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Implementation of a risk-stratified opioid weaning protocol in a pediatric intensive care unit☆

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ABSTRACT

Purpose: Opioids are important in the care of critically ill children. However, their use is associated with complications including delirium, dependence, withdrawal, and bowel dysfunction. Our aim was to implement a risk-stratified opioid weaning protocol to reduce the duration of opioids without increasing the incidence of withdrawal.

Methods: A pre- and post-interventional prospective study was undertaken in a large children's hospital pediatric ICU where we implemented a risk-stratified opioid weaning protocol. Patients were included if exposed to ≥7 days of scheduled opioids. The primary outcome was duration of opioids and secondary outcome was hospital LOS.

Results: One hundred seven critically ill children met the inclusion criteria (68 pre-, 39 post-intervention). Demographics, risk factors, and confounders did not differ between groups. Patients in the post-intervention group had shorter duration of opioids (17 vs. 22.5 days, $p = 0.01$) and opioid wean (12 vs. 18 days, $p = 0.01$). Despite the shorter duration of opioid wean, there was no increase in withdrawal incidence. There was no difference in the LOS (29 vs. 33 days, $p = 0.06$).

Conclusions: We implemented a risk-stratified opioid weaning protocol for critically ill children that resulted in reduction in opioid exposure without an increase in withdrawal. There was no difference in the LOS.

1. Introduction

Opioid infusions are commonly used to manage patients admitted to the pediatric intensive care unit (PICU) [1]. Children with prolonged exposure to opioids frequently develop dependence to these drugs, which may result in symptoms of withdrawal after these medications are weaned or stopped [1,2]. Additional complications associated with the use of opioids include delirium and opioid-induced bowel dysfunction [3,4]. In combination, these complications can lead to increased morbidity in critically ill children, including prolonged hospitalization. In addition, there is growing concern that opioids may have a negative effect on long-term neurodevelopmental outcomes of children who have been exposed [5,6].

Although there is limited clinical evidence of the long-term neurodevelopmental effects of narcotics and sedatives in pediatric patients [7,8], animal studies have convincingly shown that anesthetics, analgesics, and sedatives, including opioids, have deleterious effects on the developing brain [5,6]. Therefore, avoiding potentially unnecessary prolonged exposure to opioids could be beneficial in the long-term.

Despite the common use of opioid infusions in the PICU and their associated complications, there is little consensus among critical care practitioners for the ideal sedation management and withdrawal prevention practices [9-11]. This has led to widely varied drug management practices in the field of pediatric critical care. One approach has been to implement goal-directed sedation protocols; while these protocols have demonstrated decreasing exposure to opioid medications, they have not altogether prevented opioid dependence, necessitating

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effective weaning guidelines [12]. Other researchers have developed methods for converting continuous opioid infusions to long acting intermittent medications, such as methadone, to minimize the risk of withdrawal [10]. Conversion tables or means of weaning intermittent drugs have also been described [13-15]. However, a protocol including risk stratification, drug conversion, withdrawal assessment, and weaning of pediatric patients has not been previously described.

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

2. Materials and methods

2.1. Study design

We conducted a single-center pre- and post-intervention prospective study in the PICU of a large children's hospital between January 2013 and March 2015. The 24-bed multidisciplinary, tertiary PICU serves a mixed population of medical, surgical, trauma, and solid-organ and hematopoietic stem cell transplantation patients. The PICU is staffed by pediatric critical care physicians, nurse practitioners, nurses, pharmacists, pediatric residents, and other support staff. The unit does not provide care for postoperative cardiac patients.

The pre-intervention period was January 1st, 2013 to January 31st, 2014. The implementation period took place between February 1st and April 30th, 2014. The post-intervention period was May 1st, 2014 to March 31st, 2015. In the pre-intervention period, the weaning of opioids was done at the discretion of the treating physicians. Sedation management in both periods was also performed at the discretion of the bedside team; no specific sedation protocol was used during the study period.

Protocol compliance data was collected prospectively through bedside audits by five study investigators (LNS, RA, KL, JK, and JR) on a bi-weekly basis. Clinical and outcomes data was extracted from the electronic health record (Cerner Kids, Kansas City, MO) and a locally developed quality improvement and clinical database (Microsoft Access, Seattle, WA) maintained by the physicians delivering care in the PICU.

This study was approved with a waiver of informed consent by the Institutional Review Board of Children's Hospital Los Angeles.

2.2. Inclusion and exclusion criteria

Patients were included for analysis if they were younger than 21 years of age, admitted to the PICU during the study period, and received scheduled opioids for 7 days or more. The 7 day time period includes both opioids given for the management of pain and sedation, as well as scheduled doses during the weaning period. Patients were excluded if they died or were transferred to another hospital or ICU before completing their opioid wean.

2.3. Protocol description

The opioid weaning protocol consisted of three main parts: (a) an algorithm to delineate a weaning schedule stratified by risk of withdrawal (low, moderate, high and very high risk) (Fig. 1), (b) a table to convert the opioid infusion to a weaning medication (Fig. 2), and (c) a bedside worksheet used by clinicians to track withdrawal symptoms as measured by the withdrawal assessment tool-1 (WAT-1).

2.3.1. Risk stratification

Patients were stratified into withdrawal risk categories based on the length of exposure to opioids. Risk categories were defined as continuous exposure to opioids *before* weaning for: 1) less than five days (low risk), 2) five to seven days (moderate risk), 3) between seven and 30 days (high risk), and 4) >30 days (very high risk). A prescribed weaning strategy was defined for each risk category. 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 weaning medication if they did not demonstrate significant withdrawal syndrome (i.e., five day wean if no withdrawal). High risk patients were weaned every other day by 20% of the original dose of the weaning medication if they did not demonstrate significant withdrawal syndrome (i.e., ten day wean if no withdrawal). Very high risk patients were weaned every other day by 10% of the original dose of the weaning medication if they did not demonstrate significant withdrawal syndrome (i.e., twenty day wean if no withdrawal).

2.3.2. Withdrawal assessment

The WAT-1 scoring system is a validated score with good inter-rater reliability that was in use and part of the standard of care in our PICU prior to this study [9]. Measurement of withdrawal symptoms by bedside nurses were done every six hours with the WAT-1 score before patients were converted to their weaning medication in order to establish baseline scores. Baseline WAT-1 scores were obtained due to the non-specific 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 four *and* two greater than the baseline WAT-1, consistent with published thresholds [9]. Additionally, patients who had received three or more rescue (PRN) doses of a medication, regardless of their WAT-1 scores in the previous 24 h, were also defined as having significant withdrawal. For patients with significant withdrawal, the protocol recommends holding the wean for that day.

2.3.3. Conversion to weaning medications

A standardized approach to converting from continuous opioid infusions to intermittent weaning medications was instituted, including PRN medications (Fig. 1). Our institution primarily uses fentanyl up to 4 mcg/kg/h, then hydromorphone for continuous opioid infusions. Moderate risk patients were recommended to convert intermittent intravenous (IV) hydromorphone (0.01 to 0.06 mg/kg based on the continuous opioid dose every 4 h). High and very high risk patients were recommended to convert to withdrawal-prevention doses of oral methadone that were not equianalgesic (0.05 to 0.15 mg/kg every 8 h) [10,13,14]. 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 to use by the pain and palliative care teams only, so high risk patients unable to tolerate oral medications were converted to intermittent IV hydromorphone (0.01 to 0.06 mg/kg every 4 h) [16].

Maximum infusion rates for opioids were set, above which patients had to be weaned down on the infusion prior to conversion to an intermittent medication. Conversion to the weaning medications was recommended prior to extubation to minimize concerns for over sedation and the risk of under-dosing withdrawal prevention medications. The conversion to intermittent dosing was treated as a wean even if equianalgesic doses were used. All patients were recommended to have IV hydromorphone as a rescue medication to treat withdrawal symptoms as needed. The administration of rescue (PRN) IV hydromorphone was determined by the bedside team in accordance to the standards of care of the PICU with the guidance of the WAT-1 scores.

2.4. Protocol implementation

Implementation of the protocol was performed in two phases. In the first phase, nurses, pharmacists, and physicians providing care in the

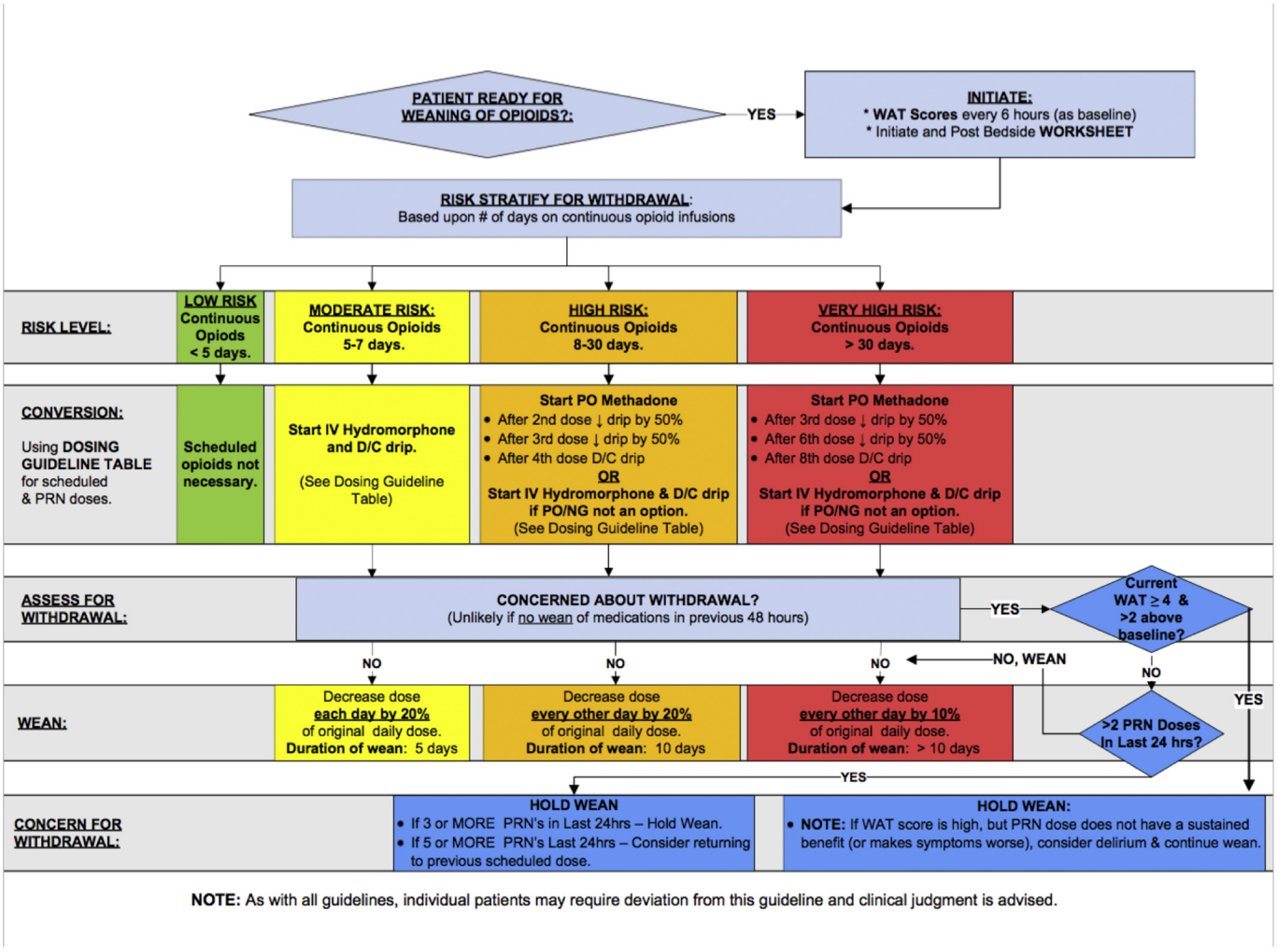

Fig. 1. Risk stratification, assessment, and weaning algorithm for patients receiving continuous opioid infusions.

PICU were educated on the weaning protocol, the screening of withdrawal symptoms using WAT-1 scores, and the recognition and differentiation of withdrawal, pain, and delirium. The protocol materials (algorithm, medication conversion tables, bedside worksheets, and protocol manual) were widely distributed. In the second phase there were several revisions made to the bedside worksheets based on provider feedback and "just-in-time" education to reaffirm previously taught principles. The staff in the pediatric wards to which patients are transferred to after their PICU stay also received training on the use of the protocol as part of the second phase.

Current Infusion Dose	Recommended Scheduled Dosing		PRN Dosing
Fentanyl Drip	**PO Methadone (preferred) (Max Dose: 10 mg)**	**IV Hydromorphone (if PO/NG not an option) (Max Dose 2 mg)**	**PRN IV Hydromorphone (Max Dose: 2 mg)**
1 mcg/kg/hr	0.05 mg/kg/dose PO Q8H	0.01 mg/kg/dose IV Q4H	0.01 mg/kg/dose IV Q2-4H PRN
2 mcg/kg/hr	0.1 mg/kg/dose PO Q8H	0.02 mg/kg/dose IV Q4H	0.02 mg/kg/dose IV Q2-4H PRN
3 mcg/kg/hr	0.1 mg/kg/dose PO Q8H	0.02 mg/kg/dose IV Q4H	0.02 mg/kg/dose IV Q2-4H PRN
4 mcg/kg/hr	0.15 mg/kg/dose PO Q8H	0.03 mg/kg/dose IV Q4H	0.03 mg/kg/dose IV Q2-4H PRN
Hydromorphone Drip	**PO Methadone (preferred) (Max Dose: 10 mg)**	**IV Hydromorphone (if PO/NG not an option) (Max dose 2 mg)**	**PRN IV Hydromorphone (Max dose 2 mg)**
0.005 mg/kg/hr	0.1 mg/kg/dose PO Q8H	0.02 mg/kg/dose IV Q4H	0.02 mg/kg/dose IV Q2-4H PRN
0.01 mg/kg/hr	0.1 mg/kg/dose PO Q8H	0.04 mg/kg/dose IV Q4H	0.04 mg/kg/dose IV Q2-4H PRN
0.015 mg/kg/hr	0.1 mg/kg/dose PO Q8H	0.06 mg/kg/dose IV Q4H	0.06 mg/kg/dose IV Q2-4H PRN
0.02 mg/kg/hr	0.15 mg/kg/dose PO Q8H	N/A	0.08 mg/kg/dose IV Q2-4H PRN
0.025 mg/kg/hr	0.15 mg/kg/dose PO Q8H	N/A	0.08 mg/kg/dose IV Q2-4H PRN
0.03 mg/kg/hr	0.15 mg/kg/dose PO Q8H	N/A	0.08 mg/kg/dose IV Q2-4H PRN

Fig. 2. Drug conversion and dosing guideline for opioids.

2.5. Outcomes

The primary outcome for this study was duration of opioid exposure. This was measured using the total length of scheduled opioids and the length of opioid weaning. The *length of scheduled opioids* was calculated as the number of days from the initiation of scheduled or infused opioids until the day of the last scheduled weaning opioid dose. The *length of opioid weaning*, a subset of the length of scheduled opioids, was calculated as the number of days from the day of peak daily scheduled opioid dose until the day of the last scheduled opioid dose. *Total exposure to opioids* was defined as the cumulative morphine equivalents (mg/kg/patient) from initiation of opioids until the last dose of scheduled weaning opioid.

The secondary outcomes included hospital length of stay, number of patients discharged home on opioids, and protocol compliance. *Protocol compliance* was measured by auditing the use of the opioid weaning protocol worksheet at the patient's bedside and defined by the number of days on a weaning schedule recorded in the opioid weaning protocol worksheet divided by the total number of days on a weaning schedule.

2.6. Risk factors and confounders

Potential risk factors and confounders of outcomes in patients in the pre- and post-intervention periods included severity of illness, admitting diagnoses, use of adjunct sedative medications, and opioid exposure prior to initiation of opioid wean. To study the severity of illness on admission the Pediatric Index of Mortality 2 (PIM-2) and the Pediatric Risk of Mortality III (PRISM III) score were calculated and compared between groups. To study the use of adjunct sedatives, the number of patients receiving benzodiazepines, clonidine, and dexmedetomidine were calculated and compared between groups. In addition, the duration of benzodiazepine use and the total benzodiazepine exposure (as lorazepam-equivalents, mg/kg/patient) and total dexmedetomidine exposure (mcg/kg/patient) were calculated.

To study the exposure to opioids used prior to weaning in patients in the pre- and post-intervention periods, the peak daily opioid dose (mg/kg/day), the length of opioids until peak daily opioid dose (days), and the cumulative opioid dose prior to weaning (mg/kg/patient) were calculated and compared between groups. Opioid doses were calculated by adding the total scheduled and infusion doses of opioids received and converted to morphine-equivalents. The conversion ratios to morphine equivalence used for fentanyl was 0.01:1 and for hydromorphone was 0.15:1 [15].

2.7. Adverse events

The major adverse event monitored was the *incidence of withdrawal* defined as any WAT-1 score equal to or over 4, consistent with prior studies [9]. Secondary adverse events monitored during the study period included the use of 2 or more rescue (PRN) doses in a day, rescue doses of naloxone for excessive opioid sedation and the incidence of unplanned extubations.

2.8. Data analysis

Data were analyzed using Stata version 13 (StatCorp, College Station, TX). Categorical variables were compared using the Yates-corrected Chi-squared test or the Fisher's exact test and continuous variables were compared using the Mann-Whitney *U* test. A p-value < 0.05 was considered statistically significant.

3. Results

3.1. Demographics, risk factors, and confounders

One hundred seven critically ill children met the inclusion criteria (68 pre- and 39 post-intervention). The age, weight, gender, primary admitting diagnoses, severity of illness scores on admission, PICU length of stay, and length of mechanical ventilation did not differ between the two groups (Table 1). There was a slightly larger proportion of Hispanic patients in the post-intervention group. The use of adjunct benzodiazepines and clonidine was not different between groups. While the number of patients exposed to dexmedetomidine was not different between interventional groups, total cumulative exposure to dexmedetomidine was lower in the post-interventional period (29.4 vs 39.2 mcg/kg/patient, $p = 0.04$). The peak daily opioid dose, the length of opioids prior to peak opioid dose, and the cumulative opioid dose prior to the weaning phase was not different between groups (Table 2). In the post-intervention group, 15 patients (38%) met moderate-risk, 23 patients (59%) met high-risk, and 1 patient (3%) met very high-risk for withdrawal criteria.

Table 1
Demographic and severity of illness characteristics of patients in the pre- and post-intervention groups.

Demographic variable	Pre-intervention	Post-intervention	p
Patients (N)	68	39	
Age, years (IQR)	2.1 (0.6, 9.8)	2.3 (0.4, 14.2)	0.94
Weight, kg (IQR)	11.8 (5.7, 27.5)	10.6 (5.9, 39.9)	0.89
Males, N (%)	40 (59.7%)	20 (50%)	0.44
Race, N (%)			
Hispanic	32 (48%)	27 (68%)	0.04
White	23 (34%)	6 (15%)	0.07
Black	6 (9%)	2 (5%)	0.75
Other/unknown	7 (10.4%)	4 (10%)	1.0
Admission diagnosis, N (%)			0.3
Respiratory failure	36 (53%)	22 (61%)	
Sepsis/multisystem	12 (18%)	7 (18%)	
Gastrointestinal	6 (9%)	1 (3%)	
Neurologic compromise	4 (6%)	1 (3%)	
Cardiovascular	3 (4%)	1 (3%)	
Other	7 (10%)	7 (18%)	
Severity of illness on admission			
PIM-2 Score (IQR)	−4 (−4.7, −3)	−4.4 (−4.9, −3.1)	0.29
PRISM III Score (IQR)	8 (3, 12)	6 (1, 13)	0.42
Length of mechanical ventilation, days (IQR)	10.5 (8, 14)	8 (7, 13)	0.1
PICU length of stay, days (IQR)	15 (11, 23)	13 (10, 20)	0.14

IQR, inter-quartile range; PIM-2, Pediatric Index of Mortality-2; PRISM III, Pediatric Risk of Mortality III.

Table 2
Exposure to opioids and other adjunct medications.

Medication exposure	Pre-intervention	Post-intervention	p
Patients (N)	68	39	
Opioid exposure before wean			
Peak daily opioid dose, mg/kg/day (IQR)	6.5 (4.4, 7.7)	5.4 (4.1, 7.2)	0.30
Duration of scheduled opioids before peak, days (IQR)	6 (4, 8)	6 (3, 8)	0.38
Total scheduled opioids before peak, mg/kg/patient (IQR)	17.1 (9.9, 36.1)	20.4 (11.6, 38.3)	0.68
Benzodiazepine exposure, total			
Benzodiazepine used, N (%)	65 (96%)	36 (92%)	0.67
Total length of scheduled benzodiazepines, days (IQR)	18 (9, 30)	14 (10, 21)	0.24
Total benzodiazepine exposure, mg/kg/patient (IQR)	12.4 (6.2, 21)	13.2 (3.8, 26.5)	0.98
Other adjunct sedative used			
Clonidine, N (%)	14 (21%)	10 (26%)	0.5
Dexmedetomidine, N (%)	44 (65%)	31 (79%)	0.13
Total dexmedetomidine exposure, mcg/kg/patient (IQR)	39.2 (13.9, 106.4)	29.4 (13.9, 37.0)	0.04

Opioid doses expressed in morphine-equivalents. Benzodiazepine doses expressed in lorazepam-equivalents. IQR, inter-quartile range.

3.2. Outcomes

3.2.1. Length of scheduled opioids, opioid wean, and total opioid exposure

Patients in the post-intervention group had significantly shorter median length of scheduled opioids (17 vs. 22.5 days, p = 0.01) and opioid wean (12 vs. 18 days, p = 0.01), and decreased total exposure to opioids (33.2 vs 48.8 mg/kg/patient, p = 0.02) than those in the pre-intervention group (Table 3, Fig. 3).

3.2.2. Secondary outcomes

There was a trend toward shorter hospital length of stay in the post-intervention group, but it did not reach statistical significance (29 vs. 33 days, p = 0.06). The number of patients discharged home on opioids was not different (2 post vs 4 pre, p = 0.87). The monthly average protocol compliance in the post-intervention group was consistently >90% (range: 80–100%).

3.3. Adverse events

There was no difference in the proportion of withdrawal symptoms between the two groups as measured by the percentage of WAT-1 scores 4 or greater (2.6% post vs. 4% pre; p = 0.29, Table 3). Additionally, there was no difference in the proportion of days with 2 or more rescue PRN opioid doses (17% post vs. 22% pre, p = 0.58). Two patients in the pre-intervention group and one patient in the post-intervention group received rescue naloxone doses (p = 0.7). One patient in the pre-intervention group and zero patients in the post-intervention group had unplanned extubations (Table 3).

4. Discussion

The primary objective for the current study was to evaluate the effectiveness of a risk-stratified opioid weaning protocol at decreasing the opioid drug burden in critically ill children. As hypothesized, we found that patients in the post-intervention group had fewer days on opioids and decreased total cumulative exposure to opioids without an increase in withdrawal symptoms compared to patients in the pre-intervention group. In addition, there was an associated trend toward a decreased hospital length of stay, although this did not achieve statistical significance.

Our finding of a decrease in opioid exposure with the use of an opioid weaning protocol is consistent with previous studies. Robertson and colleagues randomized 20 patients into a protocol-based or a non-protocol opioid weaning regimen and found the protocol group to have a significantly shorter opioid wean than those in the non-protocol group (9 vs. 20 days, p < 0.001) [17]. In addition, our finding that pediatric patients are able to tolerate shorter weaning schedules without increased withdrawal is also consistent with prior studies. Meyer and colleagues implemented a 10-day enteral methadone wean for fentanyl-tolerant children and found it to be effective in preventing withdrawal symptoms [14]. Bowens and colleagues randomized 74 patients who received 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 on both groups equally likely to complete the 10-day wean (56 vs. 62%, p = 0.79) [13]. Berens and colleagues prospectively randomized 37 patients to a 5-day or a 10-day methadone wean schedule and found both regimens to be equally effective [18].

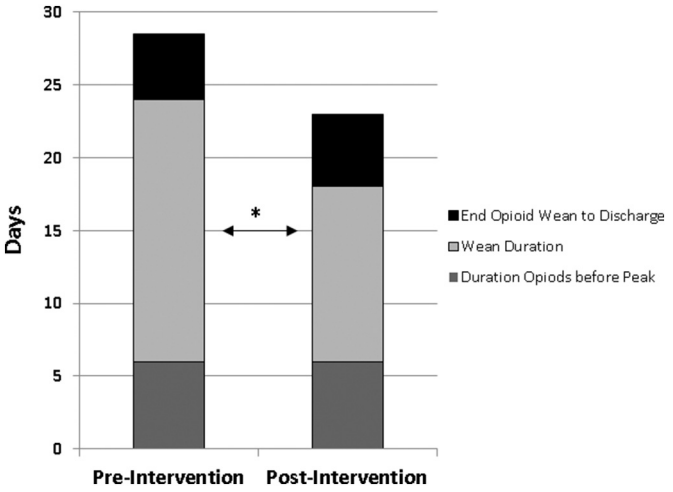

Fig. 3. Duration to peak daily opioid dose, duration of weaning phase (peak to end opiod), and duration after opioids until hospital discharge stratified by intervention period (in days). The duration of weaning phase was significantly shorter post-intervention (*p = 0.01).

Table 3
Outcomes and adverse events.

	Pre-intervention	Post-intervention	p
Number of patients (N)	68	39	
Outcomes:			
Length of scheduled opioids (total), days (IQR)	23 (16, 34)	17 (13, 23)	0.01
Length of opioid wean, days (IQR)	18 (11.5, 26.5)	12 (10, 19)	0.01
Length of opioids after extubation, days (IQR)	11 (5.5, 17)	7 (5, 10)	0.02
Total opioid exposure, mg/kg/patient (IQR)	48.8 (27.1–74.5)	33.2 (21.6–48.5)	0.02
Hospital length of stay, days (IQR)	33 (21, 52)	29 (16, 42)	0.06
Patients discharged home on opioids, N (%)	4 (5.8%)	2 (5.1%)	0.87
Adverse events:			
% WAT-1 score ≥4 (IQR)	4 (0, 14.5)	2.6 (0, 10.5)	0.29
% days ≥ 2 rescue PRN doses (IQR)	22% (11–31%)	17% (8–31%)	0.58
Inadvertent extubations, N (%)	1 (1.4%)	0 (0%)	1.0
Naloxone use, N (%)	2 (2.9%)	1 (2.5%)	0.9

Opioid doses expressed in morphine-equivalents. All results are medians (IQR) or N (%). IQR, inter-quartile range.

A few novel approaches of our risk-stratified opioid weaning protocol are notable. The utilization of a baseline WAT-1 score allows a more specific assessment of withdrawal symptoms in patients who exhibit signs that overlap with withdrawal even when not being weaned off opioids (e.g., emesis or hyperthermia). This allows patients to continue the weaning process with fewer interruptions. Furthermore, the risk stratification of patients creates a customized approach to the weaning process more specific to the patient. Finally, this is the largest study of a standardized opioid weaning protocol in critically ill pediatric patients.

The reduction in exposure to opioids may have several positive effects. Reduced drug exposure has been associated with decreased risk of complications, including delirium, bowel dysfunction, feeding intolerance, and overdose [3,4]. There are human and animal studies demonstrating potential negative effects of opioids and sedatives in the developing brain [6]. Because well-controlled clinical studies assessing the long-term neurodevelopmental effects of opioids in children are unlikely to be performed [5], reducing exposure to these potentially harmful medications is a sensible goal. Our study demonstrates that the length of opioid weans can be safely decreased by a third without increased withdrawal or other apparent complications. While goal-directed sedation protocols can decrease upfront exposure to opioids, a standardized weaning guideline can further decrease exposure in the weaning phase for patients with opioid dependence. Furthermore, guidelines such as those used in the RESTORE study, do not stratify the weaning process based upon risk, hence exposing higher risk patients to a wean that is likely too rapid [12]. As such, a goal-directed sedation protocol and the weaning guidelines presented here may serve as complementary parts of the sedation management process.

In general, protocol-based opioid weans seem to be effective, but as other authors have noted, there is little consensus among critical care practitioners in regards to opioid and sedative medication weaning and there is large variability in practice within and across institutions [9,10]. Perhaps the most 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 length of opioid weans in the post-intervention group. Furthermore, the educational intervention, and multidisciplinary approach, cannot be understated in operating such a protocol.

4.1. Limitations

The vast majority of patients in the post-intervention group were classified into the moderate and high-risk group of our risk-stratified protocol. As such, we were unable to fully evaluate the advantage of having a risk-stratified protocol with the current study population, specifically the very high-risk group. However, our study population is consistent with prior literature suggesting most patients at risk for opioid withdrawal in a PICU fall into the moderate and high risk-groups [13,14,17,18]. In addition, this was a single-center study. Practices differ across institutions and this variation can have a significant impact in some of the outcomes measured in our study. Also, practice over time may have varied within our institution due to initiation of this protocol, but the lack of difference in exposure to adjunct medications, including benzodiazepines, nor exposure to opioids prior to weaning, suggests this was not the case. If anything, there was decreased dexmedetomidine exposure in the post-intervention group. Finally, while this is the largest such study in pediatric patients, a larger post-interventional patient population may have been more sensitive to detect changes in our secondary outcome of hospital length of stay.

5. Conclusion

We successfully implemented a risk-stratified opioid weaning protocol in the PICU of a large children's hospital. The protocol led to a significant reduction in the length of opioid exposure in critically ill children without an increase in withdrawal symptoms nor other adverse outcomes. No difference was observed in the hospital length of stay. External validation of these results in other PICU populations is warranted before this can be generalized as a standard protocol.

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