub>), and erection (one patient in Group BN<sub>3</sub>). The incidence of these side-effects was similar in the four groups.

## Discussion

Neostigmine, a cholinesterase inhibitor has been found to provide analgesia by both intrathecal as well as epidural routes.<sup>[15-17]</sup> It inhibits the breakdown of endogenous acetylcholine and thus indirectly stimulates both muscarinic and nicotinic receptors to produce analgesia.<sup>[18,19]</sup> This effect is mediated via spinal M<sub>1</sub> muscarinic receptors and supraspinal M<sub>1</sub> and M<sub>2</sub> muscarinic and nicotinic cholinergic receptors.<sup>[20]</sup>

Lauretti *et al.* were the first investigators to report that epidural neostigmine in combination with lignocaine produced a dose-independent analgesic effect as well as reduction in postoperative

rescue analgesic consumption in adults.<sup>[16]</sup> In children Abdulatif first reported the efficacy of caudal neostigmine to prolong the duration of postoperative analgesia provided by local anesthetic alone.<sup>[9]</sup> Since then other investigators have confirmed that caudal neostigmine alone as well as in combination with local anesthetics provides prolonged postoperative analgesia.<sup>[10,11,21,22]</sup> The commonly used dose of caudal neostigmine is 2  $\mu\text{g}\cdot\text{kg}^{-1}$  as an adjuvant to local anesthetic and it has been observed to prolong the duration of analgesia for up to 16-22h.<sup>[10,11]</sup>

We studied the effect of 2, 3 and 4  $\mu\text{g}/\text{kg}$  of neostigmine on the duration of analgesia in children undergoing surgery for hypospadias and found that the addition of neostigmine to caudal bupivacaine did not affect the duration of analgesia or the requirement of supplemental analgesic. The following factors may explain the inefficacy of caudal neostigmine in prolonging the duration of postoperative analgesia in our study.

The site of surgical procedure is known to affect the duration of analgesia after CEB. The same volume of caudal bupivacaine produces longer duration of analgesia after penoscrotal surgery compared to inguinal surgery.<sup>[23]</sup> This is probably due to a higher segmental block required for hernia surgery and thus faster regression of the block at the operative site. In our study, the duration of analgesia provided by bupivacaine itself was probably long enough to mask the efficacy of neostigmine.

The volume of the local anesthetic used can also affect the efficacy of caudal adjuvant drug. Mahajan *et al* found 2-4  $\mu\text{g}\cdot\text{kg}^{-1}$  of caudal neostigmine to be effective in prolonging the analgesia, possibly because the smaller (0.5  $\text{ml}\cdot\text{kg}^{-1}$ ) volume of bupivacaine used resulted in a short duration of analgesia allowing the analgesic effect of neostigmine to become perceptible.<sup>[22]</sup>

In the present study the data was right-censored in more than a quarter of patients, i.e. supplemental analgesic was not required till the end of the study period. The proportion of such patients was significantly higher in Groups B (34.6%) and BN<sub>4</sub> (44.8%). This led to wide interquartile ranges in these groups and ambiguous results (time to first analgesic in Group B was similar

Table 2: Analgesic profile

	Group B (n=27)	Group BN <sub>2</sub> (n=29)	Group BN <sub>3</sub> (n=30)	Group BN <sub>4</sub> (n=29)
Time to first analgesic (min) (median [IQR])	540 (240 - 1441)	450 (240 - 720)	600 (360 - 1020)	990 (420 - 1441)*
Number (Percent) [95% CI] of patients not requiring analgesic	9 (34.6) [16.3 to 52.9]†	4 (13.8) [1.2 to 26.3]	4 (13.3) [1.2 to 25.5]	13 (44.8)‡
Number of analgesic doses (mean $\pm$ SD) <sup>§</sup>	2.2 $\pm$ 1.0	1.8 $\pm$ 0.6	1.6 $\pm$ 0.7	1.8 $\pm$ 1.1

\*Log rank analysis: Group BN<sub>2</sub> vs. BN<sub>4</sub>  $P=0.008$ , Group BN<sub>3</sub> vs. BN<sub>4</sub>  $p=0.031$ , †One patient received analgesic eight-hourly, hence only 26 patients in this group were included in these analyses. ‡Chi-square: Groups B and BN<sub>4</sub> vs. BN<sub>2</sub> and BN<sub>3</sub>:  $p=0.012$ , §The mean number of analgesic doses were calculated only in patients who were administered rescue analgesic in the first 24h (Group B: n=17, BN<sub>2</sub>: 25, BN<sub>3</sub>: n= 26, BN<sub>4</sub>: n=16)

Table 3: Number (percent) of patients who were sedated or had vomiting

	Patients with laryngeal mask airway				Patients with tracheal tube			
	B (n=23)	BN <sub>2</sub> (n=22)	BN <sub>3</sub> (n=24)	BN <sub>4</sub> (n=20)	B (n=4)	BN <sub>2</sub> (n=7)	BN <sub>3</sub> (n=6)	BN <sub>4</sub> (n=9)
Sedation score > 1	2 (8.7)	6 (27.3)	6 (25.0)	4 (20.0)	0	1 (14.3)	1 (16.7)	5 (55.6)
Vomiting more than once	5 (21.7)	5 (22.7)	5 (20.8)	5 (25.0)	0	3 (42.9)	3 (50.0)	0

to that in groups BN<sub>2</sub>, BN<sub>3</sub> and BN<sub>4</sub>; at the same time, the time to first analgesic in Groups BN<sub>2</sub> and BN<sub>3</sub> was shorter compared to Group BN<sub>4</sub>). Similar findings have been reported earlier with the mean duration of analgesia in the range of 9-11h, and a number of patients not requiring any supplemental analgesic for 24h.<sup>[24,25]</sup> A study with a longer period of observation may be able to provide definite results regarding the duration of analgesia.

Epidural neostigmine acts by being absorbed into the CSF. Neostigmine is a hydrophilic substance and approximately one-tenth of its epidural dose penetrates into the CSF.<sup>[16]</sup> Intrathecal neostigmine in doses of 5-10 µg is required to provide effective analgesia in adults.<sup>[15]</sup> Thus in an average adult patient weighing 50 kg the amount of epidural drug required will be 100-150 µg. The proportion of epidural neostigmine that crosses to subarachnoid space in children is not known. However, if the same fraction of the drug is transferred as in adults, the usual dose of 2 µg/kg of epidural drug used in children weighing about 10-20 kg will result in 2-4 µg of neostigmine in the CSF. We do not know whether this amount of neostigmine will be sufficient for analgesic effect as the minimum effective intrathecal dose of the drug in children is not known.

We used both LMA and endotracheal tube for airway management in this study. Children with endotracheal tube received muscle relaxants intraoperatively, the residual effect of which was reversed at the end of the procedure using intravenous neostigmine. Administration of neostigmine by intravenous as well as caudal route could result in higher incidence of muscarinic side-effects. Therefore we have analyzed the incidence of side-effects in patients using LMA separately from those using T.T. However, we found that neither the addition of caudal neostigmine alone, nor that of both caudal and intravenous neostigmine affected the incidence of sedation and vomiting. Epidural neostigmine was shown to cause dose-dependent sedation in women undergoing Caesarean section in one study and was probably due to increased central cholinergic receptor stimulation.<sup>[26]</sup> However, increased sedation due to caudal neostigmine has not been reported in children.<sup>[9,10,21,22]</sup> The overall incidence of vomiting (22.6%) in our study was similar to the incidence reported earlier.<sup>[9,10,22]</sup>

Other side-effects that can occur following intravenous neostigmine include arrhythmia, bradycardia, bronchospasm, increased bronchial secretions and salivation, increased motility of the intestines, nausea and vomiting. We observed diarrhea, increased oropharyngeal secretions, pruritus, laryngospasm and erection. The incidence of these side-effects was similar in all the groups. Bradycardia, arrhythmias or bronchospasm were not observed in any patient in our study. All the children had a urinary catheter *in situ*; therefore the incidence of urinary retention could not be assessed.

One of the limitations of our study was the use of two different pain scores to assess postoperative analgesia. As pain is a subjective phenomenon, patient-rated pain scales such as numerical rating scale (NRS) and visual analogue scale (VAS) are considered to be accurate indicators of pain. However, only children above four to five years of age can use these scales. As

the age range was wide in our study, we used OPS for children below five years of age and NRS for older children. A study in children within a narrower age range in which a single pain score is used would provide better results.

## Conclusion

Addition of 2-4 µg/kg of neostigmine to 1.875 mg/kg of caudal bupivacaine did not result in prolongation of duration of analgesia following hypospadias surgery in children. Caudal bupivacaine alone in a volume of 0.75 ml/kg was sufficient to provide adequate analgesia for 24h in more than one-third of the patients. Prophylactic antiemetic is recommended in patients undergoing hypospadias surgery.

## References

1. Markakis DA. Regional anesthesia in pediatrics. *Anesthesiol Clin North Am* 2000;18:355-81.
2. Lourey CJ, McDonald IH. Caudal anaesthesia in infants and children. *Anaesth Intensive Care* 1973;1:547-8.
3. Krane EJ, Tyler DC, Jacobson LE. The dose response of caudal morphine in children. *Anesthesiology* 1989;71:48-52.
4. Constant I, Gall O, Gouyet L, Chauvin M, Murat I. Addition of clonidine or fentanyl to local anaesthetics prolongs the duration of surgical analgesia after single shot caudal block in children. *Br J Anaesth* 1998;80:294-8.
5. Breschan C, Krumpholz R, Likar R, Kraschl R, Schalk HV. Can a dose of 2 micro.kg (-1) caudal clonidine cause respiratory depression in neonates? *Pediatr Anaesth* 1999;9:81-3.
6. Ansermino M, Basu R, Vandebek C, Montgomery C. Nonopioid additives to local anaesthetics for caudal blockade in children: A systematic review. *Pediatr Anaesth* 2003;13:561-73.
7. Cook B, Grubb DJ, Aldridge LA, Doyle E. Comparison of the effects of adrenaline, clonidine and ketamine on the duration of caudal anaesthesia produced by bupivacaine in children. *Br J Anaesth* 1995;75:698-701.
8. Malinovsky JM, Cozian A, Lepage JY, Mussini JM, Pinaud M, Souron R. Ketamine and midazolam neurotoxicity in the rabbit. *Anesthesiology* 1991;75:91-7.
9. Abdulatif M, El-Sanabary M. Caudal neostigmine, bupivacaine and their combination for postoperative pain management after hypospadias surgery in children. *Anesth Analg* 2002;95:1215-8.
10. Turan A, Memis D, Basaran UN, Karamanlioglu B, Sut N. Caudal ropivacaine and neostigmine in pediatric surgery. *Anesthesiology* 2003;98:719-22.
11. Kumar P, Rudra A, Pan AK, Acharya A. Caudal additives in pediatrics: A comparison among midazolam, ketamine and neostigmine co administered with bupivacaine. *Anesth Analg* 2005;101:69-73.
12. Hannallah RS, Broadman LM, Belman AB, Abramowitz MD, Epstein BS. Comparison of caudal and ilioinguinal/iliohypogastric nerve blocks for control of postorchiopey pain pediatric ambulatory surgery. *Anesthesiology* 1987;66:832-4.
13. Tyler DC, Tu A, Douthit J, Chapman CR. Towards validation of pain assessment tools for children: A pilot study. *Pain* 1993;52:301-9.
14. Doyle E, Harper I, Morton NS. Patient-controlled analgesia with low dose background infusions after lower abdominal surgery in children. *Br J Anaesth* 1993;71:818-22.
15. Lauretti GR, Reis MP, Prado WA, Klamt JG. Dose-response study of intrathecal morphine versus intrathecal neostigmine, their combination or placebo for postoperative analgesia in patients undergoing anterior and posterior vaginoplasty. *Anesth Analg* 1996;82:1182-7.
16. Lauretti GR, de Oliveira R, Reis MP, Juliao MC, Pereira NL. Study of three different doses of epidural neostigmine co administered with lidocaine for postoperative analgesia. *Anesthesiology* 1999;90:1534-8.
17. Lauretti GR, Gomes JM, Reis MP, Pereira NL. Low doses of epidural ketamine or neostigmine, but not midazolam improves morphine analgesia in epidural terminal cancer pain therapy. *J Clin Anesth* 1999;11:663-8.

18. Iwamoto ET, Marion L. Characterization of the antinociception produced by intrathecally administered muscarinic agonists in rats. *J Pharmacol Exp Ther* 1993;266:329-38.
19. Yaksh TL, Dirksen R, Harty GJ. Antinociceptive effects of intrathecally injected cholinomimetic drugs in the rat and cat. *Eur J Pharmacol* 1985;117:81-8.
20. Naguib M, Yaksh TL. Antinociceptive effects of spinal cholinesterase inhibition and isobolographic analysis of the interaction with  $\mu$  and  $\alpha_2$  receptor systems. *Anesthesiology* 1994;80:1338-48.
21. Bātra YK, Arya VK, Mahajan R, Chari P. Dose response study of caudal neostigmine for postoperative analgesia in paediatric patients undergoing genitourinary surgery. *Pediatr Anaesth* 2003;13:515-21.
22. Mahajan R, Grover VK, Chari P. Caudal neostigmine with bupivacaine produces a dose-independent analgesic effect in children. *Can J Anesth* 2004;51:702-6.
23. Warner MA, Kunkel SE, Offord KO, Atchison SR, Dawson B. The effects of age, epinephrine and operative site on duration of caudal analgesia in pediatric patients. *Anesth Analg* 1987;66:995-8.
24. Khalil S, Campos C, Farag AM, Vije H, Ritchey M, Chuang A. Caudal block in children: Ropivacaine compared with bupivacaine. *Anesthesiology* 1999;91:1279-84.
25. Baris S, Karakaya D, Kelsaka E, Guldogus F, Ariturk E, Tur A. Comparison of fentanyl-bupivacaine or midazolam-bupivacaine mixtures with plain bupivacaine for caudal anaesthesia in children. *Pediatr Anaesth* 2003;13:126-31.
26. Kaya FN, Sahin S, Owen MD, Eisenach JC. Epidural neostigmine produces analgesia but also sedation in women after cesarean delivery. *Anesthesiology* 2004;100:381-5.

**Source of Support:** Nil, **Conflict of Interest:** None declared.

### Author Help: Online Submission of the Manuscripts

Articles can be submitted online from <http://www.journalonweb.com>. For online submission articles should be prepared in two files (first page file and article file). Images should be submitted separately.

- 1) **First Page File:**  
Prepare the title page, covering letter, acknowledgement, etc., using a word processor program. All information which can reveal your identity should be here. Use text/rtf/doc/pdf files. Do not zip the files.
- 2) **Article file:**  
The main text of the article, beginning from Abstract till References (including tables) should be in this file. Do not include any information (such as acknowledgement, your names in page headers, etc.) in this file. Use text/rtf/doc/pdf files. Do not zip the files. Limit the file size to 400 kb. Do not incorporate images in the file. If file size is large, graphs can be submitted as images separately without incorporating them in the article file to reduce the size of the file.
- 3) **Images:**  
Submit good quality colour images. Each image should be less than **400 kb** in size. Size of the image can be reduced by decreasing the actual height and width of the images (keep up to about 4 inches) or by reducing the quality of image. All image formats (jpeg, tiff, gif, bmp, png, eps, etc.) are acceptable; jpeg is most suitable. The image quality should be good enough to judge the scientific value of the image. Always retain a good quality, high resolution image for print purpose. This high resolution image should be sent to the editorial office at the time of sending a revised article.
- 4) **Legends:**  
Legends for the figures/images should be included at the end of the article file.