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Effect of a Sedation Weaning Protocol on Safety and Medication Use among Hospitalized Children Post Critical Illness

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ABSTRACT

Background: Best practice guidelines for the safe and compassionate care of critically ill children necessitates the use of sedation to ensure adequate ventilation, patient safety and comfort. Prolonged use of sedation can result in tolerance, physical dependence and iatrogenic withdrawal syndrome if medications are weaned too quickly.
Problem: In the context of medication errors related to parent administration of outpatient sedation weans, we set out to improve the safety of children weaning from sedatives.
Methods: A retrospective analysis was completed. Quality improvement was guided by using Plan-Do-Study-Act cycles.
Interventions: An evidence-based post PICU sedation weaning guideline was created and implemented over time with ongoing education, and review of progress with staff members with pre-post evaluation.
Results: Post intervention, there were significant differences in the numbers of patients discharged on home weaning from both opioids and benzodiazepines (11%, n = 24/219 pre; 3%, n = 7/233 post; $p < 0.005$). The number of patients discharged with a methadone wean decreased (7%, n = 16/219 pre; 0%, 0/233 post; $p = 0.03$). Despite these differences, there were no significant differences in the median hospital length of stay (42 pre; 39 post; $p = 0.35$). Post implementation more children had mild to moderate symptoms of withdrawal (11% pre; 21% post; $p < 0.005$) as compared to pre-implementation, however, the percentage of severe symptoms remained consistently low (0.6% pre; 1% post; $p = 0.11$).
Conclusions: Implementation of an evidence-based post PICU weaning guideline significantly reduced the number of patients discharged on potentially dangerous medications with modest increases in mild-moderate symptoms of withdrawal and no significant change in length of stay or the incidence of severe symptoms of withdrawal.

Problem description

Best practice guidelines for the safe and compassionate care of critically ill children necessitates the use of sedation to ensure adequate ventilation, patient safety and comfort. To achieve adequate sedation, medications such as opioids, benzodiazepines, and/or alpha-agonists are administered. Prolonged use of sedatives can result in iatrogenic withdrawal syndrome (IWS) if medications are weaned too quickly (Duceppe et al., 2019). On the other hand, prolonged weaning necessitates either lengthy hospitalizations with risks of hospital borne infections or continued weaning of sedatives after eventual discharge home with risks of dosing errors especially for children receiving liquid medication (Yin, Parker, Sander, et al., 2016).

Prior to implementation of a sedation weaning protocol, our institution had no hospital-wide guidelines for sedation weaning, thus practice varied in terms of the rate of the wean, the order of medications weaned and whether a wean was completed in the inpatient or outpatient setting. Commonly, patients who received prolonged sedatives while in the pediatric intensive care unit were transferred to a patient ward and were ultimately discharged home on several medications including methadone and/or benzodiazepines adding complexity to the

Abbreviations: ICU, intensive care unit; LOS, length of stay; IWS, iatrogenic withdrawal syndrome; WAT-1, Withdrawal Assessment Tool-Version 1; EMR, electronic medical record.

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home regimen. In the context of serious medication errors related to parent administration of outpatient sedation weans, we set out on this quality improvement effort to improve the safety of children weaning from sedatives.

Available knowledge

A consequence of prolonged administration of sedatives is the development of tolerance and physical dependence. Tolerance is a decreased medication effect after prolonged administration, requiring increased dosing to maintain the clinical effect. Physical dependence is a physiologic state produced by repeated medication administration, requiring continued administration to prevent iatrogenic withdrawal syndrome (Franck, Naughton, & Winter, 2014). Patients with tolerance and physical dependence are at greater risk of iatrogenic withdrawal.

Iatrogenic withdrawal syndrome is common in children recovering from a critical illness (Best, Wypi, Asaro, & Curley, 2017). In order to minimize the incidence and severity of tolerance and physical dependence, opioids and benzodiazepines should be used at the minimum effective dose as clinically indicated and incrementally reduced when no longer required (Curley, Wypij, et al., 2015). For most children with tolerance and physical dependence, iatrogenic withdrawal is associated with short term, mildly uncomfortable symptoms, such as mild diaphoresis or fussiness which is responsive to swaddling or holding. However, when high doses of opioids and benzodiazepines are abruptly stopped or tapered too quickly after prolonged administration, iatrogenic withdrawal may be more severe and in some cases associated with cardiovascular or respiratory compromise (Franck et al., 2014).

Signs and symptoms of withdrawal may vary in number, presentation, and severity; individual patients may be affected by various factors including the dose and medications administered, time of exposure, patient age, cognitive state, and medical condition (Amigoni et al., 2017; Franck, Harris, Soetenga, Amling, & Curley, 2008). Children with poor respiratory or cardiac reserve, such as those with single ventricle physiology or pulmonary hypertension due to significant lung disease, are unable to tolerate increases in heart rate, blood pressure, respiratory rate or pulmonary vascular resistance and may be at increased risk of developing hemodynamic or respiratory instability with withdrawal symptoms, thus warranting a more prolonged wean. Therefore the consensus guidelines had to allow for weaning at different rates depending on the child's condition.

Rationale

The Plan-Do-Study-Act model (PDSA) was the framework used to guide this quality improvement effort (Langley et al., 2009). An interdisciplinary taskforce planned the initiative by reviewing adverse events and creating a driver diagram outlining the key components of the initiative. This group developed and implemented guidelines. We measured weaning practices and implemented changes to the guidelines where clarification was needed. We provided education programs for targeted groups as needed.

Specific aims

The primary aim of this evidence-based initiative was to decrease patients with prescriptions for high-risk medications (opioids, benzodiazepines and clonidine) at discharge. The secondary aims were to standardize the care of patients weaning from sedatives and to increase the pace of weaning without increasing severe signs and symptoms of withdrawal.

Context

This quality improvement initiative was developed within a 410-bed academic pediatric tertiary care center with four intensive care units (ICUs) and with 24/7 in-hospital coverage by the Pain Treatment Service nurse practitioners with an on-call attending. The Pain Service was consulted for weaning patients before discharge from the ICU.

Interventions

We convened a taskforce comprised of nurses, nurse practitioners, physicians and pharmacists from the intensive care units (ICUs), Pain Treatment Service, and general care units that care for weaning patients with a goal of developing evidence-based and consensus guidelines for weaning within our institution. The taskforce met over time to review Plan- Do-Study-Act (PDSA) cycles. The interventions included: 1) sedation weaning guidelines based on a multicenter pediatric trial of sedation and weaning (Curley, Wypij, et al., 2015); 2) weaning worksheets created in Excel to calculate the decrements for specific medication based on the previously mentioned guidelines; 3) electronic medical record (EMR) changes that allowed for improved documentation of signs and symptoms of withdrawal; 4) review of measures; 5) interprofessional education; 6) parent education. Instead of converting patients to methadone as was our previous practice, most patients were weaned from their original opioid without changing to methadone.

The weaning guidelines (Table 1) provided a framework for weaning sedatives by a percentage of the maximum dose (Curley, Wypij, et al., 2015). For example, for patients physiologically able to tolerate some signs and symptoms of withdrawal, opioids were weaned by 10% of the maximum dose every 8 h until off, with a goal of discontinuing opioids in 3.5 days. Benzodiazepines were weaned by 20% of the maximum dose daily with a goal of discontinuing in 5 days. When patients were able to tolerate enteral medications, they were switched from intravenous medications to enteral and weaned at the same rate. Patients on clonidine weaned by 20% of the maximum dose daily after opioids and benzodiazepines were weaned completely off. High risk weaning patients were defined as patients who either had a long exposure to sedatives due to long intubation or those who were unable to tolerate increases in heart rate, blood pressure, respiratory rate or pulmonary vascular resistance (Table 2). High risk weaning patients were weaned more slowly than those with normal risk (Table 2).

Changes in practice were communicated via electronic and in-person clinician education. Parent education was an important part of the initiative since parents are typically actively involved in the care of their children. During daily rounds, parent education was delivered using paper-based information sheets with verbal reinforcement. The paper-based information sheets contained details on why weaning is necessary as well as common signs and symptoms of withdrawal. On daily rounds, decisions about weaning were made with input from parents and based on the clinical judgment of the Pain Treatment Service team and primary service, with the overall goal of consistent weaning based on the protocol. Throughout the process, the Pain Treatment Service, consulted on high risk weaning patients who had transferred to the non-ICU setting. Each patient was evaluated formally on daily rounds by the Pain Treatment Service team with repeated evaluations before and after medication weans.

Study of the interventions

The study of the interventions was based on the specific aims of the initiative. Clinical practice was measured and reported back to staff with discussions for improvement monthly and then quarterly. A key aspect of staff education was changing expectations about managing the signs and symptoms of withdrawal. Previously, our practice was to pharmacologically treat all signs and symptoms of withdrawal, even mild symptoms. With implementation of this new sedation weaning guideline, we emphasized for both parents and clinicians that mild signs of withdrawal are expected throughout the weaning process. Mild signs of withdrawal are now managed with non-pharmacologic comfort measures (for example swaddling and decreasing environmental

Table 1
Weaning guideline.

	Low Risk	Normal Risk	High Risk
Mechanical Ventilation (in days)	<5 days	5-20 days	>20 days
Physiologically able to tolerate withdrawal	Yes	Able to tolerate mild to moderate signs of withdrawal.	No Includes patients with poor respiratory or cardiac reserves and/or hemodynamic instability, unable to tolerate significant increases in HR, BP, RR or PVR, including those with single-ventricle physiology, myocardial dysfunction and or pulmonary hypertension.
Weaning plan • Wean ONE medication at a time • Wean benzodiazepines first for patients with a moderate to severe source of pain AND infants <1 year old. • If patient has moderate to severe signs of withdrawal, slow the wean and consider adding or increasing the clonidine	No wean. Stop medication and monitor patient for signs and symptoms of withdrawal.	• Wean morphine 10% q8 hours. GOAL = Off in 3 days * • Wean benzodiazepine 20% q24 hours. GOAL = Off in 5 days* • Wean clonidine 20% q24hours. GOAL = Off in 5 days*	• Start initial wean 10% q24 hours for morphine, methadone, benzodiazepine, clonidine.* • Increase to 15-20% q24 hours if patient tolerates.*

Percentage of the maximum dose (for example, for a patient with a maximum dose of 10 mg of morphine, wean 1 mg every 8 h until off).

stimuli) while moderate to severe withdrawal are managed with either a rescue dose or increased doses of medications. This study (2013–2018) follows patients to discharge or the end of the inpatient wean, whichever came first.

Notably, at the same time as our efforts, the cardiac ICU team implemented a system to ensure that patients weaned according to the same guidelines outlined in Curley et al. while in the ICU. However, the other 3 ICUs continued their usual practice which is similar to these guidelines.

Measures

Retrospective data were obtained for a 5 year period (7/1/2013–6/30/2018) to allow for data points before and after the intervention with time for PDSA cycles. This report combines a practical account of the implementation activities following the Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0).

We developed an operational definition for "weaning patients" to identify patients in the electronic medical record (EMR). "Weaning patients" were defined as: intubated for ≥120 consecutive hours (5 days) and received three decreasing doses of sedatives [morphine, methadone, hydromorphone, fentanyl, lorazepam, midazolam, diazepam, clonidine, dexmedetomidine, pentobarbitol]. In order to ensure accuracy of this measure, we compared the patients selected with this operational definition with a review of currently critically ill patients. Based on these reports, adjustments were made to the logic of the automatically generated report until results were at least 95% accurate in identifying weaning patients. All patients that met these requirements were included in the study. Patients solely with neonatal abstinence syndrome were not included in the sample.

Once the denominator was defined, measures were developed to monitor targeted changes in practice based on their importance to patient safety. We measured the number of patients discharged home on methadone and other sedative medications and length of stay (LOS) to ensure that this was not negatively impacted by the intervention.

We measured the signs and symptoms of withdrawal using nurse-documented WAT-1 (Withdrawal Assessment Tool-Version 1) from the electronic medical record (Franck et al., 2014). The WAT-1 is an 11 item, 12-point scale validated to quantify signs and symptoms of opioid and benzodiazepine withdrawal (Franck et al., 2008). The score is the sum of 11 indicators with a higher score indicating more withdrawal. Typically scores greater than three indicate clinically important withdrawal that requires intervention (Franck et al., 2008). All patients had WAT-1 scoring performed by the PICU nurse and subsequently by the general nurses after transfer to the care unit.

Table 2
Pretest (4 quarters before) and posttest (final 4 quarters) comparison after implementation.

Demographics	Pretest n = 219	Posttest n = 233	p-Value
Age (years) median; IQR	0.2; 0.01–1.4	0.8; 0.04–6.1	0.26
Female (%)	114 (52%)	105 (45%)	0.53
Reasons for ICU admission			
Medical management	70 (32%)	100 (43%)	0.34
Surgery (cardiac)	88 (40%)	72 (31%)	0.28
Surgery (non-cardiac)	53 (24%)	44 (19%)	0.33
Measures			
Patients discharged with methadone	16 (7%)	0 (0%)	0.03*
Patients discharged with opioid & benzodiazepine prescription	24 (11%)	7 (3%)	0.003*
Length of stay (days) median; IQR	42; 29–77	39; 24–70	0.35
Mild–moderate WAT-1 scores (4–7) (%)	11%	21%	0.002*
Severe WAT-1 scores (≥8) (%)	0.6%	1%	0.11

* p value is <0.05.

Analysis

Although the measures were reviewed prospectively, the pretest/posttest analysis was retrospective. We analyzed the demographics of all weaning patients over 5 years. We compared the first 4 quarters of data (pretest) and the last (posttest) with 3 years in between. Three years after implementation, we were confident that the protocol was consistently implemented throughout the institution after review of the measures which were graphed monthly then quarterly targeting the goals of this initiative: specifically, discharge home weaning high risk medications, LOS, and withdrawal signs and symptoms. A paired sample *t*-test compared the means of age, patients discharged with methadone, opioids and Benzodiazepine prescriptions, LOS, WAT-1 scores.

Results

Over a 5-year period from July 1, 2013 through June 30, 2018, 1080 patients were identified as weaning patients. These patients accounted for 1487 weaning events (some patients weaned more than once during the same admission). Almost 19% (208 of 1080) had more than one weaning event during the admission.

Most weaning patients were infants (63%), males (58%) and Caucasian (50%). Many weaning patients (41%, n = 474) had congenital heart disease and required prolonged ventilatory support after a surgical procedure (36%, N = 411) or for medical management of their congenital heart disease (5%, n = 63). More than one-third (36%, n = 425) were admitted to an ICU for medical management of a critical illness including respiratory failure (12%, n = 143); sepsis (5%, n = 62). Approximately one-quarter (23%, n = 269) were admitted to the ICU after non-cardiac surgeries (Table 2). Most weaning events included sedation with both an opioid and a benzodiazepine (97%). In addition, alpha-2 adrenergic agonists were frequently administered including dexmedetomidine (60%, n = 708) and clonidine (55%, n = 645). During this 5-year period, 124 total patients were discharged home with a methadone wean. The median days of invasive ventilation for these previously defined weaning patients (with a minimum of 5 days intubated) was 10.8 days with an inter-quartile range of 7.2–16.8 days.

Patients were sedated in the ICU with opioids, benzodiazepines, dexmedetomidine and occasionally on pentobarbital based on their medical condition, level of sedation and expected duration of mechanical ventilation. ICU nurses titrated medications based on the child's level of sedation using the State Behavioral Scale (Curley, Harris, Fraser, Johnson, & Arnold, 2006). After the patients were no longer critically ill, they were transferred from the ICU to a general care unit where weaning continued. WAT-1 scores were completed by nurses in the general care unit. None of these patients had delirium when weaning in the general care unit.

We compared the 4 quarters immediately before implementation (pretest, n = 219) with the last 4 quarters of the study period (posttest, n = 233) (Table 2). There were no significant differences in the age, sex, or reason for admission to the ICU pretest versus posttest. Before implementation, none of the patients received the intervention.

During the last 4 quarters of the study period, all patients were weaned according to the newly implemented guidelines. Post-intervention there was a significant difference in the number of patients discharged on home weaning from both opioids and benzodiazepines (11%, n = 24/219 pre; 3%, n = 7/233 post; $p < 0.005$). Patients discharged with a methadone wean decreased (7%, n = 16/219 pre; 0%, 0/233 post; p = 0.03) (Fig. 1). Despite keeping patients in the hospital to wean, there were no significant differences in the median hospital LOS (42 pre; 39 post; p = 0.35) and the median LOS decreased throughout the study period (Table 2). Post implementation more children had mild to moderate symptoms of withdrawal (11% pre; 21% post; $p < 0.005$), however, the percentage of severe symptoms remained consistently low (0.6% pre; 1% post; p = 0.11) (Fig. 2).

Summary

In this 5-year study of practice, we describe a paradigm change in how IWS can be managed safety and effectively across a complex pediatric hospital. We were able to demonstrate that weaning guidelines decreased unnecessary variation in practice and allowed for complex weans to be managed within the hospital without increasing LOS. In addition, we demonstrated that this change could be sustained over time and that an interprofessional cross-unit group could successfully work together on a common ICU-related problem.

Because patients weaned more rapidly, we significantly reduced the number of patients being discharged home to wean high-risk medications (opioids and benzodiazepines) without increasing LOS. This is an important safety finding for several reasons. The age of patients weaning from sedatives was young. Sixty-three percent were infants and 86% were <8 years old. Small children who are weaning from enteral medications require liquid medications both because the inability to swallow tablets and because the relatively small decrements (due to weight based dosing). Liquid medications drawn up by parents are associated with miscalculation and dosing error (Yin et al., 2016). Dosing errors with high-risk medications, such as opioids and benzodiazepines, can have serious or even life threatening consequences. Methadone is a particularly dangerous medication in young children as even exploratory ingestions of small volumes have been associated with severe toxicity and fatalities (Torrents, Picot, Glaizal, et al., 2015). Pediatric ICU admissions for opioid toxicity in children have increased significantly, and nearly 20% of these admissions in children < 6 years old were secondary to methadone ingestions (Kane, Colvin, Bartlett, & Hall, 2018).

In addition, limited studies in infants report short and long term neurodevelopmental delays following postnatal opioid exposure (de Graaf, van Lingen, Simons, et al., 2011; Ferguson, Ward, Paule, Hall, & Anand, 2012; Steinhorn, McPherson, Anderson, et al., 2015). Therefore, decreasing opioid exposure through more rapid weaning of sedatives after critical illness may decrease these deleterious effects on the developing brain.

Interpretation

This effort builds on previous work that describes the effects of a protocolized sedation and weaning guideline resulting in less opioid exposure with comparable WAT-1 scores in an ICU setting (Curley, Wypij, et al., 2015). It is important to note that these guidelines allowed for extending the time of weaning if a patient has signs and symptoms of withdrawal.

Best practice for the care of hospitalized, recently critically ill children is an interdisciplinary model of care. One of the major challenges

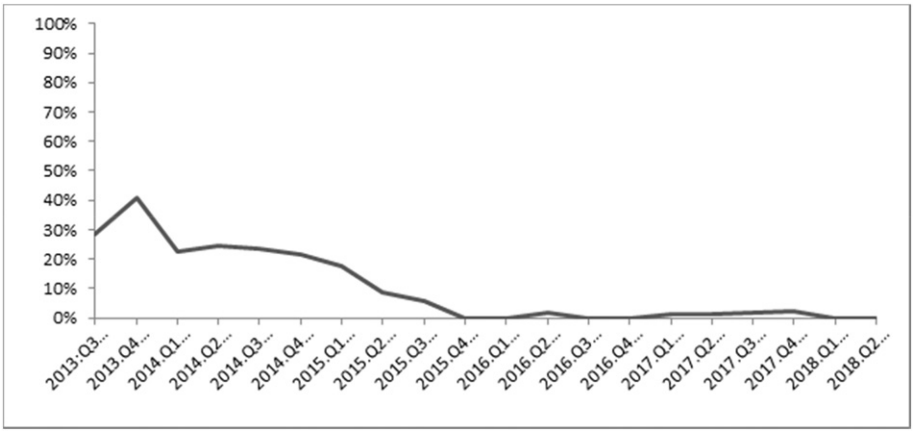

Fig. 1. Percentage of patients discharged with methadone.

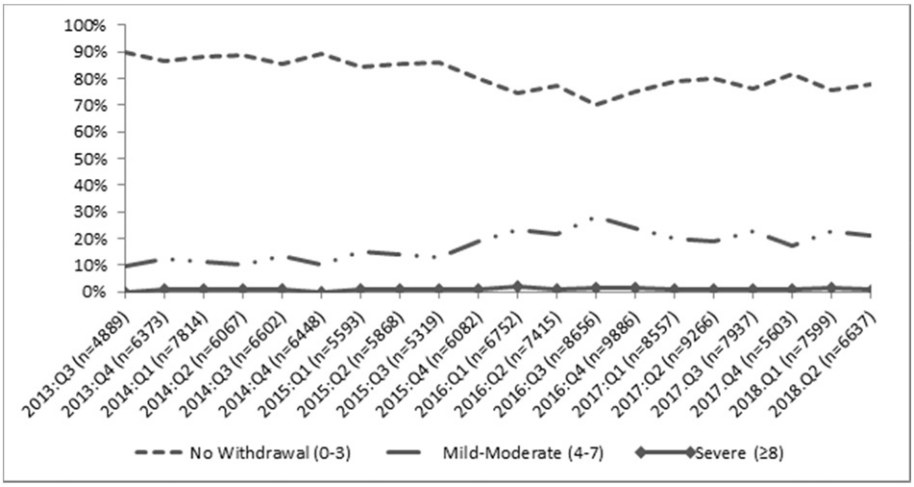

Fig. 2. Percentage of patients with symptoms of withdrawal as measure by WAT-1 scores.

to implementation of this quality improvement effort was having clinicians follow the guidelines. The effort required ongoing education of clinicians and parents as well as resources and references to guide practice. Moreover, this effort required a change in expectations. Previously, we treated patients for mild signs of withdrawal, with pharmacological interventions, while now we expect mild signs of withdrawal as a sign that the pace of weaning is reasonable and only intervene with pharmacological interventions when patients exhibit moderate to severe withdrawal. When consulted, the Pain Treatment Service nurse practitioners were the primary liaison for the general care units with weaning difficulties. This small group of clinicians guided and maintained this change over time. There were no additional costs to the institution to have the Pain Treatment Service manage these patients, because the service was already in place before the initiative.

Limitations

There are several limitations of this study. Data was collected retrospectively from documentation within the electronic medical record. In addition, this quality improvement effort was implemented in a single institution with 24/7 in-hospital coverage by the Pain Treatment Service nurse practitioners with an on-call attending. Results may vary in different settings. We also did not collect detailed patient-level data that would allow risk-adjustment of our LOS data. Delirium was not monitored while patients were in the ICU. Secular trends such as improvements in clinician knowledge could provide a competing hypothesis for our results.

Conclusion

Protocolized weaning guidelines can decrease variation in clinical practice and reduce the number of patients discharged home on potentially dangerous medications with only a modest increase in mild to moderate withdrawal and no significant change in the incidence of severe withdrawal. This can be done even within a complex hospital system.

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CRediT authorship contribution statement

Jean C. Solodiuk: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Visualization, Project administration. **Christine D. Greco:** Conceptualization, Methodology, Writing - review & editing. **Katherine A. O'Donnell:** Conceptualization, Methodology, Writing - review & editing. **Dominick R. Morrill:** Validation, Data curation. **Martha A.Q. Curley:** Conceptualization, Formal analysis, Writing - review & editing, Supervision.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

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