Implementation of a Risk-Stratified Opioid and Benzodiazepine Weaning Protocol in a Pediatric Cardiac ICU

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Objectives: Opioids and benzodiazepines are commonly used to provide analgesia and sedation for critically ill children with cardiac disease. These medications have been associated with adverse effects including delirium, dependence, withdrawal, bowel dysfunction, and potential neurodevelopmental abnormalities. Our objective was to implement a risk-stratified opioid and benzodiazepine weaning protocol to reduce the exposure to opioids and benzodiazepines in pediatric patients with cardiac disease.

Design: A prospective pre- and postinterventional study.

Patients: Critically ill patients less than or equal to 21 years old with acquired or congenital cardiac disease exposed to greater than or equal to 7 days of scheduled opioids ± scheduled benzodiazepines between January 2013 and February 2015.

Setting: A 24-bed pediatric cardiac ICU and 21-bed cardiovascular acute ward of an urban stand-alone children's hospital.

Intervention: We implemented an evidence-based opioid and benzodiazepine weaning protocol using educational and quality improvement methodology.

Measurements and Main Results: One-hundred nineteen critically ill children met the inclusion criteria (64 post intervention, 55 pre intervention). Demographics and risk factors did not differ between groups. Patients in the postintervention period had shorter duration of opioids (19.0 vs 30.0 d; $p < 0.01$) and duration of benzodiazepines (5.3 vs 22.7 d; $p < 0.01$). Despite the shorter duration of wean, there was a decrease in withdrawal occurrence (% Withdrawal Assessment Tool score ≥ 4, 4.9% vs 14.1%; $p < 0.01$). There was an 8-day reduction in hospital length of stay (34 vs 42 d; $p < 0.01$). There was a decrease in clonidine use (14% vs 32%; $p = 0.02$) and no change in dexmedetomidine exposure (59% vs 75%; $p = 0.08$) in the postintervention period.

Conclusions: We implemented a risk-stratified opioid and benzodiazepine weaning protocol for critically ill cardiac children that resulted in reduction in opioid and benzodiazepine duration and dose exposure, a decrease in symptoms of withdrawal, and a reduction in hospital length of stay. (*Pediatr Crit Care Med* 2018; 19:1024–1032)

Key Words: benzodiazepines; cardiac critical care; clinical protocol; opioids; pediatrics; withdrawal syndrome

Analgesia, anxiolysis, and sedation are frequently accomplished with the use of opioids and benzodiazepines in critically ill children in the cardiac ICU (CICU) (1). However, cumulative long-term exposure to these drugs is fraught with undesired effects including dependence, withdrawal syndrome, bowel dysfunction, and exacerbation of delirium (1–4). These effects are in turn associated with prolonged hospitalization and potential negative impact on neurodevelopmental outcomes (5, 6). This includes evidence of long-term neurocognitive deficits associated with exposure to these medications (7).

There is clinical evidence that patients with complex congenital heart disease (CHD) are at risk for poor neurodevelopmental outcomes at baseline, further exacerbated by exposure to cardiopulmonary bypass (8, 9). As such, the increasing evidence that narcotics and sedatives may be harmful to the neurologic outcomes of pediatric patients is even more concerning in this subset of children (10, 11).

Previous literature has reported the benefits of using a goal-directed sedation protocol in decreasing exposure to opioids and benzodiazepines (12). These guidelines have not altogether prevented dependence on opioids and benzodiazepines, so a

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standardized process for weaning pediatric patients who develop dependence on opioids and/or benzodiazepines remains an important gap (13–15). We recently reported how a comprehensive risk-stratified opioid weaning protocol decreased hospital length of stay (LOS) and opioid exposure in an older population of general PICU patients (16). The protocol takes advantage of previously proven methods for converting continuous opioid infusions to long-acting intermittent medications using conversion tables to minimize the risk of withdrawal (14, 17–19).

Prior to our first study of general PICU patients, a complete protocol that includes risk stratification, drug conversion, withdrawal assessment, and weaning of medications had not been described in pediatrics. However, the safety of such a protocol has not been evaluated in a pediatric CICU, where children tend to be younger and have higher risk of developing complications such as feeding intolerance and neurodevelopmental abnormalities. Furthermore, given the increasing evidence of the risks of exposure to benzodiazepines, an effective benzodiazepine weaning protocol was needed (20, 21).

The primary objective for this investigation was to study the effectiveness of a comprehensive, risk-stratified opioid and benzodiazepine weaning protocol at decreasing drug burden without increasing withdrawal symptoms in critically ill children at risk for withdrawal in a pediatric CICU. Our hypothesis was that following the implementation of a standardized protocol, children would have shorter duration of opioids and benzodiazepines and a reduction in their hospital LOS.

MATERIALS AND METHODS

Study Design

We conducted a single-center prospective study in the pediatric CICU at Children's Hospital Los Angeles between January 2013 and February 2015. The 24-bed tertiary CICU cares for over 1,000 surgical and medical pediatric patients annually, including those with CHD, arrhythmias, cardiac failure, cardiac assist devices, and transplantation. The CICU is staffed by pediatric critical care physicians, nurse practitioners, nurses, pharmacists, pediatric critical care and cardiology fellows, and other support staff.

The preintervention time period was January 1, 2013, to January 1, 2014. The implementation period took place January 1, 2014, to January 31, 2014. The postintervention period was February 1, 2014, to February 1, 2015. In the preintervention period, the weaning of opioids and benzodiazepines was done at the discretion of the treating physicians with minimal compliance to a prior weaning protocol. Sedation management in both periods was also performed at the discretion of the bedside team; no specific sedation protocol was used during the study.

All clinical and outcomes data were extracted digitally from the electronic health record (Cerner, Kansas City, MO) and a locally developed quality improvement and clinical database (Microsoft Access, Seattle, WA). Care providers were blinded of all data collection until completion of the intervention period. Protocol compliance data were collected through bedside audits by four investigators (R.A., L.N.S-P, J.Y.K., J.W.R.) on a biweekly basis.

This study was approved with a waiver of informed consent by the local Institutional Review Board.

Inclusion and Exclusion Criteria

Patients were included if they were younger than 21 years old, admitted to the CICU during the study period, and received scheduled opioids for 7 days or more (as infusions and/or scheduled doses). The 7-day time period includes opioids given for the management of pain and sedation, as well as scheduled doses during the weaning period, in order to include patients at risk for withdrawal (1, 2). Benzodiazepine exposure was not used as the inclusion criteria since patients in our CICU receive either opioids exclusively or in combination with benzodiazepines. Patients were excluded if they died or were transferred to another hospital before completing their wean.

Protocol Description

We have previously published a similar protocol in a general PICU population that only included the opioid weaning process (16). The opioid and benzodiazepine weaning protocols consisted of three main parts: 1) an algorithm to delineate a weaning schedule stratified by risk of withdrawal (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A761—**legend**, Supplemental Digital Content 5, http://links.lww.com/PCC/A765; and **Supplemental Fig. 2**, Supplemental Digital Content 2, http://links.lww.com/PCC/A762—legend, Supplemental Digital Content 5, http://links.lww.com/PCC/A765); 2) a table to convert opioid and benzodiazepine infusions to intermittent weaning medications (**Table 1**); and 3) a bedside worksheet used to track withdrawal symptoms measured by the Withdrawal Assessment Tool-1 (WAT-1) and daily decisions regarding the weaning process (**Supplemental Fig. 3**, Supplemental Digital Content 3, http://links.lww.com/PCC/A763—legend, Supplemental Digital Content 5, http://links.lww.com/PCC/A765; and **Supplemental Fig. 4**, Supplemental Digital Content 4, http://links.lww.com/PCC/A764—legend, Supplemental Digital Content 5, http://links.lww.com/PCC/A765).

Risk Stratification. In the postintervention period, patients were stratified into withdrawal risk categories based on duration of exposure to opioids and/or benzodiazepines, defined as the total duration of exposure to scheduled or infusion medications at the initiation of weaning: 1) less than 5 days is defined as low risk, 2) 5–7 days is defined as moderate risk, 3) between 7 and 30 days is defined as high risk, and 4) more than 30 days is defined as very high risk. Low-risk patients did not have a weaning schedule recommended. Moderate-risk patients had a daily wean of 20% of the original dose of the medication if they did not demonstrate significant withdrawal syndrome (i.e., 5 d wean if no withdrawal). High-risk patients were weaned every other day by 20% of the original dose of the medication if they did not demonstrate significant withdrawal syndrome (i.e., 10 d wean if no withdrawal). Very high risk patients were weaned every other day by 10% of the original dose of the medication if they did not demonstrate significant withdrawal syndrome (i.e., 20 d wean if no withdrawal). These risk categories were based upon available literature regarding pediatric risk for withdrawal (1, 2, 17).

TABLE 1. Opioid and Benzodiazepine Infusion to Intermittent Dosing Conversion Table

Current Infusion and Infusion Rate	Opioid Infusions		
	Recommended Scheduled Dosing		Recommended PRN Dosing
	PO/NG Methadone (Preferred Agent, Maximum Dose = 10 mg)	IV Hydromorphone (If PO/NG Route Unavailable, Maximum Dose = 2 mg)	PRN IV Hydromorphone (Maximum Dose = 2 mg)
Fentanyl infusion, μg/kg/hr			
1	0.05 mg/kg/dose PO/NG Q8H	0.01 mg/kg/dose IV Q4H	0.01 mg/kg/dose IV Q2–4H
2	0.1 mg/kg/dose PO/NG Q8H	0.02 mg/kg/dose IV Q4H	0.02 mg/kg/dose IV Q2–4H
3	0.1 mg/kg/dose PO/NG Q8H	0.02 mg/kg/dose IV Q4H	0.02 mg/kg/dose IV Q2–4H
4	0.15 mg/kg/dose PO/NG Q8H	0.03 mg/kg/dose IV Q4H	0.03 mg/kg/dose IV Q2–4H
	PO/NG Methadone (Preferred Agent, Maximum Dose = 10 mg)	IV Hydromorphone (If PO/NG Route Unavailable, Maximum Dose = 2 mg)	PRN IV Hydromorphone (Maximum Dose = 2 mg)
Hydromorphone infusion, mg/kg/hr			
0.005	0.1 mg/kg/dose PO/NG Q8H	0.02 mg/kg/dose IV Q4H	0.02 mg/kg/dose IV Q2–4H
0.01	0.1 mg/kg/dose PO/NG Q8H	0.04 mg/kg/dose IV Q4H	0.04 mg/kg/dose IV Q2–4H
0.015	0.15 mg/kg/dose PO/NG Q8H	0.06 mg/kg/dose IV Q4H	0.06 mg/kg/dose IV Q2–4H
0.02	0.15 mg/kg/dose PO/NG Q8H	Wean infusion	0.08 mg/kg/dose IV Q2–4H
0.025	0.15 mg/kg/dose PO/NG Q8H	Wean infusion	0.08 mg/kg/dose IV Q2–4H
0.03	0.15 mg/kg/dose PO/NG Q8H	Wean infusion	0.08 mg/kg/dose IV Q2–4H

Current Infusion and Infusion Rate	Benzodiazepine Infusion	
	Recommended Scheduled Dosing	Recommended PRN Dosing
	IV Lorazepam (Maximum Dose = 4 mg)	PRN IV Lorazepam (Maximum Dose = 4 mg)
Midazolam Infusion, mg/kg/hr		
0.06	0.05 mg/kg/dose IV/PO/NG Q4H	0.05 mg/kg/dose IV/PO/NG Q2–4H
0.12	0.1 mg/kg/dose IV/PO/NG Q4H	0.1 mg/kg/dose IV/PO/NG Q2–4H
0.18	0.15 mg/kg/dose IV/PO/NG Q4H	0.15 mg/kg/dose IV/PO/NG Q2–4H
0.24	0.25 mg/kg/dose IV/PO/NG Q4H	0.25 mg/kg/dose IV/PO/NG Q2–4H

PO/NG = oral/nasogastric enteral route, PRN = as needed dose, Q_H = every _ hours.
IV to PO conversion: hydromorphone IV:PO conversion 1:5; lorazepam IV:PO conversion 1:1.

Withdrawal Assessment. Withdrawal symptoms were measured by bedside nurses every 6 hours with the WAT-1 score before patients began weaning in order to establish baseline scores. The WAT-1 scoring system is a validated score with good interrater reliability that was part of the standard of care in our CICU prior to this study (13). Baseline WAT-1 scores were obtained given the nonspecific nature of withdrawal symptoms (e.g., vomiting or temperature > 37.8°C). Patients were defined as having significant withdrawal if their WAT-1 score was equal or greater than 4, consistent with published thresholds, and 2 greater than the baseline WAT-1 (13). Additionally, patients who had received three or more rescue (as needed dose [PRN]) doses, regardless of their WAT-1 scores, were defined as having withdrawal. The protocol warns that excessive PRNs should prompt evaluation for other diagnoses (e.g., delirium). For patients with significant withdrawal, the protocol recommends holding the wean that day.

Conversion to Weaning Medications. A standardized conversion from continuous infusions to intermittent weaning medications was instituted, including PRN medications (Table 1). Our institution primarily uses fentanyl up to 4 μg/kg/hr and then converts to hydromorphone if higher doses are needed. We use scheduled around-the-clock lorazepam for benzodiazepines as the standard in our CICU.

For opioids, moderate-risk patients were converted to intermittent IV hydromorphone. High and very high risk patients were recommended to convert to withdrawal prevention doses of oral methadone that were not equianalgesic (14, 17, 18). The longer half-life of methadone allows more steady state opioid

levels and minimizes breakthrough withdrawal symptoms. The algorithm had specific directions on how to wean the continuous infusions while starting the methadone. Our institution restricts IV methadone use to the Pain and Palliative Care teams, so high-risk patients unable to tolerate oral medications were converted to intermittent IV hydromorphone (22). Table 1 and Supplemental Figure 1 (Supplemental Digital Content 1, http://links.lww.com/PCC/A761—legend, Supplemental Digital Content 5, http://links.lww.com/PCC/A765) summarize opioid conversions. For benzodiazepines, the patients were converted to IV or oral route lorazepam, every 4 hours, regardless of the risk level (Table 1; and Supplemental Fig. 2, Supplemental Digital Content 2, http://links.lww.com/PCC/A762—legend, Supplemental Digital Content 5, http://links.lww.com/PCC/A765).

Maximum infusion doses were set for all opioid and benzodiazepine infusions, above which infusions had to be weaned to the maximum dose prior to conversion to an intermittent medication. Conversion to weaning medications was recommended prior to extubation. All patients were recommended to have as needed IV hydromorphone and as needed IV lorazepam for opioids and benzodiazepines, respectively, as rescue medications to treat withdrawal symptoms (23). With the guidance of the WAT-1 scores, the administration of PRN medications was by the bedside nurse.

Protocol Implementation

Implementation of the protocol was performed in two cycles. First, the entire cohort of providers providing care in the CICU and the cardiac acute care unit were educated on the weaning protocol, screening for withdrawal symptoms using WAT-1 scores, and differentiation of withdrawal, pain, and delirium. Educational interventions included one-on-one and lecture-based learning, online and hard-copy resources, pre- and post-educational testing, and review of gaps in education noted on pretesting. All providers were required to complete education and testing specific to their discipline. The protocol materials (algorithm, medication conversion tables, bedside worksheets, and protocol manual) were distributed. In the second cycle, there were revisions made to the bedside worksheets based on provider feedback and combined with "just-in-time" education to reaffirm previously taught principles.

Definitions and Calculations

To study exposure to opioids and benzodiazepines, the prewean phase was defined as onset of opioids and benzodiazepines until the peak daily dose of each, respectively. The weaning phase was defined as the duration of time following the peak daily dose to discontinuation of scheduled medications. Total duration of exposure was defined as the sum of the prewean and weaning phases. Post wean to hospital discharge phase was defined as the duration of time after the discontinuation of scheduled medications until discharge from the hospital.

Opioid and benzodiazepine doses were calculated by adding the scheduled and infusion doses received as recorded in the electronic medical records and converting to morphine equivalents and lorazepam-equivalents respectively (expressed as mg/kg/patient). The conversion ratios to morphine equivalence used for fentanyl was 0.01:1 and for hydromorphone was 0.15:1 (19). The conversion to lorazepam equivalence used for midazolam was 1:2 (24). Data extraction and calculations were automated, and a convenience sample was checked by team members (R.A., L.N.S-P.) to validate the data.

Demographics and Risk Factors

In addition to comparison of demographics including age, weight, sex, and race of the patients, potential risk factors in patients in the pre- and postintervention periods were compared including severity of illness, admitting diagnoses, length of mechanical ventilation, ICU LOS, and the prewean exposure of opioids and benzodiazepines.

To study the severity of illness at admission, the Pediatric Index of Mortality (PIM)–2 score was calculated. To study the diagnostic risk categories for patients admitted to the CICU, the percent of patients with a Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) mortality category of 4 or greater was determined. In both intervention periods, the duration (days) and cumulative opioid and benzodiazepine doses (mg/kg/patient) in the prewean phases were calculated and compared in order to determine baseline withdrawal risk.

Primary Outcomes

The primary outcome for this study was duration of opioid and benzodiazepine exposure. The total duration of scheduled opioids and benzodiazepines was compared between intervention periods. The duration of opioid and benzodiazepine weaning, that is, the number of days during the weaning phase, was also compared. Total dose exposure to opioids and benzodiazepines (mg/kg/patient) during the total duration of exposure was also calculated and compared.

Secondary Outcomes

The secondary outcomes included hospital LOS, number of patients discharged home on a wean, postwean to hospital discharge duration, hospitalization cost, and protocol compliance. Protocol compliance involved auditing the weaning worksheet at the patient's bedside to determine both 1) worksheet indicating appropriate initiation of the protocol and 2) the number of wean days recorded in the weaning worksheet divided by the duration of the wean phase.

Total accrued cost of hospitalization was determined for each patient during the study. The median cost per patient was compared between intervention periods. Adjusting for the different number of patients in each intervention period, the adjusted cost savings was determined.

Adverse Events and Adjunct Exposure

The major adverse event monitored was the occurrence of withdrawal defined as any WAT-1 score equal to or over 4 (13). Secondary adverse events monitored were two or more PRN doses in a day, rescue doses of naloxone for excessive opioid sedation, the occurrence of unplanned extubations, and increased use of adjunct medications. The use of adjunct sedatives included

comparison of the number of patients receiving clonidine and dexmedetomidine between interventional periods. In addition, total dexmedetomidine dose exposure (μg/kg/patient) was compared between periods.

Data Analysis

Data were analyzed using Stata Version 13 (StatCorp, College Station, TX). Categorical variables were compared using the Yates-corrected chi-square test or the Fisher exact test, and continuous variables were compared using the Mann-Whitney *U* test. A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Demographics and Risk Factors

One-hundred nineteen critically ill children with cardiac disease met the inclusion criteria (55 pre intervention and 64 post intervention). Of these patients, 63 were exposed to benzodiazepines (34 pre intervention and 29 post intervention). Post hoc analysis demonstrated no patients exposed to 7 days or more of benzodiazepines without concurrent exposure to 7 days or more of opioids, validating the use of opioid exposure as the primary inclusion criteria.

The age, weight, sex, race, PIM-2 severity of illness score, STAT mortality category, length of mechanical ventilation, and CICU LOS did not differ between the two groups (**Table 2**).

Opioid and Benzodiazepine Prewean Exposure

The average daily morphine equivalent exposure per patient in the prewean phase was not different between pre- and postintervention periods. The duration of opioids and the cumulative opioid dose exposure in the prewean phases were also not different between periods (**Table 3**).

There was no difference in the daily lorazepam equivalents per patient, the duration of benzodiazepine exposure, nor the total lorazepam equivalent exposure in the prewean phase between interventional periods (Table 3).

Outcomes

Primary Outcomes. *Opioids.* Patients in the postintervention period had shorter total duration of scheduled opioids and duration of opioid wean phase both by 11 days ($p < 0.001$) and decreased total dose exposure to opioids by over 17 mg/kg/patient ($p < 0.001$) than those in the preintervention group (**Table 4**). Notably, there was also less variability in these metrics in the postintervention period as indicated by relatively narrow interquartile ranges (IQR). For example, the IQR for total duration of opioids decreased from 32 to 15 days (Table 4).

Patients in the postintervention period had significantly shorter duration of total scheduled benzodiazepines by 19 days ($p < 0.001$), shorter benzodiazepine weans by 13 days ($p = 0.01$), and decreased total dose exposure to benzodiazepine by 2.6 mg/kg/patient ($p < 0.01$) than those in the preintervention group (Table 4). Again, relatively narrow IQR was noted for these outcomes in the postintervention period.

Secondary Outcomes. The hospital LOS in the postintervention group was shorter by 8 days ($p < 0.01$), with no difference in the prewean phase, nor the postwean to hospital discharge phase (**Table 5** and **Fig. 1**). The number of patients discharged home on opioids was not different. The monthly average protocol compliance in the postintervention group was consistently greater than 95% after the intervention period (range, 90–100%). Finally, the cost per patient decreased by approximately $17,000 after the intervention ($p = 0.04$), with an adjusted actual cost-savings of approximately 2 million dollars (Table 5).

TABLE 2. Demographic and Severity of Illness Characteristics of Patients by Intervention Group

Variables	Pre Intervention	Post Intervention	*p*
Patients, *n*	55	64	
Age, d, median (interquartile range)	10 (2–166)	10 (1–170)	0.88
Weight, kg, median (interquartile range)	4.2 (3.5–5.7)	3.9 (3.3–6.0)	0.34
Males, *n* (%)	29 (52.7)	45 (70.3)	0.06
Race, *n* (%)			
Latino	29 (53)	33 (52)	0.44
White	18 (33)	16 (25)	
Black	5 (9)	6 (9)	
Other/unknown	3 (5)	9 (14)	
Pediatric Index of Mortality-2 score, median (interquartile range)	−4.1 (−4.9 to −3.2)	−4.1 (−4.9 to −3.2)	0.62
Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery mortality category ≥ 4, *n* (%)	34 (61.8)	38 (59.4)	0.79
Length of mechanical ventilation, d, median (interquartile range)	11 (9–18)	11 (8–17.5)	0.21
ICU length of stay, d, median (interquartile range)	20 (14–30)	17 (13–23.5)	0.09

TABLE 3. Prewean Opioid and Benzodiazepine Exposure, by Intervention Period

Variables	Opioids			Benzodiazepines		
	Pre Intervention	Post Intervention	*p*	Pre Intervention	Post Intervention	*p*
Patients, *n*	55	64		34	29	
Daily prewean equivalents (average mg/kg/d per patient), median (interquartile range)	1.8 (1.4–2.7)	1.7 (1.4–2.2)	0.54	0.21 (0.12–0.31)	0.18 (0.14–0.25)	0.31
Duration of prewean (d), median (interquartile range)	4 (2–10)	5 (3–8)	0.37	5 (0–12)	2 (0–5)	0.27
Prewean total equivalents (mg/kg/patient), median (interquartile range)	18.2 (9.1–26.2)	16.4 (8.5–24.6)	0.40	1.7 (0.8–2.8)	0.8 (0.4–2.1)	0.07

Opioids are in morphine equivalents, benzodiazepines are in lorazepam equivalents. Comparisons are between intervention periods for each class of medication. Benzodiazepine patients are a subgroup of the opioid patients.

TABLE 4. Wean Phase and Total Opioid and Benzodiazepine Exposure, by Intervention Period

Variables	Opioids			Benzodiazepines		
	Pre Intervention	Post Intervention	*p*	Pre Intervention	Post Intervention	*p*
Patients, *n*	55	64		34	29	
Total duration of exposure (d), median (interquartile range)	30 (19–51)	19 (13–28)	**< 0.001**	24 (8.7–60.6)	5 (1.8–17.0)	**< 0.001**
Duration of wean phase (d), median (interquartile range)	23 (15–35)	12 (7–16.5)	**< 0.001**	15 (7.2–28.2)	2 (2.1–10.4)	**< 0.001**
Total equivalents (mg/kg/patient), median (interquartile range)	48.4 (31.2–91.6)	31.2 (21.4–44.2)	**< 0.001**	3.9 (1.7–10.3)	1.3 (0.4–3.0)	**< 0.01**

Opioids are in morphine equivalents, benzodiazepines are in lorazepam equivalents. Comparisons are between intervention periods for each class of medication. Benzodiazepine patients are a subgroup of the opioid patients.

Boldface values signify those items that demonstrate statistically significant difference between intervention periods.

TABLE 5. Secondary Outcomes

Variables	Pre Intervention	Post Intervention	*p*
Patients, *n*	55	64	
Hospital length of stay (d), median (interquartile range)	42 (35–75)	34 (25–50)	**< 0.01**
Discharged on wean, *n* (%)	9 (16.4)	4 (6.3)	0.14
Postwean to hospital discharge, median (interquartile range)	8 (3–21)	13 (5–22)	0.25
Total hospitalization costs per patient (U.S. dollar), median (interquartile range)	$207,000 ($62,000–$313,000)	$190,000 ($133,000; $258,000)	**0.04**
Adjusted cost savings after intervention	$2,095,465[a]		

[a]The total difference in cost between pre- and postinterventional periods as adjusted for different patient numbers in each period.

Secondary outcomes are for the entire cohort (all opioid patients and subgroup of benzodiazepine patients).

Boldface values signify those items that demonstrate statistically significant difference between intervention periods.

Adverse Events

There were fewer patients with symptoms of withdrawal in the postintervention period as measured by the percentage of WAT-1 scores 4 or greater ($p < 0.01$). Additionally, there was no difference in the proportion of days with two or more rescue PRN doses, unplanned extubations, nor patients receiving rescue naloxone doses between the intervention periods (**Table 6**).

Fewer patients had use of adjunct clonidine in the postintervention period ($p = 0.02$). Although the number of patients exposed to dexmedetomidine trended toward fewer in the

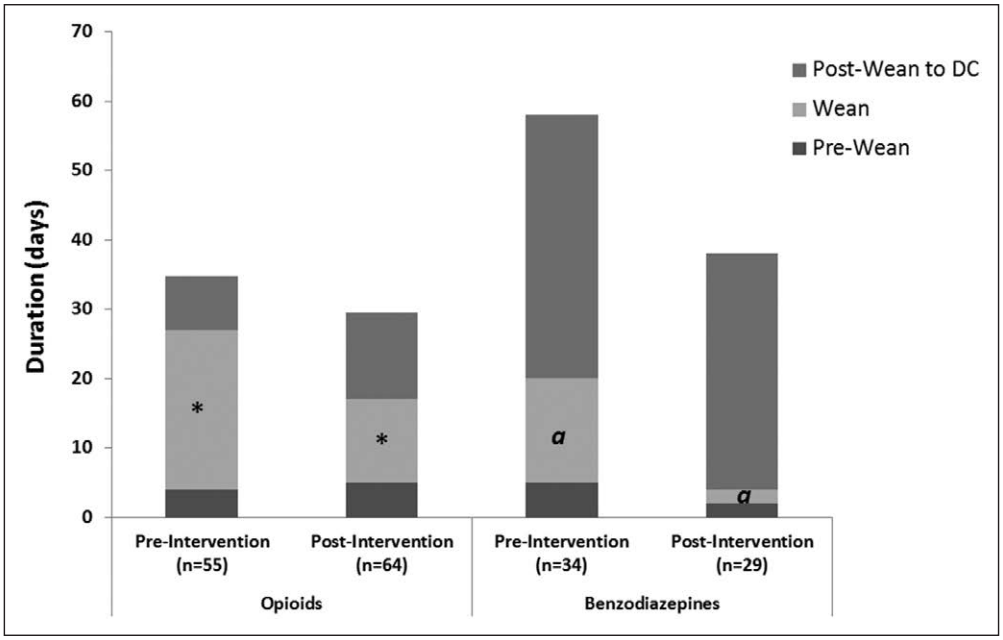

Figure 1. Median duration (days) of prewean phase, weaning phase, and post wean to hospital discharge (DC) stratified by medication class and intervention period (*n* values noted). Only the duration of the weaning phase was significantly shorter post intervention for opioids ($^{*}p < 0.001$) and benzodiazepines ($^{a}p < 0.001$). The sum of phases do not necessarily add to hospital length of stay given that patients are not necessarily exposed to opioids and benzodiazepines from admission and that these are median values of each phase. Benzodiazepine-exposed patients are a subset of the total opioid-exposed patients.

postintervention period, it did not reach statistical significance ($p = 0.08$). Total cumulative dose exposure to dexmedetomidine per patient was not different between interventional periods (Table 6).

DISCUSSION

Our objective for this study was to determine the effectiveness of a risk-stratified opioid and benzodiazepine weaning protocol in decreasing the drug burden in critically ill children in a CICU. As hypothesized, patients in the postintervention period had fewer days on opioids and benzodiazepines. Additionally, in comparison with patients in the preintervention period, patients in the postintervention period had decreased cumulative dose exposure to opioids and benzodiazepines, with the percent of elevated WAT-1 scores decreasing in the postintervention period (less withdrawal). Patients also had shorter hospital LOS (more than a week) leading to an adjusted cost savings of over 2 million dollars in the postintervention period.

We replicated similar findings of decreased exposure to opioids in an older, general PICU population using the opioid weaning protocol described here (16). The results of this investigation demonstrate the benefits and potential generalizability of a weaning protocol in a population of younger patients with differing diagnoses in the CICU. Given the baseline high risk for neurodevelopmental injuries in patients with CHD, decreased exposure to opioids and benzodiazepines may be of great importance to their long-term outcomes (8, 9). This study also corroborates that a standardized approach to benzodiazepine weans can have similar benefits as seen with opioids. With increasing evidence that benzodiazepines are associated with delirium, decreased exposure to

TABLE 6. Adverse Events and Adjunct Exposure

Variables	Pre Intervention	Post Intervention	*p*
Patients, *n*	55	64	
Adverse events, median (interquartile range)			
Percent of Withdrawal Assessment Tool-1 score ≥ 4	14.1 (3.9–22.1)	4.9 (0–12.4)	**< 0.01**
Percent of days with ≥ 2 as needed doses	13.3 (8.0–23.5)	13.2 (8.5–18.8)	0.99
Inadvertent extubations, *n* (%)	2 (3.6)	3 (4.6)	0.78
Naloxone use, *n* (%)	1 (1.8)	0 (0)	0.46
Exposure to adjunct medications			
Clonidine, *n* (%)	18 (32)	9 (14)	**0.02**
Dexmedetomidine, *n* (%)	41 (75)	38 (59)	0.08
Total dexmedetomidine exposure, μg/kg/patient, median (interquartile range)	195 (45–336)	181 (77–329)	0.32

Adverse events and adjunct exposures are for the entire cohort (all opioid patients and subgroup of benzodiazepine patients).
Boldface values signify those items that demonstrate statistically significant difference between intervention periods.

this class of medication, including an efficient weaning process, could help mitigate exacerbation of delirium (21, 25). This study also substantiates prior smaller studies showing the benefit of using protocol-based opioid weaning schedules (26).

Although decreasing patients' exposure to opioids and benzodiazepines is important, avoiding unintended consequences is also essential. In the current study, we demonstrated pediatric patients can not only tolerate shorter weaning schedules without increased withdrawal, but we even found decreased withdrawal symptoms in the postintervention period. These results replicate those in our previous study (15). Similarly, Meyer et al (18) used a 10-day enteral methadone wean for fentanyl-dependent children and found it effective in preventing withdrawal symptoms. Bowens et al (17) randomized 74 patients on 5 or more days of opioid infusion into a 10-day low-dose, weight-based methadone wean or a 10-day high-dose, formula-based methadone wean and found patients in both groups were equally likely to complete the 10-day wean (56 vs 62%; $p = 0.79$). Furthermore, Berens et al (27) prospectively randomized 37 patients to a 5- or 10-day methadone wean and found both to be equally effective. Although two of these studies did not specifically evaluate the degree of withdrawal symptoms, the successful completion of these protocols may imply no significant increase in symptoms leading to protocol termination. The additional finding of decreased withdrawal in these results may be due to the risk-stratified approach preventing rapid weans in higher risk patients.

We also demonstrated that a weaning protocol can avoid other potential complications, such as inadvertent extubation, opioid narcotization, or increases in the use of adjunct medications. We found less exposure to clonidine and a trend toward fewer patients on dexmedetomidine in the postinterventional group. The decreased use of adjunct medications may not be surprising given increasing evidence that opioid and benzodiazepine exposure may exacerbate signs and symptoms of delirium; worsening delirium often leads providers to add more medications, whether it is more opioids or additional agents, such as dexmedetomidine (21, 25).

The benefits of reduced exposure to opioids and benzodiazepines include reduction in associated complications. Decreasing opioid and benzodiazepine exposure has been associated with reduction in delirium, bowel dysfunction, feeding intolerance, and overdose (3, 4, 21, 25). Given human and animal studies demonstrating the potential negative effects of opioids and benzodiazepines in the developing brain, reducing exposure to these potentially harmful medications is a sensible goal (5, 6).

Novel aspects of our risk-stratified opioid and benzodiazepine weaning protocols are notable. Baseline WAT-1 scores obtained prior to weaning led to a more customized assessment of withdrawal symptoms. For example, although not specifically studied here, patients with other diagnoses such as delirium frequently have elevated WAT-1 scores at baseline because of the overlap in symptoms. Baseline WAT-1 scores allow continued weaning, even if the WAT-1 is 4 or greater but not significantly different than baseline. In the example of delirious patients, this could translate to ongoing reduction in some of the potential triggers for their delirium. Another novel aspect, the stratification of patients into risk categories, further customizes the weaning process. Also, to our knowledge, this is the most comprehensive withdrawal prevention protocol for critically ill children, combining evidence from prior studies into a complete weaning process for both opioids and benzodiazepines. Finally, this is the largest study of a standardized weaning protocol in critically ill pediatric patients, and the only one of its kind in a CICU population.

Some evidence exists that goal-directed sedation protocols may decrease upfront exposure to sedation medications. However, a standardized weaning guideline can further decrease exposure in the weaning phase for patients with dependence. Additionally, guidelines such as the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study did not include some of the features in our protocol, including customization of the weaning process based on risk and using a baseline WAT-1 score, hence potentially exposing high risk patients to a wean that is likely too rapid and vice versa (12). Goal-directed sedation protocols and risk-stratified weaning guidelines, such as the one presented here, may result in even lower exposure to analgesics and sedatives as a part of a comprehensive sedation management process. This would be a valuable future investigation.

Although protocol-based weans seem to be effective, little consensus exists among practitioners with regard to opioid and benzodiazepine weaning, with significant variability in practice within and across institutions (13, 14). An important effect of our protocol implementation and educational intervention was the reduction in variability in the practice of providers, as evidence by the reduced range in the duration of weans in the postintervention group for both opioids and benzodiazepines.

A few limitations of this study are notable. A large proportion of patients in the postintervention group were classified into the moderate- and high-risk group of our risk-stratified protocol. Although we could not fully evaluate the advantage of having a risk-stratified protocol with the current study population, particularly for the smaller very high-risk group, our population was consistent with literature suggesting most patients at risk for withdrawal fall into the moderate- and high-risk groups (17, 18, 26, 27). Also, this was a single-center study, not fully able to account for practices variation across institutions. We are reassured that the opioid weaning protocol has demonstrated similar benefits in two separate ICUs at our institution, staffed by different physicians and nurses, providing single institutional validation of the protocol.

Finally, upfront sedation practices may have changed over time at our institution as a result of education relating to the protocol. The lack of significant differences in exposure to opioids and benzodiazepine prior to the weaning phase suggests this was not a major effect, albeit worthy of consideration. Also, there did not appear to be a shift in medication use. For example, there was not an increase in dexmedetomidine use, in fact, there was a trend toward fewer patients on this agent, and no change in overall dose exposure to the drug.

As with any quality improvement endeavor, sustainability of change can be an important challenge to the long-term

success of the project. As such, since the conclusion of the initial validation phase of this protocol, we have begun methods to integrate the protocol into the electronic medical records and devised a computer decision-support tool, both of which are currently being studied.

CONCLUSIONS

We implemented a risk-stratified opioid and benzodiazepine weaning protocol in the CICU of a large children's hospital. The education and implementation of the protocol led to a reduction in the duration of opioid and benzodiazepine exposure and cumulative dose exposure in critically ill cardiac children, while decreasing withdrawal symptoms, decreasing hospital LOS by over one week, and leading to major hospitalization cost savings. External validation of these results in other pediatric CICU populations would be needed to validate this protocol.

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