Review

Pro/con debate: Should synthetic colloids be used in patients with septic shock?

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Abstract

You have recently heard reports that synthetic colloids may be associated with renal failure and other morbidities in certain populations of critically ill patients. You have been asked by the hospital chief of staff whether there should be a suspension of the use of synthetic colloids until further information is available. You need to make a decision.

Statement for debate

'Until further data are available, synthetic colloids should not be used in critically ill patients with sepsis.'

Introduction

Colloid solutions are commonly used to replenish or maintain intravascular volume status in a variety of clinical settings. Human albumin is a natural and relatively safe colloid [1] but its high cost has driven a search for safe synthetic alternatives. Three types of synthetic colloids are currently used worldwide: (a) hydroxyethyl starches (HESs), (b) gelatins, and (c) dextrans.

Hydroxyethyl starches

HESs are modified natural polymers of amylopectin. HES solutions are distinguished by (a) their molecular weight (MW), (b) their molar substitution ratio, and (c) their C2/C6 substitution ratio. These characteristics determine the rate of metabolism of the HES molecules, which in turn affects both the half-life and the side effects of the solution.

The average MW of the HES molecules in the solution (measured in kilodaltons) is inversely correlated with colloidal activity because HES solutions are supplied in weight-based concentrations (usually 6% or 10%). Low-MW solutions contain more molecules of HES for a given concentration and thus have a higher oncotic pressure, but they have a shorter half-life *in vivo* because they are more quickly broken down by serum amylase to 50-kDa molecules that can be excreted in the urine. Solutions are typically divided into three weight categories: high MW (approximately 450 kDa) (for example, Hespan®), medium MW (200 to 260 kDa) (for example, HemoHES® and Pentaspan®), and low MW (70 to 130 kDa) (for example, Voluven®).

To slow metabolism by amylase, HES molecules have hydroxyethyl radical groups substituted onto individual glucose units. The degree of hydroxyethyl substitution is expressed by the molar substitution ratio, which is simply a ratio of the number of substituted glucose molecules to the total number of glucose molecules. Highly substituted HES solutions have a ratio of 0.6 to 0.7 and are metabolized slowly. Less substituted HES solutions have a ratio of 0.4 to 0.5 and are metabolized quickly. Finally, the point of attachment of the hydroxyethyl group is also important. Hydroxyethyl groups attached at the C2 position on the glucose ring slow metabolism more than those attached at the C6 or C3 position. Thus, a high C2/C6 ratio (>8) slows metabolism more than a low C2/C6 ratio (<8).

Gelatins

Gelatins are polypeptides derived from bovine collagen. Modern gelatin preparations are chemically modified in various ways to reduce viscosity while maintaining their oncotic effect. Gelatins are smaller molecules than HESs (approximately 35 kDa) and therefore are more rapidly broken down and eliminated. However, there is no published dose limitation for gelatins as there are for HES and dextrans [2].

ARF = acute renal failure; HES = hydroxyethyl starch; MW = molecular weight; VISEP = Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis.

Dextrans

Dextrans are a polysaccharide mixture derived from the bacterium *Leuconostoc mesenteroides*, typically used in solutions of either 40- or 70-kDa molecules. Dextrans have a high water-binding capacity and are very effective for reducing blood viscosity [3].

Pro: There is no justification for using synthetic colloids in patients with septic shock

Investigators have long known about the potential risks of synthetic colloids, including renal failure, coagulopathy, anaphylactoid reactions, reticuloendothelial dysfunction, hepatic dysfunction, and severe pruritus [4]. As described in the section above, the synthetic colloids represent a group of products with different properties, and studies of one product may not be representative of the group as a whole. However, numerous investigators have concluded that synthetic colloids are safe (or superior to albumin or crystalloids) on the basis of small studies using surrogate, biochemical, or hemodynamic endpoints and often very brief follow-up [5-15].

On the other hand, two large prospective randomized trials with lengthy follow-up and hard endpoints have now shown that HES is associated with a significantly increased risk of acute renal failure (ARF), coagulopathy, and possibly mortality in patients with septic shock. Schortgen and colleagues [16] randomly assigned 129 patients to receive either HES 200/0.62 or 3% gelatin for intravascular volume expansion and followed them for 34 days. They found that the HES group had a significantly higher incidence of ARF (defined as a twofold increase in creatinine, 42% versus 23%; $P = 0.028$), and in a multivariate analysis, the use of HES was associated with an odds ratio of 2.57 for ARF. The investigators were careful to respect the dose limitations recommended by the manufacturer, giving an average of 14 mL/kg (range of 10 to 26) on day 1 and less than 20 mL/kg for the next 3 days. HES was not administered after the fourth day.

In the more recent VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) study, Brunkhorst and colleagues [17] randomly assigned 537 patients with severe sepsis or septic shock to receive either HES 200/0.5 or Ringer lactate as part of a 96-hour protocol to maintain a central venous pressure of greater than 8 mm Hg, a central venous O_2 saturation of greater than 70%, and a mean arterial pressure of greater than 70 mm Hg. Again, patients in the HES group had a higher incidence of renal failure requiring dialysis (31.0% versus 18.8%; $P = 0.001$). The protocol specified a daily limit of 20 mL/kg of HES [17] but this was exceeded in approximately 35% of patients in the HES group, mostly on day 1. When the investigators looked only at the patients who had received less than 20 mL/kg of study fluid daily, there was still a significantly higher incidence of renal failure requiring dialysis. The investigators also identified a clear dose effect of HES. Higher cumulative doses of HES were correlated with both a higher 90-day mortality rate and a higher incidence of renal failure requiring dialysis. This dose effect was not seen in the Ringer lactate group.

While other investigators did not detect a significant increase in the incidence of ARF or mortality, this may have been due to their shorter follow-up (that is, less than 5 days). Data from the latter two studies suggest that differences in the incidence of ARF and mortality may not become apparent until 5 and 30 days, respectively [18].

HES administration is also associated with a deterioration in renal function in patients undergoing cardiovascular surgery [9,19] and kidney donation [20]. The mechanism of renal injury from HES is unclear, but possible explanations include osmotic injury [20], ischemic injury from hyperviscosity [21], or injury related to significant HES uptake by the reticuloendothelial system in the kidney [22,23].

Some have argued that the increased incidence of renal failure can be attributed to either the long half-life or crystalloid solvent of some HES solutions, suggesting that newer low-MW HES [24] or 'balanced' solvents [25] might be safe. However, studies of low-MW HES in cardiac surgery patients show evidence of impaired postoperative glomerular filtration rate [9] and elevated serum markers of renal function [19], and patients who received low-MW HES during abdominal surgery showed greater elevations in α1-microglobulin levels than those who received medium-MW HES [10]. Furthermore, a study comparing a 'balanced' and 'unbalanced' HES solution in patients undergoing abdominal surgery demonstrated no difference, with no renal dysfunction or coagulopathy in either group [6]. Thus, the advantages of low-MW HES or 'balanced' solvents are certainly not proven [6].

There are no large, published, randomized controlled trials of dextrans or gelatins in patients with sepsis, but the data from other clinical settings are not encouraging [26]. In patients undergoing cardiac surgery, gelatin shows an effect similar to HES on markers of renal dysfunction [19] and is associated with higher rates of ARF than crystalloid [27] and HES [28]. Studies of dextrans also show an association with renal failure [29,30]. There is no evidence to suggest that gelatins and dextrans are associated with a lower risk of renal dysfunction than crystalloid.

High- and medium-MW HES preparations cause coagulopathy primarily by reducing levels of factor VIII and von Willebrand factor and by interfering with platelet function [24,31]. In the VISEP study, patients in the HES group developed worse coagulopathy, as demonstrated by a higher Sequential Organ Failure Assessment (SOFA) coagulation score, and a greater need for transfusion of packed red blood cells compared with the crystalloid group (median of 6 units versus 4 units) [17]. Low-MW HES preparations do not appear to show the same effects on factor VIII and von Willebrand factor [24]. Again, fewer studies have examined

the bleeding risks associated with dextrans and gelatins but both appear to be associated with impaired coagulation and increased bleeding risk [2,32].

Synthetic colloids are effective volume expanders but their use in septic shock cannot be justified in light of the adverse effects. Even 'safe' doses are associated with significant morbidity; newer generation colloids appear to cause adverse reactions similar to the older colloids, and 'balanced' solvent solutions are unproven. Until a large randomized trial with hard endpoints and adequate follow-up demonstrates that one of these solutions is safe and effective, we must conclude that the only safe dose for synthetic colloids is zero.

Con: Synthetic colloids should be used but not abused

A policy to ban synthetic colloids in the treatment of critically ill patients with septic shock is certainly not supported by the current data. The argument revolves largely around two randomized controlled trials [16,17], both of which used a clinically unlikely regimen: in the HES arm, the starch appeared to be administered as the sole intravenous fluid for many patients (up to a daily maximum level). In the real-life situation, colloids are usually used as intermittent boluses in conjunction with concomitantly administered crystalloid fluids. A study arm in which colloid was the predominant intravenous fluid provided is not generalizable to usual clinical practice. Furthermore, the dose of colloid administered in the VISEP study was far higher than that used clinically, with a median dose of 2.4 L (and a maximum dose of 13 L!) on the first day of therapy [33]. In clinical practice, it is uncommon to administer near the maximal dosage. A further confounding issue is the fact that, in the VISEP study, 26.6% of patients in the crystalloid arm received some form of colloid, either the study HES or another colloid product [17].

Studies of HES used as an adjunct to crystalloid fluid therapy, to facilitate reaching hemodynamic targets, have shown benefit. A study of septic and trauma patients, in which HES was given with crystalloid (administered in a volume ratio of approximately 1:3.5), showed clear benefits in terms of hemodynamic improvement and oxygen delivery [5]. Long-term renal function was not assessed in this study. The absence of an association of HES with renal failure in usual clinical practice was demonstrated in a large European observational study of over 3,000 patients [34]. One third of these patients (1,075 patients) received HES with a median dose of 555 mL per day (median total dose of 1,000 mL in 2 days). Although the incidence of renal failure was higher in this group, there was no association between HES and dialysis in a multivariable model. Patients who received HES were also older, were more likely to be surgical patients, and had a higher severity of illness.

Others have reported a lack of association between the use of HES and renal failure in clinical use, in which HES is combined with crystalloid therapy [35]. In a study of 62 patients undergoing abdominal aortic surgery, a reduced incidence of renal injury was noted in patients randomly assigned to received one of two HES products (HES 200/0.62 or HES 130/0.4) compared with gelatin [36]. All patients received concomitant infusions of normal saline, amounting to approximately twice the volume of colloid. Only one patient in each HES group required renal replacement therapy (4.8%) compared with three in the gelatin group (15%). A recent study evaluated renal effects in 33 patients with pre-existing mild renal dysfunction who were randomly assigned to receive 6% HES (130/0.4) or gelatin (in addition to at least 1.5 L/day crystalloid) for perioperative volume replacement for abdominal aortic surgery [37]. Five patients (15%) in the HES arm developed severe renal impairment that was not different from the gelatin-treated arm, although this does not exclude the possibility that both the HES and gelatin caused some renal dysfunction.

Furthermore, a comprehensive ban on all synthetic colloids would overlook the important differences between older and newer synthetic colloids. Neither of the above-mentioned randomized trials studied one of the new low-MW HES solutions. No study has demonstrated a link between low-MW HES solutions and an increased need for dialysis, and while high-MW HES solutions are clearly associated with coagulopathy, the low-MW HES solutions are not [24,38,39]. A study of renal function in cadaveric renal transplant recipients compared donors resuscitated with a 200/0.6 hetastarch and those resuscitated with a new-generation 130/0.4 product in a retrospective matched paired study [40]. The group that received the 130/0.4 hetastarch had a significantly reduced incidence of delayed graft failure (22% versus 33%). Furthermore, animal studies suggest that HES solutions containing a more physiologically 'balanced' solvent (for example, Ringer lactate) might cause less renal impairment and coagulopathy than one containing normal or hypertonic saline [25]. One study in patients undergoing abdominal surgery found that a 'balanced' HES solution produced a smaller acid-base disturbance than an 'unbalanced' solution [6].

The results of Schortgen and colleagues [16] and Brunkhorst and colleagues [17] should warn clinicians not to exceed the recommended daily dose of synthetic colloid and to use a balanced approach to fluid resuscitation that includes crystalloid solutions. They should not serve as the basis of a comprehensive ban on synthetic colloids in any patient population.

Conclusions

We cannot support a comprehensive ban on synthetic colloids on the basis of only two trials [16,17] but these two trials represent the best evidence currently available (in terms of randomization, endpoints, and follow-up). Since both suggested that the use of medium-MW HES solutions is associated with harm in patients with septic shock, these

solutions should not be used routinely for this indication. Synthetic colloids are potent volume expanders but they may be harmful and are probably unnecessary for most patients.

The current data should alert clinicians to potential concerns with the administration of high volumes of HES, particularly the medium-MW HES solutions favoured in many parts of the world. Synthetic colloids definitely should not be used as the sole source of intravenous fluid in critically ill patients, and ordering physicians should be aware of the potential adverse effects, including allergic reactions, renal dysfunction, and coagulopathy. Maximum dosages for these products should be made known to all users and strictly monitored whenever possible. Newer-generation low-MW HES solutions or balanced crystalloid solvents may be safer but this has never been conclusively demonstrated.

Competing interests

The authors declare that they have no competing interests.

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