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ORIGINAL RESEARCH PEDIATRIC ANESTHESIA

Caudal epidural morphine versus intravenous morphine for postoperative analgesia in pediatric cardiac surgery

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Abstract

Background & objective: Traditionally, analgesia after heart surgery is obtained with the use of intravenous opioids (particularly morphine). Continuous infusion of narcotic analgesics results in a more constant level of analgesia, but slow accumulation may cause excessive sedation. The caudal epidural narcotics, alone or with local anesthetics have been advocated following lower abdominal and thoracic surgery in children. We compared the analgesic effect and safety of caudal epidural morphine (CEM) after heart surgery with intravenous morphine infusion.

Methodology: Sixty children, aged 6 months to 5 y, undergoing elective cardiac surgery under general anesthesia were enrolled in the study. The patients were randomly allocated to one of the two groups to receive either 0.06 mg/kg CEM at induction of anesthesia (study group or CEM group) or postoperative morphine infusion at a rate of 0.025 mg/kg/h intravenously (control group or PIVM group). Postoperative pain scores were assessed according to the COMFORT behavior scale. Two patients were excluded from the study after randomization and 58 patients completed the study.

Results: Time from pediatric intensive care unit (PICU) admission to the need of intravenous morphine boluses was significantly longer in the CEM group compared with the control group (16-20 h vs 38 min; $P < 0.0001$). In CEM group, 68.97% of patients did not require additional morphine and the total intravenous morphine consumption over the 48 h postoperatively was lower ($P < 0.0001$). Moreover, the use of CEM resulted in earlier extubation and earlier discharge from the PICU ($P = 0.011$). Over-sedation was recorded in the control group on the first postoperative day. The incidence of adverse events was low in both groups. Respiratory depression was not seen in CEM group patients.

Conclusion: A single dose of morphine 0.06 mg/kg in caudal epidural, preoperatively in pediatric cardiac surgery, had a significant intravenous morphine sparing effect as compared to a postoperative morphine infusion at a rate of 0.025 mg/kg/h, and was associated with a low incidence of adverse events after pediatric cardiac surgery. Effective analgesia was achieved for 16-20 h after surgery.

Key words: Caudal epidural morphine; COMFORT behavior scale; Opioid–related adverse events; Pediatric cardiac surgery; Analgesia, Postoperative

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1. Introduction

Traditionally, analgesia after heart surgery has been obtained with the use of intravenous opioids (particularly morphine).[1,2] Due to various factors, acute pain in infants and children still remains undertreated, despite progress in perioperative analgesia in the previous few decades.[3] Intense pain without adequate analgesia will not only cause unacceptable sympathetic response at the time of

intervention, it may be associated with poor quality of recovery and long-lasting pain memory and even behavioral disorders.[4,5] Unfortunately, pain intensity after cardiac surgery is often underestimated and undertreated.[2,6]

Continuous intravenous infusion of morphine results in a more constant level of analgesia but slow accumulation may cause excessive sedation, which needs to be monitored.[7] The safety and efficacy of caudal epidural morphine (CEM) administration following lower abdominal and thoracic surgery has been studied by various authors.[8-11]

This randomized controlled trial compared CEM with conventional intravenous infusion of morphine for pain control after cardiac surgery in pediatric population. The hypothesis was that CEM would be associated with less morphine consumption over the first 48 h after surgery. Secondary outcomes included time to first analgesic request, pain scores, adverse opioid reactions, and the time period to discharge.

2. Methodology

This prospective, randomized, comparative pilot study was carried out in the Cardiovascular Anesthesia Department at Hue Central Hospital, Vietnam, from February 2016 to October 2017.

Institutional review board approval was obtained from Hue Central Hospital's Ethics Committee and the University Medicine of Greifswald. Parental informed consent was also secured. A total of 60 pediatric patients scheduled for open heart surgery were randomly assigned to one of the two groups; the control group (PIVM group) to receive intravenous infusion of morphine for pain control after cardiac surgery, or to the study group (CEM group) to receive a preoperative caudal injection of preservative free morphine, as described below. There were 30 patients in each group.

The patients were between 6 months to 5 y of age, scheduled to undergo open heart surgery such as closure of atrial septal defect (ASD) or ventricular septal defect (VSD) under cardiopulmonary bypass (CPB). Exclusion criteria included emergency cardiac surgery or re-sternotomy, parental refusal, previous cardiac surgery, hemodynamic instability, intraoperative deep hypothermia, skin or soft tissue infection, anticoagulant therapy, platelet counts less than 100×10^3 / μL, bleeding diathesis, abnormalities of the sacrum or vertebral column. Patients perioperatively treated with extra corporeal membrane oxygenation or given intravenous morphine without using the COMFORT behavior scale (CBS) for analgesia assessment were also excluded.

Anesthesia was induced with midazolam 0.3 mg/kg, and maintained with rocuronium 0.6 mg/kg and sevoflurane 1.5%. In both groups, patients received a total of 0.005 mg/kg fentanyl in the operating room divided into three doses, e.g., 0.002 mg/kg at induction, 0.002 mg/kg before sternotomy, and 0.001 mg/kg before CPB. If required, fentanyl 0.001 mg/kg was supplemented. After sternotomy and placement of perfusion cannulae, heparin 3 mg/kg was administered intravenously.

After induction of anesthesia, intubation of the trachea and placement of central venous and arterial catheters, patients in the CEM group received 0.06 mg/kg of preservative-free morphine diluted in 0.5 mL/kg saline via caudal epidural space with a 20 or 22G catheter (Vasofix Braunüle, B.Braun®) in the lateral position. For patients randomized to receive conventional postoperative intravenous morphine (control group), a bolus dose of 0.05 mg/kg morphine was given postoperatively followed by a continuous infusion of 0.025 mg/kg/h of morphine, when CBS ≥ 17. If the patient was still uncomfortable after 1 h of continuous morphine infusion, another bolus dose of 0.05 mg/kg was administered.

Postoperatively, all patients were transferred to PICU for ventilation, continuous monitoring of vital signs and pain assessment.

The study protocol covered the first 72 h after surgery. Pain was hourly evaluated using the CBS. The CBS consists of six behavioral items: alertness, calmness, respiratory response (for ventilated children) or crying (for spontaneously breathing children), body movements, facial tension and muscle tone. Each item has five response alternatives, rated 1 to 5, describing the different intensities of the behavior in question. Summating the six ratings leads to a total score ranging from 6 to 30.[12-14]

Postoperatively, all patients received oral acetaminophen (15 mg/kg; maximum 650 mg) every 6 h. Rescue morphine bolus of 0.05 mg/kg was administered intravenously when the CBS scores indicated that the patient was in pain (CBS ≥ 17).

Patient's demographic data, type of surgery, anesthetic drug doses, time to first postoperative supplemental morphine administration and analgesic doses as well as opioid related adverse events (e.g., respiratory depression, nausea and vomiting, pruritus) were recorded.

CBS score was recorded by registered nurses 16 times per patient in both groups (at 0h, 0.5h, 1h, 2h, 4h, 8h, 12h, 16h, 20h, 24h, 32h, 40h, 48h, 56h, 64h and at 72h postoperatively). Pain and sedation were simultaneously evaluated using the same scale.[15-17] Based on these scores, patients were classified as 'excessively sedated' (over-sedation, score between 6 and 10), 'sedated' (adequately sedated, score between 11 and 22) and

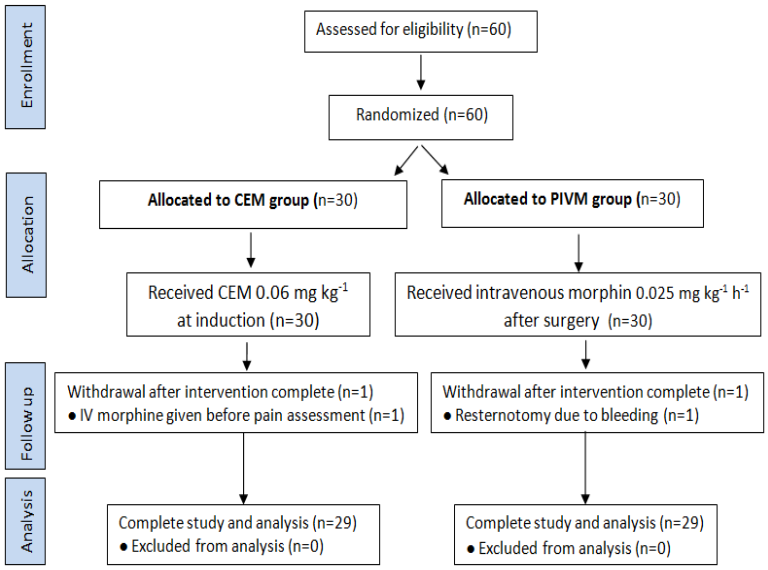

Figure 1: CONSORT flow diagram

'insufficiently sedated' (under-sedation, higher than 23).[15]

Delayed passage of stool as well as lack of bowel sounds were considered as signs of temporary impairment in gastrointestinal motility.[18,19] Abdominal auscultation was carried out every 15 min postoperatively. Time from PICU administration to first passage of stool was noted by the parents or nursing staff.

Of the 60 patients enrolled, two patients were excluded; one patient in the control group because of his emergency sternotomy within a few hours of PICU admission due to severe bleeding, and the other one in the CEM group, withdrawn because IV morphine was started on arrival in the PICU without using the CBS. Fifty-eight patients completed the final analysis.

Statistical analysis

The SPSS for Windows 20.0 software program and Excel (Microsoft Cooperation, Redmond, WA, USA) were used for statistical analysis. Data are represented as mean ± SD. A χ^2 test was used for categorical variables. The Student's t-test or two-tailed Fisher's exact test were used for continuous normally distributed data and the Mann-Whitney U test for continuous abnormally distributed data. $P < 0.05$ was considered statistically significant. The mean time of first intravenous morphine and of the recovery of gastrointestinal motility from PICU admission were analyzed using Kaplan-Meier estimations and tested by the log-rank test between the two groups.

3. Results

A total of 29 patients in each group were studied (Figure 1). There were no significant differences between groups with respect to their demographic data, clinical characteristics and surgical time. Patients in both groups received similar anesthetic doses except for a higher intraoperative dosage of fentanyl in the control group (10 µg/kg vs 5 µg/kg; $P < 0.0001$). There were no relevant intraoperative hemodynamic changes (Table 1).

The mean time to the first intravenous morphine administration after surgery was significantly longer ($P < 0.0001$) in the CEM group compared to PIVM group, 16-20 h vs 38 min respectively (Figure 2).

In terms of pain scores, a higher difference was found in PIVM group patients versus those in CEM group (19.9 vs 12.4; $P < 0.001$) after the first 30 min (Figure 3). Most patients in both groups experienced no pain (CBS < 17) after 2 h. However, over-sedation was observed in patients in PIVM group from 4 to 16 h postoperatively (CBS ≤ 10). At the 48-h time point, the pain scores of each group began to trend back together.

Regarding postoperative analgesia, there were differences among the groups with respect to morphine supplementation. Mean total doses of intravenous morphine were higher in control group ($P < 0.05$). The postoperative use of acetaminophen was not different

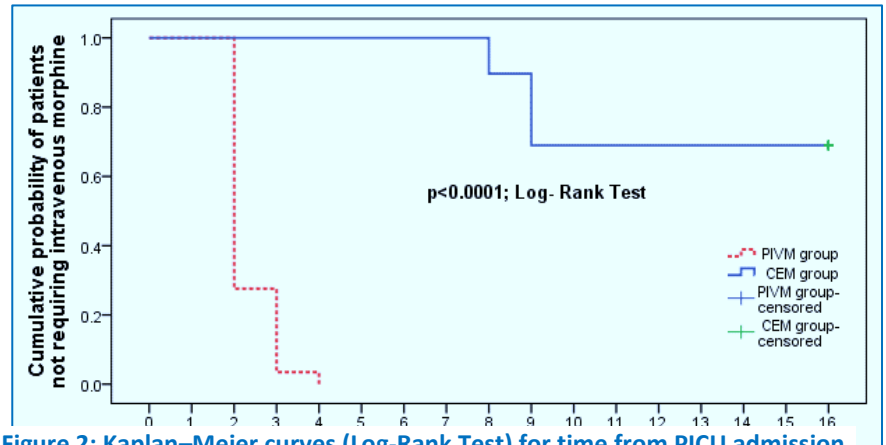

Figure 2: Kaplan–Meier curves (Log-Rank Test) for time from PICU admission to first rescue intravenous morphine administration.

Table 1: Demographic, clinical characteristics and intraoperative data of patients.

Demographic and clinical characteristics	PIVM group (n = 29)	CEM group (n = 29)	P value
Gender (female/male)	10/19	16/13	0.065#
Age	1.41 ± 0.93	1.34 ± 0.84	0.779
Height	76.30 ± 14.308	71.52 ± 10.305	0.150
Weight	9.397 ± 3.493	8.086 ± 2.264	0.096
Ejection Fraction (%)	65.10 ± 3.277	64.45 ± 2.443	0.392
Systolic pulmonary artery pressure (mmHg)	35.69 ± 13.210	38.28 ± 13.646	0.466
Atrial / Ventricular septal defect	6 / 23	5 / 24	0.738#
Anesthetics			
Midazolam (mg)	3.36 ± 1.37	2.67 ± 1.42	0.07
Rocuronium (mg)	14.40 ± 9.34	13.56 ± 6.37	0.69
Fentanyl (mcg)	100.86 ± 47.53	41.00 ± 11.94	0.0001#
Fentanyl (mcg/kg)	10.32 ± 2.77	5.07 ± 0.43	0.0001#
Intra-operative Data:			
Lowest temperature °C	34.07 ± 1.11	33.50 ± 1.61	0.12
Cardiopulmonary-bypass time (min)	49.30 ± 14.39	53.13 ± 16.10	0.33
Cross- clamp time (min)	26.47 ± 10.65	30.83 ± 13.67	0.17
Operation time (min)	161.21 ± 21.41	151.55 ± 19.09	0.075
Heart Rate (bpm)			
After induction	118.22 ± 14.48	117.07 ± 14.37	0.75
After skin incision	116.53 ± 12.79	115.97 ± 13.41	0.90
After sternotomy	115.71 ± 14.99	116.48 ± 11.92	0.84
20 min after CPB	119.38 ± 13.04	117.31 ± 13.79	0.65
After sternal closure	122.17 ± 14.42	119.24 ± 10.98	0.41
Mean Blood Pressure (mmHg)			
After induction	65.56 ± 7.79	63.97 ± 5.86	0.37
After skin incision	56.66 ± 7.01	54.93 ± 6.19	0.26
After sternotomy	51.90 ± 6.36	51.24 ± 5.23	0.56
20 min after CPB	60.62 ± 6.01	57.76 ± 6.68	0.06
After sternal closure	63.03 ± 6.47	61.10 ± 4.08	0.11

Data are expressed as mean ± SD or number of patients # Mann- Whitney U Test
CEM: caudal epidural morphine; PIVM: conventional postoperative intravenous morphine

between the groups. Of the 29 patients who received CEM at induction of anesthesia, 20 (68.97%) did not require any additional morphine in the PICU (Table 2). Time to tracheal extubation was shorter for patients in the study group versus control group (6.3 h vs 10.8 h; P < 0.05) (Table 3). The CEM group was associated with shorter ICU length of stay (3.34 vs 4.03 days; P = 0.011). With respect to postoperative hospital length of stay no difference between groups was found (11.72 vs 13.52; P = 0.224).

The time to return of bowel sounds was 29.5 ± 15.3 min for caudal group and 54.9 ± 25.8 min for control group, and to first defecation 1.44 ± 0.14 and 3.12 ± 0.17 days, respectively (P < 0.05; Table 3).

The incidence of opioid adverse events was very low in both groups. Vomiting occurred more frequently in the control group (13.79% vs 3.45%; P = 0.039) (Table 3). Respiratory depression was seen in one 5-year-old patient in the control group with an arterial PCO_2 55 mmHg after extubation. None of the patients needed to be reintubated. One patient in the study group had itching.

Table 2: Postoperative cumulative analgesic consumption

Variables	PIVM group (n = 29)	CEM group (n = 29)	P value
Number of patients not administrated postoperative intravenous morphine	0 (0 %)	20 (68.97 %)	< 0.0001
Morphine Consumption (mg)			
0-4 h	1.43 ± 0.67	0	< 0.0001
0-12 h	3.74 ± 1.81	0	< 0.0001
0-24 h	6.00 ± 2.94	0.18 ± 0.29	< 0.0001
0-48 h	6.60 ± 3.76	0.25 ± 0.37	< 0.0001
Paracetamol Consumption (mg)			
0 – 24 h	461.55 ± 232.28	450.34 ± 127.77	0.821
0 – 48 h	963.62 ± 459.23	920.00 ± 251.50	0.655
0 – 72 h	1486.03 ± 712.11	1393.10 ± 378.15	0.537

Values are presented mean ± standard deviation
CEM: caudal epidural morphine; PIVM: conventional postoperative intravenous morphine

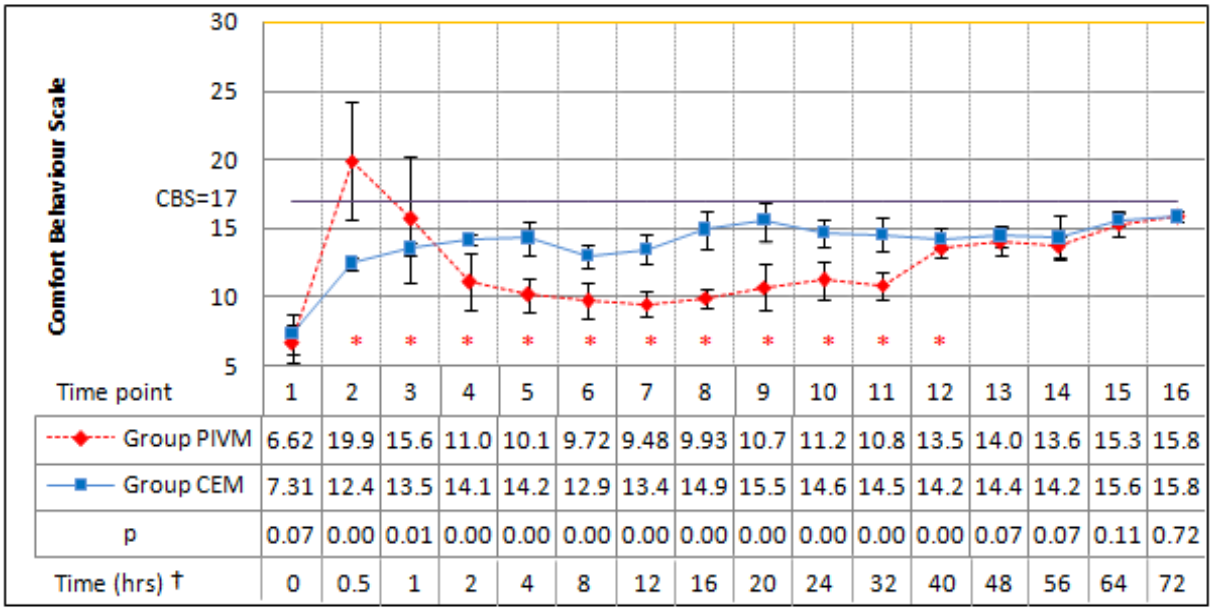

Figure 3: Kaplan–Meier curves (Log-Rank Test) for time from PICU admission to first rescue intravenous morphine administration.

4. Discussion

To improve postoperative pain management after pediatric cardiac surgery we compared two analgesic regimens. Both regimens provided good pain relief in most of the children postoperatively. However, single-shot CEM was superior to routine continuous infusion of morphine after surgery when evaluated by pain scores (CBS) and supplemental morphine. We found that the time to the first postoperative intravenous morphine dose was significantly longer in the CEM group. A CEM dose of 0.06 mg/kg had a significant sparing effect parenteral morphine use over the first 16-20 postoperative hours. Although caudal epidural morphine did not provide total pain relief following surgery, total morphine requirements were significantly reduced for 48 h. Supplementary intravenous morphine was also not required in the majority of the patients (68.97 %) receiving CEM. More importantly, patients in control group appeared excessively sedated on the first postoperative day. Additionally, the use of CEM resulted in earlier extubation and earlier discharge from the PICU. Therefore, administration of CEM seems to be a

Table 3: Other postoperative Data

Postoperative Data	PIVM group (n = 29)	CEM group (n = 29)	P value
Time to extubation (h)	10.8	6.3	0.006
Discharge from ICU (days)	4.03 ± 1.21	3.34 ± 0.72	0.011
Length of postoperative hospital stay (days)	13.52 ± 7.29	11.72 ± 2.76	0.224
Opioid-related adverse events			
Vomiting	4 (13.79%)	1(03.45%)	0.039
Pruritus	0 (0%)	1(03.45%)	0.05 **
Respiratory depression	1 (03.45%)	0 (0%)	0.05 **
Recovery of gastrointestinal motility			
Time to return of bowel sound (min)	54.9 ± 25.8	29.5 ± 15.3	0.0001
Time to first passage of stool (days)	3.12 ± 0.17	1.44 ± 0.14	0.0001

*Data are expressed as mean ± SD ; **Fisher's exact test; (.) in percent*
CEM: caudal epidural morphine; PIVM: conventional postoperative intravenous morphine

suitable means of postoperative pain management for children undergoing cardiac surgery.

Intubated and electively ventilated children are difficult to assess with respect to postoperative pain.[20] Currently there are no clinically useful or practical scores for the estimation of pain in these patients.[21] There is limited literature on pain assessment in the PICU; the available studies concern the validation of instruments such as the COMFORT scale,[12,22] the COMFORT behavior scale,[13,14,23,24] the FLACC scale[25-27] and the Multidimensional Assessment Pain Scale (MAPS).[15,28,29] The well-established, validated COMFORT behavior scale (CBS) is especially recommended in critically ill children. The CBS is one of the standardized sedation assessment tools with proven validity, reliability and clinical utility. In 2016 the European Society of Pediatric and Neonatal Intensive Care (ESPNIC) has recommended that all children in the PICU be monitored for pain and sedation by using the CBS (grade of recommendation - A).[15] This is why the CBS was chosen for pain and sedation assessment in this study.

Early extubation of the trachea in pediatric patients following cardiac surgery is not a new approach.[30-33] It was a common practice in the 1960s and 1970s, based on the patient population and limited availability of drugs and ventilator technology.[34] Stuth and colleagues conducted a randomized control trial to compare the effect of high-dose caudal morphine and intravenous morphine on early extubation and postoperative analgesic requirements for stages 2 and 3 in single ventricle palliation. They concluded that CEM not only delayed the need for rescue analgesia in stage 3 patients, but also made early extubation feasible.[35] We observed an intraoperative dosing of fentanyl and the total intravenous morphine consumption over 48 postoperative hours were significant lower in the CEM group ($P < 0.0001$). The administration of caudal morphine to patients prior to cardiac surgery, by producing intense analgesia in the immediate postoperative period, may therefore facilitate early extubation and beneficially affect outcome. Patients in the CEM group spent less time in the ICU, but length of time spent in the hospital was similar in both.

Side effects were infrequent in both groups. Respiratory depression, the most notorious side effect of CEM was first reported by Krane and co-workers, in a child after a 0.10 mg/kg caudal dose of epidural morphine.[36] Baduni and colleagues also observed postoperative respiratory depression in three patients who had received 0.07 mg/kg of caudal epidural morphine, but they all responded to supplemental oxygen supplementation only and no naloxone was required.[37] Valley and Bailey also reported respiratory depression in 11 children receiving caudal epidural morphine (0.07 mg/kg) at the end of surgery and involving a caudal catheter with intraoperative caudal local anesthetics or receiving intraoperative supplemental intravenous opioids. Ten of them were younger than 1 year.[38]

The CEM dose 0.06 mg/kg was chosen with the purpose of providing adequate analgesia at a less risk of respiratory depression. None of the patients showed respiratory depression despite the young average age of 1.34 years at this dose, in contrast to other studies with the same dose.[11]

The incidence of other adverse effects in CEM group was low; 3.45% patients had vomiting as compared to 13.79 % in the PIVM group. This could be due to less generous administration of supplemental opioids in the CEM group. Though pruritus is not life-threatening, it

can severely impact recovery quality in patients receiving opioids. Only one patient in the CEM group had itching.

Co-administration of epidural morphine and local anesthetic is a common and effective method of postoperative pain control and an important component of the ERAS protocol.[39,40] Although it is well established that postoperative epidural morphine reduces gastrointestinal motility,[41-43] we illustrated the beneficial effect of CEM on recovery of gastrointestinal motility when used for pain control after pediatric cardiac surgery. Thus, the present study has confirmed that CEM confers the benefits of shorter ICU length of stay.

5. Limitations

Limitations to the study include the small sample size, which may explain the lack of statistical significance in secondary outcomes. Therefore, caution should be taken when interpreting these results. Future prospective, blinded, randomized, controlled multicenter trials are needed to truly assess the beneficial effects of caudal epidural morphine in children undergoing cardiac surgery. This study only selected patients with simple heart defects (ASD, VSD) but in reality caudal epidural injections were placed for more complex open heart cases and had some benefits in those cases not addressed in this study. Moreover, to prove the efficacy of caudal morphine, we could have compared it with other new additives. Another limitation included the inability to assess urinary retention, one of adverse side effects of using morphine, as many of our patients were catheterized.

6. Conclusion

In conclusion, the preoperative single-shot caudal epidural morphine 0.06 mg/kg in 0.5 mL/kg saline solution is suitable for achieving postoperative pain relief lasting for 16-20 h in children with uncomplicated open heart surgery with few side effects, notably without respiratory depression. However, it is necessary to carry out more prospective studies in order to draw definitive conclusions.

7. Data availability

The numerical data generated in the course of this study is available with the authors.

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9. Conflict of interests

The authors declare that they have no conflict of interest.

10. Authors' contribution

TDN: study design, patient recruitment, acquisition of data, or analysis and interpretation of data; drafting the article or revising it critically for important intellectual content; final approval; agreement to be accountable for all aspects of the work.

DN: Patient recruitment, acquisition of data, final approval.

NHP and TJ: language correction, work's critical revision for important intellectual content; final approval; agreement to be accountable for all aspects of the work.

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