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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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Abstract

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

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

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

Conclusions: AWP occurs in a significant minority of mechanically ventilated ED patients. Potential associations of AWP with ED care and increased perceived threat warrant further evaluation.

INTRODUCTION

Background

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

Prospective studies have estimated prevalence of AWP during general anesthesia to be approximately 0.1-0.2%;[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 AWP in the OR include: 1) intravenous anesthetic approach (versus use of inhaled anesthetics),[8,9] 2) underdosing of anesthesia,[10] 3) administration of longer-acting NMBAs,[2,5,11] and 4) lack of protocolized sedation depth monitoring.[3] While extensive research has been conducted on AWP in the OR, this has yet to extend to other areas, such as the emergency department (ED), potentially placing mechanically ventilated patients at higher risk for this complication.

In the United States, clinicians have historically managed mechanically ventilated ED patients in a way that could predispose them to AWP.[12,13] These patients exclusively receive

intravenous analgosedation and are frequently under-dosed.[14] This includes induction agents during rapid sequence intubation (RSI), particularly in obese patients.[15,16] Several studies have shown that 10-54% of ventilated patients receive no sedation after RSI,[14,17–21] and there can be substantial delay (up to 50 minutes) in the provision of post-intubation sedation.[18,22] Approximately 90% of patients receive NMBAs for intubation in the ED, with an increasing use of longer-acting agents (e.g. rocuronium) as opposed to succinylcholine.[23] After intubation, approximately 10-25% of mechanically ventilated ED patients receive additional, longer-acting NMBAs without any increase in sedation.[18,19] Literature has demonstrated that for ED patients receiving longer-acting NMBAs such as rocuronium, post-intubation sedation is initiated at lower doses and with greater delays compared to those who receive succinylcholine.[21,22] Finally, a lack of protocol-driven management of sedation is common, and up to 33% of mechanically ventilated ED patients receive no sedation depth assessment.[18,19]

Importance

These data describe a historical precedent of management in the ED that is discordant to recommendations for prevention of AWP. 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 6-50%.[24–27] This prior research on AWP in ED patients is limited secondary to small sample sizes, methodological limitations, and use of non-validated and never-before used questionnaires to assess for awareness. Despite a lack of studies examining AWP in ED patients, prior data regarding analgosedation practices suggest that these patients could be at a higher risk for AWP 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 AWP in mechanically ventilated ED patients.

METHODS

Study Design & Setting

We conducted a single-center, prospective cohort study from June 2019 to May 2020 at a large (annual ED volume ~ 90,000 patients visits) academic, residency-affiliated, tertiary care center in St. Louis, Missouri. These results are reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Appendix E1).[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 mechanically ventilated patients via 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 via an endotracheal tube

in the ED. Intubation could have occurred either in the ED or prior to arrival, such as prehospital or at a transferring facility. Exclusion criteria were: 1) death before discontinuation of mechanical ventilation, 2) presence of neurological injury with residual deficit that precluded assessment for AWP (e.g. cerebrovascular accident, traumatic brain injury, cardiac arrest with hypoxic brain injury), 3) transfer to another facility, and 4) attrition or refusal to answer the questionnaire.

Methods of Measurement

All measurements and clinical data were gathered from chart review and collated using REDCap electronic data capture tools.[30,31] All variables were objective and easily abstracted from the electronic medical record. A trained team member 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 (e.g. plausible ranges for all values). A second team member performed periodic monitoring throughout the study on 20% of REDCap patient records. Prior to 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, gender, race, weight, height, pre-existing 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 (i.e. schizophrenia, bipolar disorder, major depression, or generalized anxiety disorder). Select laboratory values included 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 NMBAs used to facilitate intubation. Post-intubation medications related to analgosedation included opiates, benzodiazepines, propofol, ketamine, etomidate, haloperidol, quetiapine, and all NMBAs. We recorded sedation depth using the Richmond Agitation-Sedation Scale (RASS) per routine care. When more than one sedation depth was recorded, the median value was used. In patients that did not have an ED RASS score recorded, the first RASS score from the intensive care unit (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, NMBAs, sedation depth, and delirium assessments using the Confusion Assessment Method for the ICU (CAM-ICU) per routine care. The incidence of acute brain dysfunction, ventilator-free days, ICU- and hospital-free days were also tracked.

Outcomes

The primary outcome was AWP. 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 OR (the only clinical arena where AWP has been rigorously studied)

compared to critically ill mechanically ventilated patients. In the OR, 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 is not only expected in mechanically ventilated patients, but in general is considered beneficial. This is in stark contrast to memories of awareness of paralysis, which carries substantial, negative psychological sequelae.[35–39] To aid in distinguishing AWP from the appropriate recall of memories while mechanically ventilated, a combination of questions from the Brice questionnaire and the ICU Memory Tool were used (Appendix E2). The Brice questionnaire is the preferred method of evaluating for AWP,[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 AWP 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/feeling of wakeful paralysis, and have documented NMBA administration. If a patient did not report memories of the period between losing consciousness and waking up but did report memories of wakeful paralysis before losing consciousness (e.g. recall of intubation), and had documented NMBA administration, then they were also considered for a possible AWP event. Events related to waking up during neuromuscular blockade and experiencing AWP before unconsciousness were considered equivalent. The study team assessed for AWP after extubation and prior to hospital discharge. During the final two months of the study, due to university-mandated clinical research restrictions related to the COVID-19 pandemic, AWP was assessed via telephone follow up after hospital discharge. AWP was independently adjudicated by three 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 NMBA. In assessing whether AWP 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 NMBA (Appendix E3). Due to the somewhat subjective nature in assessing for AWP these instructions were used to provide some standardization for adjudicators regarding the background of the study, how awareness and memories were assessed for, and to make sure they were looking at the accounts through a similar lens. Each expert reviewer adjudicated events as either no AWP, possible AWP, or definite AWP. The primary outcome of AWP was determined when at least two experts were in agreement. If all experts had held opposing views, then it was planned for a fourth reviewer to assist in the adjudication process.[40] The use of 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 AWP 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 (i.e. on the causal pathway) for the development of PTSD symptoms.[46–49]

Analysis

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

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

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 two groups. Prior to conduct of the study, we noted a dearth of literature regarding AWP 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 OR had a prevalence of AWP approaching 1% during routine care.[9] Since data demonstrate that our population could be at even higher risk, we estimated a prevalence of 1-2%, 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 in order to accrue an adequate sample size and reduce the chance that any seasonal trends would skew the data. Based on our prior work in mechanically ventilated ED patients, we expected 2.1 patients per day to satisfy inclusion criteria, and estimated approximately half would ultimately be excluded, leaving just over one patient per day enrolled (n= 383).[18,19,50–52] With a sample size of 383, if only one AWP event were detected, the corresponding event rate of 0.26% is similar to that seen in the OR, where sedation depth is monitored more diligently.[3] Based on known risk factors for AWP 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

Figure 1 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 (27/383) reported memories of wakeful paralysis and were assessed for AWP. Adjudicators of AWP events had high agreement (intraclass correlation coefficient, 0.72; 95% CI 0.55 to 0.85). After adjudication, the prevalence of possible or definite AWP was 2.6% (10/383; 95% CI, 1.3-4.7%). Clinical summaries, analgosedation data, and adjudication information for the 10 patients with possible or definite AWP are presented in Table 2. The summaries for all 27 patients reporting wakeful paralysis is available in Table E1. A description of analgosedation practices in the ED (RSI and post-intubation sedation) is presented in Table 3. There was no documented NMBA use for thirty-eight (9.9%) patients. The prevalence of possible or definite AWP among patients with documented NMBA exposure was 2.9% (10/345; 95%

CI, 1.4-5.3%). Exposure to rocuronium at any time point in the ED (i.e. combining RSI and post-intubation) was significantly different between patients who experienced AWP (70%) versus the rest of the cohort (31.4%) (odds ratio, 5.1; 95% confidence interval [CI], 1.30 to 20.1).

Patients experiencing AWP had higher mean (standard deviation) values on the threat perception scale, denoting a higher degree of perceived threat, as compared to patients that did not experience AWP [13.4 (7.7) vs. 8.5 (6.2), mean difference 4.9; 95% CI 0.94 to 8.8].

LIMITATIONS

This study has several limitations. While it is the largest non-OR study to date focusing on AWP, the overall sample is small and derived from a single center. Therefore, all results from this observational single-center cohort study with ten 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 AWP. While our rigorous methodology in adjudicating AWP and similar prevalence as a recent multi-center 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 AWP cases, which could provide more reliable estimates of ED-based factors associated with AWP, and allow for the conduct of interventional trials going forward. There is also some subjectivity in the assessment of AWP and interpretation of our results should take into account the fact that unmeasured variables (e.g. 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 a fourth reviewer was never needed during the adjudication process. Further, the objective demonstration of higher perceived threat suggests the patients' experiences of AWP were indeed real. Patients with definite and possible AWP were combined in the assessment of the total event rate. This approach has been done in major trials from the OR which 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. However, seven cases of definite AWP (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 AWP (1.2%) is still factors higher than that seen 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. As these patients were not administered the questionnaire or included in the analysis, we cannot be sure that their characterisitics, treatment, or possible event rate for AWP is not systematically different from our study population. The receipt of a NMBA was a requirement for consideration of an AWP event. Thirty-eight patients never received a NMBA, and exclusion of these patients would increase the event rate to 2.9%. We elected to use 383 as the denominator to err on the side of conservative estimates, and because our over-arching goal was to inform practicing clinicians regarding AWP across a full spectrum of patients requiring mechanical ventilation in the ED. Because AWP in the ED has not been rigorously examined before, our research methods are largely extrapolated from similar studies in the OR, e.g. the utilization of the modified Brice questionnaire.[42] While these

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

DISCUSSION

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

First, the prevalence of AWP in our cohort was 2.6%, a figure substantially higher than that reported from the OR, 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 AWP events related to both endotracheal intubation and the postintubation phase of care, including vivid memories of painful procedures performed in the ED. While this event rate may seem low, when considering the shear volume of patients intubated in the ED, this could translate into more than 6,000 annual cases of AWP related to the ED.[12,13] The estimated prevalence of AWP in the ED from four prior studies was substantially higher than our estimate, ranging from 6-50%.[24–27] We believe these estimates were likely inflated secondary to: 1) methodological limitations, including non-validated questionnaires to assess for AWP, 2) small sample sizes (combined $n = 123$), and 3) inconsistent and non-standard definitions of AWP. To try and avoid these limitations, we used the modified Brice questionnaire, the preferred method of assessing for AWP and powered our study to detect a prevalence of 1-2%. Finally, we defined AWP specifically as recall of wakeful paralysis with record of administration of an NMBA. All clinical data and questionnaire responses were adjudicated independently by three experts to make all AWP determinations rigorous.

Second, exposure to rocuronium in the ED was significantly different between patients who experienced AWP versus the rest of the cohort. These findings are biologically plausible and congruent with prior work, as studies from the OR demonstrate that longer-acting NMBAs are an important risk factor for AWP.[2,5,11] In this study, all patients with AWP events which

appear temporally associated to the post-intubation phase of care had a longer-acting NMBA administered. The use of rocuronium in the ED has increased substantially in recent years, and prior work demonstrates that these paralyzed patients typically receive less analgesia and sedation, lower doses, and in a delayed fashion when compared to patients receiving succinylcholine.[21–23] As 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 time 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.

Our last significant finding concerns the psychological sequelae attributed to experiencing AWP. Historically, patients reporting AWP from the OR 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 AWP had a higher degree of perceived threat, as compared to patients that did not experience AWP. 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] While the subjective accounts provided by the patients demonstrate the negative consequences of AWP, elevated perceived threat also shows objectively an increased risk of adverse psychological effects, including PTSD. This underscores the importance of further studying AWP in the ED and instituting interventions to protect patients from this complication and the commensurate psychological sequelae that can result.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial Support

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833 mechanically ventilated ED patients assessed for eligibility

450 excluded:
- 252 acute neurologic injury with residual deficit
    - 29 acute ischemic stroke
    - 48 cardiac arrest
    - 94 intracranial hemorrhage
    - 9 status epilepticus
    - 65 traumatic brain injury
    - 7 other
- 131 death before discontinuation of mechanical ventilation
- 26 transfer to another facility from the ED
- 41 attrition

383 mechanically-ventilated ED patients included in final analysis

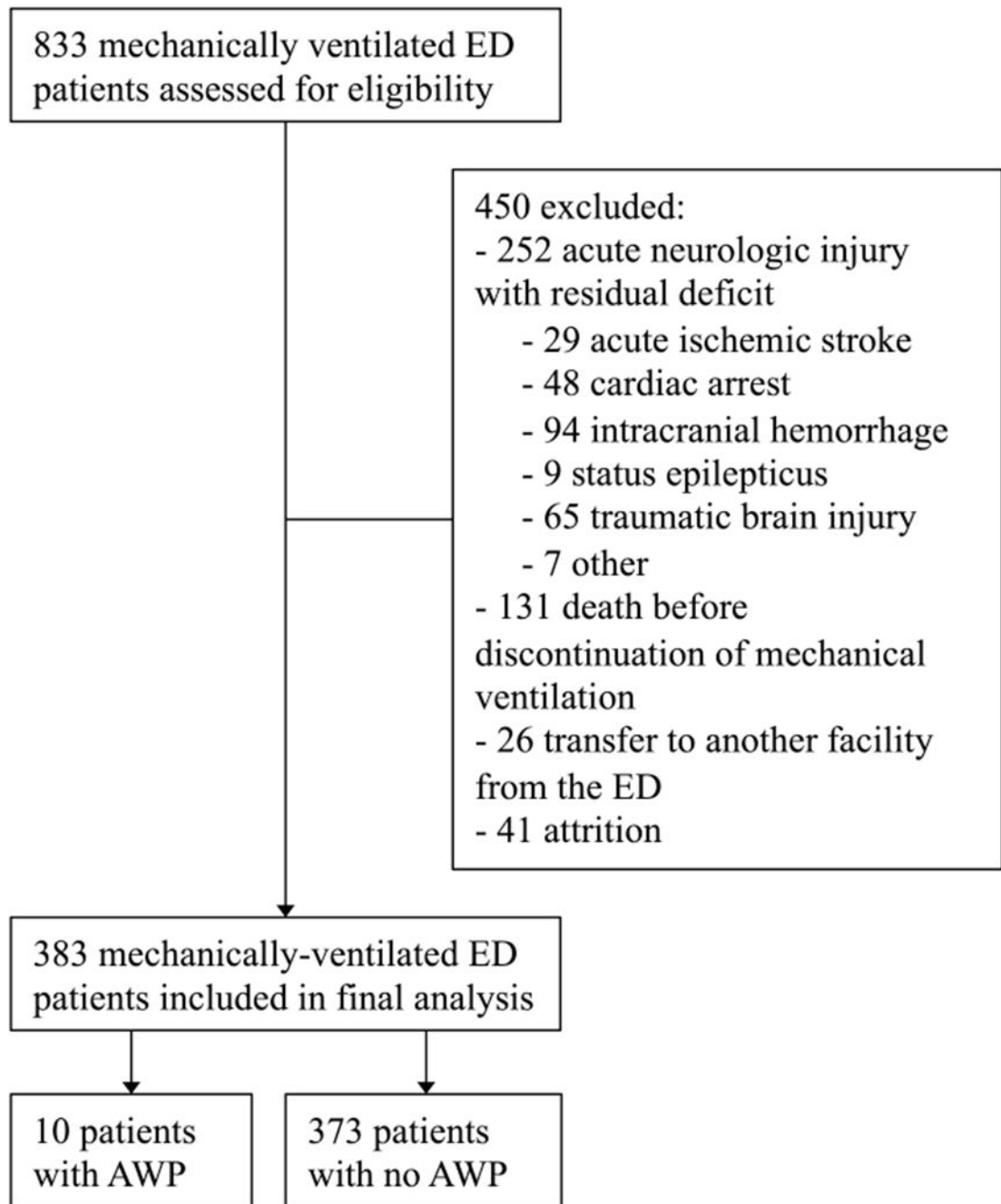10 patients with AWP

373 patients with no AWP

Figure 1.
Study flow and final study population. AWP, Awareness with paralysis.

Table 1.

Characteristics of included study participants.

Baseline Characteristics	All Subjects (n = 383)	Patients with AWP (n = 10)	Patients without AWP (n = 373)
Age (years)[2]	54 (37-63)	65 (53-67)	53 (37-63)
Female, n (%)	132 (35)	4 (40)	128 (34)
BMI[2]	26.9 (22.3-31.7)	30.4 (22.9-36.4)	26.6 (22.3-31.6)
Race, n (%)			
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, n (%)			
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[a]	71 (19)	2 (20)	69 (19)
Intubation Data, n (%)			
Location of Intubation			
Emergency Department	309 (81)	9 (90)	300 (80)
Transferring Facility	44 (11)	1 (10)	43 (12)
Prehospital	30 (8)	0	30 (8)
Indication for Intubation			
Trauma	106 (28)	4 (40)	102 (27)
Medical	277 (72)	6 (60)	271 (73)
Temperature (°C)[2]	36.5 (36.0-36.9)	36.6 (36.0-37.1)	36.5 (36.0-36.9)
Heart Rate (bpm)[1]	99 (25)	92 (24)	99 (25)
Mean Arterial Pressure (mmHg)[1]	98.8 (24.4)	105.6 (28.2)	98.7 (24.3)
Lactate (mmol/L)[2]	2.8 (1.6-5.1)	2.4 (1.4-3.1)	2.8 (1.6-5.2)

Baseline Characteristics	All Subjects (n = 383)	Patients with AWP (n = 10)	Patients without AWP (n = 373)
Creatinine (mg/dL)[2]	1.1 (0.9-1.5)	1.5 (1.0-1.6)	1.1 (0.9-1.5)
Bilirubin (mg/dL)[2]	0.4 (0.3-0.7)	0.2 (0.2-0.5)	0.4 (0.3-0.8)
SOFA[2]	2.0 (0-4.0)	2.5 (1.8-4.2)	2.0 (0-4.0)
ED Process of Care Variables			
Length of Stay (hours)[2]	5.1 (3.3-7.0)	4.1 (3.0-5.8)	5.2 (3.3-7.0)
Vasopressor Infusion, n (%)	86 (23)	3 (30)	83 (22)

AWP = awareness with paralysis, BMI = body mass index, ESRD = end-stage renal disease, COPD = chronic obstructive pulmonary disease, SOFA = Sequential Organ Failure Assessment

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

[1]Continuous variables are reported as mean (standard deviation)

[2]Continuous variables are reported as median (interquartile range)

Table 2.

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

ID	Gender, Age (yr) (Weight)	Drugs for Intubation	Post-Intubation Analgosedation	Clinical Scenario	Reported Memory / Awareness Experience	Determination of Awareness (definite, possible, no)	
						3 Expert Reviewers	Overall
1	M, 67 (62 kg)	Ketamine 100 mg Rocuronium 60 mg	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 mechanically ventilated. Remembered feeling scared, tried to open eyes and move, but couldn't. Patient had no further details regarding this memory.	Possible Possible Possible	Possible
3	F, 65 (110 kg)	Etomidate 30 mg Rocuronium 100 mg	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, like she was paralyzed. - Stated she felt as though she woke up once in the ED but couldn't move anything except for maybe her fingers. She felt 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 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 kg)	Ketamine 100 mg Succinylcholine 60 mg	Fentanyl, propofol, and midazolam infusions One 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 kg)	Ketamine 80 mg Rocuronium 70 mg	Fentanyl, propofol infusions One 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 if he ever felt the sensation of feeling paralyzed, he answered "yes". Stated "I came to the ER 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 kg)	Etomidate 20 mg Succinylcholine 200 mg	Propofol boluses, 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, like he was paralyzed. - He remembers waking up with someone pulling very hard on his injured leg, which caused severe pain. He thinks he was in the emergency room. The patient said this was the worst pain he has ever had and 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 one person pulling hard on his injured leg. - Records note that patient's open fracture/dislocation was reduced in the ED	Possible Definite Definite	Definite

ID	Gender, Age (yr) (Weight)	Drugs for Intubation	Post-Intubation Analgosedation	Clinical Scenario	Reported Memory / Awareness Experience	Determination of Awareness (definite, possible, no)	
						3 Expert Reviewers	Overall
					after intubation and prior to transfer; reported "spike in blood pressure" during this event.		
18	F, 67 (114 kg)	Etomidate 20 mg Succinylcholine 100 mg	Fentanyl and propofol infusions	Fell and had open tib/fib 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 mechanically ventilated. - Stated that she remembered the physicians telling her they need to put in a breathing tube, and they began to give her medication through the IV. For "about a minute" she experienced paralysis where she "couldn't move anything, not even my eyes." She said that then she passed out.	Possible No Possible	Possible
20	F, 57 (80 kg)	Ketamine 100 mg Rocuronium 100 mg	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, like she was paralyzed. - Said she remembered, "coming into the ER 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 couldn't 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
21	M, 41 (92 kg)	Ketamine 100 mg Succinylcholine 100 mg	Fentanyl and midazolam infusions; one 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, like he was paralyzed. - Patient states he was in the emergency department and heard a female nurse say, "we are trying to bring you back, just stay calm." He remembers laying on the bed and feeling like he was in a dream, but he knew that this 'dream' was actually happening in real life. He stated he felt out of his own body and couldn't move. He stated he couldn't even open his eyes or breathe on his own. He states he saw himself on the bed almost like he was outside his own body. He said he had a breathing tube in his throat and was trying to move and talk but couldn't. - He stated the worst part about having the breathing tube and being aware in the ED was: "I 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 kg)	Etomidate 20 mg Succinylcholine 100 mg	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, like he was paralyzed. - Patient stated he remembers being in a hospital room, he thinks it was the emergency department, and the breathing tube was being inserted into his throat while he was awake. The patient remembers he didn't think he could move. However, the patient stated that he was able to open his eyes and look around at people and felt like he was able to turn his head "a little bit."	Definite Definite Possible	Definite
27	F, 65 (68 kg)	Etomidate 20 mg Rocuronium 90 mg	Fentanyl and propofol infusions	Altered with COPD, hypercapnia and	- Reported remembering things in between losing consciousness and waking up and reported a sensation of not being able to move, like she was paralyzed. - "I was in the ER and I had a mask blowing air into my mouth to help me breath. I remember the doctors telling me that I would need to be put on the	Definite Definite Definite	Definite

ID	Gender, Age (yr) (Weight)	Drugs for Intubation	Post-Intubation Analgosedation	Clinical Scenario	Reported Memory / Awareness Experience	Determination of Awareness (definite, possible, no)	
						3 Expert Reviewers	Overall
				hypoxia, failed NIPPV	breathing machine. When I woke up, I was lying flat and I could hear everybody's voices around me. I tried to move and breath 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." - States her worst memory was waking up and not being able to move.		

M = male, F = female, ED = emergency department, NIPPV = non-invasive positive pressure ventilation, DKA = diabetic ketoacidosis, COPD = chronic obstructive pulmonary disease

Table 3.

Emergency department analgosedation variables.

Variable	Patients with AWP (n = 10)	Patients without AWP (n = 373)	Between-Group Difference (95% CI)
RSI Variables			
Induction Agent			
Etomidate, n (%)	5 (50)	173 (46.4)	3.62 (−27.8 to 35.0)
Dose (mg)	20 (20-25)	20 (20-20)	0.60 (−4.63 to 5.82)
Weight-Based Dose (mg/kg)	0.27 (0.19-0.29)	0.28 (0.24-0.34)	0.05 (−0.3 to 0.13)
Ketamine, n (%)	5 (50)	126 (33.8)	16.2 (−15.1 to 47.6)
Dose (mg)	100 (90-100)	100 (100-150)	38.1 (23.9 - 52.3)
Weight-Based Dose (mg/kg)	1.25 (1.02-1.64)	1.43 (1.10-1.97)	0.36 (−0.37 to 1.08)
Midazolam, n (%)	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, n (%)	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, n (%)	0	21 (5.6)	−5.63 (−7.97 to −3.29)
Paralytic			
Succinylcholine, n (%)	5 (50)	196 (52.5)	−2.55 (−34.0 to 28.9)
Dose (mg)	100 (100-160)	100 (100-100)	−21.9 (−75.7 to 31.8)
Weight-Based Dose (mg/kg)	1.08 (0.96-2.47)	1.23 (1.06-1.52)	−0.27 (−1.35 to 0.82)
Rocuronium, n (%)	5 (50)	102 (27.3)	22.7 (−8.7 to 54.0)
Dose (mg)	90 (65-100)	100 (80-100)	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, n (%)	0	39 (10.5)	−10.5 (−13.6 to −7.35)
ED Post-Intubation Variables			
Fentanyl, n (%)	8 (80)	294 (78.8)	1.18 (−24.0 to 26.3)

Variable	Patients with AWP (n = 10)	Patients without AWP (n = 373)	Between-Group Difference (95% CI)
Cumulative Dose (mcg)	250 (138-300)	288 (150-500)	115 (−118 to 348)
Weight-Based Dose (mcg/kg)	2.8 (1.8-4.4)	3.4 (2.0-6.4)	1.64 (−1.39 to 4.67)
Propofol, n (%)	8 (80)	267 (71.6)	8.42 (−16.8 to 33.6)
Cumulative Dose (mg)	660 (290-1340)	510 (290-980)	−391 (−1382 to 600)
Weight-Based Dose (mg/kg)	7.5 (3.8-11.9)	6.6 (3.6-12.0)	−5.6 (−19.3 to 80.0)
Midazolam, n (%)	2 (20)	128 (34.3)	−14.3 (−39.6 to 10.9)
Cumulative Dose (mg)	6 (6-6)	5 (4-10)	1.4 (−6.9 to 9.7)
Weight-Based Dose (mg/kg)	0.08	0.07 (0.04-0.13)	0.01 (−0.09 to 0.11)
Lorazepam, n (%)	0	46 (12.3)	−12.3 (−15.7 to −9.0)
Cumulative Dose (mg)	-	2 (2-4)	-
Weight-Based Dose (mg/kg)	-	0.03 (0.02-0.06)	-
Ketamine, n (%)	3 (30)	57 (15.3)	14.7 (−13.9 to 43.4)
Cumulative Dose (mg)	70	100 (60-118)	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[a], n (%)	2 (20)	22 (5.9)	14.1 (−10.8 to 39.0)
Cumulative Dose (mg)	100 (100-100)	100 (50-100)	−11 (−103 to 81)
Weight-Based Dose (mg/kg)	1.09	1.11 (0.47)	-
Sedation Depth Variables			
Median RASS in ED	−1.5 (−2.3 to 1.3)	−1.7 (−3 to 0)	−0.8 (−2.1 to 0.5)
Deep Sedation, n (%)	2 (20)	146 (39)	−19.1 (−44.4 to 6.14)

AWP = awareness with paralysis, CI = confidence interval, RSI = rapid sequence intubation, ED = emergency department, RASS = Richmond Agitation–Sedation Scale

[a] Refers to paralytic given as additional bolus after RSI

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