The ED-AWARENESS Study: A Prospective, Observational Cohort Study of Awareness With Paralysis in Mechanically Ventilated Patients Admitted From the Emergency Department

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Study objective: Awareness with paralysis is a devastating complication for patients receiving mechanical ventilation and risks long-term psychological morbidity. Data from the emergency department (ED) demonstrate a high rate of longer-acting neuromuscular blocking agent use, delayed analgosedation, and a lack of sedation depth monitoring. These practices are discordant with recommendations for preventing awareness with paralysis. Despite this, awareness with paralysis has not been rigorously studied in the ED population. Our objective is to assess the prevalence of awareness with paralysis in ED patients receiving mechanical ventilation.

Methods: This was a single-center, prospective, observational cohort study on 383 mechanically ventilated ED patients. After extubation, we assessed patients for awareness with paralysis by using the modified Brice questionnaire. Three expert reviewers independently adjudicated awareness with paralysis. We report the prevalence of awareness with paralysis (primary outcome); the secondary outcome was perceived threat, a mediator for development of posttraumatic stress disorder.

Results: The prevalence of awareness with paralysis was 2.6% (10/383). Exposure to rocuronium at any point in the ED was significantly different between patients who experienced awareness with paralysis (70%) versus the rest of the cohort (31.4%) (unadjusted odds ratio 5.1; 95% confidence interval 1.30 to 20.1). Patients experiencing awareness with paralysis had higher mean values on the threat perception scale, denoting a higher degree of perceived threat, compared with patients who did not experience awareness with paralysis (13.4 [SD 7.7] versus 8.5 [SD 6.2]; mean difference 4.9; 95% confidence interval 0.94 to 8.8).

Conclusion: Awareness with paralysis occurs in a significant minority of ED patients who receive mechanical ventilation. Potential associations of awareness with paralysis with ED care and increased perceived threat warrant further evaluation. [Ann Emerg Med. 2021;77:532-544.]

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INTRODUCTION

Background

Awareness with recall of paralysis is the recollection of sensory perceptions while under the influence of a neuromuscular blocking agent. Studies examining outcomes of patients who experience awareness with paralysis in the operating room have documented disturbing long-term psychological sequelae occurring in up to 70% of cases, including posttraumatic stress disorder (PTSD), clinical depression, and complex phobias.[1-4]

Prospective studies have estimated prevalence of awareness with paralysis during general anesthesia to be approximately 0.1% to 0.2%[5,6]; this figure approaches 1.0% in high-risk patients given only intravenous anesthesia.[7] Risk factors for higher prevalence and greater severity of awareness with paralysis in the operating room include intravenous anesthetic approach (versus use of inhaled anesthetics),[8,9] underdosing of anesthesia,[10] administration of longer-acting neuromuscular blocking

Editor's Capsule Summary

What is already known on this topic

Awareness with paralysis is a potential complication for patients receiving mechanical ventilation and may be associated with long-term psychological consequences.

What question this study addressed

What is the prevalence of awareness with paralysis among emergency department (ED) patients receiving mechanical ventilation?

What this study adds to our knowledge

In this prospective study of 383 patients, 10 (2.6%) experienced an episode of awareness with paralysis.

How this is relevant to clinical practice

Awareness with paralysis occurs in a small but important number of ED patients receiving mechanical ventilation.

agents,[2,5,11] and lack of protocolized sedation depth monitoring.[3] Although extensive research has been conducted on awareness with paralysis in the operating room, this has yet to extend to other areas, such as the emergency department (ED), potentially placing patients receiving mechanical ventilation at higher risk for this complication.

In the United States, clinicians have historically managed ED patients receiving mechanical ventilation in a way that could predispose them to awareness with paralysis.[12,13] These patients exclusively receive intravenous analgosedation and are frequently underdosed.[14] This includes induction agents during rapid sequence intubation, particularly in obese patients.[15,16] Several studies have shown that 10% to 54% of patients receiving ventilation receive no sedation after rapid sequence intubation,[14,17-21] and there can be substantial delay (up to 50 minutes) in the provision of postintubation sedation.[18,22] Approximately 90% of patients receive neuromuscular blocking agents for intubation in the ED, with an increasing use of longer-acting agents (eg, rocuronium) as opposed to succinylcholine.[23] After intubation, approximately 10% to 25% of ED patients receiving mechanical ventilation receive additional, longer-acting neuromuscular blocking agents without any increase in sedation.[18,19] Literature has demonstrated that for ED patients receiving longer-acting neuromuscular blocking agents such as rocuronium, postintubation sedation is initiated at lower doses and with greater delays compared with those who receive succinylcholine.[21,22] Finally, a lack of protocol-driven management of sedation is common, and up to 33% of ED patients receiving mechanical ventilation receive no sedation depth assessment.[18,19]

Importance

These data describe a historical precedent of management in the ED that is discordant with recommendations for prevention of awareness with paralysis. However, only a few small studies have examined awareness in this vulnerable cohort. Four prospective cohort studies (combined n=123) assessed for recall of intubation and demonstrated a prevalence ranging from 6% to 50%.[24-27] This prior research on awareness with paralysis in ED patients is limited as a result of small sample sizes, methodological limitations, and use of nonvalidated and never-before-used questionnaires to assess for awareness. Despite a lack of studies examining awareness with paralysis in ED patients, prior data regarding analgosedation practices suggest that these patients could be at a higher risk for awareness with paralysis and justify the conduct of more rigorous studies.

Goals of This Investigation

To address this critical knowledge gap, we conducted the ED-AWARENESS study to estimate the prevalence of awareness with paralysis in ED patients receiving mechanical ventilation.

MATERIALS AND METHODS

Study Design and Setting

We conducted a single-center, prospective cohort study from June 2019 to May 2020 at a large (annual ED volume ≈90,000 patient visits), academic, residency-affiliated, tertiary care center in St. Louis, MO. These results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement (Appendix E1, available online at http://www.annemergmed.com).[28] Our institutional review board approved this study and waived requirement to obtain a signed informed consent form; the study team obtained verbal informed consent from each subject. A detailed description of the methods has been published.[29]

Selection of Participants

The study team prospectively identified patients receiving mechanical ventilation through an automated screening alert and enrolled consecutively, 24 hours per day. Patients were eligible if they were aged 18 years or older and underwent mechanical ventilation through an endotracheal tube in the ED. Intubation could have

occurred either in the ED or before arrival, such as out-of-hospital or at a transferring facility. Exclusion criteria were death before discontinuation of mechanical ventilation, presence of neurologic injury with residual deficit that precluded assessment for awareness with paralysis (eg, cerebrovascular accident, traumatic brain injury, cardiac arrest with hypoxic brain injury), transfer to another facility, and attrition or refusal to answer the questionnaire.

Methods of Measurement

All measurements and clinical data were gathered from chart review and collated with Research Electronic Data Capture (REDCap) tools.[30,31] All variables were objective and easily abstracted from the electronic medical record. A trained team member (RDP) entered data from the electronic medical record into REDCap. This team member was also experienced in the methodology, given prior experience extracting similar data.[19] We performed data quality control using both automatic and manual methods, and controlled REDCap fields by enforcing reference ranges for all data entered (eg, plausible ranges for all values). A second team member (BMF) performed periodic monitoring throughout the study on 20% of REDCap patient records. Before statistical analysis, the complete database was electronically searched for out-of-range and implausible values, and all flagged data were rechecked in the electronic chart to ensure accuracy.

Baseline characteristics included age, sex, race, weight, height, preexisting comorbidities, initial ED vital signs, and laboratory values. Comorbid conditions included dementia, diabetes mellitus, cirrhosis, heart failure, end-stage renal disease, chronic obstructive pulmonary disease, immunosuppression, malignancy, alcohol abuse, and psychiatric illness (ie, schizophrenia, bipolar disorder, major depression, or generalized anxiety disorder). Select laboratory values included levels of lactate, creatinine, bilirubin, platelets, hemoglobin, and blood gases. ED length of stay and data related to mechanical ventilation were collected.

All sedation-related data in the ED were collected, including induction agents and neuromuscular blocking agents used to facilitate intubation. Postintubation medications related to analgosedation included opiates, benzodiazepines, propofol, ketamine, etomidate, haloperidol, quetiapine, and all neuromuscular blocking agents. We recorded sedation depth with the Richmond Agitation-Sedation Scale in accordance with routine care. When more than one sedation depth was recorded, the median value was used. For patients who did not have an ED Richmond Agitation-Sedation Scale score recorded, the first such score from the ICU was used as a surrogate, consistent with prior approaches.[18,19] Data were also collected from the first 48 hours of ICU stay, including all analgesics, sedatives, neuromuscular blocking agents, sedation depth, and delirium assessments with the Confusion Assessment Method for the ICU according to routine care. The incidence of acute brain dysfunction, ventilator-free days, and ICU- and hospital-free days was also tracked.

Outcome Measures

The primary outcome was awareness with paralysis. In the assessment of the primary outcome, an important distinction had to be recognized with respect to the management goals for anesthetized patients in the operating room (the only clinical arena in which awareness with paralysis has been rigorously studied) compared with critically ill patients receiving mechanical ventilation. In the operating room, the goal is to typically achieve unconsciousness and a lack of movement during a course of periodic painful stimuli. In contrast, data from patients in the ED and ICU demonstrate that light levels of sedation are associated with improved outcome.[18,19,32-34] Therefore, memory and recall of events are not only expected in patients receiving mechanical ventilation but also in general are considered beneficial. This is in stark contrast to memories of awareness of paralysis, which carry substantial negative psychological sequelae.[35-39] To aid in distinguishing awareness with paralysis from the appropriate recall of memories while patients receive mechanical ventilation, a combination of questions from the Brice questionnaire and the ICU Memory Tool was used (Appendix E2, available online at http://www.annemergmed.com). The Brice questionnaire is the preferred method of evaluating for awareness with paralysis,[3,40-42] and the ICU Memory Tool is a validated questionnaire to assess memory of events in critically ill patients.[43-45]

To be considered for a possible awareness with paralysis event, patients had to report memories of the period between losing consciousness and waking up (Brice questionnaire item 3 answered as yes), report a sensation or feeling of wakeful paralysis, and have documented neuromuscular blocking agent administration. If patients did not report memories of the period between losing consciousness and waking up but did report memories of wakeful paralysis before losing consciousness (eg, recall of intubation), and had documented neuromuscular blocking agent administration, then they were also considered for a possible awareness with paralysis event. Events related to waking up during neuromuscular blockade and experiencing awareness with paralysis before

unconsciousness were considered equivalent. The study team assessed for awareness with paralysis after extubation and before hospital discharge. During the final 2 months of the study, because of university-mandated clinical research restrictions related to the coronavirus disease 2019 pandemic, awareness with paralysis was assessed by telephone follow-up after hospital discharge. Awareness with paralysis was independently adjudicated by 3 expert reviewers who were provided patient responses to the questionnaire, qualitative reports of patient experiences, and pertinent clinical information, including data regarding analgesics, sedatives, and neuromuscular blocking agent. In assessing whether awareness with paralysis occurred, the reviewers were instructed to consider such things as details and consistency of the reported memories, along with pertinent clinical information, such as type or dose of neuromuscular blocking agent (Appendix E3, available online at http://www.annemergmed.com). Because of the somewhat subjective nature in assessing for awareness with paralysis, these instructions were used to provide some standardization for adjudicators regarding the background of the study and how awareness and memories were assessed for, and to ensure they were looking at the accounts through a similar lens. Each expert reviewer adjudicated events as no awareness with paralysis, possible awareness with paralysis, or definite awareness with paralysis. The primary outcome of awareness with paralysis was determined when at least 2 experts were in agreement. If all experts held opposing views, then it was planned for a fourth reviewer to assist in the adjudication process.[40] A fourth reviewer was not needed.

The secondary clinical outcome was perceived threat, which was assessed with a previously validated measurement tool (scale 0 to 21, with higher scores denoting a greater degree of perceived threat).[46,47] A link between awareness with paralysis and perceived threat exists because perceived threat (conceptualized as a self-measured sense of life endangerment and personal vulnerability) during a medical emergency has previously been identified as a mediator (ie, on the causal pathway) for the development of PTSD symptoms.[46-49]

Primary Data Analysis

Patient characteristics are reported with descriptive statistics and frequency distributions. Data normality was assessed by inspection of Q-Q plots and the Kolmogorov-Smirnov test.

Awareness with paralysis was calculated as the proportion of patients with either possible or definite awareness events. The agreement among adjudicators of awareness with paralysis events was assessed with the use of a 2-way, random-effects, intraclass correlation coefficient for absolute agreement according to the following: 0=no awareness with paralysis, 1=possible awareness with paralysis, and 2=definite awareness with paralysis.

We previously published a detailed rationale regarding our sample size.[29] Given the observational design of the study, the primary outcome is more descriptive rather than a hypothesis test between 2 groups. Before conduct of the study, we noted a dearth of literature regarding awareness with paralysis from the ED domain, which raised the potential that no events would be detected. However, we noted that patients receiving intravenous (not inhaled) anesthesia in the operating room had a prevalence of awareness with paralysis approaching 1% during routine care.[9] Because data demonstrate that our population could be at even higher risk, we estimated a prevalence of 1% to 2%, recognizing that the sample size needed to be large enough to observe an event with a high degree of probability and with sufficient precision. We decided a priori to enroll patients for approximately 12 months to accrue an adequate sample size and reduce the chance that any seasonal trends would skew the data. According to our prior work in ED patients receiving mechanical ventilation, we expected 2.1 patients per day to satisfy inclusion criteria and estimated approximately half would ultimately be excluded, leaving just over 1 patient per day enrolled (n=383).[18,19,50-52] With a sample size of 383, if only 1 awareness with paralysis event were detected, the corresponding event rate of 0.26% would be similar to that observed in the operating room, where sedation depth is monitored more diligently.[3] According to known risk factors for awareness with paralysis and prior literature regarding ED sedation practices, we were confident that the sample size would be large enough to observe at least one event with sufficient precision.

RESULTS

Characteristics of Study Subjects

The Figure shows the study flow and final study population. Baseline characteristics are reported in Table 1.

Main Results

There were 383 patients included in the study. Seven percent of patients (27/383) reported memories of wakeful paralysis and were assessed for awareness with paralysis. Adjudicators of awareness with paralysis events had high agreement (intraclass correlation coefficient 0.72; 95% confidence interval [CI] 0.55 to 0.85). After adjudication, the prevalence of possible or definite awareness with paralysis was 2.6% (10/383; 95% CI 1.3% to 4.7%). Clinical summaries, analgosedation data, and adjudication information for the 10 patients with possible or definite awareness with paralysis are presented in Table 2. The

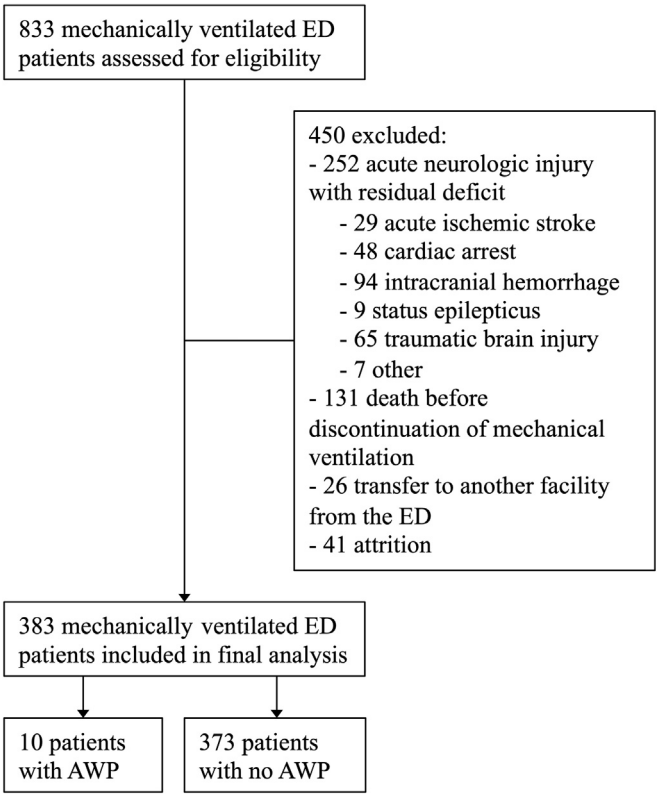

Figure. Study flow and final study population. *AWP*, Awareness with paralysis.

summaries for all 27 patients reporting wakeful paralysis are available in Table E1. A description of analgosedation practices in the ED (rapid sequence intubation and postintubation sedation) is presented in Table 3. There was no documented neuromuscular blocking agent use for 38 patients (9.9%). The prevalence of possible or definite awareness with paralysis among patients with documented neuromuscular blocking agent exposure was 2.9% (10/345; 95% CI 1.4% to 5.3%). Exposure to rocuronium at any time in the ED (ie, combining rapid sequence intubation and postintubation) was significantly different between patients who experienced awareness with paralysis (70%) versus the rest of the cohort (31.4%) (odds ratio 5.1; 95% CI 1.30 to 20.1).

Patients experiencing awareness with paralysis had higher mean values on the threat perception scale, denoting a higher degree of perceived threat, compared with those who did not experience it (13.4 [SD 7.7] versus 8.5 [SD 6.2]; mean difference 4.9; 95% CI 0.94 to 8.8).

LIMITATIONS

This study had several limitations. Although to our knowledge it is the largest nonoperating room study to date focusing on awareness with paralysis, the overall sample was small and derived from a single center. Therefore, all results from this observational single-center cohort study with 10 events for the outcome of interest are exploratory and hypothesis generating only. Our design also limits generalizability to other centers and could lead to an overestimation of the true event rate for awareness with paralysis. Although our rigorous methodology in adjudicating awareness with paralysis and prevalence similar to that of a recent multicenter ICU-based trial enhance face validity of our results,[53] larger, multicenter studies from the ED are needed. Large, prospective, multicenter, cohort studies would provide a higher number of awareness with paralysis cases, which could provide more reliable estimates of ED-based factors associated with awareness with paralysis, and allow for the conduct of interventional trials. There is also some subjectivity in the assessment of awareness with paralysis, and interpretation of our results should take into account the fact that unmeasured variables (eg, inducing false memories) could confound responses given by participants. However, we are encouraged by the fact that good agreement existed between the independent reviewers and that a fourth reviewer was never needed during the adjudication process. Furthermore, the objective demonstration of higher perceived threat suggests the patients' experiences of awareness with paralysis were indeed real. Patients with definite and possible awareness with paralysis were combined in the assessment of the total event rate. This approach has been used in major trials from the operating room that demonstrated similar reports of distress among patients with definite versus possible awareness.[41] However, this raises the possibility that our reported event rate is inflated. Nevertheless, 7 cases of definite awareness with paralysis (1.8%) remains worrisome and meaningful. The exclusion of a large number of neurologically injured patients could have also inflated the event rate. However, even if all eligible patients were included as the denominator, the resulting prevalence of awareness with paralysis (1.2%) is still factors higher than that observed in other domains, placing thousands of patients at risk annually. With respect to excluded patients, 9.1% (n=41) of exclusions were due to attrition. Because these patients were not administered the questionnaire or included in the analysis, we cannot be sure that their characteristics, treatment, or possible event rate for awareness with paralysis was not systematically different from that of our study population. The receipt of a neuromuscular blocking agent was a requirement for consideration of an awareness with paralysis event. Thirty-eight patients never received a neuromuscular blocking agent, and their exclusion would increase the event rate to

Table 1. Characteristics of included study participants.

Baseline Characteristics	All Subjects (n=383)	Patients With AWP (n=10)	Patients Without AWP (n=373)
Age, y*	54 (37–63)	65 (53–67)	53 (37–63)
Women, No. (%)	132 (35)	4 (40)	128 (34)
BMI, kg/m^2*	26.9 (22.3–31.7)	30.4 (22.9–36.4)	26.6 (22.3–31.6)
Race, No. (%)			
Black	224 (59)	3 (30)	221 (59)
White	151 (38)	7 (70)	144 (38)
Asian	5 (2)	0	5 (2)
Not reported	3 (1)	0	3 (1)
Comorbidities, No. (%)			
Dementia	9 (2)	0	9 (2)
Diabetes mellitus	86 (23)	3 (30)	83 (22)
Cirrhosis	8 (2)	0	8 (2)
Heart failure	76 (20)	2 (20)	74 (20)
ESRD	28 (7)	1 (10)	27 (7)
COPD	71 (19)	3 (30)	68 (18)
Immunosuppression	14 (4)	2 (20)	12 (3)
Malignancy	41 (11)	1 (10)	40 (11)
Alcohol abuse	44 (12)	0	44 (12)
Psychiatric†	71 (19)	2 (20)	69 (19)
Intubation data, No. (%)			
Location of intubation			
ED	309 (81)	9 (90)	300 (80)
Transferring facility	44 (11)	1 (10)	43 (12)
Out-of-hospital	30 (8)	0	30 (8)
Indication for intubation			
Trauma	106 (28)	4 (40)	102 (27)
Medical	277 (72)	6 (60)	271 (73)
Temperature (°C)*	36.5 (36.0–36.9)	36.6 (36.0–37.1)	36.5 (36.0–36.9)
Pulse rate, beats/min‡	99 (25)	92 (24)	99 (25)
Mean arterial pressure, mm Hg‡	98.8 (24.4)	105.6 (28.2)	98.7 (24.3)
Lactate, mmol/L*	2.8 (1.6–5.1)	2.4 (1.4–3.1)	2.8 (1.6–5.2)
Creatinine, mg/dL*	1.1 (0.9–1.5)	1.5 (1.0–1.6)	1.1 (0.9–1.5)
Bilirubin, mg/dL*	0.4 (0.3–0.7)	0.2 (0.2–0.5)	0.4 (0.3–0.8)
SOFA*	2.0 (0–4.0)	2.5 (1.8–4.2)	2.0 (0–4.0)
ED process-of-care variables			
Length of stay, h*	5.1 (3.3–7.0)	4.1 (3.0–5.8)	5.2 (3.3–7.0)
Vasopressor infusion, No. (%)	86 (23)	3 (30)	83 (22)

BMI, Body mass index; *ESRD*, end-stage renal disease; *COPD*, chronic obstructive pulmonary disease; *SOFA*, sequential organ failure assessment.
*Continuous variables reported as median (interquartile range).
†Psychiatric if patient received a diagnosis of schizophrenia, bipolar, major depression, or generalized anxiety disorder.
‡Continuous variables reported as mean (SD).

2.9%. We elected to use 383 as the denominator to err on the side of conservative estimates, and because our overarching goal was to inform practicing clinicians regarding awareness with paralysis across a full spectrum of patients requiring mechanical ventilation in the ED.

Because awareness with paralysis in the ED has not been rigorously examined before to our knowledge, our research methods are largely extrapolated from similar studies in the operating room (eg, the use of the modified Brice questionnaire).[42] Although these methods are the current

Table 2. Patients reporting wakeful paralysis and adjudicated to have possible or definite awareness with paralysis.

ID	Sex, Age (Years) (Weight in Kilograms)	Drugs for Intubation, Milligrams	Postintubation Analgosedation	Clinical Scenario	Reported Memory/Awareness Experience	Determination of Awareness (Definite, Possible, No)	
						3 Expert Reviewers	Overall
1	M, 67 (62)	Ketamine 100 Rocuronium 60	Fentanyl infusion	Brought to ED for dyspnea, failed NIPPV	No memory of anything in between losing consciousness and waking up. Answered yes to question regarding a sensation of feeling paralyzed while receiving mechanical ventilation. Remembered feeling scared, tried to open eyes and move, but could not. Patient had no further details regarding this memory.	Possible Possible Possible	Possible
3	F, 65 (110)	Etomidate 30 Rocuronium 100	Propofol infusion	Altered mental status, DKA, and possible seizure	Reported remembering things in between losing consciousness and waking up and reported a sensation of not being able to move, as if she were paralyzed. Stated she thought she woke up once in the ED but could not move anything except for maybe her fingers. She thought she could open her eyes and saw lights but could not move the rest of her body. Reported that she remembered voices and specific conversations, and remembered her bed being pushed/transported. Believed her event took place in the ED because she remembered a lot of commotion occurring when she had her moment of awareness, and that she had significant pain. Patient stated that then after a short time everything went dark again.	Definite Definite Possible	Definite
4	M, 72 (60)	Ketamine 100 Succinylcholine 60	Fentanyl, propofol, and midazolam infusions 1 dose ketamine (80 mg) and etomidate (10 mg) after intubation	Brought to ED for dyspnea, failed NIPPV	No memory of anything in between losing consciousness and waking up. Patient did not remember anything after losing consciousness but described procedural awareness of intubation ("I remember the breathing tube going in"). Stated, "I had a mask on my face"; then he was given medications. Before he went to sleep, he remembered "something opening my mouth up and the tube going in my mouth and down my throat." Stated that this experience was his worst memory of his entire period of mechanical ventilation.	Possible Possible Definite	Possible
5	M, 64 (84)	Ketamine 80 Rocuronium 70	Fentanyl, propofol infusions 1 dose ketamine (10 mg) after intubation	Angioedema-fiberoptic nasotracheal intubation with multiple attempts	No memory of anything in between losing consciousness and waking up. Reported last memory was of recall of the procedure of intubation. When asked whether he ever had the sensation of feeling paralyzed, he answered yes. Stated, "I came to the [ED] because my tongue was swollen. I remember them putting the breathing tube down, but I could not move. I remember the breathing tube actually going in and being panicked. It was terrible and traumatic. I was panicking inside. Then I went to sleep." Stated his worst memory was "being paralyzed and remembering it."	Definite Definite Definite	Definite

11	M, 37 (68)	Etomidate 20 Succinylcholine 200	Propofol boluses and then infusion Given 20 mg vecuronium after intubation	Fall from a roof and sustained bilateral lower extremity fractures, including an open distal tibia fracture/dislocation. Intubated in ED of transferring facility.	Reported remembering things in between losing consciousness and waking up and reported a sensation of not being able to move, as if he were paralyzed. He remembered waking up with someone pulling very hard on his injured leg, which caused severe pain. He thinks he was in the ED. The patient said this was the worst pain he had ever had and it was unbearable, and said he felt "scarred" by going through such intense pain. Reported that he tried to move but could not. He remembers hearing alarms, hearing and seeing 3–4 people standing around his bed and 1 person pulling hard on his injured leg. Records noted that patient's open fracture/dislocation was reduced in the ED after intubation and before transfer; reported "spike in blood pressure" during this event.	Possible Definite Definite	Definite
18	F, 67 (114)	Etomidate 20 Succinylcholine 100	Fentanyl and propofol infusions	Fell and had open tibia/fibula fracture with extensive blood loss	No memory of anything in between losing consciousness and waking up. Reported last memory before unconsciousness was being in the ED, asking for pain medication. Answered yes to question regarding a sensation of feeling paralyzed while receiving mechanical ventilation. Stated that she remembered the physicians telling her they needed to put in a breathing tube, and they began to give her medication through the IV line. For "about a minute" she experienced paralysis in which she "couldn't move anything, not even my eyes." She said that then she passed out.	Possible No Possible	Possible
20	F, 57 (80)	Ketamine 100 Rocuronium 100	Propofol infusion	Inhalation injury after house fire. Intubated in ED; then bronchoscopy performed.	Reported remembering things in between losing consciousness and waking up and reported a sensation of not being able to move, as if she were paralyzed. Said she remembered "coming into the [ED] after the fire and my throat hurt. They said they were worried about my breathing, so they needed to put a breathing tube in." Said that when she woke up, she could not move but could hear people talking about "putting a camera down to look in my lungs." She felt a lot of pain in the back of her throat and inside her chest from something going down the tube. "When I woke up, it felt like the same room and I heard the same voices. I felt that pain inside my chest before I went to sleep again." Said her worst memory was waking up and not being able to move and feeling the pain of endotracheal tube being suctioned.	Definite Definite Possible	Definite

Table 2. Continued.

ID	Sex, Age (Years) (Weight in Kilograms)	Drugs for Intubation, Milligrams	Postintubation Analgosedation	Clinical Scenario	Reported Memory/Awareness Experience	Determination of Awareness (Definite, Possible, No)	
						3 Expert Reviewers	Overall
21	M, 41 (92)	Ketamine 100 Succinylcholine 100	Fentanyl and midazolam infusions; 1 bolus dose of rocuronium 100 mg ("patient biting tube")	Pedestrian struck by car; open tibia fracture was reduced, splinted, and placed in traction after intubation	Reported remembering things in between losing consciousness and waking up and reported a sensation of not being able to move, as if he were paralyzed. Patient stated he was in the ED and heard a female nurse say, "We are trying to bring you back; just stay calm." He remembered lying on the bed and feeling as if he were in a dream, but he knew that this "dream" was actually happening. He stated he felt out of his own body and could not move. He stated he could not even open his eyes or breathe on his own. He stated he saw himself on the bed almost as if he were outside his own body. He said he had a breathing tube in his throat and was trying to move and talk but could not. He stated the worst part about having the breathing tube and being aware in the ED was that he "…felt like if I stopped breathing, I would die right there on the bed, and it would be all over."	Definite Definite Possible	Definite
23	M, 67 (96)	Etomidate 20 Succinylcholine 100	Fentanyl and propofol infusions	Altered mental status and severe cervical stenosis	Reported remembering things in between losing consciousness and waking up and reported a sensation of not being able to move, as if he were paralyzed. Patient stated he remembered being in a hospital room—he thought it was the ED—and the breathing tube was being inserted into his throat while he was awake. The patient remembers he did not think he could move. However, he stated that he was able to open his eyes and look around at people and felt as if he were able to turn his head "a little bit."	Definite Definite Possible	Definite
27	F, 65 (68)	Etomidate 20 Rocuronium 90	Fentanyl and propofol infusions	Altered with COPD, hypercapnia and hypoxia, failed NIPPV	Reported remembering things in between losing consciousness and waking up and reported a sensation of not being able to move, as if she were paralyzed. "I was in the [ED] and I had a mask blowing air into my mouth to help me breathe. I remember the doctors telling me that I would need to be put on the breathing machine. When I woke up, I was lying flat and I could hear everybody's voices around me. I tried to move and breathe but could not and it was terrifying. I heard people in the room talking and I remember seeing the curtains and the lights in the room. I don't know how long this lasted but it felt like forever. Then I went to sleep again and the next thing I remember was waking up in the room in the ICU." Stated her worst memory was waking up and not being able to move.	Definite Definite Definite	Definite

M, male; *NIPPV*, noninvasive positive-pressure ventilation; *F*, female; *DKA*, diabetic ketoacidosis.

Table 3. ED analgosedation variables.

Variable	Patients With AWP (n=10)	Patients Without AWP (n=373)	Between-Group Difference (95% CI)
RSI variables			
Induction agent			
Etomidate, No. (%)	5 (50)	173 (46.4)	3.62 (−27.8 to 35.0)
Dose, mg	20 (20 to 25)	20 (20 to 20)	0.60 (−4.63 to 5.82)
Weight-based dose, mg/kg	0.27 (0.19 to 0.29)	0.28 (0.24 to 0.34)	0.05 (−0.3 to 0.13)
Ketamine, No. (%)	5 (50)	126 (33.8)	16.2 (−15.1 to 47.6)
Dose, mg	100 (90 to 100)	100 (100 to 150)	38.1 (23.9 to 52.3)
Weight-based dose, mg/kg	1.25 (1.02 to 1.64)	1.43 (1.10 to 1.97)	0.36 (−0.37 to 1.08)
Midazolam, No. (%)	0	10 (2.7)	−2.68 (−4.32 to −1.04)
Dose, mg	—	8.9 (5.1)	—
Weight-based dose, mg/kg	—	0.11 (0.06)	—
Propofol, No. (%)	0	10 (2.7)	−2.68 (−4.32 to −1.04)
Dose, mg	—	129 (52)	—
Weight-based dose, mg/kg	—	1.47 (0.78)	—
None, No. (%)	0	21 (5.6)	−5.63 (−7.97 to −3.29)
Paralytic			
Succinylcholine, No. (%)	5 (50)	196 (52.5)	−2.55 (−34.0 to 28.9)
Dose, mg	100 (100 to 160)	100 (100 to 100)	−21.9 (−75.7 to 31.8)
Weight-based dose, mg/kg	1.08 (0.96 to 2.47)	1.23 (1.06 to 1.52)	−0.27 (−1.35 to 0.82)
Rocuronium, No. (%)	5 (50)	102 (27.3)	22.7 (−8.7 to 54.0)
Dose, mg	90 (65 to 100)	100 (80 to 100)	10.9 (−15.5 to 37.3)
Weight-based dose, mg/kg	1.05 (0.22)	1.17 (0.33)	0.12 (−0.18 to 0.42)
None, No. (%)	0	39 (10.5)	−10.5 (−13.6 to −7.35)
ED postintubation variables			
Fentanyl, No. (%)	8 (80)	294 (78.8)	1.18 (−24.0 to 26.3)
Cumulative dose, μg	250 (138 to 300)	288 (150 to 500)	115 (−118 to 348)
Weight-based dose, μg/kg	2.8 (1.8 to 4.4)	3.4 (2.0 to 6.4)	1.64 (−1.39 to 4.67)
Propofol, No. (%)	8 (80)	267 (71.6)	8.42 (−16.8 to 33.6)
Cumulative dose, mg	660 (290 to 1,340)	510 (290 to 980)	−391 (−1,382 to 600)
Weight-based dose, mg/kg	7.5 (3.8 to 11.9)	6.6 (3.6 to 12.0)	−5.6 (−19.3 to 80.0)
Midazolam, No. (%)	2 (20)	128 (34.3)	−14.3 (−39.6 to 10.9)
Cumulative dose, mg	6 (6 to 6)	5 (4 to 10)	1.4 (−6.9 to 9.7)
Weight-based dose, mg/kg	0.08	0.07 (0.04 to 0.13)	0.01 (−0.09 to 0.11)
Lorazepam, No. (%)	0	46 (12.3)	−12.3 (−15.7 to −9.0)
Cumulative dose, mg	—	2 (2 to 4)	—
Weight-based dose, mg/kg	—	0.03 (0.02 to 0.06)	—
Ketamine, No. (%)	3 (30)	57 (15.3)	14.7 (−13.9 to 43.4)
Cumulative dose, mg	70	100 (60 to 118)	54 (−42 to 150)
Weight-based dose, mg/kg	0.83 (0.63)	1.41 (0.88)	0.58 (−0.45 to 1.61)
Rocuronium,* No. (%)	2 (20)	22 (5.9)	14.1 (−10.8 to 39.0)
Cumulative dose, mg	100 (100 to 100)	100 (50 to 100)	−11 (−103 to 81)
Weight-based dose, mg/kg	1.09	1.11 (0.47)	—
Sedation depth variables			
Median RASS score in ED	−1.5 (−2.3 to 1.3)	−1.7 (−3 to 0)	−0.8 (−2.1 to 0.5)
Deep sedation, No. (%)	2 (20)	146 (39)	−19.1 (−44.4 to 6.14)

RSI, Rapid sequence intubation; *RASS*, Richmond Agitation-Sedation Scale.
Continuous variables are reported as mean (SD) and median (interquartile range).
*Refers to paralytic given as additional bolus after rapid sequence intubation.

standard for assessing awareness with paralysis, the modified Brice questionnaire may not perform in the same manner for our cohort as when applied to postsurgical patients. We therefore made extensive efforts to separate memories from wakeful paralysis. We also did not serially assess patients for awareness with paralysis, as some operating-room-based studies have done.[40,41] In preparing for this study, we did not think this was necessary because all patients would be interviewed typically after multiple days of receiving mechanical ventilation and days after exposure to neuromuscular blockers, which would encompass multiple interview periods from operating-room-based studies. In accordance with prior literature from the operating room, had we interviewed at day 30, there would have been a chance that we could have uncovered more cases of awareness with paralysis, which is a consideration for future studies.

DISCUSSION

Awareness with paralysis is a potentially devastating but largely preventable complication of mechanical ventilation that has been well studied only in the operating room.[5,6] Rigorous studies examining this complication have yet to be performed in the ED. Research on analgosedation practices for ED patients receiving mechanical ventilation demonstrate a pattern of delayed intravenous sedation,[14-22] frequent administration of longer-acting neuromuscular blocking agents,[18,19,23] and an overall lack of protocolized sedation monitoring,[18,19] all of which are known risk factors for awareness with paralysis.[3] To address this gap in the literature, we conducted a single-center, prospective, cohort study on ED patients receiving mechanical ventilation to determine the prevalence of awareness with paralysis and explore risk factors and adverse psychological effects related to this complication. There were several important findings.

First, the prevalence of awareness with paralysis in our cohort was 2.6%, a figure substantially higher than that reported from the operating room and comparable to the prevalence reported from a recent ICU-based study regarding neuromuscular blockers in acute respiratory distress syndrome (1.8%).[53] Clinical summaries demonstrate awareness with paralysis events related to both intubation and the postintubation phase of care, including vivid memories of painful procedures performed in the ED. Although this event rate may seem low, when considering the sheer volume of patients intubated in the ED, this could translate into more than 6,000 annual cases of awareness with paralysis related to the ED.[12,13] The estimated prevalence of awareness with paralysis in the ED from 4 prior studies was substantially higher than our estimate, ranging from 6% to 50%.[24-27] We believe these estimates were likely inflated as a result of methodological limitations, including nonvalidated questionnaires to assess for awareness with paralysis; small sample sizes (combined n=123); and inconsistent and nonstandard definitions of awareness with paralysis. To try to avoid these limitations, we used the modified Brice questionnaire, the preferred method of assessing for awareness with paralysis, and powered our study to detect a prevalence of 1% to 2%. Finally, we defined awareness with paralysis specifically as recall of wakeful paralysis with record of administration of a neuromuscular blocking agent. All clinical data and questionnaire responses were adjudicated independently by 3 experts to make all awareness with paralysis determinations rigorous.

Second, exposure to rocuronium in the ED was significantly different between patients who experienced awareness with paralysis versus the rest of the cohort. These findings are biologically plausible and congruent with prior work as studies from the operating room demonstrate that longer-acting neuromuscular blocking agents are an important risk factor for awareness with paralysis.[2,5,11] In this study, all patients with awareness with paralysis events that appeared temporally associated with the postintubation phase of care had a longer-acting neuromuscular blocking agent administered. The use of rocuronium in the ED has increased substantially in recent years, and prior work has demonstrated that compared with patients receiving succinylcholine, these paralyzed patients typically receive less analgesia and sedation, at lower doses, and in a delayed fashion.[21-23] Because sedation depth cannot reliably be monitored clinically during periods of neuromuscular blockade, our results suggest that clinicians should be cognizant that rocuronium use could increase patient-centered complications related to a vulnerable period of care. However, until larger studies are conducted, we urge caution in interpreting these results and they should be viewed as exploratory and hypothesis generating.

Third, there was the significant finding of the psychological sequelae attributed to experiencing awareness with paralysis. Historically, patients reporting awareness with paralysis from the operating room have been at risk for a number of adverse psychological conditions, most notably PTSD but also major depression and complex phobias.[1-4] We found that in our cohort, patients experiencing awareness with paralysis had a higher degree of perceived threat compared with those who did not experience it. Perceived threat is defined as a measure of the patient's perceived vulnerability during the hospital stay and after discharge, and the literature shows that perceived threat is common in critically ill patients and is predictive of developing PTSD.[49,54-56] Although the subjective accounts provided

by the patients demonstrate the negative consequences of awareness with paralysis, elevated perceived threat also shows objectively an increased risk of adverse psychological effects, including PTSD. This underscores the importance of further studying awareness with paralysis in the ED and instituting interventions to protect patients from this complication and the commensurate psychological sequelae that can result.

In conclusion, awareness with paralysis had a prevalence of 2.6% in this cohort of ED patients receiving mechanical ventilation and was associated with rocuronium exposure in the ED. Given the known consequences attributed to awareness with paralysis, future studies are warranted to further quantify this complication in the ED population and explore targeted interventions to reduce the risk of awareness with paralysis in this vulnerable cohort.

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