

## Caudal Neostigmine and Bupivacaine Facilitates Early Extubation and Provides Prolonged Postoperative Analgesia in Children Undergoing Open Heart Surgery

Sayed Kaoud Abd-Elshafy\*, Esam abdalla, Mohamed Ali and Hesham Mohamed

Department of Anesthesia, College of medicine, Assiut University, Assiut, Egypt

\*Corresponding author: Dr. Sayed Kaoud Abd-Elshafy, Department of Anesthesia, College of medicine, Assiut University, Assiut, Egypt, Tel: 002 01007098665; E-mail: [sayed\\_k\\_72@yahoo.com](mailto:sayed_k_72@yahoo.com)

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### Abstract

**Objective:** This study was designed to examine the effect of single shot of caudal neostigmine with bupivacaine on early extubation versus standard intravenous fentanyl regimen without caudal block.

**Design:** Prospective, randomized double blind controlled clinical trial

**Setting of the study:** Children University Hospital

**Patients:** 80 children (4 to 12 years) undergoing correction of congenital heart defects

**Methods:** Patients were randomized into two equal groups (caudal neostigmine group and non-caudal group); Anesthesia was provided with sevoflurane, midazolam, plus fentanyl 5 mcg/kg and cisatracurium 0.1 mg/kg and maintained with sevoflurane, fentanyl 1 mcg/kg/h. and cisatracurium 0.05 mg/kg. In caudal group; caudal block with bupivacaine (0.125%) in a dose of 1.5 ml/kg plus neostigmine in a dose of 2 mcg/kg was performed after endotracheal intubation in the caudal group only. In non-caudal group intravenous fentanyl was continuously infused postoperatively until weaning from mechanical ventilation.

**Measurements and Main Results:** Both groups were comparable as regard age, sex, weight, and bypass and aortic cross clamp times. In the caudal neostigmine group patients were early extubated, with shorter Pediatric Intensive Care Unit (PICU) stay and prolonged postoperative analgesia. Eleven patients had nausea and vomiting in caudal versus four in non-caudal group.

**Conclusion:** Single dose of caudal bupivacaine with neostigmine provided optimum conditions for extubation and good control of postoperative pain in children undergoing cardiac surgery.

**Keywords:** Early extubation; Caudal; Neostigmine; Children; Cardiac surgery

### Introduction

Early weaning from mechanical ventilation in children undergoing repair of congenital cardiac disease was associated with improved cardiac performance and reduced incidence of postoperative pulmonary complications such as atelectasis [1].

Fast-tracking in cardiac surgery refers to the concept of early extubation, mobilization and hospital discharge in an effort to reduce costs and perioperative morbidity [2,3].

Fast-tracking for pediatric cardiac cases requires an anesthetic technique that allows safe early extubation either at the end of the procedure in the operative theater, or within a few hours in the Pediatric Intensive Care Unit (PICU) [4].

A high-dose opioid technique is typically not used for this approach. Neuraxial techniques have been used to minimize the use of intravenous opioid administration and to improve post operative outcome in a fast-track protocol. However, there is major controversy

about the safety, and benefits (outcome measures) of such approaches [5,6].

Compared to an indwelling epidural catheter, the risk of epidural hematoma associated with a single shot technique should be even lower. Neuraxial techniques have been shown to blunt the stress response to surgery and CPB [7,8], improved analgesia [9,10], shorter time to extubation [11,12], improved pulmonary function [13], reduced time with mechanical ventilatory support and consequently reduced costs.

Previous studies suggest that an opioid-sparing effect can be achieved postoperatively using a pharmacologically diverse variety of non-opioid adjuvants i.e., clonidine [14], dexmedetomidine [15], dexamethasone [16], magnesium [17], ketamine [18], midazolam [19]. Also neostigmine as adjuvant to caudally administered local anesthetic significantly increases the pain relief time in routine clinical practice in pediatric patients [20-24].

In fast-track regimen, it is important to have good selection of adjuvant drugs to local anesthetic that allows early extubation and avoids prolonged anesthetic effects [25].

## Aim of the Study

This study was designed to examine the effect of single shot of caudal neostigmine with bupivacaine on early extubation versus standard intravenous fentanyl regimen without caudal block as a primary outcome. The secondary outcome measures included pain and sedation assessment, hospital stay, the occurrence of re-intubation and side effects.

## Patients and Methods

After obtaining approval from the Local Research Ethics Committee of college of Medicine of Assiut university and informed parents' consent eighty children undergoing open heart surgery were studied. Children aged from 2 to 10 years. Patients were randomly allocated into two equal groups (caudal neostigmine group and non-caudal group) by using computer generated random numbers.

Children having chest problems, severe pulmonary hypertension, renal insufficiency, severe liver disease, history of seizure or stroke or any contraindication for regional techniques such as: infection near the site of the needle insertion, coagulopathy, anti-coagulation therapy, pilonidal cyst, congenital anomalies of the lower spine because of the unclear or impalpable anatomy or allergy to the local anesthetic drugs used were excluded from the study.

The sealed envelopes of randomization were opened early in the morning of surgery by the anesthetist who is going to give caudal block, and post-operative follow up of this patients were done by ICU doctors who were unaware by the type of randomization.

Standard anesthetic technique was used in the form of premedication with 0.5 mg/kg oral midazolam and 10 mcg/kg atropine. Anesthesia was induced with sevoflurane plus fentanyl 5.0 mcg/kg and cisatracurium 0.1 mg/kg and maintained with sevoflurane, fentanyl 1.0 mcg/kg/hr. and cisatracurium 0.05 mg/kg/dose.

ECG, invasive blood pressure, heart rate, temperature, oxygen saturation, exhaled CO<sub>2</sub> (end tidal CO<sub>2</sub>) and train of four of peripheral nerve stimulator for muscle relaxation monitoring; all were continuously monitored during the procedure.

After induction of anesthesia and before skin incision, patients in the caudal group received caudal epidural block in the left lateral position using a 23-gauge short-beveled needle under sterile conditions using a standard loss of resistance technique (maximum of 30 ml) with bupivacaine (0.125%) in a dose of 1.5 ml/kg plus neostigmine in a dose of 2 mcg/kg. Two milliliter of the bupivacaine (0.125%) (Subtracted from the total volume of the study medication) was initially administered with epinephrine 1:200,000 as a test dose and this was followed by rest of the study medication, which had been previously prepared. All operations were carried out by the same team of cardiac surgeons.

Management strategy of cardio-pulmonary bypass (CPB) was standardized for all the patients in the two groups. Heparin in a dose of 400 IU/kg was given to the patient and this usually after 60 minutes from caudal epidural anesthesia, and once activated clotting time (ACT) of  $\geq 450$  seconds, CPB was initiated.

A recruitment maneuver was carried out prior to weaning from cardiopulmonary bypass to prevent atelectasis. Ventilation was started,

hemodynamics and arterial blood gases were stabilized and patients were weaned from CPB at nasopharyngeal temperature 37°C. Protamine was administered to reverse heparin in a dose of 1mg protamine for every 100 IU heparin.

Fentanyl infusion stopped after weaning from CPB before transportation to postoperative cardiac intensive care (PICU) in the caudal neostigmine group. The last dose muscle relaxation was given before starting closure of the sternum and continuous re-warming by warm mattress at 37°C till transported to PICU.

The PICU physician was kept blinded to the randomization group where the criteria for extubation were as the standards for postoperative cardiac patients in the form of adequate level of consciousness, hemodynamic stability, and absence of arrhythmias, adequate airway reflexes, normothermia, acceptable mediastinal drainage blood loss and acceptable arterial blood gas analysis (appropriate for specific CHD lesion).

After endotracheal extubation patients were assessed for postoperative pain by using an Objective Pain Score (OPS) (Appendix 1) [26]. Intravenous (IV) paracetamol (15 mg/kg/dose) was given as rescue analgesia when OPS  $\geq 4$  and IV morphine (0.1 mg/kg) was given for persistent pain.

In the postoperative period patients were assessed for side effects especially sedation by using Richmond Agitation Sedation Scale (RASS) (Appendix 2) [27], and postoperative vomiting (if occurred it was treated as needed with IV ondansetron 0.06 mg/kg every 4 hours if needed).

## Statistical analysis

Based on the preliminary study, a power analysis was done to find a sufficient sample size in determining a significant difference in duration of post-operative mechanical ventilation by using an alpha value of 0.05 and a power of 80%. This established that a sample size of 36 patients was adequate per group so we enrolled 40 patients in each group.

Data were computerized and analyzed using the (SPSS 16.0 software, Chicago, IL, USA) computer program. The normality of the data was assessed by Kolmogorov-Smirnov test. Data was presented as mean  $\pm$  SD or numbers and percentages when appropriate. Comparison between groups was done by Independent Samples *T* test or Mann-Whitney *U* test when appropriate.  $\chi^2$  test or Fisher's Exact Test was used to assess group differences for categorical variables. *P*-value was considered significant if *P*-value < 0.05.

## Results

Both groups were comparable as regard age, sex, weight, and bypass and aortic cross clamp times (Table 1). In the caudal neostigmine group patients were early extubated ( $67.62 \pm 53.03$  vs.  $106.02 \pm 73.04$  in the non-caudal group, *P*=0.009), with shorter Pediatric Intensive Care Unit (PICU) stay ( $2.45 \pm 0.54$  vs.  $2.75 \pm 0.70$  in the non-caudal group, *P*=0.024) and prolonged postoperative analgesia ( $12.74 \pm 7.53$  vs.  $2.62 \pm 1.67$  in the non-caudal group, *P*<0.001) (Table 2).

Items	Caudal neostigmine group	Non caudal group	P- value
Age range (24-96 months)	50.53 ± 0.52	54.06 ± 0.70	0.48
Weight (kg)	15.32 ± 5.86	15.75 ± 5.22	0.73
Sex-Number (%)			
Male	25 (62.5%)	28 (70%)	0.23
Female	15 (37.5%)	12 (30%)	0.34
Diagnosis-Number (%)			
ASD	16 (40%)	10 (25%)	0.23
VSD	13 (32.5%)	13 (32.5%)	1
TOF	11 (27.5%)	17 (42.5 %)	0.24
CPB (minute)	81.22 ± 32.24	92.95 ± 28.59	0.08
Cross clamp time (minute)	47.85 ± 23.56	53.42 ± 21.19	0.26
Operative time (hours)	210.25 ± 49.69	213.5 ± 43.15	0.76
ASD: Atrial Septal Defect; VSD: Ventricular Septal Defect; TOF: Tetralogy of Fallot; CPB: Cardio-Pulmonary Bypass			
Data was described as means ± SD by using Independent sample T test and described as number of patients (percentage) by using Fisher's exact test for nominal and ordinal variables			

**Table 1:** Demographic data and different intraoperative times in both caudal neostigmine group and non caudal group

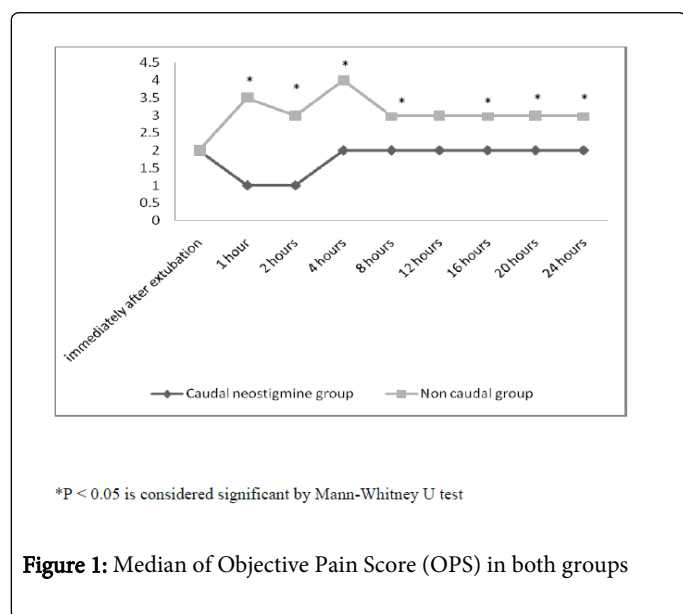
More patients were extubated within the 1st hour in caudal neostigmine group [25 patients] compared with non-caudal group [14 patients], P=0.025. Also, decreased number of patients who extubated after 2 hours in caudal neostigmine group compared to non-caudal fentanyl group [6 (15%), and 17 (42.5%) respectively, P=0.013 by Fishers' exact test (Table 2).

Variable	Caudal neostigmine group	Non caudal group	P-value
Total mechanical ventilation time (minutes)	67.62 ± 53.03	106.02 ± 73.04	0.009*
Fast Track-Number (%)			
A	25 (62.5%)	14 (35%)	0.025*
B	9 (22.5%)	9 (22.5%)	1
C	6 (15%)	17 (42.5%)	0.013*
Duration of postoperative analgesia (hours)	12.74 ± 7.53	2.62 ± 1.67	<0.001*
Total paracetamol consumption (mg)	300 (1080)	675 (1350)	<0.001*
Patients received morphine-Number (%)	2(5%)	10(25%)	0.025*
PICU stay (days)	2.42 ± 0.55	2.75 ± 0.70	0.024*
Hospital stay (days)	4.55 ± 1.06	4.8 ± 0.94	0.186
A=weaning from mechanical ventilation within the first hour in PICU			
B=weaning from mechanical ventilation within the second hour in PICU			
C=weaning from mechanical ventilation after the second hour in PICU			
Data was described as means ± SD by using Independent sample T test and described			
as number of patients (percentage) by using Fisher's exact test for nominal and ordinal			

variables
*P Value was considered significant if <0.05.

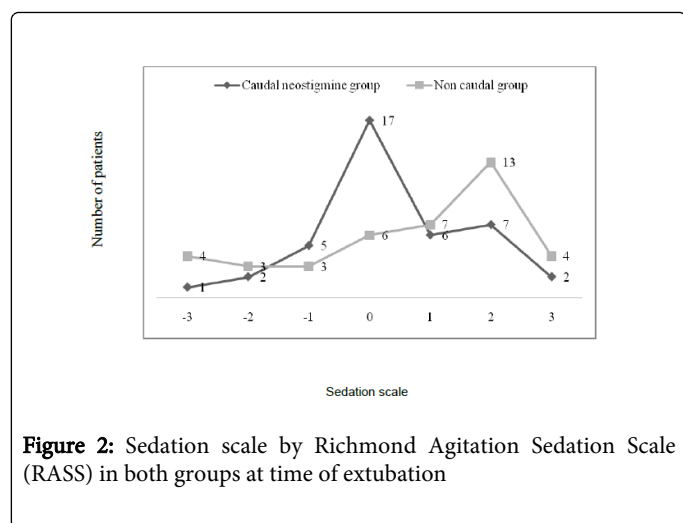
**Table 2:** Post operative data in caudal neostigmine group and non caudal group

Objective pain score showed a significant decrease in caudal neostigmine group when compared with non-caudal group at all times except immediately after extubation, and at 12 hours postoperatively (Figure 1). Total IV paracetamol and number of patients received IV morphine as rescue postoperative analgesia were significantly less in caudal neostigmine group when compared with non-caudal group (Table 2).



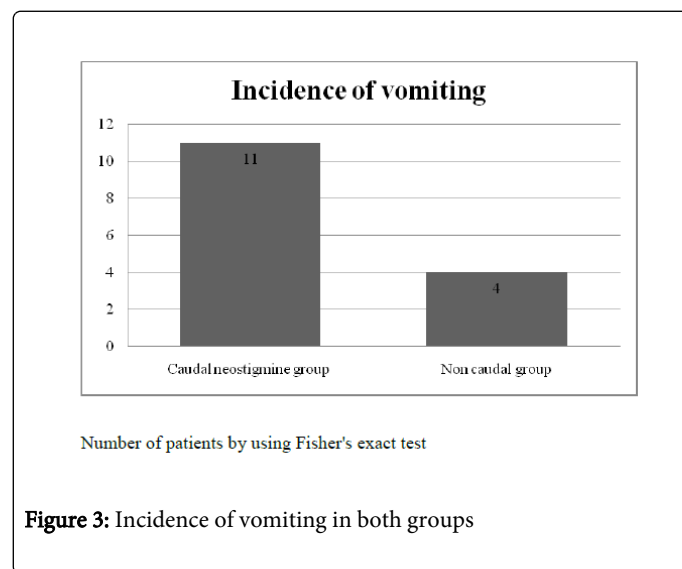
**Figure 1:** Median of Objective Pain Score (OPS) in both groups

As regard to side effects our results showed no significant difference between both groups in sedation scale, although results revealed a high percent of patients 17 (42.5%) in the caudal neostigmine group were alert and calm, whereas in the non-caudal group, results revealed that most of patients 13 (32.5%) were restless and agitated (Figure 2).



**Figure 2:** Sedation scale by Richmond Agitation Sedation Scale (RASS) in both groups at time of extubation

Eleven patients had postoperative vomiting in caudal neostigmine group versus four in non-caudal group (P=0.09) by Fisher's Exact Test (Figure 3). None of the patients in both groups had any neurological toxicity manifestation or required re-intubation.



**Figure 3:** Incidence of vomiting in both groups

## Discussion

In this study we are describing our experience of early extubation of children undergoing cardiac surgery in pediatric cardiac unit of Assiut University Hospital.

Our study showed that caudal neostigmine group patients were early extubated, with shorter ICU stay and prolonged postoperative analgesia. When the need for systemic opioids are reduced, cardiac surgery patients are able to be extubated early with reduced length of stay in the intensive care unit [28], as well as a faster recovery of bowel and bladder function [29].

The criteria for tracheal extubation include hemodynamic stability, normothermia, minimal bleeding, adequate neuromuscular and pulmonary function, return of consciousness and good analgesia

Several studies have addressed the use of caudal anaesthesia for fast-track management [11,30,31]. Leyvi et al., in 2005 retrospectively reviewed the medical records of 169 patients undergoing congenital heart surgery with CPB under general or general plus caudal anesthesia in an attempt to discern whether caudal anesthesia affects postoperative outcomes. They found no differences in PICU stay and hospital length of stay between caudal and non-caudal groups for the 3 most common pathologic repairs: ASD, VSD, and TOF. Also they showed that mechanical ventilatory times were significantly shorter in the ASD and TOF caudal groups compared with the corresponding non-caudal groups. Pain scores and postoperative morphine requirements were not different between caudal and non-caudal

patients, but only a small number of patients were included in their analysis [11].

Peterson et al., in 2000 reviewed the records of children receiving a regional anesthetic for cardiothoracic surgery at Stanford Medical Center between January 1993 and February 1997. In their study all patients were targeted for early tracheal extubation, where a variety of regional techniques were used and time to extubation, control of pain, incidence of respiratory depression and other complications, and length of hospital stay were determined. They found that regional anesthesia was safe and effective in the management of pediatric patients undergoing cardiac surgery [30].

Laussen et al., in 1996 retrospectively reviewed 102 cases of ASD repair and found no difference in cost except for decreased cost of mechanical ventilation in the group of patients who were extubated in the operative room. Their patients were treated with a combination of general anesthesia and caudal morphine [31].

Also, Shayevitz et al., in 1996 compared the outcomes of 27 patients with congenital heart repairs given general anesthesia and lumbar epidural morphine infusion with those in 27 similar patients given intravenous opioid medications. They reported that patients receiving lumbar epidural morphine were more quickly extubated and transferred from the PICU [32].

Our study revealed that the duration of postoperative analgesia and first dose of rescue analgesic was significantly longer with caudal neostigmine than non-caudal group. Our findings are in line with the results of previous reports that used caudal neostigmine for postoperative analgesia in children [22-24].

Neostigmine is a hydrophilic molecule similar to morphine. The analgesic effects of caudal neostigmine can be attributed to either to the direct action at the spinal cord level after transdural diffusion to cerebrospinal fluid (CSF) or a peripheral antinociceptive at the surgical site after systemic absorption [33]. The effectiveness of small dose of caudal neostigmine 2 mcg/kg suggests a spinal rather than a peripheral mechanism of action.

More patients experienced post operative vomiting in the caudal neostigmine group in our study (11 patients in the caudal neostigmine group vs. 4 patients in non-caudal group,  $P=0.09$ ). Similarly, Abdulatif and colleagues, found that neostigmine was associated with an unacceptably high incidence of vomiting (30%, 10% and 25% for neostigmine, bupivacaine and neostigmine+bupivacaine, respectively), which may preclude its use [22]. In addition, others [23,24] revealed that the incidence of vomiting with the use of caudal bupivacaine neostigmine was 20%.

No neurological toxicity and this in line with previous studies [22,23] with 2 mcg/kg of neostigmine, which have not mentioned any behavioural changes from epidural administration of neostigmine with methyl and propyl of paraben as preservatives in a glucose containing solution.

## Conclusion

Caudal neostigmine can be used safely as a model of fast-track anesthesia for congenital heart surgery; also it provides effective analgesia with opioid sparing effects. This allows faster recovery of patients, and helps to provide an efficient and cost-effective service. However, better control of postoperative vomiting by antiemetic prophylaxis after caudal neostigmine is required.

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