Original Article
The assessment of bupivacaine-tramadol and levobupivacaine-tramadol combinations for preemptive caudal anaesthesia in children: a randomized, double-blind, prospective study

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Abstract: Caudal block is the regional anesthetic technique that is used most frequently in pediatric surgery and bupivacaine and levobupivacaine are widely utilized in this technique. Opioid drugs have been added to local anesthetic solutions to prolong duration of analgesia but ideal combination were not found. We compared the postoperative analgesic efficacy of equal concentrations of bupivacaine or levobupivacaine plus tramadol in pediatric patients. Sixty eight children aged 2 to 7 years who were undergoing inguinal herniorrhaphies or orchidopexies received bupivacaine 0.25% plus tramadol 2 mg/kg (1 ml/kg) (BT group) or levobupivacaine 0.25% plus tramadol 2 mg/kg (1 ml/kg) (LT group) by the caudal route after laryngeal mask anesthesia. The primary outcome of the study was to compare the duration and quality of postoperative analgesia. The postoperative pain relief was evaluated by the Children and Infants Postoperative Pain Scale (CHIPPS) at 2, 4, 6, 12, and 24 h postoperatively. In addition, the time of first analgesic requirement was noted. The CHIPPS scores were not statistically different between the groups. The duration of analgesia and requirements for rescue analgesia was similar. Urinary retention was observed more often in the BT group. There were no significant differences between groups for arterial pressures and heart rate values after caudal block and during the operation. Caudal bupivacaine plus tramadol and levobupivacaine plus tramadol have similar postoperative analgesic efficacy. But the use of bupivacaine plus tramadol may cause a greater frequency of urinary retention.

Keywords: Bupivacaine, levobupivacaine, tramadol, anaesthesia, caudal

Introduction

Caudal block is the regional anesthetic technique that is used most frequently in pediatric surgery [1], and bupivacaine and levobupivacaine are widely utilized in this technique. A large number of clinical studies have proven the clinical effectiveness and safety of bupivacaine and levobupivacaine [2-4]. Genitourinary and lower abdominal surgery is often associated with moderate to severe postoperative pain [5]. However, the single caudal block with local anesthetics provides only a short duration of analgesia and can lead to inadequate postoperative pain control in these operations. Opioid or nonopioid drugs as tramadol have been added to local anesthetic solutions to prolong caudal analgesia by a single injection [6, 7].

Tramadol, a synthetic 4-phenyl-piperidine analogue of codeine, has only a weak opioid receptor effect, and the analgesic effect is mainly attributable to the inhibition of monoamine reuptake. Animal studies have suggested that tramadol has a selective spinal action [8]. Despite publications describing the use of caudal tramadol with and without levobupivacaine or bupivacaine [2, 4, 6, 9-13], no randomized studies have compared the effects of caudal levobupivacaine plus tramadol and bupivacaine plus tramadol.

When planning this study, we hypothesized that levobupivacaine and bupivacaine plus tramadol may have different synergistic effects and different analgesic efficacy. To this aim, we planned this prospective randomized study to

Table 1. Children and Infants Postoperative Pain Scale

Item	Structure	Points
Crying	None	0
	Moaning	1
	Screaming	2
Facial expression	Relaxed/Smiling	0
	Wry mouth	1
	Grimace	2
Posture of the trunk	Neutral	0
	Variable	1
	Rear up	2
Posture of the legs	Neutral	0
	Kicking about	1
	Tightened legs	2
Motor restlessness	None	0
	Moderate	1
	Restless	2

compare postoperative analgesic efficacy and side effects of bupivacaine plus tramadol and levobupivacaine plus tramadol administered caudally in equal concentrations to children undergoing minor urological procedures.

Material and methods

Ethical approval for this study (Ethical Committee Nº 2010/94) was provided by the Ethical Committee of Duzce University on 02 December 2010. Information about the study was given and received written consent of parents.

A total of 68 ASA status I children aged 2 to 7 years who were scheduled for elective inguinal herniorrhaphy or orchidopexy were enrolled. Children in whom caudal block was contraindicated (infection at the site of block, bleeding diathesis, pre-existing neurological or spinal disease, or abnormalities of the sacrum) or with a known allergy to local anesthetics were excluded.

Patients were randomly assigned using a computer-generated random number table to one of the two groups (http://www.graphad.com/quickcalcs/RandMenu.cfm): Bupivacaine-tramadol (BT) group and levobupivacaine-tramadol (LT) group. The investigators, attending anesthetists and patients were blinded to the computer-generated randomization schedule. Patients were fasted for 6 h before the procedure. Clear fluids were allowed up to 3 h before the

procedure. Patients received premedication with rectal midazolam 0.5 mg/kg (maximum 15 mg) 30 min before surgery. Peripheral I.V. access was secured and I.V. induction with propofol 2 mg/kg and alfentanil 20 µg/kg was administered. Anaesthesia was maintained with 50% air in 50% oxygen plus 2-2.5% sevoflurane by laryngeal mask airway. After induction of anesthesia and before surgery so as preemptive, patients were placed in a left lateral position and caudal blockade was performed under sterile conditions using a 25 G pediatric caudal needle (Epican Paed, Braun, Germany). Verification of successful needle placement was based on four predictors: ability to locate sacral hiatus, pop on piercing the ligament, lack of resistance to injection, and lack of subcutaneous swelling. The children in the bupivacaine-tramadol (BT) group received a caudal injection of bupivacaine 0.25% plus tramadol 2 mg/kg (maximum doses; 35 mg bupivacaine plus 35 mg tramadol), while those in the levobupivacaine-tramadol (LT) group received a caudal injection of levobupivacaine 0.25% plus tramadol 2 mg/kg (maximum doses; 35 mg levobupivacaine plus 35 mg tramadol), resulting in a total volume of 1 ml/kg at maximum volume of 15 ml. Study drugs were prepared by an anesthetist not involved in the trial using unlabeled syringes. The study remained blind until completion and researchers were only made aware of group allocations after statistical analysis.

Heart rate, noninvasive arterial pressure and peripheral oxygen saturation were recorded before anaesthesia and at 5 min intervals after caudal block. A skin incision was performed 15-20 min after caudal anaesthesia. Effective analgesia was defined as an absence of gross movements and a hemodynamic reaction < 20% as compared with baseline values in response to surgical incision. In case of inadequate perioperative analgesia, supplementary fentanyl 1 µg/kg was administered (these patients were excluded from study). After surgery, patients were transferred to the recovery room.

The primary goal of our study was to compare the duration and quality of postoperative analgesia and adverse effects with tramadol added to bupivacaine and levobupivacaine for caudal anaesthesia. The postoperative pain relief was evaluated using Children's and Infants'

Figure 1. CONSORT flowchart summarizing enrollment and retention in the study protocol.
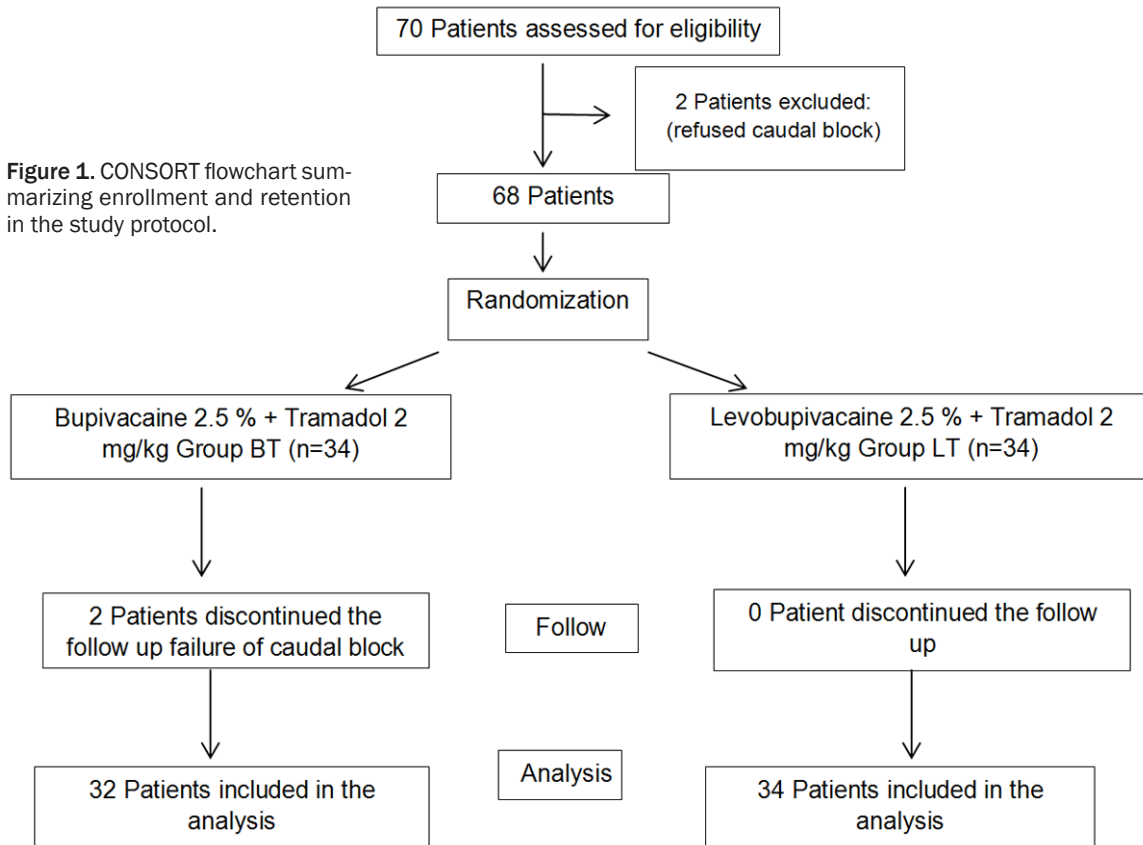
Postoperative Pain Scale (CHIPPS) [14] and by measuring the duration of analgesia at 2, 4, 6, 12, and 24 h following recovery from anaesthesia (**Table 1**). At the same time, staff nurses and parents evaluated children's behaviors and sleep quality with reference to a three-point scale (calm/cheerful, score 1; restless, score 2; tense/tearful, score 3). Postoperative assessments were made by nursing staff unaware of group allocation. Residual motor block was evaluated using a modified Bromage Scale (no motor block, score 0; able to move knees and feet, score 1; able to move feet, score 2; complete block of motor limb, score 3) 2 hours after surgery. In the case of a CHIPPS score of 4 or more, paracetamol 30 mg/kg was administered rectally. The duration of analgesia was defined by noting the time from caudal injection to the time of first analgesic requirement. Side effects (emesis, urinary retention, motor weakness, and sedation), time prior to first analgesic, and the total number of analgesic doses required in the first 24 h were recorded. All patients were observed in the hospital for at least 24 h because of the possible side effects of caudal blocks.

Statistical analysis

To achieve a power of 90% with a type I error rate of 0.05, the first analgesic requirement time was considered as the primary outcome and the sample size was calculated as 25 patients for each group. Likelihood ratio and chi-square tests were used to examine the relationships between categorical demographic data and groups. Quantitative demographic characteristics were compared using ANOVA. In addition, differences between groups in terms of hemodynamic parameters were assessed with an ANOVA and periodic changes in each group were examined using a repeated measure ANOVA. CHIPPS scores, sleep quality, and behavioral scores were compared using a Mann-Whitney U test among the groups and the relationships between these groups were examined using a Likelihood ratio chi-square test.

Results

A total of 68 children were enrolled in the study, with 2 patients in the BT group excluded due to

Table 2. Patients' clinical characteristics

	Group BT (n=32)	Group LT (n=34)	p
Age (years)	5.1 ± 2.3	4.64 ± 2.17	0.40
Weight (kg)	18.53 ± 5.3	17.11 ± 5.07	0.27
Duration of operation (min)	52 ± 13.9	58.9 ± 25.4	0.18
Type of Surgery: Orchidopexy/inguinal herniorrhaphy	12/20	16/18	0.22
Gender (n) (male/female)	27/5	27/7	0.35

Table 3. CHIPPS scores for the first 24 postoperative hours[*]

Time İntervals	Group BT (n=32)		Group LT (n=34)		p
	Mean ± SD	Median	Mean ± SD	Median	
2 h	1.06 ± 2.01	0	0.5 ± 1.46	0	0.287
4 h	0.70 ± 1.51	0	0.47 ± 1.29	0	0.986
6 h	0.46 ± 0.8	0	0.69 ± 1.23	0	0.440
12 h	0.60 ± 0.89	0	0.88 ± 1.75	0	0.975
24 h	2.13 ± 2.58	0	1.83 ± 2.92	0	0.573

[*]Mann-Whitney U test used.

Table 4. The first analgesic requirement times and numbers of receiving paracetamol postoperatively[*]

	Group BT (n=32)	Group LT (n=34)	p
Time to first analgesic	10.26 ± 3.09	8.55 ± 1.67	0.402
Number of doses of paracetamol received			0.653
0	11	15	
1	19	17	
2	2	2	

[*]Likelihood Ratio test was used.

The assessment of sleep quality and behavioral scores by the nurses and parents was similar between the two groups.

Side effects such as urinary retention were observed significantly more often in the BT group (3 patients (8.8%) in the BT group, 0 patients in the LT group; p=0.05). In these patients, external manual compression over the bladder was able to express urine; no patients required bladder catheterization. Other side effects (respiratory depression, nausea, vomiting, or pruritics) were not observed in any of the patients.

failure of the caudal block (**Figure 1**). There were no significant differences in age, weight, sex, or duration of surgery among the groups (**Table 2**).

No statistically significant difference in CHIPPS pain scoring between groups could be detected at any measurement time (**Table 3**). Eleven patients in the BT group and 15 patients in the LT group did not receive any analgesics during the study period. The amount of paracetamol given per patient did not differ between the two groups. The first analgesic requirement was similar between groups (**Table 4**). Additionally, postoperative pain relief, which was the primary end-point of the study, was similar between the two groups.

No significant difference in residual block degree between groups could be found 2 h postoperatively, and no patient achieved the maximum Bromage scoring of three.

There were no significant differences between groups for arterial pressures and heart rate values after caudal block and during the operation.

Discussion

The results of our study have shown that a caudal block with tramadol 2 mg/kg added to bupivacaine 0.25% or to levobupivacaine 0.25% yields a similar quality and duration of postoperative pain relief in pediatric patients undergoing minor urological procedures.

Tramadol injected into the epidural space has a prolonged duration of action because of sustained release from epidural fat and other relatively poorly perfused tissues [15]. Senel et al [9] suggested that the duration of analgesia was longest in children receiving concurrent tramadol 1.5 mg/kg and bupivacaine 0.25%. Prakash et al [10] compared three doses of tra-

madol, administered caudally with bupivacaine. In that study, tramadol 2 mg/kg combined with bupivacaine 0.25% provided a longer duration of postoperative analgesia and reduced the requirement for rescue analgesics as compared with tramadol 1 mg/kg or 1.5 mg/kg in children. In these studies, the mean duration of analgesia was 12-13 h. In addition, we found that the mean duration of analgesia was found 10 h group bupivacaine plus tramadol. Only one study reported that the addition of tramadol did not significantly prolong the action of caudal bupivacaine [11]. The reason for this difference may be due to postoperative pain being assessed for only 12 h after the caudal block.

A literature search revealed only one study describing the addition of tramadol to levobupivacaine in a caudal block. Yildiz et al [6] reported that the addition of tramadol 1.5 mg/kg to levobupivacaine 0.125% administered caudally provided postoperative analgesia for up to 9 h in children after inguinal hernia repair. In our study, the concentration of levobupivacaine was determined as 0.25% equal doses of bupivacaine. In this situation, we found that the mean duration of analgesia was 9 h in the LT group (levobupivacaine plus tramadol).

Engelman and Marsala [16] suggested that there could be a synergistic effect between the local anesthetics and the additives, such as tramadol, rather than simply an additive effect, as the higher the dose of local anesthetics, the greater the additional anesthetic effect. In the literature, there are studies in rats exploring a synergistic interaction between intrathecal clonidine and lidocaine [17, 18].

One limitation of this study is that we used local anesthetic concentrations of 0.25%. Comparison of local anesthetic potency has been standardized by the use of the minimum local anesthetic concentration (MLAC or ED_{50}) [4]. To our knowledge, the MLAC of local anesthetics has not been assessed in pediatric patients receiving caudal block [2]. Yao et al [19] described a dose-response relationship for levobupivacaine with caudal analgesia, and 0.15% levobupivacaine appeared to represent the optimum clinical dose for caudal block. However, the researchers did not evaluate levobupivacaine concentrations of more than 0.18%. In another study, Ivani et al [12] found that 0.20% levobupivacaine may give the best caudal block in children. The local anesthetic

concentrations used ranged from 0.2-0.25%, and the higher level may have reached the upper flat portion of the dose-response curve where both local anesthetics are effective and potency differences are obscured [2].

The residual motor blockade must increase with increasing concentrations of local anesthetics, but recent studies have reported contrasting results. Astuto et al [20] did not observe motor blockade after surgery and during the study period using ropivacaine 0.25% or levobupivacaine 0.25%. In contrast to these results, Frawley et al [4] found 7% motor block in a group receiving 0.25% bupivacaine as compared with an 11% motor blockade in the levobupivacaine 0.25% group at 120 min following caudal anaesthesia. Locatelli et al [2] demonstrated that bupivacaine 0.25% produced a significant incidence of residual motor block at recovery from anaesthesia as compared with levobupivacaine 0.25% and there was no significant difference between groups at 3 h after blockade. However, our study found no residual block at the postoperative second hour in either group, but we did not evaluate motor blockade at recovery.

Postoperative dysuria affected 2% of children after caudal block for inguinal hernia procedures [16]. In our study, three patients in the BT group (bupivacaine plus tramadol) had urinary retention, but none of these patients required bladder catheterization. In Engelman and Marsala's meta-analysis study [16], seven of the nine tramadol studies reported urinary difficulties. Pappas et al suggested that a distinct correlation between urinary retention and surgery type exists, with patients undergoing hypospadias repair having the highest incidence of urinary retention that requires therapeutic intervention [21].

In summary, the addition of tramadol to both levobupivacaine and bupivacaine yields similar postoperative analgesic efficacy, but the use of bupivacaine plus tramadol may cause a greater frequency of urinary retention.

Disclosure of conflict of interest

None.

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