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ORIGINAL ARTICLE

Effects of caudal sufentanil supplemented with levobupivacaine on blocking spermatic cord traction response in pediatric orchidopexy

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Abstract
Purposes Caudal block is one of the most commonly used anesthetic techniques in subumbilical and genitourinary procedures. However, traditional administration of caudal levobupivacaine was inadequate on blocking peritoneal response during spermatic cord traction. The aim of this study was to evaluate whether the addition of caudal sufentanil to levobupivacaine provided better analgesia for children undergoing orchidopexy.
Methods Sixty-two patients, scheduled for right orchidopexy, received caudal block after induction. Group LS ($n = 31$) received levobupivacaine 0.25 % 1 ml/kg plus sufentanil 0.5 μg/kg, and group L ($n = 31$) received levobupivacaine 0.25 % 1 ml/kg only. HR or MAP fluctuation >20 % or entropy increase >15 % during spermatic cord traction was defined as inadequate anesthesia and was treated with increasing sevoflurane concentration. The number of children who needed sevoflurane rescue was counted, and postoperative side effects and quality of sleep were also recorded.
Results There were no statistically significant differences between the two groups in age, weight, and duration of surgery. Two (6.45 %) children in group LS required inspired sevoflurane rescue to block hemodynamic fluctuation during spermatic cord traction, as compared with 12 (38.71 %) patients in group L ($P < 0.001$). At the time of exerting spermatic cord traction, the median HR was, respectively, 134 and 145 ($P < 0.001$); the corresponding response entropy (RE) and state entropy (SE) was 65 and 54, respectively, in group LS versus 76 and 65 in group L ($P < 0.001$).
Conclusion In pediatric orchidopexy, the addition of sufentanil to levobupivacaine for caudal blockade offers clinical benefit over levobupivacaine alone in blocking the spermatic cord traction response.

Keywords Caudal · Levobupivacaine · Pediatric · Sufentanil

Introduction

Caudal anesthesia is an effective and safe method for patients undergoing subumbilical and genitourinary region operations [1, 2]. This technique can be easily performed after general induction (by either inhalation or IV administration) in children and is a useful adjuvant to general anesthesia [1–3]. We conventionally used levobupivacaine 0.25 % 1 ml/kg for caudal analgesia and found it is not always adequate, requiring an increase in the inspired concentration of sevoflurane during spermatic cord traction. Aside from appropriate dose, volume, and concentration of local anesthetics, a combination of caudally administered adjunct drugs, including nonopoids and opioids, was used to reduce local anesthetic requirements while promoting the intensity of intraoperative analgesic effects [4, 5]. Our goal was to identify the analgesic efficacy of caudal addition of sufentanil, a highly lipophilic opioid, to levobupivacaine in children undergoing unilateral orchidopexy.

Previous studies that focused on caudal efficacy were mostly conducted by using measures including heart rate, mean blood pressure, or body movements. Aside from

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these traditional parameters, entropy (namely, state entropy and response entropy) was introduced in the current study to assess general anesthetic drug effects on the central nervous system so as to assess analgesia of caudal blockade, because analyzing raw EEG signals in real time during anesthesia is difficult. Entropy is a nonlinear statistic parameter quantifying the randomness of the raw EEG signals using entropy principles [6], presenting the content in a numeric value from 0 to 100: 0 indicates the deepest level of anesthesia and 100 represents the awake state of a patient. In this randomized, double-blinded, and prospective study, we applied entropy to measure the depth of general anesthesia. The device generates two indices: the state entropy (SE), computed from an EEG-dominant frequency range (0.8–32 Hz), in addition to the response entropy (RE), computed from a broader range (0.8–47 Hz), including both the EEG and electromyogram domain. This monitoring technique was thereby expected to determine the intraoperative effects of addition of sufentanil to levobupivacaine in caudal block.

Methods

After approval of the institutional review board (IRB) and obtaining informed parental consent, 62 ASA status I pediatric patients, aged from 1 to 6 years old, who were scheduled for right orchidopexy were enrolled in the current study. This study was registered online (http://www.chictr.org) with the registration number ChiCTR-TRC-12002170. According to the urologist's evaluation, the undescended testis in each case was readily palpable in a low position (superficial inguinal position). Patients with any known history of allergy to the study medicine or any contraindication to caudal anesthesia were excluded from this study. Each patient was randomly allocated to one of the two groups via a computer-generated randomization table. Two different anesthesiologists with the same urologist participated in the care of the children during the surgeries. All staff involved were blinded to each patient's group assignment.

The children were premedicated with oral midazolam 0.5 mg/kg 30 min before surgery. Anesthesiologist A performed the induction of general anesthesia using sevoflurane 8 % in oxygen 100 % by face mask and inserted a laryngeal mask airway (LMA) of appropriate size after the eyelash reflex of the child disappeared. All patients maintained spontaneous breathing, and manually assisted ventilation was performed when necessary to keep end-tidal CO_2 between 35 and 45 mmHg. Anesthesiologist B, who was not involved in subsequent management of the child, performed a single-dose caudal block using a 22 G needle. Group LS patients received a mixture of levobupivacaine 0.25 % and sufentanil 0.5 μg/kg in normal saline 1 ml; group L patients were injected with 1 ml/kg levobupivacaine 0.25 % and 1 ml normal saline. The levobupivacaine solutions were freshly prepared before injection.

Anesthesia was maintained with the same volatile agent by anesthesiologist A, who was unaware of the formula of local anesthetic injected to the caudal space. Adequate analgesia was defined as indicated by an increase or decrease in mean arterial pressure (MAP) or heartrate (HR) <20 %, in addition to entropy fluctuation <15 % compared with baseline values acquired just before surgical incision. The inspired concentration was adjusted from 1.5 % to 3 % in cases of hypertension or tachycardia. No other anesthetics or analgesics were administered in the study period.

Surgery was allowed to begin approximately 15 min after the caudal injection. The caudal block was considered successful if there was no significant increase (>20 %) in HR or MAP in response to the skin incision. An identical stimulus, including digital traction on the spermatic cord, was used in each case by the same urologist to evaluate analgesic effect and level of the caudal blockade. The surgeon was aware of the necessity to exert a uniform traction force, and followed a standardized surgical procedure, consisting of using his thumb and index finger to take the undescended testicle down into the scrotal sac. Sevoflurane administration was discontinued at the closure of the skin. After emergence from anesthesia, the LMA was removed, and the children were transferred to the postanesthesia care unit (PACU) where they all received a nurse-controlled analgesia (NCA) pump (no background infusion with a bolus of 0.5 μg/kg fentanyl and a 60-min lockout period).

In the PACU, postoperative adverse events were treated and recorded by an experienced nurse who was unaware of the study solutions. Postoperative recordings included incidence of vomiting, urine retention, respiratory depression, and quality of night rest [7] (Table 1).

Heart rate (HR), oxygen saturation (SpO_2), and end-tidal sevoflurane concentrations were monitored continuously during the whole operation. Noninvasive mean arterial blood pressure (MAP) was assessed every 5 min. Monitoring for entropy was established before any drug administration. The skin of the child's forehead had been carefully wiped off with an alcohol swab and left to dry. After sensors were placed onto the temporofrontal area of the forehead according to the manufacturer's instruction, SE and RE were calculated and recorded in intervals of 10 s by the Datex-Ohmeda S/5 Entropy Module throughout the time of anesthesia.

Seven different anesthetic steps were defined in this investigation: before induction of anesthesia (T_0), inserting LMA (T_1), after reaching stable end-tidal sevoflurane

Table 1 Postoperative adverse events

	Group L ($n = 33$)	Group LS ($n = 33$)	P value
Quality of night rest	2.2 ± 0.7	1.6 ± 0.7	0.002*
Incidence of vomiting	2	2	1
Urine retention	1	0	1
Respiratory depression	0	0	1

Value reported as mean ± SD, as frequency (%)

Scores: quality of night rest: 1 = normal sleep, 2 = occasionally interrupted, 3 = frequently interrupted, 4 = awake

Group L levobupivacaine group, *group LS* levobupivacaine-sufentanil group

* Significantly different ($P < 0.001$) compared with group L

concentration (T_2), incision of the skin (T_3), traction on spermatic cord (T_4), end of the surgery (T_5), and emergence from anesthesia (T_6). All data (RE, SE, MAP, and HR) at those steps were recorded, and comparative analysis of these data for the step of interest (T_4) was performed to differentiate the anesthetic depth of patients between the two groups.

Statistical analysis

Sample size calculation was based on data obtained from preliminary studies that revealed the incidence of requiring an increase in sevoflurane concentration to be approximately 40 % in children who received caudal analgesia with levobupivacaine 0.25 % 1 ml/kg. Thirty-one patients in each group allowed detection of a 30 % reduction with an α risk of 0.05 and a power of 0.8.

Data are expressed as means (SD) or medians (ranges). For SE, RE, MAP, and HR, 90 %, 75 %, 50 %, 25 %, and 10 % percentiles were calculated for every investigated step. The two-sample Student's t test will detect differences in age, weight, and duration of surgery. The nominal data were analyzed by chi-square tests and Fisher's exact test. Because the response variables are times to events and do not meet Gaussian distribution, we used the nonparametric Mann–Whitney U test of significance. A Mann–Whitney U test was also used to compare incidence of vomiting, urine retention, respiratory depression, and quality of night rest. A P value < 0.05 was considered statistically significant in all analyses.

Results

A total of 62 patients were admitted in this study. Relevant patient data and a CONSORT flow diagram, respectively, are shown in Table 2 and Fig. 1. There were no statistical differences ($P > 0.05$) between the two groups with respect to age (years), weight (kg), and surgery time (min).

In the PACU, all children in group LS had a better night's rest compared with those in group L (Table 1). No significant difference was found between the two groups in the incidence of vomiting. The number of patients requiring urinary catheterization was the same in both groups. No patient recorded an episode of $SpO_2 < 95$ % that required manual ventilation or emergent intubation.

At the time of T_4, only 2 patients in group LS had an increase in heart rate or blood pressure more than 20 % and therefore required an acute increase in the concentration of sevoflurane. In group L, 12 patients (38.71 %) needed sevoflurane rescue ($P < 0.001$) (Table 2). Also, a significantly lower incidence of entropy fluctuation was revealed in group LS with a P value less than 0.001.

Changes of MAP, HR, RE, and SE during the investigated anesthetic steps are shown in Figs. 2 and 3. Figure 2 demonstrated that the median values of HR at T_4 were 134 bpm (IQR 13) in group LS and 145 bpm (IQR 16) in group L. The corresponding values for MAP were 71 mmHg (IQR 13.5) and 73 mmHg (IQR 13), respectively. In other words, HR values ($P < 0.001$), but not the MAP values ($P = 0.787$), were useful to discriminate statistical difference between the study groups.

In Fig. 3, we noted that RE at T_4 (traction on spermatic cord) was 65 (IQR 8.5) in group LS and 76 (IQR 17) in group L, whereas SE was 54 (IQR 10) and 65 (IQR 15.5), respectively. Thus, RE ($P < 0.001$) and SE ($P < 0.001$) values were significantly lower in group LS compared with group L while exerting spermatic cord traction.

Discussion

A number of clinical studies have suggested that levobupivacaine has been effectively and safely used with various techniques, including caudal anesthesia, in pediatric patients [8]. Furthermore, caudal administration of bupivacaine 0.25 % supplemented with light general anesthesia provides reliable intraoperative analgesia in children undergoing genitourinary procedures [1]. However, local anesthetics given epidurally do not always furnish sufficient analgesia with a dose that avoids risks of incurring toxicity or inadvertent high block [9].

Insofar as orchidopexy is concerned, the testicle receives sensory innervation not only from the aortic and renal plexuses but also from sympathetic fibers attaching to the T10 and T11 segments of the spinal cord via the thoracic splanchnic nerves. Moreover, peritoneal stimulus derived from spermatic cord traction needs a higher level

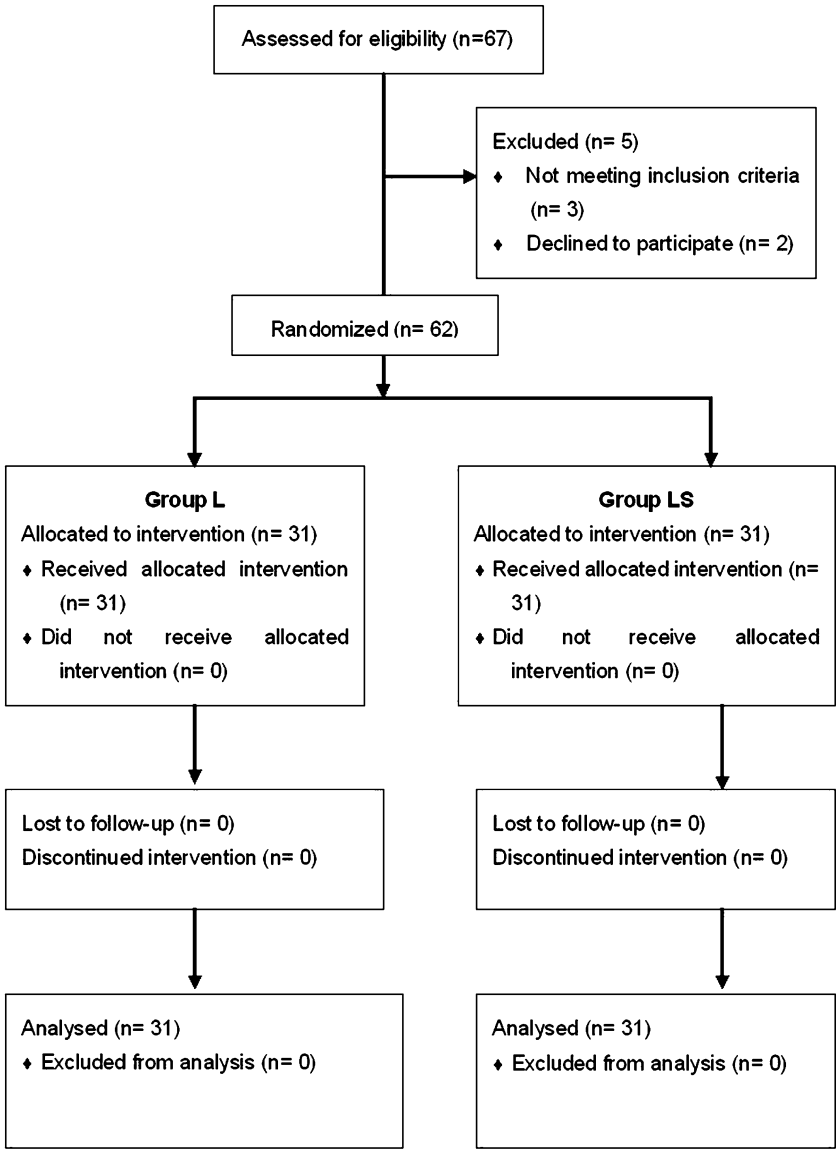


Fig. 1 CONSORT statement

Table 2 Demographic data and intraoperative characteristics

	Group L ($n = 33$)	Group LS ($n = 33$)	*P* value
Age (months)	28.5 ± 13.0 (14–70)	31.9 ± 13.5 (12–69)	0.312
Weight (kg)	14.9 ± 3.6 (10–28)	15.7 ± 3.3 (11–25)	0.379
Duration of surgery (min)	59.3 ± 12.0	59.1 ± 11.0	0.949
Sevoflurane rescue	11 (33.33 %)	2 (6.06 %)	<0.001*
Entropy fluctuation	17 (51.52 %)	4 (12.12 %)	<0.001*

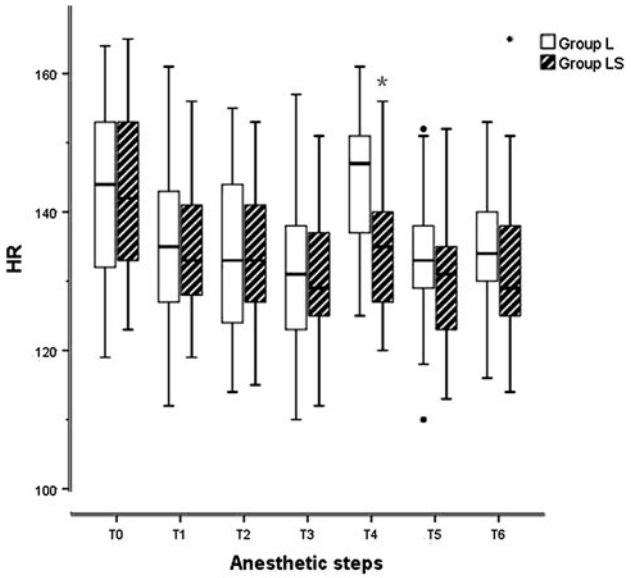
Value reported as mean ± SD, or as frequency (%)

Group L levobupivacaine group, *group LS* levobupivacaine-sufentanil group

* Significantly different ($P < 0.001$) compared with group L

of blockade (T4–T6); that may be a reasonable explanation why levobupivacaine 0.25 % 1 ml/kg sometimes fails to block peritoneal response, which is evidenced by tachycardia or hypertension. Traditionally, the general anesthetic level was increased to inhibit the response.

Although the hemodynamic fluctuation during spermatic cord traction is transient, inadequate analgesia during peritoneal stimuli carries the risk of inducing laryngeal spasm in the first place; metabolic and neuroendocrine reactions caused by this mechanical noxious stimulation would be triggered inevitably thereafter. On the other hand, it is commonly accepted by scientists and anesthesiologists that exposure to a high concentration of volatile anesthetics brings about a series of risks, including respiratory inhibition that needs close monitoring intra- or postoperatively, delayed emergence from anesthesia, organ toxicity, and



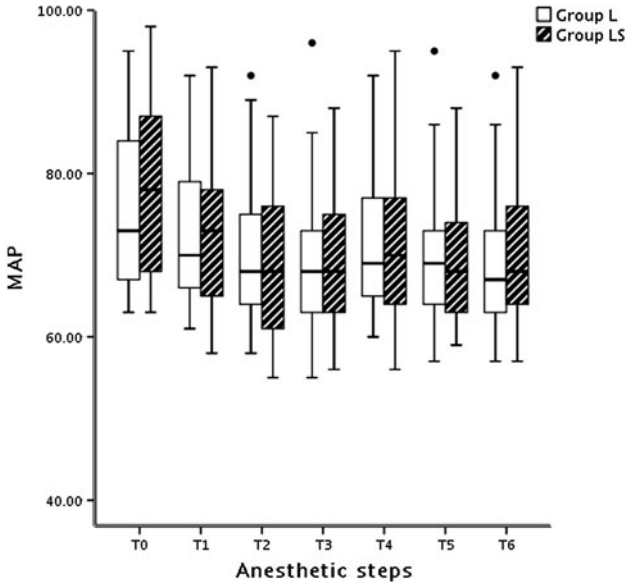
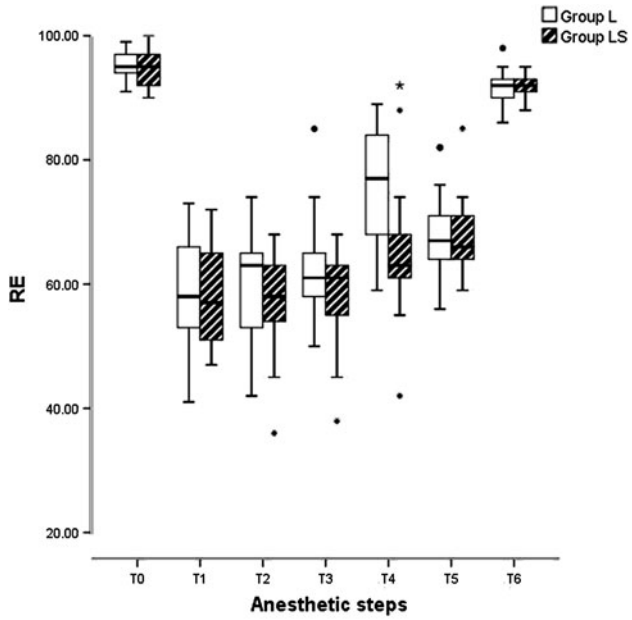


Fig. 2 Heartrate (HR) and mean arterial pressure (MAP) at predetermined time points. *Box plot* (median, *end of box*: 25th and 75th percentiles, *error bars*: 10th and 90th percentiles, outliers) of the MAP and HR at different anesthetic steps. *Asterisk* denotes group LS (levobupivacaine 0.25 % 1 ml/kg plus sufentanil 0.5 μg/kg) compared to group L levobupivacaine 0.25 % 1 ml/kg only), $P < 0.001$



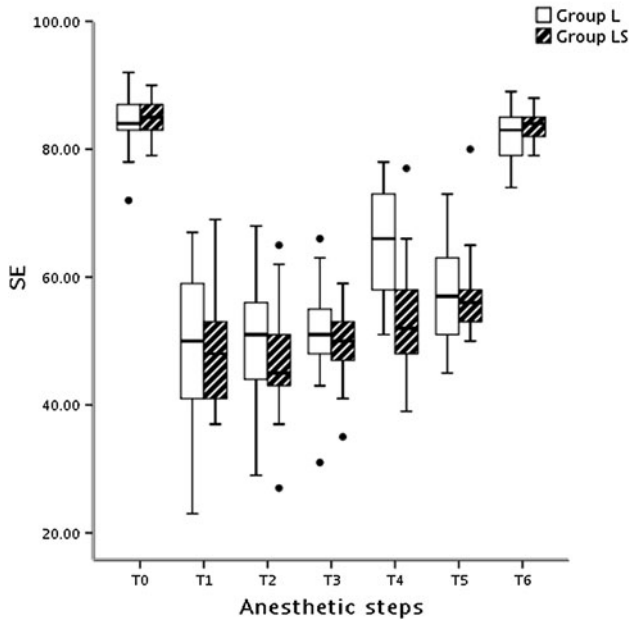


Fig. 3 Response entropy (RE) and state entropy (SE) values at predetermined time points. *Box plot* (median, *end of box*: 25th and 75th percentiles, *error bars*: 10th and 90th percentiles, outliers) of the RE and SE at different anesthetic steps. *Asterisk* represents group LS vs. group L, $P < 0.001$

emergence agitation (EA) [10–13]. Thus, we conducted this current study to find a better solution of preemptively blocking spermatic cord traction response rather than simply handling it with general anesthesia.

To prevent inadequate spinal block and to avoid possible risks of volatile anesthetics, low-dose local anesthetic solutions combined with intrathecal opioids have been shown to be safe and effective. Sufentanil is one of the commonly used opioids for this purpose [14]. Low-dose diluted bupivacaine with sufentanil 5 μg was proved to be superior to bupivacaine with fentanyl 25 μg in the quality of the spinal block in patients undergoing transurethral prostatectomy [15]. Moreover, bupivacaine in combination with sufentanil under unilateral spinal anesthesia can make knee surgery possible, avoiding risk factors such as hemodynamic instability and prolonged suffering [16]. Thus, this approach seems to be an attractive alternative in anesthesia procedures today.

Epidural opioids induce analgesic effects through the following mechanisms: transport to supraspinal specific

receptors via cerebrospinal fluid, vascular uptake to supraspinal receptors after systemic absorption, and direct activation of spinal opioid receptors. Previous studies proved that rostral cerebrospinal fluid transport seems unlikely to have contributed much to the analgesia of highly soluble opioids [17, 18]. When used alone, sufentanil apparently produces analgesia mainly through systemic uptake and redistribution to the central nervous system [19, 20]. However, Joris and coworkers [21] confirmed that sufentanil appears to augment epidural analgesia by a synergistic reaction with local anesthetics via a spinal mechanism, as shown in previous animal studies.

In the present study, 2 of the children in group LS required rescue treatment by increasing the inspiratory concentration of sevoflurane, as compared with 12 in group L ($P < 0.001$). The remarkable benefit of sufentanil may be produced by possible mechanisms, as already mentioned.

Theoretically, epidural opioids may carry the risk of nausea, vomiting, itching, urinary retention, prolonged sedation, and respiratory depression. However, highly lipophilic opioids, such as sufentanil, are rarely connected with respiratory inhibition and other adverse events [22, 23]. Because of rapid onset of analgesia with a rapid clearance from the cerebrospinal fluid (CSF), sufentanil allows less cephalic spread, which means fewer occurrences of side effects in analgesic doses, as compared to other opioids. The addition of 0.5 μg/kg sufentanil to 0.25 % bupivacaine for caudal block did not affect duration of analgesia in lower abdominal surgery and induced no greater incidence of nausea and vomiting; also, respiratory depression is rare with lipid-soluble opiates (e.g., sufentanil) [24]. In pediatric patients, no greater incidence of nausea and vomiting, or of any other side effects such as sedation or respiratory depression, was observed at a dose of 0.25 % bupivacaine 2 mg/kg plus 0.5 μg/kg sufentanil [25], but postoperative respiratory monitoring is still needed [22–26]. No case of respiratory inhibition was found in our study, thus further confirming the safety of caudal sufentanil.

A case report from De Kock et al. [27] of severe respiratory depression after epidural sufentanil in an adult patient was probably caused by direct intravascular injection or high systemic resorption.

As a more explicit index in reflecting the hypnotic state of patients, our findings in entropy monitoring showed that statistically fewer patients who received caudal sufentanil had entropy fluctuations at the time of traction on the spermatic cord. This finding indicates that entropy value is also a reliable indicator for predicting responses to peritoneal stimuli.

Although the reliability of SE values or bispectral index (BIS) as a depth-of-anesthesia monitor is still controversial, entropy, an appropriate index of the hypnotic state of patients, may be helpful to investigate the analgesic efficacy of caudal block. Schmidt and colleagues reported that the SE index correlated better with sedation levels than BIS [28]. Moreover, SE might be more useful than BIS in predicting both loss of consciousness and loss of verbal contact [29]. A clinical study by Davidson et al. revealed that both entropy and BIS were significantly different for children under the age of 1 year compared with older children [30]. Therefore, we enrolled pediatric patients from 2 to 6 years old, and investigated SE and RE changes, in addition to the traditional parameters MAP and HR, during the seven different anesthetic steps. SE and RE decreased after induction of anesthesia and then increased during emergence. The key finding of the present study is that, in group LS, SE and RE values as well as HR revealed a lesser increase while traction was being exerted on the spermatic cord.

In a word, our results suggest significant advantages of sufentanil as an adjunct to levobupivacaine in caudal anesthesia with regard to blocking peritoneal response to spermatic cord traction in pediatric orchidopexy. Entropy may also be a reliable indicator for predicting responses to peritoneal stimulation in children.

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