Original Article

Assessment of Stress Response Attenuation with Caudal Morphine Using a Surrogate Marker During Pediatric Cardiac Surgery

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ABSTRACT

Background: Measurement of biomarkers representing sympathetic tone and the surgical stress response are helpful for objective comparison of anesthetic protocols.

Aims: The primary aim was to compare changes in chromogranin A levels following pump pediatric cardiac surgery between children who received bolus caudal morphine and those who received a conventional intravenous narcotic-based anesthesia regime. The secondary objectives were to compare hemodynamic responses to skin incision and the magnitude of the rise in blood sugar values between the groups.

Settings and Design: A prospective observational study at a tertiary cardiac center.

Measurements and Methods: Sixty pediatric cardiac surgical patients were randomized to Group I [n = 30] to receive intravenous narcotic-based anesthesia and Group II [n = 30] to receive single-shot caudal morphine. Baseline and postoperative chromogranin A levels, the hemodynamic response to skin incision, changes in blood sugar levels, and the total intravenous narcotic dose administered were recorded for each participant.

Statistical Analysis: Pearson's Chi-squared test was used for comparison of categorized variables, and Mann–Whitney test was used for the analysis of continuous data.

Results: Changes in chromogranin A levels and blood sugar levels were comparable in both groups. Group II received a lower narcotic dosage ($P \leq 0.001$), and the response to skin incision as reflected by systolic pressure rise was less ($P = 0.006$).

Conclusions: Surgical stress response attenuation was similar to caudal morphine as compared with intravenous narcotic-based anesthesia techniques as reflected by a similar increase in chromogranin A levels.

Keywords: Anesthesia, cardiac surgical procedures, caudal/methods, chromogranin A, chromogranins/blood, congenital/surgery, heart defects, physiological/blood, stress

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INTRODUCTION

The noxious stimuli caused by surgical trauma trigger a stress response.[1] Biomarkers representing sympathetic tone and the surgical stress response can be measured for objective evaluation of anesthetic protocols.[2,3]

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Historically, it is known that epidural opioids provide improved perioperative analgesia.[4] Caudal morphine in pediatric cardiac surgery has been in vogue for some time.[5] The research question addressed in this prospective observational study was whether caudal morphine administered as a bolus before skin incision attenuates the surgical stress response of cardiac surgery in pediatric age groups compared to conventional intravenous analgesia protocols. Toward this end, chromogranin A (CgA) was identified as a surrogate biomarker for assessing stress response.[6] The study hypothesized that caudal morphine may not attenuate surgical stress as measured by a surrogate marker, i.e., CgA compared to conventional narcotic-based anesthetic techniques. The primary aim was to compare the change in the median CgA levels in children who received conventional narcotic-based anesthetic techniques versus those who received caudal morphine as the primary analgesic technique. CgA levels were measured immediately after the administration of general anesthesia and following the completion of on-pump cardiac surgery. The secondary objectives were to compare hemodynamic responses to skin incision, the magnitude of the rise in blood sugar values, and the duration of mechanical ventilation between the groups.

MATERIALS AND METHODS

After obtaining institutional scientific research committee approval (SRC#69/2017), pediatric cardiac surgical patients below 5 years of age, undergoing elective open-heart surgery were prospectively enrolled in the study. The children were randomized by computer-generated random numbers prior to administration of anesthesia, to Group I (control group, n = 30 patients) to receive intravenous narcotic-based anesthesia and Groups II (study group, n = 30) to receive caudal morphine as the primary technique for analgesia. Babies with bleeding diathesis, deranged liver function, preoperative mechanical ventilation, and narcotic infusions, emergency pediatric surgeries, and those with preoperative hemodynamic instability were excluded. It was agreed at the outset that if there was a traumatic tap during caudal morphine administration, the surgical procedure would be postponed. All children were premedicated as per institutional protocols. Under the standard American Society of Anesthesiologists' recommended monitoring modalities, general anesthesia was administered in both groups with intravenous anesthetics, i.e., ketamine (2 mg/kg), fentanyl (1 to 2 μg/kg), midazolam (0.1 mg/kg), and thiopentone (1–2 mg/kg/min) supplemented with sevoflurane. A blood sample for estimation of baseline CgA levels was obtained in all children. Children in Group I continued to receive intravenous fentanyl (2/μg/kg/h) along with continuous dexmedetomidine hydrochloride infusion (0.6 μg/kg/h) and sevoflurane (up to 1 MAC). In Group II, the caudal space was accessed after the administration of anesthesia under strict aseptic precautions under ultrasound guidance. A bolus of preservative-free morphine (50 μg/kg) in 1 mL/kg normal saline was deposited in the caudal space at least 30 min before skin incision. Full body heparinization was done at least 60 min after the caudal injection. Intraoperative sedation was maintained with sevoflurane (up to I MAC) and dexmedetomidine hydrochloride infusion (0.6 μg/kg). A bodyweight-adjusted dose of cis-atracurium besylate was used for muscle relaxation in both groups. In the caudal morphine group, intravenous fentanyl was used only during the induction of anesthesia. Additional boluses of fentanyl 1 to 2 μg/kg were administered intravenously if the blood pressure and heart rate increased >10% above baseline.

Bispectral index (BIS) was used to monitor the depth of anesthesia in both groups, targeting values between 40 and 60. Demographic data such as age, weight, duration of cardiopulmonary bypass, and duration of mechanical ventilation were recorded. The basic and composite Aristotle scores were calculated in both groups for a complexity adjustment. The hemodynamic response to skin incision in terms of changes in blood pressure (systolic/diastolic/mean) and heart rate, the highest blood sugar levels as compared to baseline values, and the total fentanyl and midazolam dose administered were also be obtained for each patient. A final blood sample for measuring the CgA levels at the end of surgery was collected in all children just before shifting them from the operating rooms to the postoperative pediatric intensive care unit. The median difference between the baseline and the final CgA levels was compared between the two groups. In the intensive care unit, all children were mechanically ventilated and tracheal extubation was done at the discretion of the pediatric intensivists. Following tracheal extubation, children were assessed for any neurological deficit with stress on the loss of motor function of lower limbs. Children in both groups received dexmedetomidine infusion up until the time of tracheal extubation. Intravenous acetaminophen (15 mg/kg) was administered every 6 h, and further rescue analgesia was provided by boluses of fentanyl 1 μg/kg intravenously.

Serum CgA levels were measured using a Human Chromogranin A ELISA Assay Kit (Eagle Biosciences, Inc. Nashua, NH) that utilizes a technique in which two antibodies bind to two epitopes of CgA. Blood samples for measuring CgA levels were collected in serum separator tubes without an anticoagulant (BD Medical Systems,

Becton, Dickinson and Company, NJ 07417-1880, USA). The tubes were immersed in ice and transported to the laboratory. All samples were stored and processed identically to ensure uniformity of measurements. The normal reference range for serum CgA levels considered was 25 to 95 ng/mL.

Statistics

The sample size was computed based on a pilot study results using the software G*Power 3 (Department of Experimental Psychology, Heinrich-Heine-University, Düsseldorf, Germany). With 1:1 allocation, a minimum of 26 subjects in each group with a total patient population of 52 was needed for an effect size of 0.70, power of 80%, and an α-error of 5%. Data were analyzed using IBM SPSS Statistics 25.0 (IBM Corp., Released 2017, IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY). Categorized variables were compared using Pearson's Chi-squared test. The differences between baseline and subsequent points of time of continuous data were compared using the non-parametric Mann–Whitney test. A *P* value of <0.05 was considered statistically significant.

RESULTS

Thirty-five patients were initially recruited in each group to allow for dropouts. Thirty patients in each group completed the study. Five patients in each group were excluded. For two patients (1 in each group), extracorporeal membrane oxygenation support had to be resorted to. Two other patients (1 in each group) had a change in operative procedure based on new intraoperative transesophageal echocardiography findings due to which the planned open-heart procedures were converted to closed heart procedures. Data collection was inadequate in 6 patients (3 patients in each group) due to misplacement of blood samples [Figure 1].

The demographic, cardiopulmonary bypass, and mechanical ventilation duration data were comparable between the groups [Table 1]. Caudal morphine groups had a significantly reduced rise in systolic pressure compared with the control group ($P = 0.006$). The Aristotle scores (both basic and composite) were comparable between the groups [Table 2]. Injection midazolam doses were comparable (0.28 ± 0.20 mg in group I vs. 0.31 ± 0.20 mg in group II, $P = 0.523$ [Chi-square test]). However, the total dose of injection fentanyl administered in the control group was significantly higher than that administered in the study group (21.78 ± 7.07 μg in group I vs. 2.57 ± 2.72 μg in group II, $P \leq 0.001$ [Chi-square test]). The increase in blood sugar levels due to surgical stress, as reflected by the difference in the baseline and highest blood sugar levels detected, was similar in both groups [Table 1]. The difference in the median value of CgA levels, as measured

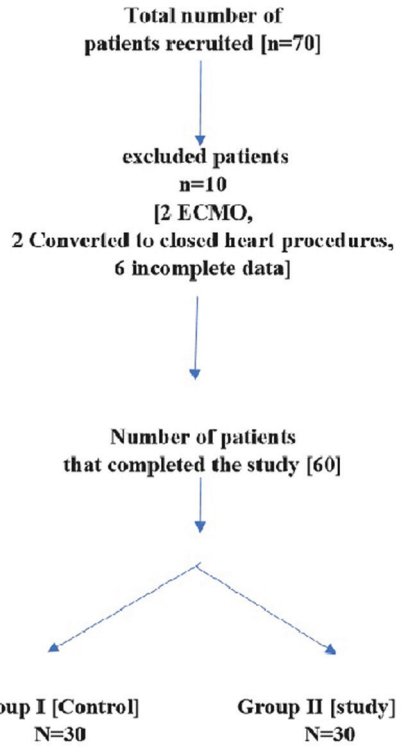

Figure 1: Patient flow chart

Table 1: Comparison of demographic data, cardiopulmonary bypass data, and clinical variables

	Group I (no caudal morphine) (*n*=30)		Group II (caudal morphine) (*n*=30)		*P**
	Median	(IQR)**	Median	(IQR)**	
Age in days	270	(2, 5110)	330	(10, 2555)	0.635
Weight	6.05	(2.70, 53.0)	7.25	(2.50, 31.0)	0.824
Duration of cardiopulmonary bypass (min)	127	(56, 225)	124	(84, 206)	0.645
Duration of mechanical ventilation (h)	12	(4, 96)	10	(4, 168)	0.307
Systolic blood pressure difference (between before and after skin incision)	13	(-17, 37)	4	(-10, 31)	0.006
Diastolic blood pressure difference (between before and after skin incision)	6.0	(-17, 30)	4.5	(-11, 33)	0.386
Mean blood pressure difference (between before and after skin incision)	10	(-17, 29)	2	(-4, 36)	0.084
Heart rate difference (between before and after skin incision)	-11	(-31, 40)	1.5	(-45, 66)	0.066
Blood sugar difference (between baseline and the highest recorded levels)	4.80	(0.80, 12.40)	3.75	(0.70, 12.60)	0.379

*Mann-Whitney test, nonparametric approach. **IQR=interquartile range

at the time of the end of the surgery, and baseline values were comparable in both groups [Table 3].

DISCUSSION

All children who completed the study were doing well at the short-term follow-up, i.e., at 3 months after the surgery. No child in the caudal morphine group had any neurological deficit. The rise in CgA levels in response to surgical stress was found to be similar in pediatric cardiac surgical patients who received caudal morphine as the primary analgesia modality as compared to those who were managed with intravenous narcotic-based anesthesia technique. The hypothesis that caudal morphine might not suppress surgical stress as compared to conventional methods was rejected.

Mittnacht *et al*. administered 50 to 100 μg/kg of preservative-free morphine into the caudal space in pediatric patients undergoing cardiac surgery to facilitate early tracheal extubation.[7] Leyvi *et al*.,[8] Sendasgupta *et al*.,[9] and Garg *et al*.[10] studied administration of narcotics, diluted in a total volume of 1 mL, to the caudal space in children undergoing cardiac surgery. In the current study, a bolus of preservative-free morphine (50 μg/kg) in 1 mL/kg normal saline was deposited in the caudal space.

Perioperative and postoperative stress responses with caudal narcotics were evaluated previously by the measurement of cortisol, blood glucose, and interleukin (IL)-6.[9,11,12] The current study assessed the stress response of surgery using CgA as a biomarker for stress. CgA is a 46 kDa protein that is stored as secretory granules in several endocrine and neuronal cells.[13] It is released primarily by the stimulation of chromaffin cells and is considered to be a reliable indicator of the activation of sympathetic tone.[14] Mahata *et al*.[15] suggested that CgA could play an important role in cardiovascular, immunometabolic, and cancer regulation. Elevated levels of immunoreactive CgA-related polypeptides were detected in patients with cardiovascular diseases such as acute coronary syndrome, myocardial infarction, primary and secondary hypertension, dilated cardiomyopathy, and hypertrophic cardiomyopathy.[15] Under conditions of acute stress, CgA is released along with catecholamines from the adrenal medulla. However, no study has been carried out to evaluate the levels of CgA in the context of patients subjected to surgical stress, making this study probably the first one to do so.

Sendasgupta *et al*.[9] reported better glycemic control in patients who had general anesthesia with caudal than those who were administered only general anesthesia. The current study suggests that the difference between the baseline and highest blood sugar levels was comparable between the groups with no additional benefit proffered by caudal morphine.

An increase in blood pressure during surgery correlates well with changes in plasma vasopressin and catecholamines levels in humans.[16] However, this may not be very specific for evaluating stress response during open-heart surgery. A sensory stimulus with a consequent sympathetic response releases catecholamines such as norepinephrine, which is a neurotransmitter of sympathetic neurons. The extent of the stress response as a result of surgery can be evaluated by comparison of levels of biomarkers in blood samples collected before and after major surgical stress. In humans, the biomarker CgA is considered a reliable indicator of markedly increased sympathetic tone and correlates with the norepinephrine release rate.[1] It was suggested that circulating CgA levels correlate closely with increased sympathetic activity both in the adrenal medulla and peripheral nerve endings.[17-19]

CgA is relatively stable in plasma compared to other neurotransmitters and can be used as a parameter to measure stress responses to surgery.[20] It is difficult to measure the levels of norepinephrine due to its short half-life in the blood. Hsiao *et al*. demonstrated that the changes in CgA plasma concentration after pheochromocytoma resection showed an initial rapid half-life time of 16 min, followed by a longer half-life of 520 min.[21] This feature makes CgA less prone to rapid fluctuations in circulating concentrations compared to many other neurohormones.

Table 2: Comparison of severity of congenital heart disease using basic and composite Aristotle score

Variables	Group I mean (SD)	Group II mean (SD)	*P**
Basic	8.15 (2.15)	7.92 (1.92)	0.645
Composite	8.65 (2.77)	8.01 (1.94)	0.271

*Independent samples '*t*' test

Table 3: Comparison of chromogranin A [CgA] levels

Variables	Median values (minimum, maximum)		*P***
	Group I (no caudal morphine) (*n*=30)	Group II (caudal morphine) (*n*=30)	
Baseline CgA levels*	97 (40, 275)	81 (25, 164)	
Final CgA levels	120.5 (46, 271)	89.5 (31.0, 193.0)	
Difference in CgA levels (between baseline and final levels)	13 (-177, 123)	8 (-280, 134)	0.652

*The normal laboratory reference range for serum CgA levels is 25 to 95 ng/mL. **Mann-Whitney test

The biochemical analysis of CgA can be readily performed using standardized and well-validated, commercially available assays.[22] Hence, CgA could be another biomarker representing sympathetic activity that might be valuable in assessing the intensity of surgical stress.

As for the hemodynamic disturbances, Bichel *et al*.[12] demonstrated no difference in hemodynamics between high-dose IV opioids (sufentanil 15 μg/kg) and caudal sufentanil (5 μg/kg). In the present study, the rise in systolic pressure in the caudal morphine group compared to the control group was significantly reduced ($P = 0.006$).

Several authors have administered narcotics in the caudal space after administration of general anesthesia in pediatric cardiac surgical patients undergoing open-heart surgery to enable early tracheal extubation.[7-10] The authors of the current study followed a similar concept taking care that full-body heparinization was done only after a minimum of 60 min had elapsed after the caudal injection. A neuraxial technique provides long-lasting analgesia with a significant opioid-sparing effect. In small children, a single-shot caudal or spinal technique provides adequate pain control for several hours following surgery, with the chances of the occurrence of an epidural hematoma being minimal especially if a small-bore needle is used. Apart from providing superior analgesia, epidural opioids have been shown to blunt the stress response posed by both cardiac surgery and cardiopulmonary bypass.[23-25] As there was an obvious narcotic sparing effect with caudal morphine with the provision of good analgesia, an attempt at assessing the efficacy of caudal morphine in obtunding the stress response to on-pump cardiac surgery was made in this study.

The mechanism by which epidural morphine produces analgesia is by its action on Mu, Delta, and Kappa opioid receptors after its uptake into the epidural fat, systemic circulation, and cerebrospinal fluid through the dura mater. Because morphine is hydrophilic, it allows for a more cephalad spread. Baduni *et al*. suggested that the mean duration of analgesia provided by 50 μg/kg caudal morphine was 13.36 ± 2.47 h.[26] The same dose was adopted in this study as the duration of surgery was not expected to last longer than 12 h.

This study was conducted in the quest for an answer to the query if a single dose of caudal morphine would produce adequate surgical stress response attenuation. The results suggest that caudal morphine appeared to produce similar attenuation of stress response to surgery as conventional intravenous narcotic-based anesthesia techniques.

The strength of this study lies in its unique aim of assessing surgical stress attenuation by caudal morphine using a biomarker of stress that remains in the circulation for an adequate amount of time to enable its levels to be measured. Instead of relying on aphysiological response, this surrogate marker helped assess the efficacy of caudal morphine suppression of stress response.

Shortcomings of the study include

1. Unpleasant side effects such as nausea, vomiting, pruritus, or urinary retention, the risk of delayed respiratory depression was not evaluated.
2. The need for rescue analgesic medication in the intensive care unit was not assessed although it was administered.

In conclusion, caudal morphine attenuated stress response that was comparable to narcotic-based anesthesia techniques. This study provides an objective method of stress attenuation in pediatric cardiac surgical patients.

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Conflicts of interest
There are no conflicts of interest.

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