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Fluid management in sepsis: The potential beneficial effects of albumin☆

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ABSTRACT

Fluid administration is a key intervention in hemodynamic resuscitation. Timely expansion (or restoration) of plasma volume may prevent tissue hypoxia and help to preserve organ function. In septic shock in particular, delaying fluid resuscitation may be associated with mitochondrial dysfunction and may promote inflammation. Ideally, infused fluids should remain in the plasma for a prolonged period. Colloids remain in the intravascular space for longer periods than do crystalloids, although their hemodynamic effect is affected by the usual metabolism of colloid substances; leakage through the endothelium in conditions with increased permeability, such as sepsis; and/or external losses, such as with hemorrhage and burns. Albumin has pleiotropic physiological activities including antioxidant effects and positive effects on vessel wall integrity. Its administration facilitates achievement of a negative fluid balance in hypoalbuminemia and in conditions associated with edema. Fluid resuscitation with human albumin is less likely to cause nephrotoxicity than with artificial colloids, and albumin infusion has the potential to preserve renal function in critically ill patients. These properties may be of clinical relevance in circulatory shock, capillary leak, liver cirrhosis, and de-escalation after volume resuscitation. Sepsis is a candidate condition in which human albumin infusion to preserve renal function should be substantiated.

1. Impact of plasma volume expansion on microvascular perfusion

Circulatory failure or shock is associated with a high risk of death and characterized by hemodynamic alterations that result in impaired tissue perfusion [1,2]. Fluid resuscitation is one of the most frequent interventions used at the bedside to improve tissue perfusion, especially in septic shock. In experimental models of sepsis, generous fluid administration is associated with improved survival [3,4]. Fluids should also be given in a timely fashion. Compared to early administration, delay in fluid administration resulted in more severe microcirculatory alterations [5], an increase in expression of proinflammatory molecules and excessive mitochondrial dysfunction [6]. Importantly, excessive fluid administration should be avoided because a positive fluid balance is associated with poor outcome [7,8]. In an observational study in more than 9000 septic patients, the amount of fluid given in the first few hours of resuscitation followed a U-shaped curve, with an optimal amount comprised between 15 and 45 mL/kg; mortality rates more than doubled with higher and lower amounts of fluid [9]. Fluids should, therefore, be given generously in the early phases but restricted at later stages, with, if possible, achievement of a negative fluid balance [10,11].

There is still intense debate as to which is the best solution for fluid resuscitation, even after inclusion of thousands of patients in large-scale randomized trials [12–14]. Differences in fluid composition can impact the magnitude and the duration of hemodynamic effects, including at the microcirculatory level. Indeed, recently, we have begun to focus more on microcirculatory alterations [15], which are key determinants of tissue perfusion and also of capillary leak [16,17]. Several studies have shown that the severity of these alterations is associated with outcome [18], and we have begun to evaluate the impact of fluid resuscitation on microvascular perfusion and capillary leakage in patients with sepsis.

1.1. The effects of fluids: basic principles

Fluids distribute not only in the intravascular compartment, the desired effect being to increase cardiac output, but also in the extravascular and intracellular compartments. The distribution between compartments is principally determined not only by the electrolyte content and oncotic properties of infused fluids but also by the degree of microvascular permeability.

The equilibrium between intravascular and interstitial compartments is regulated by the endothelium, which is impermeable to large molecules, such as albumin and other proteins, but can be crossed freely by water and electrolytes (Fig. 1). Active transfer of albumin

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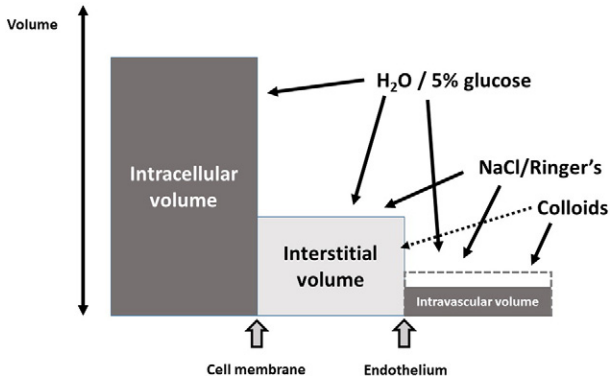

Fig. 1. Schematic distribution of fluids in the intravascular, extravascular, and intracellular compartments. Water and electrolytes cross compartments freely. Isotonic solutions, such as Ringer's lactate, have little movement across cellular membranes and distribute in the vascular and interstitial spaces. The endothelium is impermeable to large molecules, such as colloids, which thus increase intravascular oncotic pressure and promote diffusion of water from the other compartments to the intravascular space. In conditions where permeability is increased, colloids may also distribute in the interstitial space (dotted arrow).

and other proteins occurs at the endothelial level but the oncotic gradient between the intravascular and extracellular spaces always remains positive because the concentration of oncotic substances is always higher in the plasma than in the interstitium. This effect helps maintain an effective intravascular volume and limits development of interstitial edema.

Of note, the permeability barrier is not solely guaranteed by endothelial cells but also by the glycocalyx. The glycocalyx is a layer of a few microns at the surface of endothelial cells and is composed of glycosaminoglycans that also contain antioxidant and anticoagulant molecules. However, the glycocalyx does not contain albumin, in part due to the negative charges of glycosaminoglycans and albumin, which thus tend to repel each other [19]. As a result, albumin tends to accumulate at the outer layer of the glycocalyx, generating a second oncotic gradient that helps to limit fluid leakage [20,21]. When the glycocalyx and/or endothelium are damaged or dysfunctional as in sepsis, vascular permeability is increased, allowing leakage of fluids but also of large molecules (including albumin) into the interstitium. Importantly, the negative charges of albumin and the glycocalyx also decrease, limiting somewhat the formation of the albumin layer at the outer glycocalyx [19]. The oncotic gradient may thus be minimized but is never reversed, as active recapture of interstitial proteins occurs, even in sepsis. Nevertheless, this increase in permeability may alter the plasma expansion properties of fluids.

The equilibrium between interstitial and intracellular compartments is driven by osmotic forces at the level of the cellular membrane. These osmotic forces are generated by electrolyte channels and transporters and remain tightly regulated, even in sepsis.

1.2. Plasma-expanding effects of fluids

Oncotic and osmotic gradients explain the different plasma-expanding properties of intravenous solutions in normal conditions. Isotonic solutions, such as normal saline or plasmalyte, and near isotonic solutions, such as Ringer's lactate and Ringer's acetate, distribute in the vascular and interstitial space with little movement of water across cellular membranes [22] (Fig. 1). These solutions have a plasma-expanding capacity that is lower than the infused volume. Colloid solutions have plasma-expanding capabilities greater than just the effect of the infused volume [23]. Indeed, their administration increases intravascular oncotic pressure, promoting diffusion of water from the other compartments into the intravascular space [24,25] (Fig. 1). This effect was nicely demonstrated by Margarson and Soni [26], who showed that administration of 200 mL of 20% albumin was immediately followed by a decrease in the hematocrit corresponding to the dilutional effect induced by adding 200 mL to the plasma, and then a further decrease, twice as large, over the next few minutes, peaking at 60 minutes and remaining stable for 240 minutes. The extent and duration of the hemodynamic effect depend on the ability of the colloid molecules to remain inside the intravascular space, a condition that is affected by the metabolism of these substances as well as the degree of leakage through the endothelium [25]. External losses of plasma proteins can also occur in other conditions, such as bleeding, burns, or nephrotic syndrome, but this is beyond the scope of this review.

1.3. Is the plasma-expanding capacity of albumin affected in conditions of increased endothelial permeability?

Administration of albumin does not decrease capillary leak [27], and part of the albumin will escape into the interstitial fluid. One may thus be concerned that albumin may be relatively ineffective in conditions associated with significant capillary leak. In a model of experimental sepsis associated with increased permeability, the expanding capacity of albumin remained 3 times higher than that of crystalloid, as in normal conditions [28]. Interestingly, Dubois et al [29] demonstrated that the administration of albumin was associated with significantly increased albumin levels in patients with septic shock, indicating that the albumin remained, at least in part, in the plasma. Similar results were observed in the ALBIOS trial [14].

In several large randomized trials in sepsis, the plasma-expanding capacity of colloids was less than in normal conditions [12,30]. In the SAFE trial, the amount of fluid was only 30% higher in the crystalloid than in the albumin group [12], and the amounts of fluid administered were similar in the 2 groups in the ALBIOS trial [14]. The total amount of fluid administered was also approximately 30% higher in the crystalloid than in the hydroxyethyl starch (HES) groups in several large trials [13,30,31]. These trials indicate that the expanding capacity of colloids is indeed decreased in sepsis.

1.4. Duration of the plasma-expanding capacity of the various solutions

In addition to the immediate change in plasma volume, the duration of the plasma expansion effect should also be considered. In patients undergoing cholecystectomy, the duration of plasma expansion was only 2 hours for gelatin and 4 hours for HES [32]. In experimental conditions, plasma expansion persisted at 6 hours but was reduced by 30% [33]. Similarly, in patients with septic shock, Margarson and Soni [26] reported that, although albumin disappeared from plasma more rapidly than in normal conditions, at 6 hours its level was still only 20% lower in septic patients than in healthy control subjects [26].

1.5. Impact of fluids on microvascular perfusion

Sepsis-associated microcirculatory alterations are characterized by heterogeneity of perfusion, with nonperfused capillaries in close vicinity to adequately perfused capillaries [15,18,34,35]. Several studies have demonstrated that fluids can improve microvascular perfusion, increasing the proportion of perfused capillaries and decreasing perfusion heterogeneity [36,37]. Of note, these microcirculatory effects are quite independent from any systemic effects. Interestingly, the earlier the fluid administration, the greater the effect on microcirculatory alterations [36], although large amounts of fluid may not be needed. In 1 study evaluating the effects of repeated fluid boluses, only the first bolus was associated with an improvement in microvascular perfusion [37].

The impact of the type of fluid on the microcirculation is debated. In experimental conditions, colloids and especially albumin had a more