Intermittent Versus Continuous and Intermittent Medications for Pain and Sedation After Pediatric Cardiothoracic Surgery; A Randomized Controlled Trial

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Objectives: Compare continuous infusions of morphine and midazolam in addition to intermittent doses with an intermittent only strategy for pain and sedation after pediatric cardiac surgery.
Design: Randomized controlled trial.
Setting: Advocate Children's Hospital, Oak Lawn, IL.
Patients: Sixty patients 3 months to 4 years old with early extubation after pediatric cardiac surgery.
Interventions: Patients received a continuous infusion of morphine and midazolam or placebo for 24 hours. Both groups received intermittent morphine and midazolam doses as needed.
Measurements and Main Results: Gender, age, bypass time, and surgical complexity were not different between groups. Scheduled ketorolac and acetaminophen were used in both groups and were not associated with adverse events. The mean, median, and maximum Faces, Legs, Activity, Cry, And Consolability score were not different between groups. There was no significant difference in number of intermittent doses received between groups. The total morphine dose was higher in the continuous/intermittent group (0.90 vs 0.23 mg/kg; $p < 0.01$). The total midazolam dose was also higher in the continuous/intermittent group (0.90 vs 0.18 mg/kg; $p < 0.01$). The hospital length of stay was longer in the continuous/intermittent group (8.4 vs 4.9 d; $p = 0.04$).
Conclusions: Pain was not better controlled with the addition of continuous infusions of morphine and midazolam when compared with intermittent dosing only. Use of continuous infusions resulted in a significantly higher total dosage of these medications and a longer length of stay. (*Crit Care Med* 2017; XX:00–00)
Key Words: analgesia; pain; pediatric; sedation; thoracic surgery

Fast track to extubation after pediatric cardiothoracic surgery is becoming more common after a number of reports showing it is safe and effective (1–4). However, it has introduced new challenges to pain control. Intubated patients require larger doses of opioids and benzodiazepines for comfort. In patients who are awake and spontaneously breathing, pain and agitation can be treated with lower doses. Some centers still administer continuous infusions of opioid and benzodiazepines to extubated patients. The historical practice at our center, after early extubation, has been low dose opioid and midazolam infusions along with intermittent boluses. However, these infusions may not be necessary and may even be harmful.

There is some evidence that pain control can be achieved without a continuous infusion (5). In a randomized trial evaluating intermittent versus continuous morphine dosing after noncardiac surgery, Bouwmeester et al (5) found no difference in stress hormone levels. In children under 1 year, there was no difference in pain scores either. However, in the 1–3-year range, those receiving intermittent dosing had higher pain scale scores. These subjects were only scheduled for low dose morphine so Bouwmeester et al (5) recommended these patients receive additional classes of analgesic medication.

Multimodal therapy may provide pain relief with fewer side effects. A loading dose of 30 mg/kg of acetaminophen is safe and reduces fever faster than 15 mg/kg (6). Additionally, in a study that evaluated morphine administration in infants following noncardiac surgery, Ceelie et al (7) reported that the cumulative median morphine dose in the paracetamol group was significantly lower (121 vs 357 μg/kg). Ketorolac is another adjunct that has been used safely in the postoperative period (8–10). A

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retrospective review by Moffett et al (9) assessing the safety of ketorolac in infants' postcardiac surgery found no adverse hematologic or renal side effects. Likewise, Gupta et al (8) reported no increased risk of bleeding complications in their randomized controlled trial of ketorolac, even though it was administered as early as 6 hours after pediatric cardiac surgery.

We hypothesized that similar levels of comfort could be achieved in patients receiving intermittent dosing versus those receiving continuous and intermittent dosing when adjunct medications are used. We further hypothesized that greater amounts of morphine and midazolam would be administered in the continuous infusion group. To test our hypotheses, we conducted a prospective, randomized, double-blinded study of intermittent dosing versus continuous infusions in addition to intermittent dosing. We compared these two treatment strategies to evaluate for differences in pain scores, total medication received, and clinical outcomes.

MATERIALS AND METHODS

Approval was obtained from the Institutional Review Board at Advocate Health Care prior to the performance of research procedures. The study was conducted under a Food and Drug Administration investigational new drug application for the use of ketorolac in a pediatric study. All patients scheduled for cardiac surgery were screened between August 2014 and May 2016. Informed consent was obtained from participants' parents prior to surgery.

Inclusion Criteria

1) Three months to 4 years old. Three months was chosen as the lower age limit for ketorolac use based on research that demonstrated safe use at that age (8). Age 4 was selected as the upper limit in order to use only one pain evaluation scale: Faces, Legs, Activity, Cry, and Consolability (FLACC) scale.
2) Early extubation, defined as within 3 hours of admission to the cardiac ICU (CICU), was used to ensure all patients started the study in a similar time frame after surgery.
3) Midline sternotomy.

Exclusion Criteria

1) Renal insufficiency (creatinine greater than 0.8 mg/dL at the preoperative visit or history of chronic renal insufficiency);
2) Bleeding disorder or gastrointestinal bleed within 2 months;
3) Chronic liver disease or alanine aminotransferase (ALT) over 300 U/L at the preoperative visit;
4) Developmental delay significant enough to prevent reliable FLACC scoring;
5) Three or more previous sternotomies (reoperations through scarring may increase pain and may not randomize equally); and
6) Admission to the PICU (excluded because sedation practices and staff sedation training differ from the CICU).

Subjects were randomly assigned to either the intermittent only or continuous/intermittent group in blocks of 10 and stratified for Down syndrome. This stratification was based on a retrospective, matched study that showed Down syndrome patients required a higher total dose of morphine by day 3 after pediatric cardiac surgery versus non-Down syndrome patients (11).

The intermittent only group received doses of morphine and midazolam in an open-label fashion. The morphine bolus dose was 0.05 mg/kg every 2 hours as needed, and the midazolam bolus dose was 0.05 mg/kg every hour as needed. Boluses were given for a FLACC score of 4 or greater but could also be given when FLACC was less than 4 if deemed appropriate. The decision to give morphine or midazolam was made by the nurse or physician and was based on whether pain or agitation was causing the patient distress. Additional doses of either could be ordered with no limit, but all boluses had to be the same 0.05 mg/kg dosage. The intermittent only group received a normal saline infusion, and providers were blinded to which infusion was being delivered. The volume of the infusion was the same in both groups.

The continuous/intermittent group received a continuous infusion of 0.03 mg/kg/hr of morphine and 0.03 mg/kg/hr of midazolam started in the CICU only after the patients were extubated. Patients in this group received morphine and midazolam boluses in the same doses and open-label fashion as the intermittent only group.

All patients in both groups received this regimen for a 24-hour period, at which point the study infusion was discontinued. Patients were then given standard care, which was transition to oral medications.

Patients in both groups received an initial rectal acetaminophen dose of 30 mg/kg in the CICU followed by 15 mg/kg every 4 hours for the first 24 hours so that every patient received six doses. Doses were switched to oral as soon as oral intake was tolerated. In order to ensure safe acetaminophen use, patients were withdrawn if the ALT rose to over 300 U/L on the immediately postoperative or postoperative day 1 laboratories (aspartate aminotransferase [AST] was initially used as well, but because AST levels rise due to hemolysis and myocardial injury, it was thought to be less specific and was removed [12]). A dose of 0.5 mg/kg of intravenous ketorolac was given every 6 hours and was started between 6 and 12 hours after arrival to the CICU. The first dose was given when chest tube drainage was not frankly bloody and was not greater than 3 mL/kg/hr for 2 consecutive hours. Patients were withdrawn from the study if they did not meet these criteria within 12 hours of arrival to the CICU to ensure similar dosing of ketorolac for all study patients. Patients were withdrawn if the platelet count was less than 80,000 or creatinine was greater than 0.8 mg/dL postoperatively or 1 day postoperatively based on thresholds consistent with the trial by Gupta et al (8).

Each patient received parasternal bupivacaine once in the operating room per our institutional practice. Dexmedetomidine use was not permitted for patients enrolled in the study since it affects pain scores. Phenobarbital for

sedation was permitted at the discretion of the treating physician because of an institutional belief that withholding it would prevent optimal pain treatment.

To enhance reliability of FLACC scoring, the nursing staff in the CICU received education by the pediatric pain service and completed a posttest prior to study implementation. The pain service provided an individual review for all staff who scored less than 100% on the posttest. Inter-rater reliability was established before the patient enrollment was initiated. In addition, inter-rater reliability cycles were periodically assessed. Remediation was provided until 100% agreement was reached.

An estimated sample size of 28 per group was calculated to achieve 80% power to detect a dose difference of 30% with an estimated SD of 0.9 and with a significance level (alpha) of 0.05 using a two sample *t* test (13). An interim analysis and safety evaluation was conducted by a data safety monitoring board (DSMB) when half of the patients completed study participation. The DSMB did not require any modifications to the study design. Continuous variables were examined by using independent groups Student *t* test; length of stay (LOS) variables were log transformed prior to *t* test. To compare FLACC assessments, the number of assessments recorded and composite scores were calculated with the sum, mean, median, and maximum of all FLACC scores over the 24-hour study period. FLACC scores were not normally distributed so median and interquartile ranges were compared using the Mann-Whitney *U* test. Dichotomous variables were examined by the chi-square or Fisher exact test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Ninety-one of 108 eligible patient's parents (84%) consented, and 60 patients completed the study (**Fig. 1**). Seven of the 91 eligible patients were not randomized as they were not extubated within 3 hours of arrival to the CICU (92% successfully extubated). Six other patients did not meet inclusion criteria (Fig. 1) prior to starting the study medication, leaving 78 who met all inclusion criteria. Four from each group were withdrawn from the study for reasons unrelated to the study intervention (Fig. 1). Four patients were withdrawn by the treating physician in the intermittent only group and six in the continuous/

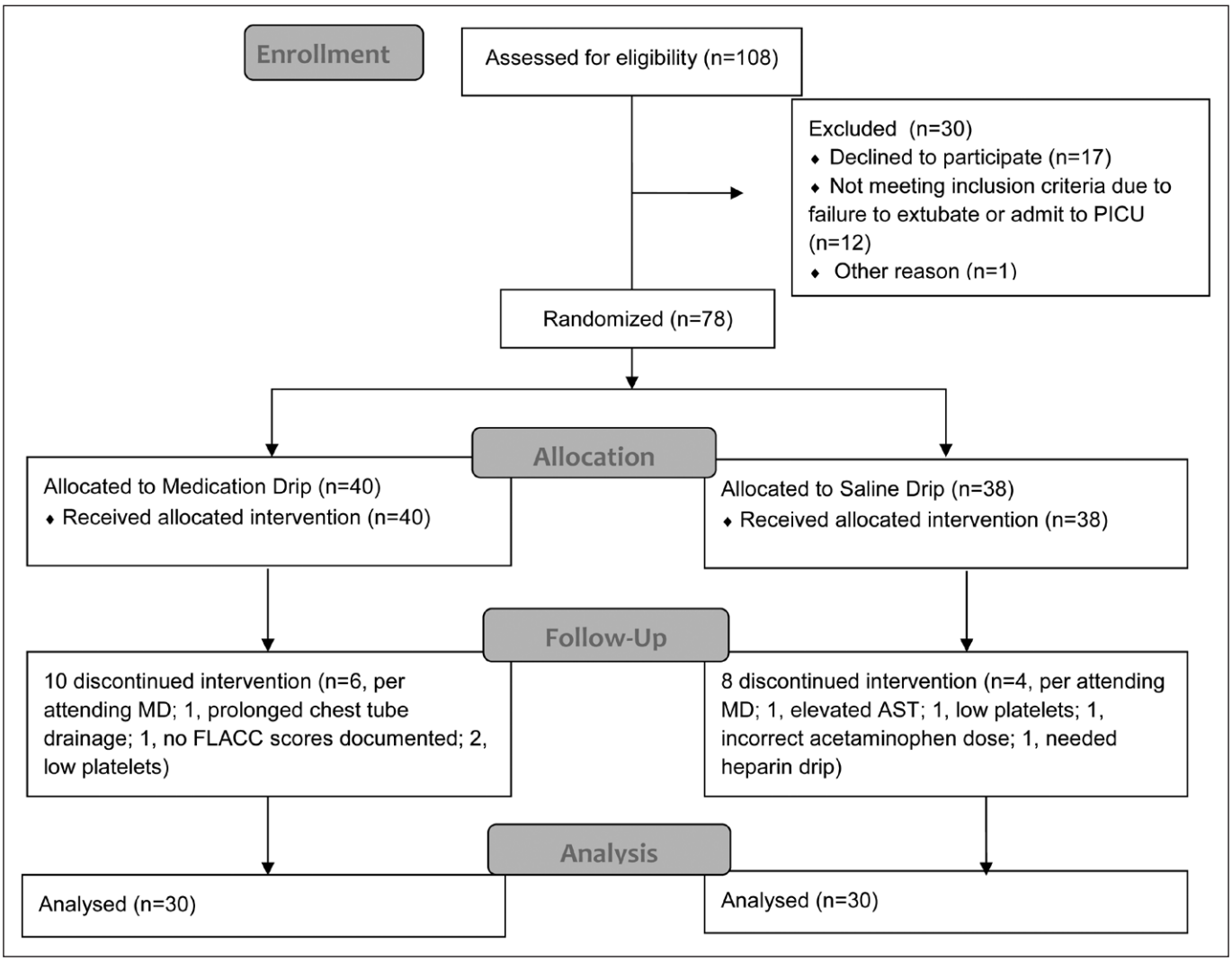

Figure 1. Consort flow diagram. AST = aspartate aminotransferase, FLACC = Faces, Legs, Activity, Cry, and Consolability, MD = medical doctor.

intermittent group primarily for concerns related to under or oversedation. One of these subjects had hypotension that progressed after withdrawal from the study. This patient had an arrest and reintubation 6 hours after removal from the study (this was the only subject who was reintubated).

Thirty patients completed the study in each group. Phenobarbital was given to three patients in the intermittent only group and two patients in the continuous/intermittent group. Gender, age, Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery mortality scores, time on cardiopulmonary bypass, and number of previous sternotomies were not different between groups as described in **Table 1**.

Documentation of the last few hours of study infusion was missing in the medical records of seven patients. It is possible that their infusions were discontinued early, but none were missing more than 4 hours. During this time, no boluses were given and no FLACC scores exceeded two for any patient regardless of group, so these patients were not excluded from analyses.

No patients had evidence of kidney injury during their hospital stay defined by an increase of 1.5 times over the preoperative creatinine with an absolute increase greater than or equal to 0.3 mg/dL. There were no cases of clinically significant gastrointestinal bleeding, postoperative ALT levels higher than 300 U/L, or sanguineous chest tube drainage greater than 3 mL/kg/hr after ketorolac.

FLACC assessment results are reported in **Table 2**. Nurses recorded FLACC scores hourly and on an "as needed" basis to document episodes of pain or agitation. The sum, mean, median, and maximum FLACC scores were not significantly different between groups (Table 2).

The total amount of intermittent morphine, and thus the number of boluses, was not different between groups as the only bolus dose amount allowed was 0.05 mg/kg for each medication (intermittent only = 0.23 mg/kg vs continuous/intermittent = 0.20 mg/kg; $p = 0.39$). Similarly, the total amount of intermittent midazolam was not different between groups (intermittent only = 0.18 mg/kg, continuous/intermittent = 0.19 mg/kg; $p = 0.8$). The total amount of both

TABLE 1. Baseline Characteristics of Study Subjects

Variables	Intermittent Only	Intermittent/ Continuous	*p*
Female gender[a], frequency (%)	18 (60.0)	17 (56.7)	0.79
Age (mo)[b], mean (SD)	16.0 (12.8)	14.8 (12.1)	0.71
Diagnosis of Down syndrome[a], frequency (%)	4 (13.3)	5 (16.7)	0.72
No. of previous sternotomies[a], frequency (%)			
Zero	16 (53.5)	9 (30.0)	0.16
One	6 (20.0)	11 (36.7)	
Two	8 (26.7)	10 (33.3)	
Sum of Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery scores[c], sum (range)	61 (1–4)	59 (1–4)	0.70
Time on cardiopulmonary bypass (min)[b], mean (SD)	83.87 (29.8)	91.40 (47.2)	0.46
Surgery[a], frequency (%)			
Aorta patch plasty	1 (3.3)	0 (0)	
ASD and coarctation of the aorta repair	2 (6.7)	0 (0)	
ASD repair	0 (0)	1 (3.3)	
Atrioventricular canal repair	3 (10)	2 (6.7)	
Bidirectional Glenn	5 (16.7)	8 (26.7)	
Fontan	8 (26.7)	7 (23.3)	
Totally anomalous pulmonary venous return	1 (3.3)	0 (0)	
Tetralogy of Fallot repair	4 (13.3)	3 (10)	
Ventricular septal defect repair	5 (16.7)	5 (16.7)	
Pulmonary valve replacement	1 (3.3)	3 (10)	
Rastelli	0 (0)	1 (3.3)	

ASD = atrial septal defect.

[a]Chi-square.

[b]Independent groups Student's *t* test.

[c]Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery mortality score.

TABLE 2. Faces, Legs, Activity, Cry, and Consolability Pain Assessment Scores

Variables[a]	Intermittent Only, Median (IQR)	Intermittent/Continuous, Median (IQR)	*p*
No. of FLACC assessments during 24 hr	28.0 (25.8–31.3)	26.5 (25.0–30.3)	0.34
Mean of all FLACC assessment scores	1.58 (0.80–2.35)	1.34 (0.62–2.02)	0.35
Median of all FLACC assessment scores	1.00 (0–2.62)	0.00 (0–2.00)	0.20
Maximum score of all FLACC assessment scores	5.50 (4.0–8.0)	5.00 (4.0–7.25)	0.80
No. of FLACC assessment scores ≥ 4	3.50 (1.0–6.0)	3.00 (1.0–5.0)	0.75
Percent of FLACC assessment scores ≥ 4	0.12 (0.04–0.19)	0.12 (0.03–0.19)	0.79

FLACC = Faces, Legs, Activity, Cry, and Consolability, IQR = interquartile range.
[a]All comparisons were tested using the Mann-Whitney *U* test.

medications received was significantly higher in the continuous/intermittent group ($p < 0.01$) as shown in **Table 3**.

Secondary Outcomes

The continuous/intermittent group had a longer mean LOS in the CICU (4.5 vs 2.7 d; $p = 0.10$) and a statistically significantly longer hospital LOS (8.4 vs 4.9 d; $p = 0.04$) than the intermittent only group (**Fig. 2**). The median and maximum inotrope scores were not different between groups (Table 3). The continuous/intermittent group had a more positive fluid balance after 24 hours (74.7 vs 45.6 cc/kg; $p = 0.02$). The mean time to first oral intake was 10.1 hours in the intermittent only group and 14.0 hours in the continuous/intermittent group ($p = 0.46$). There was no difference in episodes of emesis, which was rare in this study.

Subgroup Analyses

To explore whether the type of surgery influenced the difference found in the LOS, subgroup analyses were used to compare LOS between groups of patients after common types of repair. We analyzed these subgroups as biventricular repair, tetralogy of fallot repair, ventricular septal defect repair, bidirectional Glenn, and Fontan and found similar LOS findings with each type of surgery, but none of the surgical subgroups were powered to reach significance. We further explored all single ventricle patients as a subgroup and found the difference in LOS remained significant ($p = 0.04$).

Down Syndrome

A subgroup comparison between patients with Down syndrome ($n = 9$) and those without ($n = 51$) showed no difference in the amount of intermittent morphine (0.23 vs 0.21 mg/kg; $p = 0.7$) or midazolam (0.16 vs 0.19 mg/kg; $p = 0.6$) needed. Mean FLACC scores were 1.4 for patients with Down syndrome and 1.6 for those without ($p = 0.8$).

DISCUSSION

Results from this study demonstrate that continuous infusions of opioid and benzodiazepines did not improve comfort

TABLE 3. Primary and Secondary Outcomes

Variables[a]	Intermittent Only, Mean (SD)	Intermittent/Continuous, Mean (SD)	*p*
Primary outcomes (dose in mg/kg)			
Total morphine	0.23 (0.14)	0.90 (0.13)	< 0.01
Total midazolam	0.18 (0.18)	0.90 (0.17)	< 0.01
Intermittent morphine	0.23 (0.14)	0.20 (0.13)	0.39
Intermittent midazolam	0.18 (0.18)	0.19 (0.17)	0.80
Secondary outcomes			
No. of ketorolac doses[b]	3.53 (0.57)	3.33 (0.66)	0.22
Fluid Balance first 24 hr (mL/Kg)[a]	45.64 (36.61)	74.69 (56.69)	0.02
Median inotrope scores first 24 hr[b]	2.07 (2.54)	3.68 (4.09)	0.12
Maximum inotrope scores first 24 hr[b]	3.87 (3.80)	5.00 (4.58)	0.47
No. of hours to first oral intake	11.96 (7.04)	13.61 (9.88)	0.46
Cardiac ICU length of stay (d)[a]	2.67 (1.15)	4.50 (4.38)	0.10
Hospital length of stay (d)[a]	4.90 (2.52)	8.37 (7.68)	0.04

[a]Comparisons were tested using independent groups Student's *t* test; length of stay data were log transformed due to nonnormality.
[b]Comparisons were tested using the Mann-Whitney *U* test due to nonnormality.

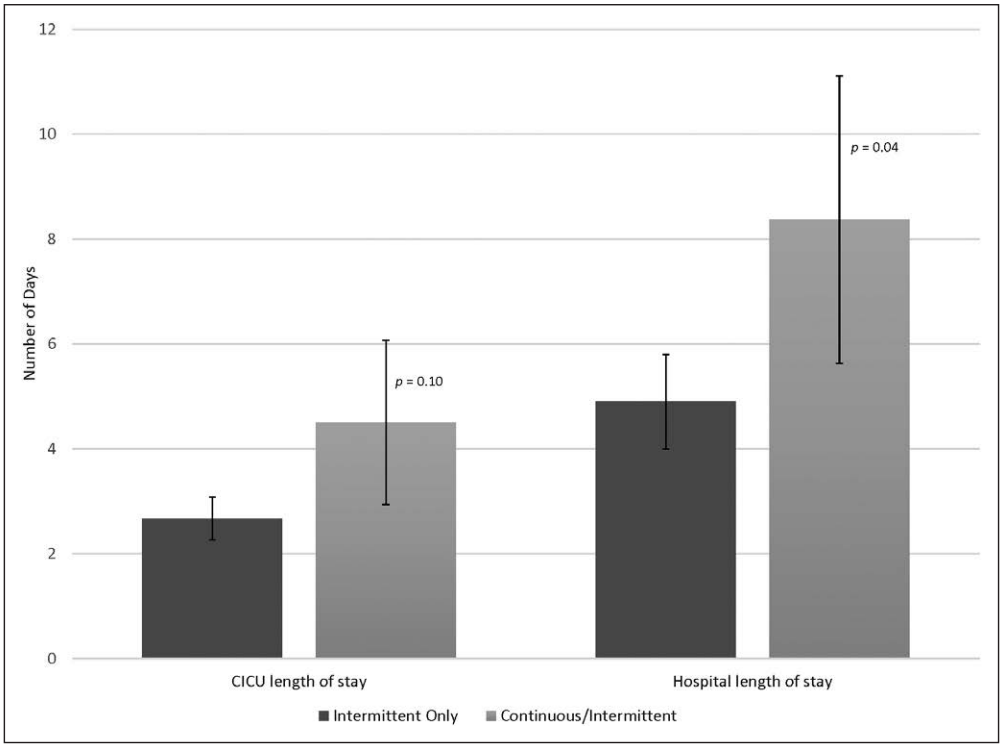

Figure 2. Length of stay difference between treatment groups. Error bars represent 95% CI, *p* values reflect analysis on log transformed data for nonnormality. CICU = cardiac ICU.

compared with intermittent dosing only. Also, continuous infusions did not reduce the number of intermittent doses needed to control pain. The outcomes assessment revealed that the use of continuous infusions prolonged the hospital LOS.

We measured comfort using FLACC scores and compared differences between groups in several ways (i.e., sum, mean, median, and maximum scores). Since FLACC scores were performed hourly and on an "as needed" basis, more pain could have translated to more frequent scoring. However, the total number of assessments did not differ between groups. The mean, median, and maximum FLACC scores were also similar.

Another gauge of comfort was the number of bolus doses received. The need for bolus medications is a strong surrogate for significant pain or discomfort. Continuous infusions did not reduce the need for these rescue medications. We speculate that pain and anxiety are episodic in nature and thus respond well to larger doses on an "as needed" basis. These episodes may be triggered by movements that cause bursts of pain at incision or chest tube sites. When not moving, or aggravating a wound, the continuous medication may not be needed.

The patients who received the continuous infusion of morphine and midazolam received four times the total dose of morphine and almost five times more midazolam than the intermittent only group. This difference was despite using a low dose infusion for only 24 hours. The use of acetaminophen and ketorolac as adjunct medications may have provided baseline pain relief that minimized or eliminated the need for a continuous infusion. They may also have contributed to the generally low pain scores in both groups. We did not reevaluate the usefulness of acetaminophen or ketorolac as they have been previously shown to reduce opioid and benzodiazepine requirements (7, 13). In the absence of adjunct medications, continuous infusions may be useful, but we did not find any adverse events that should preclude their use.

We found no difference between patients with and without Down syndrome. Though based on a small sample size, FLACC scores and the number of bolus medications needed were similar between the nine patients with Down syndrome and the rest. This is consistent with two previous retrospective and observational studies (14, 15) that showed no difference in medications needed for patients with Down syndrome despite a widespread perception that more is required.

The use of continuous infusions significantly prolonged the hospital LOS. Upon arrival to the CICU, all variables that we measured that may be expected to contribute to a prolonged LOS were similar between groups. After surgery, the continuous infusion group had a more positive fluid balance at 24 hours. This group may have required more fluid resuscitation or had lower urine output or a combination of both of these. This may be due to the significantly higher doses of opioid and midazolam that the continuous infusion group received. It is possible that despite randomization, the continuous infusion group had sicker patients and this led to the longer LOS. However, given that there was no difference in expected level of illness prior to the intervention, it is more likely that the difference between groups arose due to the intervention.

Other factors could also have contributed to the difference in LOS. The additional medication in the continuous infusion group may have impeded early mobilization. It could also have delayed the ability to receive good nutrition, which is critical for healing. This study was not powered to detect differences in amount of nutrition taken in, but future studies could examine if that contributes to a longer LOS.

Our study findings were concordant with previously published studies (8–10) in that none of our patients experienced kidney injury or significant chest tube bleeding after ketorolac was initiated. The acetaminophen dose for the first day was 105 mg/kg with no early indication of liver injury.

We were limited in our ability to discern exactly why the continuous/intermittent group had a longer LOS. We did not anticipate the difference in fluid balance, but future studies

should incorporate this in the design. More data on activity, early mobilization and quantity of oral intake would have been helpful. A larger study could have examined differences between surgical types. A larger study could also be powered to detect a difference in CICU LOS. We did not include a control group to prove the effectiveness of the acetaminophen and ketorolac regimen, but we believe that previously published literature has already established their effectiveness.

CONCLUSIONS

Continuous infusions of morphine and midazolam did not improve patient comfort over intermittent dosing when adjunct medications were used. Length of hospital stay was prolonged by the use of continuous infusions. After early extubation following pediatric cardiothoracic surgery, routine administration of continuous infusions of opioid and benzodiazepine is not warranted.

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