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Severe agitation among ventilated medical intensive care unit patients: frequency, characteristics and outcomes

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Abstract *Objective:* To determine the frequency, characteristics and outcomes of severe agitation among ventilated medical intensive care unit (MICU) patients. *Design:* Prospective cohort study. *Setting:* Eighteen-bed MICU in 964-bed tertiary care center. *Patients:* All ventilated patients, aged 18 years or older and admitted for more than 24 h between January 1, 2001 and May 8, 2001. *Interventions:* None. *Measurements:* Data were collected daily by concurrent chart abstractions. Variables included sociodemographic, clinical, laboratory, pharmacologic and non-pharmacologic interventions, ventilator settings and adverse events. Severe agitation, the main outcome variable, was defined as two or more Motor Activity Assessment Scale (MAAS) scores above 4 in a 24-h period and sedative and/or narcotic doses above the established sedation and analgesia protocol or a combination of two or more sedatives. *Results:* Twenty-three (16.1%) of 143 enrolled patients exhibited severe agitation. Agitated patients were younger (hazard ratio [HR] 1.32), more likely to be admitted from an outside hospital ICU (HR 2.48), had lower pH (HR 1.55) and PaO_2/FIO_2 less than 200 mmHg (HR 2.59). Agitated patients had longer MICU stays (median 12 versus 5 days, $p<0.0001$) and more ventilator days (median 14 versus 6, $p<0.0001$). Agitated patients were more likely to self-extubate (26% versus 6%, $p=0.002$). Benzodiazepines, narcotics and neuromuscular blocking agents were administered more frequently and at higher doses, but haloperidol was not. *Conclusion:* Severe agitation occurs commonly in critically ill patients and is associated with adverse events including longer ICU stays, duration of mechanical ventilation and self-extubation.

Keywords Sedation · Agitation · Mechanical ventilation · Critically ill · Medical intensive care unit

Introduction

Stress and mechanical ventilation contribute to the frequent need for sedative and/or analgesic agents [SAAs] as well as non-pharmacologic management of pain, anxiety and agitation [1, 2, 3, 4, 5]. Recently, we found 85% of ventilated patients received SAAs [6]. Clinical experience has shown that subsets of patients have agitation that is difficult to manage. In the absence of an evident medical cause, clinicians often respond to ongoing or severe agitation by increasing doses of SAAs and by using multiple medications. Occasionally, a neuromuscular blocking agent may be required to facilitate mechanical ventilation. High doses and/or multiple medications come with increased likelihood of adverse drug reactions, weaning time and ICU length of stay [5, 7, 8, 9]. Yet, if the patient's agitation is not managed, he/she may be compromised physiologically and is at greater risk of disrupting critical therapies.

The use of guidelines regarding ICU sedation, analgesia and neuromuscular blocking agents confer benefits, such as fewer ventilator days [6, 10]. In spite of the risks of agitation in ventilated ICU patients, little is known regarding its frequency, associated risk factors, practice patterns or clinical outcomes. Understanding patient risk factors allows clinicians to identify high-risk patients early and implement appropriate, targeted interventions.

Our hypothesis is that severe agitation in intubated patients will have an impact on selected outcomes such as: mortality, ICU length of stay and interruption of therapy. Thus, the aims of this prospective cohort study were to determine the frequency of severe agitation in intubated MICU patients; to identify patient characteristics associated with severe agitation; to describe associated non-pharmacologic and pharmacologic measures (i.e., medicated within the MICU guidelines) and to determine clinical outcomes associated with severe agitation.

Methods

Setting

The study took place in a closed, 18-bed medical intensive care unit (MICU) within The Cleveland Clinic Foundation (CCF), a 964-bed tertiary referral center. Patients are admitted under the direct care and supervision of the MICU medical staff consisting of board certified, attending pulmonary/critical care staff, pulmonary/critical care fellows and residents and interns from the internal medicine program. Interdisciplinary rounds are conducted daily and house officers write all orders.

The nurse-to-patient ratio is 1:2. Nurses assess each patient's level of agitation and assign a score using the Motor Activity Assessment Scale (MAAS), a 7-point scale ranging from 0 (unresponsive, does not move to noxious stimuli) to 6 (dangerously agitated) (Table 1) [11] that has been tested for inter-rater reliability in our MICU [12]. Nurses assess and document each patient's level of sedation and motor activity every 4 h and with changes in sedation. House staff use the MICU Sedation and Analgesia Guidelines, adapted from the American College of Critical Medicine (See the electronic supplementary material) [5, 7] and indicate the targeted sedation score or activity level, e.g., MAAS 1–3; the nurse administers the amount of medication judged necessary to maintain the patient within the targeted score. The sedation goal is reassessed daily, along with attempts to decrease the dose of sedatives/analgesics; daily interruption of sedation is not practiced [13]. For patients who received a neuromuscular blocking agent, nurses evaluate physiological variables, endotracheal tube placement, hemodynamic status, pain status, train-of-four measurement and sedation score (See the electronic supplementary material). All patients who receive a neuromuscular blocking agent are administered sedatives and analgesics. The decision to utilize paralysis was based on the attending physician's judgement and individualized in every patient. A critical care clinical pharmacist monitors the daily doses and type of SAAs, and the sedation score.

Typically, before the patient with agitation is treated with medications, the nurse and physician perform a comprehensive evaluation to rule out organic reasons for the agitation, such as severe hypoxemia, pain or a new neurologic event. Besides

Table 1 Motor Activity Assessment Scale

Score	Description	Definition
0	Unresponsive	Does not move with noxious stimulus[a]
1	Responsive only to noxious stimuli	Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs with noxious stimulus[a]
2	Responsive to touch OR name	Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs when touched or name is loudly spoken
3	Calm and cooperative	No external stimulus is required to elicit movement AND patient is adjusting sheets or clothes purposefully and follows commands
4	Restless and cooperative	No external stimulus is required to elicit movement AND patient is picking at sheets or tubes OR uncovering self and follows commands
5	Agitated	No external stimulus is required to elicit movement AND attempting to sit up OR moves limbs out of bed AND does not consistently follow commands (e.g., will lie down when asked but soon reverts back to attempts to sit up or move limbs out of bed)
6	Dangerously agitated, uncooperative	No external stimulus is required to elicit movement AND patient is pulling at tubes or catheters OR thrashing side to side OR striking at staff OR trying to climb out of bed AND does not calm down when asked

[a] Noxious stimulus, suctioning OR 5 s of vigorous orbital, sternal or nail bed pressure
Adapted from: Crit Care Medicine (1999) 27 (7):1271–1275

pharmacologic measures, nurses utilize a variety of non-pharmacologic measures to reduce or manage agitation, such as: minimizing noise and light and using quiet music. Protocols for management of invasive mechanical ventilation and weaning/discontinuation are used in all patients receiving mechanical ventilation [14]. The modality of mechanical ventilation used is volume cycle assist control.

Participants

All consecutively admitted patients from January 8, 2001 through May 8, 2001, who were 18 years old or more and received mechanical ventilation were eligible for enrollment in the study. The only exclusion criterion was length of stay less than 24 h. Participants or their family members provided informed consent prior to any data collection. The institutional review board approved the study. No effort was made to disguise the study from the medical and nursing staff.

Outcome measures

The primary outcome measure was severe agitation. There is no well-accepted definition of severe agitation in the literature; we based our definition on two components: hyperactive behavior judged to be dangerous and doses of SAAs higher than the recommended guideline dosages [6]. Severe agitation was prospectively defined as: (1) two or more MAAS scores higher than 4 in a 24-h period, (Table 1) [5, 11] and (2) SAA doses above the MICU Sedation and Analgesia Guidelines *or* (3) the combination of two sedatives within the same 24-h period (i.e., lorazepam and propofol) because maximal doses of one of the sedatives did not achieve adequate sedation. Prior to the study, four external intensivists agreed that the proposed definition was adequate. A panel of MICU clinicians confirmed the classification of patients (agitated or non-agitated) and to assure the absence of inadequate sedation due to underdosing.

Data collected on admission included demographic characteristics, admission source, baseline severity of illness as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II [15], admitting diagnoses, alcohol or drug use, history of smoking, selected psychiatric diagnoses (manic depression, depression, anxiety, schizophrenia), and reason for ventilation.

Daily data collection included: the last recorded arterial blood gases with corresponding ventilator settings, laboratory values (white blood count, sodium, potassium, glucose, magnesium, phosphate, hematocrit, liver function tests, creatinine, blood urea nitrogen, albumin, total protein), nursing interventions (music, relaxation television channel, encourage family visitation, position for comfort, post orienting objects, reorientation, physical restraints), and total doses of sedatives, analgesics or neuromuscular blocking agents. Documented new conditions or adverse events occurring during the MICU stay included: ethanol withdrawal, encephalopathy, delirium, psychosis, acute renal failure, gastrointestinal bleeding, pneumothorax, sepsis, nosocomial infection, new stroke, adverse drug reaction, new pulmonary embolism, deep vein thrombosis, metabolic acidosis, tracheotomy or other event. Finally, we recorded discharge disposition, length of stay, weaning status and patient-disruption of endotracheal tubes, arterial lines or nasogastric tubes.

Trained ICU registered nurses using standardized data collection instruments gathered all information daily. Weekly quality checks were conducted by one of two investigators (JW, RM) to ensure inter-rater reliability. The data were coded and entered by the personnel in the Department of Biostatistics and Epidemiology. Chart audits were performed for all suspicious or missing data. Data were then transferred to SAS data sets for analysis.

Statistics

Descriptive statistics included frequencies and percentages for categorical variables and means, standard deviations and medians and ranges for continuous level variables. Cox-proportional hazards with time-varying covariates were used to model the time until patients became agitated [16]. The resulting estimates are reported as hazard ratios (95% confidence interval). Probability values test the hypothesis that the hazard ratios =1.0. Outcomes were examined between the two groups by using chi-square tests for categoric variables and Wilcoxon-rank sum tests for skewed variables. All time-to-event analyses were performed using S-PLUS 6.1 (Insightful, Seattle, WA). All other analyses were performed using SAS software (version 8.0, SAS Institute, Cary, NC).

Results

Characteristics of the study group

During the study, 350 patients were admitted to the MICU. One hundred forty-three consecutive patients were enrolled; no eligible patient was excluded. Fifty percent were men and the median age was 62.0 years (range 22.5–98.1 years). Twenty-five percent were admitted from outside hospitals. Hypoxic respiratory failure was the most frequent admitting diagnosis and most frequent reason (58%) for mechanical ventilation. The mean tidal volume was 6.6 ml/kg (SD=2) of actual body weight. Fifty-two patients (36.3%) had findings consistent with acute lung injury or the acquired respiratory distress syndrome at 24 hours of admission [17]. The median APACHE II score on admission was 20 (range 6–38). The median length of MICU stay was 6.0 days (range 1–40 days). The median duration of mechanical ventilation was 7 days (range 1–44 days). Nine percent extubated themselves. Sixty-eight percent were discharged to one of the hospital general units and the MICU mortality was 28%.

Occurrence of severe agitation

Twenty-three patients, 16.1% (95% CI 10.9–23.0%) of ventilated patients admitted to the MICU, were severely agitated at some point during their MICU stay. Ten (7%) patients became severely agitated during their first 24 h in the MICU. The long-term rate of agitation (the probability of experiencing severe agitation if in the MICU for longer than 14 days) was estimated to be 33.5% (95% CI 13.4–49.0%).

Features associated with severe agitation

Table 2 shows patients' characteristics at the time of admission to the MICU. The characteristics that differed significantly between those who developed severe agita-

Table 2 Characteristics of severe agitation and non-agitated patients on admission to the medical intensive care unit

Characteristic	Severe agitation (n=23)	Non-agitated (n=120)
Age		
Mean (SD), years	50.2 (19.0)	62.6 (±16.7)
Median (range), years	44.6 (22.5–79.8)	66.0 (22.5–98.1)
Sex, number of males (%)	13 (57%)	58 (48%)
Admission source, n (%)		
Emergency department	4 (17%)	27 (23%)
Nursing home	0	5 (4%)
Other hospital	11 (48%)	25 (21%)
Within hospital, general unit	4 (17%)	48 (40%)
Within hospital, other ICU	4 (17%)	15 (13%)
Reason for mechanical ventilation[a], n (%)		
Hypoxic respiratory failure	13 (57%)	70 (58%)
Hypercapnic respiratory failure	5 (22%)	19 (16%)
Acute respiratory failure on chronic pulmonary disease	5 (22%)	17 (14%)
Airway protection	7 (30%)	38 (32%)
Pneumonia	11 (48%)	35 (29%)
Cardiac arrest	0	15 (13%)
Pulmonary embolism	0	6 (5%)
Drug overdose	0	3 (3%)
Diagnoses present on admission[b], n (%)		
Liver disease	3 (13%)	17 (14%)
Renal failure	5 (22%)	45 (38%)
Gastrointestinal bleed	1 (4%)	9 (8%)
Heart failure	3 (13%)	17 (14%)
Neurologic disorder	1 (4%)	19 (16%)
Ethanol dependency	3 (13%)	22 (18%)
Smoker	10 (43%)	42 (35%)
APACHE II score: mean (SD); median (range)	18.9 (±7.2); 17.0 (6.0–34.0)	20.7 (±6.3); 20.0 (10.0–38.0)
PaO_2/FIO_2 (mmHg) at entry, mean (SD)	155.7 (±99)	256.6 (±137)
Median	122	243

[a] More than one reason for mechanical ventilation could be documented
[b] More than one diagnosis could be present at admission

tion versus those who did not were younger age (50.2 versus 62.6 years, p=0.0016) and more frequently admitted from an outside hospital (48% versus 21%, p=0.0158). Those admitted from outside hospitals were more likely to develop severe agitation within the first 24 h of admission compared to patients admitted from other sources (17% versus 4%, p 0.0085).

Features on admission significantly associated with the development of severe agitation included younger age, admission from an outside hospital, marijuana use and currently not married (Table 3). Over the course of the hospitalization, features preceding or concurrent with the onset of severe agitation included: (1) increased FIO_2, (2) PaO_2/FIO_2 below 200 mmHg and (3) decreased pH. Multivariate models showed that younger age, admission from another hospital, lower pH and PaO_2/FIO_2 below 200 mmHg were associated with severe agitation (Table 4).

Notably, no associations with laboratory indices or onset of adverse events before the onset of severe agitation were found. There was no significant difference between the two groups in term of ventilator settings including size of the tidal volume and the level of positive end-expiratory pressure. During the MICU stay, 2 (8.7%) of the severely agitated patients and 6 (5%) of the non-agitated patients had delirium noted in the medical records.

Management

Both benzodiazepines and opiates were administered more frequently and in greater doses to those experiencing severe agitation both prior to or on the day of agitation onset as well as throughout the MICU stay as compared to those who did not experience severe agitation (See Table in ESM). For example, 96% of the severely agitated patients received lorazepam at some point during their MICU stay compared to 75% of non-severe agitation patients (p=0.028), and 91% of the severely agitated patients received lorazepam by continuous intravenous infusion compared with 26% of non-severe agitation patients (p<0.001). Haloperidol was administered to only 4% of severely agitated patients prior to or on the day of onset. Thirty percent of severely agitated patients received haloperidol at some point during their MICU stay compared to 20% of non-severely agitated patients (p=0.27). Neuromuscular blocking agents were administered to 48% of the severely agitated patients versus to 11% of the non-severely agitated patients (p<0.0001). In all patients, the indication for the use of a neuromuscular

Table 3 Univariate analysis of factors associated with severe agitation in mechanically ventilated patients

Variable	Hazard ratio	95% Confidence interval	p value
Variables on admission			
Younger age (minus 10 years)	1.51	1.18–1.93	0.0012
Admitted from outside hospital	2.66	1.17–6.04	0.02
Marijuana use	7.94	1.82–34.73	0.007
Not currently married	2.91	1.14–7.39	0.025
Variables collected daily			
Increased FIO_2 (1%)	1.32	1.11–1.57	0.0013
Decreased pH (0.1 unit)	1.62	1.18–2.22	0.0028
PaO_2/FIO_2 lower than 200 mmHg	1.81	1.16–2.84	0.0092

Table 4 Multivariate analysis of factors associated with severe agitation among ventilated medical intensive care unit patients

Variable	Hazard ratio	95% Confidence interval	p value
Younger age (minus 10 years)	1.32	1.01–1.72	0.040
Admitted from outside hospital	2.48	1.06–5.78	0.035
Lower pH (minus 0.1 unit)	1.55	1.05–2.31	0.028
PaO_2/FIO_2 lower than 200 mmHg	1.61	1.02–2.54	0.041

Table 5 The effect of severe agitation on medical intensive care unit (*MICU*) patient outcomes

	Agitation	Non-agitation	
Variable	(*n*=23)	(*n*=120)	p value
MICU survival	70%	72%	0.77
MICU length of stay			
Median	12	5	<0.0001
Range	2–40	1–35	
Days ventilated			
Median	14	6	<0.0001
Range	2–44	1–43	
Weaned in MICU	48%	57%	0.44
Patient self-extubated	26%	6%	0.002
Any patient disruption of therapy	30%	8%	0.003

blocking agent was to facilitate mechanical ventilation. Patients that were severely agitated received more continuous intravenous infusions of opiates and in higher doses when compared with the non-agitated group (See ESM Table, S2). No association with nursing interventions prior to or after severe agitation onset was found.

Outcomes associated with severe agitation

Outcomes associated with having severe agitation included (Table 5): longer ICU stay (12 versus 5 days, *p*<0.0001), longer duration of mechanical ventilation (14 versus 6 days, *p*<0.0001) and greater frequency of self-extubation (26 versus 6%, *p*=0.002). Eighty-six percent of agitated patients who self-extubated from mechanical ventilation required reintubation as compared to 17% of non-agitated patients who self-extubated (Fisher's exact test *p*=0.029). No significant difference in ICU survival rates was observed.

Discussion

Severe agitation in mechanically ventilated patients is a significant clinical issue confronting critical care nurses and physicians. The main findings of this prospective cohort study were: (1) severe agitation occurs in 16% of mechanically ventilated patients; (2) correlates of severe agitation were younger age, transfer to the ICU from another hospital, acidemia and worsened oxygenation; and (3) the occurrence of severe agitation was associated with adverse outcomes including longer ICU stay, longer du-

ration of mechanical ventilation and a higher rate of self-extubation, but was not associated with higher mortality.

Fraser et al. [18] observed severe agitation more frequently (46%) among ICU patients; unlike our findings, they observed no age-related differences in the occurrence of severe agitation. Possible explanations for these discrepancies include differences in inclusion criteria (e.g., we studied only mechanically ventilated patients, while Fraser et al. [18] studied ventilated and non-ventilated patients), definition of severe agitation and our use of a protocol [6] to manage SAAs. Indeed, to the extent that such protocols can lessen the frequency of severe agitation, we speculate that the lower frequency in our series may reflect this practice. Also, to the extent that agitation represents a hyperactive subtype of delirium [19, 20, 21], the lower rate of such delirium among patients older than 65 years may contribute to the higher frequency of agitation observed among younger patients [20, 21].

Our observation that severe agitation was more common among patients transferred from other hospitals invites comment. The possibility that such transferred patients were sicker than those admitted from within our hospital or emergency department is belied by similar APACHE II scores (data not shown). On the other hand, others have shown that patients transferred from outside hospitals experience a higher rate of mortality that is not reflected in APACHE scores. Presumably the higher rate of mortality reflects post-admission developments that prompt transfer for management, but which are not present, and therefore not captured by APACHE ratings, at the time of initial ICU admission [22, 23, 24]. Recently, Rosenberg et al. [24] found that patients transferred to the MICU of a tertiary center have a longer hospital stay and higher mortality rate compared with patients admitted directly to the MICU. Another plausible explanation is that variation in practices may account for the severe agitation in the transferred group; it is unknown to what extent sedation and analgesia protocols were utilized by referring hospitals.

The association of severe agitation with PaO_2/FIO_2 lower than 200 mmHg may reflect the contribution of severe hypoxemia to the development of agitation [19]. Also, the worse acidemia in severely agitated patients may reflect their greater degree of illness or their having received high-dose intravenous lorazepam, which can cause metabolic acidosis mediated by the large volumes of infused propylene glycol as the vehicle for lorazepam [25]. While severe hypoxemia and acidemia are markers of severe lung dysfunction and the need for greater

ventilatory support, there was no significant difference between the groups in terms of ventilatory settings, including tidal volume and level of positive end-expiratory pressure.

Because severely agitated patients received higher doses of sedatives and analgesics (see ESM Table, S2) and because continuous infusions of sedatives has been associated with longer duration of mechanical ventilation [7], it is conceivable that medication use contributed to longer mechanical ventilation. The length of ICU stay for the non-agitated group was within the range reported recently by others [10, 13, 26]. The overall incidence of therapy disruption among severely agitated patients was higher than that of non-agitated patients and reflects findings by others of the association of agitation with therapy disruption [27, 28, 29, 30, 31]. Though not observed in this series, self-extubation has been associated with a higher ICU mortality rate [26]. Also, patient-initiated device removal incurs higher ICU costs [27, 32].

Several authors have suggested the use of non-pharmacologic measures, such as minimizing noise and light, may be helpful in the management of the agitated critical care patient [1, 5, 33, 34, 35]. There was no difference in the frequency of use of these measures by the nurses. Rather, our team relied on pharmacologic measures. Non-pharmacologic strategies for the treatment of delirium have been underutilized in hospital and ICU settings [33, 34]. In the future, it will be important to assess the impact that these measures have on the management and outcomes of the severely agitated patient.

Intensive care unit clinicians are confronted with the paradox of a subset of patients who, despite the fact of their having received higher doses of SAAs, disrupt their therapy more frequently and remain for a longer period of time in the MICU on mechanical ventilation. It is clear that our current sedation and analgesia protocol, based on the previous and the most recent practice guidelines of the ACCCM [5, 35], is inadequate to manage the severely agitated patient. Clinicians need to modify the diagnostic strategy and therapy to improve the management of these patients. Patients should be systematically evaluated for the presence of delirium and, in the presence of delirium, the choice of haloperidol should be increased in this patient population [2, 20, 36, 37].

Several potential shortcomings of the current study warrant mention. First, at the time of this study there was no systematic assessment for delirium among mechanically ventilated patients [2, 36]. Indeed, few patients in our sample were diagnosed as having delirium, a finding reported in studies of hospitalized patients [38, 39, 40]. Because the diagnosis of delirium would prompt the administration of haloperidol rather than analgesics or sedatives, it is conceivable that the occurrence of severe agitation among mechanically ventilated patients despite the use of a protocol may, in part, reflect this. A second potential limitation of our study is that the results from our ICU, based in a tertiary care institution and with active use of a protocol to guide sedation, may not generalize to other settings. We did not disguise the study from the medical and nursing staff, therefore staff may have altered their behavior. This is unlikely; our unit has used the same sedation protocol and agitation guidelines for the last 7 years. Lastly, because this is an observational study, we are unable to offer new insights in terms of the pathogenesis, prevention and management of severe agitation.

In conclusion, notwithstanding these potential limitations, our results confer better understanding of the frequency, correlates and outcomes associated with severe agitation. Both the frequency of severe agitation and the gravity of consequences suggest the need for greater strategies to lessen its occurrence among mechanically ventilated patients. Physicians' and nurses' assessment of delirium and early pharmacologic approaches to treat agitation are essential.

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