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Sedation Management for Critically Ill Children with Pre-Existing Cognitive Impairment

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The authors declare no conflicts of interest.

Randomized Evaluation of Sedation Titration for Respiratory Failure (*RESTORE*) Study Investigators*

Abstract

Objective: To compare current analgesia and sedation management practices between critically ill children with pre-existing cognitive impairment and critically ill neurotypical children, including possible indicators of therapeutic efficacy.

Study design: This study used secondary analysis of prospective data from the *RESTORE* clinical trial, with 2449 children admitted to the pediatric intensive care unit (PICU) and receiving mechanical ventilation for acute respiratory failure. Subjects with a baseline Pediatric Cerebral Performance Category (PCPC) ≥3 were defined as CI subjects, and differences between groups were explored using regression methods accounting for PICU as a cluster variable.

Results: This study identified 412 subjects (17%) with CI. Compared with NT subjects, CI subjects were older (median, years, 6.2 vs 1.4; $P<.001$) with more severe pediatric acute respiratory distress syndrome (40% vs 33%; $P=.009$). They received significantly lower cumulative doses of opioids (median, mg/kg, 14.2 vs 16.2; $P<.001$) and benzodiazepines (10.6 vs 14.4; $P<.001$). Three non-verbal CI subjects received no analgesia or sedation. Subjects with CI were assessed as having more study days awake and calm and fewer study days with an episode of pain. They were less likely to be assessed as having inadequate pain/sedation management or unplanned endotracheal/invasive tube removal. CI subjects had more documented iatrogenic withdrawal symptoms than NT subjects.

Conclusions: Subjects with CI in this study received less medication, but it is unclear whether they have authentically lower analgesic and/or sedative requirements or are vulnerable to inadequate assessment of discomfort due to the lack of validated assessment tools. We recommend the development of pain and sedation assessment tools specific to this patient population.

Keywords

Analgesia; sedation; neurodevelopmental disability; cognitive impairment; pediatric; critical care

Hospitalization is challenging for children with pre-existing cognitive impairment (CI), who often require more healthcare resources and experience longer hospitalizations than neurotypical (NT) children.(1,2) In the pediatric intensive care unit (PICU), children with CI constitute an estimated 25% of the patient population,(3,4) but their unique needs are understudied. Children with CI may lack the ability to communicate pain or the cognitive capacity to understand what is happening to them,(5) making the use of critical care analgesia and sedation essential for the safety and comfort of these patients.

In previous analyses, approaches to pain and sedation management in the general PICU population have been clinician dependent;(6,7) it is likely that current practice is similarly variable for critically ill children with CI. Clinicians may be reluctant to prescribe typical doses of opioids and benzodiazepines to children with CI due to concerns about a higher risk for adverse events, particularly airway compromise.(8) In addition, well-validated and reliable pain and sedation assessment tools specifically designed for critically ill children

with CI are currently lacking,(5,9,10) which poses a significant barrier to understanding whether their analgesic and sedative needs are being met in the PICU.

The effectiveness of current strategies for analgesia and sedation in children with CI has not been evaluated. Such information is vital to ensuring humane and equitable care for this vulnerable patient group, and it also will serve as a foundation for future research on proactive approaches to tailoring sedation management for critically ill children with CI. Therefore, the purpose of this study is to describe current analgesia and sedation management for critically ill children with CI, compare it with that of NT children, and evaluate possible indicators of analgesic and sedative efficacy.

Methods

This study was a secondary analysis of data from the Randomized Evaluation of Sedation Titration fOr Respiratory FailurE (*RESTORE*) study, a multicenter cluster randomized clinical trial testing the impact of a nurse-led, goal-directed sedation protocol on length of mechanical ventilation in critically ill pediatric patients with acute respiratory failure.(11) Subjects were enrolled at 31 sites from June 2009 to December 2013. Consent for prospective data collection was obtained from subjects' parents and/or legal guardians, and institutional review boards (IRBs) at each site approved the *RESTORE* study protocol.

All participating sites used the same pain, sedation, and withdrawal assessment instruments. Subjects enrolled at sites randomized to the intervention had their analgesic and sedative medications prescribed according to the published *RESTORE* protocol.(11) Sedative medications were titrated and weaned based on a daily prescribed sedation target (ie, State Behavior Scale [SBS] score(12)) and withdrawal symptoms score (i.e., Withdrawal Assessment Tool – version 1 [WAT-1] score(13)). Subjects enrolled at sites randomized to the control arm received unrestricted usual care, in which the process of sedation and weaning was left to provider discretion and analgesics and sedatives were selected, prescribed, and titrated according to local practice norms.

Study population:

Patients aged 2 weeks (≥42 weeks postmenstrual age) to 17 years were enrolled in the *RESTORE* study if they were receiving invasive mechanical ventilation for acute airway and/or parenchymal lung disease. Detailed inclusion and exclusion criteria are published elsewhere.(11) This secondary analysis included subjects from both intervention and control groups (n=2449) without applying any additional inclusion or exclusion criteria and was exempt from IRB review.

Variables and measures:

The operational definition of CI was based on previous research with a validated tool, the Pediatric Cerebral Performance Category (PCPC).(14,15) The measure is a scale of increasing cognitive disability with scores ranging from 1 to 6, representing a continuum from normal function to death. Baseline PCPC score and Pediatric Overall Performance Category (POPC) score (for measurement of functional impairment) were collected during the *RESTORE* study as measures of pre-illness functioning. Subjects with a baseline PCPC

≥3 were defined as those with pre-existing cognitive impairment ("CI group") and subjects with baseline PCPC scores of 1 or 2 were classified as typically developing or neurotypical ("NT group"). This cutoff was chosen based on the subject's presumed degree of visible impairment; that is, children with PCPC scores of 2 have mild disability that may only manifest in the classroom and otherwise engage in age-appropriate interactions.

In the *RESTORE* study, clinical data were collected from endotracheal intubation (Day 0) until 72 hours after the last opioid dose, hospital discharge, or Day 28 (whichever occurred first). All subjects were assessed at regular intervals for pain, sedation/agitation and iatrogenic withdrawal symptoms using age-appropriate standardized assessment tools, according to study protocol.(11) Specifically for pain assessment, the recommended pain scale depended on the subject's chronological age, as follows: the FLACC (Faces, Leg, Activity, Cry and Consolability) scale in nonverbal children 0 to 6 years of age (16); the Wong-Baker Faces Pain Scale in verbal children ≥3 years (17); and the INRS (Individualized Numeric Rating Scale) in nonverbal cognitively impaired children ≥6 years of age (18). On days when subjects received neuromuscular blockade, nurses used their clinical judgement to differentiate pain (i.e., assume pain present, or APP) from agitation (i.e., assume agitation present, AAP) when subjects demonstrated ≥20% increase in heart rate or blood pressure when stimulated. Demographic information was obtained at study entry. Severity of illness was assessed using the Pediatric Risk of Mortality (PRISM) III-12.(19) Sedation data were captured daily, including opioid dosage (morphine equivalents per kilogram),(11) benzodiazepine dosage (midazolam equivalents per kilogram), (11) and all other sedative medications (e.g., dexmedetomidine, ketamine) administered during the study period.

Each *RESTORE* site collected data on adverse events that could be used to assess the efficacy of analgesia and sedation provided to study subjects.(20) Inadequate pain management was defined as a pain score >4/10 using an age-appropriate pain assessment tool, or nurse-reported APP, for two consecutive hours unrelated to planned extubation. Inadequate sedation management was defined as agitation, based on an SBS score >0, or nurse-reported AAP, for 2 consecutive hours unrelated to planned extubation.

Statistical Analyses:

Descriptive statistics, including medians and interquartile ranges for continuous variables and frequency counts and percentages for categorical variables, were generated for the CI and NT groups. Differences between groups were explored using linear, cumulative logit, logistic, multinomial logistic, proportional hazards, and Poisson regression for continuous, ordinal, binary, nominal, time-to-event, and rate variables, respectively. All regression analyses except for multinomial logistic regression accounted for PICU as a cluster variable using generalized estimating equations. Log transformations were used as necessary for continuous variables. Comparisons of sedation profiles and adverse events were adjusted for age group (2 weeks to <6 months, 6 months to <2 years, 2 to <6 years, and 6 to <18 years) and severity of illness. All comparisons with $P < .05$ were considered statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, N.C.).

Results

In the *RESTORE* study, 412 of 2449 subjects (17%) had baseline PCPC scores indicating CI. Compared with the NT group, subjects with CI were older, majority non-Hispanic white, and had a worse severity of illness upon admission (Table I). A higher proportion of subjects with CI had severe pediatric acute respiratory distress syndrome (PARDS) within 48 hours of intubation, and more subjects with CI had pneumonia or aspiration pneumonia as their primary diagnosis. Subjects with CI were more functionally impaired than NT subjects, based on POPC scores, and fewer subjects with CI were able to verbally communicate pain at baseline.

After adjusting for age and severity of illness, doses of opioids and benzodiazepines administered to subjects with CI were significantly lower than those administered to the NT subjects (Table II), including lower doses administered starting their first full study day. Despite receiving lower doses, subjects with CI tended toward a longer duration of exposure to opioids compared with NT subjects, but this difference was not statistically significant (median, days, 10.5 vs 9, $P=.052$) and likely reflected their longer PICU stays (12.9 vs 9.1; $P<.001$). More CI subjects had no primary opioid or benzodiazepine agent administered during the study period. Of these, there were 15 CI subjects who did not receive opioids during the study period, most of whom were ≥16 months old and non-verbal at baseline. Three non-verbal subjects with CI (one intervention subject with a chronic tracheostomy, two control subjects with endotracheal tubes) did not receive any analgesic or sedative medications. Subjects with CI received fewer different classes of sedative medications.

Regarding measures of wakefulness, pain, and agitation, subjects with CI had more study days assessed as being awake and calm and fewer study days with an assessed episode of pain compared with NT subjects (Table II). The FLACC scale was the most common primary pain assessment tool used among all subjects (92% of both CI and NT subjects), followed by the INRS (5% of CI subjects and 2% of NT subjects). Compared with CI patients scored using the FLACC, CI patients scored using the INRS were older (median, years, 13.4 vs 5.1; $P<.001$) and received lower cumulative doses of opioids (median, mg/kg, 3.0 vs 15.1; $P=.01$) and benzodiazepines (3.9 vs 11.8; $P<.001$). They also had more study days assessed as being awake and calm (median [IQR], %, 91 [80–100] vs 80 [60–100]; $P<.001$). Neuromuscular blockade was used for the entire day for 11% of study days for the CI group and 14% of study days for the NT group. On these days, there were no differences between the CI and NT groups in the number of hours per day APP (both groups: median [IQR], 1 [0–3]; $P=.94$) or the number of hours per day AAP (both groups: 1 [0–3]; $P=.99$).

Regarding iatrogenic complications and adverse events, a higher proportion of subjects with CI exhibited signs and symptoms of iatrogenic withdrawal syndrome (IWS), including higher peak WAT-1 scores and a greater proportion of study days with WAT-1 scores indicative of IWS (Table II). Fewer subjects with CI received antidelirium medications in this study. Across both groups, 15% of subjects were assessed as having inadequate pain management and 22% of subjects were assessed as having inadequate sedation management (Table III). CI subjects were not more likely to be assessed as having inadequate pain or sedation management, unplanned extubation, or removal of any invasive tube compared with

NT subjects. A higher proportion of subjects with CI required reintubation within 24 hours for extubation failure, but few CI subjects (n/total=4/45, 9%) were considered to have insufficient respiratory effort due to over-sedation.

The proportion of subjects in the *RESTORE* intervention group (i.e., protocolized sedation) was not different between the CI and NT groups (Table I). Adjustment for *RESTORE* intervention group did not appreciably change group comparisons of sedation profiles and adverse events.

Discussion

In this large prospective study of analgesia and sedation in critically ill children, children with CI were assessed to have more study days awake and calm and fewer days with an episode of pain while receiving lower doses of opioids and benzodiazepines compared with critically ill NT children. We also found that these children could be managed safely without an increase in adverse events associated with agitation but did exhibit more symptoms of IWS than NT children. Our findings could suggest that children with CI can be safely managed using less analgesia and sedation while receiving mechanical ventilation for acute respiratory failure, though alternatively these findings may indicate that our assessment tools are not sensitive in detecting discomfort in this vulnerable population.

The FLACC instrument, which has not been validated for use in children with neurodevelopmental disabilities, was used to assess a majority of subjects with CI. The issue of pain assessment in this study reflects the broader challenges of caring for children with CI in the PICU: there is limited evidence supporting the use of validated assessment tools among critically ill children with CI. There are four published observational assessment tools designed to assess pain in hospitalized non-verbal children with CI,(18,21–23) but none of them have been validated for use specifically in the PICU. Because many of the available tools rely on behavioral cues or are lengthy, they may be difficult to apply in the busy PICU environment where subjects are often intubated, sedated, and/or pharmacologically paralyzed. The INRS is the most promising tool for nursing assessment in the PICU, because it was designed by critical care nurses to be used in non-verbal patients, is brief, and draws on parental input to populate a 0–10 scale with the child's typical pain behaviors.(18,24) However, it was used for few subjects with CI in this study, suggesting that further work needs to be done to incorporate it into routine nursing practice in the PICU.

In addition to finding that subjects with CI received lower doses of analgesics and sedatives, three subjects with CI received neither analgesia nor sedation, both of which are concerning results given that most clinicians would agree that endotracheal intubation is an uncomfortable experience. Although it could be argued that the 1 child with a chronic tracheostomy may not have required analgesia and sedation in order to tolerate mechanical ventilation, failing to provide analgesia and sedation to the two children with endotracheal tubes is a less tenable position, particularly when there are documented episodes of pain for those subjects. As a recent opinion piece noted, some clinicians question whether children with severe neurologic impairments experience pain, despite emerging literature suggesting

that they do.(25) The more important focus should be on identifying and treating pain in these patients, so the question that remains in this study is: were these children correctly assessed as being comfortable with less medication, or were clinicians misinterpreting atypical signs of pain and/or agitation in subjects with CI? Our study design limits the ability to draw direct associations between pain and/or sedation scores and subsequent medication administration, and although our data allow new insights into the problem, they do not provide a straightforward answer.

Adverse events typically associated with agitation (i.e., unplanned extubation or device removal) were not more frequent in the population of subjects with CI, which suggests that these patients may have been adequately sedated at lower medication doses. However, this interpretation relies on a potentially faulty assumption, that lack of movement is a proxy for comfort. It is also possible that functional impairment associated with their neurodevelopmental disabilities prevented subjects with CI from dislodging devices, independent of their level of pain or agitation. Attributing fewer agitation-related adverse events to adequate sedation is further complicated by the observed higher rate of extubation failure in subjects with CI. The most obvious interpretation of this finding is that it reflects greater sensitivity to analgesia and sedation in subjects with CI, which also would explain their reported comfort on lower doses of opioids and benzodiazepines. Yet over-sedation was not the primary reason cited by clinicians for reintubation in these subjects, and the fact that children with CI were assessed to have a higher proportion of study days awake and calm also argues against over-sedation. It is possible that the subjects requiring reintubation had other risk factors for extubation failure that were independent of their analgesic or sedative exposure, such as underlying neuromuscular impairments. This question regarding the adequacy of sedation provided to critically ill patients with CI requires additional prospective research, because the possibility that any of these children could be receiving insufficient analgesia and sedation while intubated, particularly those patients who are non-verbal, is alarming.

More subjects with CI in this study exhibited symptoms of IWS than NT subjects. The importance of obtaining baseline WAT-1 scores and following changes in patients' behavior during sedative titration is especially important in this patient population, considering that there may be some misattribution of baseline behaviors to signs of IWS in patients with CI. However, the median duration of exposure to opioids for both groups was greater than the threshold of five days, which is a well-established risk factor for IWS.(26–28) In addition, as we have argued previously,(29) it is possible that children with CI have existing alterations in neurotransmitter function that are exacerbated by prolonged administration of opioids and/or benzodiazepines, which may have put them at greater risk for experiencing IWS than NT children with similar durations of exposure. Specifically, the inhibitory neurotransmitter γ-aminobutyric acid (GABA), along with other neurotransmitters, is hypothesized to be involved in imbalances in excitatory and inhibitory signaling that may underlie global changes in cognition and behavior in several neurodevelopmental disabilities.(30–32) This suggestion also has been made in the emerging literature on risk factors for delirium, for which children with CI have been found to be at high risk.(33,34) Subjects in the *RESTORE* study were not routinely screened for delirium, and our results showed that a lower proportion of subjects with CI received antidelirium medications than NT subjects, though

antidelirium medications were rarely used across both groups. Delirium has been described in children weaning from analgesia and sedation, and both delirium and IWS could reflect an “acute-on-chronic” brain dysfunction process in the critically ill child with CI. Further research is needed to better elucidate the neurobiological mechanisms underlying the delirium-IWS relationship in children with CI and the potential role of pharmacotherapy in precipitating these iatrogenic complications of PICU care.

The primary limitation of this study is the inability to directly assess the relationship between pain and/or sedation scores and medication administration in study subjects. Clinician decision-making with regards to analgesic and sedative administration is complex and multi-factorial, and it is impossible to know why subjects with CI in this study may have been given lower medication doses without knowing more about the immediate context of administration. This study was a secondary analysis of existing data, and although the parent study collected data on analgesic and sedative administration in critically ill children, it was not designed to answer this specific study question. Finally, the cohort of subjects with CI was defined based on a previously published measure of baseline cognitive functioning, the PCPC,(14,15) but it is possible that this approach failed to fully capture the entire population of critically ill children with CI. For example, because we categorized subjects based on their pre-admission cognitive status, our analysis did not account for children who may have suffered new-onset cognitive impairment during the study period.

This study describes analgesic and sedative administration in the largest published cohort of critically ill children with CI, with highly generalizable findings based on the recruitment of subjects from 31 PICUs across the United States. Despite the observation that subjects with CI received lower doses of opioids and benzodiazepines while in the PICU, these subjects also had more documented iatrogenic withdrawal symptoms. The data also suggest that comfort for subjects with CI may have been achieved with less medication, based on available measures and documented assessments of wakefulness, pain and agitation, but these conclusions are limited by the lack of assessment instruments specific to children with CI. Although this study establishes an important foundation for understanding current practice in providing analgesia and sedation for critically ill children with CI, additional work is needed to improve our awareness of whether the needs of this unique population are being met and to optimize outcomes for these vulnerable children. Specifically, we recommend that future research prioritizes instrument validation studies to ensure that pain and agitation can be precisely assessed in critically ill children with CI. This research should be followed by prospective studies evaluating administration of analgesic and sedative medications to critically ill children with CI and focusing on discerning whether disparities in medication administration are the result of adequate response at lower doses, or other factors.

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Table I.

Baseline characteristics by group

Variable	CI* (N = 412)	NT (N = 2037)	*P* value†
Age at PICU admission			
Median (IQR), y	6.2 (1.8–12.3)	1.4 (0.3–6.8)	<.001
N (%)			<.001
2 wk to <6 mo	26 (6)	686 (34)	
6 mo to <2 y	84 (20)	469 (23)	
2 to <6 y	93 (23)	325 (16)	
6 to <18 y	209 (51)	557 (27)	
Female, n (%)	192 (47)	909 (45)	.38
Race/ethnicity, n (%)			.002
Non-Hispanic white	238 (58)	995 (49)	
Non-Hispanic black	59 (14)	443 (22)	
Hispanic (any race)	87 (21)	449 (22)	
Other/unknown	28 (7)	150 (7)	
Baseline POPC, n (%)‡			<.001§
1–2	0	1991 (98)	
3	177 (43)	37 (2)	
4	233 (57)	9 (<1)	
5	2 (<1)	0	
Able to verbally communicate pain at baseline, n/total (%)¶	72/350 (21)	891/1034 (86)	<.001
PRISM III-12 score, median (IQR)	8 (4–13)	7 (3–12)	.04
Risk of mortality based on PRISM III-12 score, median (IQR), %	3.9 (1.3–14.0)	3.8 (1.0–12.3)	.49
Primary diagnosis, n (%)‖			<.001
Pneumonia	214 (52)	613 (30)	
Bronchiolitis	46 (11)	610 (30)	
Acute respiratory failure related to sepsis	61 (15)	296 (15)	
Asthma or reactive airway disease	13 (3)	194 (10)	
Aspiration pneumonia	60 (15)	89 (4)	
Other	18 (4)	235 (12)	
Intervention group, n (%)	214 (52)	1011 (50)	.33
PARDS based on worst OI or OSI on days 0 to 1, n (%)			.01
At risk (OI <4.0 or OSI <5.0)	59 (14)	318 (16)	
Mild (OI=4.0–7.9 or OSI=5.0–7.4)	78 (19)	455 (22)	
Moderate (OI=8.0–15.9 or OSI=7.5–12.2)	110 (27)	586 (29)	
Severe (OI ≥16.0 or OSI ≥12.3)	165 (40)	678 (33)	
Neuromuscular blockade for the entire duration of days 0 to 2, n (%)	27 (7)	147 (7)	.65

[*] Cognitive impairment (CI) was defined as baseline Pediatric Cerebral Performance Category (PCPC) score ≥3.

[†] *P* values for comparison between groups were calculated using linear, cumulative logit, logistic and multinomial logistic regression for log-transformed continuous, ordinal, binary and nominal variables, respectively. All regression analyses except for multinomial logistic regression accounted for PICU as a cluster variable using generalized estimating equations.

[‡] Pediatric Overall Performance Category (POPC) score is dependent on PCPC score (14), POPC score must be equal to or greater than PCPC score.

[§] This *P* value was calculated using Fisher's exact test.

[¶] Able to verbally communicate pain at baseline includes only patients aged 16 months or older.

[//] Other primary diagnoses include pulmonary edema, thoracic trauma, pulmonary hemorrhage, laryngotracheobronchitis, acute respiratory failure after bone marrow transplantation, acute chest syndrome/sickle cell disease, pertussis, pneumothorax (nontrauma), acute exacerbation lung disease (cystic fibrosis or bronchopulmonary dysplasia), acute respiratory failure related to multiple blood transfusions, pulmonary hypertension (not primary), and other.

CI, cognitive impairment; IQR, interquartile range; NT, neurotypical; OI, oxygenation index; OSI, oxygen saturation index; PARDS, pediatric acute respiratory distress syndrome; PCPC, Pediatric Cerebral Performance Category; PICU, pediatric intensive care unit; POPC, Pediatric Overall Performance Category; PRISM III-12, Pediatric Risk of Mortality score from first 12 hours in the PICU.

Table II.

Sedation profiles by group

Variable	CI (N = 412)	NT (N = 2037)	*P* value*
Sedatives administered			
Primary opioid agent(11), n (%)			.37†
Morphine	155 (38)	837 (41)	
Fentanyl	241 (59)	1179 (58)	
Other (hydromorphone or remifentanil)	1 (<1)	12 (<1)	
None	15 (4)	9 (<1)	
Opioid exposure, median (IQR)			
Mean daily dose, mg/kg	1.2 (0.4–2.5)	1.5 (0.8–2.8)	<.001
Peak daily dose, mg/kg	2.9 (1.3–6.2)	3.7 (1.9–6.7)	<.001
Cumulative dose, mg/kg	14.2 (3.7–43.0)	16.2 (5.7–46.6)	<.001
Number of exposure days	10.5 (5–21)	9 (5–18)	.052
Maximum number of daily bolus doses	6 (3–10)	7 (5–10)	<.001
Day 1 dose, mg/kg‡	1.7 (0.9–3.2)	2.2 (1.2–3.4)	<.001
Primary benzodiazepine agent(11), n (%)			<.001
Midazolam	344 (84)	1752 (86)	
Lorazepam	61 (15)	273 (13)	
None	7 (2)	12 (<1)	
Benzodiazepine exposure, median (IQR)			
Mean daily dose, mg/kg	0.9 (0.4–2.3)	1.4 (0.7–2.6)	<.001
Peak daily dose, mg/kg	2.3 (1.1–6.0)	3.2 (1.6–6.5)	<.001
Cumulative dose, mg/kg	10.6 (2.7–42.3)	14.4 (5.2–41.9)	<.001
Maximum number of daily bolus doses	6 (3–10)	7 (4–10)	<.001
Day 1 dose, mg/kg‡	1.3 (0.5–2.4)	1.8 (0.8–2.8)	<.001
Secondary sedatives, n (%)			
Dexmedetomidine	138 (34)	745 (37)	.01
Propofol	67 (16)	241 (12)	.49
Barbiturates	64 (16)	304 (15)	.13
Ketamine	95 (23)	534 (26)	<.001
Clonidine	44 (11)	268 (13)	.01
Methadone	77 (19)	439 (22)	.79
Chloral hydrate	36 (9)	179 (9)	.004
Number of different sedative classes received, n (%)			
0	3 (<1)	0	
1	7 (2)	12 (<1)	
2	169 (41)	801 (39)	
3	119 (29)	644 (32)	

Variable	CI (N = 412)	NT (N = 2037)	*P* value*
4	65 (16)	366 (18)	
5–7	49 (12)	214 (11)	
Median (IQR)	3 (2–4)	3 (2–4)	<.001
≥3 sedative classes, n (%)	233 (57)	1224 (60)	<.001
Hypnotic medications, n (%)	42 (10)	121 (6)	.22
Antidelirium medications, n (%)	6 (1)	40 (2)	.03§
Neuromuscular blockade to manage agitation, n (%)	91 (22)	525 (26)	.22
Measures of wakefulness, pain, and agitation, median (IQR)			
Study days awake and calm (modal SBS score −1 or 0), %	80 (60–100)	80 (56–100)	.003
Days to first awake/calm state	2 (1–4)	2 (1–4)	.045
Study days with modal pain score <4, %	100 (100–100)	100 (100–100)	.53
Study days with an episode of pain (highest pain score ≥4), %	33 (13–56)	38 (14–60)	.005
Study days with an episode of agitation (highest SBS score +1 or +2), %	50 (18–71)	50 (25–75)	.57
Occurrence of iatrogenic withdrawal			
Iatrogenic withdrawal syndrome (WAT-1 score ever ≥3), n (%)	120/168 (71)	668/991 (67)	.01
Peak WAT-1 score, median (IQR)	4 (2–6)	4 (2–5)	.04
Study days with WAT-1 score ≥3, median (IQR), %	30 (0–50)	25 (0–50)	.002

**P* values for comparison between groups were calculated using logistic, linear and proportional hazards regression accounting for PICU as a cluster variable using generalized estimating equations for binary variables, log-transformed continuous variables (except percentage of study days variables) and time-to-event variables, respectively, adjusting for age group and PRISM III-12 score.

†This *P* value compares primary agent morphine vs fentanyl between groups.

‡Not available for 5 patients (1 CI, 4 no CI) who were study discharged on day 0.

§This *P* value adjusts for three-category age group, with the two youngest age groups collapsed due to small cell sizes.

CI, cognitive impairment; IQR, interquartile range; NT, neurotypical; SBS, State Behavioral Scale; WAT-1, Withdrawal Assessment Tool-Version 1.

Table III.

Sedation-related adverse events by group

Variable	CI (N = 412)	NT (N = 2037)	*P* value*
Inadequate pain management, n (%)	69 (17)	300 (15)	.58
Inadequate sedation management, n (%)	110 (27)	437 (21)	.35
Unplanned ETT extubation, n (%)	14 (3)	91 (4)	.61
Extubation failure (reintubation within 24 h), n (%)	45 (11)	156 (8)	<.001
Unplanned removal of any invasive tube (other than an endotracheal tube), Number of events/100 device days	0.09	0.15	.11

**P* values for comparison between groups were calculated using logistic and Poisson regression accounting for PICU as a cluster variable using generalized estimating equations for binary and rate variables, respectively, adjusting for age group and PRISM III-12 score.

CI, cognitive impairment; ETT, endotracheal tube; NT, neurotypical.