

## Commentary

# Pro/con clinical debate: Hydroxyethylstarches should be avoided in septic patients

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### Abstract

There are few issues in critical care medicine that have a less clearly defined standard of care than the intravenous fluid choice for resuscitation. Natural colloids (such as albumin) became popular during the Second World War when there was a need to develop a portable, easily stored, blood substitute. Early successes led to widespread use and a multibillion dollar industry. It is not surprising given the large demand, high costs and potential adverse effects of natural colloids that synthetic colloids have emerged. In the present article, two groups of clinical investigators remind us of the controversies surrounding the use of synthetic colloids.

**Keywords** fluid resuscitation, hydroxyethylstarches, intensive care unit, sepsis

### The scenario

A septic patient is in your intensive care unit and you are concerned that he is behind on his intravascular volume. For a variety of reasons you have decided you would like to give

him intravenous colloids. The only colloid available in your intensive care unit is hydroxyethylstarch.

### Pro: Yes, hydroxyethylstarches should be avoided in septic patients

Frédérique Schortgen and Laurent Brochard

Capillary leakage during sepsis is a reason for recommending the use of macromolecules that could preserve the colloid osmotic pressure (COP). The high cost of albumin has facilitated the widespread use of hydroxyethylstarches (HES). Outcome studies on sepsis are scarce, and the reasons why we should use HES remain speculative or based on short-term physiological data. The reason why we should avoid HES is much better documented. We will briefly describe how uncertain are the clinical benefits of these products and, by contrast, how strong is the evidence for numerous adverse effects.

Both crystalloids and colloids have a similar ability to achieve sufficient volume loading when the volume administered takes into account the capacity of the solution to remain in the intravascular space [1]. To achieve an equivalent plasma volume expansion, a fourfold greater volume of crystalloid may be needed in comparison with 5% albumin [1].

Maintaining COP by administration of HES could, in theory, reduce pulmonary oedema. One study including septic patients found a higher incidence of pulmonary oedema after crystalloids than after HES [2]. Most clinical results have

been disappointing, however, and a meta-analysis showed that pulmonary oedema occurrence is similar with colloids or crystalloids [3]. Indeed, in the context of a free course of macromolecules across a damaged alveolocapillary membrane, the Starling equation indicates that colloidal forces can no longer stop fluid shift.

An attractive, although unproven, pharmacological effect of HES comes from experimental studies suggesting that HES could improve microcirculation [4]. Clinical studies were again disappointing. Boldt and colleagues found a better intramucosal pH in patients receiving HES in comparison with albumin [5], but two recent studies in septic hypovolaemic patients showed that HES did not improve splanchnic circulation whereas gelatins did [6,7].

The case for adverse events secondary to administration of HES is much stronger and concerns coagulation disorders, acute renal failure, liver failure and pruritis [8–12]. Initially shown in a situation of ischaemia reperfusion (i.e. renal transplant recipients) [8], the nephrotoxicity of hydroxyethylstarch has been demonstrated in a randomised study during severe sepsis [9]. In comparison with gelatins, HES 200 kDa/0.6 induced a twofold higher incidence of acute renal failure.

The adverse effects of HES may depend on the molecular weight and the degree of substitution (proportion of hydroxyethyl groups on glucose molecules) [13]. The conflicting results coming from coagulation studies cast doubts whether an optimal combination for these two parameters has yet been found. Comparing HES 200 kDa/0.5 and 130 kDa/0.4, Jamnicki and colleagues found the same disturbances in *in vitro* coagulation tests [14]. A recent meta-analysis in cardiac surgical patients showed that postoperative bleeding was more frequent with HES, whatever the molecular weight, than with albumin [11]. Concerning acute renal failure, no comparative study supports the hypothesis that the newer compounds are safer. In a prospective randomised study including 150 postoperative patients with sepsis, a 50% increase in the serum creatinine was found at day 3 in the hydroxyethylstarch 200 kDa/0.5 group against only a 6% increase with albumin [15]. This difference was not significant, but this result again suggests that doing no harm should be our primary goal.

If the only colloids available are HES, the actual equipoise regarding efficacy means that we choose crystalloids to avoid adverse effects on organ function.

## Con: No, hydroxyethylstarches should not be avoided in septic patients

Ellen Burnham and Greg S Martin

Fluid exchange across the capillary endothelium obeys Starling's Law  $\{V = K_f[(P_C - P_i) - \sigma(\pi_C - \pi_i)]\}$ , which describes the forces governing fluid flux across a semipermeable membrane, such as the human vasculature [16]. Hydrostatic pressure and COP ( $\pi$ ) are the primary determinants of fluid flux in this system. When these forces are in balance, homeostasis between the intravascular and extravascular fluid compartments is maintained. The difference in hydrostatic pressure ( $P_{\text{capillaries}} - P_{\text{interstitium}}$ ) pushes fluid out of the vasculature, while the difference in COP ( $\pi_{\text{capillaries}} - \pi_{\text{interstitium}}$ ) draws fluid into the vasculature. The relative effect of oncotic pressure is modulated by the reflection coefficient ( $\sigma$ ), describing the integrity of the capillary wall in preventing translocation of proteins.

Colloids were developed as a durable alternative to crystalloids and blood products for patients requiring fluid resuscitation. Colloids exist in two general forms: natural and synthetic. In practical terms, this translates into albumin versus starches, gelatins, dextrans or combination solutions. Because of cost differentials, conflicting evidence and the underemphasis of COP in shock states, the solution of choice for resuscitating patients is controversial. The utilisation of a crystalloid solution in volume resuscitation, especially in situations where patients are hypoproteinemic, such as sepsis, may promote extravasation of volume out of

the vascular space and into the interstitium, where it is of little help in rectifying hypotension [1].

Physiologically, the use of resuscitative fluid containing osmotically active molecules of low molecular weight that are biodegradable with a moderate half-life would be ideal in septic patients, who have greater capillary permeability and, frequently, a low COP. HES are such agents. HES solutions contain molecules with a wide range of molecular weights and have an effect on intravascular volume lasting about 24 hours. In the intravascular compartment, HES are progressively hydrolysed into smaller fractions that are ultimately excreted by the kidneys [4].

Colloidal agents are more efficacious at restoring plasma volume compared with crystalloids, per unit of fluid given [1,17]. Furthermore, HES continue to provide volume expansion even in states of capillary permeability [18]. Investigators have demonstrated that, in hypovolaemic shock, resuscitation with starches or albumin results in a lower incidence of pulmonary oedema, compared with crystalloids [2]. Additionally, maintenance of COP may prevent complications of critical illness, including refractory acidosis [19], acute respiratory distress syndrome, prolonged mechanical ventilation and mortality associated with crystalloid resuscitation [20].

Apart from being pure volume expanders, HES have specific pharmacologic properties that may be beneficial in sepsis, such as lowering the circulating levels of adhesion molecules [21], and thus potentially reducing endothelial activation and damage. In septic patients, endogenous vasopressor production is decreased in patients receiving HES compared with other colloids [22]. Additionally, HES may exert useful effects on the microvascular coagulation cascade of these patients by elevating levels of protein C and protein S [23].

### Pro's response

Frédérique Schortgen and Laurent Brochard

In the absence of abnormally high hydrostatic pressure, low COP does not promote lung fluid accumulation [24]. Whereas a low COP may induce soft tissue oedema, several effective mechanisms protect against alveolar flooding. Low COP is rather a marker of severity for capillary leakage and of the amount of volume needed before acute respiratory distress syndrome onset. The ability of plasma expanders to

The use of HES as a resuscitative fluid in this patient with septic shock makes sound physiologic sense, particularly if COP is already reduced. Experimental data have demonstrated the efficacy of HES in the restoration of intravascular volume, and the unique pharmacologic properties of HES may provide additional benefit. Finally, prevention of the sequelae from sepsis could neutralise any acquisition cost associated with colloids.

reverse microvascular damages is not limited to starches, or even to colloids. Similar beneficial effects have been shown using hypertonic crystalloids [25]. One might not forget that the best way to reverse low COP and microvascular damages in sepsis remains early and adequate anti-infectious treatment.

### Con's response

Ellen Burnham and Greg S Martin

For improving outcomes in critically ill patients with severe sepsis there is an absence of evidence regarding intravenous solutions. Colloids have physiologic advantages over crystalloids, but suffer from higher acquisition costs. In light of recent evidence specifically regarding HES, advocating their use in patients with severe sepsis is problematic. Although HES may be the economic colloids of choice, we must focus our prescribing choices on patient-centred

outcomes. Association does not indicate causation and, until clinical trials evaluating appropriate clinical outcomes are performed, we will continue to deliver imprecise critical care. Intensivists should prescribe intravenous therapy based upon patient-specific factors, recognising that newer starches might obviate the associated risks, which are also absent with natural colloids.

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