J Anesth (2010) 24:700–704
DOI 10.1007/s00540-010-0979-1

ORIGINAL ARTICLE

Epidural ropivacaine versus ropivacaine plus tramadol in postoperative analgesia in children undergoing major abdominal surgery: a comparison

Kerem Inanoglu · Dilek Ozcengiz · Yasemin Gunes · Hakki Unlugenc · Geylan Isik

Received: 4 March 2010 / Accepted: 1 June 2010 / Published online: 28 July 2010

Abstract
Purpose In this study, we aimed to compare the effects of ropivacaine alone and ropivacaine plus tramadol administered epidurally for postoperative analgesia in children.
Methods Following Ethics Committee approval and informed parent consent, 44 children aged between 2 and 12 years, with ASA physical status I or II, who were undergoing major abdominal surgery were included in the study. Following tracheal intubation, patients were placed into lateral decubitus position and an epidural catheter (22–24 G) was inserted by using a Tuohy needle. Patients were randomly divided into two groups to receive either ropivacaine alone (0.2%), 0.7 ml/kg, in group I, or ropivacaine (0.2%) plus tramadol (2 mg/kg), with total volume 0.7 ml/kg, in group II, epidurally in both groups. Hemodynamic variables, pain and sedation scores, duration of analgesia, and side effects were recorded postoperatively.
Results The duration of analgesia was significantly longer in group RT than in group R (298.6 ± 28 and 867.9 ± 106.8 min in group I and II, respectively) ($P < 0.05$). CHEOPS scores were significantly lower in group RT at 30 min, 45 min, and 3 h postoperatively than in group R ($P < 0.05$). However, sedation scores were similar between the two groups. Twenty-two patients (100%) in group R and 13 patients (59%) in group RT needed supplemental analgesia postoperatively. There were no significant differences in side effects between the groups.
Conclusion In children undergoing major abdominal surgery, epidural tramadol, added to epidural ropivacaine, provided lower pain scores, longer duration of analgesia, and lower postoperative analgesic requirement.

Keywords Epidural analgesia · Ropivacaine · Tramadol · Pediatrics

K. Inanoglu (✉)
Department of Anesthesiology, School of Medicine, Mustafa Kemal University, MKU Arastirma Hastanesi, Serinyol, 31100 Hatay, Turkey
e-mail: kinanoglu@yahoo.com

D. Ozcengiz · Y. Gunes · H. Unlugenc · G. Isik
Department of Anesthesiology, School of Medicine, Cukurova University, Adana, Turkey

Introduction

Tramadol has been licensed for use in children older than 1 year of age in many European countries since 1997. It acts at the opioid receptors and also appears to modify transmission of pain impulses by inhibition of monoamine reuptake. Tramadol is a racemic mixture of two enantiomers [1]. The (+) enantiomer has a moderate affinity for the mu receptor, greater than that of the (−) enantiomer. In addition, the (+) enantiomer inhibits serotonin reuptake and the (−) enantiomer is a norepinephrine reuptake inhibitor [2–4]. These effects result in a synergistic antinociceptive interaction between the two enantiomers. Thus, the opioid has a striking lack of respiratory depressant effect despite an analgesic potency approximately equal to that of pethidine [5].

Tramadol has been shown to provide effective, long-lasting analgesia after epidural administration in both adults and children [6–8]. Epidural blockade is recently the choice of postoperative pain management in children undergoing major abdominal surgery [9–11]. Ropivacaine, a new local anesthetic agent, has been reported to have lower toxic effects on the cardiovascular and central nervous systems [12, 13]. Although tramadol, a weak opioid

synthesized in recent years, has been reported to be effective in caudal blockade in children, studies regarding its use in lumbar epidural blockade are rare [14–17]. On the other hand, previous studies have also shown that epidural or caudal tramadol can be free from postoperative analgesia-related side effects [6–8].

Epidural anesthesia via the thoracic, lumbar, or sacral route has been commonly used in children. Lumbar epidural anesthesia has been shown to provide postoperative analgesia following pediatric abdominal or urological surgery in previous studies [18, 19].

Thus, we aimed to compare the effects of ropivacaine alone with ropivacaine plus tramadol administrated epidurally on postoperative analgesia in children.

Materials and methods

Forty-four children, aged between 2 and 12 years with ASA physical status I or II, who were undergoing elective abdominal or urological surgery were included in the study after approval by the ethics committee. Patients who were taking regular medications or had a history of major back problems, coagulation abnormality, or neurological disease were excluded. Patients received no premedication.

After application of standard monitoring, general anesthesia was induced by mask with sevoflurane 6–7% in oxygen/N_2O mixture (fraction of inspired oxygen = 0.5); anesthesia was maintained with sevoflurane (0.5–2.5%) in O_2 and N_2O mixture. An intravenous cannula was placed into a peripheral vein and a mixture of 5% dextrose in water and lactate Ringer's solution (2.5% dextrose, 0.41% sodium chloride, 0.22% sodium lactate) was administered at a rate of 5 ml/kg/h. Endotracheal intubation was facilitated with vecuronium 0.1 mg/kg.

Monitoring included noninvasive arterial blood pressure (BP), heart rate (HR), pulse oximetry, end-expired carbon dioxide, and end-expired (Esev) sevoflurane concentrations. After tracheal intubation, the patients were placed in the left lateral decubitus position. The epidural space was identified with a 19-gauge Tuohy needle with the bevel directed cephalad via the midline approach in the L3–L4 or L4–L5 vertebral space, and following determining of the epidural space by the loss of resistance, a catheter was advanced up to 3 cm in cephalic direction into the epidural space. The catheter was aspirated to exclude intrathecal or i.v. placement and then secured. The patients was then returned to the supine position.

All patients were randomly divided into two groups using a random number table to epidural ropivacaine 0.2% (group R) or ropivacaine 0.2% plus 2 mg/kg tramadol (group RT). Ropivacaine or ropivacaine plus tramadol, diluted in 0.9% saline to a total volume of 0.7 ml/kg, was given into the epidural space. The total ropivacaine dose was 1.4 mg/kg. HR, SpO_2, SBP, and DBP was recorded every 5 min during the operation.

SBP, DBP, HR, SpO_2, respiratory rate (RR), sedation, and pain scores were recorded at 5, 10, 15, and 30 min, and at 1, 2, 3, 4, 6, 12, and 24 h following recovery from anesthesia. Wake-up time was defined as the time between the end of surgery and the first evidence of one of the following: spontaneous movement, spontaneous eye opening, crying, grimacing, restlessness, and cooperation on talking to the child. In the postanesthesia care unit (PACU), a blinded observer recorded modified Aldrete scores for every 2 min. The time to discharge from recovery room was defined as time to first Aldrete score $\geq$9. All the children stayed at least 30 min in the recovery room independent of whether they met discharge criteria sooner. The analgesic effect of epidural block was evaluated by using the Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (Table 1) [15], which assigns values for crying, facial expression, verbal response, touching the wound and torso, and leg position.

Duration of analgesia was defined as the time from epidural injection to the first need for epidural analgesic. When the patient needed supplemental analgesic, we applied 0.2% ropivacain 0.35 ml/kg via epidural catheter. A pain score <7 was considered adequate analgesia. Sedation was assessed using a sedation 5-point test: 0 = awake, 1 = mild sedation, 2 = slipping into sleep, 3 = sleeping, but able to wake, and 4 = deep sleeping, unable to wake. These observations were made by an experienced anesthesiologist blinded to the treatment groups.

Sample size was calculated based on a previous study [20]. For an α-level of 0.05 and a power of 80%, 22 patients were needed in each group to detect a minimum 30% difference in the need for rescue analgesia.

Statistical analyses were performed using data from the intent-to-treat population using the statistical package SPSS v. 11.0 for Windows. Statistical comparisons between two groups were performed by using the unpaired *t* test. The incidence of complications was analyzed by

Table 1 Modified Children's Hospital of Eastern Ontario pain scale (mCHEOPS)

Score	0	1	2
CRY	No cry	Crying, moaning	Scream
FACIAL	Smiling	Composed	Grimace
VERBAL	Positive	None or other complaint	Pain, complaint
TORSO	Neutral	Shifting, tense, upright	Restrained
LEGS	Neutral	Kick, squirm, drawn-up	Restrained

Table 2 Demographic characteristics of the groups, duration of surgery, and anesthesia

Parameter	Group R ($n = 22$)	Group RT ($n = 22$)
Age (years)	7.6 ± 3.6	6.4 ± 3.0
Sex (boy/girl)	11/11	12/10
Weight (kg)	23.8 ± 11.1	20.1 ± 10.1
Height (cm)	100.4 ± 33.3	97.6 ± 27.7
Duration of surgery (min)	179.6 ± 22.0	217.5 ± 22.8
Duration of anesthesia (min)	191.3 ± 23.2	231.5 ± 23.6
Wake-up time (min)	9.6 ± 2.3	10.2 ± 2.4
PACU time (min)	18.6 ± 4.3	19.5 ± 4.4
Type of surgery		
Reimplantation of ureter	7	8
Nephrectomy	6	3
Intestinal	6	9
Other abdominal	3	2

Group R children receiving only ropivacaine, *group RT* children receiving ropivacaine plus tramadol, *PACU* postanesthesia care unit

$P > 0.05$

using the Chi-square and Fisher exact test. Unless otherwise specified, data are mean ± SD, SD, and $P < 0.05$ was defined as significant.

Results

There was no difference between the two groups in age, weight, height, ASA physical status, baseline arterial BP or HR, duration of anesthesia, surgery, wake-up time, and PACU time ($P > 0.05$). After surgical incision, the groups did not differ in intraoperative vital signs (SBP, DBP, HR, SpO_2, RR). Demographic data, duration of surgery and anesthesia, wake-up and PACU times, and types of surgery are shown in Table 2.

None of the children received intraoperative narcotics. Sevoflurane requirements were the same in the groups and decreased progressively during the operation ($P > 0.05$). None of the children developed a hemodynamic problem, respiratory difficulty, or any other adverse side effect. Sedation scores were the similar in the groups ($P > 0.05$) (Table 3). We did not observe any deep sedation in the groups.

Postoperative analgesia duration was significantly longer in group RT at $P < 0.05$: 298.6 ± 28 vs. 867.9 ± 106.8 min. CHEOPS scores recorded at 30 min, 45 min, and 3 h postoperatively were significantly lower in group RT ($P < 0.05$) (Table 4). Twenty-two patients (100%) in group R and 13 patients (59%) in group RT needed supplementary analgesics. There were no significant side effects in the patients.

Table 3 Postoperative sedation scores of the two groups

Sedation scores	Group R	Group RT
At 5 min	1.2 ± 13	0.8 ± 1.2
At 10 min	0.6 ± 1.0	0.5 ± 1.0
At 15 min	0.2 ± 0.7	0.4 ± 0.9
At 30 min	0.1 ± 0.4	0.2 ± 0.6
At 45 min	0.1 ± 0.5	0.1 ± 0.3
At 1 h	0.1 ± 0.5	0.0 ± 0.0
At 2 h	0.1 ± 0.4	0.0 ± 0.0
At 3 h	0.0 ± 0.0	0.0 ± 0.0
At 4 h	0.0 ± 0.0	0.0 ± 0.0
At 6 h	0.0 ± 0.0	0.0 ± 0.0
At 12 h	0.0 ± 0.0	0.0 ± 0.0
At 24 h	0.0 ± 0.0	0.0 ± 0.0

Group R children receiving only ropivacaine, *group RT* children receiving ropivacaine plus tramadol

$P > 0.05$

Table 4 Postoperative mCHEOPS data in the groups

CHEOPS	Group R ($n = 22$)	Group RT ($n = 22$)
At 5 min	6.8 ± 1.2	7.0 ± 1.6
At 10 min	6.4 ± 0.9	6.3 ± 0.9
At 15 min	6.4 ± 1.2	6.1 ± 0.7
At 30 min	6.3 ± 0.9	6.0 ± 0.5*
At 45 min	6.5 ± 1.0	5.9 ± 0.6*
At 1 h	6.5 ± 1.4	5.6 ± 0.7
At 2 h	6.0 ± 0.9	5.7 ± 0.9
At 3 h	5.8 ± 0.7	5.0 ± 1.0*
At 4 h	6.1 ± 1.2	4.8 ± 0.9
At 6 h	5.7 ± 0.8	4.7 ± 0.9
At 12 h	5.9 ± 1.2	4.8 ± 1.1
At 24 h	5.5 ± 0.8	4.6 ± 0.9

Group R children receiving only ropivacaine, *group RT* children receiving ropivacaine plus tramadol

* $P < 0.05$: group RT compared to group T

Discussion

Increasingly, it is obvious that children undergoing surgery need effective pain treatment to avoid unnecessary suffering. When feasible, epidural analgesia by the continuous catheter technique provides one of the most effective treatments for pain relief. This effect was also noticed in the present trial, as epidural analgesia performed well in all children. This present study showed that epidural ropivacaine plus tramadol provided more effective and longer analgesia than epidural ropivacaine alone in children.

Bösenberg et al. [21] reported that continuous epidural infusion of ropivacaine 0.2% (0.2–0.4 mg/kg/h) for

48–72 h provided satisfactory postoperative pain relief in infants aged 0–362 days. In neonates, plasma concentrations of unbound ropivacaine were well below threshold concentrations associated with systemic central nervous system (CNS) toxicity in adults (≥0.35 mg/l). In neonates, observed unbound ropivacaine levels were higher but still remained below toxic concentrations. However, because of the higher variability of plasma concentrations of ropivacaine in neonates, all those who underwent surgery during the first week of life, this group should be treated with caution. Although the T_{max} and C_{max} of ropivacaine were reported to be greater in infants with the single-shot technique [22], the ropivacaine dosages used in the present study have been used safely in caudal and lumbar epidural anesthesia [12, 23]. We did not observe any side effects related to local anesthetic concentration in our study.

Berde et al. [24] reported that epidural ropivacaine 0.4 mg/kg/h could be safely administered to children 1–9 years of age for up to 72 h. Koinig et al. [25] showed that the duration of analgesia was significantly longer with 0.5% ropivacaine than 0.25% ropivacaine (1,440 and 208 min, respectively). Within the 24-h observation period, fewer children required additional analgesia in the 0.5% ropivacaine group compared with the other group. Analgesia was adequate in 52% of the patients for 24 h. In the present study, 22 patients (100%) in group R and 13 patients (59%) in group RT needed supplementary analgesics. However, we used the lumbar epidural route, and ropivacaine concentration was 0.2%.

The relevance of a vasoconstrictive effect of ropivacaine is debatable. Some believe this effect is present only at low concentrations whereas others do not. It has been reported, especially in children, that the intrinsic vasoconstrictive property of ropivacaine leads to prolonged analgesia and might not require the concomitant use of epinephrine [26–28]. This effect could have prolonged the analgesic action of tramadol used in our study.

Tramadol is an analgesic assumed to lack a respiratory depressant effect and has been shown to provide effective, long-lasting analgesia after epidural administration in adults and children [6–8, 15, 16]. Caudal administration of bupivacaine with the addition of tramadol resulted in superior analgesia for a longer period without demand for additional analgesia compared with caudal bupivacaine and tramadol alone [29]. Prosser et al. [6] demonstrated that caudal tramadol (2 mg/kg) provided very effective analgesia for more than 10.7 h and only 6.7% of patients required additional analgesia within 1 h. Delilkan and Vijayan [7] also reported that tramadol 100 mg given epidurally, in adult patients, had a long duration of action compared to 0.25% bupivacaine (9.4 vs. 6 h) and gave very effective analgesia. Prakash et al. [17] suggested that addition of tramadol to bupivacaine administered caudally provided a dose-related increase in postoperative analgesia. The dosage of 2 mg/kg of tramadol was significantly more effective than 1 and 1.5 mg/kg. In the present study we also found that tramadol with ropivacaine produced a very long duration of analgesia (869 min) in most patients when administered by the lumbar epidural route. There was no difference in postoperative sedation between the groups as evidenced by the time to spontaneous eye opening and sedation scores at 1 and 4 h after operation.

It is not clear whether the prolonged duration of action of caudal tramadol is caused by slow absorption across the dura or slow uptake of tramadol from the epidural space into the systemic circulation. As our institution lacks the facilities to estimate serum tramadol concentrations, it was not possible to do so in our study. However, lower plasma levels after epidural administration of tramadol have been reported in most clinical studies. Chrubasik and colleagues [8], in their study of 21 patients given epidural tramadol infusion, found mean plateau serum concentrations of about 300 mg/ml that were far lower than those seen with i.v. tramadol treatment. The data from the study by Murthy and colleagues [5] suggest that injection of tramadol in the epidural space appears to act only as a depot for immediate and delayed systemic absorption. Tramadol has hydrophilic properties similar to morphine; thus, it binds less to fat and provides a higher concentration gradient that enhances absorption into the cerebrospinal fluid (CSF) [30]. Gunes and colleagues [31] concluded that caudal tramadol (2 mg/kg) provided better and long-lasting postoperative analgesia (>24 h) than i.v. tramadol 2 mg/kg (2.20 h). The majority of patients (30 of 34 patients) receiving tramadol i.v. needed supplementary analgesia, whereas no boys given caudal tramadol required postoperative analgesia during the 24-h study period. Tramadol has been reported to depress the spinal nociceptive receptors in the rat, indicating that, similarly to morphine, it acts at the spinal level [32].

In the present study, pain scores of the children receiving epidural ropivacaine plus tramadol were higher than the group receiving ropivacaine alone 5 min postoperative and then gradually decreased in a time-dependent manner. We thought that in part this finding can result from the complication of pain scores by emergence agitation following sevoflurane anesthesia at the early postoperative period and the reduction of noxious stimuli in time.

In conclusion, our study demonstrated that, in major abdominal surgery, ropivacaine (0.2%) plus tramadol provided more effective and longer-duration analgesia than ropivacaine alone: also, fewer patients needed supplementary postoperative analgesia.

References

1. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL, Jacoby HI, Selve N. Complementary and synergistic antinociceptive interaction between the enantiomers of tramadol. J Pharmacol Exp Ther. 1993;267:331–40.
2. Gobbi M, Mennini T. Release studies with rat brain cortical synaptosomes indicate that tramadol is a 5-hydroxytryptamine uptake blocker and not a 5-hydroxytryptamine releaser. Eur J Pharmacol. 1999;370:23–6.
3. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an atypical opioid analgesic. J Pharmacol Exp Ther. 1992;260:275–85.
4. Driessen B, Reimann W. Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain in vitro. Br J Pharmacol. 1992;105:147–51.
5. Murthy BV, Pandya KS, Booker PD, Murray A, Lintz W, Terlinden R. Pharmacokinetics of tramadol in children after i.v. or caudal epidural administration. Br J Anaesth. 2000;84:346–9.
6. Prosser DP, Davis A, Booker PD, Murray A. Caudal tramadol for postoperative analgesia in paediatric hypospadias surgery. Br J Anaesth. 1997;19:293–6.
7. Delilkan AE, Vijayan R. Epidural tramadol for postoperative pain relief. Anaesthesia. 1993;48:328–31.
8. Chrubasik J, Warth L, Wust H, Zindler M (1987) Analgesic potency of epidural tramadol after abdominal surgery. Pain 1987(Suppl 4) (abstract 296).
9. Uguralp S, Mutus M, Koroglu A, Gurbuz N, Koltuksuz U, Demircan M. Regional anesthesia is a good alternative to general anesthesia in pediatric children surgery: experience in 1,554. J Pediatr Surg. 2002;37:610–3.
10. Markakis DA. Regional anesthesia in pediatrics. Anesthesiol Clin N Am. 2000;18:355–81.
11. Williams DG, Howard RF. Epidural analgesia in children. A survey of current opinions and practices amongst UK paediatric anaesthetists. Paediatr Anaesth. 2003;13:769–76.
12. Morton NS. Ropivacaine in children. Br J Anaesth. 2000; 85:344–6.
13. McClure JH. Ropivacaine. Br J Anaesth. 1996;76:300–7.
14. Wilder-Smith CH, Wilder-Smith OH, Farschtschian M, Naji P. Preoperative adjuvant epidural tramadol: the effect of different doses on postoperative analgesia and pain processing. Acta Anaesthesiol Scand. 1998;42:299–305.
15. Gunes Y, Secen M, Ozcengiz D, Gunduz M, Balcioglu O, Isik G. Comparison of caudal ropivacaine, ropivacaine plus ketamine and ropivacaine plus tramadol administration for postoperative analgesia in children. Paediatr Anaesth. 2004;14:557–63.
16. Gunduz M, Ozcengiz D, Ozbek H, Isik G. A comparison of single dose caudal tramadol, tramadol plus bupivacaine and bupivacaine administration for postoperative analgesia in children. Paediatr Anaesth. 2001;11:323–6.
17. Prakash S, Tyagi R, Gogia AR, Singh R, Prakash S. Efficacy of three doses of tramadol with bupivacaine for caudal analgesia in paediatric inguinal herniotomy. Br J Anaesth. 2006;97:385–8.
18. Ingelmo P, Locatelli BG, Frawley G, Knottenbelt G, Favarato M, Spotti A, Fumagalli R. The optimum initial pediatric epidural bolus: a comparison of four local anesthetic solutions. Paediatr Anaesth. 2007;17:1166–75.
19. Ecoffey C, Dubosset A-M, Samii K. Lumbar and thoracic epidural anesthesia for urologic and upper abdominal surgery in infants and children. Anesthesiology. 1986;65:87–90.
20. Boccara G, Chaumeron A, Pouzarette Y, Mann C. The preoperative administration of ketoprofen improves analgesia after laparoscopic cholecystectomy in comparison with propacetamol or postoperative ketoprofen. Br J Anaesth. 2005;94:347–51.
21. Bösenberg AT, Thomas J, Cronje L, Lopez T, Crean PM, Gustafsson U, Huledal G, Larsson LE. Pharmacokinetics and efficacy of ropivacaine for continuous epidural infusion in neonates and infants. Paediatr Anaesth. 2005;15:739–49.
22. Dalens B. Some open questions in pediatric regional anesthesia. Minerva Anestesiol. 2003;69:451–6.
23. Ivani G, Lampugnani E, De Negri P, Lonnqvist PA, Broadman L. Ropivacaine vs. bupivacaine in major surgery in infants. Can J Anaesth. 1999;46:467–9.
24. Berde CB, Yaster M, Meretoja O, McCann ME, Huledal G, Gustafsson U, Larsson LE. Stable plasma concentrations of unbound ropivacaine during postoperative epidural infusion for 24–72 hours in children. Eur J Anaesthesiol. 2008;25:410–7.
25. Koinig H, Krenn CG, Glaser C, Marhofer P, Wildling E, Brunner M, Wallner T, Grabner C, Klimscha W, Semsroth M. The dose-response of caudal ropivacaine in children. Anesthesiology. 1999;90:1339–44.
26. Gherardini G, Samuelson U, Jernbeck J, Aberg B, Sjostrand N. Comparison of vascular effects of ropivacaine on isolated rings of human arteries. Acta Anaesthesiol Scand. 1995;39:765–8.
27. Kopacz DJ, Carpenter RL, Mackey DC. Effect of ropivacaine on cutaneous capillary blood flow in pigs. Anesthesiology. 1989; 71:69–74.
28. Nakamura K, Toda H, Kakuyama M, Nishiwada M, Yamamoto M, Hatano Y, Mori K. Direct vascular effects of ropivacaine in femoral artery and vein of the dog. Acta Anaesthesiol Scand. 1993;37:269–73.
29. Senel AC, Akyol A, Dohman D, Solak M. Caudal bupivacaine–tramadol combination for postoperative analgesia in paediatric herniorrhaphy. Acta Anaesthesiol Scand. 2001;45:786–9.
30. Castro DS, Silva MF, Shih AC, Motta PP, Pires MV, Scherer PO. Comparison between the analgesic effects of morphine and tramadol delivered epidurally in cats receiving a standardized noxious stimulation. J Feline Med Surg. 2009;11:948–53.
31. Gunes Y, Gunduz M, Unlugenc H, Ozalevli M, Ozcengiz D. Comparison of caudal versus intravenous tramadol administered either preoperatively or postoperatively for pain relief in boys. Paediatr Anaesth. 2004;14:324–8.
32. Carlsson KH, Jurna I. Effects of tramadol on motor and sensory responses of the spinal nociceptive system in the rats. Eur J Pharmacol. 1987;139:1–10.