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Cost-Benefit Analysis of a Pediatric ICU Sedation Weaning Protocol

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OBJECTIVE A risk stratified sedation weaning protocol improved patient outcomes in a pediatric intensive care unit (PICU). We sought to determine the protocol effect on medication costs.

METHODS This was a retrospective observational cohort study in an academic tertiary care children's hospital PICU (2018–2020) comparing the cost when weaning benzodiazepine, alpha agonist, and/or opioid infusions in intubated children <18 years of age.

RESULTS There were 84 total sedation weaning instances (pre-protocol n = 41 and post-protocol n = 41); 2 patients had 2 encounters, 1 in each phase. The total cost (in 2022 United States Dollars) of sedation weaning was $400,328.87 ($15,994.44/kg) pre-protocol compared with $170,458.85 ($11,227.52/kg) post-protocol. The median cost of sedation wean per patient for pre-protocol patients was $3197.42 (IQR: $322.66–$12,643.29) and post-protocol patients was $1851.44 (IQR: $425.05–$5355.85; p = 0.275). A linear regression model estimated the expected cost of sedation wean for post-protocol patients to be $5173.20 lower than for pre-protocol patients of the same weight and overall drug risk (p = 0.036). The proportion of withdrawal symptoms in the pre-protocol patients (16%) was not significantly different from the proportion in the post-protocol patients (14%; p = 0.435).

CONCLUSIONS Implementation of a PICU sedation weaning protocol in a single-center conferred cost benefit without negatively impacting patient outcomes. A larger multicenter study would provide insight to the applicability to PICUs in varied settings with differing patient populations.

ABBREVIATIONS CHEERS, the consolidated health economic evaluation reporting standards; IRB, institutional review board; PICU, pediatric intensive care unit; QALYs, quality adjusted life years; REDCap, Research Electronic Data Capture; USD, United States Dollars; WAT-1, Withdrawal Assessment Tool

KEYWORDS clinical protocol; cost-benefit analysis; deep sedation; intensive care units; pediatric

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Introduction

Sedation is important for the safety and comfort of intubated pediatric patients. Sedation use is not standardized in many pediatric intensive care units (PICUs). Our knowledge of the sequelae of sedation exposure for pediatric patients is still growing. Exposure to agents such as benzodiazepines in the short term is associated with delirium and increased length of stay.[1,2] Standardization of sedation weaning may reduce exposure to these agents and therefore reduce their deleterious consequences. Emerging pediatric literature supports improved patient outcomes associated with sedation weaning protocols, and recent pediatric guidelines recommend protocolized sedation weaning.[3–10] In addition to achieving medical goals more efficiently, protocol implementation can provide cost savings.[11] Specifically, protocolizing sedation in 1 adult ICU had an associated cost savings of over $900 per hospitalization.[12] Few pediatric studies look at the cost of a sedation weaning protocol. Only 1 study specifically evaluated the total hospitalization cost associated with a weaning protocol in one pediatric cardiac ICU.[13] Variation in practice between providers is a known phenomenon and can influence cost, as demonstrated in the study by Garland et al,[14] which had a mean difference of $1003 in discretionary costs in an adult ICU based on which provider was managing care. While quality adjusted life years (QALYs) is the gold standard to assess how a practice change such as a protocol impacts a patient, this is not easily achieved in pediatrics for many reasons. For example, the health state classification tools do not account for child development and exclude children less than 5 years old in addition to the many confounders that occur when asking a parent to measure their child's health and value.[15] Additionally, the long-term impact that sedation exposure has on QALYs on the developing pediatric brain does not yet exist in the literature.[16] This study sought to assess the cost benefit of implementing

a sedation weaning protocol in the PICU. We hypothesized that the cost to the hospital would be reduced after implementation of a sedation weaning protocol without an increase in patient withdrawal symptoms.

Materials and Methods

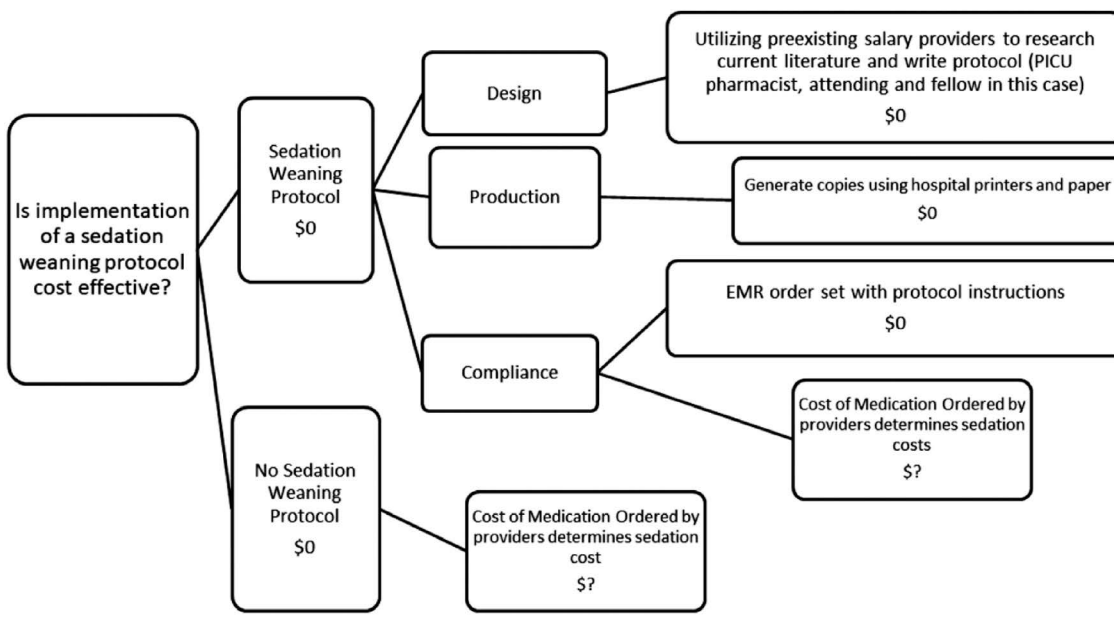
Study Design and Patient Population. This study was a single-center, retrospective observational cohort study in a 42-bed tertiary care academic children's hospital PICU. A risk stratified sedation weaning protocol was created by PICU pharmacists and physicians and implemented unit wide in September 2019 as part of a quality improvement initiative (Supplemental Figures S1, S2, and S3). The protocol delineated a risk stratification system based upon duration of sedation exposure with a recommended timeline to wean infusion and initial habituation medication dose (if patient qualified for one).[10] In addition, the protocol included parameters to modify the wean if a patient experienced withdrawal symptoms. Pre-protocol patients were weaned based upon individual physician preference with no consistent timeline for wean or guideline for initiation of habituation medication.

Patients were screened for eligibility using a pharmacy generated list of PICU patients with orders for an alpha agonist, benzodiazepine, or opioid infusion during a 12-month period before the protocol (January 2018–December 2018) and a 12-month period after protocol implementation (September 2019–August 2020). Patients <18 years of age were included if they were intubated and required a sedative or analgesic infusion for at least 3 days. Patients chronically exposed to any of the medication classes pre-admission, transfer patients who were already undergoing a sedation wean, and those receiving sedative and analgesic infusions for comfort care at end of life were excluded from the study.

Relevant data were collected from electronic medical records and pharmacy billing data. Collected demographic data included primary admitting diagnosis (respiratory, cardiac, neurological, trauma, toxin, infectious, and other), age, sex, and dosing weight. Clinical data included number of days on sedative and analgesic infusions and days weaning infusions, infusion doses, amount of each habituation medication, cost of each medication, withdrawal symptoms, PICU length of stay, hospital length of stay, and if patient was discharged on habituation medications. If a medication dose was given for an indication other than treatment of withdrawal (for example, lorazepam but given for seizure abortion), it was excluded. Withdrawal treatment in those on more than 1 infusion was based on clinical judgement with consideration of weaning pattern and patient response to an as needed dose of the drug class. Using the predefined sedation weaning protocol risk categories based on infusion exposure duration, patients were categorized as low risk (less than 5 days), moderate risk (5–7 days), high risk (8–30 days) and very high risk (greater than 30 days) for each individual drug class.

Outcomes. This cost analysis was guided by the consolidated health economic evaluation reporting standards (CHEERS).[17] A decision tree diagram (Figure 1) showed that implementation of the sedation

Figure 1. Decision tree for implementing a sedation weaning protocol.



EMR, electronic medical record; PICU, pediatric intensive care unit

weaning protocol cost $0 with the assumptions specified and therefore comparing the variable cost of medications ordered with and without the protocol described the total cost difference in this study. The primary outcome of interest was comparison in medication costs prior to and after implementation of a sedation and analgesia weaning protocol. An institutional perspective was taken in which health care costs and costs to produce and maintain the protocol were included. Of note, the opportunity cost of the time, the value of time used in terms of wage that takes away from the time of the employee to complete other job duties, used by the personnel is not described quantitatively. A health economic analysis plan was not developed for this economic evaluation. Cost was defined as the amount in United States Dollars (USD) that the hospital incurred for the total amount of the medication that the patient received for weaning purposes. Cost calculation began when the infusion began to be tapered with documentation of intent to wean off and not titrate to sedation goal. Cost calculation included tapering infusions and habituation medications initiated during tapering of the infusion. Data were collected on patients until the last dose of habituation medication or until discharge from the hospital, whichever occurred first.

Secondary outcomes included the presence of withdrawal symptoms. Withdrawal symptoms were evaluated to determine if patients experienced more adverse side effects with use of the protocol. A validated pediatric assessment tool for withdrawal, the Withdrawal Assessment Tool (WAT-1), was used.[18,19] A score greater than 3 was considered a clinically significant withdrawal necessitating rescue medications. All recorded WAT-1 scores were included, and the proportion WAT-1 scores >3 (calculated by dividing number of scores >3 divided by total number of WAT-1 scores collected) were used to describe withdrawal. Data were retrieved from patient electronic medical records then stored and managed using REDCap (Research Electronic Data Capture) tools hosted at Vanderbilt University. REDCap is a secure, web-based software platform designed to support data capture for research studies (https://projectredcap.org/).[20] Cost data were obtained from the pharmacy department and reflected the direct cost to the hospital pharmacy for the medication during the study years of 2018 to 2020 without accounting for the cost of compounding the medication (see Supplemental Table S1). The cost of medications was the same in the pre-protocol and post-protocol periods.

Statistical Analysis. Patient demographics were compared using descriptive statistics. Categorical data were reported with frequencies and percentages and continuous variables were described with means, SDs, medians, and IQRs. Differences in categorical variables were assessed via χ^2 test and differences in continuous variables were assessed via the Student *t* test. The individual drug class costs, total cost of sedation wean, and costs by drug class risk category of the 2 groups were compared using means, SDs, medians, and IQRs along with the non-parametric Wilcoxon rank sum test (continuity-corrected in presence of ties). The total cost for each patient was determined by calculating the cost of the total milligrams (or micrograms) infused from the time that the weaning of the infusion was started until discontinuation of the infusion plus the cost of all medication doses given for withdrawal treatment or prevention during the remaining hospital stay; for example, the total cost of benzodiazepines was the cumulative cost of the midazolam and/or lorazepam infusion once weaning was initiated plus intermittent lorazepam. The total cost for each patient was then divided by the patient weight in kilograms to create weight based cost. Weight-adjusted cost was compared to allow the cost difference to account for pediatric dosing in which the size of patient determined the dose and affected the cost. A p value of 0.05 or less was considered statistically significant.

A linear model was fit to quantify the difference in total cost of sedation wean between the pre- and post-protocol periods. Patient weight and overall risk score were included in the model as covariates. An overall drug risk score was used in the model to account for multiple drug risk categories in some patients. A patient's overall risk score was an aggregation of the patient's opioid, benzodiazepine, and dexmedetomidine risk categories. Low risk corresponded to a value of 1, moderate risk 2, high risk 3, and very high risk 4 for each drug category. The maximum possible overall drug risk score was 12. A formal uncertainty analysis was not performed due to the small sample size and limited data that exists concerning QALYs and pediatric sedation exposure. An acceptable alternative of a decision analysis was employed to describe the cost-utility of protocol implementation. All statistical analyses were performed using R version 4.2.2.

Results

Eighty-two patients met study inclusion criteria, with 41 treated during the pre-protocol period and 41 treated in the post-protocol period. Two patients had 2 encounters, 1 in each phase, for a total of 42 pre-protocol encounters and 42 post-protocol encounters with no crossover between pre-protocol and post-protocol. Table 1 describes patient demographics and clinical variables, with no statistically significant differences in the age, weight, sex primary diagnosis, or sedation risk categories. Of the 84 total encounters, 4 (2 pre-protocol, 2 post-protocol) were on only 1 infusion, 44 (23 pre-protocol, 21 post-protocol) were on 2 infusions, and 36 (17 pre-protocol, 19 post-protocol) were on 3 infusions. There were 48 encounters (27 pre-protocol, 21 post-protocol) where intermittent weaning

Table 1. Patient Demographics

	Pre-Protocol (N = 42)	Post-Protocol (N = 42)	p value*
Age, mo	60.0 [11.8–120]†	34.5 [4.25–105]	0.443
Weight, kg	19.1 [8.44–37.9]	15.5 [5.12–31.7]	0.288
Sex (female), n (%)	21 (50.0%)	21 (50.0%)	1
Primary Diagnosis, n (%)			
Respiratory	21 (50.0%)	24 (57.1%)	
Trauma	6 (14.3%)	5 (11.9%)	
Neurological	5 (11.9%)	2 (4.8%)	
Infectious	2 (4.8%)	6 (14.3%)	
Cardiac	0 (0%)	0 (0%)	
Other	8 (19.0%)	5 (11.9%)	
Hospital length of stay, days	27 [16–36]	25 [17–37]	0.822
ICU length of stay, days	17 [12–24]	17 [12–24]	0.965
Discharged home on medications, n (%)	19 (45.2%)	18 (42.9%)	1

ICU, intensive care unit

* P-value derived from 2-sample *t* test for numeric variables and χ^2 test for categorical variables.

† Values shown are median [first, third IQR].

medications were not used: 10 opioid (7 pre-protocol, 3 post-protocol) infusion exposures, 11 benzodiazepine (8 pre-protocol, 3 post-protocol) infusion exposures, and 27 alpha-agonist (12 pre-protocol, 15 post-protocol) infusion exposures (Supplemental Table S2). The total cost of sedation weaning was $400,328.87 in the pre-protocol cohort compared with $170,458.85 in the post-protocol cohort with a median total cost per patient for pre-protocol patients of $3197.42 (IQR: $322.66–$12,643.29) compared with $1851.44 (IQR: $425.05–$5355.85) post-protocol (p = 0.275; Supplemental Table S2). The results of a regression model indicated that the expected cost of sedation wean for patients with a particular weight was $190.56 more than patients weighing 1 fewer kilogram but with the same protocol classification (pre/post-protocol group) and overall drug risk profile (p = 0.001), and the expected cost of sedation wean for patients in a particular risk category was $2304.98 more than a patient in the adjacent, lower risk category with the same protocol classification and weight (p < 0.001; Supplemental Table S3). Since patient weight and risk category influenced the cost, they were included in the linear regression model, which estimated a reduction of expected cost of sedation wean of $5173.20 for post-protocol patients compared with pre-protocol patients of the same weight and overall drug risk (p = 0.036).

Regarding the risk categories, the protocol provided significant savings in the high risk opioid group with a median pre-protocol cost of $2.82/kg (1.23–4.71) and $1.17/kg (0.39–4.25) post-protocol (p = 0.049; Table 2). The weight-adjusted infusion wean costs were significantly reduced for opioids (p = 0.008) and benzodiazepines (p = 0.015; Supplemental Table S2). Although the alpha agonist infusion dexmedetomidine is notably more expensive than the other infusions, the number of times infusions were used in both groups were not starkly different and there was no statistically significant difference in the cost. Withdrawal symptoms, as denoted by proportion of WAT-1 scores greater than 3, did not differ significantly between the 2 groups with 0.164 pre-protocol and 0.138 post-protocol (p = 0.435; Figure 2). No readmissions for withdrawal treatment occurred in either group.

Discussion

Sedation is an unavoidable exposure for most mechanically ventilated children in the PICU. Efficient, structured weaning of sedation may improve patient clinical outcomes, as well as confer cost savings. Linear regression analysis indicated an expected cost savings of $5173.20 in the post-protocol patients of the same weight and overall risk profile. In addition, the protocol did not increase patient withdrawal symptoms in order to achieve these cost savings. This study adds to the growing evidence supporting the benefits of protocolized sedation weaning in critically ill children.

The protocol had the most significant impact on the cost in the high risk opioid group. This could be reflective of the larger number of patients in this drug class and risk group and thus more power to delineate differences between the pre- and post-cohorts. Further analyses with more patients is warranted to determine if the protocol functions the best for a specific drug or risk category.

Prior pediatric studies have observed clinical benefits with sedation weaning protocols.[3,4,6,7,9,10] Adult studies have observed cost savings with protocolized weaning as well.[11,12] Compared with the adult study cost savings of about $900 per hospitalization, this study showed a predicted savings of around $5000 per hospitalization. This difference could be accounted for with different targeted depth of sedation and therefore different quantity used or potentially that different sedation and analgesia medications are used with large cost differences among the different agents. Further studies are needed to clarify reasons for potential cost savings differences between adult and pediatric patients. This

Table 2. Cost Comparison by Risk Category of Drug Class

	Pre-Protocol	Post-Protocol	p value
Opioid			
Low risk, n	1	0	
	$0.48/kg		
Moderate risk,* n	10	12	0.381
	$0.97/kg [0.26–1.42]	$1.10/kg [0.65–2.17]	
High risk, n	27	26	**0.049**
	$2.82/kg [1.23–4.71]	$1.17/kg [0.39–4.25]	
Very high risk, n	2	3	0.4
	$21.30/kg [16.40–26.20]	$44.00/kg [27.80–55.40]	
Benzodiazepine			
Low risk, n	5	5	0.666
	$0.09/kg [0–0.14]	$0.54/kg [0–0.81]	
Moderate risk, n	8	12	0.238
	$1.73/kg [0.98–2.11]	$0.72/kg [0.23–1.48]	
High risk, n	14	9	0.877
	$3.62/kg [2.24–4.99]	$2.74/kg [1.78–5.72]	
Alpha agonist			
Low risk, n	7	7	0.522
	$44.40/kg [35.80–194.00]	$79.00/kg [17.30–99.00]	
Moderate risk, n	7	6	0.101
	$183.00/kg [155.00–292.00]	$56.80/kg [35.30–165.00]	
High risk, n	17	24	0.312
	$382.00/kg [199.00–674.00]	$231.00/kg [144.00–531.00]	
Very high risk, n	2	2	0.333
	$1,800.00/kg [1,760.00–1,840.00]	$139.00/kg [123.00–155.00]	

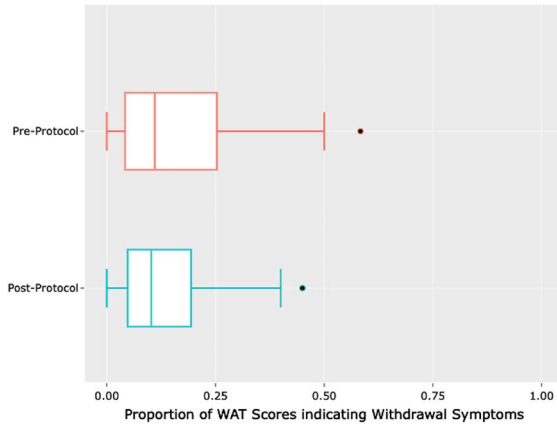
Bold indicates statistically significant.

* For each risk category, median [first quartile, third quartile] is displayed.

is one of the only pediatric studies to assess cost savings with a sedation weaning protocol. Protocolizing the wean resulted in less time on sedative and analgesic infusions, which resulted in cost savings. The inclusion of titration orders and instructions based upon the desired depth of sedation and presence of withdrawal symptoms in the protocol allowed for faster, goal-oriented adjustment of infusions. Although not assessed in this study, there is an opportunity to study whether sedation weaning protocols contribute to reduced need for intravenous access and potentially central lines, and as such potentially lowering infection risk and allowing for earlier and more extensive patient mobility.

This study has several limitations. Patients were not followed after discharge and as such this study does not account for the cost of the weaning medications once discharged from the hospital. Similar numbers of patients were discharged home on weaning medications (19 [45%] patients in the pre-protocol group and 18 [43%] patients in the post-protocol group). Our primary outcome of interest was cost incurred by our hospital, and discharge medications were not provided by our inpatient pharmacy, so as such these medications did not apply to our direct costs. Future studies should include discharge medications as well to more fully describe total cost burden. Other limitations include

Figure 2. Box and whisker plot describing each sedation instances recorded proportion of withdrawal symptoms elevated to a level that would need clinical intervention.



WAT, Withdrawal Assessment Tool

small sample size, and further studies should assess cost savings over a longer period to assess true effect. At our institution, we implemented the protocol without increased staff or resources. This may not be possible at other institutions or hospitals, and as such cost savings may vary based on environment. The influence and presence of contract discounts, 340b pricing, and/or a 503b utilization discount on the gross price of medications is unknown, so that is not generalizable to other institutions. Future studies should assess multicenter protocolization and associated patient outcomes and cost savings.

Conclusion

Implementation of a risk-stratified PICU sedation weaning protocol conferred cost savings. Future studies are needed to assess effects in a large population and applicability to varied health care settings.

Article Information

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Disclosure. For the affiliation with the Air Force for the first author, Chiara Velez, the views expressed are those of the author and do not reflect the official policy or position of the United States Air Force, Department of Defense or the United States Government. Otherwise, the authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethical Approval and Informed Consent. Given the nature of this study, institutional review board/ethics committee review and informed consent were not required. This study was IRB #212123 at the Vanderbilt IRB and was deemed exempt from full review with approval to proceed granted.

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