Commentary

Pro/con clinical debate: Do colloids have advantages over crystalloids in paediatric sepsis?

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Abstract

Despite decades of resuscitating patients with intravenous fluids in intensive care units, it is somewhat surprising that very little consensus exists regarding the type of fluid physicians should choose. Factors that influence decisions are often local culture or politics, hospital administrators, history (i.e. 'I've always done it this way') and budgets, as opposed to strong evidence. In the present issue of *Critical Care* we are presented with compelling arguments for and against the administration of colloids (as opposed to crystalloids) in paediatric sepsis. One point that appears to be clear is that the ideal choice of intravenous fluid goes beyond the simple haemodynamic effect. As such, in the future, clinicians will need to consider other factors when making their decision. In addition, large-scale quality randomised studies are desperately needed to guide clinicians.

Keywords crystalloids, colloids, sepsis

The scenario

A 5-year-old girl is admitted to the paediatric intensive care unit with meningococcal sepsis. She is hypotensive and requires fluid resuscitation. You are trying to decide which type of fluid to choose (crystalloids or natural colloids [albumin]).

Pro: Yes, colloids have advantages over crystalloids in paediatric sepsis

Puran Khandelwal and Desmond Bohn

Meningococcal sepsis is a fulminant form of Gram-negative sepsis associated with profound shock. The release of endotoxins (lipopolysaccharides) from the bacterial cell wall initiates a cascade of events resulting in the release of cytokines (IL-1, IL-6, tumour necrosis factor alpha), which in turn causes endothelial cell injury with capillary leak and loss of vasomotor tone [1].

Plasma proteins, including albumin, and water from the intravascular compartment leak into the interstitium, resulting in hypovolaemia and hypotension [2]. Fleck and colleagues [3] showed that there is an increase of 300% in the albumin escape rate from the vascular to the interstitial space, associated with hypoalbuminaemia, in septic patients. Hypoalbuminaemia is also associated with increased mortality in critically ill patients [4].

Holland and colleagues [5] found albumin fragments of approximately 45 kDa, 25 kDa, and <20 kDa in the urine of children with meningococcal sepsis and associated purpura. They suggested that exogenous or endogenous proteases, or both, may be released in severe meningococcal sepsis and, in association with an inadequate antiprotease response, result in albumin degradation. This may be a contributory factor to the rapid shock, hypocalcaemia, and rash seen in meningococcal sepsis.

IL = interleukin.

Early fluid resuscitation in paediatric septic shock improves outcome [6], but there is ongoing controversy over the type of fluid to be used [7–10]. Two published meta-analyses, by the Cochrane group, of randomised trials that compared crystalloids with colloids or crystalloids with albumin attracted considerable attention [8,10]. They concluded that the use of both colloids was associated with increased mortality in critically ill patients. Most of the trials were small studies that were insufficiently powered to address mortality. There were only six paediatric studies analysed, five of which were in neonates, one was in burns in children. None were in patients with sepsis. Despite the concerns raised by the publication of these papers, early aggressive fluid resuscitation with albumin, specialist advice and transfer to a paediatric intensive care unit for patients with meningococcal sepsis in the UK has reduced mortality from 50% in severely ill patients to less than 5% [11].

Understanding of the distribution of colloids and crystalloids in the different fluid compartments is fundamental to fluid resuscitation. Ernest and colleagues [12] studied the distribution of normal saline and 5% albumin in septic patients. Normal saline increases the extracellular fluid compartment 1:1 ratio with only 20% remaining with the intravascular space, whereas 5% albumin increases extracellular fluid more than twice and is distributed equally intravascularly and interstitially. Volume for volume, two to three times as much crystalloid needs to be used as colloid for the same haemodynamic effect.

Dengue shock syndrome has a similar pathophysiology of increased capillary leak to meningococcal sepsis. A recent randomised, controlled trial showed greater improvements in haematocrit, pulse pressure, and cardiac index among children with Dengue shock syndrome who received colloid compared with a crystalloid [13]. Metabolic acidosis with high lactate is a common finding during presentation of these children. The use of a large volume of and rapid infusion of normal saline will produce hyperchloraemic acidosis and has the potential to worsen acidosis [14,15]. This dilutional acidosis may impair myocardial function and make inotropes less effective.

Con: No, colloids do not have advantages over crystalloids in paediatric sepsis

Joseph A Carcillo and Neal J Thomas

It is well accepted that fluid resuscitation in paediatric septic shock is critical. Carcillo and colleagues [6] reported a decade ago that paediatric patients in septic shock had reduced mortality with rapid fluid administration, initially with crystalloids but with one-third of the total fluid given as colloid. The advantages of vigorous fluid resuscitation have also been demonstrated in septic animals [16]. However, the debate continues concerning the optimum initial fluid to utilise. After reviewing the available literature concerning primary fluid options, we present facts that refute the statement 'colloids have advantages over crystalloids in paediatric sepsis'.

To defend the statement that colloids are superior, one must prove their benefit in the clinical setting described: paediatric septic shock. Because of the lack of literature available in this patient subset, a broad base of literature review must cover adult patients in a wide variety of clinical situations, including sepsis. Multiple systemic reviews have been published recently. Choi and colleagues [7] reviewed 17 studies encompassing 814 patients that compared isotonic crystalloids with colloids for fluid resuscitation. The authors concluded that there was no advantage in terms of outcome or length of stay with colloids. In an attempt to determine whether a larger amount of colloid or crystalloid remained in the intravascular compartment, Ernest and colleagues [12] randomised septic adult patients to receive either normal saline or 5% albumin. They concluded that there was no advantage in the haemodynamics of patients who received albumin.

To further this argument, we present the case that colloids may actually be harmful to patients. Castro and colleagues [17] raised concerns about the adverse rheologic effects with colloid infusions, citing that hydroxyethyl starch increases blood viscosity and has the potential to impair microvascular flow during sepsis. Additionally, a recent meta-analysis of 30 randomised, controlled trials including 1149 patients concluded that, in addition to no evidence suggesting that mortality was improved with albumin administration, there was a strong suggestion that albumin may actually increase mortality [10]. Another meta-analysis [8] revealed an increased absolute risk of mortality of 4% in patients resuscitated with colloids. These studies have prompted the Food and Drug Administration to issue a warning: "… the FDA urges treating physicians to exercise discretion in use of albumin …" (http://www.fda.gov/cber/ltr/albumin.htm).

In this age of cost containment, attention must also be paid to the utilisation of health care dollars. The cost of initially administering colloid solutions can be tremendous. Crystalloid solutions can generally be acquired at $1/500 ml, in comparison with hydroxyethyl starch ($45/500 ml) or 5% albumin ($76/100 ml) [18]. It is easy to see that the utilisation of crystalloid solutions for initial resuscitative measures can result in significant cost savings.

Based on the lack of evidence documenting improved outcome, potential deleterious effects, and substantial economic strain on the health care system, we agree with the recent review by Alderson and colleagues [19]. They concluded "it is hard to see how their (colloids) continued use in these patient types (critically ill) can be justified outside the context of randomized controlled trials".

Pro's response

Puran Khandelwal and Desmond Bohn

Carcillo and Thomas noted that colloid was used when crystalloids failed to improve perfusion or blood pressure, or for correcting coagulation. Ernest and colleagues [12] used 5% albumin or normal saline to achieve a similar haemodynamic target (pulmonary artery occlusion pressure = 15 mmHg), and found albumin more efficient (122% versus 21%).

Meta-analyses are limited in their ability to examine the effects of crystalloids or colloids for fluid resuscitation. The heterogeneity in the study population, selection criteria and different outcome measures included in the meta-analysis can influence the result. It is interesting to note, however, that Wilkes and Navickis [9] have shown in their meta-analysis that albumin has no effect on mortality.

An appropriately powered and clinically relevant randomised, controlled clinical trial is needed to resolve these issues.

Con's response

Joseph A Carcillo and Neal J Thomas

Khandelwal and Bohn present some excellent arguments to support their view that colloids should be administered as resuscitative fluids in this child. However, the prime question concerning whether colloids will improve outcome in this type of patient remains unanswered.

We agree that the literature is limited with regards to paediatric septic shock, but this should not cause us to ignore the data that has been generated by our adult colleagues and to recommend a therapy that may in fact be harmful. Instead, it should invite us to answer the question in our distinct population of children with septic shock by a well-planned, randomised, controlled trial.

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