Association Between Deep Sedation from Continuous Intravenous Sedatives and Extubation Failures in Mechanically Ventilated Patients in the Pediatric Intensive Care Unit

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OBJECTIVE The primary objective of this study was to determine whether an association exists between deep sedation from continuous infusion sedatives and extubation failures in mechanically ventilated children. Secondary outcomes evaluated risk factors associated with deep sedation.

METHODS This was a retrospective cohort study conducted between January 1, 2009, and October 31, 2012, in the pediatric intensive care unit (PICU) at Duke Children's Hospital. Patients were included in the study if they had been admitted to the PICU, had been mechanically ventilated for ≥ 48 hours, and had received at least one continuous infusion benzodiazepine and/or opioid infusion for ≥ 24 hours. Patients were separated into 2 groups: those deeply sedated and those not deeply sedated. Deep sedation was defined as having at least one documented State Behavioral Scale (SBS) of -3 or -2 within 72 hours prior to planned extubation.

RESULTS A total of 108 patients were included in the analysis. Both groups were well matched with regard to baseline characteristics. For the primary outcome, there was no difference in extubation failures in those who were deeply sedated compared to those not deeply sedated (14 patients [22.6%] versus 7 patients [15.2%], respectively; $p = 0.33$). After adjusting for potential risk factors, patients with a higher weight percentile for age (odds ratio [OR] 1.02; 95% confidence interval [CI] 1.00-1.03), lower Glasgow Coma Score (GCS) score prior to intubation (OR 0.85; 95% CI 0.74-0.97), and larger maximum benzodiazepine dose (OR 1.93; 95% CI 1.01-3.71) were associated with greater odds of deep sedation. A higher GCS prior to intubation was significantly associated with increased odds of extubation failure (OR 1.19; 95% CI 1.02-1.39).

CONCLUSIONS While there was no statistically significant difference in extubation failures between the 2 groups included in this study, considering the severe consequences of extubation failure, the numerical difference reported may be clinically important.

ABBREVIATIONS ERT, extubation readiness test; GCS, Glasgow Coma Scale; SBS, State Behavioral Scale

KEYWORDS airway extubation; deep sedation; extubation failure; sedation; sedatives

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Introduction

Analgesia and sedation are integral components in the management of critically ill patients, with over 90% of children supported by mechanical ventilation receiving sedative medications.^{1,2} Sedation provides amnesia, reduces anxiety, minimizes stress response, and improves tolerance to mechanical ventilation. However, when studied in critically ill children and adults, continuous infusion sedation has been associated with adverse outcomes such as increased rates of extubation failure, prolongation of mechanical ventilation, increased risk for the development of ventilator-associated pneumonia, and increased intensive care unit and hospital length of stay.³⁻⁶

In an attempt to mitigate these deleterious effects, the degree of sedation should be frequently evaluated. Patients can be assessed using standardized, validated tools that describe a patient's behavioral state, and this assessment can be used to titrate sedation infusions.⁷ The State Behavioral Scale (SBS) is a reliable tool used to assess the level of sedation in mechanically ventilated pediatric patients.⁷ This scoring system describes the sedation-agitation continuum, with more negative numbers (-3) reflecting a more sedated state and more positive numbers ($+2$) reflecting a more agitated state (Table 1). Most mechanically ventilated pediatric patients have a target SBS of -1 (responsive to gentle touch or voice) or 0 (awake and able to calm).^{2,5}

The overall goal for most patients supported by me-

Table 1. State Behavioral Scale*

-3	Unresponsive
-2	Responsive to noxious stimuli
-1	Responsive to gentle touch or voice
0	Awake and able to calm
+1	Restless and difficult to calm
+2	Agitated

*Score is based on patient's response to voice, then touch, and then noxious stimuli⁷

chanical ventilation is to attain a calm, yet responsive and arousable, state, thereby protecting the patient from self-harm.^{2,5} However, the selection and method of administering sedative and analgesic medications are highly variable.³ Continuous infusions are frequently used in critically ill patients as a means to provide controlled administration and a continuous level of sedation; however, optimum management of continuous infusion sedation remains unknown.^{8,9} The recently completed RESTORE study¹⁰ compared protocolized sedation management in pediatrics compared with standard of care and found no difference in mechanical ventilation days or hospital length of stay. However, the investigators did not specifically look at levels of sedation and extubation failure.

In the adult population, continuous infusion sedation has been associated with increased risk for extubation failure. Extubation failure has been defined¹¹ as the requirement for reintubation within 24 to 48 hours after elective extubation. Rates of extubation failure in pediatric intensive care units range from 2.7% to 22%.¹²⁻¹⁴ Risk factors for extubation failure, identified in critically ill adults, include upper airway obstruction, pulmonary insufficiency, cardiac dysfunction, neurological impairment, poor muscle strength, and excessive sedation.^{13,14} Limited literature exists regarding pediatric sedation and extubation failure. Predictors identified in pediatric patients include age less than 3 months, duration of mechanical ventilation of greater than 15 days, lower tidal volumes, higher oxygen requirements, higher peak inspiratory pressure, or low compliance; however, level of sedation has not been evaluated as a risk factor for extubation failure in pediatric patients.¹²⁻¹⁴ Fontela and colleagues¹⁴ did determine that pediatric patients on intravenous sedation greater than 10 days were at a higher risk for extubation failure, but they did not specifically look at levels of sedation as a predictor for extubation failure. Therefore, the primary objective of this study was to determine whether an association exists between deep sedation from continuous infusion sedatives and extubation failures in mechanically ventilated children.

Materials and Methods

After institutional review board approval was re-

ceived, a retrospective chart review was conducted. Patients were included in the study if they had been admitted to the pediatric intensive care unit between January 1, 2009 and October 31, 2012; if they had been mechanically ventilated for longer than 48 hours; and if they had received at least one continuous infusion benzodiazepine and/or opioid infusion for longer than 24 hours. Patients were identified utilizing a data repository. Patients who were neurologically devastated, opioid or benzodiazepine tolerant (defined as receiving scheduled benzodiazepine or opioid medications longer than 24 hours prior to intubation), who had received continuous infusion neuromuscular blockade, who had been placed on extracorporeal membrane oxygenation support, or who underwent mechanical ventilation via tracheostomy were excluded from the study. Patients were also excluded if medical records were incomplete or if the patient died during hospitalization. Patients with multiple eligible hospital admissions were only included once in the study.

Data collected included age, weight, sex, height, Glasgow Coma Scale (GCS) prior to intubation, primary diagnosis at the time of intubation, dates of mechanical ventilation, extubation readiness test (ERT) results, and extubation outcome. Continuous infusion administration, bolus dosing, and SBS data were collected up to 7 days prior to elective extubation. Intravenous opioid medications were converted to fentanyl equivalents and intravenous benzodiazepine medications were converted to midazolam equivalents utilizing standard conversions.^{15,16}

Patients were separated into 2 groups: those deeply sedated and those not deeply sedated. The primary outcome of the study was the incidence of extubation failure among patients who were deeply sedated compared to those who were not. Deep sedation was defined as having at least one documented SBS of -3 (unresponsive) or -2 (responsive to noxious stimuli) within 72 hours prior to extubation. Extubation failure was defined as the need for reinstitution of ventilator support within 48 hours of a planned endotracheal tube removal. Secondary outcomes included evaluation of risk factors associated with deep sedation and extubation failure. Risk factors evaluated included age, sex, weight percentile by age, daily opioid dose, daily benzodiazepine dose, GCS prior to intubation, duration of mechanical ventilation, duration of continuous infusions, and number of failed ERTs. Extubation readiness tests were performed daily on all intubated patients meeting the following criteria: spontaneous respiratory drive, dead space volume to tidal volume ratio of <0.6 from the previous blood gas, FiO₂ less than 50%, stable or decreased ventilator support in the previous 12 hours, and hemodynamic stability. The patients' SpO₂ values, tidal volumes, and respiratory rates were monitored for 60 to 90 minutes. Patients must have remained in the age-specified ranges for respiratory

Table 2. Patient Demographics

Characteristic	Deeply Sedated (n = 62)	Not Deeply Sedated (n = 46)	p Value
Male, n (%)	39 (62.9)	29 (63.0)	0.961
Median age, yr (IQR)	3.3 (0.5-13.6)	1.1 (0.2-9)	0.090
Median weight, percentile for age (IQR)	50 (10-75)	17.5 (7.5-50)	0.075
Median GCS prior to intubation, score (IQR)	7 (6-11)	9 (7-13)	0.070
Diagnosis at time of intubation (%)			
Pulmonary	11	3	
Cardiovascular	4	2	
Neurological	9	4	
Infectious disease/sepsis	10	13	
Congenital anomaly	1	10	
Gastrointestinal	4	2	
Oncology/bone marrow transplant	4	4	
Trauma	13	5	
Metabolic	2	1	
Surgery/transplant	4	2	

GCS, Glasgow Coma Scale; IQR, Interquartile Range

rate and SpO₂ with tidal volumes greater than 5 mL/kg to pass the ERT.

A sample size of 180 patients was estimated to provide 82% power to detect a 15% absolute increase in extubation failures for deeply sedated patients, assuming an extubation failure rate for pediatric patients who are not deeply sedated of 10%. Baseline demographics were analyzed using a chi-square test for categorical variables and a non-parametric Wilcoxon Rank Sum test for continuous variables. The primary endpoint was evaluated using a 1-sided chi-square test at a significance level of $p = 0.05$. The risk factor analysis utilized univariate and multivariate logistic regression. Covariance-adjusted odds ratios and their corresponding 95% confidence intervals were estimated for the final set of risk factors in the models. Analyses were completed using SAS v9.3 (SAS Institute, Cary, NC).

Results

One hundred twenty-nine patients were originally identified for inclusion. Of those, 21 patients were excluded (11 patients due to tracheostomy, 7 who died during hospitalization, 2 who received continuous infusion sedation for less than 24 hours, and 1 who was neurologically devastated). A total of 108 patients were included in the analysis, representing 62 deeply sedated patients and 46 patients who were not deeply sedated. Both groups were generally well matched with regard to baseline characteristics, although more patients admitted for pulmonary disease or trauma were included in the deeply sedated group and more patients with congenital anomalies were included in

the not deeply sedated group (Table 2). Additionally, patients in the deeply sedated group tended to be older and heavier, although the differences were not statistically significant. One hundred and six (98%) patients received a continuous infusion of fentanyl, 106 (98%) patients received a continuous infusion of midazolam, and 4 (4%) patients received a continuous infusion of morphine within 7 days prior to extubation.

There was no statistically significant difference in extubation failures between deeply sedated patients (14, 22.6%) and those who were not deeply sedated (7, 15.2%; $p = 0.33$). Additional cohort results are listed in Table 3. After adjusting for potential risk factors, patients with a higher weight percentile for age (odds ratio [OR] 1.02; 95% confidence interval [CI] 1.00-1.03), lower GCS score prior to intubation (OR 0.85; 95% CI 0.74-0.97), and larger maximum benzodiazepine dose per day (OR 1.93; 95% CI 1.01-3.71) were associated with greater odds of deep sedation. There was no difference in terms of ERT failures in patients who were deeply sedated compared to those who were not deeply sedated (13 patients [21.0%] versus 8 patients [17.4%], respectively). Higher GCS score prior to intubation was associated with increasing odds of extubation failure (OR 1.19; 95% CI 1.02-1.39). Longer durations of mechanical ventilation (OR 1.10; 95% CI 0.97-1.25) and larger maximum benzodiazepine dose per day (OR 1.47; 95% CI 0.71-3.05) were not associated with greater odds of extubation failure.

Discussion

Rates of extubation failure in this study were consistent with those reported in the literature.¹²⁻¹⁴ Recent

Table 3. Results by Cohort

Characteristic	Deeply Sedated (n = 62)	Not Deeply Sedated (n = 46)	p Value
Median maximum opioid dose in fentanyl equivalents, mg/kg/day (IQR)			
Continuous	0.061 (0.038-0.089)	0.071 (0.045-0.108)	0.334
Bolus as needed	0.006 (0.002-0.013)	0.004 (0.002-0.011)	0.450
Total	0.072 (0.045-0.096)	0.081 (0.052-0.121)	0.280
Median maximum benzodiazepine dose in midazolam equivalents, mg/kg/day (IQR)			
Continuous	2.460 (1.431-4.755)	1.596 (0.722-4.431)	0.176
Bolus as needed	0.898 (0.523-2.321)	0.957 (0.488-1.800)	0.777
Total	4.477 (2.102-6.911)	3.108 (1.355-5.518)	0.165
Duration of mechanical ventilation, days [†]	6.64 ± 4.9	6.76 ± 4.9	0.995
Extubation readiness test failure, n (%)	13 (21.0)	8 (17.4)	0.642
Duration of opioid infusion, days [†]	4.94 ± 3.7	5.71 ± 4.6	0.468
Duration of benzodiazepine infusion, days [†]	5.20 ± 4.9	5.16 ± 5.0	0.765

IQR, Interquartile Range

[†]Mean ± SD

pediatric studies and multiple adult studies report serious consequences of extubation failure, including longer intensive care unit and hospital length of stay, increased costs, and increased mortality.¹⁷⁻²⁵ Esteban et al²³ demonstrated a significant increase in mortality for children failing extubation compared to successful extubations (20% versus 2% respectively; $p < 0.001$). In our study, more deeply sedated patients failed extubation compared to numbers of those not deeply sedated. Although this trend was not statistically significant, it may be clinically significant given the substantial consequences of failed extubations in pediatric patients. Unfortunately, our study was underpowered to evaluate this difference. Additionally, the pediatric literature does not provide an evident, reliable method of assessing readiness for weaning and predicting extubation success.²⁵

Patients with a higher weight percentile for age, larger maximum benzodiazepine dose per day, and lower initial GCS prior to intubation were at greater odds for deep sedation. These data suggest benzodiazepine continuous infusion dosing and dosing in heavier children may need to be reevaluated. Some of our results were inconsistent with our initial hypothesis. Based on the literature,²⁶ we expected patients with neurologic impairment, or a lower GCS prior to intubation, to be at greater risk for extubation failure. On the contrary, this study demonstrated that those patients with a better neurologic prognosis had statistically significant increased odds of extubation failure. This trend could potentially reflect differences in management of patients with lower initial GCS assessments, including closer monitoring or more conservative sedation administration and extubation decisions. Surprisingly, larger maximum opioid dose per day and longer durations of opioid continuous infusion were non-significantly

associated with lower odds for deep sedation. This observation may be due to tolerance or tachyphylaxis. The use of fentanyl in this study may have contributed to this finding, given that synthetic opioids have an increased affinity for the μ -opioid receptor and more rapid development of tolerance than is associated with morphine.^{26,27}

The recently completed RESTORE study¹⁰ evaluated a sedation protocol versus standard of care and found no differences in duration of mechanical ventilation or extubation failure. In general, the patients in the intervention group were less deeply sedated than were those in the control groups. However, the authors did not specifically address the patient's level of sedation as a risk factor for extubation failure or prolonged intubation.

Our study has several limitations. As a result of the retrospective nature of the study, we were only able to include a total of 108 patients in our study, instead of the planned 180 patients. We included every patient who met criteria during the specified time frame, but our time frame was limited by the initiation of SBS scoring at our institution. Additionally, no standardized sedation protocol existed at our institution during the study period, thereby creating variability in sedation practices. Sedation for each individual patient was at the discretion of the provider. Additionally, although SBS scores were recorded multiple times per day for each patient, they were not necessarily used to titrate sedative medications. The 72-hour time period prior to extubation for classifying patients as deeply sedated is also a potential limitation. The patients may have been deeply sedated at the 72-hour mark but not so at a time closer to extubation, thereby influencing the effects of deep sedation upon extubation. Consistent deep sedation in the period prior to extubation may

be a better predictor of extubation failure. Although sedation is typically weaned prior to extubation, no standard weaning protocol exists at our institution. The method of sedation weaning may have had an effect on the rates of extubation failure. Additionally, we only evaluated benzodiazepine and opioid use in our patient population, as these were our most common agents used during the study time period. The use of other sedatives or intermittent paralytics may have also affected the results of this investigation. Although other sedatives and intermittent paralytics were used in our patients, the use was erratic and inconsistent, thereby limiting our ability to draw conclusions on the effects of these agents on extubation failure.

In this retrospective analysis, there was no statistically significant difference between rates of extubation failure in this investigation; however, there was a numerical increase in rates of extubation failure in patients who were deeply sedated versus patients who were not deeply sedated. Given the substantial morbidity associated with extubation failures, levels of sedation for the pediatric patient should be assessed and kept as low as possible, especially around the peri-extubation period, to optimize extubation success. Additional studies with larger sample sizes are required to further investigate the impact of deep sedation and specific sedation medications on extubation failure rates in pediatric patients.

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REFERENCES

- Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. *JAMA*. 2000;283(11):1451-1459.
- Marx CM, Rosenberg DI, Ambuel B, et al. Pediatric intensive care sedation: survey of fellowship training programs. *Pediatrics*. 1993;91(2):369-378.
- Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306.
- Rello J, Diaz E, Roque M, Valles J. Risk factors for developing pneumonia within 48 hours of intubation. *Am J Respir Crit Care Med*. 1999;159(6):1742-1746.
- Durbin CG. Sedation in the critically ill patient. *New Horiz*. 1994;2(1):64-74.
- Kollef MH, Levy NT, Ahrens TS, et al. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest*. 1998;114(2):541-548.
- Curley MA, Harris SK, Fraser KA, et al. State Behavioral Scale: a sedation assessment instrument for infants and young children supported on mechanical ventilation. *Pediatr Crit Care Med*. 2006;7(2):107-114.
- Deeter KH, King MA, Ridling D, et al. Successful implementation of a pediatric sedation protocol for mechanically ventilated patients. *Crit Care Med*. 2011;39(4):683-688.
- Gupta K, Gupta VK, Jayashree M, Singhi S. Randomized controlled trial of interrupted versus continuous sedative infusions in ventilated children. *Pediatr Crit Care Med*. 2012;13(2):131-135.
- Curley MAQ, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. *JAMA*. 2015;313(4):379-389.
- Baisch SD, Wheeler WB, Kurachek SC, Cornfield DN. Extubation failure in pediatric intensive care incidence and outcomes. *Pediatr Crit Care Med*. 2005;6(3):312-318.
- Khan N, Brown A, Venkataraman ST. Predictors of extubation success and failure in mechanically ventilated infants and children. *Crit Care Med*. 1996;24(9):1568-1579.
- Farias JA, Alía I, Retta A, et al. An evaluation of extubation failure predictors in mechanically ventilated infants and children. *Intensive Care Med*. 2002;28(6):752-757.
- Fontela PS, Piva JP, Garcia PC, et al. Risk factors for extubation failure in mechanically ventilated pediatric patients. *Pediatr Crit Care Med*. 2005;6(2):166-170.
- Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. *Crit Care Med*. 2000;28(6):2122-2132.
- Ashburn MA, Lipman AG. *Principles of Analgesic Use in the Treatment of Acute Pain and Chronic Cancer Pain*. 5th ed. Glenview, IL: American Pain Society; 2003.
- Manczur T, Greenough A, Pryor D, Rafferty GF. Comparison of predictors of extubation from mechanical ventilation in children. *Pediatr Crit Care Med*. 2000;1(1):28-32.
- Farias JA, Retta A, Alía I, et al. A comparison of two methods to perform a breathing trial before extubation in pediatric intensive care patients. *Intensive Care Med*. 2001;27(10):1649-1654.
- Epstein SK, Ciubotaru RL. Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation. *Am J Respir Crit Care Med*. 1998;158(2):489-493.
- Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest*. 1997;112(1):186-192.

21. Demling RH, Read T, Lind LJ, Flanagan HL. Incidence and morbidity of extubation failure in surgical intensive care patients. *Crit Care Med.* 1988;16(6):573-577.
22. Edmunds S, Weiss I, Harrison R. Extubation failure in a large pediatric ICU population. *Chest.* 2001;119(3):897-900.
23. Esteban A, Alía I, Tobin MJ, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. *Am J Respir Crit Care Med.* 1999;159(2):512-518.
24. Kurachek SC, Newth CJ, Quasney MW, et al. Extubation failure in pediatric intensive care: a multiple-center study of risk factors and outcomes. *Crit Care Med.* 2003;31(11):2657-2664.
25. Newth CJ, Venkataraman S, Willson DF, et al. Weaning and extubation readiness in pediatric patients. *Pediatr Crit Care Med.* 2009;10(1):1-11.
26. Cho HH, O'Connell JP, Cooney MF, Inchiosa MA Jr. Minimizing tolerance and withdrawal to prolonged pediatric sedation: case report and review of the literature. *J Intensive Care Med.* 2007;22(3):173-179.
27. Kanwaljeet AJ, Willson DF, Berger J, et al. Tolerance and withdrawal from prolonged opioid use in critically ill children. *Pediatrics.* 2010;125(5):e1208-e1225.