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Relative analgesic potencies of bupivacaine, ropivacaine and levobupivacaine for caudal analgesia in children

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Abstract : *Background :* Caudal epidural analgesia (CEA) is used in children undergoing lower abdominal surgery. Although ropivacaine, levobupivacaine and bupivacaine are commonly used, their relative potency remains poorly defined in case of CEA. The aim of this prospective, randomized, double-blind trial was to determine the minimum local analgesic concentration (MLAC) for each of these three molecules.

Material and methods : Ninety-two children (between 1-8 years old) scheduled for lower abdominal surgery under sevoflurane anesthesia were included and randomized to receive CEA with ropivacaïne, levobupivacaine or bupivacaine. One mL Kg^{-1} of the "study solution" was injected in the epidural space. Skin incision was allowed 15 minutes after injection. Movements and hemodynamic variability ("clinical response") associated with skin incision were used to determine the efficacy of the CEA. In all groups, the starting local anesthetic concentration was 0.16% and subsequent concentrations were determined by the clinical response of the previous patient to skin incision using the Dixon's up-and-down sequential allocation. Increments and decrements were 0.02% for each drug. Secondary endpoints were duration of analgesia, incidence of motor block and side effects (postoperative nausea and vomiting, agitation, urinary retention). Isotonic regression method was used to calculate efficient dose in 50% of patients (ED 50) and in 95% of patients (ED 95).

Results : From the 92 randomized children, 87 were finally included in the protocol. Demographic characteristics were not different between groups. The ED 50 and ED 95 for bupivacaine, ropivacaine and levobupivacaine were, respectively: 0.122% and 0.179%, 0.111% and 0.176%, 0.171% and 0.216%. No difference was observed between the 3 groups in term of efficacy, duration of analgesia, muscular blockade, agitation, and postoperative nausea and vomiting.

Conclusions : In the conditions of our study, MLAC of ropivacaine, and bupivacaine were comparable, much lower than that of levobupivacaine.

Key words : Caudal analgesia, Pediatric, ropivacaine, levobupivacaine, bupivacaine.

Introduction

Caudal epidural analgesia (CEA) in children is useful for providing intraoperative and postoperative analgesia in urological or lower abdominal procedures (1).

This technique allows reducing the amount of opioid administration, the dose of inhaled and intravenous anesthetic agents, the stress response to surgery, and it facilitates a rapid and smooth recovery (2, 3).

The minimal local analgesic concentration (MLAC) concept has been developed to determine the relative potency of a local anesthetic agent. In neuraxial anesthesia, it has become a benchmark for epidural dosing during labor (4). In the context of pediatric anesthesia, MLAC is defined individually for local anesthetic agents in neuraxial analgesia (5-8). Knowledge of the MLAC also identifies the concentration of local anesthetic agent associated with the best benefit-to-risk ratio (less side effects including motor block, with better analgesia).

MLAC studies describe one point of the dose-response curve, the effective dose in 50% of the population, and do not typically provide information about the shape or slope of the curve. The 95%

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effective concentration is often more clinically relevant (9).

Bupivacaine (0.125-0.175%; max 1-2 mg Kg^{-1}) is the most frequently used local anesthetic agent in pediatric surgery, because it provides a long-acting analgesia (10). However, its use is potentially associated with some side effects including motor block, responsible for postoperative discomfort in children. In addition, cardiotoxic and neurotoxic side effects have been demonstrated.

Ropivacaine and levobupivacaine provide a better differentiation between sensory and motor effects, as compared to bupivacaine. Levo-bupivacaine (the S-enantiomer of bupivacaine) and ropivacaine (an amide structurally related) have been promoted as an alternative to racemic bupivacaine. The concentration of ropivacaine used in caudal analgesia ranges from 0.1% to 0.5% (max 1.5-3 mg Kg^{-1}) (10). The average concentration for levopubivacaine ranges from 0.1 to 0.25% (max 2-3 mg kg^{-1}) (10).

Several studies have compared the efficacy of these three local anesthetic agents, and have reported a reduced incidence of postoperative motor block with the new agents (11-13). However, these studies did not consider the relative potency of the studied molecules. The best way to determine this relative potency is to estimate of the minimum local analgesic concentration (MLAC) for each of the three molecules in a single protocol. Hence, we performed a prospective, randomized, double-blind study to determine the MLAC of bupivacaine, ropivacaine, and levobupivacaine for CEA in children under sevoflurane general anesthesia.

Methods

After Institutional Ethics approval (internal reference of the Ethics Comity: 22/06) and parental written informed consent, 92 healthy boys and girls (ASA I, II), aged between 1 and 8 years, and weighing less than 25 Kg were enrolled in this prospective, randomized, double-blind controlled study.

All children were scheduled for elective lower abdominal surgery under sevoflurane anesthesia combined with CEA. All procedures were scheduled for a one-day surgery program.

Exclusion criteria were emergency surgery, hemostasis disorders, history of hypersensitivity to amide local anesthetics, history of active and severe renal, hepatic, respiratory, or cardiac disease, neurological or neuromuscular disorders, history of chronic pain or analgesic drugs use, local skin infections in the caudal area, and parent refusal to beneficiate from a CEA for their child.

Children were randomized to receive one local anesthetic using sealed envelopes. An anesthesiologist, not involved in patient's management, prepared the randomization and the studied solution injected through the caudal needle. The anesthetist in charge of the patient was blinded to the type and the concentration of the local anesthetic agent used.

All children were fasted according to local rules (six hours for solids and 2 hours for clear liquids). Thirty minutes before surgery, they were premedicated with midazolam 0.5 mg Kg^{-1}, either intrarectally or orally. Patients were monitored with a precordial stethoscope, three leads electrocardiography, non-invasive arterial blood pressure and pulse oxymetry. Anesthesia was induced using sevoflurane in 50% oxygen-air through a facemask. An intravenous catheter was placed and an infusion of Ringer's Lactate was started using the 4/2/1 rule (14). Under adequate anesthetic depth (end-tidal sevoflurane concentration of 5%), a weight-based sized laryngeal mask airway (LMA) was inserted. End-tidal CO_2 and rectal temperature were monitored. Lungs were mechanically ventilated using a volume control mode (8 ml Kg^{-1}) to maintain an end-tidal CO_2 between 33 and 38 mmHg.

Thereafter, patients were placed in a left lateral position, and a senior anesthetist performed the CEA using anatomic landmarks (15). Under sterile conditions, a 22-Gauge intravenous catheter (Smiths medical Jelco®) with an inner stylet was inserted through the sacrococcygeal ligament into the caudal space over 0.5-1 cm.

Gentle aspiration was then performed to confirm the absence of blood/cerebrospinal fluid. The injection into the epidural space started with one 10^{th} of the total dose of the studied solution, while observing vital signs and absence of complication. Thereafter, the remaining amount of the solution was slowly administered (16). A total of 1 ml Kg^{-1} was injected to achieve a T10 sensitive level (10). The catheter was removed after the injection.

According to the literature (10), the starting concentration for the first child in each group was 0.16%. The subsequent concentrations were determined by the analgesic response of the previous patient after skin incision using the Dixon's up-and-down sequential allocation. The increments and decrements in concentration were 0.02% for each drug. The preparations of local anesthetic agent were performed by a third anesthesiologist. The anesthesiologist in charge of the patient and the

one who collected the data were blinded to patient allocation.

Skin incision was performed exactly 15 minutes after the caudal block, under general anesthesia, with an age-adjusted 0.5 minimum alveolar anesthetic concentration (MAC) (17). The fraction of inspired oxygen was set at 50%.

Blood pressure and heart rate were recorded immediately before and after surgical incision. After skin incision, the children were observed for signs of gross purposeful muscular movement and hemodynamic variability for at least 1 minute.

Two outcomes were possible :

- Effective : absence of any muscular movement and no increase in blood pressure or heart rate of more than 20% compared with baseline values obtained immediately before surgical incision. An effective result led to a decrement of 0.02% in the concentration of local anesthetic agent for the next child randomized to that group.
- Ineffective : signs muscular movement and/or increase in blood pressure or heart rate of more than 20% compared with baseline values in response to surgical incision. Ineffective meant that analgesic level was inadequate. As a consequence, a rescue intravenous analgesia with 0.2 µg Kg^{-1} of sufentanil was administered, and the depth of anesthesia was increased with either a bolus of propofol and/or an increase in inhaled sevoflurane. A result defined as ineffective led to an increase of 0.02% in the concentration of local anesthetic agent for the next patient randomized to that group.

In case of technical failure of the regional technique, the patient was excluded from the study. In that case, the same concentration was repeated for the next child in that group.

After the recording phase, 15 mg Kg^{-1} of paracetamol was administered intravenously.

At the end of surgery, sevoflurane was discontinued and the LMA removed. The children were transferred to the post-anesthesia care unit (PACU). Postoperative pain was evaluated using the Children's Hospital Eastern Ontario Pain Scale (CHEOPS) for children below 6 years of age or the visual analogue scale (VAS) for children aged between 6 and 8 years old.

If CHEOPS was above 7 or VAS above 3 in the PACU, ketorolac 0.5 mg Kg^{-1} was administered intravenously. If ketorolac was ineffective at controlling pain after 30 minutes, 2 mg Kg^{-1} of tramadol was administered intravenously.

Residual motor blockade was evaluated using the modified Bromage scale as used by Breen (18). We also recorded the incidence of nausea and vomiting, agitation, and analgesic duration (defined as the amount of time between caudal injection and first analgesic supplement). Parents were systematically called the day after surgery to collect information about the postoperative evolution of their child. At that time, data on analgesic requirements and/or first micturition (or time of first wet nappy) were recorded.

Statistical analyses

Quantitative data are presented as mean (SD) and qualitative data as number (percentage-%). One-way ANOVA for independent samples was used to test for differences in age, weight, height, duration of surgery, first urination time, and first analgesic requirement time. Gender, motor blockade, nausea vomiting, agitation and number of analgesic supplements were analyzed using a chi-square test. A two-tailed threshold for statistical significance was set at $P < 0.05$.

For each local anesthetic agent, up-and-down sequences were analyzed using an isotonic regression method, based on the modified Dixon's method (19-21), using the R software (R 3.0.1. for Windows) to obtain the efficient doe in 50% of patients (ED 50), in 95% of patients (ED 95) and the associated 95% confidence limits (95% CI) (22). Obtained estimates of ED 50 and ED 95 by means of isotonic regression by group were compared using a confidence interval overlap test (23), available in the composed function in the R package, using the ED 50 or ED 95 parameters and their standard errors as input.

Results

Ninety-two children were enrolled in the study, 87 were analyzed (29 in the bupivacaine group, 29 in the ropivacaine group, and 29 in the levobupivacaine group), while 5 were excluded (Fig. 1). Three were excluded because of CEA technical difficulties (one in each group), one for surgical problem in the ropivacaine group, and one for protocol violation in the bupivacaine group.

Patients' clinical characteristics are given in Table 1. The distribution of the different types of surgeries is summarized in Table 2. Surgical duration was the longest in the levobupivacaine

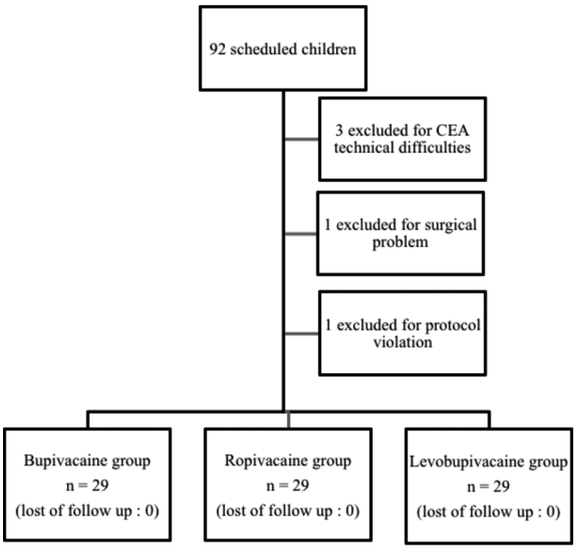

Fig. 1. — Chart Flow.

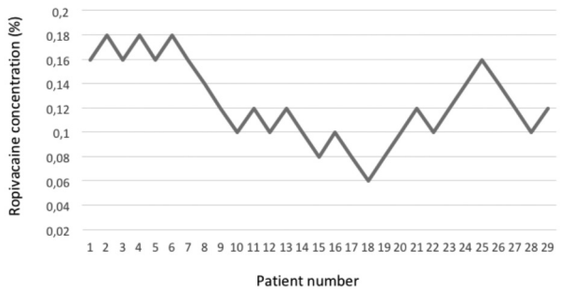

Fig. 2. — Sequence of effective and ineffective analgesia for ropivacaine.

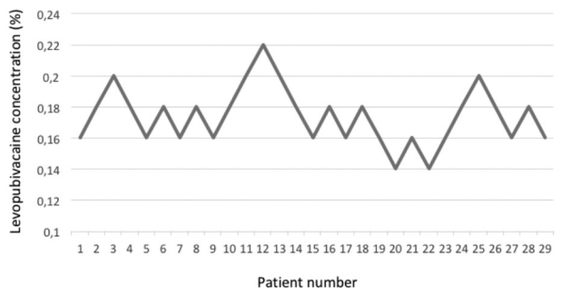

Fig. 3. — Sequence of effective and ineffective analgesia for levobupivacaine.

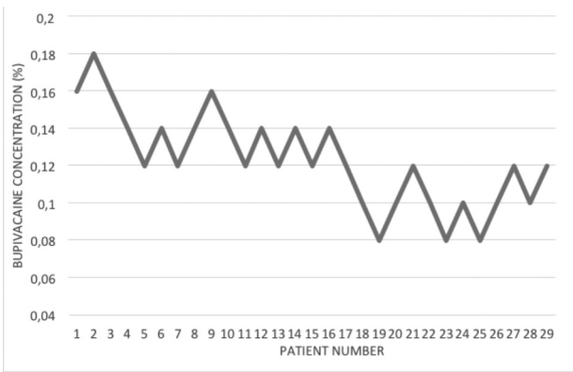

Fig. 4. — Sequence of effective and ineffective analgesia for bupivacaine.

Table 1

Demographic data

	Bupivacaine n = 29	Ropivacaine n = 29	Levobupivacaine n = 29	P
Sexe male (%)	27 (93)	24 (82)	25 (86)	0.48
Age (month)	47 ± 25	46 ± 21	39 ± 19	0,37
Weight (kg)	16 ± 4	16 ± 4	15 ± 4	0,33
Height (cm)	99 ± 15	103 ± 13	97 ± 15	0,35
Surgery Time (min)	37 ± 20	33 ± 19°	47 ± 22	0,04
ASA I / II	28 / 1	27 / 2	28 / 1	0.77

Data are presented as mean ± SD or rough numbers (%). With ASA : American Society for Anesthesiologists, ° $p < 0.05$ between levobupivacaine and ropivacaine.

Table 2

Types of surgery

	Bupivacaine (n = 29)	%	Ropivacaine (n = 29)	%	Levobupivacaine (n = 29)	%	Total %
Unilateral inguinal repair	10	34.5	17	58.5	10	34.5	42.5
Bilateral inguinal repair	1	3.5	1	3.5	0	0	2.3
Unilateral orchidopexy	8	27.5	3	10	10	34.5	24.1
Minor hypospadias repair	3	10	7	24	1	3.5	12.6
Bilateral orchidopexy	0	0	1	3.5	2	7	3.4
Spermatic cord cyst	7	24	0	0	3	10	11.5
Hydrocele testis	0	0	0	0	3	10	3.4
	29	99.5	29	99.5	29	99.5	99.8

Data are presented as rough numbers and %

Table 3

Postoperative data

T0 : arrival in PACU ; T1 : after 1h ; T2 : after 2h ; T3 : after 3h.

	Bupivacaine n = 29	Ropivacaine n = 29	Levobupivacaine n = 29	P
Efficacy (%)	15 (52)	16 (55)	14 (48)	0.70
Motor blockade T0 (%) (Bromage < 4)	5 (17)	3 (10)	3 (10)	0.55
Motor blockade T1 (%) (Bromage < 4)	1 (3)	3 (10)	0 (0)	0.22
Motor blockade T2 (%) (Bromage < 4)	0 (0)	1 (3)	0 (0)	
PONV (%)	4 (14)	0 (0)	5 (17)	0.06
Agitation – T0 (%)	8 (27)	9 (31)	7 (24)	0.88
Agitation – T1 (%)	4 (14)	5 (17)	1 (3)	0.25
Agitation – T2 (%)	0 (0)	3 (10)	1 (3)	0.16
Agitation – T3 (%)	1 (3)	2 (7)	0 (0)	0.36
First urination time (min)	335 ± 191	312 ± 130	293 ± 154	0.70
Analgesia duration (min)	554 ± 519	551 ± 560	482 ± 573	0.87
Analgesia supplement 0 / 1 / >1	10 / 10 / 9	9 / 9 / 11	10 / 12 / 7	0.15

group as compared to the two other groups. No serious adverse event related to the anesthetic drugs occurred.

The sequences of effective and ineffective caudal analgesia are shown in Figures 2 to 4.

The ED 50 of bupivacaine was 0.122% (95% CI 0.096-0.143%) using the isotonic regression method. The ED 50 of ropivacaine was 0.111% (95% CI 0.096-0.140%), and the ED 50 of levobupivacaine was 0.171% (95% CI 0.164-0.184%). The ED 95 of bupivacaine, ropivacaine, and levobupivacaine were respectively 0.179% (95% CI 0.159-0.179%), 0.176% (95% CI 0.166-0.179%), 0.216% (95% CI 0.207-0.219%).

Postoperative data are presented in the Table 3. No child needed urinary catheterization.

Discussion

This randomized, double-blind study determined the MLAC of ropivacaine, levobupivacaine, and bupivacaine when used through CEA in children undergoing lower abdominal surgery.

The concept of MLAC reminds the widely used concept of MAC for inhaled anesthesia (minimum alveolar concentration required for the abolition of a motor response in 50% of patients, in response to skin incision). CEA in children provides an ideal, stable, and safe model for comparing local anesthetic agent potency, because it concerns a relatively homogenous population, with infrequent pharmacological interactions and physiological confounding factors. CEA is generally performed under general anesthesia (inhaled or intravenous). General anesthetic agents inevitably interact with the clinical effect of local anesthetic agents. This condition is specific to the anesthetic management of pediatric patients. It means that comparing the potency of a local anesthetic agents in that case necessitates identical general anesthesia protocols in all compared groups. The relative potency of the three molecules has been well studied in adults (mostly during labor epidural analgesia). Due to the differences of the physiologic pain system and metabolism in children, one cannot transpose the adult doses to the pediatric population (24).

In children, a few studies have attempted to describe a dose-response curve for ropivacaine and levobupivacaine (5-8), but none attempted to determine the MLAC for bupivacaine. No study assessed the ED 50 of the three molecules in the same study.

In our study, the ED 50 for bupivacaine was 0.122% (95% CI 0.096-0.143%). To our knowledge, there is no other study that determined the ED 50 for this agent when used for CEA. The ED 50 for ropivacaine was 0.111% (95% CI 0.096-0.140%). This result is similar to the one reported by Deng et al. In their first study, Deng et al. (5) determined the potency of ropivacaine at 0.110%, with a mixed enflurane 0.5 MAC induction and propofol anesthesic maintenance. In their second study (6), they determined the ED 50 at 0.107% under 0.7 MAC of sevoflurane. This level of anesthesia was very close to the one used in our protocol. They also suggested that school-age children (6 to 12

years old) needed a higher concentration than pre-school children (1 to 5 years old), with respectively 0.143% (95% CI 0.132-0.157%) and 0.107% (95% CI 0.089-0.122%) (6).

Ingelmo et al. (8) compared ropivacaine and levobupivacaine. They reported lower ED's for the children at the same group of age (ED 50 of ropivacaine: 0.075%). Two major factors may explain the lower ED 50 they observed. First, their general anesthesia protocol was deeper than our (1 MAC sevorane as compared with 0.5 MAC in our protocol). Second, there was a 20-minute latency between caudal injection and surgical incision, while this latency was shorter in our study. This may have increased the number of false negative responses. In our study, the ED 50 of levobupivacaine was 0.171% (95% CI 0.164-0.184%). These values appear much higher than those obtained by Ingelmo et al. (0.069%, 95% CI 0.058-0.092%) (8).

The only one study comparing the three molecules simultaneously enrolled a neonatal population (infants of less than 55-week post-menstrual age) undergoing inguinal hernia repair under spinal anesthesia alone (25). The authors concluded that bupivacaine is estimated to be more potent than either ropivacaine or levobupivacaine, at both the ED 50 and ED 95. In our study, levobupivacaine and ropivacaine had similar potency ratios, at both ED 50 and ED 95. Most pediatric regional anesthesia studies, where the quality of postoperative analgesia was used as a measure of effectiveness, suggested that levobupivacaine and ropivacaine may be less potent than racemic bupivacaine, but are not markedly different from each other (26-29). Overall, the ED 50 for levobupivacaine appeared to be higher than the ED 50 of bupivacaine and ropivacaine. The difference between the two drugs was not observed by Ingelmo, who found comparable ED 50 for each molecule, using a similar methodology than ours. The only reason that may account for the difference in the observed ED 50 between ropivacaine and levobupivacaine in our study, and not in Ingelmo's study, is the time allowed between CEA injection and surgical incision. As this time was 5 minutes shorter in our study than in the Ingelmo's study, we hypothesize that a slower onset of action for levobupivacaine may be responsible for a higher ED 50. However, other uncontrolled factors may have played a role, as the speed of injection (30). Finally, it should be noted that the ED 95 for ropivacaine and levobupivacaine appears quite comparable in both studies.

The incidence of postoperative motor block was low and similar between the three groups, which is in accordance with the current literature (31, 32). We did not observe any effect on the incidence of urinary retention. All three investigated local anesthetic agents were found to be clinically comparable, with regard to length of analgesia (13). However, these results are difficult to interpret, due to the nature of the study design (in all groups, children for whom the CEA was considered ineffective received sufentanil at surgical incision).

Finally, our results should be interpreted taking account into some constraints:

- The ED 50 and ED 95 were determined under 0.5 MAC sevoflurane to have the least possible effect on the motor neuron response. This sevoflurane concentration is correlated with sufficient depth of sedation and prevented unintended awareness for minor surgical procedures (33). In addition, Prabhakar et al. reported a *response* and *state entropy* around 60 under 0.5 MAC sevoflurane in a similar population (34). In our experience, the use of this concentration is safe and not associated with any complication.
- The incision was allowed 15 minutes after CEA injection. This period may influence the rate of success/failure of the block. However, on a daily clinical practice, a longer waiting time would not be acceptable for surgeons.
- The ED 50 was determined but it is clinically less interesting than the ED 95. Most up-down studies attempt to extrapolate a high quantile (ED 95) effect/dose concentration from the median point (ED 50) of the tolerance distribution curve, despite sparse data points in this range. The limited number of patients enrolled in up-down studies, with relatively few in the upper dose ranges, generates a potential biasing estimation of the ED 95 (35). For a clinical purpose, the ED 95 should be determined in a future study including a larger cohort of patients.
- An important confounding factor to consider is the volume of solution injected in the epidural space. The most common volume used for pediatric surgery requiring an anesthetic level below the T-10 sensitive level is 1mL Kg^{-1}. It is well established that a larger volume of diluted local anesthetic agent provides better quality, longer analgesia duration, and fewer motor blockade than a smaller volume of a more concentrated medication (30, 36). Also, in an attempt to reduce the heterogeneity of surgical procedures, we chose to study

children undergoing sub-umbilical surgical procedures.

– A potential problem regarding our study design is related to the fact that the local anesthetic agents provides analgesia but also some degree of motor block (37). A drug associated with motor block could be incorrectly identified as effective if the evaluation of effectiveness is only based on the motor response.

In conclusion, this study attempted to determine the ED 50 and ED 95 of the three most commonly used local anesthetic agents for CEA in children aged between 1 and 8 years under 0.5 MAC of sevoflurane. The ED 50 of ropivacaine and bupivacaine appeared quite comparable and lower than the one of levobupivacaine. Further prospective studies are required to confirm these results and to define more precisely the ED 95 of the three agents.

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