JPPT | Single Center Retrospective Study

Impact of Intravenous Methadone Dosing Schedule on Iatrogenic Withdrawal Syndrome in a Pediatric Intensive Care Unit

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OBJECTIVE To compare median Sophia Observation withdrawal Symptoms scale (SOS) scores between intravenous methadone dosing scheduled every 6 hours or every 8 hours for iatrogenic withdrawal syndrome (IWS).

METHODS This single-center, retrospective chart review evaluated patients aged 4 weeks through 18 years treated with intravenous methadone for IWS. Children admitted to the pediatric intensive care unit (PICU) of a tertiary care children's hospital between August 2017 and July 2021 and treated for IWS for at least 48 hours were eligible for inclusion. Methadone dosing schedules were compared, with a primary outcome of median Sophia Observation withdrawal Symptoms (SOS) score during the first 24 hours after cessation of continuous fentanyl infusion. Secondary outcomes included PICU and general pediatric unit lengths of stay, extubation failure rates, and mortality.

RESULTS Twenty patients met inclusion criteria, with 9 in the 6-hour dosing group. There was no difference in median SOS score, extubation failure, length of stay, or mortality between the 2 groups.

CONCLUSIONS During the first 24 hours after cessation of continuous fentanyl, there appears to be no difference in IWS severity, as determined by bedside nurse scoring, between patients treated with intravenous methadone every 6 hours compared with every 8 hours.

ABBREVIATIONS EMR, electronic medical record; IWS, iatrogenic withdrawal syndrome; OCH, John R. Oishei Children's Hospital; PICU, pediatric intensive care unit; SOS, Sophia Observation withdrawal Symptoms scale

KEYWORDS fentanyl; iatrogenic withdrawal syndrome; methadone; methadone dose frequency; opioid withdrawal; pediatric

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Introduction

Children admitted to the pediatric intensive care unit (PICU) are frequently treated with intravenous opioids for sedation and analgesia. Patients receiving invasive forms of mechanical ventilation usually receive these medications via continuous infusion, often for days or weeks at a time. Although the benefits of therapy (e.g., pain control, ventilator synchrony, reduction of tissue oxygen demands) are clear, intravenous opioid administration is not without consequence.[1,2] Patients exposed to higher doses and/or longer durations are at risk of developing tolerance and physical dependence, especially from continuous infusion.[2–5] In US PICU settings, fentanyl is the most commonly prescribed opiate for these purposes.[6] Data have shown that most children treated with fentanyl infusions for 5 consecutive days will develop withdrawal symptoms after cessation of therapy. Importantly, this risk remains for briefer exposures to sufficiently high, cumulative doses (approximately 1.5 mg/kg); it rises to near certainty for infusions lasting roughly 9 days and/or delivering a total fentanyl burden of 2.5 mg/kg.[7]

Iatrogenic withdrawal syndrome (IWS) presents with central nervous system irritability (e.g., agitation, tremors, insomnia), sympathetic dysregulation (e.g., fever, tachycardia, diaphoresis), and gastrointestinal dysfunction (e.g., vomiting, diarrhea).[8] Pediatric critical care guidelines recommend the use of validated scoring systems such as the Sophia Observation withdrawal Symptoms scale (SOS) to evaluate IWS severity and guide treatment.[9] Our institution utilizes this bedside assessment tool, which contains fifteen equally weighted signs and symptoms of opioid and benzodiazepine withdrawal, tabulated to obtain a cumulative withdrawal score. Values above 3 are considered IWS-symptomatic.[10]

Clinicians have several options for IWS therapy, including morphine, clonidine, methadone, buprenorphine, transdermal fentanyl, gabapentin, and even propofol.[5,11,12] However, not all these agents are standard options in the pediatric population. Therapeutics specific to opiate withdrawal include methadone and extended-release oxycodone or morphine.[9] The ideal medication would have a longer half-life (decreasing the requisite dosing frequency) and favorable oral bioavailability. Methadone has a half-life exceeding 18 hours with reasonable oral bioavailability (75%–80%), making it a viable choice in many intensive care units.[13] Despite this, however, there still exists considerable practice variability regarding timing of initiation, dosing schedules, and bedside monitoring.[9] Data comparing these strategies are lacking.

To our knowledge, no study has evaluated the comparative efficacy of IWS treatment between differing intravenous methadone schedules for children weaned from continuous opioid infusions in a PICU setting. We hypothesize that intravenous methadone administered every 6 hours, beginning 24 hours prior to cessation of a fentanyl infusion, would result in lower SOS scores during the subsequent 24 hours than a dosing schedule of 8 hours.

Materials and Methods

Study Design, Setting, and Patient Population. This was a single-center, retrospective chart review conducted at John R. Oishei Children's Hospital (OCH), a 185-bed, urban, tertiary care, and level 1 trauma center. The OCH operates a 20-bed, medical-surgical PICU that serves patients of all disease phenotypes and subspecialty needs except cardiac surgery.

Medical records for all patients admitted to the PICU between August 1, 2017, and July 31, 2021, were screened, with those children receiving intravenous methadone for IWS eligible for inclusion. The start date was chosen based on our incorporation of SOS scoring into the electronic medical record (EMR). For study inclusion, patients had to be between 4 weeks and 18 years of age at the time of PICU admission and have received intravenous methadone (dosed every 6 or 8 hours) for at least 48 hours with a documented indication of IWS. Children were excluded if they were admitted with severe hypoxic-ischemic or traumatic brain injury; they were also excluded if they had documentation of sympathetic/thalamic "storming," pregnancy, or were still supported by invasive mechanical ventilation 24 hours after starting intravenous methadone. Incomplete SOS documentation (i.e., fewer than 3 scores in the first 24 hours following liberation from opioid infusion) or treatment with a non-fentanyl opioid infusion (e.g., morphine) also warranted exclusion. Per OCH PICU policy, bedside nurses are tasked with SOS documentation every 4 hours once a provider order is placed in the EMR. Our standard practice is placement of this order with discontinuation of any continuous opioid infusing for at least 96 hours. Our previous methadone dosing guideline was a calculation-based model, focused on fentanyl dose required, derived in part from a publication from our institution that used exclusively extended interval dosing (e.g., every-8-hour dosing).[14] Therapy for IWS was started 24 hours prior to anticipated extubation. Conversion from intravenous to enteral methadone typically occurs when SOS scores are 3 or less and is treated as the first opioid wean due to bioavailability of enteral methadone. Over time, attending physicians who joined our team from other institutions had a preference for shorter interval dosing (e.g., every-6-hour dosing).

Data Collection. The EMR queries generated a list of patients admitted to the OCH PICU during the study period who received intravenous, every-6-hour or every-8-hour dosing of methadone for IWS. Demographic data collection included age and weight at start of intravenous methadone, as well as sex and length of stay. Pharmacologic data collection included maximum doses and durations of all sedatives and analgesics, intravenous and enteral methadone dosing information, and details of any "rescue" therapies for breakthrough IWS symptoms. Outcome data included median SOS score for the first 24 and 48 hours following extubation, median SOS score for the first 24 hours following conversion to enteral methadone dosing, extubation failure, and hospital mortality. For the purposes of this study, failure was defined as the replacement of an endotracheal tube within 24 hours of its removal, irrespective of causality.

Study Outcomes. The primary outcome was the median SOS score for the first 24 hours after cessation of continuous fentanyl. Secondary outcomes included PICU and hospital lengths of stay, extubation failure, and mortality. Exploratory outcomes were median SOS score of intravenous methadone dosing schedule on IWS during the first 48 hours and enteral methadone during the first 24 hours upon initiation in each respective cohort.

Statistical Analysis. Descriptive statistics were used to summarize demographic and clinical characteristics of patients. Nominal, categoric data were analyzed using the Fisher exact test. Continuous, nonparametric data were analyzed using the Wilcoxon rank sum. The *a priori* level of significance was 0.05 for all statistical analyses. Data analysis was completed using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics. Of the 178 patients identified receiving intravenous methadone during the 4-year time frame, 20 patients met inclusion criteria for this evaluation. Of these, 9 were treated with every-6-hour dosing and 11 were treated with every-8-hour dosing. The most common reasons for exclusion

were intravenous methadone for less than 48 hours, inadequate documentation of SOS scores, and treatment with non-fentanyl opioid infusion (Table 1). The 2 groups did not differ by age or sex (Table 2). Nearly all (95%; n = 19) study patients were concurrently treated with dexmedetomidine infusions while on fentanyl; fewer than half (45%; n = 9) were treated with midazolam. There was no difference between the groups in receipt of adjunctive therapies (p = 0.93 and 0.99, respectively).

Treatment Characteristics. There was no difference in maximum dose or duration of fentanyl, dexmedetomidine, or midazolam between the 2 groups (Table 2). However, there was a statistically significant increase in the initial intravenous (0.41 vs 0.23 mg/kg/day) and enteral conversion (0.30 vs 0.20 mg/kg/day) methadone dosing in the 6-hour dosing group, compared with the 8-hour dosing group (p = 0.02). Patients initially dosed with intravenous methadone every 6 hours were also treated with enteral formulations for longer (5.9 vs 4.1 days, p = 0.02). There was no difference in the total duration of methadone wean between the 2 groups. The number of "rescue" interventions for breakthrough IWS (e.g., intravenous morphine) did not differ between the 2 groups, nor did the number of deviations from scheduled methadone dosing (e.g., ordered dose withheld, extra dose administered).

Outcomes. There was no difference in median SOS scores between the 2 dosing groups in the first 24 hours after fentanyl discontinuation (Table 3). Likewise, there was no difference between the dosing groups for hospital length of stay, although the latter had a very slight trend toward significance (10 vs 13 days, p = 0.19). There was also no difference in the exploratory outcomes between the dosing groups (Table 3).

Table 1. Reasons for Exclusion

	No. of Patients Excluded (N = 158)
Intravenous methadone for <48 hr	46
Incomplete SOS documentation	33
Concomitant treatment with non-fentanyl opioid infusion	27
Invasive mechanical ventilation 24 hr after starting intravenous methadone	20
Age either <4 wk or >18 yr	14
Indication other than IWS	11
Severe hypoxic-ischemic or traumatic brain injury	6
Sympathetic/thalamic "storming"	1

IWS, iatrogenic withdrawal syndrome; SOS, Sophia Observation withdrawal Symptoms scale

Discussion

The results of this study show no difference in median SOS score for intravenous methadone dosed every 6 or 8 hours in children who received continuous fentanyl infusion at risk for the development of IWS. The shorter duration of general pediatric unit length of stay observed in the 8-hour dosing group may be attributed to patients having a shorter duration of enteral methadone and shorter total duration of methadone wean. Although not evident via presentation of data by median (likely due to sample size), there was a shorter duration of enteral methadone and total duration of methadone wean in the 8-hour group represented by evaluating the midspread or IQR of the data collected. Inversely, the shorter duration in the 8-hour dosing group could be attributed to the statistically significant increase in the initial intravenous and subsequently enteral methadone dose in the 6-hour dosing group contributing to a longer duration of methadone wean to minimum dose. The significant increase in the initial intravenous methadone is due to specific provider practice at our institution by converting fentanyl total daily dose to methadone total daily dose and dividing the total daily methadone dose by 3 for every-8-hour dosing. Some providers added a fourth dose to make a 6-hour dosing schedule, whereas others preferred a less calculation-based approach with dosing of 0.05 or 0.1 mg/kg/dose. This resulted in a higher total daily methadone dose than the previously proven effective conversion from fentanyl to methadone.[14] In regard to timing of transition from intravenous to enteral methadone, transition occurs, in general, when SOS scores are 3 or less. Because of the variability in bioavailability reported with methadone, the change from intravenous to enteral at the same dose is considered the first step in the methadone wean at our institution. It is also common practice at our institution to wean only 1 agent at a time in the first 24 hours, and thus methadone is often weaned to enteral after a patient is transitioned off dexmedetomidine, if applicable. The time to transition to enteral methadone was not different between the 2 groups. Median SOS score of enteral methadone over the first 24 hours upon initiation in each respective cohort was collected to assess if there was any or continued difference in median SOS scores when converted from intravenous to enteral. In addition, there are many indicators of IWS that typically do not include re-intubation or mortality; however, this was a multidisciplinary effort and the medical team was interested in these additional outcomes.

Support for the extension of methadone dosing intervals (e.g., from every 6 hours to every 8 hours) has been published in several pharmacokinetic studies in

Table 2. Patient Baseline and Treatment Characteristics

	Six-Hour Interval (n = 9)	Eight-Hour Interval (n = 11)	p value
Male, n (%)	5 (56)	2 (18)	0.22
Age at start of treatment, median (IQR), mo	14 (8–55)	43 (19–179)	0.09
Weight at start of treatment, median (IQR), kg	8.8 (7.4–19.9)	13.4 (8.8–45)	0.15
Required first adjunctive therapy with dexmedetomidine, n (%)	9 (100)	10 (91)	0.93
Required second adjunctive therapy with midazolam, n (%)	4 (44)	5 (45)	0.99
Maximum fentanyl dose, median (IQR), mcg/kg/hr	5 (4.5-6)	5 (4-6)	0.71
Maximum dexmedetomidine dose, median (IQR), mcg/kg/hr	0.80 (0.7–1)	0.95 (0.7–1)	0.55
Maximum midazolam dose, median (IQR), mg/kg/hr	0.1 (0.075–0.125)	0.05 (0.04–0.10)	0.43
Duration of fentanyl, median (IQR), hr	145 (109–194)	146 (124–199)	0.56
Duration of dexmedetomidine, median (IQR), hr	197 (115–259)	164 (111–188)	0.60
Duration of midazolam, median (IQR), hr	92 (44–133)	90 (36–232)	0.73
Total duration of sedation, median (IQR), days	8.3 (5.9–11.3)	7.9 (6.5–9.3)	0.88
Number of as-needed doses throughout sedation course, median (IQR)			
Fentanyl	22 (17–30)	21 (19–21)	0.56
Benzodiazepines	16 (11–19)	7 (4–24)	0.29
Morphine	0 (0–3)	0 (0-1)	0.82
Number of additional doses of methadone, median (IQR), doses/PICU stay	0 (0-1)	0 (0–1)	0.99
Number of held doses of methadone, median (IQR), doses/PICU stay	0 (0–1)	0 (0)	0.19
Intravenous methadone, median (IQR), mg/kg/day	0.41 (0.20–0.43)	0.23 (0.14–0.33)	0.02
Enteral methadone, median (IQR), mg/kg/day	0.30 (0.22–0.39)	0.20 (0.15–0.30)	0.02
Duration of intravenous methadone, median (IQR), days	2.6 (2.1–3.6)	3.1 (2.7–7.2)	0.12
Duration of enteral methadone, median (IQR), days	5.9 (5.3–10.4)	4.1 (3.2–5.7)	0.02
Total duration of methadone wean, median (IQR), days	8.5 (8.1–14.3)	8.6 (6.8–11.5)	0.50

PICU, pediatric intensive care unit

the pediatric population.[13,15,16] However, the literature is scant on assessment of this dosing extension in the setting of active IWS prevention or therapy in critically ill children, focusing instead on the efficacy of a protocolized weaning practice or various "amount-per-dose" strategies.[17–23] In a work by Steineck and colleagues,[18] 8-hour interval was initiated in patients with minimal risk of withdrawal, defined as duration of opioid infusion less than 5 days, and 6-hour interval was initiated in patients with moderate risk of withdrawal, defined as duration of opioid infusion for 5 or more days. This study was also evaluating a pharmacist-managed methadone taper and found that their protocol resulted in earlier discontinuation of methadone and earlier discontinuation of additional opioid infusions.[18] Although the current study cannot conclude a significant difference between extended interval dosing of methadone, it provides valuable insights into the comparison of different intravenous methadone dosing schedules. The findings of this study, which demonstrate no significant difference in median SOS score between the 6- and 8-hour dosing groups, suggest that an extended dosing interval

Table 3. Primary, Secondary, and Exploratory Outcomes

	Six-Hour Interval (n = 9)	Eight-Hour Interval (n = 11)	p value
SOS score: first 24 hr of intravenous methadone, median (IQR)	1 (0–3)	1 (0–2)	0.86
SOS score: first 48 hr of intravenous methadone, median (IQR)	1 (1–2.5)	1 (0–2)	0.38
SOS score: first 24 hr of enteral methadone, median (IQR)	0 (0–1)	0 (0)	0.24
PICU length of stay, median (IQR), days	15 (14–27)	16 (11–31)	0.84
General pediatric unit length of stay, median (IQR), days	13 (11–20)	10 (7–14)	0.19
Failure of extubation, n (%)	2 (22)	0 (0)	0.60
Mortality, n (%)	0 (0)	0 (0)	0.99

PICU, pediatric intensive care unit; SOS, Sophia Observation withdrawal Symptoms scale

may be considered. Furthermore, the observation of a numerically shorter duration of general pediatric unit stay in the 8-hour dosing group highlights the potential benefit of extended interval dosing.

Strengths of our study include being the first to directly compare SOS scores between different intravenous methadone dosing schedules for the prevention of IWS, and an otherwise homogeneous population for comparison. Patients treated with non-fentanyl opioid or supported by mechanical ventilation 24 hours after the start of intravenous methadone were excluded to result in a more accurate representation of SOS scores for the time of methadone conversion and taper by eliminating the potential confounder of additional sedation. In addition, pharmacotherapy for concomitant sedation and analgesia was collected for representation of sedation needed between the 2 groups for the assessment of a possible confounder if decreased methadone dosing or SOS scores were observed. Publication of the first Society of Critical Care Medicine–endorsed guidelines[9] addressing sedation and withdrawal in PICU patients occurred during the data analysis phase of this study and did not affect study design or results.

Limitations of our study include the retrospective nature of the design, precluding randomization or preintervention and postintervention comparisons. The relatively small sample size, due to the paucity of early SOS scoring in the medical record, may have resulted in a type II error and prevented rejection of the null hypothesis equating early intravenous methadone strategies. The divergence of SOS documentation from ICU policy certainly suggests an opportunity for improvement and quality assurance study. The lack of an appreciable SOS difference between every-6-hour and every-8-hour intravenous methadone intervals may have presented itself if our methodology had followed these patients for a longer duration, which is also an area for future examination. The investigators did not assign or extract SOS scores based on other chart documentation for patients who did not have SOS scores documented. Our practice to prophylactically treat for withdrawal in high-risk patients had long predated our implementation of a validated scoring tool into practice and EMR documentation. Prior to SOS scoring, our institution's therapy plans for rescue doses, wean, or no change for pharmacotherapy for IWS were based on overall assessment of the patient by providers, nurses, and discussion on interdisciplinary rounds. Although vital signs and objective signs of IWS may help include more patients by assigning an SOS score, documentation of more subjective portions of the scoring system are not easily extractable and may result in falsely lower SOS scores if assigned retrospectively. Other common reasons for excluding patients included using intravenous methadone for less than 48 hours and using non-fentanyl opiate infusions prior to the methadone transition. Overall, reconsideration of the inclusion criteria and primary outcome may help to include more patients to achieve the aim in future investigations. There was consideration to extend investigating SOS scores beyond 24 hours, so one of the exploratory outcomes was median SOS score during the first 48 hours. However, consideration of investigating median SOS score during a longer time period may need to be considered in future examinations. Although the SOS scoring system has been validated in children 16 years old or younger, it—like other bedside tools—is imperfect; therefore, any conclusions drawn from its data are subject to those limitations. However, including children up to 18 years of age reflects clinical practice. In addition, significantly higher total dose in the 6-hour dosing group certainly could confound the conclusions because dose rather than frequency could have made a difference in SOS scores, if a difference had been found. The PICU provider discretion in the starting dosages likely influenced the results, and subsequent

research may benefit from the establishment of a standardized or risk-stratified approach. Finally, continuation of dexmedetomidine infusions after extubation for patients deemed "high risk" for IWS is customary practice in our PICU. The continued presence of an α2 agonist may have blunted SOS scores and mitigated the effect of a difference in intravenous methadone intervals despite a lack of significance between groups for dexmedetomidine dose or duration. Unfortunately, duration of dexmedetomidine continuation after extubation was not collected or compared between groups. Providers may have reluctance to wean more than 1 agent at once, preventing the first wean from intravenous to enteral methadone for patients who were still receiving dexmedetomidine. Although fentanyl dose and duration were not different between groups, it is possible that the half-life of continuous infusion fentanyl after several days could have caused lower SOS scores after 24 hours as well. It is also important to consider the potential influence of coadministered medications on the metabolism of methadone. Other medications that are concurrently administered during a patient's PICU stay may have acted as inhibitors or inducers of methadone metabolism, which could affect effectiveness.[24] Inhibitors of methadone metabolism can potentially increase the plasma concentrations and prolong effects, whereas inducers may lead to decreased methadone concentrations and reduce efficacy.[25]

Conclusion

For children receiving fentanyl via continuous infusion, there was no appreciable difference in IWS symptomatology, as determined by SOS scoring, during the first 24 hours after fentanyl cessation for those managed with intravenous methadone every-6-hour dosing and those treated every-8-hour dosing. The current study provides initial evidence that warrants further investigation of effectiveness and additional evaluation of cost based on methadone dosing schedule in the pediatric population because prospective studies during a longer period among other considerations are needed to ascertain the veracity of these findings.

Article Information

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