Journal of Critical Care 29 (2014) 1011–1015

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Volume of fluids administered during resuscitation for severe sepsis and septic shock and the development of the acute respiratory distress syndrome ☆

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ARTICLE INFO

Keywords:
Sepsis
Acute respiratory distress syndrome
Resuscitation
Fluid balance

ABSTRACT

Purpose: The purpose of this study was to examine the association between the volume of intravenous (IV) fluids administered in the resuscitative phase of severe sepsis and septic shock and the development of the acute respiratory distress syndrome (ARDS).
Materials and methods: This was a retrospective cohort study of adult patients admitted with severe sepsis and septic shock at a large academic public hospital. The relationship between the volume of IV fluids administered and the development of ARDS was examined using multivariable logistic regression analysis.
Results: Among 296 patients hospitalized for severe sepsis and septic shock, 75 (25.3%) developed ARDS. After controlling for confounding variables, there was no significant association between the volume of IV fluids administered in the first 24 hours of hospitalization and the development of ARDS (odds ratio [OR], 1.05; 95% confidence interval [CI], 0.95-1.18). Serum albumin (OR, 0.52; 95% CI, 0.31-0.87) and Acute Physiology and Chronic Health Evaluation II score (OR, 1.08; 95% CI, 1.04-1.13) on admission were the most informative covariates for the development of ARDS in the regression model.
Conclusions: For patients hospitalized for severe sepsis and septic shock, fluid administration to improve end-organ perfusion should remain the top priority in early resuscitation despite the potential risk of inducing ARDS.

1. Introduction

Severe sepsis and septic shock are the most severe manifestations of the sepsis syndrome and characterized by end-organ hypoperfusion and hypotension due to infection [1]. Previous studies have shown that early goal-directed resuscitation of patients with severe sepsis and septic shock improves mortality [1,2]. One of the key interventions in early goal-directed therapy is aggressive administration of intravenous (IV) fluids using physiologic targets to assess for improvements in end-organ perfusion [2]. For patients with severe sepsis or septic shock, the Surviving Sepsis Guidelines recommend an initial bolus of 30 mL/kg of fluid followed by repeated fluid administration as long as there are continued responses in hemodynamic parameters [1]. The rationale for these recommendations is that, in the resuscitative phase of severe sepsis and septic shock, restoring intravascular volume and maintaining end-organ perfusion are the top priorities. However, one concern regarding aggressive volume resuscitation is that it may increase the risk for complications due to volume overload, such as the acute respiratory distress syndrome (ARDS) [3–5].

Acute respiratory distress syndrome is a devastating complication of sepsis that affects its clinical management and outcomes [6–8]. Previous studies have shown that interventions that minimize the administration of IV fluids in hemodynamically stable patients with ARDS decrease the duration of mechanical ventilation and intensive care unit (ICU) stay without compromising end-organ perfusion [9]. As such, the fluid management strategies for ARDS can become discordant with those of sepsis when pulmonary edema complicates the early resuscitative phase of the sepsis syndrome.

Given the increased propensity of the lungs to develop pulmonary edema during sepsis, it is possible that the effects of positive fluid balance during fluid resuscitation in patients admitted with severe sepsis and septic shock may increase the risk for developing ARDS.

☆ Research support: none.
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http://dx.doi.org/10.1016/j.jcrc.2014.06.005
0883-9441/

The objective of this study was explore this risk by examining the association between the volume of IV fluids administered in the first 24 hours of hospitalization for severe sepsis or septic shock and the development of ARDS. We hypothesized that increased IV fluid administration is associated with a greater incidence of ARDS despite controlling for known predisposing factors.

2. Materials and methods

2.1. Study design and patients

This was a retrospective observational study of patients with severe sepsis or septic shock admitted to the emergency department of a large academic county hospital (Harbor-UCLA Medical Center, Torrance, CA) between December 2011 and January 2013. The cohort of patients with severe sepsis and septic shock was identified by retrospective chart review of all patients seen in the emergency department using the clinical definition from the Surviving Sepsis Guidelines and the Society of Critical Care Medicine/European Society of Intensive Care Medicine/American College of Chest Physicians International Sepsis Definitions Conference [1,10]. Specifically, *sepsis* was defined as a probable and suspected infection as documented by a physician in the medical record with at least 2 manifestations of a systemic inflammatory response (temperature > 38.3°C or <35.6°C, heart rate > 90 beats per minute, respiratory rate > 20/min, or white blood cell count > 12.0×10^3 or <4.0×10^3, or normal white blood cell count with > 10% immature band forms). *Severe sepsis* was defined as sepsis with organ dysfunction or tissue hypoperfusion (systolic blood pressure < 90 mm Hg, mean arterial pressure < 70 mm Hg, lactate above the upper limit of normal, urine output < 30 mL/h despite initial fluid resuscitation, creatinine > 2.0 mg/dL, bilirubin > 2 mg/dL, platelet count < 100,000, international normalized ratio > 1.5). *Septic shock* was defined as sepsis-induced hypotension resulting in a systolic blood pressure less than 90 mm Hg or mean arterial pressure less than 70 mm Hg requiring vasopressor support despite IV fluid administration [1,10].

We examined the association between the total volume of IV fluids administered in the first 24 hours of hospitalization and the development of ARDS within 72 hours of hospital admission in patients admitted with severe sepsis and septic shock. The total volume of IV fluids administered was determined from nursing flow sheets that documented the total fluid intake and output for each patient. The development of ARDS was identified by chart review using the Berlin definition of *ARDS* [11,12]. Specifically, patients were identified as having ARDS if they had bilateral opacities on chest radiograph, acute onset of respiratory failure not fully explained by cardiac failure, and Pao_2/Fio_2 ratio less than 300 mm Hg within 72 hours of admission for severe sepsis or septic shock.

2.2. Risk factors for the development of ARDS

The primary predictor variable for the development of ARDS was the volume of IV fluids (liters) administered in the first 24 hours of hospitalization. Secondary variables included the administration of an initial fluid bolus of greater than 20 mL/kg and the volume of IV fluids given in the first 6 hours of hospitalization. Additional risk factors that were examined included patient demographics (age, sex, race/ethnicity), medical comorbidities (Charlson Comorbidity Index), presenting vital signs and laboratory data (serum sodium, bicarbonate, glomerular filtration rate, albumin, lactate), medications, use of blood products, composite scores for severity of illness (Acute Physiology and Chronic Health Evaluation [APACHE] II, Sequential Organ Failure Assessment [SOFA]), and suspected source of sepsis. Additional clinical outcomes that were examined include hospital and ICU mortality. Laboratory studies that were not normally distributed were log transformed for statistical analysis. The APACHE II and SOFA scores were calculated from the clinical data available on admission. All data were collected by retrospective chart review by 2 of the investigators (RH and NH) using a structured data abstraction form. Patient identifiers were removed from aggregated data and were coded using a numeric identifier. The list of numeric codes and corresponding patient identifiers was maintained in a password-protected computer by one of the investigators (DWC). The study was approved as an exempt protocol by the John G Wolf Institutional Review Board at the Los Angeles Biomedical Research Institute. The need for informed consent was waived.

2.3. Statistical analysis

The primary analysis compared the volume of IV fluids administered in the first 24 hours of hospitalization in patients who developed ARDS vs those who did not. The Student *t* test was used to compare the volume of fluids administered to each group at 6 and 24 hours. The secondary predictor variables, volume of fluids administered in the first 6 hours of hospitalization and the administration of an initial fluid bolus, were analyzed using a *t* test or χ^2 test, as appropriate. A *P* value < .05 was used to define statistical significance. To control for factors that may confound the relationship between the volume of fluids administered in the first 24 hours (primary predictor variable) and the development of ARDS (primary outcome variable), multivariable logistic regression analysis was performed [13,14]. Prior to multivariable analysis, univariate analysis was performed on all covariates to identify those with the strongest association with the development of ARDS. All covariates that were significant at a level of $P < .10$ were considered for multivariable analysis [15]. For multivariable regression analysis, 2 models were generated. First, all covariates of interest were included in a comprehensive model that contained any factors that showed an association in the univariate analysis. Next, the same covariates were included in stepwise logistic regression analysis to generate a parsimonious model that contained only the most informative covariates. These 2 models were used as complementary approaches to control for the influence of confounding factors on the relationship between primary and secondary predictor variables and the development of ARDS. The volume of IV fluids administered in the first 24 hours (primary variable of interest) and the administration of an initial fluid bolus (secondary variable) were included in all models. The administration of an initial fluid bolus was included in the multivariable models despite the lack of association in univariate analysis because this variable was of clinical interest as a potential risk factor for ARDS. The volume of IV fluids administered in the first 6 hours of hospitalization (secondary variable) was not included in the multivariable models because it was collinear with the volume of IV fluids administered in the first 24 hours. We evaluated the models for multicollinearity using a correlation coefficient matrix of the covariates [15]. All covariates included in the models showed a correlation of less than 0.60. The values of the variables in the models are reported as adjusted odds ratios (ORs) with 95% confidence intervals (CIs). A *P* value < .05 was used for statistical significance in the model variables. The data analysis was performed using JMP version 11.0 (SAS Institute, Cary, NC).

3. Results

3.1. Baseline characteristics between the ARDS and control groups

The study cohort consisted of 296 patients who were admitted with severe sepsis or septic shock. Of these, 75 patients (25.3%) developed ARDS within 72 hours of hospital admission. There were multiple differences in the baseline characteristics between patients that developed ARDS and those that did not develop ARDS (Table 1). The ARDS group was older (mean age, 71.5 vs 62.9 years; $P = .004$). In addition, the ARDS group had a lower proportion of Hispanic patients compared to the no-ARDS group (17.3% vs 38.9%, $P < .001$). The serum