Awareness With Paralysis Among Critically Ill Emergency Department Patients: A Prospective Cohort Study*

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OBJECTIVES: In mechanically ventilated patients, awareness with paralysis (AWP) can have devastating consequences, including post-traumatic stress disorder (PTSD), depression, and thoughts of suicide. Single-center data from the emergency department (ED) demonstrate an event rate for AWP factors higher than that reported from the operating room. However, there remains a lack of data on AWP among critically ill, mechanically ventilated patients. The objective was to assess the proportion of ED patients experiencing AWP and investigate modifiable variables associated with its occurrence.

DESIGN: An a priori planned secondary analysis of a multicenter, prospective, before-and-after clinical trial.

SETTING: The ED of three academic medical centers.

PATIENTS: Mechanically ventilated adult patients that received neuromuscular blockers.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: All data related to sedation and analgesia were collected. AWP was the primary outcome, assessed with the modified Brice questionnaire, and was independently adjudicated by three expert reviewers. Perceived threat, in the causal pathway for PTSD, was the secondary outcome. A total of 388 patients were studied. The proportion of patients experiencing AWP was 3.4% ($n = 13$), the majority of whom received rocuronium ($n = 12/13$; 92.3%). Among patients who received rocuronium, 5.5% ($n = 12/230$) experienced AWP, compared with 0.6% ($n = 1/158$) among patients who did not receive rocuronium in the ED (odds ratio, 8.64; 95% CI, 1.11–67.15). Patients experiencing AWP had a higher mean (SD) threat perception scale score, compared with patients without AWP (15.6 [5.8] vs 7.7 [6.0]; $p < 0.01$).

CONCLUSIONS: AWP was present in a concerning proportion of mechanically ventilated ED patients, was associated with rocuronium exposure in the ED, and led to increased levels of perceived threat, placing patients at greater risk for PTSD. Studies that aim to further quantify AWP in this vulnerable population and eliminate its occurrence are urgently needed.

KEY WORDS: awareness with paralysis; emergency department; mechanical ventilation; neuromuscular blockers; post-traumatic stress disorder; sedation

In critically ill mechanically ventilated patients, awareness with recall of paralysis can cause intense fear, pain, feelings of impending death, and thoughts of suicide (1–6). Long-term psychologic consequences are common and include depression, anxiety, post-traumatic stress disorder (PTSD), and debilitating phobias (3, 4). Awareness with paralysis (AWP) has been studied extensively in the operating room, yet very little data exist from the emergency department (ED),

*See also p. 1541.

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KEY POINTS

- **Question:** What is the proportion of ED patients that experience AWP and do modifiable variables associated with its occurrence exist?
- **Findings:** In this pre-planned secondary analysis of a multicenter, prospective, before-after clinical trial, 3.4% of patients experienced AWP. Rocuronium was used in 12/13 (92.3%) patients and was independently associated with AWP. AWP patients experienced higher levels of perceived threat, placing them at increased risk for post-traumatic stress disorder.
- **Meaning:** These findings suggest that AWP is present in a concerning proportion of mechanically ventilated ED patients and should be targeted for prevention.

where mechanical ventilation is delivered to hundreds of thousands of patients annually (3, 7–10).

Historical practice patterns related to management of sedation and neuromuscular blockade in the ED place patients at high risk for AWP. These include: 1) high frequency of neuromuscular blockade use in the ED, with an increase in use of longer acting agents (e.g., rocuronium) (11, 12), 2) underdosing of IV analgesia and sedation (13–15), 3) high proportion of patients that receive no sedation after intubation (12, 15–19), 4) delays in provision of sedation after neuromuscular blockade (16, 19, 20), and 5) inconsistent monitoring and documentation of sedation depth (12, 16, 21). For these reasons, our research group conducted the ED-AWARENESS Study to estimate the frequency of AWP in mechanically ventilated ED patients and assess modifiable risk factors associated with its occurrence (22, 23). AWP occurred in 2.9% of patients exposed to neuromuscular blockers (approximately 25 times higher than that in the operating room) and was more common in patients receiving rocuronium. However, that study was single center, limiting generalizability. It also remains the only ED-based AWP study to rigorously assess and adjudicate awareness events in a fashion similar to large-scale trials from the operating room (3, 24, 25). Therefore, a persistent knowledge gap with respect to AWP in mechanically ventilated ED patients remains.

To address some of these limitations and further report on this important patient-centered complication, we planned a priori to prospectively assess for AWP during the conduct of an ED-based clinical trial regarding targeted sedation in the postintubation period (26). The objectives of the current work were to: 1) further estimate the frequency of AWP in mechanically ventilated ED patients, 2) identify risk factors associated with AWP, and 3) compare perceived threat between patients experiencing AWP and those without the complication. We hypothesized that AWP would be associated with modifiable variables related to sedation and neuromuscular blockade in the ED, and perceived threat would be higher in patients with AWP.

MATERIALS AND METHODS

Study Setting and Design

This was an a priori planned secondary analysis of AWP events collected during the ED-SED Pilot Trial, a multicenter, prospective, before-and-after pilot, and feasibility trial that examined the implementation and impact of ED-based targeted sedation for mechanically ventilated patients (26, 27). The study was conducted at three academic, tertiary medical centers from September 2020 to August 2021. These results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (**Supplemental Digital Content 1**, http://links.lww.com/CCM/H173). The study was approved with waiver of informed consent (Board Name: Human Research Protection Office; Approval Number: 201909100; Approval Date: July 1, 2020; Study Title: The ED-SED Pilot Trial). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as most recently amended. The ClinicalTrials.gov identifier is NCT04410783. A detailed description of the trial protocol has been published, as have results of the primary analysis (26, 27).

Participants

Consecutive mechanically ventilated ED patients were screened. Patients were eligible if they: 1) were age greater than or equal to 18 years, 2) received mechanical ventilation in the ED via an endotracheal tube,

and 3) received a neuromuscular blocker (i.e., during rapid sequence intubation or the postintubation phase of care). Patients with missing data regarding the receipt of neuromuscular blockers (n = 16, majority intubated at transferring EDs) were included in the analysis. This was done because approximately 90% of ED patients receive neuromuscular blockers either for intubation or in the postintubation phase of care; we, therefore, thought it reasonably safe to assume a neuromuscular blocker was given (12). We also aimed to provide conservative estimates for AWP. The exclusion criteria were: 1) acute neurologic injury (acute ischemic stroke, intracranial hemorrhage, traumatic brain injury, sudden cardiac arrest, status epilepticus, fulminant hepatic failure, and drug overdose), 2) death or transition to comfort measures within 24 hours, 3) transfer from the ED directly to the operating room, 4) transfer to another hospital, and 5) chronic/home mechanical ventilation.

Assessments and Outcome Measures

Research Electronic Data Capture (REDCap) tools were used to collate and manage data, which were abstracted from the electronic medical record (28, 29). Based on our prior work in mechanically ventilated ED patients, a data entry study manual was developed and used to train and guide team members in entering data from the medical record into REDCap (12, 16, 22, 23, 30–32). Quality control was achieved with manual and automatic methods, examining for outliers, and by enforcing plausible reference ranges in REDCap fields. Prior to data analysis, all data were electronically validated to verify accuracy.

Demographics and baseline variables comprised age, sex, race, weight, comorbid conditions, vital signs, and pertinent laboratory variables. Process of care variables included location of intubation and indication for mechanical ventilation, ED length of stay, receipt of antibiotics, and vasopressor use. Illness severity was assessed with the modified Sequential Organ Failure Assessment (SOFA) score (33, 34).

All data related to sedation and analgesia in the ED were collected. This included induction agents and neuromuscular blockers given for intubation. Medications during the postintubation phase of care included fentanyl, propofol, midazolam, dexmedetomidine, lorazepam, ketamine, etomidate, haloperidol, and neuromuscular blockers. Depth of sedation was recorded per existing scales at each site during the study period. This included the Richmond-Agitation Sedation Scale (RASS) or the Sedation-Agitation Scale (SAS). Deep sedation was defined as RASS of –3 to –5, or SAS of 1–3 (12, 35, 36).

AWP was the primary outcome. The modified Brice questionnaire was used to evaluate for AWP, as done in multiple studies from the operating room and our prior ED-based work on AWP (3, 22–25, 37). To be considered for a possible AWP event, patients had to report a memory of wakeful paralysis, which could have occurred after losing consciousness (i.e., waking up while under paralysis) or before unconsciousness (i.e., memory of paralysis during intubation). AWP was assessed by study team member after extubation and occurred either before hospital discharge or via telephone follow-up after discharge. Screening and adjudication of AWP were consistent with large clinical trials from the operating room and our prior approach (22, 24, 25). Three independent reviewers were provided questionnaire responses and reports of patients' experience. Important clinical information was also provided, including analgesia and sedation, neuromuscular blockers, and their dose. Reviewers were also provided an instruction sheet of the standard operating procedures regarding adjudication of awareness events. Reviewers adjudicated events as definite AWP, possible AWP, or no AWP; when two or more reviewers were in agreement, the patient was adjudicated as having AWP or not (22, 24, 25). In cases of no agreement (i.e., all reviewers held opposing views), an a priori plan for a fourth reviewer was in place, but was not needed. To distinguish between AWP and appropriate recall of memories, the ICU memory tool was combined with the Brice questionnaire during the assessment for AWP. The ICU Memory Tool is a previously validated instrument used to assess recall of events in the critically ill (38–40). The questionnaire used to assess for AWP, and the adjudicator instruction sheet is provided in **Supplemental Digital Contents 2** and **3** (http://links.lww.com/CCM/H173).

The secondary outcome of interest was perceived threat, the self-measured sense of personal vulnerability and life endangerment, and previously identified to be in the causal pathway for PTSD development (41–44). It, therefore, serves as a link, or mediator, between AWP and long-term psychologic morbidity. A previously validated measurement tool, on a scale of

0–21 with higher scores indicating greater threat, was used to asses this outcome (41, 44).

Statistical Analysis

Descriptive statistics and frequency distributions were used to assess patient characteristics. Continuous variables were compared using independent samples *t* test or Mann-Whitney *U* test, whereas categorical variables were compared using chi-square or Fisher exact test.

The proportion of patients with possible or definite AWP was used to calculate the primary outcome. To examine potential variables associated with AWP, a multivariable logistic regression model was used. In anticipation of a small number of events, we took several factors into consideration. First, any results from the model would be exploratory and hypothesis-generating. Second, we elected to use a parsimonious model and followed recommendations to select covariates a priori, based on prior knowledge (22, 45–47). We, therefore, selected these predictors for the model: 1) illness severity (i.e., SOFA score), 2) ED exposure to rocuronium (during intubation or postintubation period), 3) depth of ED sedation (deep vs light), and 4) age. Third, we used multivariable logistic regression with Firth bias-reducing penalized likelihood method. Different from conventional maximum likelihood estimation, the Firth log likelihood is penalized by the determinant of the information matrix, provides bias reduction for a small number of events, and yields finite and consistent estimates even in the case of separation (48–57).

A link between AWP and perceived threat was also explored. We hypothesized that AWP would be associated with increased perceived threat, placing patients at greater risk for developing PTSD symptoms (22, 26). To test the association between AWP and perceived threat, we used multivariable linear regression. We again followed recommendations that covariates be selected for inclusion a priori and adjusted our model for the following: 1) age, 2) illness severity, 3) prior history of psychiatric illness, and 4) indication for intubation (i.e., medical [reference] vs trauma) (42, 46, 47, 58–60). Our model used conservative robust standard errors in order to reduce the risk of type I error.

Agreement among adjudicators of AWP events was assessed with two-way, random-effects, intraclass correlation coefficient per prior approach (22, 25). All tests were two-tailed with an alpha of 0.05 to indicate statistical significance. Sample size rationale was based off of the parent trial (26). Based on our prior work regarding AWP in mechanically ventilated ED patients, we were confident during the planning of the trial that enough AWP events would be detected in order to conduct analyses with sufficient precision (22, 23).

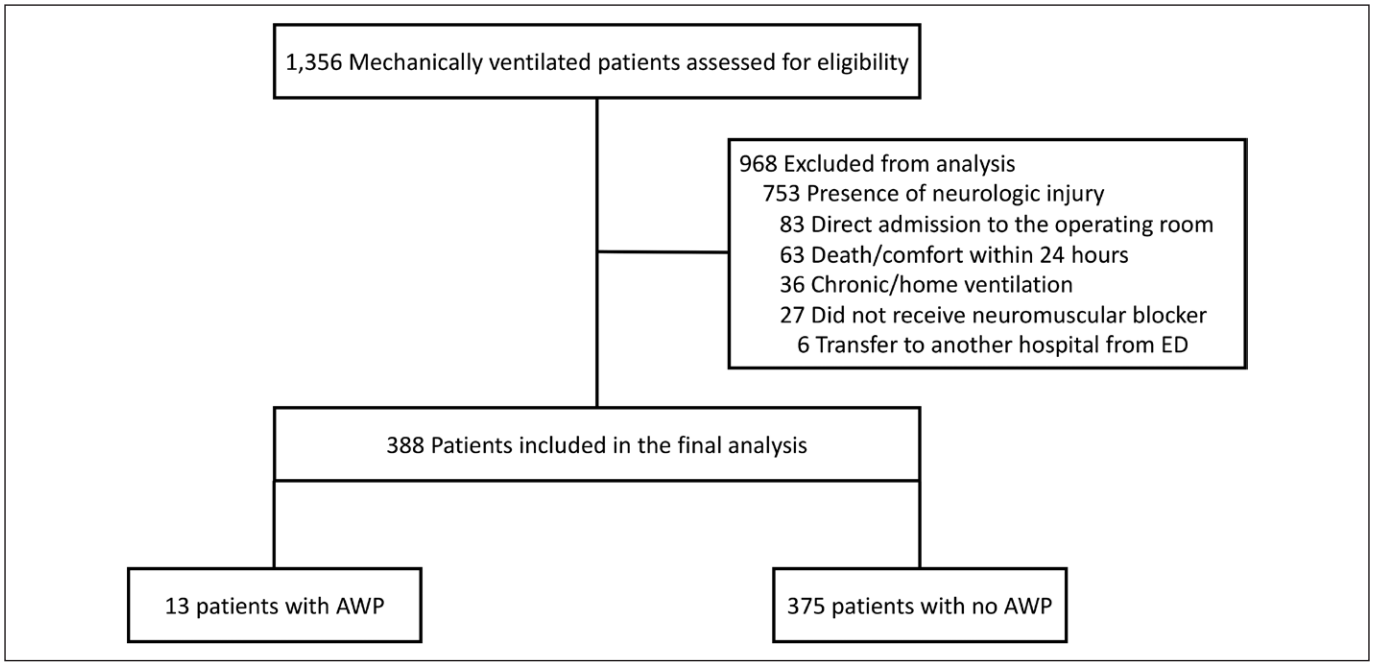

Figure 1. Study flow diagram. AWP = awareness with paralysis, ED = emergency department.

TABLE 1.
Characteristics of Included Study Participants

Baseline Characteristics	All Subjects (*n* = 388)	Patients With AWP (*n* = 13)	Patients Without AWP (*n* = 375)
Age (yr)	60 (45–72)	51 (46–58)	60 (45–72)
Female, *n* (%)	148 (38.1)	3 (23.1)	145 (38.7)
Body mass index	27.7 (23.9–33.8)	29.0 (23.3–37.0)	27.7 (23.8–33.7)
Race, *n* (%)			
White	190 (49.0)	11 (84.6)	179 (47.7)
Black	154 (39.7)	1 (7.7)	153 (40.8)
Hispanic	30 (7.7)	1 (7.7)	29 (7.7)
Asian	9 (2.3)	0 (0.0)	9 (2.4)
Native American	2 (0.5)	0 (0.0)	2 (0.5)
Other	3 (0.8)	0 (0.0)	3 (0.8)
Comorbidities, *n* (%)			
Dementia	17 (4.4)	0 (0.0)	17 (4.5)
Diabetes mellitus	116 (29.9)	3 (23.1)	113 (30.1)
Cirrhosis	25 (6.4)	1 (7.7)	24 (6.4)
Heart failure	83 (21.4)	2 (15.4)	81 (21.6)
End-stage renal disease	13 (3.4)	0 (0.0)	13 (3.5)
Chronic obstructive pulmonary disease	81 (20.9)	3 (23.1)	78 (20.8)
Immunosuppression	28 (7.2)	1 (7.7)	27 (7.2)
Malignancy	51 (13.1)	1 (7.7)	50 (13.3)
Alcohol abuse	51 (13.1)	5 (38.5)	46 (12.3)
Psychiatric[a]	97 (25.0)	6 (46.2)	91 (24.3)
Intubation data, *n* (%)			
Location of intubation			
Emergency department	321 (82.7)	9 (69.2)	312 (83.2)
Transferring facility	42 (10.8)	2 (15.4)	40 (10.7)
Prehospital	25 (6.4)	2 (15.4)	23 (6.1)
Indication for intubation			
Trauma	81 (20.9)	3 (23.1)	78 (20.8)
Medical	307 (79.1)	10 (76.9)	297 (79.2)
Temperature (°C)	36.6 (36.1–37.1)	36.9 (36.5–37.6)	36.6 (36.0–37.1)
Mean arterial pressure (mm Hg)	98.8 (24.3)	104.8 (27.9)	98.8 (24.2)
Lactate (mmol/L)	2.7 (1.5–4.8)	1.8 (1.6–4.1)	2.7 (1.5–4.8)
Sequential Organ Failure Assessment	4.0 (3.0–7.0)	3.0 (2.0–4.0)	4.0 (3.0–7.0)
Emergency department process of care variables			
Length of stay (hr)	5.8 (3.9–8.7)	4.9 (2.6–12.4)	5.8 (3.9–8.6)
Vasopressor infusion, *n* (%)	150 (38.7)	2 (15.4)	148 (39.5)
Blood transfusion, *n* (%)	47 (12.1)	3 (23.1)	44 (11.7)
Central venous catheter, *n* (%)	105 (27.1)	4 (30.8)	101 (26.9)
Antibiotics, *n* (%)	198 (51.0)	4 (30.8)	194 (51.7)

AWP = awareness with paralysis.

[a]Psychiatric if diagnosed with schizophrenia, bipolar, major depression, or generalized anxiety disorder.

Continuous variables are reported as mean (SD) and median (interquartile range).

RESULTS

Study Population

One thousand three hundred fifty-six patients were screened, and 388 were included as the final study population (**Fig. 1**). The baseline characteristics of the study cohort are in **Table 1**. Baseline differences existed for several variables. Patients experiencing AWP in general were younger, and there were a greater proportion that were male, White, and with a history of alcohol abuse and psychiatric illness. In addition, AWP patients were less severely ill (i.e., lower SOFA score and need for vasopressors). Three hundred sixty-four (93.8% of total cohort) patients had COVID-19 test results available; one of 13 AWP patients (7.7%) tested positive for COVID and 40 of 351 (11.4%) of the remainder of the cohort tested positive for COVID ($p = 0.68$).

Main Results

Twenty (5.2%) of the 388 patients reported memory of wakeful paralysis and were assessed by independent adjudicators for potential AWP events. Clinical summaries for these 20 patients are provided in **Supplemental Digital Content 4** (http://links.lww.com/CCM/H173). The intraclass correlation coefficient (95% CI) between adjudicators was 0.65 (0.42–0.83). After adjudication, the proportion of patients experiencing AWP was 3.4% (13/388; 95% CI, 1.8–5.7). Clinical summaries and adjudication results for the 13 AWP patients are in **Supplemental Digital Content 5** (http://links.lww.com/CCM/H173). There were 58 patients (14.9%) that died in the hospital. The proportion of surviving patients experiencing AWP was 3.9% (13/330; 95% CI, 2.1–6.6%). Data regarding analgesia, sedation, and neuromuscular blocker use in the ED are in **Table 2**. Three hundred seventy-two patients received neuromuscular blockers for rapid sequence intubation, and 16 during the postintubation period. No significant differences existed between the two groups, except for rocuronium use. The majority of patients with AWP received rocuronium ($n = 12/13$; 92.3%). Among patients who received rocuronium, 5.5% ($n = 12/230$) experienced AWP, compared with 0.6% ($n = 1/158$) among patients who did not receive rocuronium in the ED (odds ratio, 8.64; 95% CI, 1.11–67.15).

The logistic regression model assessing for predictors of AWP is shown in **Table 3**. Exposure to rocuronium in the ED was a statistically significant predictor of AWP (adjusted odds ratio, 7.22; 95% CI, 1.39–37.58).

Threat perception scores differed significantly between the two groups. Patients experiencing AWP had higher mean (SD) threat perception, when compared with patients without AWP (15.6 [5.8] vs 7.7 [6.0]; $p < 0.01$), indicating a greater degree of perceived threat. In the multivariable model assessing the relationship between AWP and perceived threat (**Table 4**), AWP was a statistically significant predictor of greater perceived threat ($\beta = 7.46$; 95% CI, 4.14–10.77).

DISCUSSION

Prior ED-based sedation research demonstrated clinical practice patterns placing patients at high risk for AWP (12, 13, 15–20, 61). Given this, the severe psychologic trauma that can result from AWP, and the paucity of ED-based data, we previously conducted the ED-AWARENESS Study to rigorously assess this complication in mechanically ventilated ED patients (22, 23). In that study, 2.9% of patients that were given neuromuscular blockers experienced AWP, with a higher proportion of AWP among patients exposed to rocuronium. Given the limitations of that single-center study and to add to the body of research, we conducted the current investigation in order to further assess AWP in this vulnerable population.

The first significant finding is that the proportion of patients experiencing AWP was 3.4%; when restricted to survivors, this proportion was 3.9%. This rate is similar to that observed from the ED-AWARENESS study, as well as a comprehensive systematic review and meta-analysis regarding AWP in mechanically ventilated patients in the ED and ICU (22, 62). Patient testimonials reflect vivid recollections of pain from procedures, being restrained, and feelings of impending death. Data from the operating room estimate the prevalence of AWP during general anesthesia to be approximately 1–2/1,000 cases (0.1–0.2%), and approximately 0.9% in high-risk patients managed with total IV anesthesia (3, 8, 9, 63). Although more work is needed, as the study of AWP in mechanically ventilated ED patients is in its relative infancy, these event rates are concerning and could translate into approximately 10,000 cases of AWP annually in the United States.

Another important finding relates to rocuronium exposure in the ED, as it was significantly higher among patients with AWP compared with those not experiencing

TABLE 2.
Data Regarding Analgesia, Sedation, and Neuromuscular Blocker Use in the Emergency Department

Variable	All Subjects (*n* = 388)	Patients With AWP (*n* = 13)	Patients Without AWP (*n* = 375)	OR or Between-Group Difference[a] (95% CI)
Rapid sequence intubation variables[b]				
Etomidate, *n* (%)	235 (60.6)	8 (61.5)	227 (60.5)	1.04 (0.34–3.25)
Dose (mg)	20 (20–30)	20 (20–30)	20 (20–30)	0.26 (–7.51 to 8.04)
Weight-based dose (mg/kg)	0.27 (0.21–0.32)	0.29 (0.18–0.31)	0.26 (0.22–0.32)	–0.02 (–0.11 to 0.07)
Ketamine, *n* (%)	131 (33.8)	5 (38.5)	126 (33.6)	1.24 (0.40–3.85)
Dose (mg)	100 (100–150)	100 (62–155)	100 (100–150)	–11.9 (–60.0 to 36.0)
Weight-based dose (mg/kg)	1.30 (1.09–1.66)	0.85 (0.59–1.79)	1.30 (1.10–1.66)	–0.37 (–0.98 to 0.23)
Succinylcholine, *n* (%)	155 (39.9)	3 (23.1)	152 (40.5)	0.44 (0.12–1.63)
Dose (mg)	100 (100–120)	125 (100–NA)	100 (100–120)	15.5 (–33.7 to 64.6)
Weight-based dose (mg/kg)	1.32 (1.12–1.51)	1.11 (0.85–NA)	1.32 (1.14–1.52)	–0.24 (–0.77 to 0.28)
Rocuronium, *n* (%)	217 (55.9)	10 (76.9)	207 (55.2)	2.71 (0.73–9.99)
Dose (mg)	100 (100–100)	100 (100–110)	100 (100–100)	3.2 (–14.2 to 20.5)
Weight-based dose (mg/kg)	1.17 (1.00–1.39)	1.06 (0.92–1.34)	1.17 (1.0–1.39)	–0.08 (–0.31 to 0.16)
ED postintubation variables				
Fentanyl, *n* (%)	331 (85.3)	12 (92.3)	319 (85.1)	2.11 (0.27–16.5)
Cumulative dose (μg)	400 (200–750)	338 (125–763)	400 (200–750)	–25 (–281 to 231)
Weight-based dose (μg/kg)	5.0 (2.0–9.1)	3.5 (1.4–9.3)	5.2 (2.0–9.1)	–1.0 (–4.34 to 2.27)
Propofol, *n* (%)	304 (78.4)	10 (76.9)	294 (78.4)	0.92 (0.25–3.42)
Cumulative dose (mg)	248 (38–663)	252 (42–1,457)	248 (37–659)	200 (–141 to 543)
Weight-based dose (mg/kg)	3.2 (0.6–8.1)	3.6 (0.6–13.4)	3.0 (0.6–8.1)	1.2 (–2.1 to 4.4)
Midazolam, *n* (%)	96 (24.7)	4 (30.8)	92 (24.5)	1.37 (0.41–4.54)
Cumulative dose (mg)	6.0 (4.0–10.0)	5.0 (2.0–5.8)	7.0 (4.0–10.0)	–4.8 (–15.9 to 6.2)
Weight-based dose (mg/kg)	0.07 (0.04–0.14)	0.05 (0.02–0.06)	0.07 (0.04–0.14)	–0.07 (–0.24 to 0.10)
Dexmedetomidine, *n* (%)	37 (9.5)	1 (7.7)	36 (9.6)	0.79 (0.10–6.21)
Cumulative dose (mg)	1.5 (0.4–3.2)	0.40 (NA)	1.5 (0.4–3.3)	–1.7 (–6.7 to 3.4)
Weight-based dose (mg/kg)	0.02 (0.01–0.04)	0.004 (NA)	0.02 (0.01–0.04)	–0.02 (–0.09 to 0.04)
Lorazepam, *n* (%)	20 (5.2)	1 (7.7)	19 (5.1)	1.56 (0.19–12.64)
Cumulative dose (mg)	2.0 (1.0–2.0)	1.0 (NA)	2.0 (1.0–2.0)	–1.3 (–5.0 to 2.4)
Weight-based dose (mg/kg)	0.03 (0.01–0.04)	0.01 (NA)	0.03 (0.01–0.04)	–0.02 (–0.07 to 0.03)
Ketamine, *n* (%)	41 (10.6)	2 (15.4)	39 (10.4)	1.57 (0.34–7.33)
Cumulative dose (mg)	100 (40–200)	75 (50–NA)	100 (40–200)	–83 (–301 to 137)
Weight-based dose (mg/kg)	1.25 (0.40–2.63)	0.65 (0.45–NA)	1.34 (0.38–2.65)	–1.05 (–3.08 to 0.98)
Rocuronium[c], *n* (%)	16 (4.1)	2 (15.4)	14 (3.7)	4.69 (0.95–23.19)
Cumulative dose (mg)	100 (53–100)	100 (100–NA)	100 (50–100)	10 (–64 to 83)
Weight-based dose (mg/kg)	0.87 (0.63–1.08)	0.88 (0.85–NA)	0.86 (0.58–1.14)	–0.06 (–0.94 to 0.82)

(*Continued*)

TABLE 2. (*Continued*).
Data Regarding Analgesia, Sedation, and Neuromuscular Blocker Use in the Emergency Department

Variable	All Subjects (*n* = 388)	Patients With AWP (*n* = 13)	Patients Without AWP (*n* = 375)	OR or Between-Group Difference[a] (95% CI)
Sedation depth variables[d]				
Median Richmond-Agitation Sedation Scale in ED	−2 (−3 to 0)	−2 (−3 to −1)	−2 (−3 to 0)	−0.3 (−2.3 to 1.6)
Median Sedation-Agitation Scale in ED	2 (1–3)	3 (2–4)	2 (1–3)	0.5 (−0.6 to 1.7)
Deep sedation, *n* (%)	194 (50.0)	7 (53.8)	187 (49.9)	1.17 (0.39–3.56)

AWP = awareness with paralysis, ED = emergency department, NA = not available, OR = odds ratio.
[a]OR is presented for binary data, and between-group difference is presented as the difference in means for the continuous data.
[b]Three total patients were given midazolam, and six were given propofol (no difference between the groups). Data are not shown due to space constraints.
[c]Refers to paralytic given as additional bolus after rapid sequence intubation.
[d]Eight hundred twenty-three sedation assessments were performed in the ED, on average 2.1 assessments per patient.
Continuous variables are reported as median (interquartile range).

the complication. Longer acting neuromuscular blockers are a known risk for AWP (2, 3, 8, 64). The current results are also congruent with the higher rates of rocuronium use in AWP patients observed in the ED-AWARENESS Study (22). Given the similar methodology of the two studies, combining the results demonstrates that AWP among patients given rocuronium was 5.4% (*n* = 19/354), compared with 1.0% (*n* = 4/417) among patients who did not receive rocuronium in the ED (odds ratio, 5.86; 95% CI, 1.97–17.40) (22, 26). These results are even more critical when considering that rocuronium use for rapid sequence intubation in the ED has increased from less than 10% to around 50% over the last 2 decades (11, 12, 65, 66). Further, the use of rocuronium in the ED has been shown to reduce the chance that patients will ever receive postintubation sedation (67). If sedation is received in the context of rocuronium use, data demonstrate that it is at lower doses and in delayed fashion (19, 20). Our results call further attention to the need for: 1) patient-centered clinical outcomes when studying endotracheal intubation and mechanical ventilation in the ED, 2) improved monitoring of both the brain and the effects of neuromuscular blockade (e.g., train-of-four monitoring), and 3) pragmatic interventions to prevent AWP (68). Although rocuronium has high rates of first-pass success during intubation, our data indicate a need to look beyond short-term surrogate outcomes if the human cost is AWP and commensurate long-term psychologic morbidity (69).

TABLE 3.
Multivariable Logistic Regression Model With Firth Bias-Reducing Penalized Likelihood Method for Small Sample Sizes

Variables	Adjusted OR (95% CI)	*p*
Rocuronium exposure in the ED[a]	7.22 (1.39–37.58)	0.02
Age	0.99 (0.96–1.02)	0.33
Sequential Organ Failure Assessment score	0.80 (0.63–1.02)	0.07
ED deep sedation	1.13 (0.39–3.25)	0.83

ED = emergency department, OR = odds ratio.
[a]Rapid sequence intubation and the postintubation phase of care. Awareness with paralysis is the dependent variable.

The final important finding relates to the psychologic footprint from AWP. Patients with AWP had higher degrees of perceived threat, and AWP strongly influenced levels of threat in multivariable analysis. This is important as perceived threat is a strong mediator for development of PTSD as it relates to medical emergencies (43, 44, 59, 70, 71). These findings objectively demonstrate the psychologic vulnerability as a result of AWP and lend weight to the call for AWP in mechanically ventilated ED patients to be a never event (69). However, as PTSD was not formally assessed in this cohort, future studies will need to confirm this link among AWP, perceived threat, and PTSD.

TABLE 4.
Multivariable Linear Regression Model Assessing the Relationship Between Awareness With Paralysis and Perceived Threat

Variable	Regression Coefficients (95% CI)	*p*
Awareness with paralysis	7.46 (4.14–10.77)	< 0.01
Age	−0.08 (−0.13 to −0.03)	< 0.01
Sequential Organ Failure Assessment	0.16 (−0.15 to 0.46)	0.31
History of psychiatric illness[a]	1.59 (−0.23 to 3.41)	0.09
Indication for intubation	−1.71 (−3.66 to 0.24)	0.09

[a]Schizophrenia, bipolar, major depression, or generalized anxiety disorder.

This report has multiple strengths, including the rigorous methodology in the assessment of AWP and the multicenter approach. However, several limitations exist. The sample size is the largest to date with respect to AWP among mechanically ventilated ED patients, yet remains small, and there were only 13 events for the primary outcome. This is reflected in the wide CIs of our analyses and draws attention to the need for larger studies. The small number of events also brings concern for statistical overfitting, which we attempted to mitigate by using a parsimonious approach and small sample methodology (Firth bias-reducing penalized likelihood method). Definite and possible AWP was combined, which could inflate the event rate. This approach is consistent with large trials from the operating room and our prior work, both of which demonstrate similar distress and perceived threat among those with possible or definite events (22, 24). The multicenter approach enhances external validity, but extrapolating these findings beyond our three sites may not be valid. Further, rocuronium use was high in the current investigation, and results may not extend to other sites, where longer acting neuromuscular blockers are given less frequently. However, our data are consistent with the well-established trend of increased rocuronium use in the ED. In addition, because reviewers were not blinded to data regarding neuromuscular blockers and sedation, it is possible that the adjudication process was biased against rocuronium (i.e., more AWP adjudicated in patients with known rocuronium exposure). Although our methodology in adjudicating AWP events is rigorous and consistent with prior approach, subjectivity exists. Because of this, our adjudicators were given instructions to assure uniformity; however, subjectivity in determining real memories from perceptions or delusions (e.g., hallucinations and medication effects) remains. In addition, given the variability in lengths of stay and ventilator duration experienced by mechanically ventilated patients, the exact timing of questionnaire administration was not standardized, which could impact reproducibility. However, our event rate for AWP is consistent with prior work, lending face validity to the results (22, 62). In addition, the Brice questionnaire has not been extensively used outside of the operating room setting, and its sensitivity may vary among the critically ill. Our consistent results with prior work, rigorous adjudication methodology, and use of the ICU Memory Tool to attempt to separate memories from AWP events lend confidence in the results. Recognizing that patients must survive to extubation to be assessed for AWP, for the primary analysis, we elected to include those patients that died in the hospital in the denominator. This was in effort to prioritize cautious estimates and again highlights the need for larger studies in the ED population. Finally, this was a secondary analysis of a previously conducted clinical trial. Although all parts of the current investigation were planned a priori, these results should be viewed as hypothesis-generating.

CONCLUSIONS

AWP was present in almost 4% of survivors of ED-based mechanical ventilation, was associated with rocuronium exposure in the ED, and led to increased levels of perceived threat, placing patients at greater risk for PTSD. Studies that aim to further quantify AWP in this vulnerable population and eliminate its occurrence are urgently needed.

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