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Plasma syndecan-1 levels identify a cohort of patients with severe sepsis at high risk for intubation after large-volume intravenous fluid resuscitation

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ABSTRACT

Purpose: Sepsis damages the endothelial glycocalyx, contributing to fluid extravasation, organ injury, and death. Our goal was to determine if syndecan-1 level is associated with the risk of intubation and modifying effect of intravenous fluids (IVFs) in these patients.
Methods: Syndecan-1 was measured at enrollment in patients underdoing protocolized resuscitation for severe sepsis or septic shock. The primary outcome was difference in syndecan-1 based on subsequent intubation status, with in-hospital mortality and acute kidney injury serving as secondary outcomes. Logistic regression was performed to evaluate the effect of IVF volume on each outcome.
Results: Syndecan-1 was measured in 175 patients. Twenty-two percent met the primary outcome, 21% died, and 57% developed kidney injury. Syndecan-1 was nonsignificantly higher in intubated patients and was significantly higher in nonsurvivors and those with kidney injury. High syndecan-1 was defined as >240 ng/mL. The IVFs did not differ significantly between high and low syndecan-1 groups. Fluid volume was not associated with intubation in patients with a low syndecan-1 level but was associated with intubation in those with high syndecan-1 levels.
Conclusions: Syndecan-1 is elevated in emergency department sepsis nonsurvivors. Patients with high syndecan-1 may represent a cohort at particular risk for intubation after large-volume fluid administration.

1. Purpose

Despite recent data suggesting some improvements in severe sepsis mortality, the risk of death in severe sepsis still exceeds 20% [1]. One of the cornerstones of early sepsis resuscitation is the administration of intravenous (IV) crystalloid [2], with the goals of restoring intravascular fluid volume loss, increasing venous return to the heart, and ultimately increasing cardiac output. Numerous studies have investigated the value of physiologic measurements to predict fluid responsiveness. Static measurements such as central venous pressure [3] and pulmonary capillary wedge pressure [4] carry significant limitations and are of unclear value. Dynamic measurements such as stroke volume variation [5] and straight leg raise [6] testing demonstrate better test characteristics but have limitations that prevent widespread adoption. Investigations related to these measurements are often limited by short-term hemodynamic outcomes and rarely address patient-centered outcomes. Although fluid boluses can lead to temporary improvements in hemodynamic measurements, a proportion of crystalloid fluid diffuses into the extravascular space, a process exacerbated in sepsis secondary to endothelial damage [7]. This extravascular fluid may promote the development of acute respiratory distress syndrome and acute kidney injury (AKI). Thus, defining the relative risks and benefits of fluid resuscitation remains a critically important area of investigation.

Clinical data regarding the relative risks and benefits of IV fluids (IVFs) in sepsis remain mixed. Implementation of resuscitation protocols has been associated with both decreased mortality and increased volume of crystalloid administration [8,9], although it is unclear whether changes in fluid management are responsible for improved outcomes. Data from 3 recent large randomized controlled trials of early quantitative resuscitation strategies suggest that the volume of crystalloids administered varies significantly internationally, with median volumes ranging from approximately 2.5 L in Australia [10] to 4 L in the United Kingdom [11] to 5 L in the United States [12]. Despite this variation, the 3 cohorts exhibited comparable mortality rates. In other settings, the Fluid Expansion as Supportive Therapy (FEAST) trial found that patients in low-resource environments and with a high predominance of anemia have an increased risk of death after fluid bolus therapy, demonstrating the importance of clinical environment and specific patient factors when assessing this therapy [13]. Finally, clinical trial data suggest that patients with acute lung injury benefit from a restrictive fluid strategy [14]. Taken together, the ideal volume and timing of crystalloid resuscitation in severe sepsis remain unclear.

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The endothelium plays several physiologic functions; one of the most critical is the separation between the intravascular and extravascular spaces. Severe sepsis damages the endothelium [15]. In the intraluminal space, the endothelium is covered with glycocalyx composed of a number of proteins including syndecan-1 [16]. The glycocalyx is hypothesized to be damaged before the endothelium itself and may be an earlier and more sensitive indicator of injury [15]. Syndecan-1 levels are elevated in patients with sepsis, particularly in nonsurvivors [15,17,18]. In this study, we wished to extend these studies by investigating the possibility that glycocalyx damage plays a direct pathophysiologic role in sepsis by predisposing patients to organ failure. We hypothesized that glycocalyx damage may contribute to increased extravascular fluid extravasation, observed clinically as an increase in the risk of intubation, that would be especially pronounced among patients receiving larger volumes of IV crystalloids.

2. Materials and methods

2.1. Patient selection

Patients from a single emergency department (ED) participating in a previously published multicenter clinical trial comparing 2 early resuscitation strategies for severe sepsis were enrolled. The study took place from 2007 to 2009 [19]. The study was approved by institutional review board, and all patients or their surrogates gave informed consent. Inclusion criteria included age >17 years, 2 or more systemic inflammatory response criteria, and either hypotension after a fluid challenge or lactate >4 mmol/L. Patients were excluded if they or a surrogate could not provide informed consent, if they had an absolute contraindication to central venous line placement, or if they required emergent surgical intervention. All patients underwent a standardized resuscitation based on serial iterative steps of IV crystalloid to achieve central venous pressure, mean arterial pressure, and either central venous oxygen saturation (Scvo2) ≥70% or lactate clearance goals. The protocol was continued until all end points were achieved or a maximum of 6 hours. The published results of this study showed a 6% (95% confidence interval [CI], −3% to 14%) in-hospital mortality difference favoring the lactate clearance group, confirming the primary hypothesis of noninferiority between the 2 strategies [19].

2.2. Syndecan-1 measurements

Blood was drawn at enrollment into EDTA tubes and processed immediately by centrifugation at 3000*g* at 4°C for 10 minutes. Aliquots were stored at −80°C without any freeze-thaw cycles until the time of measurement. Investigators blinded to the clinical status of the patient measured syndecan-1 using enzyme-linked immunosorbent assay (Abcam, Cambridge, MA) in duplicate, and results were averaged. The lower limit of the detection for the test was 4.94 ng/mL.

2.3. Clinical outcomes

All clinical data including demographics and therapies administrated, including volume of IVF administered in the ED, were recorded prospectively. The primary outcome of this study was the difference in syndecan-1 levels among patients who did and did not require endotracheal intubation. Secondary outcomes included differences in syndecan-1 among in-hospital survivors and nonsurvivors and those who did and did not develop AKI. AKI was defined as a creatinine increase of >50% at any point during the hospitalization, consistent with the "risk" component of the Risk of renal failure, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage renal failure (RIFLE) criteria [20]. Timing of intubation and development of AKI were not collected prospectively, and the relationship of these outcomes to the time of blood draw was not available for this analysis.

2.4. Data analysis

Simple descriptive statistics, χ^2 and Fisher exact tests, and Wilcoxon rank sum were used to analyze the data as appropriate. A receiver operating characteristic curve using intubation as the dependent variable was created, and the area under the curve was calculated. An optimum cutoff was chosen, and patients were grouped into high and low syndecan-1 groups accordingly. To assess the potential of high syndecan-1 levels as a predictor variable, a multivariable logistic regression model was constructed using intubation as the dependent variable. Candidate variables for the model were chosen based on the results of the univariate analysis comparing patients who did and did not meet the primary outcome. Initial variables included those variables with a *P* value <.1 and other variables logically expected to increase the risk of intubation (such as a history of chronic obstruction pulmonary disease). Sequential organ failure assessment (SOFA) score [21] was not placed in the model as a whole because of the potential for collinearity, as the respiratory component of the SOFA score is highly reflective of the dependent variable of interest (intubation), and the central nervous system component is based on the Glasgow Coma Score, which may be artificially inaccurate in intubated patients secondary to sedative medications and has been shown to have low interrater reliability [22]. We forced the variable of IVF volume administered into the final logistic regression model. The model was refined using backwards stepwise elimination, maintaining variables with a $P < .1$. Model diagnostics included jackknife and bootstrap replications, which demonstrated similar results. The final model was checked for overfitting using the method of Hosmer and Lemeshow.

Finally, logistic regression of patients with high and low syndecan-1 levels was performed to evaluate the risk of intubation associated with the administration of IVF in each of these subgroups of patients. These data were visualized using the Lowess smoothing function and are presented in Fig. 2. All analyses were conducted using STATA 10.0 (College Station, TX). Tests were 2-sided, and *P* values ≤.05 were considered significant.

3. Results

One hundred ninety-three patients were enrolled, and 175 had plasma available for analysis from the time of enrollment. Fifty-two patients (22%) met the primary outcome of intubation, and 34 (21%) died. One hundred (57%) met the study definition of AKI. Baseline demographics and clinical characteristics of the entire cohort and those meeting primary outcome are summarized in Table 1. Intubated patients tended to be older and were more likely to have dementia and require dialysis. They also had a higher severity of illness, longer lengths of stay, and a higher mortality rate.

Median syndecan-1 levels were 152 ng/mL (interquartile range [IQR], 49-345), with a range from undetectable (<4.94 ng/mL; 14 patients) to 1870 ng/mL. Levels of syndecan-1 were nonsignificantly higher in intubated patients (181 ng/mL [IQR, 61-568] vs 141 ng/mL [IQR, 46-275]; $P = .06$) and significantly higher in nonsurvivors (223 ng/mL [IQR, 67-464] vs 142 ng/mL [IQR, 38-294]; $P = .04$) (Figs. 1A and B). Syndecan-1 levels were significantly higher in patients with evidence of AKI (193 ng/mL [IQR, 63-441] vs 93 ng/mL [IQR, 23-187]; $P < .001$) (Fig. 1C).

High syndecan-1 was significantly associated with intubation (odds ratio [OR], 2.3; 95% CI, 1.1-4.6), which remained a significant independent predictor in our final multivariable model (OR, 2.7; 95% CI, 1.3-5.6; $P < .01$). Other variables in the final model included history of hypertension (OR, 2.4; 95% CI, 1.1-5.0), dementia (OR, 10.5; 95% CI, 3.0-36.1), and total IVF volume administered in the ED (OR, 1.2 per L of fluid; 95% CI, 1.0-1.5). These data are summarized in Table 2.

The area under the curve to predict the primary outcome of intubation was 0.58 (95% CI, 0.49-0.68), indicating that syndecan-1 level alone is a poor predictor of the need for intubation. Based on the receiver