CHEST

Impact of Vasoactive Medications on ICU-Acquired Weakness in Mechanically Ventilated Patients

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BACKGROUND: Vasoactive medications are commonly used in the treatment of critically ill patients, but their impact on the development of ICU-acquired weakness is not well described. The objective of this study is to evaluate the relationship between vasoactive medication use and the outcome of ICU-acquired weakness.

METHODS: This is a secondary analysis of mechanically ventilated patients (N = 172) enrolled in a randomized clinical trial of early occupational and physical therapy vs conventional therapy, which evaluated the end point of ICU-acquired weakness on hospital discharge. Patients underwent bedside muscle strength testing by a therapist blinded to study allocation to evaluate for ICU-acquired weakness. The effects of vasoactive medication use on the incidence of ICU-acquired weakness in this population were assessed.

RESULTS: On logistic regression analysis, the use of vasoactive medications increased the odds of developing ICU-acquired weakness (odds ratio [OR], 3.2; $P = .01$) independent of all other established risk factors for weakness. Duration of vasoactive medication use (in days) (OR, 1.35; $P = .004$) and cumulative norepinephrine dose (μg/kg/d) (OR, 1.01; $P = .02$) (but not vasopressin or phenylephrine) were also independently associated with the outcome of ICU-acquired weakness.

CONCLUSIONS: In mechanically ventilated patients enrolled in a randomized clinical trial of early mobilization, the use of vasoactive medications was independently associated with the development of ICU-acquired weakness. Prospective trials to further evaluate this relationship are merited.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT01777035; URL: www.clinicaltrials.gov

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ABBREVIATIONS: APACHE = Acute Physiology and Chronic Health Evaluation; ICU-AW = ICU-acquired weakness; OR = odds ratio

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Generalized neuromuscular weakness is a common complication of critical illness. It is estimated that at least 25% of patients who require prolonged mechanical ventilation develop ICU-acquired weakness (ICU-AW).[1-3] ICU-AW can lengthen the duration of mechanical ventilation and is associated with increased mortality.[4-6] The functional impairments resulting from ICU-AW can persist for years after discharge.[7]

Many risk factors for the development of ICU-AW have been described, including pharmacologic interventions used in the treatment of critically ill patients, such as glucocorticoids and neuromuscular blocking agents.[8] It is unclear what role other pharmacologic agents used in the ICU, such as vasoactive medications, have in the development of ICU-AW.

Vasoactive medications are used commonly in the treatment of critically ill patients with shock, a life-threatening condition of circulatory failure. Their use allows sustained perfusion to vital organs while the underlying cause of the shock is treated. A portion of patients who receive vasoactive medications will experience adverse effects related to their use. It is well recognized that increased adrenergic stimulation associated with vasoactive medication use can lead to cardiac consequences such as increased rates of arrhythmias and myocardial ischemia.[9,10]

Clinically, an association between the use of vasoactive medications and critical illness polyneuropathy has been described, but little remains known about the impact of this class of medications on the development of clinically apparent weakness.[11,12] In addition, a limited number of studies show that in animal models, stimulation of β-adrenergic receptors at high doses in vivo can lead to apoptosis and necrosis in skeletal muscles, similar to what is seen in cardiac myocytes.[13-15] This work suggests biologic plausibility for a link between the use of vasoactive medications in the ICU and skeletal muscle injury that may increase the risk of developing ICU-AW. To further investigate this, we performed a secondary analysis of the association between the use of vasoactive medications and the occurrence of ICU-AW in mechanically ventilated patients enrolled in a clinical trial of early mobilization.

Methods

Study Design and Patients

This study is a secondary analysis of a randomized controlled trial (N = 172) of patients in the medical ICU randomized to receive early physical and occupational therapy within 72 h of mechanical ventilation (early mobilization) or standard care with therapy as ordered by the primary team.[16] Patients included were those enrolled in a completed trial of short-term outcomes of an early mobility intervention (n = 104) and patients enrolled in an ongoing trial (ClinicalTrials.gov: NCT01777035) with the same protocol examining the long-term outcomes of an early mobility intervention (n = 68).[16] Adult patients greater than 18 years old and admitted to the medical ICU were eligible. Inclusion criteria for early mobility were mechanical ventilation for greater than 24 h but less than 72 h at the time of enrollment. The baseline functional status of all patients was assessed using the Barthel Index, with a score greater than 70 required for study inclusion.[17,18] Exclusion criteria included rapidly changing neurologic conditions, cardiac arrest, elevated intracranial pressure, more than one absent limb, pregnancy, terminal condition (life expectancy less than 6 months), traumatic brain injury, multiple limb fractures or open wounds, or severe chronic pain syndrome on admission. The institutional review board for human studies approved the protocols (11-0218), which were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments, and written consent was obtained from the subjects or their surrogates.

All enrolled patients who were mechanically ventilated received daily interruption of sedatives,[19] protocol-based weaning from mechanical ventilation,[20] and enteral feeding. Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission and change in Sequential Organ Failure Assessment (SOFA) score from admission to 48 h.[21-25] All patients received daily assessment for the presence of sepsis.[26] The initiation and choice of specific vasoactive medications were determined by the primary medical service. The type and dose of vasoactive medication received were recorded daily for all enrolled patients.

All patients had an assessment by physical and occupational therapists blinded to randomization assignment on hospital discharge. The strength of three muscle groups in each upper and lower extremity was measured by Medical Research Council (MRC) score, using a scale from 0 to 5.[27,28] ICU-AW was diagnosed at the time of this assessment when an awake and attentive patient had a muscle strength sum score < 48 out of a maximal score of 60.[1]

Statistical Analysis

Data were analyzed with Stata 14.1 (StataCorp LP) software. Baseline and outcomes variables were depicted as medians (interquartile ranges). We used the Wilcoxon-Mann-Whitney two-sample rank-sum test to compare continuous variables and the χ^2 test or Fisher exact test where appropriate to compare categorical variables. A univariable analysis of the outcome of interest, occurrence of ICU-AW on hospital discharge, was performed, evaluating the effect of early mobilization, currently established risk factors for ICU-AW, and the use of vasoactive medications. To assess the effect of vasoactive medication use on the occurrence of ICU-AW, logistic regression analysis was performed, correcting for risk factors that showed a trend toward significance ($P \leq .1$) on univariable analysis and others that were linked to the outcome on a biologically plausible basis. Hierarchical entry of each variable was performed. Goodness of fit was assessed by the Hosmer-Lemeshow test. Using this model, additional logistic regression analysis was performed to assess the effect of vasoactive medication duration of use (days) and dose (normalized by weight) on the occurrence of ICU-AW.

Assessment of a dose-dependent response to norepinephrine was performed by grouping patients according to low, medium, or high total dose requirement, with analysis using χ^2 for trend.

As a sensitivity analysis, a Fine-Gray competing risk regression was performed using the time of discharge with weakness as the outcome and time of death as the competing risk, with the same confounding variables as the logistic regression. Further evaluation was done with a subgroup analysis of patients who survived to hospital discharge. Logistic regression was performed to assess the effect of vasoactive medication use on ICU-AW in the subgroup of survivors, using the variables selected in original model.

Results

Univariable Analysis

A total of 80 of the 172 patients demonstrated ICU-AW on hospital discharge. Baseline characteristics of patients in the control and early mobilization treatment groups were comparable. Patients with ICU-AW were older, had higher APACHE II scores, a higher incidence of sepsis, longer hospital length of stay, and longer duration of mechanical ventilation (Table 1). Importantly, the use of steroids and neuromuscular blockers did not differ between the groups.

Patients with ICU-AW had lower mean arterial pressure by area under the curve analysis during the ICU admission [79 (73-87) vs 86 (79-93) mm Hg; $P = .0008$]. Correspondingly, more patients with ICU-AW received vasoactive medications during their hospitalization compared with patients who did not demonstrate ICU-AW (73.8% vs 33.7%; $P = < .0001$). Norepinephrine was the most commonly used medication. Sixty percent of patients with ICU-AW received norepinephrine compared with 24% of patients without ICU-AW ($P < .0001$). Patients with ICU-AW also received vasopressin (48% vs 22%; $P = .0002$) and phenylephrine (31% vs 5%; $P < .0001$) more frequently than patients without ICU-AW. Dobutamine, dopamine, and epinephrine were used less frequently and were not significantly different between the groups (e-Table 1).

Multivariable Analysis

Based on the univariable analysis and biologic plausibility, the following independent variables were

TABLE 1] Univariable Analysis of Baseline and Outcome Characteristics

Variable	ICU-AW (N = 80)	No ICU-AW (N = 92)	*P* Value
Baseline characteristics			
Age, y	61 (49-72)	50 (31-64)	.0002
Female, No. (%)	41 (51.3%)	45 (48.9%)	.76
BMI, kg/m^2	28.1 (23.7-34.4)	27.5 (24.4-33.5)	.96
APACHE II	24 (20-30)	17 (13-22)	< .0001
Sepsis	66 (82.5%)	60 (65.2%)	.01
Diabetes	24 (30%)	26 (28.3%)	.8
Outcome characteristics			
Early mobility	33 (41.3%)	50 (54.4%)	.09
Ventilator use, d	5 (2.8-8.3)	2.9 (1.7-4.6)	< .0001
Hospital length of stay, d	17.1 (9-27.9)	10.6 (6.7-15.9)	.0001
ΔSOFA (0-48 h)	0 (−2 to 2)	0 (−2 to 1)	.24
MRC score on hospital discharge	34.5 (0-43.5)	56 (51-59)	< .0001
Mean arterial pressure[a]	79 (73-87)	86 (79-93)	.0008
Median glucose[b]	135 (116-152)	125 (113-142)	.11
Medications received			
No. (%) receiving corticosteroids in ICU	55 (68.8%)	62 (67.4%)	.85
No. (%) receiving neuromuscular blocker	5 (6.25%)	3 (3.3%)	.35
No. (%) receiving vasopressors	59 (73.8%)	31 (33.7%)	< .0001
No. (%) receiving multiple vasopressors	45 (56.3%)	17 (18.5%)	< .0001

Data represent No. (%) or median (IQR). APACHE = Acute Physiology and Chronic Health Evaluation; ICU-AW = ICU-acquired weakness; IQR = interquartile range; MRC = Medical Research Council; SOFA = Sequential Organ Failure Assessment.
[a]Median area under the curve of mean arterial pressure (mm Hg) during ICU stay.
[b]Median glucose during ICU stay (mg/dL).

included in the multivariable analysis for the outcome of ICU-AW: early mobilization, age, severity of illness as defined by APACHE II score, sepsis, duration of mechanical ventilation, hospital length of stay, mean arterial pressure, and vasoactive medication use. Since patients included in the analysis were enrolled in two different studies, this was accounted for in the model as well. There was no multicollinearity among the predictors. The model was well calibrated by the Hosmer-Lemeshow test ($P = .77$), and the area under the receiver operating characteristic curve for ICU-AW on hospital discharge was 0.86.

In the multivariable analysis, use of vasoactive medications was associated with a more than threefold increase in the odds of developing ICU-AW on hospital discharge (odds ratio [OR], 3.2; 95% CI, 1.29-7.95; $P = .01$), independent of other established risk factors for ICU-AW (Table 2). APACHE II score, hospital length of stay, and age were also independently associated with increased odds of developing ICU-AW. Early mobility intervention independently decreased the odds of developing ICU-AW. Further, for every day that a patient received a vasoactive medication the odds of developing ICU-AW increased 35% (OR, 1.35; 95% CI, 1.1-1.65; $P = .004$).

Given the hypothesis that the type of vasoactive medication used may have a differential effect on skeletal muscle via the β-adrenergic receptor, a multivariable analysis was performed with vasoactive medications separated into two variables: those that stimulate the β-adrenergic receptor (norepinephrine, epinephrine, dopamine, and dobutamine) and those that do not (phenylephrine and vasopressin). In this multivariable analysis only the β-adrenergic group was significantly associated with the outcome of ICU-AW (OR, 3.67; 95% CI, 1.44-9.36; $P = .006$). In order to further assess this, the cumulative doses of norepinephrine (μg/kg/d), phenylephrine (μg/kg/d), and vasopressin (units/d) were analyzed. For every 1-μg/kg/d dose of norepinephrine a patient received, the odds of developing ICU-AW increased 1% (OR, 1.01; 95% CI, 1.001-1.02; $P = .04$). A dose-dependent response was evident, with increasing incidence of ICU-AW seen with increasing cumulative norepinephrine dose (Fig 1). This relationship was not seen with vasopressin (OR, 1.01; 95% CI, 0.99-1.04; $P = .28$) or phenylephrine (OR, 1.97; 95% CI, 0.52-7.44; $P = .32$). The numbers of patients in groups receiving cumulative doses of dopamine, dobutamine, and epinephrine were small and not significantly different when comparing patients with and without ICU-AW, and thus were not included in the analysis.

TABLE 2] Multivariable Analysis of ICU-Acquired Weakness

Variable	OR	95% CI	*P* Value
Vasoactive medication	3.2	1.29-7.95	.01
APACHE II	1.08	1.01-1.15	.02
Sepsis	0.91	0.32-2.62	.85
Hospital length of stay, d	1.05	1.01-1.08	.009
Age, y	1.03	1.0-1.05	.03
Ventilator use, d	1.07	0.98-1.16	.15
Early mobilization	0.38	0.17-0.85	.02
Mean arterial pressure[a]	0.97	0.92-1.02	.21
Study group	0.34	0.14-0.8	.01

APACHE II = Acute Physiology and Chronic Health Evaluation II; OR = odds ratio for developing ICU-acquired weakness.
[a]Median area under the curve of mean arterial pressure (mm Hg) during ICU stay.

Subgroup Analysis

In order to assess for death as a competing risk for the detection of ICU-AW we performed a competing risk regression that showed use of vasoactive medications remained independently associated with ICU-AW (subdistribution hazard ratio, 2.45; $P = .006$). Additional analysis of patients who survived to hospital discharge with ICU-AW (N = 46) and without ICU-AW (N = 92) was also performed. In this multivariable analysis, the use of vasoactive medications was associated with

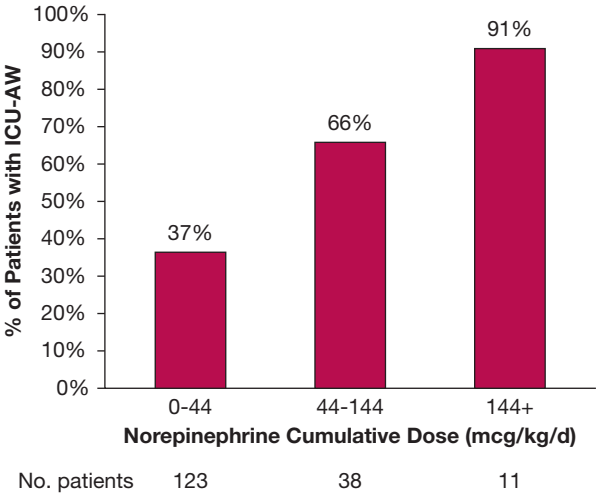

Figure 1 – *Incidence of ICU-acquired weakness (ICU-AW) with increasing cumulative dose of norepinephrine. *The proportion of patients with ICU-AW significantly increases with increasing cumulative dose of norepinephrine (χ^2 for trend $P < .0001$).*

significantly increased odds of developing ICU-AW (OR, 5.37; 95% CI, 1.65-17.5; $P = .005$) (e-Table 2).

Discussion

As survivorship of critical illness continues to improve, there is an increasing emphasis on improving the outcomes of these survivors. ICU-AW is known to have detrimental effects on both short- and long-term outcomes, and therefore understanding the pathogenesis and identifying those at highest risk of developing neuromuscular weakness are critical. The role vasoactive medications may play has been unclear to this point.

We show in a population of critically ill, mechanically ventilated patients that the use of vasoactive medications is independently associated with the diagnosis of ICU-AW at hospital discharge. In fact, each day a patient received a vasoactive medication significantly increased the odds of developing neuromuscular weakness. In addition to the duration of vasopressor support, the cumulative dose of the β-agonist norepinephrine significantly increased the odds of developing ICU-AW. Importantly, this effect is independent of other known risk factors for ICU-AW, which include sepsis and markers of severity of illness, such as APACHE II score, and duration of mechanical ventilation. Other risk factors such as steroid use and neuromuscular blockade did not differ significantly between the groups and did not significantly impact outcomes in our analysis. The effect of vasoactive medication use remained significant when evaluating the subgroup of patients that survived to hospital discharge. This suggests that vasoactive medications, above and beyond being a marker for other risk factors associated with ICU-AW, may have a direct and independent effect on the development of neuromuscular weakness.

The role adrenergic stimulation may play in the outcomes, neuromuscular and otherwise, of critically ill patients is important to consider. An increase in circulating catecholamines is the natural and necessary response to shock, but in some critically ill patients, excess adrenergic stimulation from both endogenous and exogenous catecholamines can have detrimental effects. Many of the adverse effects of elevated circulating catecholamines appear to be mediated through the β-adrenergic receptor. The effect of β-adrenergic stimulation on the heart can lead to elevated heart rate, increased rates of arrhythmias, myocardial ischemia, and direct toxic effects on cardiac myocytes leading to apoptosis and fibrosis.[9,10,29-31]

While these are the most well-known adverse effects of adrenergic stimulation, there is significant evidence supporting effects on other organ systems as well. There is a growing body of evidence supporting the potentially detrimental immunomodulatory effects of norepinephrine use, which is believed to be mediated through activation of the β-adrenergic receptor.[32] In the coagulation system, induction of a hypercoagulable state occurs in a dose-dependent response to epinephrine.[29,33] The metabolic system is also affected, with evidence supporting numerous metabolic effects of adrenergic stimulation including catecholamine-induced hyperglycemia.[29,34,35]

Given the presence of adrenergic receptors on skeletal muscle (predominantly β-adrenergic receptors), it is not surprising that skeletal muscle may be susceptible to adverse effects of excess adrenergic stimulation as well. The results of our study show an association between the cumulative dose of norepinephrine (but not vasopressin or phenylephrine) and the development of ICU-AW. This finding supports the theory introduced in animal models that stimulation of β-adrenergic receptors by vasoactive medications may have a toxic effect on skeletal myocytes.[13-15,36,37] Although these studies provide biologic plausibility for an independent detrimental effect of excessive β-adrenergic stimulation on skeletal muscle, further studies are clearly needed in this area to confirm the association between specific vasoactive medication use and the development of neuromuscular weakness in humans and to elucidate the mechanism underlying this association. Given that the Surviving Sepsis Campaign guidelines recommend norepinephrine as the initial vasoactive of choice, future trials that aim to illuminate a potential causal role of β-adrenergic stimulation in the development of neuromuscular weakness may have important implications.[38]

Limitations

This is a retrospective study, and therefore carries the limitations of this type of analysis. The analysis included the characteristics known to affect the development of ICU-AW, but there can be no guarantee that it was not confounded by inherent differences between the patients with and without ICU-AW and/or those requiring vs not requiring vasoactive drugs that were not accounted for in the model. As an exploratory analysis, unmeasured confounding related to clinician's choice to initiate specific vasoactive medications may also affect these findings. A retrospective independent association

does not prove causation. Therefore, these findings need to be evaluated in prospective manner.

An additional limitation of this study is that the patient population analyzed is from a single-center randomized controlled trial, which could lead to exclusion of some patients. Both of these factors can introduce selection bias and therefore limit the generalizability of the findings to a broader patient population.

Conclusions

In a population of critically ill, mechanically ventilated patients enrolled in a clinical trial of early mobility, the use of vasoactive medications was independently associated with the development of ICU-AW. This effect is related to both the duration of vasoactive support and cumulative dose of norepinephrine received.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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