Review Article

Fluid Therapy in Sepsis

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Abstract

Fluid resuscitation is one of the cornerstones of management of patients with severe sepsis. However considerable controversy remains when it comes to deciding the targets and endpoints of resuscitation, hemodynamic and microcirculatory goals to be achieved , and nature and amount of fluid to be administered. The article briefly addresses the various aspects of fluid resuscitation in sepsis,and attempts to highlight the recent evidences and areas which hold promise for future research.

Key Words: Fluid resuscitation, Sepsis, Hemodynamic goals

Introduction

Sepsis continues to be a major cause for intensive care unit admission and mortality in the developed and developing world. In fact, as much as 20-30% of admissions in ICU have severe sepsis[1]. Fluid therapy either alone or in combination with vasopressors continues to be among the mainstays of management of patients with septic shock. However till date there remains considerable debate regarding the targets and endpoints of fluid resuscitation, ideal fluid to be administered, heamodynamic goals to be achieved and quantity of fluid to be administered.

A landmark study by Rivers et al[2] advocated early goal directed fluid therapy in the initial six hours of septic shock targeting specific hemodynamic endpoints of central venous pressure, mean arterial pressure, urine output and central venous oxygen saturation to reduce mortality and severity of organ dysfunction.This led to adoption of guidelines targeting aggressive fluid resuscitation in sever sepsis patients in the subsequent surviving sepsis guidelines. However more recent trials published since then (ProCESS, ARISE, ProMISe) have reported no mortality benefit with early goal directed fluid therapy[3-5]. The increased de-emphasis on central venous pressure guided fluid therapy had led to revision of the 6-hour bundle in septic shock[6]. This review attempts to have a relook at the emerging evidence regarding fluid resuscitation in sepsis patients, and tries to highlight the latest areas of research and controversies.

Monitoring fluid responsiveness

The goal of fluid resuscitation in septic shock patients is to optimize cardiac output and organ perfusion. While suboptimal fluid resuscitation in severe sepsis patients can worsen end organ dysfunction and increase vasopressor requirements, excess of positive fluid balance can also have deleterious consequences[6,7]. Hence researches have focused on finding the subset of patients with sepsis who would benefit the most from fluid resuscitation,the so called "fluid– responders". Fluid responsiveness has been defined as those patients who would respond with a 10-15% increase in cardiac output following 250 ml or 3ml.kg^{-1} of crystalloid infused over 10-15 minutes[8]. Patients who respond positively can be given additional boluses of fluid till the response is attenuated. Alternatively a mini fluid challenge test, which involves infusing 100 ml of crystalloid over 1 minute, can also be used[10]. It has shown good sensitivity and specificity of 95% and 78%, respectively, with an area under the receiver operating characterizing curve (AUC ROC) of 0.92 [95% confidence interval (CI): 0.78– 0.98].

Static Parameters

Historically central venous pressure was used to guide fluid therapy. However, subsequent evidence found central venous pressure to be a very poor indicator of volume status and requirement of fluid therapy[10]. The use of Pulmonary artery catheterization has shown a steady decline owing to its invasiveness and complications associated with its use[11]. The major criticism of static parameters is their inability to predict whether the heart is operating on the steep or flat position of the Frank-Starling's curve.

The poor reliability of static parameters in assessment of volume status has generated increased interest in research and clinical application of dynamic indices of fluid responsiveness to guide fluid therapy in the septic patient.

Dynamic Parameters

Dynamic indices of fluid responsiveness rely on the heart lung interactions that occur during the respiratory

cycle. The inspiratory increase in intrathoracic pressure during positive pressure mechanical ventilation leads to a decreased right ventricular preload (due to decreased venous return) and an increased right ventricular afterload (due to increased transpulmonary pressures). Decreased RV ejection translates to a decreased left ventricular filling and cardiac output after 2-3 beats during expiratory phase. The cyclical fall in LV stroke volume during expiration and rise during inspiration is aggravated in a patient with pre-existing hypovolemia.

Dynamic parameters such as Stroke volume variation (SVV) and pulse pressure variation (PPV) make use of the phasic changes in cardiac output during respiration to assess fluid responsiveness. Since arterial pulse depends on cardiac output PPV correlates well with changes in LV stroke volume[12]. A cut-off value of 13% for PPV can predict fluid responsiveness with a sensitivity of 94% and specificity of 96%(AUC ROC of 0.94 and 0.84 for PPV and SVV) [14,15].

The Pleth Variability Index" (PVI) (Masimo Corporation, Irvine, CA) relies on the dynamic changes in plethysmographic amplitude and peak that occurs during a respiratory cycle.The PVI can predict fluid responsiveness noninvasively in mechanically ventilated patients who do not have an arterial line in situ[15].

Limitations

Dynamic indices of preload responsiveness are not without limitations. They are unreliable in presence of spontaneous breathing efforts making it essential for all breaths to be delivered mechanically. They require large tidal volumes(>8ml.kg-1) rendering them invalid during low tidal volume lung protective ventilation. Finally they are unreliable in the presence of arrhythmias or high heart rate, which are quite common in the critically ill[16-18]. All these factors limit their usefulness in ICU patients making them more useful in the operation theatre.

Echocardiographic Indices

Currently Echocardiography is considered as the first line in the hemodynamic assessment of any patient with shock and can be used for assessment of fluid responsiveness[19]. Both transthoracic and transesophageal echocardiography can be used for the purpose. While static measures of cardiac chamber volume and filling pressures have the same limitations as other static measures of volume responsiveness, it is the dynamic markers that have achieved reliability and reproducibility in managing septic shock patients. Echocardiography can be used to measure LV stroke volume using pulsed wave Doppler by multiplying the velocity time integral (VTI) by LV outflow tract diameter. The VTI is estimated by tracing the area of subaortic blood flow in pulsed Doppler and represents the distance travelled by red blood cells during systole. Since the aortic outflow tract diameter remains constant changes in VTI has been used to predict fluid responsiveness[20-21].

An excellent applicability of aortic blood flow velocity in predicting fluid responsiveness is the Passive Leg Raising (PLR) test. A form of reversible autotransfusion, PLR relies on venous return from the legs and abdominal compartment during a 45 degree leg elevation and the consequent changes in aortic blood flow velocity measured by esophageal Doppler.The test has excellent value in predicting fluid responsiveness in the critically ill patients, area under the receiver operating characteristic curve of 0.95[22].

Respiratory variations in inferior venacava diameter imaged by transthoracic echocardiography have also been used to differentiate between fluid responders and non-responders. Patients with distensibility index of inferior venacava (dIVC) greater than 18% were most likely to respond to fluids (90% sensitivity and 90% specificity)[23]. The collapsibility of the SVC imaged by trans esophageal echocardiography can be used alternatively.

Of the various echocardiographic modalities, PLR is the easiest to perform and has stood the test of time. A >10% change in aortic blood flow velocity following a PLR test predicts fluid responsiveness with a sensitivity of 97% and a specificity of 94%.In comparison. A similar 12% change in pulse pressure following a PLR is easier to perform but has a significantly lower sensitivity (60%) and specificity (85%)[24]. Though not as reliable as VTI ,yet non availability of bedside echocardiography or inadequate technical expertise in performing echocardiography makes pulse pressure change following PLR a more practical and attractive option for assessing fluid responsiveness. Recently a 5% change in End tidal CO_2 was found to reliably predict a fluid induced increase in Cardiac Index greater than 15 % with sensitivity of 71 % (95 % confidence interval: 48-89 %) and specificity of 100% (82-100)%[25]. This might be an attractive option as $EtCO_2$ monitoring is widely available and requires no expertise.

Microcirculatory dysfunction in Sepsis

Optimization of blood pressure and cardiac output remains the broad goals of hemodynamic resuscitation in septic shock. However even achieving target mean arterial pressure and cardiac output values have often failed to reverse the end organ dysfunction that accompanies inadequate tissue perfusion. Researches have focused on analyzing the microcirculatory flow in small blood vessels. Impaired microcirculatory flow may persist despite normalization of MAP or CO.

The ProCESS study is a case in point, which demonstrated resuscitation based on clinical parameters of urine output, skin mottling, mental status and lactate levels had the same mortality and end organ dysfunction as more advanced hemodynamic indices[3].

While normalizing microcirculatory dysfunction remains an attractive endpoint of fluid resuscitation, finding an appropriate tool to assess and treat microcirculatory dysfunction is still elusive. The lactate clearance over the first 12 hours of resuscitation has been evaluated as a potential marker for effective resuscitation with favorable results[26,27]. Normalization of lactate levels has been correlated with reduced mortality[28]. Splanchnic circulation is often compromised during the early stages of sepsis-induced hypoperfusion to maintain blood supply to the vital

organs. Determination of gastric mucosal pH by gastric tonometry has been used to assess the adequacy of splanchnic circulation. It has proven to be useful in critically ill, trauma and patients with acute pancreatitis[29-31]. Other methods of assessing tissue perfusion such as near infrared spectroscopy and sidestream dark field imaging have been tried in critically ill, but limited availability restricts their use[32-35].

Ideal fluid in sepsis

Fluid resuscitation is central to management of patients with sepsis. However the choice of fluid is still a matter of considerable debate. While recent evidence favours the use of crystalloids over colloids like hydroxyethyl starch/pentastarch, there has been no conclusive evidence to choose between crystalloids and albumin[36-41].

Crystalloid versus Colloid versus albumin

In the CHEST trial, patients admitted to the ICU were randomized to receive either 6% HES (molecular weight 130 kD , molar substitution ratio 0.4) in 0.9% sodium chloride or 0.9% normal saline.7% patients in the HES group required renal replacement therapy compared to 5.8% patients in the normal saline group[39]. Renal failure due to hydroxyethyl starch was more for 200kd and substitution ratio of >0.4 which are not in production any more. Pentastarch use was also associated with a trend towards increased 90 day mortality in another study[40].

The landmark SAFE study recruited 6997 critically ill patients to receive normal saline or 4% albumin for upto 28 days of admission. There was no difference in mortality between the two groups[37]. However in the subgroup of patients with severe sepsis albumin use was associated with reduced mortality. This additional benefit with albumin could be due to its anti-inflammatory and anti-oxidant profile. In addition, it protects the endothelial glycocalyx layer which acts as the key barrier to trans-vascular fluid efflux. The recent surviving sepsis guidelines favour the use of albumin as replacement of crystalloids as part of fluid resuscitation.

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The ALBIOS trial did not show any benefit of albumin over crystalloids[37]. There was no difference in 28 day and 90 day mortality in patients receiving 20% albumin targeted to a serum albumin concentration more than 30g/litre. Albumin may have a probable role in large volume fluid resuscitation as replacing albumin creates better fluid balance.The questionable mortality benefit of albumin in outcomes needs to be considered in addition to its significantly higher cost when used in resuscitating septic shock patients.

The Ideal Crystalloid

While crystalloids may be better than colloids when it comes to fluid resuscitation, considerable difference exists between different crystalloid formulations. Historically 0.9% normal saline was considered as the fluid for resuscitation. However supraphysiological concentrations of chloride and sodium makes normal saline far from an ideal fluid for resuscitation. Excessive infusion of normal saline is associated with a reduction in strong ion difference (SID) and resultant hyperchloremic metabolic acidosis.The hyperchloremia has detrimental effects on renal blood flow by promoting profound intrarenal vasoconstriction[42]. In addition it has proinflammatory effects, reduces neutrophil chemotaxis, impairs macrophage function and worsens heamodynamic instability[43].

The balanced crystalloid solutions have a composition more physiological akin to plasma and may be beneficial in large volume resuscitation.They do not lower body SID and may produce transient alkalemia.In a study comparing acetate and lactate based ringers solution in patients undergoing gynaecological surgery,both the fluids were equivocal in terms of haemodynamic stability and use of vasopressors.The acetate based solutions however produced a greater stability in plasma SID[44].

Amount of fluid:
The optimal amount of fluid for resuscitation in sepsis patients remains unknown. While earlier studies reported a mean volume of 3-5 litres to reach the target of early goal directed therapy, more recent studies report lower volumes of 2-3 litres[2-4]. While liberal fluid resuscitation is essential in septic shock excess injudicious fluid administration can have detrimental effects of its own[45]. Patients having ARDS with sepsis in particular may benefit from a restrictive fluid protocol.

In conclusion, fluid resuscitation stands as one of the cornerstones of effective management of sepsis. However the clinical context needs to be examined closely before starting resuscitation. An early onset of fluid resuscitation within 6 hours of sepsis onset seems beneficial. It also seems prudent to assess clinical signs of adequate tissue perfusion during resuscitation in addition to reaching predetermined hemodynamic targets, as microcirculatory dysfunction is increasingly being recognized as a major factor causing end organ dysfunction. The choice of fluid seems to be between balanced crystalloid solutions and albumin. The significantly higher cost of albumin and lack of measurable mortality benefit might restrict its use to resuscitations requiring large volume replacements. Normal saline and starch based solutions have clearly fallen out of favour due to their purported adverse effects. Dynamic indices of fluid responsiveness and echocardiographic modalities should be used to identify the subgroup of sepsis patients who would benefit the most from aggressive fluid resuscitation.

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