

A randomized-controlled, double-blind study to evaluate the efficacy of caudal midazolam, ketamine and neostigmine as adjuvants to bupivacaine on postoperative analgesic in children undergoing lower abdominal surgery

Musa Shirmohammadi¹, Alireza Ebrahim Soltani², Shahriar Arbabi², Karim Nasseri¹

¹Department of Anesthesiology, Kurdistan University of Medical Sciences, Sanandaj, Iran; ²Tehran Children Medical Center, Tehran University of medical Sciences, Tehran, Iran

Summary. *Background:* Caudal epidural is the most commonly used technique for the management of postoperative pain in children. The aim of the present study was to assess and compare the efficacy of caudal bupivacaine as a postoperative analgesic alone or combined with midazolam, ketamine, and neostigmine in pediatric patients undergoing lower abdominal surgery. *Methods:* Eighty pediatric patients categorized under the American Society of Anesthesiologists Physical Status I and II Classification System, who have been scheduled to undergo lower abdominal surgery were randomly designated into four groups to receive caudal block with either 1 ml/kg of 0.25% caudal bupivacaine for group B, 1 ml/kg of 0.25% caudal bupivacaine mixed with 2 µg/kg neostigmine for group BN, 1 ml/kg of 0.25% caudal bupivacaine mixed with 0.5 mg/kg ketamine for group BK or 1 ml/kg of 0.25% caudal bupivacaine mixed with 50 mcg/kg midazolam for group BM. Postoperative analgesia was examined by a blinded anesthetist utilizing a Revised Faces Pain Scale. Consumption of the total amount of rescue analgesic each 24 h, postoperative time to requirement of the first dose and any adverse effects were noted. *Results:* The four groups were comparable as regards age, sex, weight, duration of surgery, heart rate, blood pressure and the time from induction of anesthesia to response to voice. The Revised Faces Pain Scale was 2.6±1.5 in group BN, 3.1±1.8 in group BM, 4.4±2.4 in group BK, and 5.6±1.3 in group B (p=0.005). Postoperative duration of analgesia was 433±68 min, 769±118 min, 1097±126 min and 1254±176 min in groups B, BK, BM and BN respectively (P=0.001). The dose of rescue analgesic within 24 h in group B was significantly higher than those of the other three groups (P<0.05). *Conclusion:* Addition of either neostigmine, midazolam, or ketamine to caudal bupivacaine extended analgesia time and decreased rescue analgesic compared to bupivacaine alone in children who underwent lower abdominal surgery. (www.actabiomedica.it)

Key words: ketamine, pediatric caudal block, bupivacaine, postoperative analgesia, neostigmine, ketamine, midazolam

Introduction

Postoperative analgesia is a major topic of interest in pediatric anesthesia. Based on the society of pediatric anesthesia recommendation, postoperative pain

relief is an essential right and has immense known benefits (1). Caudal blockade is considered the most popular regional anesthetic procedure used in children, and it is an applicable method for providing postoperative analgesia after lower abdominal surgeries. It

can reduce the amount of inhaled and intravenous anesthetic requirement, attenuate the stress response of anesthesia and surgery, and provide excellent immediate postoperative analgesia (2).

Caudal bupivacaine is frequently used for perioperative pain relief after surgery in children (1). Although it is the local anesthetic with the longest duration of action that is currently available, however, it provides short duration of action (2-4 h) after a single injection (3). Many agents including different opioids, epinephrine, ketamine, midazolam, neostigmine, and $\alpha 2$ agonists have been added to caudal bupivacaine when used as a single-shot technique to lengthen the period of analgesia (4, 5). Though, caudal opioids may lengthen postoperative analgesia, nevertheless it may produce delayed respiratory depression (6). There are also controversy over the efficacy and side effects of non-opioid adjuvants (6-7).

The aim of this double-blinded randomized study was to compare the effects of co-administration of three non-opioid drugs (midazolam, ketamine, and neostigmine) and caudal bupivacaine on postoperative analgesia and the side effects in pediatric patients scheduled for lower abdominal surgery.

Materials and Methods

After approval by the ethics and research committee of our department, and subsequently obtaining the written informed consent of the parents of the children, a randomized double-blinded study was carried out in 80 American Society of Anesthesiologists Physical Status I and II child in the age bracket of 1-3 years undergoing elective inguinal herniorrhaphy, and or urethroplasty for hypospadias.

Children with contraindications to caudal block, bleeding diathesis, preexisting neurological or spinal disease, and those with known allergy to local anesthetics were excluded from the study.

The children were starved for 6 h after milk and 2 h after clear fluids were given, and no premedication was administered. In the operating room, monitoring procedures, which was composed of electrocardiography, pulse oximetry, heart rate, and noninvasive arterial blood pressure (NIBP) were started. After induction of

general anesthesia with sevoflurane and airway maintenance with tracheal tube, a peripheral IV line was secured and the children were hydrated with 3 mL/kg of 0.45% saline in 5% dextrose, and intravenous fluids administration was continued at a rate of 6 ml/kg/h intraoperatively and 4 ml/kg/h postoperatively. Anesthesia was maintained utilizing 50% nitrous oxide in oxygen, sevoflurane 1.5-2.5%, and intravenous atracurium of 0.1 mg/kg. No intraoperative intravenous analgesic was administered in any child. Thereafter, the patient was turned into the left lateral position, and caudal blockade was achieved under sterile conditions using a 23 gauge short beveled needle.

The patients were assigned randomly into one of four equal groups (n=20) by means of a computer-generated random list. Group B patients received 1 ml/kg of 0.25% caudal bupivacaine (AstraZeneca Australia) alone, group BN patients received 1 ml/kg of 0.25% caudal bupivacaine mixed with 2 μ g/kg neostigmine (ROCHE Germany), group BK patients received 1 ml/kg of 0.25% caudal bupivacaine mixed with 0.5 mg/kg ketamine (Ketanset Pfizer, Germany) and group BM patients received 1 ml/kg of 0.25% caudal bupivacaine mixed with 50 mcg/kg midazolam (Dermicum Hoffmann la roche, Basel, Schweiz)). Drugs were prepared by one of the investigators. The parents of the patients and the anesthetist who administered the caudal drugs and conducted the postoperative assessments were blinded. Surgical intervention commenced 15 min after caudal injection. At the end of the surgery, the duration of surgery was noted, and the neuromuscular blockade was reversed with neostigmine of 0.05 mg/kg and 0.025 mg/kg of atropine. The tracheal tube was removed and the child was transferred to the recovery room. The time between the induction of anesthesia and response to voice was recorded (anesthesia time). Postoperative pain was examined using a Revised Faces Pain Scale (R- FPS) (8), which is a self-report (parents report) measure developed to assess the intensity of pain in children. It was adapted from the Faces Pain Scale, which makes it possible to score the sensation of pain on the widely accepted 0 to 10 number scale, which noted by children parents. All patients received acetaminophen suppository 125 mg each 6 hr for 24 hr. A postoperative pain score of 4 or more was treated with meperidine of 0.3 mg/kg IV as required. The time

at which postoperative rescue analgesia was first administered and the amount of meperidine doses given each 24 h of postoperative surgery care were also recorded. Assessments were made at 1 h intervals for the first 4 h, and at 8, 12, and 24 h after recovery from anesthesia.

Based on $\alpha=0.05$ for two-sided Chi-squared test, $\beta=0.5$ to detect a difference in efficacious caudal analgesia and study power which was 90%, the sample size calculated was made up of 20 patient per group. Pain scores, time for first postoperative rescue analgesic demand and the number of rescue analgesic consumption were compared with all groups using analysis of variance, Chi-square test, and Fisher's exact test appropriately. A p value <0.05 was considered statistically significant. (SPSS version 12.0, SPSS Inc., Chicago, IL, USA)

Results

In this study, a total of 87 children were scheduled for caudal block following lower abdominal surgery. Two of the patients could not satisfy the entry criteria. The parents of four of the children were not willing

to participate in the study, and the surgery of 1 of the patients was canceled. The caudal block was efficacious in all the remaining 80 patients and the data associated with these patients were analyzed.

There were no significant differences in terms of age, gender, weight, duration of surgery, and the time from induction of anesthesia to response to voice among the four groups (Table 1).

The intraoperative heart rate and blood pressure was not significantly different in the four groups. Postoperative pain evaluation commenced from the recovery room and continued for 24 hours in the surgical ward. Addition of neostigmine to bupivacaine for caudal block resulted in superior analgesia compared to the other three groups. Revised Faces Pain Scale was 2.6 ± 1.5 in BN, which was significantly lower in comparison with other three groups ($P<0.05$). Postoperative duration of analgesia (duration for first analgesic demand) was $433\text{ min}\pm 68\text{ min}$ in group B, but it was $769\text{ min}\pm 118\text{ min}$, $1097\text{ min}\pm 126\text{ min}$ and $1254\text{ min}\pm 176\text{ min}$ in groups BK, BM and BN respectively ($P=0.001$). The dose of rescue analgesic in 24 h in group B was also higher than that of the other three groups ($P<0.05$) (Table 2).

Table 1. Characteristics of patients (mean \pm SD)

	B group (N=20)	BK group (N= 20)	BM group (N=20)	BN group (N=20)	P-value
Age; months	21 \pm 2	22 \pm 1	22 \pm 1	22 \pm 1	0.532
Gender (M/F)	13/7	13/7	12/8	12/8	0.746
Weight; kg	12.3 \pm 4.6	14.1 \pm 3.8	13.4 \pm 3.2	13.1 \pm 3.1	0.863
Duration of surgery; min	115 \pm 34	118 \pm 17	111 \pm 21	109 \pm 21	0.911
Time to response to voice; min	135 \pm 41	141 \pm 32	137 \pm 33	139 \pm 35	0.324

Anova test were used to compare quantitative variables among four groups

Table 2. Postoperative pain profile of patients (mean \pm SD)

	B group (N=20)	BK group (N= 20)	BM group (N=20)	BN group (N=20)	P-value
Face pain scale revised in 24 hr	5.6 \pm 1.3	4.4 \pm 2.4	3.1 \pm 1.8	2.6 \pm 1.5	0.0001
Time of first complain of pain (min)	433 \pm 68	769 \pm 118	1097 \pm 126	1254 \pm 176	0.0001
Amount of rescue analgesic (meperidine mg)	13 \pm 4.5	11 \pm 2.1	9 \pm 5.1	7 \pm 1.6	0.04
Time of first rescue analgesic administration (min)	455 \pm 98	830 \pm 145	1150 \pm 140	1315 \pm 209	0.001

Anova test were used to compare the variables among four groups

No child had hypotension, bradycardia, pruritus and respiratory depression in the first 24 postoperative hours. Vomiting occurred in the recovery room in 1 (5%), 1 (5%), 3 (15%) and 5 (25%) of the patients in B, BM, BK and BN groups respectively ($P < 0.01$)

Discussion

Postoperative pain relief is of great concern to anesthesiologists in various types of surgery in patients of all age group (1). Caudal block is a simple and safe method that is used frequently in pediatric surgery. Bupivacaine is the most common local anesthetic used for caudal analgesia with limited duration of action. We investigated the addition of ketamine, midazolam, and neostigmine to 0.25% caudal bupivacaine on the duration of postoperative analgesia and analgesics requirement for pain relief in children undergoing lower abdominal surgery. The result of our study showed that all three adjuvants lengthened the duration of analgesia, though the effect of neostigmine was significantly more than that of midazolam while the effect of midazolam was more than that of ketamine.

In line with the results of the current study, co-administration of 2 $\mu\text{g}/\text{kg}$ neostigmine and 1 ml/kg of caudal bupivacaine of 0.25% in children who endured hypospadias surgery extended the duration of the postoperative analgesia significantly and reduced the need for oral paracetamol (9).

In another study, children who underwent herniorrhaphy surgery received bupivacaine of 0.5 ml/kg , caudal bupivacaine of 0.25% alone or combined with 1.5 mcg/kg neostigmine, 3 mcg/kg neostigmine, or 6 mcg/kg neostigmine. The mean duration of postoperative analgesia was shorter in the group receiving pure bupivacaine (4.7 h) compared to those receiving bupivacaine combined with 1.5 mcg/kg , 3 mcg/kg , or 6 mcg/kg neostigmine (16.35, 16.8 and 16.65 h ($p < .05$)) (1).

Kumar et al., compared the efficacy of pure caudal bupivacaine with ketamine (0.5 mg/kg), midazolam (50 $\mu\text{g}/\text{kg}$), and neostigmine (2 $\mu\text{g}/\text{kg}$) combined with bupivacaine on intraoperative and postoperative pain relief therapy in eighty children aged 5-10 yr undergoing unilateral inguinal herniorrhaphy (6). The time for the first analgesic administration (paraceta-

mol syrup) was longer ($P < 0.05$) in the bupivacaine-neostigmine group and the bupivacaine-midazolam group than those groups receiving bupivacaine-ketamine or bupivacaine alone. They concluded that caudal co-administration of bupivacaine-neostigmine and bupivacaine-midazolam extended the postoperative pain relief period (6). The result of our study is in consonance with the above mentioned studies. Despite the fact that many published studies have affirmed the analgesic effects of caudal neostigmine, at least one study showed diametrically opposed results (11). In 120 boys aged 1-12 years undergoing urethroplasty, the addition of 2, 3 or 4 $\mu\text{g}/\text{kg}$ of neostigmine to 1.875 mg/kg bupivacaine did not significantly delayed the time for first rescue analgesic, or altered the supplementary analgesic and the required number of analgesic doses in comparison with patients receiving the same dose of bupivacaine without additive (10).

Intrathecal neostigmine was first reported for artificial insemination in a paraplegic man in 1956. In 1996, the effects of intrathecal neostigmine on somatic and visceral pain was reported by Lauretti GR, who also reported the analgesic effect of epidural neostigmine in 1999 (11). Thereafter, the successful use of epidural neostigmine led to its evaluation in pediatric caudal block (12).

The principal mechanism of caudally administered neostigmine on pain relief is not fully known, however it may act directly on muscarinic M1 and M2 receptors at the spinal cord level (6).

Like neostigmine there is no agreement on the role of caudal midazolam on block properties and postoperative analgesia. At least two randomized clinical study supported the use of midazolam as adjuvant to bupivacaine in lengthening the duration of postoperative analgesia (6, 13). In their study, Pradhan and Bajracharya concluded that caudal midazolam of a 50 $\mu\text{g}/\text{kg}$ dose provides equivalent analgesia to 0.25% bupivacaine (14). In contrast to these studies, Baris et al., noted that caudal block combined with bupivacaine and midazolam provides no further analgesic advantages to bupivacaine alone when administered for caudal block in children undergoing inguinal herniorrhaphy (15).

Lamina II in the dorsal horn has an important role in the processing of nociceptive information; it

seems that caudally administered midazolam affect this region through the gamma-aminobutyric acid-A/benzodiazepine system and impose analgesic effects through this means (14).

Results of the current study showed that addition of ketamine to caudal bupivacaine in comparison with plane bupivacaine could lengthen the duration of pain relief, though this effect is lower than that of neostigmine and or midazolam.

The result of the present study as regards the effects of caudally injected ketamine is in consonance with previous studies by Kumar et al. (6), Martindale et al. (16), Naguib et al. (17) and Lönnqvist et al. (18), confirmed and buttressed the positive influences of caudally injected ketamine on postoperative pain.

Caudal ketamine exerts its effect through blockade of N-Methyl-D-aspartate receptors situated in the substantia gelatinosa of the spinal cord (19, 20).

The results of our study showed that all three adjuvant drugs (neostigmine, midazolam, and ketamine) reduced the amount of rescue analgesic, and the time for first rescue analgesic administration in comparison to pure bupivacaine.

Addition of neostigmine, midazolam, and ketamine to caudal bupivacaine was safe, and there was no statically significant differences regarding incidence of complications such as hypotension, bradycardia, pruritus, vomiting, and respiratory depression in the first 24 h of postoperative surgery care in four study groups.

Conclusion

The results of this study made us to conclude that the addition of 2 µg/kg neostigmine, 50 mcg/kg midazolam, or 0.5 mg/kg ketamine as an adjuvant to 1 ml/kg of 0.25% caudal bupivacaine could lengthen the duration of postoperative analgesia in children undergoing lower abdominal surgeries without increasing the incidence of side effects. However, neostigmine offered a significant advantage over midazolam and ketamine in this regard.

References

1. Khahil SN, Hanna F, Farag A, et al. Presurgical caudal block attenuates stress response in children. *Middle East J Anaesthesiol* 2005; 18(2): 391-400.
2. Markakis DA. Regional anesthesia in pediatrics. *Anesthesiol Clin North Am* 2000; 18: 355-81.
3. Serbulent GB. Comparison of postoperative analgesic efficacy of caudal block versus dorsal penile nerve block with levobupivacaine for circumcision in children. *Korean J pain* 2011; 24(1): 31-35.
4. Bhardwai N, Yaddanapudi S, Ghai B, Wig J. Neostigmine does not prolong the duration of analgesia produced by caudal bupivacaine in children undergoing urethroplasty. *PGJM* 2007; 3: 161-165.
5. Memis D, Turan A, Karamanlioglu B, et al. Caudal neostigmine for postoperative analgesia in pediatric surgery. *Paediatr Anaesth* 2003; 13(4): 324-328.
6. 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.
7. Krane EJ. Delayed respiratory depression in a child after caudal epidural morphine. *Anesth Analg* 1988; 67: 79-82.
8. Hicks CL, von Baeyer CL, Spafford P, van Korlaar I, Goodenough B. The Faces Pain Scale - Revised: Toward a common metric in pediatric pain measurement. *Pain* 2001; 93: 173-183.
9. Mohamed A, Mohga El-S. Caudal Neostigmine, Bupivacaine, and Their Combination for Postoperative Pain Management After Hypospadias Surgery in Children. *Anesthesia & Analgesia* 2002; 95(5): 1215-1218.
10. Bhardwaj N, Yaddanapudi S, Ghai B, Wig J. Neostigmine does not prolong the duration of analgesia produced by caudal bupivacaine in children undergoing urethroplasty. *J Postgrad Med* 2007 Jul-Sep;5 3(3): 161-5.
11. Lauretti GR, de Oliveira R, Reis MP, Julião MC, Pereira NL. Study of three different doses of epidural neostigmine coadministered with lidocaine for postoperative analgesia. *Anesthesiology* 1999; 90(6): 1534-8.
12. Abdulatif M, El-Sanabary M. Caudal neostigmine, bupivacaine, and their combination for postoperative pain management after hypospadias surgery in children. *Anesth Analg* 2002; 95(5): 1215-8.
13. Mahajan R, Batra YK, Grover VK, Kajal j. A comparative study of caudal bupivacaine and midazolam-bupivacaine mixture for post-operative analgesia in children undergoing genitourinary surgery. *Int J Clin Pharmacol Ther* 2001; 39(3): 116-20.
14. Pradhan B1, Bajracharya GR. Midazolam for caudal analgesia in children: Comparison with caudal bupivacaine. *Kathmandu University Medical Journal* 2008; 2(22): 166-172.
15. Baris S, Karakaya D, Kelsaka E, Güldogus F, Ariturk E, Tür A. Comparison of fentanyl-bupivacaine or midazolam-

- bupivacaine mixtures with plain bupivacaine for caudal anaesthesia in children. *Paediatr Anaesth* 2003; 13(2): 126-31.
16. Martindale SJ, Dix P, Stoddart PA. Double-blind randomized controlled trial of caudal versus intravenous S (+)-ketamine for supplementation of caudal analgesia in children. *Br J Anaesth*. 2004;92:344-7.
17. Naguib M, Sharif AM, Seraj M, el Gammal M, Dawlatly AA. Ketamine for caudal analgesia in children: Comparison with caudal bupivacaine. *Br J Anaesth* 1991; 67: 559-64.
18. Lönnqvist PA. Adjuncts to caudal block in children--Quo vadis? *Br J Anaesth* 2005; 95: 431-3.
19. Smith DJ, Bouchal RL, Desactis CA. Properties of the interaction between ketamine and opiate binding sites in vivo and in vitro. *Neuropharmacology* 1985; 24: 1253-60.
20. Martin D, Lodge D. Ketamine acts as a non-competitive N-methyl D-aspartate antagonist on frog intrathecal cord in vitro. *Neuropharmacology* 1985; 24: 999-1003.

Received: 26 September 2016

Accepted: 3 October 2018

Correspondence:

Settings Karim Nasser

Department of Anesthesiology,

Kurdistan University of Medical Sciences

Sanandaj, Iran

E-mail: bihoshi@gmail.com