American Journal of Emergency Medicine 33 (2015) 439–443

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Brief Report

The relationship of intravenous fluid chloride content to kidney function in patients with severe sepsis or septic shock☆,☆☆,★

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ARTICLE INFO

Article history:
Received 30 October 2014
Accepted 9 December 2014

ABSTRACT

Background: Previous studies suggest a relationship between chloride-rich intravenous fluids and acute kidney injury in critically ill patients.
Objectives: The aim of this study was to evaluate the relationship of intravenous fluid chloride content to kidney function in patients with severe sepsis or septic shock.
Methods: A retrospective chart review was performed to determine (1) quantity and type of bolus intravenous fluids, (2) serum creatinine (Cr) at presentation and upon discharge, and (3) need for emergent hemodialysis (HD) or renal replacement therapy (RRT). Linear regression was used for continuous outcomes, and logistic regression was used for binary outcomes and results were controlled for initial Cr. The primary outcome was change in Cr from admission to discharge. Secondary outcomes were need for HD/RRT, length of stay (LOS), mortality, and organ dysfunction.
Results: There were 95 patients included in the final analysis; 48% (46) of patients presented with acute kidney injury, 8% (8) required first-time HD or RRT, 61% (58) were culture positive, 55% (52) were in shock, and overall mortality was 20% (19). There was no significant relationship between quantity of chloride administered in the first 24 hours with change in Cr ($\beta = -0.0001$, $t = -0.86$, $R^2 = 0.92$, $P = .39$), need for HD or RRT (odds ratio [OR] = 0.999; 95% confidence interval [CI], 0.999-1.000; $P = .77$), LOS >14 days (OR = 1.000; 95% CI, 0.999-1.000; $P = .68$), mortality (OR = 0.999; 95% CI, 0.999-1.000; $P = .88$), or any type of organ dysfunction.
Conclusion: Chloride administered in the first 24 hours did not influence kidney function in this cohort with severe sepsis or septic shock.

1. Introduction

Acute kidney injury (AKI) is prevalent in patients with severe sepsis and septic shock [1–7]. Research has shown that AKI due to sepsis is associated with higher mortality, increased ventilator dependency, greater need for vasopressors, and higher length of stay (LOS) than other causes of AKI [8–10]. Intravenous fluid administration is central to sepsis management, but controversies exist regarding the effects of fluid type and volume on kidney function [6,11,12].

Fluid optimization is necessary for adequate renal perfusion in preshock and shock states; however, several factors associated with fluids have been postulated to impair kidney function. Chloride (Cl) content in particular has been shown to have a negative effect on kidney function [13]. This is clinically relevant given the commonplace use of 0.9% saline (NS), a Cl-rich solution, in daily practice. Cl-rich fluids have been demonstrated to cause arteriolar vasoconstriction resulting in a decrease in renal blood flow and glomerular filtration rate [14,15]. A study by Yunos et al. [13] showed that eliminating Cl-rich fluids from the intensive care unit (ICU) results in a reduction in AKI according to the risk, injury, failure, loss end-stage classification, and less need for renal replacement therapy (RRT). Others have noted hyperchloremic metabolic acidosis, fluid retention, and decreased urine output as reasons for avoiding Cl-rich fluids in critically ill patients [16].

Separately, patients with severe sepsis or septic shock in the emergency department (ED) are prone to overresuscitation and fluid

☆ Study Site: All patients were enrolled at UF Health Jacksonville, 655 West 8th Street, Jacksonville, FL 32209.
☆☆ Author contributions: FWG, DJW, MH, and RLW conceived the study. FWG, DJW, AAB, AS, NP, CJK, AEJ, and RLW supervised the data collection and chart reviews. RLW, SD, CJK, and AEJ provided methodological and statistical advice on study design and data analysis. AEJ and SD provided expertise on clinical trial design, and AAB and AS provided clinical expertise regarding the subject matter. FWG, MH, DJW, AAB, AS, and NP drafted the manuscript, and all authors contributed substantially to its revision.
★ Funding was provided by a UF Faculty Dean's Fund Grant.
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http://dx.doi.org/10.1016/j.ajem.2014.12.013
0735-6757/

overload because reliable measures of fluid status are not always readily available [17]. Fluid overload is associated with poor outcome and increased mortality particularly when greater than 10% [18–21]. Fluid overload is also associated with decreased survival, increased ventilator and ICU days [22], and in patients with AKI, it has been associated with lack of renal recovery at 1 year [23].

The primary objective of this study was to evaluate the relationship of fluid Cl content to kidney function in patients undergoing a quantitative resuscitation protocol for severe sepsis or septic shock in the ED and ICU. Secondarily, we also hoped to determine the effect of total fluid volume in the first 24 hours on kidney function.

2. Materials and methods

2.1. Study design and setting

This study was a retrospective extension of a prospective cohort study in which patients with severe sepsis or septic shock were monitored for a 6-hour period of quantitative resuscitation. The following data were recorded at 0, 3, and 6 hours: vital signs, $ETCO_2$, $SCVO_2$, central venous pressure, urine output, lactate levels, FiO_2, ventilator settings, suspected source of infection, and disposition. To determine the relationship between chloride content and renal outcomes, we retrospectively determined baseline and discharge creatinine as well as type and amount of fluid administered. The prospective study took place from June 1, 2012, to May 30, 2014, in the adult ED and ICU at University of Florida (UF) Health Jacksonville. The UF Health Jacksonville ED is a high-acuity, academic, urban ED that treats approximately 90 000 patients per year. The medical ICU is a 28-bed closed unit. The research protocol was approved by the UF College of Medicine, Jacksonville, Institutional Review Board.

2.2. Patient selection

Patients with suspected severe sepsis or septic shock presenting to the ED were assessed for the following inclusion criteria: (*a*) adult 18 years or older; (*b*) documented severe sepsis (as defined by 2 of 4 Systemic Inflammatory Response Syndrome (SIRS) criteria plus a suspected or confirmed source of infection with a lactate greater than 4 mg/dL or end-organ dysfunction) or septic shock (defined as hypotension not responsive to 30 mL/kg intravenous fluids), and (*c*) candidate for treatment with early quantitative resuscitation. Patients were excluded if they were incarcerated, were pregnant, required emergency surgery, were receiving treatment with noninvasive ventilation, had preexisting end-stage renal disease (ESRD), or received greater than 1 L of fluids of unknown type.

2.3. Measurements

2.3.1. Early quantitative resuscitation for patients with severe sepsis or septic shock

At UF Health Jacksonville, early quantitative resuscitation involves two potential treatment protocols: invasive or noninvasive. Patients who maintain a mean arterial pressure (MAP) greater than 65 and are without other signs of hemodynamic instability are treated with the noninvasive protocol. This includes the placement of two large bore intravenous catheters to achieve goals for fluid resuscitation (as indicated by inferior vena cava sonographic measurement), urine output, and lactate clearance of 10% or greater over a 2-hour period. Patients with signs of hemodynamic instability as indicated by a MAP less than 65 or who are showing a lack of improvement or clinical deterioration after initiation of the noninvasive protocol receive an Edwards PreSep Central Venous Oximetry Catheter (Edwards Lifesciences, Irvine, California) placed in either the internal jugular or subclavian vein for continuous central venous oxygen saturation ($SCVO_2$) and central venous pressure monitoring. For patients in need of $SCVO_2$ monitoring but without a PreSep catheter, $SCVO_2$ is measured via venous blood gas from the distal port of the central venous catheter drawn every 2 hours. In addition, as part of early quantitative resuscitation, patients treated with both protocols received bolus antibiotics within 1 hour, MAP monitoring, Foley catheters to measure urine output and temperature, and serial lactate levels.

2.3.2. Chart review and primary end points

The Principal Investigator (PI) and a trained Research Assistant (RA) performed a chart review of enrolled patients using a standard methodology [24,25] to assess the following: (1) quantity and type of bolus intravenous fluids (NS, lactated ringers, or any other type), (2) serum creatinine (Cr) at presentation and upon discharge, and (3) need for emergent hemodialysis (HD) or RRT during admission. Duplicate reviews were performed by the PI and a trained RA on a 10% subsample of patients to assess reliability. Chart review also included ED and inpatient medical records to confirm sepsis diagnosis and determine age, sex, ethnicity, patient disposition (discharged to home, nursing home, rehabilitation facility, hospice, or death), hospital LOS, comorbidities (diabetes mellitus, chronic obstructive pulmonary disease, ESRD, active malignancy, organ transplant, and HIV status), source of infection, culture results, organ dysfunction, and the presence of shock. Organ dysfunction was defined according to the 2012 Surviving Sepsis Guidelines and the Mortality in ED Sepsis score [6,26].

The primary outcome of our analysis was change in Cr (admission–discharge Cr). Secondary outcomes were need for HD/RRT, LOS, mortality, organ dysfunction. To determine if total fluid volume in the first 24 hours adversely affected kidney function, we analyzed the same outcomes but substituted total fluid volume as the independent variable.

2.3.3. Predictor variables

The total volume of fluid administered from admission to 24 hours was determined and separated by fluid type. The quantity of Cl per liter of NS (154 mEq), LR (109 mEq), albumin (0 mEq), or any other fluid type was multiplied by liters administered in the first 24 hours after ED presentation to determine the total quantity of Cl administered in the first 24 hours. For total fluid volume, the total number of liters administered was summed.

2.3.4. Data collection and storage

Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the UF [27]. REDCap is a secure, Web-based application designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for importing data from external sources. Graphical and statistical analyses were performed using Stata Version 12 (StataCorp LP, College Station, Texas).

2.3.5. Sample, power calculation, and data analysis

The original prospective study (comparison of $ETCO_2$ to $SCVO_2$ and lactate) was institutional review board–approved to enroll 115 patients. Preliminary data suggested a linear relationship; therefore, based on linear regression of our primary end points ($ETCO_2$ and $SCVO_2$), a sample size of 70 patients was calculated to achieve 80% power to detect a regression coefficient of greater than or equal to 0.36 based on estimates of standard deviation from our pilot cases (SD of $ETCO_2$ ~ 4.00, $SCVO_2$ ~ 4.50) and a two-sided significance level of .05. Institutional review board approval was obtained to enroll an additional 45 patients to determine the relationship between $ETCO_2$ and lactate.

For the relationship of Cl and fluids to our primary and secondary outcomes, scatter plots were examined to inform the choice of regression models. For the primary analysis, we constructed a linear regression model in which change in Cr was the dependent variable and mEq of Cl was the independent (or predictor) variable. We constructed logistic regression models for each of the dichotomous secondary