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Comparison of Caudal Levobupivacaine versus Levobupivacaine plus Morphine Mixture for Postoperative Pain Management in Children

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Abstract

Backgrounds: In childhood, the most performed emergency abdominal operation is appendectomy. In this study, we aimed to evaluate a combination of levobupivacaine and morphine via caudal route in the management of postoperative pain after open appendectomy in children.

Methods: A total of 120 children with ASA I-II physical status, aged 3-7 years and undergoing open appendectomy, were randomly allocated to two groups; only 0.5% levobupivacaine 1.5 mL/kg (Group L) and 0.5% levobupivacaine 1.5 mL/kg plus morphine 50µg/kg (Group LM). After the surgery, pain management was quantified with Modified Eastern Ontario Children's Hospital pain scale (mCHEOPS) up to 24 hours postoperatively Side effects of the procedure and test drugs were also recorded.

Results: A total of 102 patients aged between 3-7 years, belonging to ASA I-IIE category were included in the study. The two groups were comparable for demographic data. On comparison of postoperative pain scores, Group L had significantly higher pain scores at 1, 2 and 3 hours postoperatively compared to Group LM (p<0.05).

Conclusion: In children undergoing open appendectomy, single-dose levobupivacaine + morphine mixture via caudal route is a simple, safe and efficient method for post-operative analgesia.

Keywords: Open appendectomy; Caudal block; Levobupivacaine; Morphine; Side effect

Introduction

Acute appendicitis is a common condition affecting all age groups with a life-time incidence between 7 and 9% [1,2] and appendectomy is one of the most commonly performed surgical procedure. Open appendectomy performed through the right lower quadrant incision was first described in 1894 [3]. It has become the standard treatment of choice for acute appendicitis, remaining mainly unchanged for 100 years due to its favorable efficacy and safety [2]. Population under 15 years of age is estimated to be at overall %1 risk of appendicitis [4]. Caudal administration of morphine is a frequently used epidural technique for postoperative analgesia in children. Epidural administration of morphine provides long term potent analgesia with dose dependent sedation and respiratory depression. Minimal effective dose of morphine via caudal route for postoperative pain relief after lower-abdominal surgery is still not determined [5-8].

Choice of local anesthetic agent is one of the fundamental factors which determine the quality, duration and spread of anesthesia and analgesia in caudal epidural block [6,9]. Bupivacaine is the most frequently preferred local anesthetic drug in pediatric regional anesthesia [9]. Levobupivacaine is an S-enanthiomer of bupivacaine [10-13]. Lower lipid solubility and intrinsic vasoactivity of S-enanthiomer provides better differential block and longer postoperative analgesic relief. So far, there is no reported significant difference of anesthetic or analgesic effect between levobupivacaine and bupivacaine in pediatric caudal anesthesia [13]. However, single-shot local anesthetic administration is limited with relatively short analgesic (4-6 hours) duration of action. Thus, a combination of local anesthetic and opioids is preferred for caudal block [14,15]. In this study, we aimed to compare the analgesic efficacy of either levobupivacaine or combination of levobupivacaine plus morphine in children undergoing open appendectomy.

Material and Methods

This study was approved by scientific ethics committee of the institute, and a written informed consent was taken from parents of the children. This prospective randomized study included 120 American Society of Anesthesiologists physical status classification (ASA) I-II children aged between 3-7 years undergoing open appendectomy according to Alvarado score [16] (Table 1). The Alvarado score is based on three symptoms, three signs and two laboratory findings.

Symptoms	Score
Migratory right iliac fossa pain	1
Nausea/vomiting	1
Anorexia	1
Signs	
Tenderness in right iliac fossa	2
Rebound tenderness in right iliac fossa	1
Elevated temperature	1
Laboratory findings	
Leucocytosis	2
Shift to the left of neutrophilis	1
Total*	10

*5-6 possible, 7-8 probable, 9-10 very probable

Table 1: Alvarado score for appendicitis[16].

Patients were included less than 60 minutes of anesthesia duration, less than 72 hours of postoperative length of hospital stay, or the first postoperative day oral fluids and a regular diet as tolerated. Patients were excluded if they had a severe systemic disease, pre-existing neurological or obvious spinal disease, bleeding diathesis, a history of seizure disorder, or a known hypersensitivity to amide-type local anesthetics. We were also interested in several complications excluding: wound infection, postoperative ileus, intraoperative bleeding (> 10 mL/kg), urinary tract infection and intra-abdominal abscess formation following open appendectomy techniques.

Premedication was performed with midazolam intramuscular 0.5 mg/kg for all patients. A 22-gauge intravenous catheter was inserted into a small vein on the dorsum of the hand in the hospital ward. Inside the operation room, standard monitoring was performed for all children (electrocardiogram, noninvasive blood pressure, peripheral oxygen saturation). Rapid sequence induction was given with propofol 2-3 mg/kg, succinylcholine 1 mg/kg was used as neuromuscular drug and fentanyl 1-2µg/kg was used as opioid. Airway was controlled by endotracheal tube. Sevoflurane 1-3% in 50% air + 50% O_2 were used for maintenance. In the left lateral decubitus position, caudal anesthesia with a 22 G caudal needle was performed after local cleaning sterile conditions.

We used closed-envelope method to randomize patients into 2 groups in this prospective, double-blind study. Drug solutions were prepared by another anesthetist. All the caudal blocks were performed by the same anesthetists. Only 0.5% levobupivacaine 1.5 mL/kg was administered to Group L, 0.5% levobupivacaine 1.5 mL/kg plus morphine 50µg/kg was administered to Group LM. Patients were taken onto operation table in supine position, covered with sterile drape and then surgery started. After first incision, hemodynamic responses up to 20% were accepted as within normal range. After the last skin suture, all the anesthetic gasses were stopped, and endotracheal tube was removed. Patients were taken to the recovery room and kept there for 30 minutes. In the recovery room, all children were observed and recorded for pain and side effects such as nausea, vomiting, itching, urinary retention, apnea and respiratory depression. Pain management was quantified with Modified Eastern Ontario Children's Hospital pain scale (mCHEOPS, Table 2) postoperatively every hour for 4 hours and then at 8, 12, 16, 20 and 24 hours. If the mCHEOPS score was ≥ 5, intravenous paracetamol 15 mg/kg was administered.

Statistics

For analysis of the findings of the study, SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used. Together with descriptive statistical methods (mean, standard deviation), Mann Whitney U-test was used for analysis of quantitative data and inter-group comparison of parameters. Intra-group comparison of pain scores with Friedman test and differences causing pain scores were used to investigate Wilcoxon sign test. On comparison of qualitative data, x^2 test was used. Results are evaluated with 95% confidence interval, p<0.05 is accepted as significance.

Power analysis was conducted on GPower 3.1 program. Test power was (1-β) 0.80 at %5 significance level.

Results

This study included 120 patients undergoing open appendectomy. Six patients in group L, eight patients in group LM for prolonged of postoperative length of hospital stay, and four patients in group LM due to wound infection were excluded from the study. Patients were divided into group L (n=54) and group LM (n=48).

The mean age of the children was 5.4 ± 1.4 years and the mean weight was 16.2 ± 3.1 kg. No significant differences existed between the groups with respect to age, weight, anesthesia duration, gender and ASA physical status (Table 3).

Patients in Group L had significantly higher pain scores at 1, 2 and 3 hours postoperatively (respectively p=0.005, p<0.0001, p=0.008). In group L the pain score was higher at 30th min compared to group LM (p=0.0001). Postoperative 4, 8, 16, 20 and 24th hour measurements revealed no significant difference between groups (p>0.05, Figure 1). Additional analgesics (24 patients in group L and 4 patients in group LM) were required less frequently in group LM (p<0.0001).

Both major (arrhythmia, hypotension, shock, or seizures) and minor complications (dural puncture, subcutaneous infiltration, vessel puncture and bleeding) were not encountered during caudal block. Nausea-vomiting was seen in two patients (3.7%) of group L and in ten patients of group LM (20.8%). Itching, motor block and urinary retention were seen only in group LM (number of patients, respectively 2, 1 and 1). No respiratory depression was seen in each group.

Demographic properties	Group L (n=54)	Group LM (n=48)	p
Age, years*	8.6 ± 3.4	9.6 ± 3.1	NS
Gender M/F	44 / 12	9 / 39	NS
ASA I-II	42 / 12	38 / 10	NS
Weight, kg*	27.3 ± 9.6	28.6 ± 9.2	NS
Anesthesia duration, minutes*	40 ± 12,7	37,3 ± 10,7	NS

* Data are presented as mean ± standard deviation. NS: not significant, p>0.05

Table 3. Distribution of demographic properties of groups.

Score	0	1	2
Crying	No crying	Crying, groan	Shriek, screaming
Facial expression	Smile	Composed, calmly	Grimace
Response to verbal stimuli	Response positive	Complaints other than pain	Complaints of pain
Body	Neutral	Unsteady, Tense, erect	Controlled back off
Lower extremity	Neutral	Kicking, agony	Controlled back off

Table 2: Modified Eastern Ontario Children's Hospital pain scale (mCHEOPS).

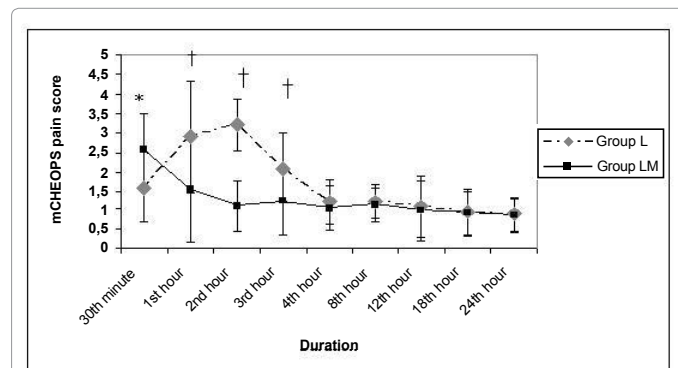
Figure 1: Distribution of postoperative pain scores of groups versus time, * 30.th minute Group L difference, p<0.0001. † 1,2,3.th hours Group L difference, p=0.005, p>0.0001, p=0.008. Group L: only 0.25% levobupivacaine 0.5 mg/kg via caudal route, Group LM: 0.25% levobupivacaine 0.5 mL/kg plus morphine 50 µg/kg via caudal route.

Discussion

Surgical procedures almost invariably cause in pain. The effect of inadequate pain relief is well known and it can result in delayed mobilization and related complications as well as psychological distress and anxiety [17]. Inadequent postoperative pain relief most commonly occurs after emergency operations. Appendectomy is one of the most common emergency surgical procedures in children.

Postoperative pain can be assessed quantitatively by the daily requirements for analgesics. Nevertheless, the various kinds of analgesics and routes of administration make it difficult to estimate pain relief [2]. We qualitatively assessed pain on the first postoperative day by means of a mCHEOPS. In this study, morphine was administered with caudal route to 48 patients of open appendectomy (Group LM). These consumed doses are different than recommended doses. In literature, there are reports of better analgesia and higher side effect incidence with these doses.

Neuroaxial morphine administration provides better and longer-term analgesic quality of analgesia than sistemic treatment even with small doses. In a study, it is reported that 30-40 µg/kg morphine administered caudal route provides 6-24 hour-long analgesic action [18]. In another study, single dose 60 µg/kg epidural morphine provided analgesia so that no additional analgesic was needed in 47% of patients for 12 hours [19]. Krane et al. [20] reported that caudal 33 µg/kg morphine provided long-term efficient analgesia for more than 8 hours. In our study, levobupivacaine plus morphine provided longer-term efficient analgesia for more than 24 hours with lower side effect incidence. Whereas, only levobupivacaine group provided similar analgesic efficiency after 4th hour. However, this analgesia level was reached with additional analgesic in 24 (44.4%) patients (intravenous paracetamol 15 mg/kg). Cesur et al. [15] reported in circumcision cases that caudal block with %1 lidocaine plus 3 different doses of morphine (10,15 and 30 µg/kg) provided excellent postoperative analgesia together with paracetamol, there was also lesser incidence of nausea-vomiting with low dose morphine. At the same time; they found that 10, 15, 30 µg/kg morphine caused nausea-vomiting in 6, 10, 20 patients (respectively 13.3%, 20%, 46.7%). Whereas in our study 50µg/kg morphine caused nausea-vomiting in 10 patients (20.8%).

Literature scan revealed that there is no study of caudal levobupivacaine and morphine combination in children. Bupivacaine is most commonly used local anesthetic in pediatric regional anesthesia [14,15]. In one of the studies using bupivacaine, caudal 50 µg/kg morphine-bupivacaine combination was compared with caudal bupivacaine; they found that morphine-bupivacaine combination had more superior analgesic action for longer time periods [21]. Similarly, in another study, morphine-bupivacaine combination was compared with caudal bupivacaine; they found that side effects were similar, and 50 µg/kg dose caudal bupivacaine-morphine groups did not need any extra analgesics postoperatively. Besides, cases of only bupivacaine group needed 53.3% additional analgesics [22]. Levobupivacaine is an isomer of bupivacaine and has some advantages. It leads to less motor blockage and longer sensorial blockage. Also, it is less toxic to the central nervous and cardiovascular systems [23,24] Our study was different from these studies; we used levobupivacaine instead of bupivacaine. In accordance, levobupivacaine-morphine combination group provided longer and more efficient postoperative analgesia. Also, less extra analgesics were needed and lesser side effect incidence was reported (Table 4, additionally administered extra analgesic ratios were 8.3% in Group LM and 44.4% in Group L).

Caudal opioid agents might lead to various adverse effects like nausea-vomiting, urinary retention, and respiratory depression. The most serious of them is depression of medullary nuclei with rostral progression of opioids [9]. Thus, it is not suitable for day-care surgeries.

According to the data which we have investigated, there was no case of respiratory depression. After caudal epidural opioids the incidence of side effects are parallel to the administered doses. After major surgeries under diaphragm, 33 µg/kg dose of morphine with caudal route leads to nausea-vomiting, itching incidence of 33-56%, 22-57% respectively [19]. In another study, caudal 50 µg/kg morphine was reported to cause 34-36% nausea-vomiting, 0-57% itching [9]. Mayhew, et al. [18] administered 30-40 µg/kg morphine with caudal route in two different doses; both groups revealed equally efficient and safe analgesia with side effects like nausea-vomiting 23%, urinary retention 3%, itching 7%. In our daily practice, morphine is used at dose of 50 µg/kg, however our side effect incidences are actually much lower than those studies (Table 4).

The most common side effect of morphine in our study is nausea-vomiting which is similar to other studies. Postoperative nausea-vomiting might lead to delayed recovery; therefore, it is especially important for children. Hospitalized children in postoperative surgical units have greater incidence of nausea-vomiting than adult patients. Following day-care surgery, overall nausea-vomiting incidence was found to be 20-30% [25]. There are lots of factors involved in this complication. Some of these factors are related to the patient; age, gender, history of previous nausea-vomiting. Other factors are related to nature and duration of surgery. These factors are mostly out of anesthetist control. Whereas some factors are under control of the anesthetist; anesthetic agents, neuromuscular blockers and antagonists, premedication and postoperative pain management. In addition, severe pain aggravates postoperative nausea-vomiting. Overall incidences of nausea-vomiting depend on these factors. The subjects of this study are only children undergoing emergent open appendectomy under general anesthesia combined with caudal block; therefore our incidences are specific to these patient groups. In addition, if propofol is used instead of sevoflurane for induction and maintenance, postoperative nausea and vomiting decreases 35-70% [15,26]. Thus, all factors should be considered for postoperative nausea-vomiting evaluation, one agent should not be blamed for it.

Nausea-vomiting significantly increases duration of hospital-stay after day-case surgeries. In addition, it might cause big problems at home. Thus, patients might come back to hospitals and re-hospitalized. Therefore, quality of postoperative pain management might decrease due to nausea-vomiting after day-case surgery even though analgesia was excellent. Besides, morphine is not suitable for day-case surgeries because of late respiratory depression due to rostral progression. The patient group which we have investigated was consisted of children who were treated a few days in pediatric surgery unit.

	Group L (n=54)		Group LM (n=48)	
	Number of patients	%	Number of patients	%
Nausea-vomit	2	3.7	10	20.8
Itching	0	0	2	4.2
Motor block	0	0	1	2.1
Urinary retention	0	0	1	2.1
Respiratory depression	0	0	0	0
Additional analgesic	24	44.4	4	8.3

Data are presented as percentage (%).

Table 4: Distribution of side effects and additional analgesic doses into groups.

In conclusion, caudal levobupivacaine plus 50 µg/kg morphine provided excellent analgesia lasting up to 24 hours, without serious side effects and minimal additional analgesics. Single dose caudal levobupivacaine plus morphine combination provides a simple, safe and effective postoperative analgesia for pediatric open appendectomies.

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