Original Article

Enhanced Recovery and Early Extubation after Pediatric Cardiac Surgery Using Single-Dose Intravenous Methadone

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Abstract

Background/Aims: Methadone may offer advantages in facilitating early extubation after cardiac surgery, but very few data are available in the pediatric population. **Setting/Design:** Community tertiary children's hospital, retrospective case series. **Materials and Methods:** We performed a retrospective analysis of all pediatric cardiac surgical patients for whom early extubation was intended. A multimodal analgesic regimen was used for all patients, consisting of methadone (0.2–0.3 mg/kg), ketamine (0.5 mg/kg plus 0.25 mg/kg/h), lidocaine (1 mg/kg plus 1.5 mg/kg/h), acetaminophen (15 mg/kg), and parasternal ropivacaine (0.5 mL/kg of 0.2%). Outcome variables were collected with descriptive statistics. **Results:** A total of 24 children [median = 7 (interquartile range = 3.75–13.75) years old, 23.7 (14.8–53.4) kg] were included in the study; 22 (92%) had procedures performed on bypass and 11 (46%) involved a reentry sternotomy. Methadone dosing was 0.26 (0.23–0.29) mg/kg. None of the children required intraoperative supplemental opioids; 23 (96%) were extubated in the operating room. The first p_aCO_2 on pediatric intensive care unit admission was 51 (45–58) mmHg. Time to first supplemental opioid administration was 5.1 (3.5–9.5) h. Cumulative total supplemental opioids (in intravenous morphine equivalents) at 24 and 72 h were 0.2 (0.09–0.32) and 0.42 (0.27–0.68) mg/kg. One child required postoperative bilevel positive airway pressure support, but none required reintubation. None had pruritus; three (13%) experienced nausea. **Conclusion:** A methadone-based multimodal regimen facilitated early extubation without appreciable adverse events. Further investigations are needed to confirm efficacy of this regimen and to assess whether the excellent safety profile seen here holds in the hands of multiple providers caring for a larger, more heterogeneous population.

Keywords: *Early extubation, enhanced recovery, enhanced recovery after surgery, ERAS, fast-track extubation, methadone, operating room extubation, pediatric cardiac surgery, pediatric open heart surgery*

Introduction

Postoperative pain in the pediatric cardiac surgical patient is hard to assess and difficult to manage. In general, postoperative pain has been shown to be most intense in the first 24 h following the procedure.[1-3] Many nonmodifiable factors contribute to the pain following cardiac surgery including surgical site incision, sternotomy, cardiac manipulations, and chest tube placement. Inevitably, the patient will experience acute pain that needs to be adequately controlled for optimum recovery outcomes.[4] Adverse consequences to inadequate pain control may include prolonged intubation times, longer hospital stays, substantial exposure to large opioid doses, and overall patient dissatisfaction.

Traditional pain management strategies have used short-acting analgesics postoperatively based on subjective patient pain scales. The obvious shortcoming of this approach is the resulting waxing and waning pain in relation to varying blood levels of the drug and ultimately very brief episodes of high-quality pain control. Repeated boluses of short-acting opiates, whether delivered by nurse administration or patient-controlled analgesia pump, may also carry the disadvantages of risks of respiratory depression and opioid-induced hyperalgesia.

The rationale for the use of methadone as an alternative strategy for analgesia after cardiac surgery is severalfold. One, its long duration of action (24–36 h of efficacy from a single dose) may provide steadier, basal pain control during the

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period of greatest surgical pain.[5,6] Its activity on the N-methyl-D-aspartate (NMDA) receptor has also been implicated as a potential mechanism in explaining studies demonstrating higher quality and more consistent pain control in the postop period after adult cardiac and noncardiac procedures,[6-8] and some evidence supports the belief that acute perioperative NMDA antagonism may reduce the development of chronic pain syndromes.[9] However, very little outcome data exist in the pediatric cardiac surgical population regarding the use of methadone as the primary analgesic agent.

The aim of this small retrospective case series was to assess the efficacy and safety of a multimodal pain regimen centered around single-dose intraoperative intravenous (IV) methadone in pediatric cardiac surgical patients.

Materials and Methods

We performed a retrospective case series analysis of all consecutive cases in which a novel analgesic regimen was used to facilitate early extubation and enhanced recovery after pediatric cardiac surgery. Cases involved all children >6 months of age undergoing surgical interventions with a single anesthesiologist and single surgeon where the likelihood of postoperative hemodynamic instability, ongoing coagulopathy, or bleeding was anticipated to be low and early extubation was planned.

We implemented a novel multimodal analgesic regimen consisting of the components detailed in Table 1. Methadone dosing was 0.2–0.3 mg/kg, rounded to a 0.5- or 1-mg increment for the purposes of minimizing operational difficulties with procedures for controlled substance tracking. Dosing was based on actual body weight except in children whose weight was >75th percentile for height, in which case the 50th percentile weight was used as an estimate of ideal body weight for dosing calculations. No other opioid analgesics were administered in the operating room (OR). Anesthesia was induced with sevoflurane and/or propofol and maintained with sevoflurane (1.0–1.2 times age-adjusted minimum alveolar concentration (MAC); muscle relaxation was achieved with rocuronium prior to incision and reversed with sugammadex prior to emergence based on train-of-four response. Orogastric suctioning was performed and a nasopharyngeal airway was placed prior to emergence in all patients.

Table 1: Analgesic regimen

Agent	Dose	Route	Timing
Methadone	0.2-0.3 mg/kg	Intravenous bolus	Prior to incision
Ketamine	0.5 mg/kg	Intravenous bolus	Prior to incision
Ketamine	0.25 mg/kg/h	Intravenous infusion	From incision to skin closure
Lidocaine	1 mg/kg	Intravenous bolus	Prior to incision
Lidocaine	1.5 mg/kg/h	Intravenous infusion	From incision to skin closure
Acetaminophen	15 mg/kg	Intravenous bolus	Prior to emergence
Ropivacaine (0.2%)	0.5 mL/kg	Parasternal infiltration	Prior to emergence

Dexamethasone (0.15 mg/kg) and ondansetron (0.1 mg/kg) were administered to all patients prior to incision and emergence, respectively, as prophylaxis for postoperative nausea and vomiting. Supplemental postoperative analgesia consisted of scheduled oral acetaminophen and IV ketorolac, plusas-needed IV fentanyl, IV morphine, and/or enteral oxycodone at the discretion of the pediatric cardiologist who assumed care for the patient after intensive care unit (ICU) admission.

Clinical and outcome variables were collected. Children were extubated in the OR and transported immediately to the pediatric intensive care unit (PICU) without any intervening observation period in the OR or postanesthesia care unit, as occurs in some institutions. Postoperative vital signs and arterial blood gas data were obtained within 30 min of arrival in the PICU.

Supplemental postoperative opioids were converted to IV morphine equivalents (fentanyl 33:1, oxycodone 2:1, hydromorphone 4:1). Clinically significant respiratory depression after the initial postoperative handoff was defined as respiratory arrest, respiratory rate <10 (a trigger for rapid response in our institution), need for manual or assisted ventilation, or reintubation. Clinically significant pruritus was defined by the administration of diphenhydramine, hydroxyzine, or nalbuphine. Postoperative nausea was defined by the use of supplemental antiemetics after prophylactic administrations that occurred intraoperatively.

This study received Institutional Review Board approval. Data are reported as median (interquartile range) unless otherwise noted. Statistics were calculated using Microsoft Excel 2016 (Version 1802; Microsoft Co., Redmond, WA, USA).

Results

A total of 24 children [7 (3.75–13.75) years old, 23.7 (14.8–53.4) kg] were included in the study. Fifteen (63%) were male; 22 (92%) had procedures performed on bypass, and 11 (46%) involved a reentry sternotomy. The youngest and smallest patient was 8 months old and weighed 6.2 kg. Four patients (17%) had single-ventricle physiology. Table 2 reports the surgical procedures represented in this cohort. Surgery and cardiopulmonary bypass duration were 222 (192–257) and 94 (65–122) min, respectively. Methadone dosing was 0.26 (0.23–0.29) mg/kg of total body weight.

No intraoperative supplemental opioid administration was required in any child. All but one patient (n = 23, 96%) were extubated in the OR at case end. One patient who

remained intubated did so without a failed extubation attempt; a team decision was made to keep the child intubated because of a concern for ongoing coagulopathy and bleeding after fourth-time sternotomy (Fontan revision and tricuspid valve repair). This patient was extubated without difficulty at approximately 4 h after PICU admission, after the aforementioned concerns proved to be well-managed.

The first recorded respiratory rate after PICU admission was 14 (11–22). The first recorded arterial partial pressure of carbon dioxide (p_aCO_2) was 51 (45–58) mmHg, with 17 (71%) of the patients having a p_aCO_2 greater than 45 mmHg; the distribution of first p_aCO2 readings is shown in Figure 1. One child (4.2%) required rescue noninvasive ventilatory support immediately upon PICU admission because of hypoventilation resulting in moderate hypoxemia (arterial saturation of oxygen 88%–91% on 6 L oxygen delivered through a simple facemask). Support consisted of bilevel positive airway pressure (BiPAP) for approximately 60 min, after which time he transitioned to 2 L of nasal cannula oxygen and had an uneventful subsequent course. None of the children experienced late respiratory depression (after care was handed over to the cardiology team in the ICU and the anesthesiologist left the patient's side). No children required reintubation at any timepoint.

The time to first supplemental opioid administration was 5.1 (3.5–9.5) h, and the distribution of times is shown in Figure 2. Cumulative total supplemental opioid dosing (expressed in IV morphine equivalents) in the first 24 and 72 h postoperatively was 0.20 (0.09–0.32) and 0.42 (0.27–0.68) mg/kg, respectively. No children experienced clinically significant pruritus; three children (13%) experienced postoperative nausea.

Table 2: Distribution of surgical procedures

Surgical procedure	No.
Aortic valve replacement, Ross procedure, or repair of subaortic stenosis	6
Fontan procedure	4
Repair of atrial septal defect, partial anomalous pulmonary venous return, or Warden procedure	3
Pulmonary valve replacement or right ventricle-to-pulmonary artery conduit	2
Repair of ventricular septal defect	2
Atrioventricular canal repair	2
Repair of interrupted aortic arch	1
Repair of vascular ring with diverticulum of Kommerell	1
Pericardiectomy	1
Reimplantation of anomalous coronary artery	1
Epicardial pacemaker revision	1

Discussion

To our knowledge, this is the first report of the routine use of IV methadone as the cornerstone of an analgesic regimen for pediatric cardiac surgery to facilitate early extubation and enhanced recovery. Methadone dosing extrapolated from the adult literature appears to be appropriate in this population, with the important note that we used ideal body weight in heavier patients. We did decrease the dose (0.15 mg/kg) for the lone child whose procedure was performed off-pump, based on the rationale that the effective volume of distribution would be lower without the bypass circuit.

This regimen involving multiple agents as a package appeared effective in facilitating early extubation and enhanced recovery, based on a high success rate of extubation in the OR (96% of children in whom we intended to do so), no occurrence of postoperative reintubation, and indications of adequate analgesia with a long interval to the first need for supplementary analgesic administration. The quantity of supplemental opioids required in this cohort is, in our view, quite modest: a median of 0.2 and 0.42 mg/kg of morphine equivalents in the first 24 and 72 h, respectively. This suggests that methadone is accomplishing the bulk of the basal pain control in the initial postoperative period.

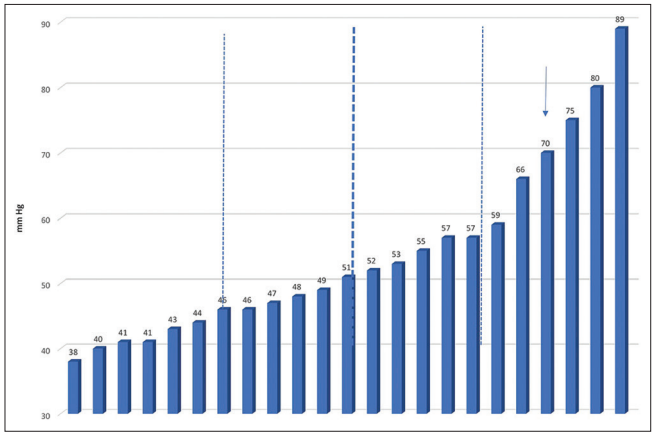

Figure 1: First recorded p_aCO_2 on PICU admission. Heavy dashed line represents median; light dashed line represents interquartile range. Arrow denotes patient who required rescue bilevel positive airway pressure

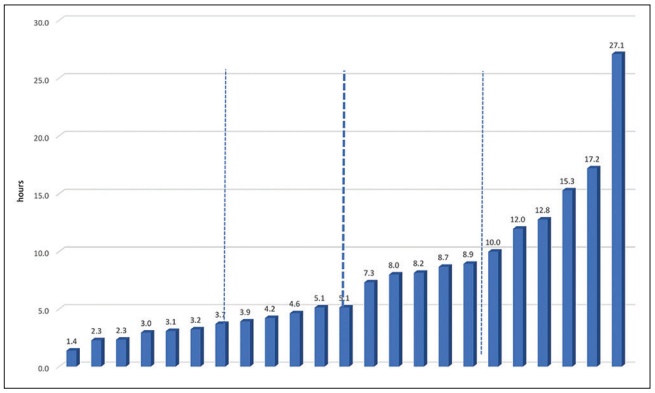

Figure 2: Time in hours from extubation to first supplemental opioid administration. Heavy dashed line represents median; light dashed line represents interquartile range

We had one patient who did not appear appropriate for extubation because of surgical factors; this, according to us, is an appropriate failure rate. If reevaluation of the plan for early extubation at case end does not occasionally result in patients who are not quite ready, we would submit that the team is not starting with a liberal enough set of criteria for patients in whom the intent to extubate in the OR is the starting point.

It is worth highlighting that this regimen was associated, on average, with some bradypnea and hypoventilation resulting in a mild respiratory acidosis (median p_aCO_2 = 51). Considering the suitability of a patient's physiology for this, anticipated transient perturbation is important in deciding to use this early extubation strategy. Single-ventricle (e.g., Fontan) patients may be more sensitive to hypercarbia because of passive pulmonary blood flow and the importance of low pulmonary vascular resistance. In our experience, mild hypercarbia is well-tolerated and the benefit from early negative pressure respiratory physiology is such that on balance, these patients benefit from this approach when possible. We might be reluctant to use this strategy in other populations that are sensitive to increases in pulmonary vascular resistance, for instance, in patients with pulmonary vasodilator-dependent pulmonary hypertension.

Several observations made in passing during the evaluation of this patient cohort are worth discussion. Qualitatively, we can describe the clinical character of most of these extubations as "deep" even though they were performed when end-tidal gas analysis revealed <0.2 MAC of residual inhaled anesthetic. It is our descriptive observation that the post-bypass period in a patient who has received this analgesic regimen appears to involve a comfortably sleeping patient who does not respond to stimuli (e.g., orogastric tube placement and removal, oropharyngeal suctioning, endotracheal tube manipulation, and removal) but has adequate respiratory mechanics. We routinely use nasopharyngeal airways, placed long before extubation, as a strategy to avoid postextubation upper airway obstruction. In the presence of this strategy, no patients required rescue placement of a nasopharyngeal, oropharyngeal, or laryngeal mask airway.

We learned two important cultural or system flaws about our system in the course of this analysis: first, our debriefing regarding the subset of patients where supplementary opioids were administered relatively early in the admission suggested that pain was already well-controlled but that certain nurses were relatively unfamiliar with early extubation and had less well-developed skills surrounding the coping strategies, family involvement, and nonpharmacologic reassurance that is routine to, for instance, postanesthesia care unit nurses. In our institution, ICU patients who are extubated in the OR go to the PACU first, so early extubation in the cardiac population presented a new challenge to PICU nurses. For instance, any spontaneous patient movement was viewed by a subset of nurses as an indication for supplementary fentanyl. Second, we set out to analyze pain scores but found the prevalence of missing or unreliable data (e.g., "baby is sleeping" but pain recorded as 10/10) to be well over 50% of all data points so we did not analyze these data. The reliability of pain scores was higher in teenage patients and seemed most poorly documented and utilized in infants and toddlers, despite the availability of nonverbal pain scales in routine nursing assessment tools. This has led to a focus on more functional assessments of pain control (e.g., whether a child is able to move in an age-appropriate fashion without limitation).

One clear limitation of this study was the nonrandomized design without a control group. A randomized trial design was not feasible in our setting, both because of systems' and family barriers to trial enrollment and because this was already standard of care in our practice and beginning an effort to randomize patient to another analgesic regimen was not felt to be ethical if our clinical judgment deemed it to be inferior. We considered using a historical control group, but this was not viable because this regimen was introduced by a new anesthesiologist on arrival to our institution. Comparisons to others' past practice would have entailed too many confounding variables to be meaningful.

This study will guide our further efforts to improve postoperative analgesia, expediting extubation and enhancing recovery for our pediatric cardiac surgical patients. For instance, patients undergoing a Glenn procedure were not included in our target cohort, but our experience here has led us to consider using a similar strategy in Glenn patients, with a goal of extubating 4–6 h after ICU admission (instead of our current standard, 18–24 hours after ICU admission). Of course, additional studies are warranted to demonstrate whether our findings are replicable in larger populations, in the hands of other surgeons and anesthesiologists, and in other institutions and patient populations.

Conclusions

This small preliminary study provides initial evidence that a novel analgesic strategy centered around the use of a single dose of a long-acting opiate, methadone, facilitates on-table extubation and enhanced recovery after pediatric cardiac surgery. Subsequent trials are needed to better determine whether this regimen is superior to others, but we believe that our experience at least offers support for the consideration of this approach.

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Conflicts of interest

There are no conflicts of interest.

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