The Reduction Rate of Serum Sodium and Mortality in Patients Undergoing Continuous Venovenous Hemofiltration for Acute Severe Hypernatremia

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ABSTRACT

Background: The excessive correction of acute hypernatremia is not known to be harmful. This study aimed to evaluate whether a reduction rate of serum sodium (RRSeNa) > 1 mEq/L/hour in acute severe hypernatremia is an independent risk factor for mortality in critically ill patients undergoing continuous venovenous hemofiltration (CVVH) treatment.

Materials and Methods: For this retrospective study, we reviewed records of 75 critically ill patients undergoing CVVH treatment for acute severe hypernatremia between March 2011 and March 2015.

Results: The 28-day mortality rate of all patients was 61.3%. In multivariate Cox regression analyses, a reduction rate of serum sodium (RRSeNa) > 1 mEq/L/hour (hazard ratio = 1.89; 95% CI: 1.03-3.47; $P = 0.04$), Acute Physiology and Chronic Health Evaluation II score and vasopressor dependency (yes or no) had a statistically significantly effect on mortality. Once we excluded patients with an RRSeNa ≤ 0.5 mEq/L/hour, only RRSeNa > 1 mEq/L/hour (hazard ratio = 2.611; 95% CI: 1.228-5.550; $P = 0.013$) and vasopressor dependency had a statistically significant influence on mortality in multivariate regression.

Conclusions: In addition to the Acute Physiology and Chronic Health Evaluation II score and vasopressor dependency, the excessive correction of acute severe hypernatremia was possibly associated with mortality in critically ill patients undergoing CVVH treatment. The optimal reduction rate of acute hypernatremia should be extensively studied in critically ill patients.

Key Indexing Terms: Hypernatremia; Continuous venovenous hemofiltration; Reduction rate of serum sodium; Mortality.
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BACKGROUND

Hypernatremia is diagnosed in 4-26% of critically ill patients.[1-6] Although the incidence of severe hypernatremia in critically ill patients is low,[2,6,7] the mortality rates are still high (67.4-87%).[8-10] Critically ill patients with hypernatremia exhibit a poor prognosis. Hypernatremia is typically regarded as both a marker of disease severity and as an independent risk factor for intensive care unit (ICU) mortality.[1,3,4,11-13]

The reduction rate of serum sodium (RRSeNa) depends on the duration of hypernatremia. The recommended RRSeNa is 1-2 mEq/L/hour for acute hypernatremia.[14,15] However, the conventional treatment for hypernatremia is often insufficient.[12,16-18] If the RRSeNa is insufficiently low in hypernatremia, it is associated with an increased risk of death.[12,14,16,18,19] In sharp contrast to the treatment of hyponatremia, where speedy correction may cause harm,[20] the existing literature for acute hypernatremia favors expeditious correction, and delayed correction is associated with harm. Therefore, we initiated continuous venovenous hemofiltration (CVVH) treatment for acute severe hypernatremia in critically ill patients.

Our retrospective study indicated that patients in the CVVH treatment group with a high RRSeNa (0.78 [0.63-1.0] mEq/L/hour) had a lower mortality rate than patients in the conventional treatment group with a low RRSeNa (0.13 [0.009-0.33] mEq/L/hour).[21] However, in the CVVH treatment group, the 28-day mortality rate was 66.7% in the patients with an RRSeNa > 1 mEq/L/hour (unpublished data). Whether the excessive correction of acute severe hypernatremia by CVVH treatment is associated with mortality is not clear.

In this study, we evaluated whether the RRSeNa of acute severe hypernatremia is an independent risk factor for the mortality of critically ill patients undergoing CVVH treatment.

MATERIALS AND METHODS

Patients

All of the critically ill patients who were admitted to the ICU of Xijing Hospital between March 2011 and March 2015 with acute severe hypernatremia and who received CVVH treatment were considered as

candidates for this study. Acute severe hypernatremia was defined as an increase in serum sodium levels from normal levels to ≥160 mEq/L within 48 hours.[13,14] We excluded patients if they met any of the following criteria: <18 years of age, hypovolemic hypernatremia and systolic blood pressure < 90 mm Hg under vasopressor dependency. The study was approved by the Ethics Committee of Xijing Hospital.

CVVH Treatment

The replacement fluid was set at 2 L/hour and the blood flow was set at 200 mL/minute. The sodium level of the replacement fluid was initially set to be lower than the serum sodium level by 8 mEq/L and was reduced by 2 mEq/L every 4 hours. A detailed description of CVVH treatment has been published previously.[22]

Data Collection

Data were retrieved from the electronic medical records of our hospital. Baseline characteristics (age and sex) were collected. The reasons for ICU admission (operation, neurologic disease and burn) were recorded before the diagnosis of acute severe hypernatremia; neurologic diseases included shock, traumatic brain injury and postoperative brain tumor. The predisposing conditions for hypernatremia included acute kidney injury, hypoalbuminemia, hyperglycemia,[23] hypokalemia, hypercalcemia, blood urea nitrogen,[24] sodium bicarbonate use, lactulose use, mannitol use[23] and loop diuretic use. The severity of illness was evaluated on the first ICU day using the Acute Physiology and Chronic Health Evaluation (APACHE) II score, the Sequential Organ Failure Assessment (SOFA) score and the Glasgow Coma Score (GCS). The following sodium-related parameters were recorded: time from admission to onset of hypernatremia, time from onset of hypernatremia to severe hypernatremia, serum sodium level before CVVH treatment, serum sodium level every 4 hours during CVVH treatment, serum sodium level before discharge or death and type of hypernatremia. Other parameters assessed at the time of CVVH treatment included the following: mechanical ventilation, vasopressor dependency and laboratory parameters. Net fluid balance was recorded from ICU admission to CVVH initiation. Patient outcomes were assessed using the following parameters: survival time and 28-day ICU mortality. We excluded blood lactate because serum lactate level was checked in only 30% of patients.

Definitions

The definition of hypernatremia was provided in a previous study.[25] The survival time was calculated from the beginning of CVVH treatment until death or censorship on the 28th day if the patient survived more than 28 days. RRSeNa (mEq/L/hour) = (serum sodium level before CVVH treatment [mEq/L] − serum sodium level after CVVH treatment [mEq/L]) / CVVH time (hours). Hypernatremia relapse was defined as serum sodium ≤ 145 mEq/L after CVVH treatment, and serum sodium > 145 mEq/L at the time of discharge or death.

Statistical Analysis

Continuous variables are presented as means and standard deviations, and categorical variables are presented as numbers (%). We used Mann-Whitney rank tests to assess continuous variables and the χ^2 test for categorical variables.

A multivariate Cox regression model was built to estimate the association between RRSeNa and mortality. The potential variables were included if they were known or suspected from clinical knowledge and literature to affect the risk of mortality. These variables included age, sex, APACHE II score, SOFA score, GCS, reasons for ICU admission, euvolemic hypernatremia, development of hypernatremia (time from admission to onset of hypernatremia), time to severe hypernatremia (time from onset of hypernatremia to severe hypernatremia), acute kidney injury, mechanical ventilation, vasopressor dependency, net fluid balance, heart rate, median arterial pressure, creatinine, glucose, serum sodium level at the time of diagnosis of acute severe hypernatremia and RRSeNa. Variables with $P <$ 0.05 by univariate analysis were entered into a multivariate Cox regression model using an Enter method. The RRSeNa was tested as a categorical variable. The midpoint between the maximum recommended reduction rate (2 mEq/L/hour) and no correction (0 mEq/L/hour) was used as the cutoff value (≤1 mEq/L/h versus >1 mEq/L/hour). The excessive correction of acute hypernatremia was defined as RRSeNa > 1 mEq/L/hour. A sensitivity analysis was performed that excluded patients with an RRSeNa ≤ 0.5 mEq/L/hour. When the RRSeNa is too low in the setting of hypernatremia, it is associated with an increased risk of death. The estimated hazard ratios (HRs), 95% CIs and P values are reported for all regression covariates.

The survival curves were produced by the Kaplan-Meier method, and a difference in the 28-day survival rate by RRSeNa was compared by the log-rank test. Patients who were alive at the end of 28 days were censored. All of the tests were 2-sided, and a $P < 0.05$ was considered significant. Statistical analysis was conducted using SPSS 16.0 (SPSS Inc., Chicago, IL).

RESULTS

Study Population

This was a retrospective study from a single center with 133 ICU beds that treats approximately 4,500 critically ill patients per year in Xijing Hospital. We consecutively recruited 95 critically ill patients with acute severe hypernatremia from the ICU who received CVVH therapy between March 2011 and March 2015. The following exclusions were made: <18 years of age ($n = 5$), hypovolemic hypernatremia ($n = 7$) and systolic blood pressure <90 mm Hg under vasopressor