[Original Research]

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.