CAUDAL LEVOBUPIVACAINE-MORPHINE AND LEVOBUPIVACAINE-TRAMADOL COMBINATIONS FOR POSTOPERATIVE ANALGESIA IN PEDIATRIC INFRA-UMBILICAL SURGERIES: *A PILOT STUDY*

Nasr M. Abdalla[1] and Ahmed H. Bakeer[2]

Abstract

Background: The aim of this study is to investigate postoperative analgesic efficacy of morphine and tramadol as adjuvants to caudal levobupivacaine in children undergoing elective infra-umbilical surgeries

Patients and Methods: This study included 90 children undergoing infra-umbilical procedures under general anesthesia. Children received caudal levobupacaine 0.25% for postoperative analgesia. They were allocated randomly into one of three drugs groups; Group L (n=30) received levobupacaine only. In Group TL (n=30) tramadol 2 mg/kg was added while in Group ML (n=30), 0.03 mg/kg morphine was added to caudal levobupivacaine. After operation, children were assessed hemodynamically and in terms of analgesic efficacy and adverse drug effects. The duration and quality of postoperative analgesia and adverse effects were compared among groups.

Results: All children were calm during the first two postoperative hours. Pain was significantly lower in Groups TL and ML compared to Group L, 3 and 4 hours after the end of surgery. Afterwards, the three groups were comparable in the pain score. The duration of analgesia was significantly longer in Group TL and Group ML compared to Group L ($p < 0.001$) and significantly longer in Group ML compared to Group TL ($p < 0.001$). The total dose of rescue analgesia during the 24 postoperative hours were significantly lower in Group TL and Group ML. Mild complications were detected in the 3 groups. No cases of respiratory depression were recorded.

Conclusion: Morphine in a dose of 30 µg/kg is a safe and effective alternative for postoperative analgesia when combined with caudal levobupivacaine in children undergoing infra-umbilical surgery.

1 MD. Lecturer of Anaesthesia, Faculty of Medicine, Cairo University.

2 MD. Lecturer of Anaesthesia and Pain Relief, National Cancer Institute, Cairo University.

Corresponding Author: Nasr M. Sief El Nasr Department of Anaesthesia, Faculty of Medicine, Egypt. Address: 13 Mohamed Shokry street-Agouza-Giza. Tel: +20233360906. E-mail: mailbox_mcs@yahoo.com

Introduction

Untreated surgical stress may produce a range of autonomic, hormonal, neurobehavioral and other consequences. In the pediatric population, regional anesthesia is considered to be the most effective technique in dampening this response[1]. Regional anesthesia is almost universally employed to provide analgesia;however, there are few prospective randomized control studies comparing regional with general anesthesia or systemic analgesics in children[2]. Caudal block is one of the most popular regional blocks used in children in many areas of the world[3-5].

The local anesthetics bupivacaine, levobupivacaine and ropivacaine are commonly employed in caudal block. Levobupivacaine, the S-enantiomer of bupivacaine, is useful in pediatric practice[6]. Its lower lipid solubility and greater intrinsic vasoactivity[7] can produce less motor block with more prolonged postoperative analgesia[8]. However, many studies of pediatric caudal anesthesia demonstrated similar effects of levobupivacaine and bupivacaine[6,9,10]. Similarly, caudal levobupivacaine and ropivacaine have a similar potency[11].

Different adjuvants are added to the local anesthetic solution to prolong postoperative analgesia. These drugs may be non-opioids as ketamine or opioids as morphine or tramadol. Tramadol is a centrally acting analgesic effect via opioid receptors[12], with an analgesic potency approximately equal to that of pethidine and lack of respiratory depressant effect[13]. Caudal tramadol was reported to prolong duration of postoperative analgesia without significant adverse effects[14,15]. Similar effects were reported when tramadol was combined with caudal bupivacaine or levobupivacaine[16].

Nevertheless, morphine added to local anesthetics for caudal block appear to be more effective than many other alternatives in different types of surgical procedures in children[17-20]. The main issues are unacceptable adverse effects including nausea, vomiting, pruritus and the risk of respiratory depression. We believe that these side effects can be controlled with smaller doses of morphine.

Therefore, in the current study, we investigated the postoperative analgesic efficacy of small dose of morphine in comparison to tramadol as adjuvants to caudal levobupivacaine in children undergoing elective infra-umbilical surgeries

Patients and Methods

This study was conducted in Cairo University Hospital from January 2016 to September 2016 after approval of Institutional Review Board and Ethical Committee of anesthesiology department and obtaining informed written parental or guardian consent. Privacy of participants and confidentiality of data were ensured according to the declaration of Helsinki. The study included ASA I and II, 90 children between 1 and 7 years of age who were undergoing elective lower abdominal or urological procedures of anticipated duration less than 2 hours. Children with bleeding diathesis, coagulopathy, neurologic or spinal disease or local skin infections were excluded from the study in addition to those receiving aspirin or any analgesic drugs in the preceding week.

Children were instructed to fast during the 6 hours before the procedure, but clear fluids were allowed up to 3 hours before surgery. No preoperative medications or opioids were administered. Anesthesia was induced via a facemask with sevoflurane 8% in 100% oxygen and maintained by sevoflurane 2-2.5% in 50% oxygen-air mixture. Upon loss of eyelash reflex, ventilation was assisted manually to maintain end tidal CO_2 at 32-36 mmHg. An intravenous line was inserted and atropine 0.01 mg/kg was given intravenously. Fluid replacement in the form of 0.45% NaCl in 5% dextrose solution was given at a rate of 3-5 ml/kg/h. Systemic blood pressure was measured automatically. Heart rate (HR) from ECG, end tidal CO_2 (P_ECO_2) and SPO_2 were monitored before induction and intraoperatively at 3-minutes intervals.

Laryngeal mask airway (LMA) was inserted then the patient was placed in the left lateral position. Under sterile conditions, caudal block was performed by a consultant anesthetist using 22-gauge needle which was advanced 0.5-1 cm for study drugs administration then a small sterile dressing was placed over the injection site in all patients. Children were allocated randomly into one of three drugs groups. Children in the first group (Group L) (n=30) received caudal levobupacaine

Table 1
Pediatric objective pain scale

Observation	Criteria	points
Blood pressure	± 10% pre-operative value	0
	> 20% pre-operative value	1
	> 30% pre-operative value	2
Crying	Not crying	0
	Crying but responds to tender loving care	1
	Crying with no response to tender care	2
Movement	None	0
	Restlessness	1
	Thrashing	2
Agitation	A sleep	0
	Mild	1
	Hysterical	2
Posture	No special posture	0
	Flexing legs and thighs	1
	Holding penis or groin	2

0.25%. In Group TL (n=30), tramadol in a dose of 2 mg/kg was added to caudal levobupivacaine 0.25%, while in Group ML (n=30), 0.03 mg/kg morphine was added to caudal levobupivacaine 0.25%. The volume of caudal solution given to each child diluted with normal saline (0.9%) was 1 ml/kg to a maximum of 20 ml. We used preservative-free drugs prepared by an anesthetist not involved in the trial using unlabeled syringes.

Caudal block efficacy during surgery was defined as absence of purposeful or non-purposeful movements or significant (> 20%) increase in arterial blood pressure, HR or RR associated with surgical incision. The incision was made 15-20 min after caudal block. In case of inadequate level of analgesia, fentanyl 1mg/kg was given and those patients were excluded from the study and replaced. After the surgery, the duration of surgery was noted and the patient was transferred to the recovery room. Recovery time was defined as the time between the end of the surgery and the first evidence of the one of the following: spontaneous eye opening, spontaneous movement, crying and co-operation on talking to the child. The systolic blood pressure (SBP), diastolic blood pressure (DBP), HR, SpO_2, and respiratory rate (RR) were monitored in the recovery room. The postoperative pain was evaluated using objective pain scale (OPS) of 10 points based on blood pressure, crying, agitatory movements and verbalization of pain.

Pain was assessed at 1, 2, 3, 4, 8, 12 and 24 hours following recovery from anesthesia. Duration of analgesia was defined as the time from caudal block to the first analgesic requirement. A pain score < 5 was considered adequate analgesia. Whenever the child has an OPS score ≥ 5, a paracetamol suppository 15 mg/kg was given (with a minimum of 4 hours time interval between successive doses of paracetamol). Rescue analgesia with IV pethidine 0.5 mg/kg was given if the OPS was still ≥ 5 within this time interval. Sedation was assessed using three-point scale (calm/cheerful score 1: restless score 2:tense/tearful, score 3). The incidence of residual motor block was evaluated using modified Bromage scale (score 0: no motor block; score 1: inability to stand unassisted; score 2: ability to flex ankle but not the knee; score 3: complete motor block in a fully awake child). Motor block score ≥ 1 after awakening and 180 min after last dose of local anesthetic was considered to be a significant residual motor blockade. The observations were made by an experienced anesthesiologist blinded to the study groups. The first analgesic dose and number of supplementary analgesics required by each child in a 24-h period and any side-effects such as emesis, urinary retention and motor weakness were recorded. After administration of caudal block, heart rate and pulse oximetry were monitored continuously and arterial pressure was monitored every 5 min. All patients were observed in the hospital for 24 hours.

The primary outcome measure was the quality of the postoperative pain control. The duration and quality of postoperative analgesia and adverse effects were compared between groups.

Sample Size calculation

In a previous study[21], caudal tramadol provided insufficient analgesia in 4.8% of cases compared to 19.2% with tramadol-bupivacaine combination. Based on the results of this study, a sample size of 22 cases

per group is required to elicit the difference at an alpha level of 0.05 and a power of the study of 95%.

Statistical methods

Statistical analysis was done using IBM© SPSS© Statistics version 22 (IBM© Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test (Fisher's exact test) was used to examine the relation between qualitative variables. Comparison between the 3 groups was done using ANOVA test, then post-Hoc "Schefe test" was used for pair-wise comparison or using Kruskal-Wallis test as appropriate. All tests were two-tailed. A p-value < 0.05 was considered statistically significant.

Results

No patients were excluded from the study after enrolment and all 90 children were analyzed (Fig. 1). The three groups were comparable regarding age, sex, weight, ASA class, and duration and type of surgery (Table 2).

All children were calm with no pain during the first two postoperative hours. Table 3 shows that the OPS score was significantly lower in Groups TL and ML compared to Group L, 3 and 4 hours after the end of surgery. Afterwards, the OPS scores were comparable among the three groups. The duration of analgesia was significantly longer in TL and ML groups compared to L group ($p < 0.001$) and significantly longer in ML group compared to TL group ($p < 0.001$). The number of doses and total doses of paracetamol consumed during the 24 postoperative hours were significantly

Fig. 1
CONSORT Flow Diagram

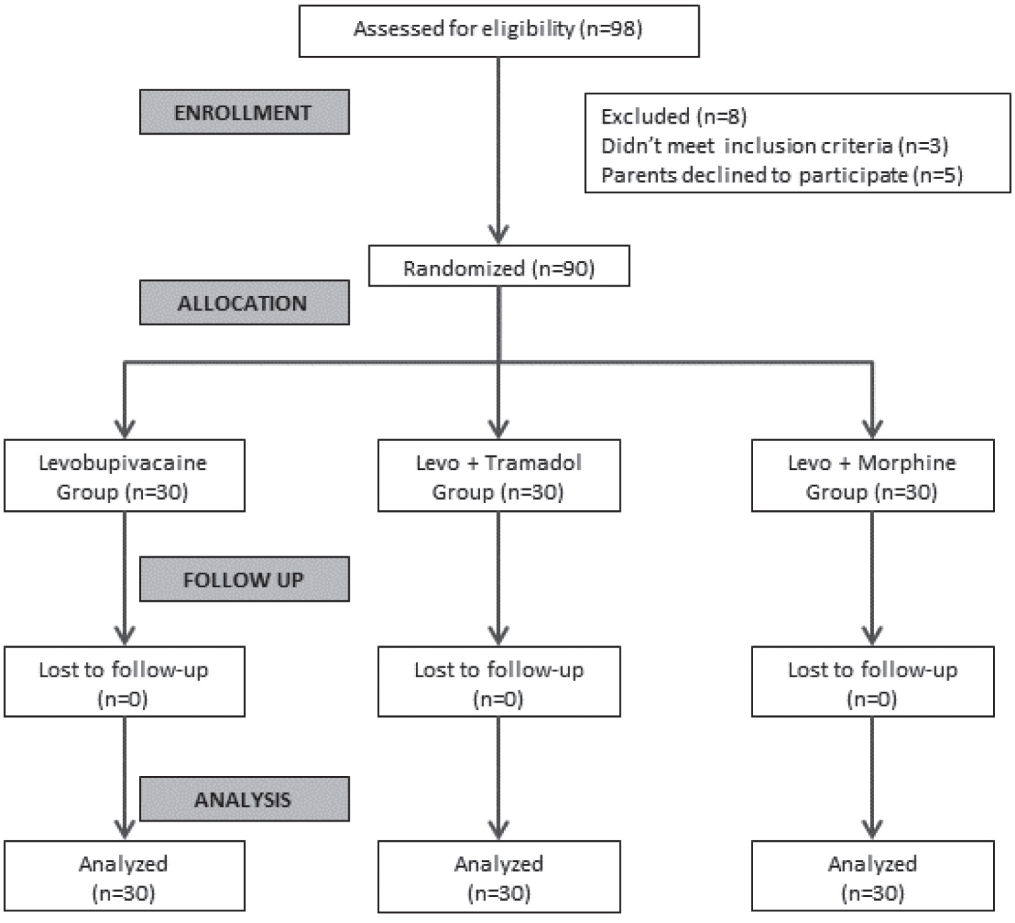

Table 2
Demographic and clinical characteristics of the three studied groups

	Group L (n=30)	Group TL (n=30)	Group ML (n=30)	p -value
Age (years)	4.3±1.6	4.5±1.5	4.5±1.6	0.823
Sex (male/female)	24/6	23/7	25/5	0.812
Weight (kg)	17.4±3.0	17.7±3.0	17.8±3.2	0.824
Duration of surgery (min)	45.2±21.5	46.3±21.9	45.7±21.1	0.978
ASA class I/II	24/6	21/9	22/8	0.664
Type of surgery				
Inguinal Hernia	20 (66.7%)	19 (63.3%)	18 (60.0%)	0.925
Hypospadias	5 (16.7%)	6 (20.0%)	8 (26.7%)	
Orchidopexy	5 (16.7%)	5 (16.7%)	4 (13.3%)	

Data presented as mean±SD, ratio, or number (%)

Table 3
Objective pain scale (OPS) in the first 24 postoperative hours in the three studied groups

	Group L (n=30)	Group TL (n=30)	Group ML (n=30)	p -value
OPS after				
3 hours	2 (0-6)	0 (0-2)*	0 (0-2)*	< 0.001
4 hours	4 (0-6)	2 (0-6)*	2 (0-6)*	0.013
8 hours	4 (2-6)	3 (2-6)	2 (2-6)	0.181
12 hours	4 (2-6)	4 (2-6)	3 (2-6)	0.067
24 hours	4 (2-6)	4 (2-6)	3 (2-6)	0.295

Data presented as median (range)
* $p<0.05$ compared to group L

Table 4
Duration of analgesia and paracetamol consumption in the first 24 postoperative hours in the three studied groups

	Group L (n=30)	Group TL (n=30)	Group ML (n=30)	p -value
Duration of Analgesia (hours)	4.1±0.3	7.2±0.4*	11.8±0.5*,^	< 0.001
Number of Paracetamol Doses	2.1±0.6	1.8±0.7*	1.3±0.5*,^	< 0.001
Total dose of Paracetamol (mg)	547±221	484±220*	343±126*,^	< 0.001

Data presented as mean±SD
* $p<0.05$ compared to group L
^ * $p<0.05$ compared to group TL

lower in TL and ML groups (Table 4).

There were no significant differences among groups in arterial pressure and heart rate values after caudal block and during the operation. Also, there was no significant difference in the degree of postoperative residual block between groups.

Mild complications were detected in the form of nausea and vomiting in one child of Group L and 2 children in Groups TL and ML. Three children in Group TL and four in Group ML complained of pruritus during the postoperative period. No cases of respiratory depression were recorded.

Discussion

This study demonstrated that caudal levobupivacaine with opioid adjuvants is safe and effective alternative for postoperative analgesia in children undergoing infra-umbilical surgery. Addition of tramadol in a dose of 2 mg/kg to caudal levobupivacaine 0.25% prolongs duration of postoperative analgesia with reduction of additional analgesic requirements. The addition of 0.03 mg/kg of morphine to caudal levobupivacaine was superior to tramadol-levobupivacaine combination in terms of duration of postoperative analgesia ($p < 0.001$) and reduction of additional analgesics.

In pediatric patients, caudal analgesia is utilized as an adjunct to general anesthesia and for postoperative analgesia. Caudal analgesia offers several advantages when combined with general anesthesia, including lower volatile anesthetic requirement, rapid and comfortable emergence, excellent analgesia and decreased blood loss[22].

Levobupivacaine was proven to be an effective agent for caudal analgesia[6,23]: however, its duration of action is relatively short[24]. Increasing the dose of local anesthetic does not increase the duration of postoperative analgesia of caudal block[25]. In the current study, caudal levobupivacaine alone was an effective analgesic only during the first three postoperative hours.

Many investigators were interested in search for an adjuvant that can prolong the duration and improve the quality of analgesia. Different agents were tried including clonidine, ketamine, morphine, fentanyl and tramadol. In the current study tramadol and morphine were safe and effective.

Tramadol is a synthetic 4-phenyl-piperidine analogue of codeine. It exerts a weak opioid receptor effect, but the analgesic effect is largely ascribed to inhibition of monoamine reuptake[16]. In a dose of 2 mg/kg, it was previously shown to be an effective adjuvant to caudal bupivacaine 0.25% or levobupivacaine 0.25%. It prolonged the duration of postoperative analgesia in children undergoing minor urological procedures[16]. Similar effects were obtained in children undergoing elective infraumblical surgeries under general anesthesia[12,15,6].

Morphine was one of the first additives used since the early 1980s. Several studies have been performed to test its efficacy and safety. The addition of morphine to caudal bupivacaine prolonged the duration of post-operative analgesia after lower abdominal and perineal surgery compared to dexmedetomidine[27]. Caudal morphine (0.03 mg/kg) provided similar quality and duration of postoperative pain relief to caudal tramadol (2 mg/kg) in children undergoing herniorrhaphy[28].

The dose of morphine selected in the current study was previously reported to provide effective analgesia with minimal side effects[29,30]. The adverse effects of morphine injected into the epidural space appear to be dose dependent. From the epidural space, morphine can diffuse to the epidural fat to the systemic circulation or it may diffuse into cerebrospinal fluid (CSF) through the dura. Its analgesic effect is mediated by mu, kappa, and delta receptors. Morphine can produce delayed respiratory depression via action on delta receptors and bradycardia, hypotension and urinary retention via action on mu1 receptors[31]. With the small dose used in the current study, we recorded no cases of respiratory depression of significant bradycardia.

Therefore, we can conclude that morphine in a dose of 30 μg/kg is a safe and effective alternative for postoperative analgesia when combined with caudal levobupivacaine in children undergoing infra-umbilical surgery. This combination was more effective than tramadol-levobupivacaine to prolong postoperative analgesia and reduce additional analgesics.

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