Impact of a Standardized Treatment Guideline for Pediatric Iatrogenic Opioid Dependence: A Quality Improvement Initiative

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OBJECTIVES: To determine whether utilization of a hospital-based clinical practice guideline for the care of pediatric iatrogenic opioid dependence (IOD) would promote a decrease in opioid exposure and improve management of opioid abstinence syndrome (AS).

METHODS: This study is a retrospective chart review of critically ill patients from a tertiary care children's hospital. Inclusion criteria included mechanically ventilated patients up to 18 years of age who received continuous opioid infusions for at least 7 days and any length of methadone administration. Data on IOD patients from January 2005 to June 2010 was divided into 3 periods: baseline, phase 1, and phase 2. Primary outcome was decrease in opioid exposure, measured by methadone duration of use and any additional opioid bolus doses used in AS management. Documentation of additional opioid bolus doses was regarded as a surrogate measure of AS. Secondary outcomes included total cumulative fentanyl dose, continuous fentanyl infusion duration of use, and hospital and pediatric intensive care unit length of stay.

RESULTS: There was a significant decrease in methadone duration of use in IOD patients from 15.3 ± 8.7 days at baseline to 9.5 ± 3.7 days during phase 1 ($p = 0.002$), to 8.1 ± 3.7 days on phase 2 (reduction not significant, $p = 0.106$) of this evaluation. Additional opioid bolus doses were significantly lower from baseline to phase 1 (5.5 ± 5.1 vs. 1.8 ± 2.3 , $p = 0.001$) and from phase 1 to phase 2 (1.8 ± 2.3 vs. 0.2 ± 1.5 , $p = 0.003$). For the remaining outcomes, differences were not observed among the evaluation periods, except for the total cumulative fentanyl dose, which was reduced from 2.8 ± 3.7 mg/kg at baseline to 1 ± 1 mg/kg only during phase 1 ($p = 0.017$).

CONCLUSIONS: Introduction of a standardized, hospital-based clinical practice guideline for children with IOD reduced the length of exposure to opioids and improved opioid AS management.

INDEX TERMS: methadone, opioid-related disorders, pediatric intensive care unit, quality improvement, treatment protocols

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INTRODUCTION

Continuous administration of intravenous (IV) opioids is considered a part of the standard practice for achieving appropriate sedation in the pediatric intensive care unit (PICU).¹ Although this intervention can reduce stress and speed recovery from critical illness, it is not devoid of complications.² Tolerance and physiologic dependence, or iatrogenic opioid dependence (IOD), can develop as a result of extended exposure to opioids and often manifests as abstinence syndrome (AS) upon drug discontinuation.^{3–15} AS is associated with neurologic, autonomic, and

gastrointestinal abnormalities and can prolong PICU stay and delay hospital discharge.^{5,15} In previous studies of children receiving continuous infusion fentanyl, development of IOD has been shown to be directly related to the total dose or the infusion duration.^{8,15,17,18} For these reasons, discontinuation of treatment should be carefully coordinated. The therapeutic goal is to provide a gradual taper of opioids while minimizing the emergence of AS, thus reducing overall patient distress.

Currently, pediatric IOD management strategies are variable and standardized protocols are lacking. Studies report opioid weaning

times ranging from days to weeks.^{13,14,19–27} Although more recent studies have described the development of clinically useful assessment tools for AS,^{28–31} variability in AS assessment persists.^{11,13,18–25,32–39} Standardization of care, including guideline-based practices, can be an important driving force for improving quality and clinical outcomes. Because pediatric patients at risk for IOD can potentially benefit from such an approach, we developed and implemented a hospital-based guideline for IOD management based on the best available scientific evidence and our hospital-specific resources. Our goals were to 1) eliminate inconsistencies, 2) define specific processes in treatment practices of known or suspected IOD among PICU patients, and 3) assess the impact of this guideline on length of exposure to opioids and opioid AS symptoms. Here, we report our experience to provide a useful framework for others attempting to optimize pediatric IOD care.

MATERIALS AND METHODS

Setting

Our institution is a 248-bed, tertiary care pediatric hospital, located in Mesa, Arizona. The 24-bed PICU has approximately 1400 admissions per year, consisting primarily of medical/surgical patients. Institutional review board approval, with waiver of informed consent for medical record review, was received before initiation of this study.

Baseline IOD Management

Prior to guideline implementation, IOD management was undertaken at the discretion of the treating physicians on a patient-by-patient basis. Fentanyl was the most commonly utilized continuous infusion, and intermittent methadone was used for IOD management in PICU patients with prolonged continuous opioid exposure. Approaches for discontinuation of opioid infusions varied. Methods for weaning intermittent opioids were also variable. Common features of methadone utilization consisted of fixed dose regimens, alternating use with other short-acting opioids, and varying weaning schedules.

Identified Need for Improvement

In 2005, the pain management team received several consultations for PICU patients with

known or suspected IOD, including requests to manage opioid AS, tapering of continuous opioids, and transition to intermittent dosing. An exploratory medical record review exposed gaps in our institution's management of IOD. Consequently, we recognized the need to improve the identification and care of pediatric IOD patients. In June 2006, an institutional quality improvement project was launched, and an interdisciplinary guideline development expert panel was formed. Physician leaders from anesthesiology, pain management, and critical care met periodically with nursing and pharmacy staffs over the next 12 months to review available evidence, identify implementation barriers, and design the guideline.

Key Aspects of the Guideline

The IOD Management Guideline resulted from the combination of an extensive review of related research studies and a consensus opinion of multiple specialists at our institution. It was intended for use in PICU patients with extended continuous IV opioid administration during mechanical ventilation.

The core components of this guideline consisted of 1) identification of patients at risk for IOD, 2) standardization of transition from continuous to intermittent opioids, 3) appropriate tapering rate and discontinuation of opioids, and 4) consistent monitoring of AS.

The opioids most frequently utilized in our PICU, fentanyl and methadone, were integrated into the IOD management algorithm (Appendix 1) to facilitate guideline adoption and promote understanding by physicians and nurses. This algorithm identifies exposure to continuous IV fentanyl administration of 7 days or more as the criterion for application of the guideline. This was based on previous reports demonstrating a direct association between prolonged continuous opioid infusion and IOD development.^{8,15,17,18} Patients meeting guideline use criterion and for whom mechanical ventilation discontinuation is anticipated within 24 to 48 hours will undergo a methadone transition, whereby their opioid regimen is converted from continuous fentanyl to intermittent methadone. This transition takes place in a structured manner so that the fentanyl is usually discontinued within a few hours of extubation. We adopted a conversion that takes into consideration differences in fentanyl and

methadone pharmacokinetic parameters, and was based on previously reported approaches by Tobias and Siddappa and colleagues.^{14,22} Both opioid incomplete cross tolerance and equipotent dosing conversion were addressed, which results in more appropriate opioid conversion approximations when compared to the utilization of fixed, weight-based dosing approaches. The methadone dose obtained is scheduled for administration every 12 hours. Tapering of fentanyl is initiated 12 hours after the first methadone dose. The fentanyl infusion rate is halved at this time and is discontinued with the third methadone dose. Intravenous methadone is switched to enteral administration (1 to 1 ratio) once patients are able to tolerate oral intake. Methadone wean duration is determined by the length of exposure to fentanyl (Appendix 1).

As standardized methods for AS assessment were not available at our institution and valid, reliable assessment tools had not been reported at the time of guideline development, we used a modified version of the Neonatal Abstinence Scale.³² Assessments were done by bedside nurses every 4 hours, or as often as hourly when patients showed signs and symptoms of AS, beginning with the first methadone dose. A patient is considered to have AS only if scored signs and symptoms are persistently elevated within a 4-hour period. If AS is confirmed, then a breakthrough methadone dose is given and AS is reassessed in 1 hour. If AS scored signs and symptoms remain elevated, then another breakthrough methadone dose is given and the attending physician is contacted for further management. A breakthrough methadone dose is equal to 20% of the methadone daily dose obtained during transition from continuous fentanyl to intermittent methadone as described above.

Guideline Implementation and Early Implementation Changes

Upon approval by appropriate institutional committees, an implementation process was initiated in March 2007 with dissemination of the IOD management algorithm (Appendix 1). The guideline development expert panel continued to meet periodically to address implementation-related issues and evaluate the need for additional resources. Encountered barriers included: 1) presence of locum physicians and temporary nursing staff in the PICU, 2) lack of physician and

staff awareness of the guideline, and 3) lack of guideline endorsement by physicians and staff. To mitigate those barriers, pain management team members performed daily PICU rounds to provide consistent support and engage all staff in the newly implemented guideline, and implementation was accompanied by in-services for all nurses routinely caring for IOD patients. In-services included dissemination of handouts containing clear definitions of each AS sign and symptom listed on the AS assessment tool we had adopted. Nurses also received written educational modules incorporating all aspects of the guideline into patient case scenarios. Physicians were educated on the guideline through educational meetings. To address guideline acceptance, a calculation tool was introduced in December 2007; it aided providers in achieving accurate and consistent methadone transition dosing (Appendix 2).

Postimplementation Monitoring

A review of guideline usage, postimplementation, revealed suboptimal compliance. This was assessed mainly by tracking adherence to the IOD management algorithm (Appendix 1) and determining whether guideline use modifications or deviations were present. The most prevalent factor for guideline use deviation was related to the transition period from continuous fentanyl to intermittent methadone. The guideline development panel presented this finding and solicited feedback from PICU physicians and nurses. To improve guideline compliance, a standardized physician order set was instituted in December of 2008. It contained specific transition orders with clear instructions on: 1) methadone starting dose and administration time, 2) fentanyl infusion rate reduction time and subsequent discontinuation, 3) methadone breakthrough dosing and use criteria, and 4) AS monitoring.

Evaluation of the Guideline

A retrospective medical record review was performed for all eligible patients, and it included 3 measurement periods. All mechanically ventilated patients, up to 18 years old, admitted to the PICU between January 1, 2005, and June 30, 2010, were eligible for inclusion if they had received continuous administration of any IV opioid for at least 7 days and 1 or more doses of methadone. All data were obtained from a computerized

data warehouse, nursing flow sheets, medication administration records, and physician and nursing progress notes. The first period (January 2005 through March 2007) was considered the baseline as there were no changes in IOD management. In the next 2 periods, phase 1 (early guideline implementation from April 2007 to September 2008) and phase 2 (postguideline implementation from October 2008 to June 2010), IOD treatment characteristics were targeted for improvement. The main outcome measure was decrease in opioid exposure as measured by methadone duration of use (days) and the number of additional opioid bolus doses (n) needed in the management of AS. Any additional opioid bolus doses were documented, and this variable was used as a surrogate measure of AS. Other IOD treatment variables evaluated were total cumulative fentanyl dose and continuous fentanyl infusion duration of use. We also assessed the influence of hospital and PICU length of stay (LOS).

Patient data collected for all measurement periods included demographic information, Pediatric Risk of Mortality III (PRISM III) score,⁴⁰ comorbidities, ventilator days, chronic ventilator use, hospital LOS, and PICU LOS. Since most IOD cases were among patients experiencing respiratory failure, diagnoses were categorized as either of respiratory or nonrespiratory etiology. Daily administration of all opioids and benzodiazepines were recorded (route, frequency, rate of delivery, cumulative dose, and exposure duration). Cumulative doses (mg/kg) were calculated by adding all intermittent and continuous infusion doses. Data on additional opioid bolus doses, used in AS management, were recorded for all opioid doses given 24 hours after initiation of methadone. All IV opioid doses were converted to equipotent fentanyl doses to facilitate data analysis. Guideline use compliance was also noted.

Statistical Analysis

The evaluation period was sorted into yearly quarters, from quarter 1 of 2005 through quarter 2 of 2010. For some analyses, data were categorized into the 3 measurement periods, which allowed us to determine the effect of practice changes introduced during and after the guideline implementation process. Differences in methadone duration and additional opioid bolus doses across all 3 periods were examined with analysis of variance. We used χ^2 tests for categorical data

and independent t-tests or one-way analysis of variance for continuous data. Multiple linear regressions were used to determine predictors of the outcomes. A 2-tailed $p \leq 0.05$ was considered significant. Statistical analyses were performed using SPSS 20.0 software (SPSS, Chicago, IL).

RESULTS

Demographics

Exposure to methadone and continuous IV opioid administration, meeting inclusion criteria, was documented in 175 patients. We excluded 3 patients with missing data on mechanical ventilation exposure. There were 4 patients who met criteria for inclusion twice, due to either repeated admissions or multiple IOD treatments under 1 admission. The final study sample consisted of 176 IOD observations with overall guideline use documented at 76% (134 IOD observations). Patient characteristics of our PICU patient population did not vary significantly over the study interval (Table 1). All patients received concurrent continuous infusions of benzodiazepines. Standardization of benzodiazepine use and weaning was not included in the IOD management guidelines. Continuous benzodiazepine infusion management and subsequent titrations were done at the discretion of PICU physicians. During the baseline period, 10 patients received continuous infusions of morphine or hydromorphone. There were no IOD cases during the third quarter of 2005 and the third quarter of 2006.

Primary Outcome

Patients in phase 1 were weaned off methadone in an average of 9.5 ± 3.7 days versus 15.3 ± 8.7 days (Table 2) for patients at baseline ($p = 0.002$). Methadone duration did not decrease significantly between phases 1 and 2. Methadone duration was independently predicted by guideline use, total cumulative fentanyl dose, continuous fentanyl duration, and additional opioid bolus doses. There was an overall 3.5-day reduction in methadone duration with guideline utilization, while each additional opioid bolus doses increased methadone duration by about 0.5 day. Figure 1, a moving average control chart for methadone duration, shows a decrease in the average methadone duration over time and decreased variability, reflected in the narrowing of the control limits. There was a 0.5-day reduc-

Table 1. Demographic and Clinical Characteristics of Iatrogenic Opioid Dependence Patients Managed Without and With Guideline

Characteristic	Management Without Guideline (N = 42)	Management With Guideline (N = 134)	p-value
Age, median (IQR), yr	1.9 (0.6-6.4)	1.1 (0.3-3.6)	0.075
Weight, median (IQR), kg	11 (7.9-19.4)	10 (4.9-15)	0.092
Gender, male, n (%)	21 (50)	76 (56.7)	0.480
Race, n (%)			0.319
Hispanic	20 (47.6)	52 (38.8)	
White	14 (33.3)	49 (36.6)	
Native American	2 (4.8)	18 (13.4)	
Black	3 (7.1)	9 (6.7)	
Asian	1 (2.4)	5 (3.7)	
Unknown	2 (4.8)	1 (0.8)	
Diagnosis, n (%), respiratory etiology	35 (83.3)	123 (91.7)	0.143
Co-morbidities, n (%)	16 (38.1)	57 (42.5)	0.720
Ventilator days, mean $\pm$ SD	12.8 $\pm$ 6.4	11.9 $\pm$ 8.3	0.117
PRISM III score, mean $\pm$ SD	6.48 $\pm$ 5.6	6.4 $\pm$ 5.8	0.437
Chronic ventilator use, n (%)	4 (11.9)	5 (3.7)	0.060
Cumulative benzodiazepine dose, mean $\pm$ SD, mg/kg	55.1 $\pm$ 42.2	50.7 $\pm$ 40.5	0.667

IQR, interquartile range; PRISM III, Pediatric Risk of Mortality III²⁹

tion in methadone duration per quarter of the evaluation interval.

There was significant reduction in additional opioid bolus doses needed in AS management in phase 1 compared with baseline (5.5 ± 5.1 vs. 1.8 ± 2.3 , $p = 0.001$, Table 2). Similar reductions occurred between phases 1 and 2 (1.8 ± 2.3 vs. 0.2 ± 1.5 , $p = 0.003$) of the evaluation period. Figure 2, a representation of the quarterly mean number of additional opioid bolus doses, demonstrates a sustained decrease in the overall mean number of additional opioid bolus doses from baseline to phase 1 to phase 2 ($p < 0.001$).

Secondary Outcomes and Guideline Use Compliance

The total cumulative fentanyl dose was significantly lower during phase 1 when compared to baseline (1 ± 0.9 mg/kg vs. 2.8 ± 3.7 mg/kg, $p = 0.017$, Table 2). Continuous fentanyl infusion duration, hospital LOS, and PICU LOS did not change significantly (Table 2).

The guideline was utilized without alterations and deviations in 90 IOD observations (67.1%). Deviations in guideline use did not improve until

after institution of the standardized physician order set in December 2008.

DISCUSSION

Pediatric intensive care unit patients receiving continuous IV opioids who were exposed to a new, multicomponent, guideline-directed, standardized approach to IOD care experienced significant reductions in opioid exposure and improved opioid AS management compared with patients at baseline. Methadone duration, as indicator of opioid exposure, was chosen over other IOD treatment outcomes (continuous fentanyl infusion duration and total cumulative fentanyl dose) that were more likely driven by patient-specific disease state and degree of critical illness rather than guideline utilization. Another indicator of opioid exposure, additional opioid bolus doses needed to manage AS, was used as a surrogate measure of AS. The reduction in additional opioid bolus doses was likely brought about by standardization of methadone dosing and weaning schedules, thus minimizing variability in dosing strategies that were common

Table 2. Outcome Measures at Baseline, Phase 1, and Phase 2 of the Guideline

Outcome	Baseline January 2005 - March 2007 (n = 30)	Phase 1 April 2007 - September 2008 (n = 48)	Phase 2 October 2008 - June 2010 (n = 98)	p-value*
Methadone duration, days	15.3 ± 8.7	9.5 ± 3.7	8.1 ± 3.7	0.002
Additional opioid bolus doses, n	5.5 ± 5.1	1.8 ± 2.3	0.2 ± 1.5	0.001†
Continuous fentanyl infusion duration, days	12.8 ± 4.8	11.0 ± 6.1	11.6 ± 6.2	0.338
Total cumulative fentanyl dose, mg/kg	2.8 ± 3.7	1.0 ± 1.0	0.8 ± 0.7	0.017
Hospital LOS, days	34.0 ± 21.7	27.1 ± 14.3	21.5 ± 14.4	0.242
PICU LOS, days	20.7 ± 12.5	17.5 ± 13.2	16.0 ± 10.6	0.576

LOS, length of stay; PICU, pediatric intensive care unit

* P values reported are related to outcomes between the baseline and phase 1. There were no statistical significant differences found in outcomes between phases 1 and 2, except for additional opioid bolus doses

† P value significant between phase 1 and 2, p = 0.003

in our PICU prior to guideline implementation. Additional opioids/benzodiazepines are commonly utilized when AS is present regardless of

IOD management approach. However, our data indicate that IOD patients managed under the guideline were less likely to have AS. After guideline

implementation, less opioids were needed to control symptoms when emergence of AS was documented. Such findings are of major clinical significance as they relate to the use of a new process that produced desirable, positive outcomes of reduced opioid AS.

Our analyses have demonstrated an independent effect from guideline utilization. At any given continuous fentanyl infusion duration, total cumulative fentanyl dose, and additional opioid bolus doses, there was a substantial reduction in methadone duration. Also, the quarterly 0.5-day reduction in methadone duration indicates a sustained change in opioid exposure after implementation of the guideline (Figure 1). The continuous fentanyl infusion duration did not change significantly during the study interval,

Figure 1. Moving average control chart of methadone duration of use over the study period.

$\bar{X}$, average; LCL, lower control limit; UCL, upper control limit.

A, guideline implementation; B, introduction of methadone transition calculation tool; C, introduction of standardized physician order set.

*Third quarter of 2005 and same quarter for 2006 (no IOD cases) omitted from the x-axis in order to make the moving average accurate.

†Numerical labels and Q, represent each year and quarter of the evaluation interval, e.g., 05 Q1 = Quarter 1 of 2005.

Figure 2. Quarterly mean additional opioid bolus doses used during the study period. A, guideline implementation; B, introduction of methadone transition calculation tool; C, introduction of standardized physician order set.
 *Numerical labels and Q, represent each year and quarter of the evaluation interval, e.g., 05 Q1 = Quarter 1 of 2005.

but there was a significant reduction in the total cumulative fentanyl dose from baseline to phase 1 (Table 2). While we cannot exclude the effect of total cumulative fentanyl dose on emergence of AS, our analysis could not confirm whether the lower total cumulative fentanyl dose observed in phase 1 could have led to a reduction in additional opioid bolus doses. Guideline use may have contributed to a lower total cumulative fentanyl dose by calling for cessation of fentanyl infusions 24 hours after initiation of methadone. This strategy minimized the continuation of opioid infusions for periods beyond mechanical ventilation cessation, a commonly noted feature of IOD management at baseline. Another component of the guideline that may have impacted opioid exposure was periodic and consistent monitoring of AS. This monitoring could have increased staff awareness of AS symptomatology, encouraging more prudent use of opioids. Complete adherence to all aspects of the guideline was achieved in approximately two-

thirds of the observations treated according to the guideline, and associations between guideline use and opioid exposure were observed despite small deviations in application of the guideline.

Clinical challenges encountered in design and implementation of the IOD Management Guideline included the use of a nonvalidated assessment tool for AS monitoring. Valid and reliable assessment tools were not available at the time of guideline implementation; however, because we considered consistent AS monitoring to be an essential aspect of IOD management standardization, we relied on a modified version of the Neonatal Abstinence Scale.³¹

Another challenge was related to the potential for incomplete opioid cross-tolerance during methadone transition. When this phenomenon is seen, the conversion from fentanyl to methadone can be inconsistent and may result in IOD treatment failure. The methadone conversion we adopted did produce relatively predictable results, since AS signs and symptoms were minimal and over sedation was not documented. This approach produced desirable outcomes within our PICU, but it is unclear whether generalization to other institutions may be possible since patient populations may differ.

Iatrogenic opioid dependence in PICU patients is an unavoidable, common occurrence associated with significant morbidity and costs.⁵ In hospitalized children, opioids are the most frequent medication class associated with adverse drug events.⁴¹ Previous studies have described hospital quality improvement processes aimed at reducing opioid-related adverse events, including reductions in AS through weaning

protocols⁴² and some studies have evaluated efforts as improving methadone dosing in IOD.^{19–27} However, we are not aware of previous reports demonstrating a multidisciplinary, collaborative, guideline-based approach to standardizing various aspects of pediatric IOD clinical management as a whole. Establishment of clear patient identification criteria, streamlining IOD care, and incorporating consistent AS monitoring were fundamental elements in achieving improvements in AS management with lower opioid exposure among our PICU patients.

Limitations in evaluation of the effectiveness of the IOD Management Guideline are largely related to the nature of retrospective data analysis, which does not fully allow for control of factors unrelated to the guideline that may have additionally influenced outcomes. This limitation is lessened by the fact that our study sample was fairly homogeneous (Table 1). In that regard, the influence of other sedatives on achieving reductions in opioid exposure is not clear. Intermittent benzodiazepines are routinely used in the management of IOD,^{5,10} and patients with simultaneous prolonged exposure to continuous benzodiazepines can also develop iatrogenic dependence and benzodiazepine-related AS.^{3,6,7,9,43–45} Benzodiazepine use may have attenuated the emergence of AS symptoms in all patients, but it is unlikely that its use affected the reduction in methadone duration and additional opioid bolus doses noted in phases 1 and 2.

A multicomponent, institutional-quality improvement initiative incorporating a standardized hospital-based clinical guideline for pediatric IOD management was associated with reductions in opioid exposure and opioid AS emergence. This guideline could serve as a stimulus for further examination of IOD management strategies and potentially contribute to future research aimed at standardization of care for pediatric IOD patients on a larger scale.

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Abbreviations AS, abstinence syndrome; IOD, iatrogenic opioid dependence; IV, intravenous; LOS, length of stay; PICU, pediatric intensive care unit; PRISM III, Pediatric Risk of Mortality III

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Appendix 1. Pediatric Iatrogenic Opioid Dependence Algorithm

1. Total fentanyl (mg) dose in previous 24 hours

Continuous = Fentanyl dose _____ (mcg) $\times$ patient weight _____ (kg) $\times$ 24 $\div$ 1000 **PLUS**

Intermittent = All intermittent fentanyl doses (mcg) $\div$ 1000

2. Methadone daily dose

Total fentanyl _____ (mg) dose in previous 24 hours $\times$ 2.5

3. Methadone 12-hour dosing

Methadone daily dose _____ (mg) $\div$ 2

4. Methadone dose for breakthrough abstinence syndrome signs and symptoms

Methadone daily dose _____ (mg) $\times$ 0.2 (administered IV)

Appendix 2. Methadone Transition Dosing Calculations