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Targeted Fluid Minimization Following Initial Resuscitation in Septic Shock

A Pilot Study

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BACKGROUND: IV fluid represents a basic therapeutic intervention for septic shock. Unfortunately, the optimal administration of IV fluid to maximize patient outcomes and prevent complications is largely unknown.

METHODS: Patients with septic shock admitted to the medical ICUs of Barnes-Jewish Hospital (January to December 2014) requiring vasoactive agents for at least 12 h following initial fluid resuscitation were randomized to usual care or to targeted fluid minimization (TFM) guided by daily assessments of fluid responsiveness.

RESULTS: Eighty-two patients were enrolled, 41 to usual care and 41 to TFM. For patients randomized to TFM, the net median (interquartile range) fluid balance was less at the end of day 3 (1,952 mL [48-5,003 mL] vs 3,124 mL [767-10,103 mL], $P = .20$) and at the end of day 5 (2,641 mL [−1,837 to 5,075 mL] vs 3,616 mL [−1,513 mL to 9,746 mL], $P = .40$). TFM appeared to be safe, as indicated by similar clinical outcomes including in-hospital mortality (56.1% vs 48.8%, $P = .51$), ventilator days (8.0 days [3.25-15.25 days] vs 5.0 days [3.0-9.0 days], $P = .30$), renal replacement therapy (41.5% vs 39.0%, $P = .82$), and vasopressor days (4.0 days [2.0-8.0 days] vs 4.0 days [2.0-6.0 days], $P = .84$).

CONCLUSIONS: This pilot study suggests that TFM in patients with septic shock can be performed using protocol-guided assessments of fluid responsiveness. Larger trials of TFM in septic shock are needed.

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ABBREVIATIONS: EVLW = extravascular lung water; IVC = inferior vena cava; IVF = IV fluid; TFM = targeted fluid minimization

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Since Rivers et al[1] demonstrated in 2001 that early goal-directed therapy improved survival in patients with septic shock, fluid resuscitation has become a mainstay for the treatment of severe sepsis and septic shock.[2] However, there is a growing body of evidence suggesting that an excessively positive fluid balance is associated with worse outcomes in ARDS,[3-5] acute renal failure,[6,7] and septic shock.[8,9] Moreover, recent prospective, randomized controlled trials have questioned the efficacy of early goal-directed therapy, because no mortality benefit was demonstrated in the Australasian Resuscitation in Sepsis Evaluation (ARISE), Protocolized Care for Early Septic Shock (ProCESS), or Protocolised Management in Sepsis (ProMISE) trials.[10-12] Although studies have been performed demonstrating no mortality benefit and possible harm with the use of dobutamine and excessive RBC transfusions in severe sepsis and septic shock,[13-15] there are no prospective, randomized controlled trials examining the role of targeted fluid minimization (TFM) following initial fluid resuscitation in septic shock.

Given the growing body of evidence that excessive fluid administration may be harmful in septic shock,[16] there has been renewed interest in predicting fluid responsiveness. Static measures, such as central venous pressure and central venous oxygen saturation, have been shown previously to be poor predictors of fluid responsiveness.[17,18] Dynamic measures, such as pulse pressure variation and inferior vena cava (IVC) distension, have shown more promise, but only under controlled situations (ie, passive positive pressure breathing with 8-10 mL/kg ideal body weight tidal volumes).[19] We hypothesized that a protocol of daily fluid status assessment resulting in TFM could be used safely in patients with septic shock deemed not to be volume responsive. Therefore, we performed a pilot study to determine the feasibility of testing the aforementioned hypothesis in patients with septic shock.

Materials and Methods

Approval of Study Design

This prospective, randomized study was approved by the institutional review board for human research at Washington University. It was conducted under the auspices of an independent safety, efficacy, and data monitoring committee (HRPO number 201503035).

Eligibility

Eligible adult patients with septic shock who presented to the medical ICU of a 1,250-bed academic tertiary care hospital from January 2014 through December 2014 were assessed for possible enrollment according to the inclusion and exclusion criteria. The criteria for inclusion were septic shock as the primary cause of hypotension and hypotension necessitating vasoactive drugs that persisted for at least 12 h after initial adequate IV fluid (IVF) administration and at the time of enrollment. Initial adequate IVF administration was defined as the administration of at least 30 mL/kg ideal body weight of normal saline or lactated Ringer solution. The criteria for exclusion from the study were prior enrollment in the study, age $<$18 years, presence of end-stage renal disease necessitating hemodialysis or peritoneal dialysis as an outpatient immediately prior to admission, pregnancy, or goals of care consistent with comfort measures only. Written informed consent was obtained from the patient when able, and if the patient was unable to provide consent, then consent was obtained from the patient's legal representative.

Study Protocol

After informed consent, patients were stratified based on the presence or absence of ARDS, then randomized to either standard (control) therapy or TFM therapy (Fig 1). Baseline parameters, including central venous pressure, mean arterial pressure, central venous oxygen saturation, pulse pressure variation, and inspiratory and expiratory IVC diameters were obtained for all patients. Stroke volume and cardiac output were also measured, using transesophageal Doppler (CardioQ; Deltex Medical) in intubated patients and transthoracic Doppler (USCOM) in nonintubated patients. Following measurement of baseline parameters in the TFM therapy group, a fluid challenge was performed by passive leg raise, or, if the primary team had already decided to administer a fluid bolus or perform an RBC transfusion, this was used in lieu of a passive leg raise. Following passive leg raise or fluid administration, parameters were repeated and fluid responsiveness was assessed. Patients were considered fluid responsive if the pulse pressure variability decreased to $<$13%, the IVC distension index decreased to $<$18%, and the stroke volume index difference increased by $>$10%.[19-21] At least two of these parameters had to be met to be considered fluid responsive. In the standard therapy group, the baseline hemodynamic data were obtained and made available to the treating medical team without data interpretation. All tests were performed and interpreted by one investigator (C. C.), and pulse pressure variation was measured only if the patient had an arterial line placed by their treating physician team.

All assessment results for patients assigned to TFM therapy were discussed directly with the primary medical team. In patients who were deemed to be fluid responsive, recommendations to continue IVF administration were made using 500 mL boluses of normal saline or lactated Ringer solution until fluid responsiveness could no longer be demonstrated. In patients who were deemed to not be fluid responsive, TFM therapy was initiated: Continuous therapeutic infusions were concentrated, maintenance IVFs were discontinued, carrier fluids were minimized, and the use of diuretic therapy or fluid removal with renal replacement therapy was discussed and encouraged with the primary team based on the patient's renal function.

Fluid responsiveness parameters were repeated daily for 5 days or until the patient was discharged from the ICU or died. In addition to the fluid responsiveness parameters, daily fluid intake and output were assessed. The APACHE (Acute Physiology and Chronic Health Evaluation) II and Sequential Organ Failure Assessment (SOFA) scores were calculated for all patients at the time of enrollment in the study. Comorbidities, including systolic and diastolic heart failure, chronic kidney disease, active malignancy, and end-stage liver disease, were also recorded.

Outcomes

The primary outcome for this pilot study was the volume of study fluids administered by days 3 and 5 and the cumulative fluid balance by days 3 and 5. Study fluids were defined as colloid and crystalloid boluses and all continuous infusions administered from study enrollment through day 5. Secondary outcomes included the frequency of renal replacement therapy, maximal vasopressor dose in μg/min, number of days requiring vasopressor use, number of vasopressor-free days, mean arterial pressure during the enrollment period, number of ventilator days, number of ventilator-free days, and in-hospital mortality.