OBSERVATIONAL STUDY

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Association of Obesity With Sedative Dosing, Sedative Response, and Clinical Outcomes in Mechanically Ventilated Critically Ill Children

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OBJECTIVES: This study aimed to investigate the impact of obesity on the use of analgesics and sedatives, rates of iatrogenic withdrawal syndrome (IWS), and outcomes in mechanically ventilated pediatric patients. Additionally, it sought to assess whether a nurse-implemented sedation protocol would be equally effective for children with and without obesity.

DESIGN: Secondary analysis of the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) pediatric multicenter clinical trial.

SETTING: Thirty-one U.S. PICUs.

PATIENTS: Children 1–17 years old, categorized as with or without obesity according to World Health Organization and Centers for Disease Control and Prevention criteria.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The study assessed various factors including medication exposure, adequacy of pain and sedation management, IWS rates, and clinical outcomes. Obesity occurred in 22% of patients. Obesity did not influence choice of opiate, but it led to extended exposure to these medications. There were no differences in dosing per kilogram of admission weight, resulting in significantly higher daily and cumulative doses in those with obesity. In the protocolized sedation arm, patients with obesity received significantly higher median opiate doses compared with the nonobesity protocolized sedation group. IWS rates did not differ; however, protocolized sedation obesity patients experienced more instances of inadequate sedation, longer time to extubation readiness, longer duration of mechanical ventilation and PICU stay, and higher 28-day in-hospital mortality than the protocolized sedation nonobesity group. These weight-based differences were not noted in the usual care arm.

CONCLUSIONS: This study underscores the significance of accounting for body habitus when selecting and dosing opiates in children with acute respiratory failure. Obesity had substantial impact on medication exposure and clinical outcomes, particularly within a structured, protocolized sedation regimen. Further research is warranted to explore the intricate relationship between medication dosing and clinical outcomes in children with obesity.

KEYWORDS: medication withdrawal; obesity; pediatric; pediatric acute respiratory failure; sedation

Sedative and analgesic medications are frequently used when managing children on mechanical ventilation. These medications come with several adverse effects, including hemodynamic instability, prolonged mechanical ventilation, drug tolerance, and iatrogenic withdrawal syndrome (IWS) (1). Determining optimal dosage in children involves various considerations such as disease state, age, weight, and body composition. Achieving optimal drug

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KEY POINTS

Question: Does obesity affect the choice and dose of analgesics and sedatives, occurrence of withdrawal, and outcomes in mechanically ventilated pediatric patients, and is a nurse-implemented sedation protocol equally effective for children with and without obesity?

Findings: Medication choice and dose per patient weight was similar for all patients. Therefore, patients with obesity had higher daily and cumulative opiate exposure. With a sedation protocol, obese patients had less adequate sedation, prolonged mechanical ventilation, and higher mortality compared with lean peers.

Meaning: Body habitus impacts medication exposure and clinical outcomes in children with acute respiratory failure, highlighting the need for tailored opiate dosing strategies.

dosing while minimizing adverse effects is a constant challenge for the care team.

The dosing recommendations for infants and children are based on predicted changes in protein binding, water content, fat stores, and renal function maturation during growth and development (2, 3). Body size descriptors like total body weight and ideal body weight (IBW) are based on "normal" body compositions within an expected age range. These descriptors may be inappropriate for children with obesity who have greater lean and fat mass, affecting drug distribution, pharmacodynamics, and response to a given dose (4). Over 30% of critically ill children requiring mechanical ventilation are overweight or obese (5, 6). Ensuring safe and effective medication dosing is essential for children with varying body compositions.

This study aims to investigate how obesity affects analgesic and sedative use, drug tolerance, IWS, and clinical outcomes in mechanically ventilated pediatric patients. Additionally, it explores whether a protocolized sedation strategy benefits children with and without obesity.

MATERIALS AND METHODS

This is a nonprespecified secondary analysis of Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE; NCT00814099), a randomized clinical trial that assessed whether a nurse-implemented, goal-directed analgesia and sedation protocol reduced ventilation duration in children with acute respiratory failure (7). RESTORE took place in 31 U.S. PICUs from 2009 to 2013 enrolling 2449 children, 2 weeks to 17 years old, who were receiving invasive mechanical ventilatory support for at least 24 hours for acute respiratory failure. Patients were cluster randomized by PICU to receive protocolized sedation or usual care. All participating institutions obtained institutional review board (IRB) approval and informed consent from legal guardians of eligible patients (IRB No. 808803, approved October 28, 2008, University of Pennsylvania, IRB Board No. 5). All RESTORE procedures followed the ethical standards of the IRB committee on human experimentation and the Helsinki Declaration of 1975. A patient's weight status did not affect enrollment.

Essential elements of RESTORE included team discussion of the patient's trajectory of illness (acute, titration, or weaning phase), prescribing a State Behavioral Scale (8) target per phase of illness, arousal assessments, titrating analgesics and sedatives at least every 8 hours, extubation readiness testing (ERT), and either discontinuing or weaning medications per target Withdrawal Assessment Tool, Version 1 (9) based on length of exposure. Assessments of pain (10, 11) and sedation (8) were standardized in all participating PICUs. Bedside care teams at intervention PICUs assigned a daily target sedation score per patient's phase of illness and nurses used an algorithm to titrate medications to achieve this goal (8). For medication dosing, the protocol stated the use of actual body weight, but recommended the prescriber consider using an adjusted dosing weight if the patient is greater than 130% of IBW or to use adult dosing for patients over 70 kg. However, only actual body weight was recorded on the data collection forms. Actual body weight most often represented the weight measured at admission to the PICU. Daily medication dosages received were recorded as total milligrams or micrograms, depending on the medication.

Patient Selection

Patients 1–17 years old with recorded admission height and weight were included. Those younger than 1 year old were excluded because of the difficulty in operationally

defining obesity due to growth variability associated with variable feeding schedules (e.g., timing of solid food initiation) and prematurity. Weight-for-height *z* scores based on World Health Organization growth charts for children younger than 2 years old and body mass index (BMI)-for-age *z* scores based on Centers for Disease Control and Prevention (CDC) growth charts for children 2 years old and older were calculated (12, 13). Each subject was categorized as either without obesity (*z* score < 1.65, < 95th percentile) or with obesity (*z* score ≥ 1.65, ≥ 95th percentile) (14). Patients with *z* score of less than –5 or greater than +5 (children < 2 yr old) or adjusted *z* score of less than –4 or greater than +8 (children ≥ 2 yr old) were excluded per CDC recommendations.

Outcome Measures

Inadequate pain and sedation management and clinically significant IWS were defined in the primary RESTORE trial and within the footnote of Table 3 of (7). To evaluate the variability in pain and sedation based on body habitus, we analyzed several variables including primary medication used to achieve desired state of calm and wakefulness, mean and peak daily doses, cumulative doses, and number of days exposed to medication and compared among the weight groups. Data for analgesic exposure was evaluated using morphine equivalents as well as separately for morphine and fentanyl given their different lipophilicity (15). For all analyses of drug exposure, comparisons were completed using dose per kilogram (as prescribed by the clinician) as well as total dose received (total milligrams or micrograms). For evaluation of dosing per kilogram analyses, the total dose in milligrams or micrograms was divided by the patient's actual body weight. We also explored measures of wakefulness, pain, and agitation and the occurrence of drug tolerance and IWS among the weight groups.

Outcomes assessed included extubation readiness, duration of mechanical ventilation, length of stay, and 28-day in-hospital mortality. Extubation readiness and success was evaluated by time to first ERT, time to first successful ERT, and successful extubation with first attempt (16).

Statistical Analysis

Linear, logistic, multinomial logistic, cumulative logit, and proportional hazards regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous, binary, nominal, ordinal, and time-to-event variables, respectively, were used to compare baseline demographic and admission variables, analgesia and sedation exposure, sedative response and weaning, and trajectory of recovery and outcomes between those with and without obesity. Analyses of trajectory of recovery and outcomes were adjusted for categorical age (1–1.99, 2–5.99, and 6–17.99 yr old) and pediatric acute respiratory distress syndrome category based on day 1 oxygenation index (OI) or oxygen saturation index (OSI) (at risk [OI < 4.0 or OSI < 5.0], mild [OI 4.0–7.9 or OSI 5.0–7.4], moderate [OI 8.0–15.9 or OSI 7.5–12.2], or severe [OI ≥ 16.0 or OSI ≥ 12.3]). Usual care and protocolized sedation arms were evaluated separately and whether RESTORE study arm modified differences in those with and without obesity was also assessed. Statistical analyses were conducted using SAS software, Version 9.4 (SAS Institute, Cary, NC); *p* value of less than 0.05 was considered statistically significant in all analyses without adjustment for multiple comparisons.

RESULTS

Of the 2449 RESTORE participants, 1183 met the inclusion criteria. Those excluded were 955 children younger than 1 year old, 273 without a height recorded, and 38 with spurious weight-for-height or BMI-for-age *z* scores outside the CDC accepted range. Obesity was present in 265 (22%) of these subjects, with a similar proportion of obesity patients in both the protocolized sedation and the usual care arms. There were no statistically significant differences between those with and without obesity regarding age, gender, race, ethnicity, baseline functional status, primary cause of respiratory failure, or Pediatric Risk of Mortality-III score. Subjects with cancer and those with chromosomal abnormalities were more prevalent in the obesity group (**Table 1**; and **eTable 1**, http://links.lww.com/CCX/B465).

Obesity was not associated with choice of primary opioid or benzodiazepine in either study arm (**Table 2**). As per protocol, morphine was the primary opioid used in the protocolized sedation arm (53%) while fentanyl was the primary opioid used in the usual care arm (84%). Midazolam was the primary sedative used in both study arms. Those with obesity were exposed to opioids for longer periods of time in both arms (median, 12 d [interquartile range, 6–19 d] vs. 9 d [5–15]

TABLE 1.
Baseline Characteristics of Participants by Weight Group

Characteristic	With Obesity ($n = 265$)	Without Obesity ($n = 918$)
Age at PICU admission, median (IQR), yr	6.0 (2.5–12.5)	6.4 (2.3–12.2)
1–1.99 yr, *n* (%)	53 (20)	201 (22)
2–5.99 yr	79 (30)	238 (26)
6–17.99 yr	133 (50)	479 (52)
Female, *n* (%)	122 (46)	436 (47)
Race, *n*/total (%)		
White	172/263 (65)	619/914 (68)
Black/African American	67 (25)	211 (23)
Asian	9 (3)	29 (3)
Native Hawaiian or other Pacific Islander	2 (1)	9 (1)
American Indian or Alaskan Native	3 (1)	5 (1)
Multiracial	10 (4)	41 (4)
Hispanic ethnicity, *n*/total (%)	59/264 (22)	160/916 (17)
Cognitive impairment (Pediatric Cerebral Performance Category > 1), *n* (%)	90 (34)	279 (30)
Functional impairment (Pediatric Overall Performance Category > 1), *n* (%)	98 (37)	332 (36)
Risk of mortality based on Pediatric Risk of Mortality III-12 score, median (IQR)	6.1 (1.7–20.1)	5.8 (1.7–18.5)
Medical history, *n* (%)		
Prematurity (< 36 wk postmenstrual age)	20 (8)	102 (11)
Asthma (prescribed bronchodilators or steroids)	51 (19)	194 (21)
Seizure disorder (prescribed anticonvulsants)	36 (14)	124 (14)
Neurologic/neuromuscular disorder putting patient at risk of aspiration[a]	21 (8)	109 (12)
Cancer (current or previous diagnosis)[a]	48 (18)	114 (12)
Known chromosomal abnormality[a]	24 (9)	45 (5)
Primary diagnosis, *n* (%)		
Pneumonia	128 (48)	455 (50)
Bronchiolitis	15 (6)	72 (8)
Acute respiratory failure related to sepsis	57 (22)	159 (17)
Asthma or reactive airway disease	26 (10)	119 (13)
Other	39 (15)	113 (12)
Pediatric acute respiratory distress syndrome based on day 1 OI or OSI, *n* (%)[b]		
At risk (OI < 4.0 or OSI < 5.0)	74 (28)	276 (30)
Mild (OI 4.0–7.9 or OSI 5.0–7.4)	68 (26)	264 (29)
Moderate (OI 8.0–16.0 or OSI 7.5–12.3)	75 (28)	212 (23)
Severe (OI > 16.0 or OSI > 12.3)	48 (18)	166 (18)

(*Continued*)

TABLE 1. (*Continued*)
Baseline Characteristics of Participants by Weight Group

Characteristic	With Obesity (*n* = 265)	Without Obesity (*n* = 918)
Enrolled in Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) protocolized sedation arm, *n* (%)	128 (48)	457 (50)

IQR = interquartile range, OI = oxygenation index, OSI = oxygen saturation index.
[a]*p* values for comparison across weight groups were calculated using linear, cumulative logit, logistic, and multinomial logistic regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous, ordinal, binary, and nominal variables, respectively. Statistically significant differences ($p < 0.05$) were found for neurologic/neuromuscular disorder putting patient at risk of aspiration ($p = 0.02$), current or previous cancer diagnosis ($p = 0.007$), and known chromosomal abnormality ($p = 0.007$).
[b]OI was calculated as (Fio_2 × mean airway pressure)/Pao_2 × 100. When an arterial blood gas measurement was not available, oxygen saturation (Spo_2) was used to estimate Pao_2 in order to calculate OSI as (Fio_2 × mean airway pressure)/Spo_2 × 100. Lower scores reflect better oxygenation.

in the protocolized sedation arm; $p = 0.01$ and 13 d [5–25] vs. 10 d [4–22] in the usual care arm; $p = 0.002$).

Regardless of study arm, when fentanyl was used as the primary opioid, the mean daily, peak daily, and cumulative fentanyl doses in micrograms per kilogram of body weight were not significantly different for those with and without obesity but as a result, the total microgram doses of fentanyl were significantly higher in those with obesity. In the protocolized sedation arm, mean daily, peak daily, and cumulative fentanyl doses (in micrograms) were higher in those with obesity vs. those without ($p < 0.001$ for each). Similarly, in the usual care arm, fentanyl doses (in micrograms) were higher in those with obesity compared with those without obesity in terms of peak daily dose ($p = 0.005$) and cumulative dose ($p = 0.001$). Similar results were noted for morphine as the primary analgesic within the protocolized sedation arm but mean and cumulative doses were not different by body habitus within the usual care study arm. **Figure 1** provides granular data of the range of cumulative fentanyl and morphine exposures as a function of age that patients with and without obesity received while intubated. Medians of medication dose for patients with obesity in the protocolized sedation arm were 65% higher for mean daily fentanyl and 41% higher for cumulative fentanyl dose (in total micrograms) compared with patients with obesity in the usual care arm ($p < 0.05$ for these interactions between weight group and study arm; Table 2).

We found weight group differences in per kilogram dosing of benzodiazepines in the usual care arm. The obesity group in the usual care arm received significantly lower mean daily dose of benzodiazepine per kilogram compared with the no obesity group ($p = 0.03$). There were no differences in peak daily or cumulative benzodiazepine exposure in either study arm.

Protocolized sedation patients with obesity had more instances of inadequate sedation management compared with those without obesity (37% vs. 24%; $p < 0.001$); however, this finding was not found in the usual care arm ($p < 0.05$ for the interaction between study arm and weight group) (**Table 3**). All other measures of wakefulness, pain, and agitation, including days awake and calm, days to reach goal sedation, number of days with episodes of pain and/or agitation and frequency of pain episodes, were not different between the weight groups in either study arm. Additionally, there was no weight group difference in occurrence of IWS in either study arm.

There were several outcome differences associated with obesity (**Table 4**). Regardless of study arm, subjects with obesity took longer to recover from acute respiratory failure. The time to first ERT and to first passing an ERT was longer in those with obesity; however, these data were only available in the protocolized sedation arm. Other key outcomes had significant associations with obesity within the protocolized sedation arm but not within the usual care arm. In the protocolized sedation arm, patients with obesity had longer duration of ventilation ($p < 0.001$) and longer duration of weaning ($p = 0.01$) compared with those without obesity, but this difference was not noted in the usual care arm. They also had longer PICU stays

TABLE 2.

Analgesia and Sedation Exposure by Weight Group and Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Arm

	Protocolized Sedation			Usual Care		
Analgesia/Sedation Exposure	**With Obesity (*n* = 128)**	**Without Obesity (*n* = 457)**	***p*[a]**	**With Obesity (*n* = 137)**	**Without Obesity (*n* = 461)**	***p*[a]**
Primary opioid agent, *n* (%)			NS[b]			NS[b]
Fentanyl	59 (46)	209 (46)		116 (85)	386 (84)	
Morphine	67 (52)	243 (53)		20 (15)	64 (14)	
Neither	2 (2)	5 (1)		1 (1)	11 (2)	
Days of opioid exposure, median (IQR)	12 (6–19)	9 (5–15)	0.01	13 (5–25)	10 (4–22)	0.002
Fentanyl as primary agent, median (IQR)						
Mean daily dose, µg/kg	22 (12–52)	28 (15–51)	NS	20 (11–32)	22 (11–35)	NS
µg	791 (448–1,695)	544 (303–1,099)	< 0.001	480 (279–973)	449 (269–884)	NS
Peak daily dose, µg/kg	54 (32–108)	72 (37–122)	NS	62 (36–96)	60 (36–100)	NS
µg	1,692 (1,100–4,226)	1,483 (792–2,462)	< 0.001	1,430 (845–2,931)	1,313 (780–2,397)	0.005
Cumulative dose, µg/kg	296 (106–924)	278 (97–715)	NS	204 (102–651)	244 (79–546)	NS
µg	7,553 (3,136–34,332)	5,496 (2,535–14,639)	< 0.001	5,351 (2,314–15,122)	4,925 (2,195–12,950)	0.001
Morphine as primary agent, median (IQR)						
Mean daily dose, mg/kg	1.1 (0.5–2.1)	1.0 (0.4–2.1)	NS	0.9 (0.4–1.4)	1.0 (0.3–2.5)	NS
mg	26.8 (12.1–63.7)	19.4 (8.4–41.4)	0.02	33.2 (12.5–61.9)	19.4 (3.9–59.2)	NS
Peak daily dose, mg/kg	2.7 (1.3–5.4)	2.9 (1.2–5.8)	NS	1.7 (1.2–4.2)	3.5 (0.8–7.0)	0.02
mg	79.6 (36.8–156.4)	58.9 (26.1–120.2)	0.01	105.5 (35.3–160.0)	58.6 (14.8–169.5)	0.04
Cumulative dose, mg/kg	16.4 (4.3–32.4)	11.5 (3.4–33.8)	NS	12.9 (3.4–31.8)	13.8 (2.3–46.2)	NS
mg	417.6 (121.1–1,338.6)	238.1 (78.7–702.5)	0.01	475.5 (148.6–1,479.4)	335.3 (33.5–1,024.2)	NS
Primary benzodiazepine agent, *n* (%)			NS[c]			NS[c]
Midazolam	114 (89)	419 (92)		126 (92)	405 (88)	
Lorazepam	12 (9)	35 (8)		9 (7)	53 (12)	
None	2 (2)	3 (1)		2 (1)	3 (1)	

(*Continued*)

TABLE 2. (*Continued*)

Analgesia and Sedation Exposure by Weight Group and Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Arm

	Protocolized Sedation			Usual Care		
Analgesia/Sedation Exposure	**With Obesity (*n* = 128)**	**Without Obesity (*n* = 457)**	***p*[a]**	**With Obesity (*n* = 137)**	**Without Obesity (*n* = 461)**	***p*[a]**
Benzodiazepine exposure, midazolam equivalent, median (IQR), mg/kg						
Mean daily dose	1.1 (0.6–2.7)	1.5 (0.6–3.0)	NS	1.4 (0.5–2.2)	1.4 (0.7–2.6)	0.03
Peak daily dose	3.0 (1.5–7.0)	3.4 (1.4–7.0)	NS	3.4 (1.6–6.3)	3.8 (1.8–7.2)	NS
Cumulative dose	15.2 (5.9–53.9)	14.6 (5.0–47.8)	NS	15.9 (4.3–46.0)	15.0 (4.8–45.5)	NS
Secondary sedatives, *n* (%)						
Dexmedetomidine	43 (34)	131 (29)	0.02	74 (54)	237 (51)	NS
Methadone	15 (12)	59 (13)	NS	58 (42)	149 (32)	0.001
Intubated on day initiated, *n*/total (%)	8/15 (53)	31/59 (53)	NS	47/58 (81)	125/149 (84)	NS
Peak Withdrawal Assessment Tool, Version 1 score on day methadone initiated, median (IQR)[d]	4.5 (1–5)	3 (1–4)	NS	2.5 (1–4.5)	2.5 (1–4)	NS
Clonidine	26 (20)	60 (13)	NS	18 (13)	63 (14)	NS
Sedative classes received, median (IQR)	3 (2–4)	3 (2–4)	NS	3 (3–4)	3 (2–4)	NS

IQR = interquartile range, NS = not significant ($p > 0.05$).

[a]*p* values for comparison across weight groups within each Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study arm were calculated using logistic, linear, and proportional hazards regression accounting for PICU as a cluster variable using generalized estimating equations for binary, log-transformed continuous (except percentage of study days variables), and number of exposure days variables, respectively.

[b]This *p* value compares primary agent morphine vs. fentanyl across weight groups. Fentanyl was recommended in patients with profound hypotension, unremitting reactive airways disease, or intolerance to morphine.

[c]This *p* value compares primary agent midazolam vs. lorazepam across weight groups. Enteral lorazepam was recommended if IV access was a problem or if the patient was tolerating enteral feedings.

[d]Withdrawal Assessment Tool, Version 1 (WAT-1) scores range from 0 to 12; higher WAT-1 scores indicate more withdrawal symptoms; WAT-1 scores ≥ 3 are associated with clinically significant withdrawal symptoms. Scores available for 48 patients (ten with obesity; 38 without obesity) in the protocolized sedation arm and 94 (24 with obesity; 70 without obesity) in the usual care arm.

TABLE 3.

Wakefulness, Pain, Agitation, and Iatrogenic Withdrawal Syndrome by Weight Group and Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Arm

Sedative Response and Weaning	Protocolized Sedation			Usual Care		
	With Obesity ($n = 128$)	Without Obesity ($n = 457$)	p[a]	With Obesity ($n = 137$)	Without Obesity ($n = 461$)	p[a]
Measures of wakefulness, pain, and agitation						
Study days awake and calm, median (IQR), %	75 (58–94)	80 (63–100)	NS	70 (33–100)	71 (50–100)	NS
Days to first awake/calm state, median (IQR)	3 (1–5)	2 (1–4)	NS	3 (1–5)	3 (1–5)	NS
Study days with an episode of pain, median (IQR), %	50 (22–67)	50 (25–67)	NS	17 (0–36)	20 (0–42)	NS
Study days with an episode of agitation, median (IQR), %	50 (25–75)	57 (29–77)	NS	30 (0–58)	33 (8–67)	NS
Inadequate pain management (pain score > 4 for 2 consecutive hr), *n* (%)	24 (19)	70 (15)	NS	17 (12)	67 (15)	NS
Inadequate sedation management (SBS score > 0 for 2 consecutive hours), *n* (%)	47 (37)	111 (24)	< 0.001	27 (20)	87 (19)	NS
SBS score occurring most often on day of event, *n*/total (%)[b]						
–3/–2	2/39 (5)	17/92 (18)	NS	3/24 (13)	10/76 (13)	NS
–1/0	29 (74)	53 (58)		13 (54)	36 (47)	
+1/+2	8 (21)	22 (24)		8 (33)	30 (39)	
Occurrence of IWS[c]						
Tolerance (doubling of day 2 opioid dose before start of weaning), *n*/total (%)	23/64 (36)	70/230 (30)	NS	11/52 (21)	36/175 (21)	NS
IWS (WAT-1 score ever ≥ 3), *n*/total (%)	42/64 (66)	146/230 (63)	NS	35/52 (67)	110/175 (63)	NS
Peak WAT-1 score, median (IQR)	3 (2–5)	3 (2–5)	NS	4 (2–6)	3 (2–5)	NS
Study days with WAT-1 score ≥ 3, median (IQR), %	26 (0–50)	22 (0–44)	NS	27 (0–47)	20 (0–50)	NS

IQR = interquartile range, IWS = iatrogenic withdrawal syndrome, NS = not significant ($p > 0.05$), SBS = State Behavioral Scale, WAT-1 = Withdrawal Assessment Tool, Version 1.

[a]*p* values for comparison across weight groups within each Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study arm were calculated using linear, proportional hazards, and logistic regression accounting for PICU as a cluster variable using generalized estimating equations for log-transformed continuous (except percentage of study days variables), time-to-event, and binary variables, respectively.

[b]Scores are from the day of inadequate sedation management event (or day of the first inadequate sedation management event if more than one event). No SBS modal score if the patient was receiving neuromuscular blockade the entire day, extubated the previous day, or scores were not collected/documented.

[c]WAT-1 scores range from 0 to 12; higher WAT-1 scores indicate more withdrawal symptoms; WAT-1 scores ≥ 3 are associated with clinically significant withdrawal symptoms. Occurrence of iatrogenic withdrawal was calculated for 294 survivors in the protocolized sedation arm and 227 survivors in the usual care arm who completed weaning from ≥ 5 d of opioids and had at least one WAT-1 assessment.

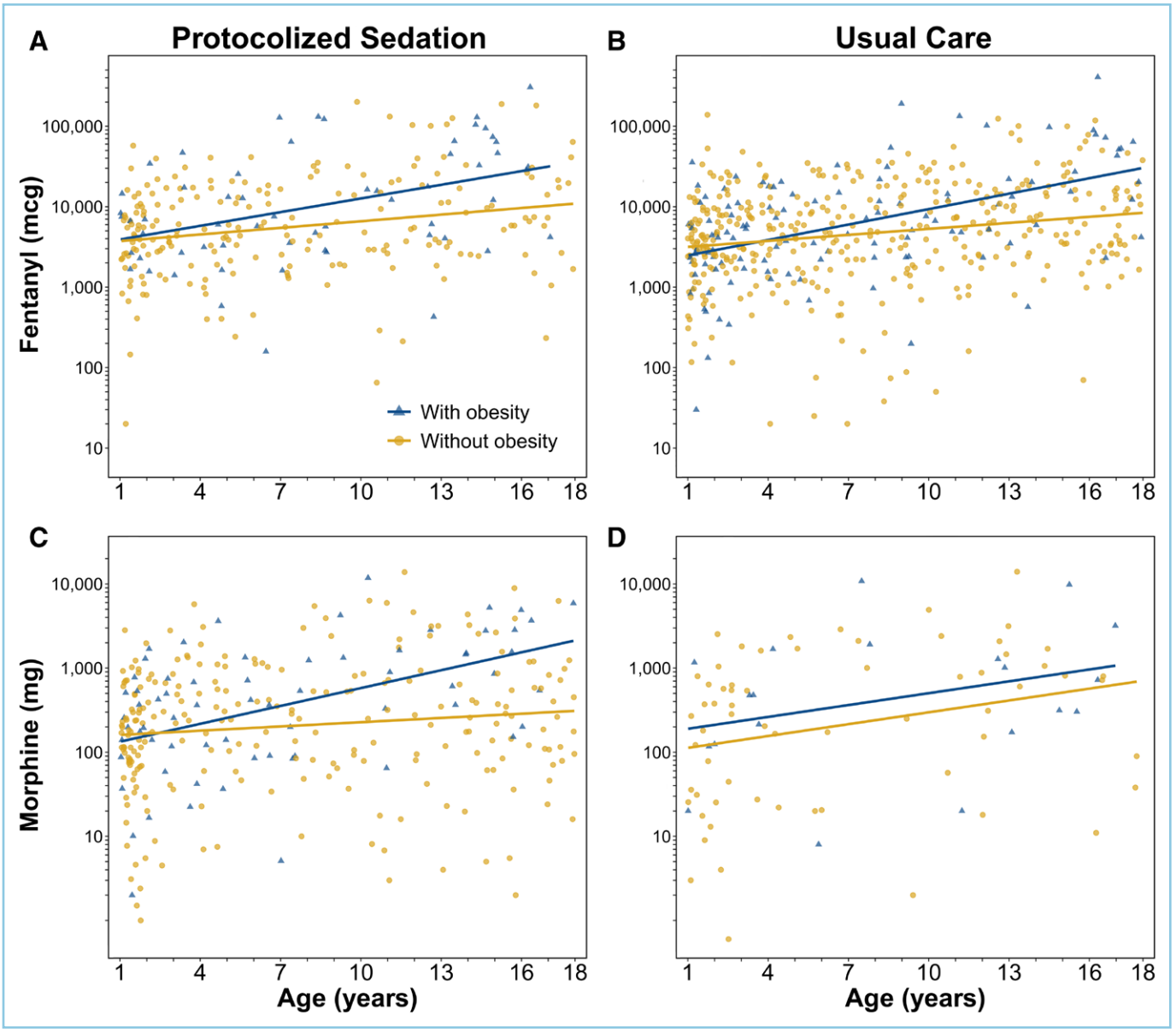

Figure 1. Trends in cumulative primary opioid agents (log scale) as a function of patient age by weight group and Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study arm. Cumulative fentanyl exposure when fentanyl is the primary agent for 59 patients with obesity and 209 patients without obesity in the protocolized sedation arm (**A**) and for 116 patients with obesity and 386 patients without obesity in the usual care arm (**B**). Cumulative morphine exposure when morphine is the primary agent for 67 patients with obesity and 243 patients without obesity in the protocolized sedation arm (**C**) and for 20 patients with obesity and 64 patients without obesity in the usual care arm (**D**).

than those without obesity (p = 0.01) and had higher 28-day in-hospital mortality compared with those without obesity (10% vs. 6%; p = 0.01). Neither PICU length of stay nor mortality were different between those with and without obesity in the usual care arm.

DISCUSSION

Twenty-two percent of children with acute respiratory failure had obesity in this study. Obesity and the lipophilic properties of medication are not accounted for when ordering sedative and analgesic infusions, leading to substantial daily and cumulative doses of opioids in children with obesity. Notably, those with obesity in the protocolized sedation arm received much higher median doses of opioids compared with those without obesity in the same study arm. Despite the differences in medication exposure, there were no differences in rates of iatrogenic withdrawal among those with and without obesity. Regarding clinical outcomes,

TABLE 4.

Trajectory of Recovery and Outcomes by Weight Group and Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Arm

Trajectory of Recovery and Outcomes	Protocolized Sedation			Usual Care		
	With Obesity ($n = 128$)	Without Obesity ($n = 457$)	p[a]	With Obesity ($n = 137$)	Without Obesity ($n = 461$)	p[a]
Days to first ERT, median (IQR)[b]	5.5 (2.8–10.3)	4.0 (2.4–7.1)	0.002	–	–	–
Days to first passed ERT, median (IQR)[c]	6.5 (3.8–11.9)	5.2 (3.3–8.2)	< 0.001	–	–	–
Days on mechanical ventilation, median (IQR)[d]	8.5 (4.7–14.6)	6.4 (3.9–11.2)	< 0.001	6.1 (3.8–14.8)	6.8 (3.7–12.5)	NS
Days to recovery from acute respiratory failure, median (IQR)[e]	4.3 (2.2–8.7)	3.1 (1.6–6.4)	0.009	3.4 (1.5–8.5)	2.9 (1.3–6.4)	0.01
Days weaning from mechanical ventilation, median (IQR)[f]	2.3 (1.0–4.2)	2.1 (1.0–4.2)	0.01	2.2 (0.9–5.0)	2.2 (1.1–5.0)	NS
Successful extubation on first attempt, *n* (%)	97 (76)	325 (71)	NS	67 (49)	258 (56)	NS
Extubation failure (reintubated within 24 hr), *n* (%)	9 (7)	32 (7)	NS	11 (8)	32 (7)	NS
Reintubated within 24 hr due to over sedation for any attempt, *n* (%)	0	0	–	0	4 (1)	–
Supported on extracorporeal membrane oxygenation, *n* (%)[g]	3 (2)	18 (4)	NS	3 (2)	15 (3)	NS
Length of stay, d, median (IQR)[h]						
PICU	13.7 (7.0–18.8)	10.1 (6.5–16.2)	0.01	10.7 (5.9–19.2)	10.0 (5.5–17.0)	NS
Hospital	20 (11.5–31.5)	15 (10–28)	0.03	20 (9–31.5)	17 (9–30.5)	NS

(*Continued*)

TABLE 4. (*Continued*)

Trajectory of Recovery and Outcomes by Weight Group and Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) Study Arm

Trajectory of Recovery and Outcomes	Protocolized Sedation			Usual Care		
	With Obesity ($n = 128$)	Without Obesity ($n = 457$)	p[a]	With Obesity ($n = 137$)	Without Obesity ($n = 461$)	p[a]
In-hospital mortality, *n* (%)						
At 28 d	13 (10)	26 (6)	0.01	8 (6)	31 (7)	NS
At 90 d	16 (13)	37 (8)	NS	13 (9)	45 (10)	NS

ERT = extubation readiness test, IQR = interquartile range, NS = not significant ($p > 0.05$).

[a]*p* values for comparison across weight groups within each Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) study arm were calculated using proportional hazards and logistic regression adjusting for categorical age and pediatric acute respiratory distress syndrome (PARDS) category and accounting for PICU as a cluster variable using generalized estimating equations for time-to-event and binary variables, respectively.

[b]Time to first ERT calculated for 101 patients with obesity and 367 patients without obesity in the protocolized sedation arm. For the RESTORE study, detailed ERT data were collected for protocolized sedation arm only.

[c]Time to first passed ERT calculated for 91 patients with obesity and 325 patients without obesity in the protocolized sedation arm.

[d]Patients were assigned 28 d if they remained intubated or were transferred or died before day 28 without remaining extubated for more than 24 hr, therefore, making this outcome equivalent to ventilator-free days.

[e]The duration from day 0 start (endotracheal intubation, initiation of assisted breathing for chronically trached patients, or PICU admission for patients intubated at an outside hospital) to the time that the patient first met criteria to be tested for extubation readiness (spontaneously breathing and oxygenation index ≤ 6). Days to recovery from acute respiratory failure excludes nonsurvivors who did not meet criteria before death. For the survivors who never met criteria, the duration of recovery was set as equal to the duration of mechanical ventilation if the patient was successfully extubated or to 28 d if the patient was still intubated on day 28 or transferred to another ICU while still intubated.

[f]Duration of weaning from mechanical ventilation excludes nonsurvivors who were not extubated for > 24 hr before death; it also excludes survivors who never met criteria and survivors still intubated on day 28.

[g]Due to small counts, *p* values for comparison across weight groups were calculated using logistic regression accounting for PICU as a cluster variable using generalized estimating equations, not adjusting for categorical age and PARDS category.

[h]PICU and hospital length of stay exclude all nonsurvivors. Patients still in the PICU or hospital on day 90 were censored at day 90.

Dashes indicate ERT was only assessed within the Protocolized Sedation study arm.

children with obesity in the protocolized sedation arm took longer to meet extubation readiness criteria, had longer duration of mechanical ventilation, took longer to recover from their illness, had longer PICU stays, and had higher mortality than their lean peers. These findings were not noted in the usual care arm.

The optimum therapeutic dose of a drug is dependent on the pharmacokinetics and pharmacodynamics of the drug, both of which can be affected by body composition and the physiological changes that occur in children with obesity. Medications that are lipophilic, such as fentanyl, midazolam, lorazepam, dexmedetomidine, and propofol, are distributed to lean and fat mass, and dosing based on actual body weight has been recommended (2, 17). Medications that are hydrophilic, including morphine and hydromorphone, are mostly distributed to lean mass (i.e., blood and solid organs) and therefore dosing based on ideal or adjusted body weight is recommended (2, 17). Physiologic factors, including inflammation and changes in lean mass, can alter glomerular filtration rate and therefore drug clearance, which must also be accounted for with medication dosing. These factors are affected by age, body habitus, and critical illness, creating substantial challenges for the pediatric intensivist in determining the optimal and safest doses of sedatives for mechanically ventilated children with and without obesity (2).

Very few studies have evaluated the interplay between obesity, sedative medication use, and clinical outcomes in children with acute respiratory failure. Johnson et al (18) evaluated initial fentanyl infusion dose and time to goal sedation in critically ill children with and without obesity. Like our findings, the fentanyl dose prescribed per kilogram was no different between the two weight groups. However, the initial dose of fentanyl infusion was more likely to achieve the goal sedation in those with obesity and less likely in those without obesity (17). Similar findings were also noted in a pilot study of 15 critically ill children with obesity and 16 without obesity, where no difference was found in initial (per kilogram) dosing or peak dosing of fentanyl infusions among the two weight groups (19). This study also noted no difference in withdrawal between the two groups but that the nonobesity group more frequently used withdrawal preventative medications such as methadone, diazepam, or transdermal fentanyl (18).

A surprising finding was the significant interaction between weight group and the RESTORE study arm. In the protocolized sedation arm, patients with obesity received much higher mean daily, peak daily, and cumulative dosing (in micrograms or milligrams) compared with those without obesity. Subsequently this subgroup took longer to meet extubation readiness criteria and had longer durations of mechanical ventilation and PICU stay than those without obesity. These findings were not evident in the usual care arm. One possible reason for this difference is the use of morphine (hydrophilic) as the primary sedative in the protocolized sedation arm compared with fentanyl (lipophilic), which was the most common opiate in the usual care arm. With medications being dosed by actual body weight for all patients, it is possible that those in the protocolized sedation arm who were treated with morphine may have been exposed to more medication than necessary. However, most dosing recommendations are based on medication half-life, which is important for initiation and weaning but likely not for maintenance when on continuous infusions. Alternatively, those treated with fentanyl (lipophilic) as a continuous infusion may have needed a lower weight-based dosing due to accumulation in their adipose tissue (20, 21). However, the patients with obesity and on fentanyl infusions in the protocolized sedation arm still received more medication than those with obesity in the usual care arm. Therefore, a third explanation is the use of adjunctive sedative medications. While both study arms were exposed to the same number of sedative classes, the timing of initiation was different. While the RESTORE protocol had clear instructions on when medications such as dexmedetomidine and methadone could be added as adjuncts, the usual care study arm had more leeway in this regard. As such, over 80% of patients in the usual care arm were initiated on methadone while still intubated compared with only 53% in the protocolized sedation arm. Further analysis is clearly needed to evaluate the impact of obesity on choice of analgesics and sedatives as well as timing and dose, and how various regimens impact outcomes.

This study has some limitations. The RESTORE study protocol had recommended using an adjusted body weight dosing for patients with obesity; however, only actual body weight was recorded. Therefore, we were unable to evaluate how often adjusted body

weights were used for medication dosing. Our finding of no significant difference in per kilogram (actual body weight) medication exposure but a great difference in total milligrams or micrograms of medication suggests that few providers used an adjusted weight for medication dosing. While the data collected in the RESTORE trial was detailed and thorough, there is no information about a subject's prior exposure to opiates and benzodiazepines, which would impact the doses needed to maintain safe sedation. Additionally, the timing and doses of secondary sedative medications, such as methadone or dexmedetomidine are not recorded to the same granularity as morphine, fentanyl, and midazolam, preventing a complete picture of drug exposure for comparison among the weight groups. In addition, some data were only available in the protocolized arm. It should also be noted that the RESTORE trial was performed over 10 years ago, and sedation practices have changed somewhat over this period. Thus, a reevaluation of the practice of using adjusted body weights and, therefore, medication exposure for patients with obesity bears reevaluation.

This study revealed that obesity is prevalent in the pediatric critical care population, and there is a lack of consistency in standard practice for weight-based dosing in this population. Some publications report dosing for medications should account for their pharmacologic properties and volume of distribution, such that lipophilic medications are dosed by actual body weight while hydrophilic medications, which have a lower volume of distribution, should an IBW (17). In contrast, other publications caution against this approach and instead recommend the most conservative dosing using IBW for all medications, with adjustments made for subsequent doses based on clinical outcomes (22). Because our study shows that medication exposure per kilogram was not different between those with and without obesity but that patients with obesity had worse outcomes (in the protocolized sedation group at least), we recommend the most conservative strategy of using IBW for initial dosing of sedation and analgesic infusions, but to adjust these doses frequently based on validated sedation and pain scoring rubrics in addition to hemodynamic responses. Standardization of IBW calculation method is also necessary since different methods yield very different weights for the same patient. In our previous work, we noted the method by McLaren and Read Walter (23) and the National Center for Health Statistics data tables (24) were most consistent with each other and most conservative in calculated IBW (25).

CONCLUSIONS

In summary, obesity is prevalent in children with acute respiratory failure, and it is not always considered when ordering sedative and analgesic infusions. This results in substantial medication exposure for children with obesity. Despite the differences in total medication exposure, we found no difference in rates of iatrogenic withdrawal among those with and without obesity. Interestingly, those with obesity in the protocolized sedation arm of the RESTORE trial received much higher doses of opiates compared with those without obesity in the same study arm. This same group also took longer to meet extubation readiness criteria, had longer duration of mechanical ventilation, took longer to recover from their illness, had longer PICU stays, and had higher mortality than their lean peers. As a result of our findings, we recommend dosing sedatives and analgesics in patients with obesity using IBW for initial dosing of sedation and analgesic infusions, but to adjust these doses frequently based on validated sedation and pain scoring rubrics in additional to hemodynamic responses. Further investigation is necessary to evaluate why medication dosing and clinical outcomes were so notably different in those with obesity who were managed with a more structured, protocolized sedation regimen.

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Drs. Ward and Curley conceived of and designed the study. All authors participated in data acquisition. Dr. Wypij, Ms. Dawkins-Henry, and Ms. Asaro conducted the data analysis. All authors contributed to the interpretation of the analysis results. Dr. Ward prepared the first draft of the article and all authors revised the draft critically. All authors have approved the final article for publication.

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