Review Article

A Concise Review of Colloids for Fluid Resuscitation in Severe Sepsis and Septic Shock

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Abstract

Objective: To provide an evidence-based review and clinical summary of colloid use for fluid resuscitation in severe sepsis and septic shock.

Data Sources: Literature retrieval was accessed through MEDLINE (1980—January 2013), Cochrane Library, and International Pharmaceutical Abstracts (1980—January 2013) using the terms sepsis, severe sepsis, shock, resuscitation, colloid, albumin, and hydroxyethyl starch. In addition, reference citations from identified publications were reviewed.

Study Selection And Data Extraction: All English-language publications identified from the data sources were evaluated. Publications deemed most relevant to the topic were included in the review.

Data Synthesis: Severe sepsis and septic shock are syndromes with high rates of morbidity and mortality. Intravascular volume deficiency due to vasodilation and increased capillary permeability and leakage leads to hypoperfusion and organ failure. Early aggressive volume resuscitation with either crystalloid or colloid fluids is essential to restore intravascular volume and improve or maintain organ perfusion. Aggressive fluid therapy, however, may lead to tissue edema and worsening organ dysfunction. Natural and synthetic colloids are high molecular weight solutions that have significantly longer intravascular half-lives and provide greater increases in central oncotic pressure when compared to crystalloid solutions. This allows for lower infused fluid volumes comparatively when titrated to the same central venous pressure endpoints. Adverse effects associated with the use of colloid solutions include allergic reactions, anaphylactic reactions, acute renal impairment, pruritus, and coagulopathies.

Conclusions: Providers should be proactive in identifying patients who may benefit from the use of natural colloid solutions in the presence of severe sepsis/septic shock. Synthetic colloids are effective volume expanders; however the risks of acute renal impairment presently outweigh the benefits of their use.

Keywords: Sepsis; severe sepsis; shock; colloid; hydroxyethyl starch; resuscitation

Introduction

Sepsis is a syndrome clinically defined as the body's systemic inflammatory response to infection [1]. Severe sepsis and septic shock are the end results of the body's maladaptive and inappropriate response to pathogenic microbes, resulting in organ dysfunction, tissue hypoperfusion and dysoxia, and ultimately death [1,2]. Mortality rates with severe sepsis and septic shock range from 25% to over 75%, with higher rates of death in patients with multi-organ dysfunction and prolonged hypoperfusion [1,3]. Severe sepsis and septic shock account for greater than 17% of all in-hospital deaths and is the eleventh leading cause of death in the United States [4,5].

Tissue dysoxia, defined as limited metabolic energy production due to a lack of oxygen supply or utilization, clinically manifests as shock [6]. In the presence of sepsis, this form of shock is typically distributive in nature, resulting in a relative hypovolemia due to systemic vascular dilation and increased capillary permeability and leakage [7]. This can lead to a decrease in oxygen uptake and utilization and result in organ failure, lactic acidosis, and tissue necrosis [7]. Oxygen uptake into the tissue (VO2) can be affected by alterations in cardiac output (CO), oxygen carrying capacity (i.e.: anemia), and oxyhemoglobin saturation (i.e.: hypoxemia). Thus, these entities have become primary targets in the early goal-directed treatment of severe sepsis and septic shock [8].

Early, aggressive volume resuscitation in septic patients with low cardiac output has been shown to modulate the inflammatory process and reduce the need for vasopressor therapy [9]. Crystalloid therapy with fluids such as 0.9% sodium chloride (saline) solution or Ringer's lactate solution have long been regarded as standard of care in severe sepsis/septic shock. The composition of these solutions, however, may be problematic in the septic patient. Saline solution has 154 mmol/L concentrations of sodium and chloride ions; when bolused aggressively in early sepsis it may lead to a hyperchloremic metabolic acidosis [10]. Ringer's lactate solution contains 4mmol/L concentration of potassium ion as well as 28mmol/L of sodium lactate. Though this may seem minimal, aggressive boluses in the presence

of acute kidney injury may lead to hyperkalemia and lactic acidosis [11]. The low molecular weights of crystalloid solutions and relatively short intravascular half-life (30 to 60 minutes) present another area of concern. Fluid requirements for resuscitation with crystalloids may be up to four times the volume required when compared to colloid solutions [12]. Evidence has shown that total fluid gain (positive fluid balance) during ICU stay is correlated with increased hospital mortality [13]. In addition, the employment of conservative fluid strategies have been shown to improve lung function, increase days without ventilator support, and reduce ICU length of stay [14].

The purpose of this article is to provide a concise review of the literature available for both natural and synthetic colloid fluids concerning their application in severe sepsis and septic shock.

Data sources

A literature review was performed via MEDLINE (1980 – January 2013), Cochrane Library, and International Pharmaceutical Abstracts (1980—January 2013) using the terms sepsis, severe sepsis, shock, resuscitation, colloid, albumin, and hydroxyethyl starch. We reviewed English-language publications, including randomized controlled trials, meta-analyses, case reports, and literature reviews. We selected publications deemed most relevant to the topic of colloids in severe sepsis/septic shock.

Natural colloids

Colloid fluids are defined as high molecular weight substances that largely remain in the intravascular compartment, generating an increase in oncotic pressure [15]. Human packed red blood cells and albumin are the two naturally occurring colloids used in severe sepsis and septic shock.

Albumin

Albumin is a natural protein colloid derived from human plasma, typically available as a solution in isotonic saline [11]. Unlike synthetic colloids, albumin has not been associated with an increased risk of renal failure or effects on coagulation. The acquisition cost of albumin is typically higher than that of synthetic colloids or crystalloids, and like other human blood products, albumin does carry a risk of allergic reaction or transmitted infection. Though some data regarding the comparative safety and efficacy of albumin exist, the role of albumin compared to that of crystalloids or synthetic colloids is not certain.

The Saline versus Albumin Fluid Resuscitation (SAFE) study compared fluid resuscitation with 4% albumin or normal saline in 6997 critically-ill patients admitted to medical or surgical ICUs [16]. Fluid resuscitation with albumin did not result in a significant reduction in 28-day mortality as compared to saline (20.9% mortality vs. 21.1%; RR 0.99; 95% CI: 0.91-1.09; p=0.87). In addition, patients in the albumin group received significantly more red blood cell transfusions.

However, a prospectively-defined subgroup analysis of the SAFE study included 1,218 patients diagnosed with septic shock. Analysis of the 919 patients (75.5%) with complete baseline data demonstrated an adjusted odds ratio for death for albumin versus saline of 0.71 (95% CI: 0.52-0.97; p=0.03), suggesting that resuscitation with albumin may provide some mortality advantage in the subgroup

of septic patients [17]. In the initial days of therapy in the SAFE study, septic patients randomized to albumin received significantly less resuscitation fluid volume and had higher central venous pressures and lower heart rates, suggesting a greater intravascular volume expansion with albumin resuscitation. Despite the apparent improvement in surrogate endpoints, these differences did not result in improved outcomes such as incidence of new single or multi-organ failure, ICU length of stay, hospital length of stay, duration of mechanical ventilation, or incidence of renal replacement therapy.

A recent meta-analysis of data from seventeen studies, including data from the SAFE study, compared fluid resuscitation with albumin to other fluid options (including starches, gelatins, and crystalloids) in patients with sepsis [18]. Resuscitation with dilute albumin solutions (4-5%) was associated with reduced mortality (OR 0.76; 95% CI: 0.61-0.95, p=0.02) compared to resuscitation with other fluids. The use of more concentrated albumin solutions (20-25%) had no significant effect on mortality (OR 1.08; p=0.73).

Hypoalbuminemia is common among critically-ill patients, though it is uncertain whether hypoalbuminemia directly contributes to poor outcomes or if it is simply a marker of other pathologic co-morbid processes (i.e. malnutrition or inflammation). It is clear that hypoalbuminemia is associated with poor clinical outcomes in critically ill patients, including increased mortality and increased ICU length of stay [19]. A meta-analysis of cohort studies and clinical trials investigated the connection between hypoalbuminemia and critical illness, concluding that each 1 g/dL decline in serum albumin increased the risk of mortality by 137%, and increased morbidity, length of stay, and resource utilization [20]. This meta-analysis suggests that complication rates may be reduced with albumin administration to target a goal of greater than 3 g/dL.

In a study of 133 patients with severe sepsis due to secondary peritonitis, a daily minimum of 25g of albumin for at least 3 days reduced 28-day mortality in hypoalbuminemic patients with a baseline albumin of less than 2 g/dL (45% vs. 76%; RR, 0.27; 95% CI, 0.09–0.83; *p* = 0.03) [21]. The mortality reduction was not sustained in patients with a baseline albumin concentration of greater than 2 g/dL. Thus, supplementing albumin may restore normal physiologic function and offer benefit in sepsis, though albumin's exact mechanism of mortality benefit in sepsis is still being explored.

Ongoing clinical trials are investigating the potential benefits of albumin administration in septic shock when targeting serum albumin levels greater than 30 mg/L (NCT00707122), and the effect of daily albumin supplements on morbidity and mortality in septic shock (NCT00327704). The PRECISE study plans to evaluate the protective effect of albumin in sepsis by measuring pro and anti-inflammatory cytokine and chemokine levels, including thrombin and protein C (NCT00819416) [22].

Synthetic colloids

Artificial, or synthetic, colloids are cheaper alternatives to human albumin as resuscitative fluids. Experimental studies have shown synthetic colloids to be more effective in restoring and maintaining circulating volume when compared to crystalloid solutions [23]. Synthetic colloids, however, have also been directly linked to renal failure and coagulopathies. Gelatins, dextrans, and hydroxyl ethyl

starches are the synthetic colloids currently available.

Gelatins and dextrans

Gelatins are the most cost effective choice of synthetic colloid, and unlike dextrans and starches, do not have an infusion ceiling. There are three newer generation (modified) gelatin solutions currently used worldwide. Succinylated or modified fluid gelatins, urea-cross-linked gelatins and oxypolygelatins [15]. Volume expansion with gelatins ranges from 70 to 80%, however its duration of action is typically shorter when compared to albumin and starches [15].

In a large observational study of 1383 surgical ICU patients Schabinski and colleagues investigated the effects of predominantly HES-based and non-HES-based fluid therapy on renal function. The two cohort groups were comprised of HES 6% 130/0.4 and 4% gelatin solution. Gelatin was found to be an independent dose-related risk factor for acute renal failure (adjusted OR, 1.99; CI, 1.05-3.79) [24]. In contrast, a nonrandomized trial of 3124 cardiac surgical patients suggested preservation of renal function with use of gelatin compared to HES 200/0.5 [25].

Schortgen and colleges measured the frequency of ARF during ICU stay in 129 patients with severe sepsis randomized to HES 200/0.5 or 3% gelatin. They reported ARF developed in 27 (42%) of the HES group and 15 (23%) in the gelatin group (OR, 2.32; 95% CI, 1.02-5.34; P=0.028), indicating a lower incidence of ARF with the use of gelatin compared to high molecular weight HES. In a prospective sequential comparison of HES 130/0.4, gelatin 4% and crystalloids in 346 severe sepsis patients AKI occurred in 47% of patients in the crystalloid group, 70% of the patients in the HES group (P=0.002) and 68% of patients in the gelatin group (P=0.025). The authors concluded that in severe sepsis patients a change in resuscitative fluid from HES or gelatin to crystalloids was associated with a significantly lower incidence of AKI and renal replacement therapy [26]. In a later study by the same investigators, the use of gelatin was found to be an independent risk factor for renal replacement therapy [27].

Dextrans are rarely used today for volume expansion due in part to adverse effects and the development of new rapidly degradable HES products [28]. The two most widely used commercially available products are a 6% solution known as dextran-40 and a 10% solution known as dextran-70. Both of these products lead to greater volume expansion when compared the HES or albumin [15]. Dextrans like other synthetic colloids have been associated with effects on coagulation, renal impairment and anaphylactic reactions.

It is hypothesized that dextran solutions precipitate renal impairment through intraluminal hyperviscosity [29]. In a cohort study including 1,013 ICU patients needing resuscitation for shock Schortgen and colleagues assessed the risks associated with hyperoncotic colloids. They found that artificial hyperoncotic colloids (dextrans and/or hydroxyethyl starches) were associated with a significant increased risk of renal adverse events [30]

Antithrombotic effects of dextrans include platelet dysfunction, accelerated conversion of fibrinogen to fibrin, facilitation of clot fibrinolysis and increased bleeding time [31,32]. Severe anaphylactic reactions may also occur with the use of dextrans, occurring at double the rate when compared to natural colloids [15,32]

Hydroxyethyl starches

Hydroxyethyl starches are synthetic colloids derived from hydrolyzed amylopectin. They have been available for more than 40 years and remain the preferred volume replacement agents over albumin in European countries due to favorable pharmacological properties and low comparative cost [33,34].

Generations of hydroxyethyl starches are primarily differentiated from one another based on average molecular weight (MW) and molar substitution (MS). The MW of the substance refers to the average weight of the starch molecules, which over time are hydrolyzed by serum amylases into particles small enough to be renally cleared (45-60 kiloDaltons). First-generation HES tend to have higher MW (range 450-670 kDa) while later generations of HES were developed with lower mean MW (130-200 kDa). The MS, or degree of hydroxyethylation of the starch, partially determines the rate at which the starch can be hydrolyzed into smaller molecules. Hydroxyethylation of the starch confers a steric hindrance that prevents hydrolysis of the molecule by serum amylase, increasing its half-life. Early generation HES had higher rates of hydroxyethylation (MS= 0.7-0.75, the hetastarches) while later generation HES employ lower ratios of substitution (MS= 0.4-0.5, the pentastarches and tetrastarches). Because the osmotic effect of HES is determined primarily by the number of osmotic particles and not their size, the later generation HES with low MW and low MS provide a greater number of osmotic particles yielding a greater osmotic effect. Additionally, the low MS allows more rapid metabolism of the molecules, generating particles with MW below the renal clearance threshold [34].

The VISEP (Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis) study compared intensive insulin therapy with conventional insulin therapy and pentastarch (HES 10%) to modified Ringer's lactate in patients with severe sepsis. The trial was suspended after the first planned interim analysis because of increased rates of renal failure and death at 90 days in the group receiving pentastarch, however no difference was found in 28-day mortality. Comparisons between single study groups suggested that the risk of acute renal failure in the intensive-therapy group was higher among patients who received pentastarch than among those who received Ringer's lactate (odds ratio, 2.9; 95% confidence interval [CI], 1.51 to 468). The need for renal-replacement therapy and the rate of death at 90 days were significantly correlated with the cumulative dose of HES (p<0.001 and p=0.001, respectively) but not with the dose of Ringer's lactate (p=0.11 and p=0.31, respectively). The authors concluded that fluid resuscitation with 10% pentastarch (HES 200/0.5) is considered harmful in patients with severe sepsis. At recommended doses, it can cause renal impairment, and at high does, it impairs long-term survival [35].

HES 130/0.4 (tetrastarch) is a third generation HES developed to provide better pharmacokinetic and safety profiles. When compared to albumin, tetrastarch may be a more cost effective alternative with a comparable degree of volume expansion [15]. The osmotic pressure obtained with tetrastarch is equivalent to that of albumin and results in 100% volume expansion. Tetrastarch has also been shown to improve volume expansion when compared to non-albumin colloids [15]. Two recent randomized control trials compared tetrastarch to

crystalloid solutions in severe sepsis/shock.

The first trial compared HES 130/0.4 to Ringer's acetate in 798 patients with severe sepsis. The primary outcome was death or dependence on dialysis 90 days after randomization. Eighty-seven patients (22%) in the HES group and 65 patients (16%) in the Ringers acetate group (RR, 1.35; 95% CI, 1.01-1.80: p=0.04) were treated with renal replacement therapy. Death at 90 days occurred in 51% of the HES group compared to 43% in the Ringer's acetate group (RR, 1.17; 95% CI, 1.01 to 1.36; P=0.030). The authors concluded that patients with severe sepsis who receive fluid resuscitation with HES 130/0.4 were more likely to require RRT and had a higher risk of death at 90 days [36].

The second and more recent clinical trial compared HES 130/0.4 to saline for fluid resuscitation in 3315 intensive care patients. The primary outcome was all-cause mortality with the incidence of acute kidney injury within 90 days as a secondary outcome. The investigators found that RRT was used in 7% of the HES group versus 5.8% in the saline group (RR 1.21; 95% CI, 1.00-1.45; P=0.04. Ninety-day mortality in the HES patients was 18% versus 17% of the saline group (RR, 1.06; 95% CI, 0.96 to 1.18; P=0.26). Renal injury occurred more frequently in the saline group (P=0.005). The authors concluded that there was no difference in 90-day mortality between the groups, but patients resuscitated with HES were treated with RRT more often [37].

A randomized control trial conducted by Dubin et al. compared saline to tetrastarch and their effects on microcirculation in septic patients. The primary outcome was microcirculatory parameters after 24 hours using sublingual capillary microvascular flow index (MFI) as a measurement. They found that after 24 hours of resuscitation the capillary MFI was higher in the HES 130/0.4 group (95% CI (-1.5- -0.4) P=0.0032). The authors concluded that in patients with sepsis induced hypoperfusion, resuscitation with HES 130/0.4 may allow for better recruitment of the microcirculation compared with saline [38].

Adverse effects

Potential side effects due to administration of HES include pruritus, renal dysfunction, and coagulopathies. Use of earlier generation HES solutions are associated with tissue depositions that cause intense pruritus unrelieved by steroids or antihistamines [34].

Renal impairment in the critically ill is associated with a 60% mortality rate [39]. It is generally thought that lower molecular weight HES solutions carry lower risks of renal failure and coagulopathies when compared to high molecular weight HES and dextrans [40]. The VISEP study, which used a pentastarch solution, was halted early due to increased incidences of acute kidney injury [35]. The CRYSTMAS study, however, compared a tetrastarch solution to saline and found no adverse effect on kidney function [41]. Though the results are inconsistent across studies, the incidence of adverse renal outcomes has been extrapolated to all HES solutions.

Hemostatic effects of HES solutions included prolonged clot formation time and decreased clot strength. A meta-analysis of postoperative blood loss in 18 randomized clinical trials of hydroxyethyl starch versus albumin for fluid management in adult cardiopulmonary bypass surgery (n=970) demonstrated

hydroxyethyl starch increased postoperative blood loss by 33.3% of a pooled SD (95% confidence interval, 18.2%–48.3%; $P < .001$). HES administration also increased risk of reoperation for bleeding and transfusion of red blood cells, fresh-frozen plasma and platelets. The effect was similar for use of hetastarch (HES 450/0.7) or pentastarch (200/0.5). There were no differences in fluid balance, ventilator time, intensive care unit stay, or mortality [42]. In contrast to hetastarch and pentastarch, Westphal and colleagues conducted a literature review on HES and found tetrastarches to have minimal effects on coagulation [34].

Summary

The optimal fluid choice for volume resuscitation in severe sepsis and septic shock remains unclear. Though crystalloids are the least costly of all fluid options, the volume of fluid needed poses risks to patients. Based on the currently available literature, human albumin appears the most promising colloid; however, its cost limits its broad use in sepsis. Currently, its use in septic patients is only recommended to minimize fluid volumes when substantial amounts of crystalloids are required. Dextrans and gelatins have limited data supporting their use in severe sepsis and septic shock, though they may have a place in therapy in other patient populations. Tetrastarches are the most promising of the synthetic colloid solutions used in the critically-ill. Unfortunately, currently available data is conflicting, leading to a more conservative approach to their use. The most recent update to the Surviving Sepsis campaign recommends against the use of synthetic colloids for fluid resuscitation, thus, their use in severe sepsis and septic shock should be avoided at this time.

It is difficult to determine the direction future studies should take in regards to synthetic colloids. Early aggressive therapy with one type of fluid clearly favors crystalloids and albumin. Perhaps a study evaluating combination therapy with both crystalloid and synthetic colloid would prove beneficial. Ultimately, the ideal resuscitative approach would minimize volume requirements and reduce the incidence of organ failure or injury at a cost that allows for broad implementation.

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