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Review Article

Early fluid loading for septic patients: Any safety limit needed?

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A B S T R A C T

Early adequate fluid loading was the corner stone of hemodynamic optimization for sepsis and septic shock. Meanwhile, recent recommended protocol for fluid resuscitation was increasingly debated on hemodynamic stability *vs* risk of overloading. In recent publications, it was found that a priority was often given to hemodynamic stability rather than organ function alternation in the early fluid resuscitation of sepsis. However, no safety limits were used at all in most of these reports. In this article, the rationality and safety of early aggressive fluid loading for septic patients were discussed. It was concluded that early aggressive fluid loading improved hemodynamics transitorily, but was probably traded off with a follow-up organ function impairment, such as worsening oxygenation by reduction of lung aeration, in a part of septic patients at least. Thus, a safeguard is needed against unnecessary excessive fluids in early aggressive fluid loading for septic patients.

Introduction

Adequate preload was the corner stone of hemodynamic optimization for sepsis and septic shock, a very complex clinical syndrome, which was lately defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] However, practices of fluid loading remained unstandardized in initial resuscitation nowadays,[2,3] although task forces for Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock took their great efforts to recommend the continually updated best practices.[4–7] Significantly, there was a trend toward more and more aggressive, but far beyond the recommendations on early fluid loading in the past two decades. This aggressive approach of fluid loading no doubt would contribute to correcting hypovolemia and minimizing hypoperfusion in early phase of sepsis, especially in patients with hemodynamic instability.[8–10] Meanwhile, a part of patients was probably placed at risk of receiving excessive unnecessary fluids,[11] which was associated with poor outcomes. In this review, the pathophysiology based rationality and safety limits of early fluid loading for septic patients were discussed.

Rationale of aggressive fluid loading

Basically, plasma volume depletion was the fundamental for aggressive fluid loading. It is well established that hypovolemia was one of the most common pathophysiological alternations in septic patients[12,13] owing to multiple factors including fever, gastrointestinal loss and immeasurable inflammatory interstitial edema as well. In addition, inflammatory mediators-induced vasodilation resulted in further inadequacy of effective blood volume, for which extra fluids were often necessary. Moreover, inadequate fluid was often administrated before admission. Notably, persisted plasma volume depletion was tightly linked to hypoperfusion, hemodynamic instability as well as sequential multiple organ dysfunction in patients with sepsis and septic shock.[14,15] Therefore, early aggressive fluid loading was rationally expected for adequate replacement circulatory volume depletion in patients with sepsis and septic shock.

Secondly, Frank-Starling principle provided a rationale for aggressive fluid loading. Based on this role, left ventricular stroke volume (SV) or cardiac output (CO) was positively responded with fluid loading while the preload was ranged at absolutely low levels (SV was functioning on ascending limb of the Frank-Starling curve). Significantly, this dose-effect potential of fluid was repeatedly confirmed in everyday practices. However, the cut goals to define “amount necessary” remained unclear for septic individuals yet.[16,17] Fluid loading was mainly guided by physiological variables as suggested in consensus at the end of 20th century, “i.e. early fluid

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loading would be recognized the best when titrated to restore tissue perfusion, which was indicated by clinical end points, such as heart rate (HR), urine output, blood pressure and maximize cardiac output (CO) in patients with septic shock".[18] Therefore, a positive fluid response, which was typically determined as a significant increase of CO after a rapidly loading 200–500 ml fluid within 15–30 min, was usually interpreted as additional fluids being needed and capable to further improve cardiac output for optimizing hypoperfusion. This might be the third reason for aggressive fluid loading.

Development of aggressive fluid loading and safety concern

In fact, EGDT trial (early goal-directed therapy, conducted by Rivers[19]) was a milestone to develop approach of aggressive fluid loading. This single center RCT (randomized control trial) reported that a significantly lower lactate concentration, less severity of organ dysfunction and higher survival rate could be achieved in patients who were administrated an average of near 1.5 L additional fluids during the initial six hours over the arm of usual care (4981 ± 2984 *vs* 3499 ± 2438, $p < 0.001$). Being a sound evidence, EGDT was adopted as the key component of the first Surviving Sepsis Campaign international guidelines for management of sepsis in 2004.[4] Moreover, more rapid and larger amount of fluid administration were studied in follow-up trials in order to reverse refractory sepsis-induced tissue hypoperfusion or organ dysfunction.[12,20–25] In a observational study for instance, Smith and Perner found that higher fluid volume (>7.5 L in total) was superior to the lower fluid volume (<7.5 L) administrated within the first 3 days in reducing 90-day mortality of patients with septic shock.[12] With increasing lovely data published, initial volume of fluid administration was significantly enlarged in each revised version of management guidelines for sepsis and septic shock.[5–7] In the latest two updates, the protocolized quantitative resuscitation of fluid bolus (30 ml/kg of crystalloid) administered within 3 h was strongly recommended when hypovolemia (or initial blood lactate concentration $\geq$ 4 mmol/L) was suspected in septic patients.[6,7] With these guidances, routine practice has been changed dramatically in early fluid therapy for septic patients now. As referred above, a retrospective study of fluid therapy for sepsis/septic shock demonstrated that the ratio of patients with fluid balance over 6000 ml/24 h was up to 43.1%.[8] However, three well-designed recent RCTs evaluating the impact of the EGDT protocol on outcomes (ProCESS, ARISE and ProMISE) failed to prove that further fluids were beneficial to septic patients.[26–28]

As well established, on the other hand, positive cumulative fluid balance was independently associated with compromised organ dysfunction and even worsened outcomes in diverse populations of sepsis.[11,26–29] Sakr Y et al.[30] found that septic patients with a higher cumulative fluid balance were associated with acute lung injury and/or acute respiratory distress syndrome more frequently. Boyd JH et al.[8] reported that a more positive fluid balance, either in early resuscitation or cumulatively over 4 days, was linked to an increased risk of mortality in septic shock. Significantly, it was strongly evidenced that a net negative fluid balance was closely tied to a reduced mortality in septic shock.[31–33] However, the real picture of our routine practice showed that about half of patients were given additional fluids, no matter what positive or negative fluid responsiveness was and often without any safety limits used, in an observational study conducted in ICUs around the world (FENICE study).[10] Therefore, to balance the efficiency of hemodynamic improvement *vs* the risk for deleteriously pathophysiological alterations in practice of early aggressive fluid loading became a big challenge in management of sepsis currently.

How much fluid is too much?

Hemodynamic responses to fluid loading were multifaceted beyond the Frank-Starling principle in septic patients. As repeated by a lot of trials, fluid responsiveness was only found in less than 50% of septic patients.[10,34] On the other hand, active water clearance of cells was impaired by inflammatory injury in sepsis, which was largely engaged in overload-induced organ dysfunction.[1,35] Accordingly, optimal fluid was hardly targeted in individuals. Improvement of hemodynamics achieved with aggressive fluid loading was therefore not always beneficial to organ function and outcomes, as commented by Marik PE.[36] For instance, the incidence of newly developed AKI (acute kidney injury) requiring renal replacement therapy was significantly higher in patients receiving the protocol-based standard therapy, who were infused with an additional 400–900 ml (in median) of fluids over other two groups in ProCESS trial.[26] Therefore, a safety limit was necessary for individualizing preload optimization in septic patients.

However, optimal goal, or the upper limit for plasma expansion, still remained as a big challenge in early fluid resuscitation for sepsis. First of all, available measures for estimating plasma volume were almost indirect. Whatever CVP (central venous pressure), PAWP (pulmonary artery wedge pressure), or left ventricular diameter at the end of diastolic period were used, the values were just regarded as a certain amount of blood volume filling heart rather than oxygenated blood flow passing cells.[37,38] The second, hardly was responsiveness of fluid challenge directly interpreted as inadequate of fluid for perfusion, or for cells with inflammatory injuries in sepsis.[39] Better information on optimizing of fluids therapy would be provide by dynamic variables, such as PPV (positive predictive value), SVV (stroke volume variation), delta $ScvO_2$ (central venous oxygen saturation) and Pv-aCO_2 (venous-to-arterial difference in pressure of CO_2) gap as well.[40–42] But, validity of them remained controversy in clinical practices. The third, the real need of fluid was heterogeneous between organs once being overwhelmed with inflammatory mediators. It was difficult to balance the volume of fluid infusion between different organs. For instance, optimal fluid for kidney perfusion might overload and harm lung.[30,43] Therefore, renovation on ways of estimating needs of blood flow in cells or organs specifically is necessary in further research on optimizing fluid loading for sepsis.

Interestedly, changes in organ function might be severed as a marker for optimizing fluid loading in sepsis today. Conducted by Caltabeloti and his colleagues, lung aeration was reported as a valid safeguard against excessive fluid loading in patients with septic shock.[44] They found that early fluid loading transitorily improved hemodynamics and oxygenation, but was positively correlated with reduction of lung aeration as shown by bedside ultrasound. But, lung has not been determined as the organ with the worst tolerance to fluid overloading yet. Little was known about functional alternations in brain, GI (Gastrointestinal) as well as kidney while fluid balance was optimized by lung physiology. Thus, an index to balance fluid tolerance between vital organs will be a novel approach for safety of fluid loading in sepsis and septic shock.

Conclusion

Fluid loading is fundamental for assessing and reversing hypovolemia in patients with sepsis and septic shock. Recently, a priority was often given to hemodynamic stability rather than organ function alternation in our practices of early fluid resuscitation for sepsis. However, practices of aggressive fluid loading, especially those far beyond recommendations of current guidelines, were risk potential to administrate excessive fluids to septic patients, which was highly associated with worse outcomes.

Therefore, a safety limit will be a big step forward to fluid optimization for septic patients.

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