ORIGINAL CLINICAL RESEARCH

# Comparing the Hemodynamic Effects of Epinephrine versus Dexmedetomidine as an Adjuvant to Bupivacaine in Caudal Anesthesia Assessed by Cardiometry: A Randomized, Double-Blind, Controlled Study

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## Abstract

**Background:** Numerous anesthetic agents have been utilized for providing caudal analgesia in pediatric patients, with lignocaine and bupivacaine being the most commonly used. The addition of different additives, such as Dexmedetomidine and Epinephrine, has been successful in prolonging the duration of caudal analgesia. It is crucial to assess the hemodynamic effects of any adjuvant drug used with local anesthetics for caudal block. This study investigated the hemodynamic effects of Dexmedetomidine compared to Epinephrine when used as an adjuvant for caudal anesthesia in children.

**Methods:** This is a randomized, controlled, double blinded trial done in uni-center teaching hospital. Recruited children were randomly assigned by a controlled, double-blinded method to one of three groups:(Group B) received general anesthesia and caudal block with bupivacaine, (Group BE) was to received general anesthesia and caudal block with bupivacaine plus epinephrine, and (Group BD) received general anesthesia and caudal block with bupivacaine plus Dexmedetomidine. The primary outcome was the percentage change in stroke volume after 20 minutes.

**Results:** The percentage change of SV after 20 minutes in caudal bupivacaine Epinephrine group was 127% ± 10 from baseline value, which was significantly different than bupivacaine alone and bupivacaine Dexmedetomidine at the same time interval (100% ± 13 and a decrease of 92 % ±10, respectively).

**Conclusion:** In conclusion, this study provides evidence that the presence of Epinephrine in caudal anesthesia may produce alterations in SV and CO in children, while dexmedetomidine does not affect SV or CO. Our data was collected using a noninvasive continuous monitor.

**Keywords:** Acute Pain Services; Analgesia; Caudal Anesthesia; Dexmedetomidine; Epinephrine.

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## Introduction

Caudal block is one of the most used regional blocks in pediatric patients because it is safe and provides efficient and adequate perioperative analgesia for most infra-umbilical and lower limb procedures.[1] However, its main disadvantage is the short duration of action. The anatomy of the caudal space is more easily appreciated in infants and children, and they typically have minimal hypotension from sympathectomy.[2] It has been proposed that the cardiovascular effects of neuraxial blocks are less marked in children than in adults because of lower systemic vascular resistance (SVR) in the pediatric population.[3]

Many anesthetic agents have been used for caudal analgesia in pediatric patients, with lignocaine and bupivacaine being the most common. The addition of various additives has achieved prolongation of caudal analgesia such as Dexmedetomidine and Epinephrine.[4]

Dexmedetomidine is a potent and highly selective α2 agonist. It has an eight-fold greater affinity for α2 adrenergic receptors than clonidine and much less α1 effects. It has sympatholytic, analgesic and sedative effects, and is remarkably free from side effects except for manageable hypotension and bradycardia.[5] Adrenaline is commonly administered with local anesthetics. It vasoconstricts blood vessels locally where the local anesthetic was administered, which prevents the anesthetic from going systemically and keeps it confined to the surgical area. It also keeps the local anesthetic from being washed away by the blood, thus prolonging its half-life.[6]

It is very essential to determine the hemodynamic effects of any drug used as an adjuvant to local anesthetics for caudal block and to explore whether it reduces the child's cardiac output.

As invasive cardiac monitors are rarely indicated in pediatric patients, and little is known about the impact of caudally administered dexmedetomidine on cardiac function, we aimed to investigate its effect on hemodynamic functions measured by Electrical Cardiometry (EC). EC estimates cardiac parameters by measuring thoracic electrical bioimpedance during the cardiac cycle using skin electrodes. It has emerged as a new non-invasive tool for the assessment of cardiac output with good accuracy in adult and pediatric anesthesia. [7]

This study aims to understand the hemodynamic consequences of the

administration of Dexmedetomidine as an adjuvant for caudal anesthesia in children compared to Epinephrine, using a non-invasive monitoring method.

## Materials And Methods

### *Study design and setting*

A single-center, randomized, controlled, double-blinded trial was conducted at Cairo University Hospital after approval of the Research and Ethics Committee. The study was conducted in accordance with the Helsinki Declaration-2013. The study was registered prior to patient enrollment at the ClinicalTrials.gov (ID: NCT05860010, Date: May 16, 2023). The study was conducted from August 2021 till July 2022.

### *Randomization*

Randomization was achieved using a computer-generated sequence. Concealment was achieved using opaque envelopes. An informed consent was obtained from all children's parents or legal guardians before surgery. Children were recruited into the trial during preoperative assessment. Recruited children were randomly assigned by a controlled, double-blinded method to one of three groups:

Patients in group B received general anesthesia and caudal block with 1 mL/kg of bupivacaine 0.25%, patients in Group BE received general anesthesia and caudal block with 1 mL/kg of bupivacaine 0.25% plus epinephrine 5µg/mL of LA, and patients in Group BD received general anesthesia and caudal block with 1 mL/kg of bupivacaine 0.25% plus 1 µg/kg Dexmedetomidine.

### *Eligibility criteria*

All pediatrics ASA I & II, aged six months to eight years, undergoing elective infraumbilical (i.e., lower abdominal or genitourinary) surgeries were included in the study. Patients ASA ≥ III, < six months or > eight years of age, with any of the following: known coagulation disorders (Platelets ≤ 150,000 and/or INR> 1.5, or on anticoagulation therapy), congenital cardiac disease, suspected or proved allergy to local or systemic anesthetics, signs of infection at the back or congenital abnormalities of lower spine or meninges e.g., spina bifida were excluded from the study. Exclusion criteria also included emergency or laparoscopic procedures, that are lengthy (>60 minutes), or with severe blood loss.

### *Procedures and interventions*

All children were anesthetized in accordance with the local policy of the Pediatric Anesthesia Unit of our institution. All children were fasting according to ASA guidelines: two hours for clear fluids, four hours for breast milk and 6-8 hours for formula and solids. All children were premedicated with oral midazolam 0.5mg/kg one hour before surgery. After preoperative examination and upon arrival to the operating room, continuous electrocardiogram (ECG), non- invasive blood pressure (NIBP) and oxygen saturation ($SpO_2$) were monitored using standard monitor (Dräger infinity vista XL) before induction of anesthesia.

Induction of anesthesia was achieved with 8% sevoflurane in 100% oxygen through spontaneous ventilation via face mask and Jackson-Rees breathing system. Intravenous (IV) access was secured with an appropriate size cannula. Muscle relaxant was given in the form of atracurium 0.5mg/kg together with fentanyl 1 µg/kg. An appropriately sized endotracheal tube was placed and secured. Lactated Ringers' solution was started as per the calculated fluid requirements at 4 mL/kg/hr.

Patients were then mechanically ventilated with volume control mode using tidal volume of 6 mL/kg and respiratory rate of 20/minute, which were further titrated to maintain an end tidal $CO_2$ of 34-40 mmHg. The ICON monitor was used as per the manufacturer's instructions. Two ECG electrodes were placed on the left chest and two on the left side of the neck. Patient's gender, height in cm and weight in kg were taken from the nursing records and entered the device. The anesthesiologist recorded the baseline cardiac output, systemic vascular resistance and stroke volume taken using the electrical cardiometry (baseline data: T0). Baseline blood pressure (SBP and MBP) and heart rate were also recorded.

The Caudal block was performed under complete aseptic precautions in the left lateral decubitus position. The back of the patients, including the sacral hiatus, was carefully sterilized with an antiseptic solution and sterile drapes were placed around the injection site. The technique was done by introducing a 23-gauge hypodermic needle at a 45-degree angle to the skin, aiming towards the head. The needle was advanced until a pop or loss of resistance was felt, indicating progression through the sacrococcygeal ligament and entrance into the epidural space. After accurate verification of caudal space and negative aspiration of blood or cerebrospinal fluid, drug mixtures were injected over 60s, according to group allocation: Group B (caudal bupivacaine

(Bucaine actavis, Egypt) 1 mL/kg 0.25%), Group BE (caudal bupivacaine 1 mL/kg 0.25% + epinephrine 5 µg/mL of LA), or Group BD (caudal Bupivacaine 1 mL/kg 0.25% + 1 µg/kg Dexmedetomidine). A small elastoplast dressing was placed over the injection site, and the child was placed supine. It was ensured that the minimum time between the caudal block and the surgical incision was at least 15 minutes. The cardiometry measurements were taken separately by an observer blinded to the study drug every ten minutes up to one hour. The measurements were stored and analyzed off-time. No other narcotics, analgesics, or sedatives were administered intraoperatively. An increase of >20% in HR or SBP after ten minutes from caudal injection, or any movement at surgical incision was considered as a failure of caudal anesthesia and patients were excluded from the study. In case of caudal block failure (i.e. an increase of >20% in HR or SBP after ten minutes from caudal injection), analgesia was supplemented with an injection of fentanyl 1 µg/kg. Intraoperative hypotension is defined as a decrease in mean arterial pressure >30% from baseline reading and was treated with fluid bolus 10 mL/kg; if there was still hypotension, ephedrine I.V injection 0.1 mg/kg was used. A decrease in HR >30% was considered as bradycardia and treated with I.V. injection of atropine 0.01 mg/kg. At the end of the surgery, muscle relaxant was reversed using neostigmine (0.05 mL/kg), patients were extubated, and transferred to the post-anesthesia care unit (PACU).

Patients' vitals were monitored by the PACU staff for two hours postoperatively. The Electrical Cardiometry device that was used is the ICON™ monitor; (the Portable Noninvasive Hemodynamic Monitor manufactured by Osypka Medical Company). The measurements were stored and analyzed off-line. The average values during three consecutive measures were considered for the analysis. In the postoperative period, all patients were assessed for severity of pain using CHEOPS pain score at 2, 4, 6, and 12 hours postoperatively. CHEOPS score ≤ six was considered adequate pain control while a score > six necessitated rescue analgesia. All patients received analgesia in the form of voltaren suppository 1mg/kg every eight hours. Paracetamol (perfelgan) 15 mg/ kg IV was used as rescue analgesia. Adverse events of agitation, urine retention, bradycardia (heart rate 30 % below baseline), hypotension (blood pressure 30 % below baseline), respiratory depression (defined as $SpO_2$ lower

than 90%), and postoperative nausea and vomiting (PONV) were recorded.

*Study outcomes*

The primary outcome was the percentage change in stroke volume after 20 minutes. Secondary endpoints included differences in cardiac parameters between the three study groups (Stroke volume, heart rate, systolic & diastolic blood pressures), CHEOPS pain scores, and duration of analgesia. Additionally, secondary outcomes included the incidence and type of complications such as bradycardia, agitation, urine retention, hypotension, respiratory depression, and postoperative nausea and vomiting.

*Statistical analysis and sample size calculation*

A sample size was calculated that could detect a mean difference of 25% between the three study groups. MedCalc Software version 14 (MedCalc Software bvba, Ostend, Belgium) was used to calculate the sample size. The primary outcome was the percentage change in stroke volume after 20 minutes. In a previous study, the mean percentage change in stroke volume in pediatric patients after caudal anesthesia using esophageal doppler was 71 ± 15.[8] Thirty-three patients (11 patients per group) at least were estimated to have a study power of 80% and an alpha error of 0.05. This number was increased to 39 patients (13 patients per group) to compensate for possible dropouts.

Data analysis was performed using Statistical package for social science (SPSS) software, version 15 for Microsoft Windows (SPSS Inc., Chicago, iL, USA). Categorical data was reported as numbers and percentages and analyzed using the chi-squared test. Continuous data was checked for normality using the Kolmogorov-Smirnov test. Normally distributed data was presented as means (standard deviations) and was analyzed using an unpaired student t-test. Skewed data was expressed as medians (quartiles) and was analyzed using the Mann Whitney U test. Repeated measures were analyzed using a two-fold (intervention and time) repeated measure analysis of the variance model. A p-value of 0.05 or less was considered significant.

**Results**

Forty-four children aged from six months to eight years scheduled for minor lower abdominal surgeries at Cairo University hospitals were screened for eligibility. Five children were excluded from

the study for not meeting the inclusion criteria: one was excluded because preoperative hemoglobin level was less than 10 gm/dL, two patients were excluded because they were more than eight years of age, and the remaining two were excluded upon their parent's refusal (Figure 1). Patients' characteristics (demographic data) including age, gender, weight, height, type of surgery, and duration of operation comparison were not statistically significant among the three groups (Table 1).

The percentage change of SV after 20 minutes in caudal bupivacaine Epinephrine group was 127% ± 10 from baseline value, which was significantly higher than bupivacaine alone and bupivacaine plus dexmedetomidine at the same time interval (100% ± 13 and a decrease of 92 % ±10, respectively) (p-value <0.001) (Figure 2). In direct comparisons between the three groups at each ten minutes time point after caudal injection, statistically significant differences were noted for SV (Figure 3), and CO (Figure 4) from 20 minute up to 50 minutes; however, no statistically significant difference was noted for the SVR.

Stroke volume comparison was statistically significant between the three groups. There was a statistically significant increase in Group BE from 20 minutes to 50 minutes.

Systemic vascular resistance comparison was not statistically significant between the three groups. Cardiac output comparison showed a statistically significant increase in Group BE compared to Group B and Group BD at 20 minutes, 30 minutes, 40 minutes and 50 minutes.

A repeated measures analysis of variance model (ANOVA) was used to compare the heart rate between groups and within each group. Heart rate comparison was not statistically significant among the three groups (Figure 5). Mean arterial blood pressure comparison was not statistically significant among the three groups (Figure 6).

Pain scores were comparable among the three groups in the first four hours postoperatively; however, patients in Group BD showed better pain scores at 6-hours and 12-hours postoperatively (P value = <0.001, 0.016, respectively). In addition, the percentage of patients who required paracetamol rescue dose in Group BD was 23% and was statistically lower than the percentage of patients in Group BE (69%) and Group B (77%). Duration of analgesia and paracetamol rescue dose were comparable among the three study groups

(Table 2). Only one patient in Group BD developed bradycardia and received 0.01 mg/kg atropine. Moreover, three patients developed postoperative nausea and vomiting, one in each group with no statistically significant differences among the three groups.

**Table 1.** Patients' demographic data.

| | | Group B (n = 13) | Group BD (n = 13) | Group BE (n = 13) | P-value |
|---|---|---|---|---|---|
| Age (years) | | 4.3 ± 1.5 | 5.1 ± 1.2 | 4.2 ± 1.7 | 0.456 |
| Weight (kg) | | 16.5 ± 3.2 | 17.1 ± 3.5 | 16 ± 2.5 | 0.534 |
| Height (cm) | | 102 ± 11.3 | 107 ± 12.4 | 101 ± 12.7 | 0.564 |
| Gender (Male) % | | 10 (66%) | 9 (60%) | 10 (66%) | 0.345 |
| Surgery | Urogenital | 6 (47%) | 5 (40%) | 6 (47%) | 0.658 |
| | Orthopedic | 3 (23%) | 4 (30%) | 4 (30%) | |
| | General | 4 (30%) | 4 (30%) | 3 (23%) | |
| Duration of surgery (minutes) | | 55 ± 12 | 58 ± 16 | 50 ± 20 | 0.754 |

Data are presented as mean ± standard deviation, or count (percentage); Group B: control Bupivacaine group; Group BD: Bupivacaine and Dexmedetomidine group; Group BE: Bupivacaine and Epinephrine group

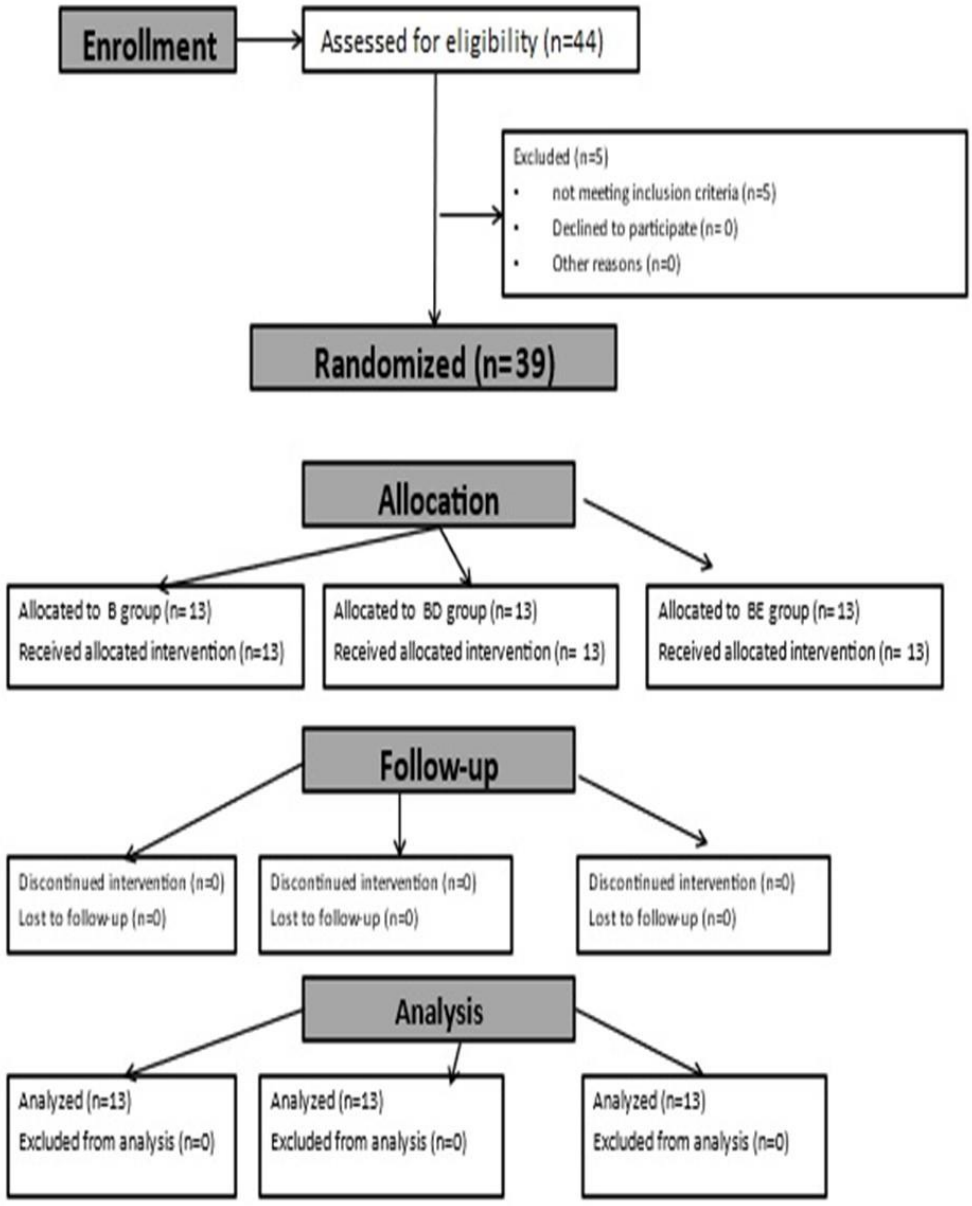


**Figure 1.** The CONSORT flow diagram of the trial.

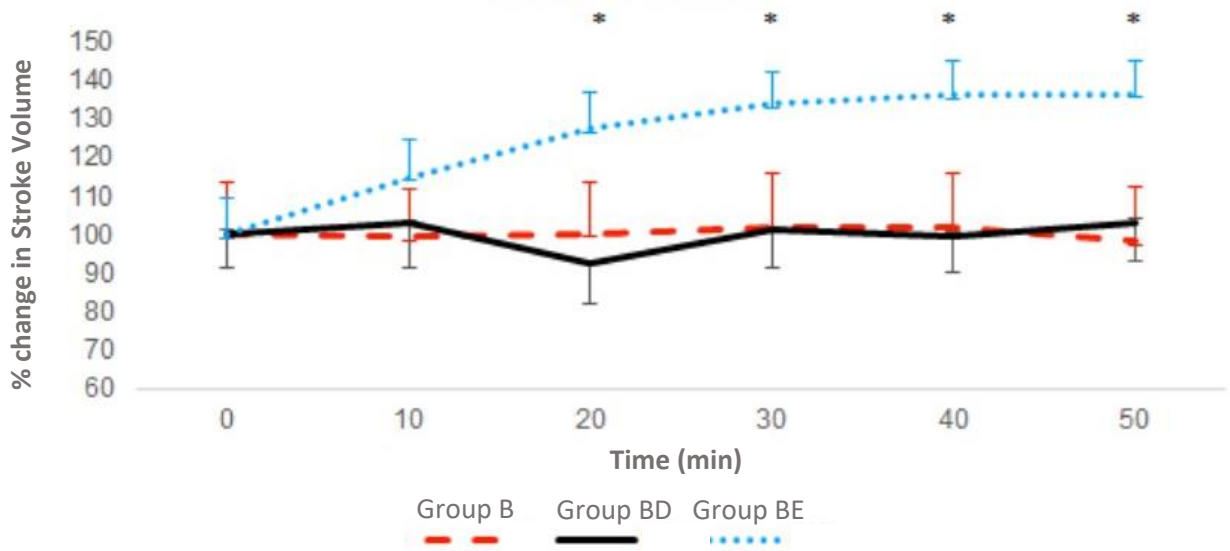


**Figure 2.** Percentage change in stroke volume.
Error bars represent standard deviation; Group B: control Bupivacaine group; Group BD: Bupivacaine and Dexmedetomidine group; Group BE: Bupivacaine and Epinephrine group; *: significance with Group BE.

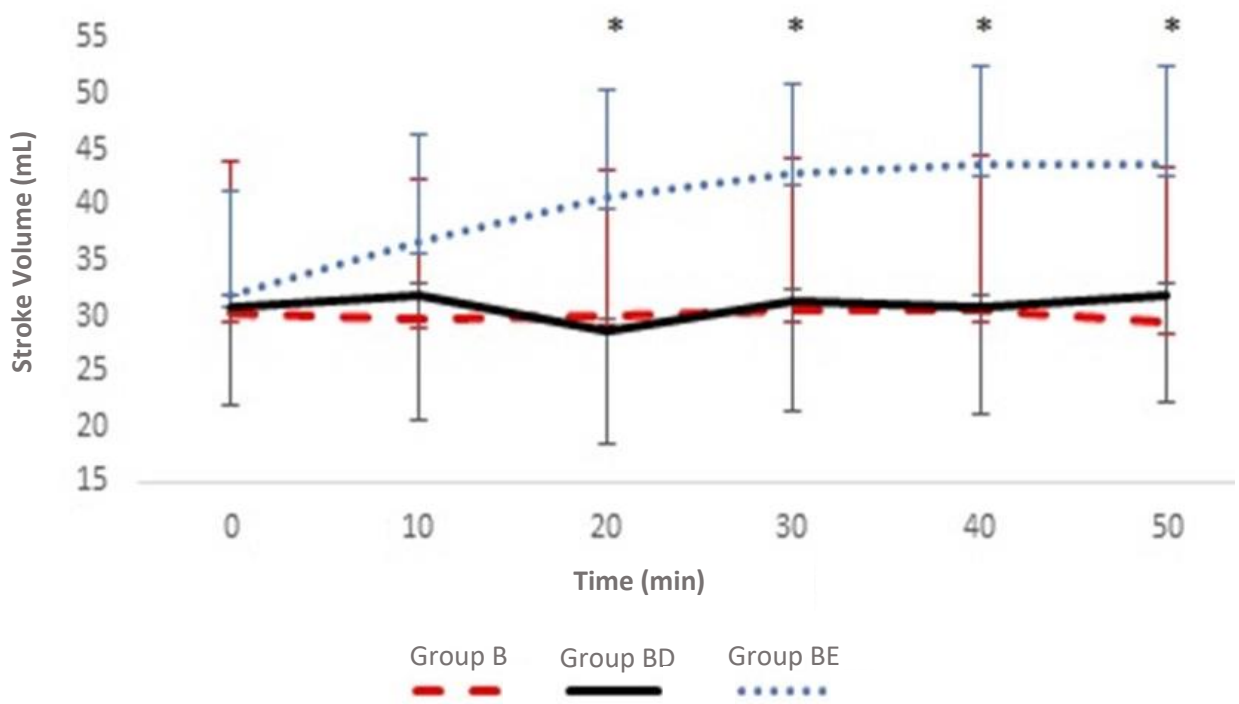


**Figure 3.** Stroke volume (ml).
Error bars represent standard deviation; Group B: control Bupivacaine group; Group BD: Bupivacaine and Dexmedetomidine group; Group BE: Bupivacaine and Epinephrine group; *: significance with the BE group.

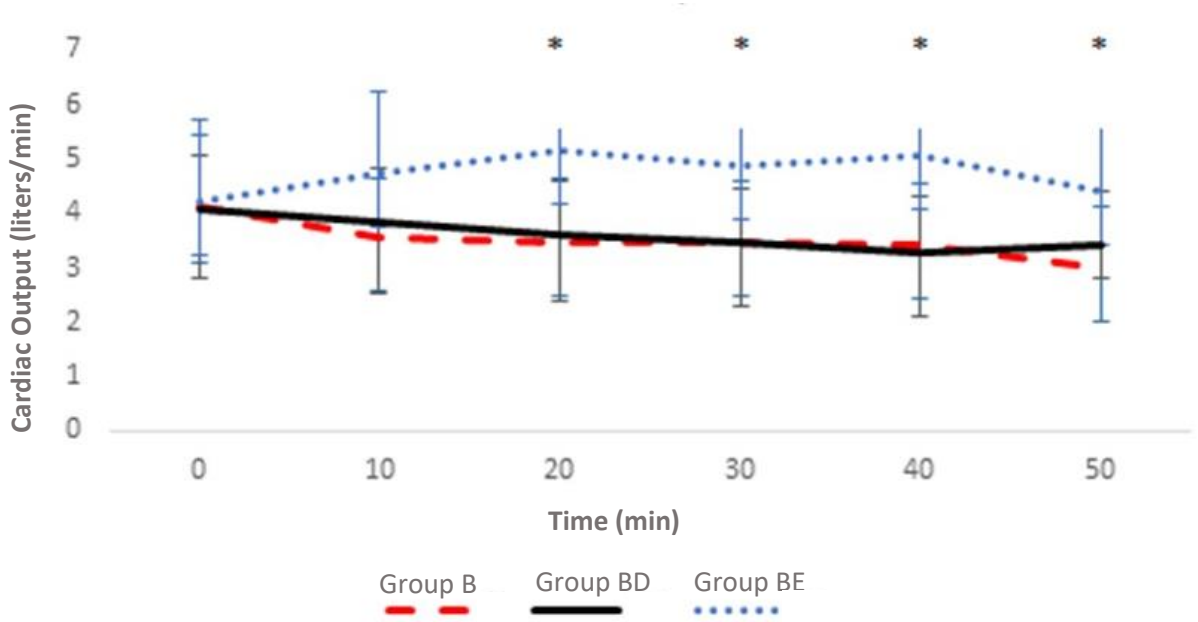


**Figure 4.** Cardiac output (liters/min).
Error bars represent standard deviation; Group B: control Bupivacaine group: Group BD: Bupivacaine and Dexmedetomidine group; Group BE: Bupivacaine and Epinephrine group; *: significance with the BE group.

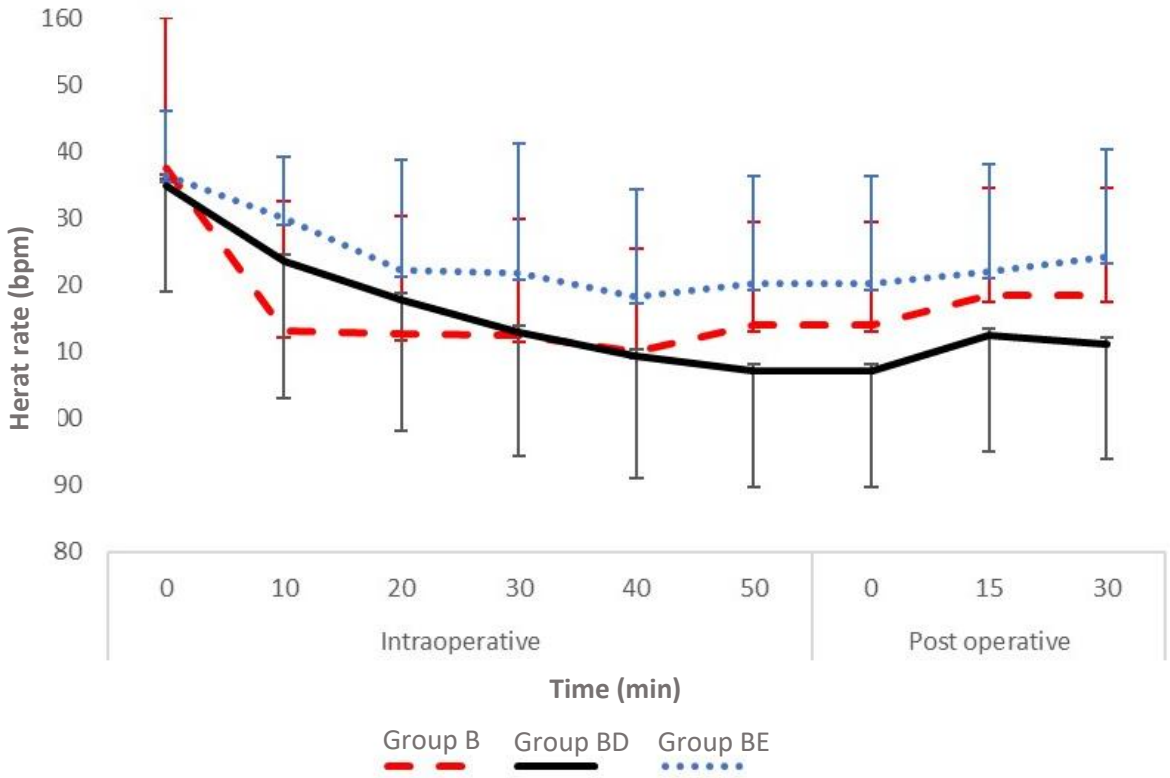


**Figure 5.** Heart rate (beats/minute).
Error bars represent standard deviation; Group B: control Bupivacaine group; Group BD: Bupivacaine and Dexmedetomidine group; Group BE: Bupivacaine and Epinephrine group.

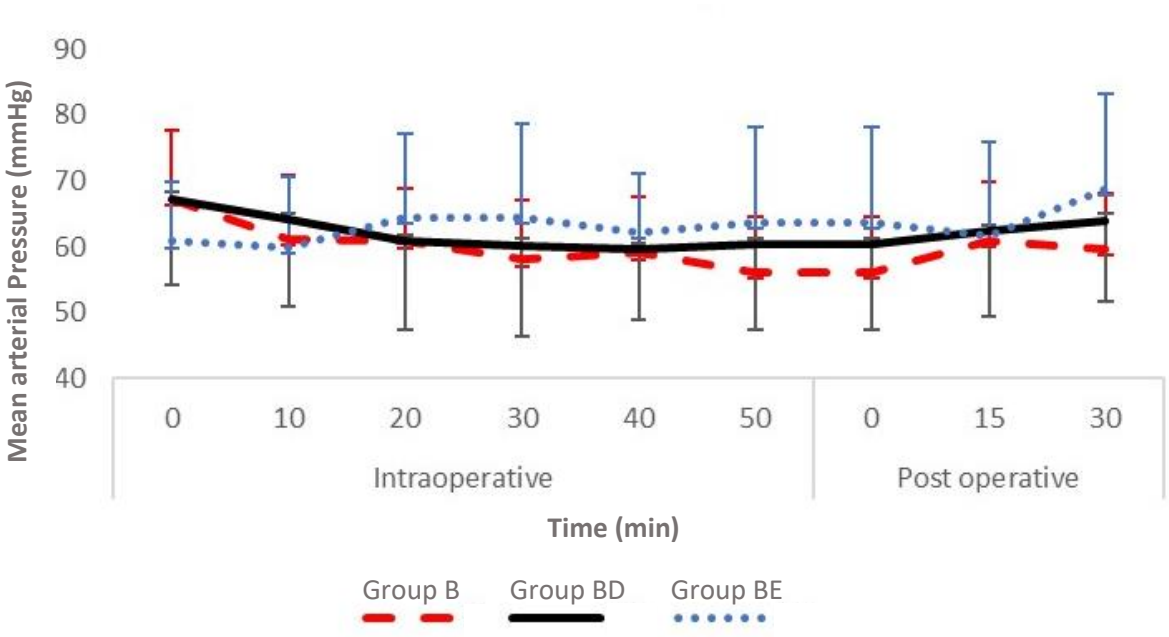


**Figure 6.** Mean blood pressure (mmHg)
Error bars represent standard deviation; Group B: control Bupivacaine group; Group BD: Bupivacaine and Dexmedetomidine group; Group BE: Bupivacaine and Epinephrine group.

**Table 2.** Pain profile, rescue analgesia given, and duration of analgesia among the three groups.

| | | Group B (n = 13) | Group BD (n = 13) | Group BE (n = 13) | P-value |
|---|---|---|---|---|---|
| **CHEOPS score** | **T0** | 4 (4 - 4) | 4 (4 - 4) | 4 (4 - 4) | 1 |
| | **T1** | 4 (4 - 4) | 4 (4 - 4) | 4 (4 - 4) | 1 |
| | **T2** | 6 (6 - 7) | 4 (4 - 5) | 6 (6 - 7) | <0.001<br>P1 <0.001<br>P2 <0.001<br>P3 <0.001 |
| | **T3** | 7 (6 - 8) | 6 (4-6) | 7 (6-8) | 0.016<br>P1 = 0.031<br>P2 <0.001<br>P3 = 0.031 |
| **Patients eho required rescue dose** | | 10 (77%) | 3 (32%) | 9 (69%) | 0.011<br>P1 = 0.019<br>P2 = 1<br>P3 = 0.049 |
| **Rescue dose of paracetamol (mg)** | | 188 ± 160 | 76 ± 161 | 166 ± 186 | 0.218 |
| **Duration of analgesia (hours)** | | 7.1 ± 1.6 | 8 ± 0 | 6.88 ± 1.65 | 0.576 |

Data are presented as median (quartiles), mean ± standard deviation, or count (percentage); Group B: control Bupivacaine group; Group BD: Bupivacaine and Dexmedetomidine group; Group BE: Bupivacaine and Epinephrine group; T0: 2-hours postoperatively; T1: 4-hours postoperatively; T2: 6-hours postoperatively; T3: 12-hours postoperatively.

**Discussion**

To our knowledge, this study is the first to examine the effect of local anesthetic with dexmedetomidine in caudal anesthesia and compare it with the effect of local anesthetic with and without epinephrine, using a noninvasive continuous CO monitor in pediatric patients. In our study, we found that the addition of epinephrine to local anesthetic in the caudal space creates a small but appreciable increase in SV and CO compared with local anesthetic alone; however, no change was found in HR or blood pressure.

Previous research has shown that when epinephrine is added to local anesthetic during caudal anesthesia, there is an observed rise in cardiac output (CO) as measured by transesophageal echocardiography[9] and electrical cardiometry,[10] compared to using only local anesthetic. Raux et al.[9] and Lui et al.[10] showed that the presence of epinephrine in caudal anesthesia using electrical cardiometry resulted in increased CO and inotropy. Similarly, Lui et al. reported similar results with caudal epinephrine when using EC.

Epinephrine is known to activate both alpha and beta-adrenergic receptors.[11] When alpha adrenergic receptors are stimulated, which are found in all blood vessels, it causes vasoconstriction leading to increased peripheral resistance and venous return to the heart.[12] On the other hand, stimulation of beta-adrenergic receptors, which are present in the heart, skeletal muscles, blood vessels, and certain arteries, causes vasodilation and a decrease in peripheral resistance.[12, 13] This results in increased stroke volume, heart rate, and cardiac output. The overall effect of epinephrine depends on which receptor system is predominantly activated, which is influenced by the concentration of epinephrine in the plasma.[13] Low concentrations of epinephrine primarily stimulate beta-adrenergic receptors, which are more sensitive to lower concentrations compared to alpha adrenergic receptors in arterial vessels.[14] When beta-adrenergic receptors are predominantly stimulated, the increase in cardiac output is counterbalanced by a decrease in peripheral resistance, leading to either no change or a slight decrease in mean arterial pressure. [13]

Previous studies have shown that there is a connection between the injection of epinephrine into the epidural space and its effects on the body.[15-17] Bonica et al.[15]

conducted a study with 19 healthy male volunteers, aged 21 to 42 years, and found that when a local anesthetic solution containing epinephrine was injected into the peridural space, the absorption of epinephrine was slow due to its local vasoconstrictor action. As a result, the levels of epinephrine in the blood primarily stimulated beta-adrenergic receptors. Ramanathan et al. [17] conducted a study with 38 healthy women in labor and found that using epinephrine with bupivacaine in epidural anesthesia for cesarean delivery increased the concentration of epinephrine in maternal venous plasma by about four times compared to using plain bupivacaine.

Steinbrook et al. [18] conducted a study on the impact of adding epinephrine to lidocaine for epidural anesthesia in 12 healthy adults who were undergoing knee surgery. They found that at 20 minutes after the start of epidural anesthesia, the group receiving lidocaine and epinephrine experienced an increase in cardiac index and total body carbon dioxide production compared to the group receiving plain lidocaine. These physiological effects observed in adults are like what we have found in children. It is likely that injecting epinephrine into the caudal space results in low systemic concentrations, primarily activating beta-adrenergic receptors, leading to increased inotropy and carbon monoxide levels in pediatric patients. However, there is currently no available data on the pharmacokinetics and plasma levels of epinephrine after caudal injection in existing literature.

To the best of our knowledge, this study is the first to evaluate the effect of dexmedetomidine in epidural space on CO and SV. In our study, we found that the addition of dexmedetomidine to local anesthetic did not affect the SV or CO. In addition, no changes in heart rate or blood pressure were noted compared to the control group. This is important as the addition of dexmedetomidine to local anesthetics in caudal anesthesia is a frequent practice. In pediatric patients, both intrathecal and epidural dexmedetomidine have been found to have analgesic properties that can prolong the effects of local anesthetics without causing nerve damage. [5]

The current study also examined the effectiveness of dexmedetomidine as an analgesic and found that the group receiving dexmedetomidine had a significant decrease in pain scores compared to the other two groups. Although the dosage and duration of analgesia were similar between all three groups, fewer patients in the

dexmedetomidine group required additional pain relief.

These findings are consistent with a previous study by El-Feky et al.,[19] which also showed a decrease in pain scores and a reduced need for analgesia in patients receiving dexmedetomidine. Other studies[20-22] have also investigated the use of dexmedetomidine as an adjuvant for caudal anesthesia and found that it significantly reduced pain scores at various time points after surgery compared to those who only received plain bupivacaine.

*Limitation*

Our study has several limitations. First, we could detect a small but appreciable increase in SV and CO but could not detect a significant change in HR and blood pressure. This may need a future larger sample size. In addition, we were also limited by the low number of blood pressure readings within the time range examined, as the blood pressure is typically measured every five not ten minutes.

**Conclusion**

In conclusion, this study provides evidence that the use of epinephrine in caudal anesthesia may produce alterations in SV and CO in children, while dexmedetomidine does not affect SV or CO. Our data collected using a noninvasive continuous monitor seems consistent with and provides additional clarity to previous findings using transesophageal echocardiography.

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None

**Conflict of interest:**

The authors declare no conflict of interest.

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