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RESEARCH REPORT

The effect of continuous wound infusion of ropivacaine on postoperative pain after median sternotomy and mediastinal drain in children

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What is already known

- Local anesthetics administered by wound catheter after median sternotomy have been effective in adults and children.

What this article adds

- Our study shows that in preschool children undergoing atrial septal closure with median sternotomy and mediastinal drain, continuous wound infusion of ropivacaine did not diminish morphine consumption or side effects compared with morphine alone.

Keywords
anesthetic techniques; regional; continuous ropivacaine infusion; analgesia; postoperative; pediatrics; surgery

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Summary

Background: Postoperative pain after median sternotomy is usually treated with i.v. opioids. We hypothesized that continuous wound infusion of ropivacaine decreases postoperative morphine consumption and improves analgesia in children who undergo cardiac surgery.
Methods: This randomized, double-blind study comprised 49 children aged 1–9 years who underwent atrial septal defect (ASD) closure. Patients received continuous local anesthetic wound infiltration either with 0.2% ropivacaine, 0.3–0.4 $mg \cdot kg^{-1} \cdot h^{-1}$ (Group R) or with saline (Group C). Rescue morphine consumption, Objective Pain Scale (OPS), time to mobilization, time to enteral food intake, and time to discharge were recorded.
Results: There were no statistically significant differences in morphine consumption at 24, 48, and 72 h postsurgery between R and C groups. There was a weak evidence for a difference in the time to the first morphine administration after tracheal extubation to be longer for Group R than Group C (186.2 vs 81.0 min; 95% CI (−236.5, 26.2), $P = 0.114$). The incidence of nausea and vomiting were comparable between the groups. No signs or symptoms of local anesthetic toxicity were registered.
Conclusions: Contrary to our hypothesis, continuous ropivacaine wound infusion did not reduce morphine consumption, pain score values, or nausea and vomiting in children who underwent ASD closure with median sternotomy and mediastinal drain.

Introduction

Atrial septal defect (ASD) closure is associated with moderate to severe postoperative pain that is related to median sternotomy and the presence of chest tubes. Standard practice to treat postoperative pain after open heart surgery is i.v. opioids, e.g., morphine. However, opioids have various side effects such as respiratory depression (1), itching, and nausea and vomiting. Regional techniques are effective for sternotomy pain but anticoagulation with heparin throughout cardiopulmonary bypass may predispose to bleeding complications (2). Paracetamol and NSAIDs as part of a multimodal analgesic approach for treating postoperative pain after sternotomy have been reported to be ineffective (3,4). In recent years, long-lasting peripheral blocks that involve the use of continuous infusion of a local anesthetic solution of the operative site have shown promising results both in adults (5,6) and in children (7–9). Tirotta and co-workers showed that continuous infusion of 0.25% levobupivacaine or bupivacaine significantly reduced postoperative morphine consumption in children who were undergoing median sternotomy (7). A local anesthetic administered to an operative site may also attenuate the local inflammatory stress response in addition to its analgesic action (10).

This prospective, randomized, trial was designed to examine whether the continuous infusion of 0.2% ropivacaine decreases daily morphine consumption for 72 h in children who were undergoing ASD closure.

Methods

Subjects

The study was approved by the Institutional Ethics Committee (Ref:15/2009) and registered with EudraCT (ref:2008:008380-94). This randomized, double-blind study was conducted at the Children's Hospital Helsinki University Hospital. We first obtained written informed consent from parents prior to recruiting the patients in this study and the study was carried out in accordance with the principles of the Helsinki Declarations. The CONSORT recommendations for reporting randomized controlled, clinical trials were followed.

We enrolled a total of 49 children aged 1–9 years of ASA physical status II–IV, who were undergoing ASD repair. Exclusion criteria included a history of developmental delay or mental retardation, any other heart defect, known allergy to any local anesthetic, and clinically significant liver or renal disease.

Anesthesia

Children received oral premedication of diazepam 0.5 $mg \cdot kg^{-1}$. After i.v. access was obtained, fentanyl 5 $\mu g \cdot kg^{-1}$ was given. Anesthesia was induced with thiopentone 3–5 $mg \cdot kg^{-1}$ i.v. All children received cisatracurium 0.1 $mg \cdot kg^{-1}$ for tracheal intubation. After tracheal intubation, an arterial line, central venous catheter, and urinary catheter were inserted. Subsequently, fentanyl 5 $\mu g \cdot kg^{-1}$ was administered prior to incision. Anesthesia was maintained with propofol 10 $mg \cdot kg^{-1} \cdot h^{-1}$ and sevoflurane. Fentanyl 1 $\mu g \cdot kg^{-1}$ was given before skin closure at the end of surgery. Patients also received paracetamol 20 $mg \cdot kg^{-1}$ i.v. and thereafter 20 $mg \cdot kg^{-1}$ every 8 h for 48 h postsurgery.

Intervention

Enrolled children were randomly assigned to a treatment by the sealed-envelope method. The study design was a series of blocks of fours, whereby a patient randomly received either a continuous wound infusion of ropivacine (Group R) or of saline (Group C). A nurse anesthetist who did not participate in the postoperative care of the enrolled children prepared all study medications according to the assigned group treatments that were stipulated in the protocol. Thus, anesthetist, surgeon, and intensive care and ward nurses were blinded regarding the drug the child received. The study used ON-Q PainBuster® pump (I-Flow Corporation, Lake Forest, CA, USA) charged with either ropivacaine 2 $mg \cdot ml^{-1}$ (Group R) or saline (Group C). The elastomeric bulb on the device administered ropivacaine or saline at a fixed rate from 1 to 7 $ml \cdot h^{-1}$ depending on the weight of a child. After sternal closure, the 12.5 cm long catheter (On-Q expansion Kit with ON-Q Socker catheter; I-Flow Corporation) was tunneled parallel into the sternal wound above periosteum. After skin closure, the surgeon injected 0.2% ropivacaine as a bolus 0.5 $ml \cdot kg^{-1}$ (Group R) or saline 0.5 $ml \cdot kg^{-1}$ (Group C) into the catheter. Thereafter, the ON-Q PainBuster® pump was connected to the catheter. The catheters were removed 47–54 h after the operation had ended. Mediastinal drain was passed through the rectus abdominis muscles just below the xyphoid area (Figure 1).

Postoperative care

Sedation was maintained by i.v. propofol during the transport from theater to the pediatric intensive care unit (PICU) until tracheal extubation. All children received continuous i.v. morphine infusion of 0.01 $mg \cdot kg^{-1} \cdot h^{-1}$ during the first postoperative night.

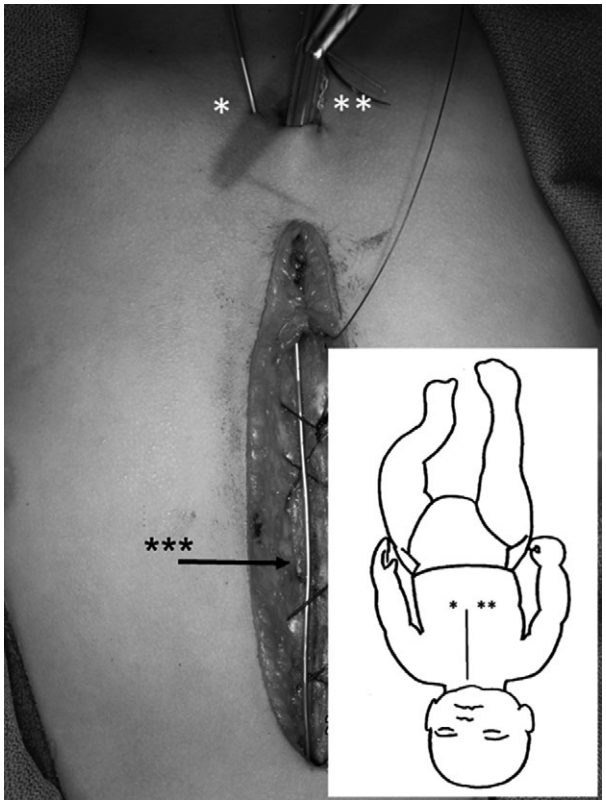

Figure 1 Catheter and mediastinal tube insertion. The catheter insertion site (*) was close to the mediastinal drain (**). The drain was positioned in the wound topically to periosteum (***).

Propofol was discontinued when the child's hemodynamic values became stable, the core temperature had corrected, and no active bleeding was observed. The trachea was extubated when the child could respond to simple commands and adequate respiratory effort existed. The rescue analgesic in the PICU was i.v. morphine 0.1 $mg \cdot kg^{-1}$. Pain was assessed by the intensive care nurse according to the behavioral Objective Pain Scale (OPS). OPS is an observer assessment score system that is based on facial expression, vocalization, movement or rigidity of the limbs and body, response to handling and irritability, and measured cardiorespiratory variables (11). In the OPS score, 0 = no pain, 1–3 = mild pain, 4–5 = moderate pain, 6–8 = severe pain, and 9 = worst possible pain. Self-assessment of pain was not used because most of the children were too young to give accurate descriptions.

The rescue analgesic was given when OPS score was ≥4. During their stay in the PICU, the highest OPS scores obtained in the preceding hour for each patient were recorded every hour. Any additional sedation required was given with midazolam 0.05–0.1 $mg \cdot kg^{-1}$. Sedation was assessed hourly using the University of Michigan Sedation scale, where 0 = completely awake, 1 = sleepy but responds appropriately, 2 = somnolent but arouses to light stimuli, 3 = asleep but responsive to deeper physical stimuli, 4 = asleep but not responsive to any stimuli. The peripheral capillary oxygen saturation (SpO_2) level and breath rates were recorded hourly. Ondansetron 0.2 $m \cdot kg^{-1}$ or dehydrobenzperidol 0.01 $mg \cdot kg^{-1}$ was given for nausea and vomiting.

The children were transferred to the ward on the first postoperative day before noon when they had become hemodynamically stable without inotropic support. The urinary catheter was removed before the patient was transferred to the ward. The rescue analgesic when the patient was in the ward was i.v. morphine 0.05 $mg \cdot kg^{-1}$. Pain, sedation, and SpO_2 were assessed every 2 h in the ward for 24–48 h and thereafter every fourth hour for 48–72 h. After 48 h, paracetamol was continued orally 20 $mg \cdot kg^{-1}$ every 8 h.

The primary outcome variable in this study was morphine consumption during the first 72 h. The secondary outcome variables were behavioral OPS scores, time to chest tube removal, time to total enteral feeding, time to mobilization, and time to discharge from hospital. In addition, side effects (nausea and vomiting, antiemetic use, itching, local anesthetic toxicity) were recorded. Special information regarding signs and symptoms of local anesthetic systemic toxicity was written in each patient's folder. The nursing staff was instructed to note any signs of dizziness; numb round mouth, fingers, and toes; focal/generalized seizures; and ventricular arrhythmia.

Statistical analysis

A targeted sample size was calculated using statistical power calculation based on previous data that were obtained from our hospital (12). The children in this study needed morphine i.v. mean (SD) 0.3 (0.15 $mg \cdot kg^{-1}$) during first 24 h postoperatively. The present study was calculated to require 23 subjects in each group to demonstrate a 40% difference ($\alpha = 0.05$, $\beta = 0.2$). A further three patients were needed to accommodate possible dropout; thus, a total of 49 patients randomly allocated to the groups in this study.

Comparisons between the groups were performed using the Student's *t*-test to compare means, the χ^2 test to compare frequencies, the Mann–Whitney *U*-test to compare distributions nonparametrically, and Fisher's exact test when appropriate. Normality of the distributions was assessed by Shapiro–Wilk W test, and depending on the results, either parametric or nonparametric analysis was performed. Data on demographics, surgery, anesthetics, and doses of drug administered were

analyzed using the Student's *t*-test. Sedation was analyzed using the Pearson's chi-squared test. Oxygen saturation and respiration rate were analyzed using the analysis of variance. Morphine consumption between the two groups and genders were analyzed by the two-way analysis of variance.

The mixed models with repeated measures were used to analyze the distinctive features of longitudinal data. Such features included within- and between-subject variation and the independence or dependence in the repeated measures. The effect of intervention on the outcome was adjusted by gender. Correlation coefficients for the relationships between the mean total morphine dose and the OPS scores were calculated. Survival analysis with Kaplan–Meier curve was used to measure severe pain.

A *P*-values of <0.05 were considered significant. All statistical analyses were performed using NCSS 9 and G* Power 3.17 (13,14).

Results

A total of 49 subjects were enrolled into the study. In Group R, one patient received dexmedetomidine infusion to counteract agitation during the first postoperative night and the other patient received oxycodone by patient-controlled analgesia (PCA) in the ward. These patients were also included in the analyses (intention-to-treat principle). The two randomly selected groups did not differ in terms of the patient characteristics data or in their surgical profiles (Table 1).

Primary and secondary outcomes

There were no statistically significant differences in morphine consumption ($P = 0.27$–0.78) (Table 2) or OPS scores ($P = 0.25$–0.52) (Figure 2) at 24, 48, and 72 h after the surgery between patients who received continuous ropivacaine wound infiltration or the placebo. The mean time to the first morphine administration after tracheal extubation was longer for Group R than for Group C (186.2 vs 81.0 min, 95% CI (−236.5, 26.2), $P = 0.114$. Figure 2 represents Kaplan–Meier curve for the time when OPS ≥6 (severe pain) for the first time ($P = 0.14$). There were no statistically significant differences between sedation scores except during 26–28 hours when more children in Group C ($P = 0.008$) slept. Furthermore, there were no differences between SpO_2 values or rate of breathing at 72 h after surgery.

There were no statistically significant differences between Group R and Group C in the time to mobilization (2.8 vs 2.9 days), the time to total enteral food intake (2.5 vs 2.6 days), or discharge from the hospital (5.4 vs 5.3 days).

The mixed models with repeated measures were used as covariates to test outcome changes over time, and treatment effect on outcome. Morphine consumption decreased significantly every subsequent 24-h interval after surgery ($P < 0.01$). However, the effect of the local anesthetic on morphine use was not significant ($P = 0.461$). Further analysis revealed significant sex-related difference in morphine consumption. During the 0- to 78-h interval, females in Group R had significantly lower mean morphine consumption (−0.102, $P = 0.010$) and during the 0- to 24-h interval, lower OPS scores (−0.477, $P = 0.015$) than males.

No patients had any signs or symptoms of local anesthetic toxicity. One child of each group had itching during the first 24-h interval after the operation. There were no pump malfunctions or disconnections during the study period. In Group C, one catheter dislodged at 38 h.

There were 15 of 26 patients (57.6%) in Group R and 18 of 23 patients (78.2%) in Group C who had nausea or vomiting during the first 24 h. The corresponding figures during the 24–48 interval were 16.6% and 21.7% for Group R and C, respectively. One child in each group vomited during the third postoperative day.

The number of doses of sedatives, antiemetics, or NSAIDs used in this study are presented in Table 2.

Table 1 Patient characteristics and intraoperative data. Data are shown as means (range) or means (SD)

	Group C ($n = 23$)	Group R ($n = 26$)
Age (year)	5.2 (2.1–7.8)	4.8 (1.3–9.7)
Weight (kg)	18.8 (5.4)	18.3 (7.8)
Height (cm)	110.2 (13.5)	106.0 (17.0)
Gender (F/M)	15/8	14/12
Duration of surgery (min)	84.8 (22.0)	85.2 (24.1)
Duration of anesthesia (min)	299.3 (109.9)	251.3 (99.9)
Time to removal of tracheal Tube (min)	198.1 (68.7)	202.6 (129.2)
Total dose of intraoperative Fentanyl ($\mu g \cdot kg^{-1}$)	9.8 (2.1)	10.7 (1.3)

C, control; R, ropivacaine.

Discussion

This randomized, placebo-controlled study involving a standardized operation showed that continuous wound infusion with 0.2% ropivacaine after median sternotomy in children undergoing ASD closure did not diminish morphine consumption or improve analgesia compared with placebo.

Our findings do not conform with the results of Tirotta *et al.* who found a significant morphine sparing effect during the first 24 h in children who had continuous wound infusion with 0.25% levobupivacaine or

Table 2 Consumption of morphine, and number of doses of sedation, antiemetics, and ibuprofen used; Midazolam 0.05 mg·kg^{-1}, dexmedetomidine 0.2–0.7 μg·kg·h^{-1}, ondansetron 0.2 mg·kg^{-1}, dehydrobenzperidol 0.01 mg·kg^{-1}, propofol 1 mg·kg^{-1} i.v., and ibuprofen 10 mg·kg^{-1} orally

	Group C (n = 23)	Group R (n = 26)	Group C vs Group R	P
Morphine consumption (mg·kg^{-1})				
Morphine: 0–24 h*	0.63 (0.30)	0.68 (0.25)	−0.05 (−0.20, 0.11)	0.559
Morphine: 24–48 h*	0.16 (0.10)	0.20 (0.18)	−0.05 (0.13, 0.04)	0.267
Morphine: 48–72 h*	0.06 (0.07)	0.07 (0.12)	−0.01 (−0.06, 0.05)	0.779
Concomitant drugs administered (n)				
0–24 h				
Midazolam	4	3		
Dexmedetomidine	0	1		
Ondansetron	19	19		
Dehydrobenzperidol	6	5		
Propofol	0	5		
24–48 h				
Ondansetron	4	6		
Dehydrobenzperidol	2	1		
Ibuprofen	1	1		
48–72 h				
Ibuprofen	4	1		

*Mean, (SD), difference in means with 95% CI and P-value of t-test.

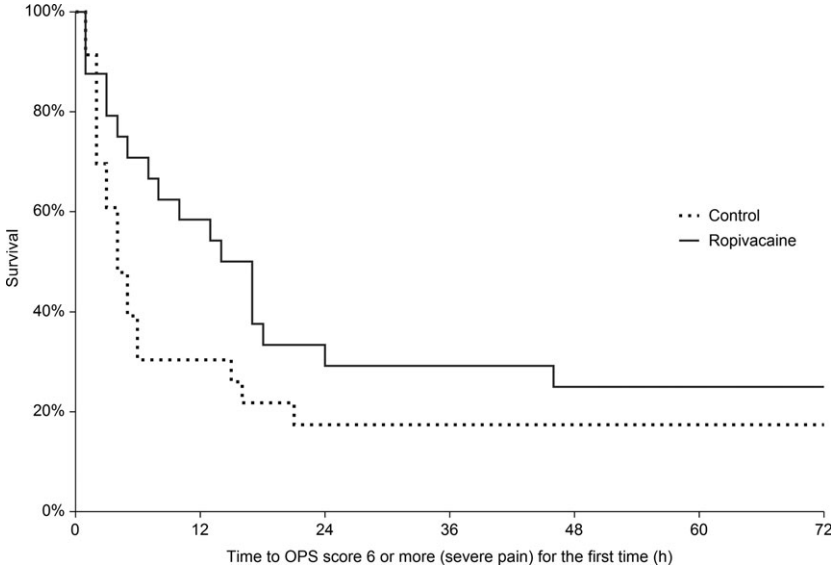

Figure 2 Kaplan–Meier curve for time to OPS score ≥ 6 (severe pain) for the first time. OPS = Objective Pain Scale as described by Eeva-Liisa Maunuksela *et al.* (11). There were no statistically significant differences between the groups.

0.25% bupivacaine compared with placebo (7). However, analgesia was not improved after local anesthetic infiltration in either our study or that of Tirotta *et al.*

A continuous wound infusion of local anesthetic has been used in postoperative pain with conflicting results (15). Two recent studies show that continuous wound infusion with ropivacaine failed to provide adequate analgesia after Cesarean section (16,17), but earlier studies after median sternotomy in adults show significant reductions in both morphine consumption and pain scores compared with placebo (5,6).

Pain after cardiac surgery is most often related to the median sternotomy or the chest drains (18). Continuous subcutaneous infusion may provide pain relief but only at the level of the wound. Therefore, in our study, local anesthesia may have been only partly effective and the mediastinal drain may have caused major discomfort in our patients. In the study by Tirotta *et al*,. 0.5 ml·kg^{-1} of local anesthetic was injected locally including chest drain sites in both the groups prior to skin closure (7). The study by Kocabas *et al.* reported that sternotomy and mediastinal drain sites that had been infiltrated with

60 ml of 0.25% levobupivacaine reduced morphine consumption within 24 h postoperatively (19). Furthermore, Dowling and co-workers put bilateral intercostal nerve blocks before inserting two catheters percutaneously (6). The authors reported that adults, who had received ropivacaine, needed less narcotic analgesia and their pain scores were lower compared with the control group. Eljezi *et al*. placed two catheters deeply under the fascia at the lateral edges of the sternum, close to the emergence points of the intercostal nerves (20). The results of their study also showed lower pain scores and reduced morphine consumption compared with the control group. This method of anesthesia, therefore, needs further studies in children who had undergone median sternotomy.

In the present study, a bolus dose of 0.2% ropivacaine 0.5 $mg \cdot kg^{-1}$ was injected through the catheter but not specifically into the mediastinal drain site. However, that bolus dose of ropivacaine may have had some effect because the time to first morphine dose tended to be longer in the ropivacaine group, although this difference was not statistically significant. The mediastinal drain was removed on the second postoperative day to avoid accumulation of pericardial fluid. After the removal of the drains, there was a nonsignificant trend toward lower OPS scores in the ropivacaine group.

In our study, the overall morphine consumption during the first 24 h was greater than that reported in the study by Tirotta *et al*. (0.66 vs 0.05 $mg \cdot kg^{-1}$ in the local anesthetic groups and 0.63 vs 0.2 $mg \cdot kg^{-1}$ in the control groups) (7). A difference between the two studies was that in the study by Tirotta *et al*., the children received dexamethasone 1 $mg \cdot kg^{-1}$ i.v. A meta-analysis on a pediatric population has shown that the dose of i.v. dexamethasone that led to pain reduction was in the range of 0.5–1.0 $mg \cdot kg^{-1}$ (21). Our children received paracetamol i.v. However, Lahtinen and co-workers have shown that paracetamol is not effective in treating postoperative pain caused by sternotomy in adults (3).

Females had lower pain scores in the present study and thus needed less morphine than males in Group R during the first 24 h after operation. This finding is not in accordance with other studies in children. Maunuksela *et al*. showed in their study that the correlation of pain ratings by the patient and observer did not differ between boys and girls (11). Other studies have shown that girls complain of pain more than boys and their coping strategy differs from that of boys (22). The study by Pestieau and colleagues found that morphine consumption after scoliosis surgery was lower and sedation score was higher in male patients compared with female patients for 96 h postoperatively (23). The elucidation of sex-related differences in postoperative analgesia and opioid consumption needs further research.

The most common side effect was postoperative nausea and vomiting (PONV), which occurred in 58–78% of the children in both the groups. It is likely that the most important reason for PONV was perioperative and postoperative opioid treatment.

Our study has limitations. First, the young age of most of the children (42 of 49 were aged <7 years) restricted the assessment of pain to behavioral Objective Pain Scale (OPS) (11). Although this Pain Rating Scale has been shown to correlate with verbal and also with two Visual Analog Scales, it may be less powerful than self-report measures of pain. Additionally, in the studies of Tirotta *et al*. and Hermansson *et al*., pain was assessed with observational pain scales and no difference in analgesia was found between children who received continuous local anesthetic wound infusion or placebo for postoperative pain treatment (7,9).

The second limitation of the study was that we did not measure the concentration of ropivacaine in plasma. Tirotta and co-workers measured the levels of levobupivacaine in plasma at 12, 24, 48, and 72 h from the beginning of the infusion (7). They found that the levels of levobupivacaine in plasma remained below the toxic threshold. Furthermore, earlier studies have not reported high plasma ropivacaine concentrations with ropivacaine 2 $mg \cdot ml^{-1}$ in either children of different ages (24–26) or adults (27). In the study of Beaussier and colleagues, ropivacaine 20 $mg \cdot h^{-1}$ was infused into adults for 48 h and both unbound and total fraction of ropivacaine decreased between 24 and 48 h, which suggested the absence of drug accumulation (27).

We conclude that the additional of continuous local anesthetic wound infiltration with 0.2% ropivacaine did not reduce morphine consumption, improve analgesia, or diminish nausea and vomiting compared with placebo in children who underwent ASD closure with median sternotomy and mediastinal drain.

Ethics approval

The study was approved by the Institutional Ethics Committee (Ref:15/2009).

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Conflict of interest

No conflict of interest to be declared.

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