Colloids and the Microcirculation
Huaiwu He, PhD,* Dawei Liu, PhD,* and Can Ince, PhD†‡

Colloid solutions have been advocated for use in treating hypovolemia due to their expected effect on improving intravascular retention compared with crystalloid solutions. Because the ultimate desired effect of fluid resuscitation is the improvement of microcirculatory perfusion and tissue oxygenation, it is of interest to study the effects of colloids and crystalloids at the level of microcirculation under conditions of shock and fluid resuscitation, and to explore the potential benefits of using colloids in terms of recruiting the microcirculation under conditions of hypovolemia. This article reviews the physiochemical properties of the various types of colloid solutions (eg, gelatin, dextrans, hydroxyethyl starches, and albumin) and the effects that they have under various conditions of hypovolemia in experimental and clinical scenarios. (Anesth Analg 2018;126:1747–54)

The composition and amount of fluid solutions used to treat hypovolemia in critical illness and anesthesia continue to be controversial, with debates continuing about various aspects of colloids versus crystalloids, balanced versus nonbalanced, and the use of different bicarbonate precursors (eg, lactate and acetate). In addition, flow-based intravenous management of fluid administration, also referred to as goal-directed administration of fluid resuscitation at the macrocirculation level, has been suggested as a standard of care for clinical practice.3,4 However, more and more evidence is emerging that fluid resuscitation, while being effective in improving the macrocirculation, does not always result in a parallel improvement in the perfusion of the microcirculation.3,4 Hence, the evaluation of global circulation on its own seems to be insufficient in guiding fluid resuscitation if the ultimate aim is, as is generally agreed on, to promote microcirculatory flow perfusion.5 That is why monitoring the microcirculation is relevant to guide fluid therapy, especially under conditions of circulatory shock.5,6

Investigation of the impact of colloid and crystalloids on tissue perfusion requires the study of the impact of the various types of the solution on microcirculatory hemodynamics under different conditions of shock and hypovolemia. The introduction of hand-held vital microscopy has allowed these issues to be investigated at the bedside by measuring the effect of such solutions on the microcirculation, measured mostly sublingually. Hand-held vital microscopy has been used to evaluate the microcirculatory response to many other interventions in critically ill patients, such as blood transfusions, vasoactive agents, and anti-inflammatory drugs. Moreover, the basic status of the microcirculation can also provide information about the potential response of microcirculation before the implementation of interventions, as well as allow evaluation of the efficacy of medical interventions.7

In this article, we review the literature on the use of colloids both experimentally and clinically in terms of their effects on microcirculatory hemodynamics, asking whether there is experimental evidence for the expected theoretical advantage of using colloids over crystalloids under conditions of hypovolemia and shock at the level of the microcirculation.

CHARACTERISTICS OF COLLOID SOLUTIONS

Colloid fluids are crystalloid electrolyte solutions containing a high molecular weight substance that retains the solution in the intravascular compartment due to colloid osmotic pressure. Crystalloids can freely pass through the vascular barrier either directly through the endothelial barrier and/or through the fenestration and pores comprising the intercellular junctions of the blood vessels in the microcirculation of the various organs. Colloids, however, would be expected to be better retained in the intravascular space. Indeed, many studies have shown that colloids have a stronger intravascular volume expansion effect and have a greater intravascular persistence when compared to crystalloids in fluid resuscitation and even under septic conditions when the vascular barrier is compromised.8,9,10 There are different types of colloid solutions; however, these may have different physiophysical properties due to their different physicochemical properties. Commonly, colloid solutions in clinical practice include gelatin, dextran, hydroxyethyl starch (HES), and human albumin.

Gelatins, which are derived mainly from bovine collagen, were the first fully artificial colloid solutions used for the treatment of shock in World War I.11 The advantages of gelatin include a significant oncotic effect, lower cost than albumin and other synthetic colloids, no limit of infusion, and rapid excretion by the kidney. The disadvantages of gelatins included anaphylactoid reactions and circulatory disturbance with increased plasma renin activity. Dextrans are derived from sucrose by Leuconostoc bacteria and have been used as a substitute for plasma for fluid resuscitation along with gelatin at the end of World War II.12 Currently, dextrans are rarely used for fluid resuscitation in clinical practice due
to several adverse effects (eg, impairment of coagulation and renal function and anaphylactic reactions). However, dextrans continue to be used to improve local microcirculatory flow by decreasing blood viscosity and impeding erythrocyte aggregation and antiplatelet activity in microsurgery. HES is derived from the starch of either potatoes or maize. Sethi et al reported that both potato- and maize-derived HES had the same effect on blood coagulation and pulmonary, renal, and hepatic function when used to prime the cardiopulmonary bypass circuit in patients undergoing coronary artery bypass grafting.

Tetraslarch, which was introduced as the third-generation production of HES to correct some of the side effects of previous-generation HES solutions, has a degree of substitution of 0.4 or 0.42 (HES 130/0.4 and 130/0.42) with fewer side effects, and is the most advanced HES solution to date and the most frequently used for perioperative settings. Recent studies, however, have suggested that HES may have deleterious effects on kidney function, requiring renal replacement therapies, however, have suggested that HES may have deleterious effects on kidney function, requiring renal replacement therapy in critically ill patients.

Human serum albumin is derived by blood fractionation from human plasma and was used to resuscitate burn patients in the Pearl Harbor attack in 1941. A 4%–5% human albumin solution is dissolved in isotonic saline, and a 20%–25% solution is dissolved in hypotonic saline. Albumin replacement compared to crystalloid resuscitation did not improve the rate of survival at 28 and 90 days in the septic patients. Frenette et al found that albumin administration was associated with a dose-dependent risk of acute kidney injury in cardiac surgery. In this context, it should be underscored that all fluid solution, irrespective of composition, can harm the kidney if the fluid is not administered to a proper target chosen according to the pathophysiological principle. The characteristics of the different types of colloids solution and normal saline are summarized in the Table.

### POTENTIAL EFFECT OF FLUID RESUSCITATION ON MICROCIRCULATORY HEMODYNAMICS

Because the improvement of microcirculatory perfusion is the ultimate aim of fluid resuscitation, investigations directed at understanding microcirculatory hemodynamics are essential to understand the functional impact of colloid solutions on the microcirculation. Microcirculatory blood flow transport of oxygen (O2)-carrying red blood cells (RBCs) to the capillaries and the passive diffusion of O2 leaving the RBCs together determine the O2 extraction capacity of the tissue cells to meet the needs of the respiring mitochondria to achieve adenosine triphosphate production by oxidative phosphorylation. Essentially, there are 2 main determinants of O2 transport to tissue at the microcirculatory level: (1) convection, which is reflected by the blood flow transport of O2-carrying RBCs to the capillaries; and (2) diffusion, which is reflected by the density of capillaries filled with flowing O2-carrying RBCs.

We previously described how microcirculatory hemodynamic measurements can be used to guide and optimize fluid administration in terms of convection and diffusion. The beneficial effects of fluid infusion on microcirculatory hemodynamics include increased microcirculatory convection flow and expanded microvascular volume to recruit the microcirculation. In doing so, care must be taken to avoid the detrimental effect of fluid infusion on microcirculatory hemodynamics. These include impairment of microcirculatory diffusion due to hemodilution and tissue edema caused by capillary leakage from high capillary pressure, both of which can reduce the functional capillary density (FCD) of microcirculation. The potential benefit and detrimental effects of fluid resuscitation are summarized in the Figure.

The current conventionally applied emphasis when choosing targets for administering fluids is on increasing global blood flow with the presumed aim of improving microcirculatory flow. However, whether this actually occurs or not in clinical practice is unknown. Maintaining mainstream flow is certainly essential for the resuscitation of microcirculatory blood flow, but only if it results in increased FCD and microcirculatory RBC convection and O2 diffusion because these processes are key components for ensuring adequate O2 transport to tissue cells. However, too much fluid administration, as can occur during excessive hemodilution and tissue edema, can decrease FCD, making it more difficult for O2 to reach the cells by diffusion. Therefore, both microcirculatory convection and diffusion function should be considered to determine an optimal volume status in fluid resuscitation.

### IMPACT OF COLLOID SOLUTIONS ON MICROCIRCULATION IN HEMORRHAGIC SHOCK

Treating hypovolemia and avoiding excessive hemodilution and tissue edema characterize the hemodynamic challenge in the fluid resuscitation of hemorrhagic shock. That is why

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<th>Table. Summary of the Properties of Commonly Used Colloid Solutions Compared With Normal Saline</th>
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**Abbreviations:** Cl−, chloride; HES, hydroxyethyl starch; K+, potassium; MW, molecular weight; NaCl, sodium chloride; Na+, sodium; N/A, not applicable

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**Figure:**

- **Microcirculatory Hemodynamics**
  - Convection
  - Diffusion
  - Hemodynamic measurements can be used to guide and optimize fluid administration.

**Table:**

- **Summary of Commonly Used Colloid Solutions Compared With Normal Saline**
  - Gelatin
    - Succinylated: 295 mOsm/kg, 27–33 mm Hg, 4–8 h, Na+ 154, Cl− 100–120
    - Nonsuccinylated: 274 mOsm/kg
  - Dextran
    - Dextran 40: 308 mOsm/kg, 168 mm Hg, N/A
    - Dextran 70: 308 mOsm/kg, 59 mm Hg, N/A
  - HES
    - HES 200/0.5 pentastarch: 308 mOsm/kg, 59–82 mm Hg, 8 h
    - HES 134/0.4 tetraslarch: 308 mOsm/kg, 36 mm Hg, 4 h
    - HES 134/0.42 tetraslarch: 277–296 mOsm/kg, 60 mm Hg, 6 h
  - Albumin
    - 4%–5%: 290 mOsm/kg, 20–29 mm Hg, 16 h
    - 20%–25%: 200 mOsm/kg, 100–120 mm Hg, 24 h
  - Normal saline: 308 mOsm/kg, 0 NaCl, 0 mm Hg, 0 h

**Abbreviations:** Cl−, chloride; HES, hydroxyethyl starch; K+, potassium; MW, molecular weight; NaCl, sodium chloride; Na+, sodium; N/A, not applicable
Colloids and the Microcirculation

Colloids present several advantages concerning microcirculation recruitment during therapeutic fluid resuscitation for treatment of hemorrhagic shock. These include a better microvascular volume expansion with low capillary leakage combined with a higher viscosity, leading to a better recruitment of capillaries when compared to crystalloids. A number of animal studies have found that colloid solutions perform better in microcirculation recruitment (ie, increased FCD) when compared to crystalloids in hemorrhagic shock models. A recent systematic review summarized 71 studies of fluid resuscitation for microcirculation in a hemorrhagic shock animal model. The authors found that 14 of 19 studies supported the idea that a high osmotic/oncotic property of the fluid solution is an important factor in achieving and restoring the microcirculatory flow, and that 10 of 12 studies supported the fact that increased fluid viscosity was superior to normal or reduced fluid viscosity in the restoration of microcirculation.

In addition, experimental studies have demonstrated that resuscitation with a hypertonic/hyperoncotic solution (hypertonic saline + HES or human albumin) could lead to a rapid recovery of microcirculatory parameters and reduce lung tissue damage and pulmonary edema in hemorrhagic shock. However, Vajda et al. found that hypertonic/hyperoncotic solution (7.2% saline + 10% HES) induces a considerable improvement of the microcirculatory flow heterogeneity in the small intestine. Makiko et al. showed that intravenous infusion of HES more effectively maintains the rabbit ear microcirculation, hemodynamics, and colloid oncotic pressure in a model of acute severe hemorrhagic shock than Ringer’s solution. Wu et al. however, recently found that intestinal microcirculation was restored only by a colloid solution (4% succinylated gelatin and 6% HES) when compared to normal saline in a rodent model of hemorrhagic shock.

Correction of blood viscosity is thought to play an important role in the restoration of the microcirculation in hemorrhagic shock. Studies have shown that blood viscosity is an independent regulator of microvascular blood flow. A low blood viscosity caused by severe hemodilution can result in microvascular flow maldistribution and impaired tissue oxygen delivery. Experimental studies have supported the idea that using colloid solutions to increase blood viscosity is beneficial for correcting microvascular flow maldistribution and recruiting perfused capillaries. Moreover, clinical studies have also found that the use of viscous fluids such as blood or colloids is an effective method of recruiting previously unfilled capillaries and increasing the FCD. On the other hand, a too-high viscosity can also increase the resistance of blood flow and impair microcirculatory flow in nonhemodilution conditions based on the physiological concept. Zimmerman et al. found that blood transfusion did not increase oxygen delivery when hematocrit was >60% with a too-high blood viscosity. A study found that an acute hemodilution (hematocrit was diluted from 57% to 30%) did not improve the impairment of sublingual microcirculatory flow and decreased the oxygen delivery in chronic polycythemia patients. Both positive and negative effects of blood viscosity on microcirculation and microcirculation should be considered in clinical practice based on the patients’ pathophysiological conditions. Here, we underscore that a high-viscosity fluid solution has potential benefit for the recruitment of microcirculation during hemodilution.

**IMPACT OF COLLOID SOLUTIONS ON MICROCIRCULATION IN SEPSIS**

Microcirculatory alterations play an important role in the complicated pathophysiological procedure of sepsis, and the typical alterations of microcirculation include abnormal heterogeneity and microcirculatory shunting. The potential mechanisms of impaired microcirculatory perfusion include increased blood viscosity, impaired RBC deformability, endothelium dysfunction, capillary leakage, leukocyte adhesion, and activation of coagulation. The effect of fluid resuscitation on microcirculation has become a hotspot in sepsis. There has been interest in the effects of colloids on microcirculation in models of sepsis. Klar et al. found that the isovolumic hemodilution effect of dextran 60 can restore the number of perfusion capillaries of pancreatic microcirculation. Hotz et al. found that using dextran could significantly increase capillary blood flow and perfused capillary percentage. Hoffmann et al. reported that HES preserved...
the FCD in comparison with saline and no resuscitation in a normotensive endotoxemia model. The study by Dubin et al\textsuperscript{42} on septic sheep showed that HES could improve sublingual and serosal intestinal microcirculation but with persistent poor perfusion in intestinal mucosal villi.

However, the use of colloid solutions for fluid resuscitation in sepsis remains controversial. Wafa et al\textsuperscript{43} found that different HES solutions did not perform better when compared to crystalloids in the microcirculation of the mesentery of colon ascendsent stent peritonitis-induced experimental sepsis in rats. A recent systematic review found that few animal model studies have investigated the microcirculatory effects of different types of fluid resuscitation for sepsis and septic shock.\textsuperscript{44} Sometimes, fluid resuscitation might not be effective in recruiting vulnerable microcirculatory beds because of impaired autoregulatory mechanisms in microcirculation, which may be different in hemorrhagic shock, in which there may be a relatively intact microcirculatory autoregulation function. Furthermore, there is a loss of hemodynamic coherence between macrocirculation and microcirculation in sepsis, and a single medical intervention (eg, fluid resuscitation/using pressor maintaining blood pressure) might be insufficient to recruit the microcirculation.\textsuperscript{45}

**IMPACT OF COLLOIDS ON MICROCIRCULATION IN GOAL-DIRECTED THERAPY STUDIES**

Conventional goal-directed fluid resuscitation therapy focuses on the restoration of global systemic hemodynamic variables and can be considered superior to the traditional, generalized algorithm-based approach to fluid administration. Use of the generalized algorithm-based approach to guide fluid infusion does not consider individual requirement at the level of macrocirculation, which masks the potential advantages of using colloid solutions when compared to the crystalloid solutions for fluid resuscitation. Interestingly, the advantages of colloid solutions in microcirculation have been shown in goal-directed therapy and experimental and clinical studies.\textsuperscript{46-50}

Hiltebrand et al\textsuperscript{46} found that goal-directed colloid administration (keeping the mixed venous \(O_2\) saturation at \(≥ 60\%\)) markedly increased microcirculatory blood flow in the small intestine and in intestinal tissue \(O_2\) tension after abdominal surgery. In contrast, goal-directed crystalloid and restricted crystalloid administration had no such effect. Kimberger et al\textsuperscript{47} reported that goal-directed colloid fluid therapy significantly increased microcirculatory blood flow and tissue \(O_2\) tension in the healthy and injured colon compared to goal-directed or restricted crystalloid fluid therapy.

Moreover, goal-directed therapy in clinical trials of the perioperative fluid therapy also demonstrated that the bolus colloid solutions could efficiently increase microcirculatory perfusion in fluid-responsive patients and have an improved outcome.\textsuperscript{48-50} A recent international statement on perioperative fluid therapy recommends “the use of a goal-directed fluid regimen containing colloid and balanced-salt solutions in major surgery” and “colloid use may be considered an approach to limiting total volumes, which may contribute to better outcomes.”\textsuperscript{51} Dubin et al\textsuperscript{52} found that fluid resuscitation with 6% HES 130/0.4 had a higher capillary microvascular flow index, percentage of perfused capillaries, and perfused capillary than normal saline to improve sublingual microcirculation in the septic patients. The authors also found that the group using colloid solutions to restore the targets of early goal-directed therapy (central venous pressure 8–12 mm Hg, mean arterial pressure \(≥ 65\) mm Hg, central venous oxygen saturation \(≥ 70\%\)) needed less than half of the fluid volume when compared to using crystalloid solutions.

It could be argued that clinical trials have not been able to demonstrate that early goal-directed therapy improves the outcome in septic shock patients.\textsuperscript{53,54} However, we feel that it needs to be emphasized that using hemodynamics at the macrocirculation level to guide fluid resuscitation, although better than the use of the generalized algorithm-based approach, may not in itself improve perfusion at the level of the microcirculation.\textsuperscript{7} Xu et al\textsuperscript{55} found, with equal success in outcome, that microcirculatory-targeted fluid resuscitation required a substantially lower amount of fluids to reach microcirculatory targets than the amount of fluids needed for correcting blood pressure in the hemorrhagic shock pig model (blood pressure–guided group with 955 mL versus sublingual partial pressure of carbon dioxide–guided group with 170 mL). This study elegantly showed that using different targets to guide fluid therapy could cause a large variation in the amount of the fluid volume used while not affecting the outcome. From this consideration, it is clear that studies are needed to investigate the potential benefit of colloid fluids based on microcirculatory goal-directed administration.

**COLOIDS AND TISSUE OXYGENATION/CELLULAR \(O_2\) UTILIZATION**

The final aim of the amplification of microcirculatory perfusion is to improve tissue oxygenation, and the final aim of increasing tissue oxygenation is to improve cellular \(O_2\) utilization to correct the cellular hypoxia according to the pathophysiological consideration. Hence, the effect of fluid solutions on tissue oxygenation and cellular \(O_2\) utilization is attractive during fluid resuscitation.

The autoregulation ability to maintain the tissue oxygenation differs in various tissue cells and organs during fluid therapy. A study reported that 3 different fluid volume regimens (low, medium, and high fluid volume groups) did not affect tissue \(O_2\) pressure in the jejunum and colon, but the high fluid volume group had a higher blood pressure, cardiac output, urine output, and subcutaneous tissue oxygenation in healthy pigs undergoing uncomplicated abdominal surgery.\textsuperscript{38} Moreover, the regulation of tissue oxygenation is also specific for different organ systems during progressive hemodilution, and the microvascular oxygenation pressure (\(\mu P_{O_2}\)) is always used to reflect the global and local redistribution of \(O_2\) delivery. Van Bommel et al\textsuperscript{37} reported that the renal \(\mu P_{O_2}\) started to decrease at a hematocrit of 38.5%, but intestinal \(\mu P_{O_2}\) decreased at a hematocrit of 17.4%, and a reduction of cardiac \(\mu P_{O_2}\) was observed at a hematocrit of 8.7% in the rat model of hemodilution.

Studies have found that using crystalloid solutions for volume replacement could reduce tissue oxygenation, while using colloid solutions could keep tissue oxygenation within the acute normovolemic hemodilution.\textsuperscript{56,59} Funk and Baldinger\textsuperscript{56} found that volume replacement with artificial
colloids yielded hemodynamic stability and adequate tissue \( \text{O}_2 \) supply, whereas administration of crystalloids alone could impair skeletal muscle tissue perfusion (perfused capillary density decreased by 62%) and \( \text{µP} \text{O}_2 \) (decreased from 19 to 8 mm Hg) in the awake hamster model of iso-volumic hemodilution. Konrad et al\textsuperscript{69} reported that a hematocrit of 15% statistically significantly impaired renal \( \text{µP} \text{O}_2 \) and renal function in the crystalloid group (using full electrolyte solution), while less tissue edema formation and an unimpaired renal \( \text{µP} \text{O}_2 \) occurred in the colloid group (using HES 6% 130/0.4) in the pig model of acute normovolemic hemodilution.

Furthermore, colloid solutions have shown a better performance in several animals in restoring tissue oxygenation during fluid resuscitation for different types of circulatory shock.\textsuperscript{60–62} Knotzer et al\textsuperscript{60} found that gelatin infusion significantly improved mucosal tissue \( \text{O}_2 \) tension of the porcine jejunum after severe hemorrhage when compared with lactated Ringer’s solution (mucosal \( \text{µP} \text{O}_2 \) 20 vs 13.8 mm Hg). Almac et al\textsuperscript{61} found that the HES 130/0.42 dissolved in acetate-balanced Ringer’s solution could restore renal blood flow back to 85% of the baseline level and most prominently improved renal microvascular oxygenation (from 24 to 50 mm Hg) when compared to normal saline and acetate-balanced Ringer’s solution in the rat model of hemorrhagic shock. Maier et al\textsuperscript{62} found that only an isotonic colloid solution (gelatin and HES) improved microvascular hemoglobin \( \text{O}_2 \) saturation when compared to a hypertonic colloid solution (HES + 7.2% saline) during hemorrhagic shock. Moreover, Wettstein et al\textsuperscript{63} reported that using highly viscous and oncotic colloid solutions with fewer RBCs could restore the FCD and resulted in a more homogeneous distribution of tissue oxygenation in the hemorrhagic shock model. The authors concluded that using highly viscous and oncotic solutions for fluid resuscitation might reduce the transfusion trigger of hemoglobin concentrations during hemorrhagic shock.

With the development of the blood substitute, hemoglobin-based \( \text{O}_2 \)-carrying solutions and perfluorocarbon-based \( \text{O}_2 \)-carrying solutions were created to solve transfusional blood availability problems and shortages and with the aim of further enhancing \( \text{O}_2 \) delivery. The viscosity and compatibility of other colloid solution play an important role in the microvascular oxygenation and perfusion when using \( \text{O}_2 \)-carrying solutions.\textsuperscript{64} Nolte et al\textsuperscript{65} reported that HES, gelatin, and human albumin are compatible with perfluorbenzene emulsion \( \text{O}_2 \)-carrying solution, but that dextran 60 was incompatible with perfluorbenzene emulsion and cause impaired capillary perfusion in the setting of acute normovolemic hemodilution.

The impairment of mitochondrial function has become a great challenge in the resuscitation of circulatory shock.\textsuperscript{66} The dysfunction of cellular \( \text{O}_2 \) utilization always occurs together with impaired microvascular oxygenation, but sometimes cellular \( \text{O}_2 \) utilization impairment could be independent of microcirculatory perfusion. Albuszies et al\textsuperscript{67} found that the restoration of macrocirculation allowed for the maintenance of gut and liver microvascular perfusion and increased capillary oxygenation after fluid resuscitation, but hepatic metabolic capacity was still impaired in a murine model of septic shock. Hence, impaired cellular \( \text{O}_2 \) utilization could be present independently of the improvement in microcirculatory perfusion during fluid resuscitation. Johannes et al\textsuperscript{68} found that redistribution of renal \( \text{µP} \text{O}_2 \) could be demonstrated when the renal blood flow and renal \( \text{O}_2 \) delivery have been restored during fluid resuscitation, and HES 130/0.4 had no influence on the renal \( \text{O}_2 \) consumption when compared to HES 200/0.5 or Ringer’s lactate. The response of cellular \( \text{O}_2 \) utilization to various types of fluid solution is required to further investigate in different clinical conditions.

**COLLOIDS AND MICROVASCULAR INFLAMMATION**

The uncontrolled inflammatory response involves the activation of cytokines, leukocytes, and cytokine storm, as well as the generation of reactive oxygen species (ROS), which together result in impairment of microcirculation. Moreover, ischemia reperfusion injury can further contribute to additional inflammation during fluid resuscitation.

Several studies have found that artifact colloid solutions might have specific anti-inflammatory properties in the context of fluid resuscitation after hemorrhagic shock by reducing leukocyte activation (stagnation, margination, and rolling) and leukocyte–endothelial interaction.\textsuperscript{69–72} Corso et al\textsuperscript{69} using intravital fluorescence microscopy found that dextran and hypertonic saline dextran attenuated leukocyte stagnation in liver sinusoids and leukocyte adherence in postischemic venules when compared to Ringer’s solution after hemorrhagic shock. Maier et al\textsuperscript{72} found that using gelatin serum protein solutions as a resuscitative fluid could reduce leukocyte adhesion. Chen et al\textsuperscript{73} also reported that fluid resuscitation with HES 130/0.4 after hemorrhagic shock ameliorated oxidative stress and the inflammatory response (lower tumor necrosis factor-\( \alpha \) and interleukin-6) in the liver, intestine, lungs, and brain compared with gelatins and HES 200/0.5. Moreover, Varga et al\textsuperscript{74} reported that HES provided a therapeutic advantage in this setting by exerting an inhibitory effect on the ischemia-reperfusion–induced local and systemic leukocyte reactions in postischemic periosteal microvascular dysfunction when compared with gelatin or dextran solutions.

In contrast, some studies have found that using artifact colloid solutions could increase inflammatory response. Wu et al\textsuperscript{75} recently found that although intestinal microcirculation was restored by only colloid solutions (4% succinylated gelatin and 6% HES) when compared to normal saline in a rodent model of hemorrhagic shock, reperfusion-induced renal ROS formation was significantly higher when synthetic colloids were used. The authors inferred that increased reperfusion-induced renal ROS formation might contribute to acute kidney injury when using synthetic colloids for fluid resuscitation. It should be noted when evaluating the literature that there are considerable differential effects between the different HES formulations. In this context, Hüter et al\textsuperscript{75} reported that 10% HES 200/0.5 had more of a proinflammatory effect compared with 6% HES 130/0.42 and caused more pronounced tubular damage than did 6% HES 130/0.42 and Ringer’s lactate in an isolated porcine renal perfusion model. In summary, the published literature supports the idea that artifact colloid solutions might have a positive effect on inflammation in the context of hemorrhagic shock resuscitation, although care should be taken on its effects on renal...
function. Such effects on kidney function may be averted if a more physiologically based target, such as the restoration of microcirculatory function, is chosen as an end point.

In animal models of sepsis, however, there is more controversy surrounding the effects of HES on inflammation. Schick et al. found that HES improved liver microcirculation but exhibited significantly increased proinflammatory cytokine levels in cecal ligation- and puncture-induced septic rodents. However, some other animal studies have found positive effects of HES on inflammatory processes in sepsis. On the other hand, it must be emphasized that all fluids probably cause inflammation. In fact, studies have also reported that Ringer’s lactate could activate neutrophils and cause an upregulation of inflammatory mediators in fluid resuscitation.

Moreover, based on the idea that inflammatory activation of HES could be controlled by the coadministration of anti-inflammatory drugs, Ergin et al. demonstrated in an endotoxin-induced septic model in the rat in which coadministration of N-acetylcysteine significantly improved renal oxygenation, O2 delivery, and O2 consumption and dampened the accumulation of neutrophil gelatinase-associated lipocalin or liver-type fatty acid-binding protein, hyaluronic acid, and nitric oxide in these septic kidneys. These studies suggest that future generations of fluids may benefit from the addition of anti-inflammatory compounds.

EFFECT OF ALBUMIN SOLUTIONS ON INFLAMMATION AND ENDOTHELIAL BARRIER

Recently, the potential benefit of albumin on inflammation and endothelial barrier function is attracting attention in fluid therapy literature. Albumin has several physiological advantages when used as a colloid during resuscitation, including antioxidant and anti-inflammatory properties, positive effects on vessel wall integrity, and ligand-biding abilities. Jacob et al. found that albumin was more effective in preventing fluid extravasation in the isolated heart model than crystalloid or artificial colloid, and that this effect was partly independent of colloid osmotic pressure and could possibly be caused by an interaction of albumin with the endothelial glyocalyx. Studies have also shown that the leakage of HES into the interstitium is greater for colloid than saline fluid loading after cardiac or hepatic surgery. The same team found that albumin supplementation abrogates the adverse effects of HES in the intestine, and that the underlying mechanism may occur via phosphorylation of Erk1/2 and Akt signal path. They inferred that albumin-containing HES solutions are superior to HES alone and may improve the suitability of HES in the clinic. Recently, Job et al. demonstrated that albumin and HES induced markedly different effects on glyocalyx mechanics and had notably different effects after glyocalyx degradation by hyaluronidase. On the other hand, several studies have shown that HES can attenuate microvascular barrier dysfunction, leading to tissue edema in septic shock with high capillary leakage. From these considerations, it is clear that there is much-needed insight into the relationship among glyocalyx function, vascular barrier integrity, inflammation, and their response to fluid resuscitation of different compositions and hemodynamic targets.

CONCLUSIONS

This article has discussed how colloid solutions not only can have a better performance on the macrocirculation but also have potential advantages for recruitment of the microcirculation, especially under conditions of hypovolemia caused by hemorrhagic shock and when administered in a goal-directed manner. Further studies are required to identify which precise goal needs to be targeted where possible microcirculatory goal-directed therapy for fluid resuscitation could improve the outcome of patients. In addition, the concept of coadministering other compounds such as anti-inflammatory drugs or even hemoglobin-based O2 carriers needs to be explored to develop a new generation of fluids to meet the challenges of perioperative and intensive care fluid management.

DISCLOSURES

Name: Huaiwu He, PhD.
Contribution: This author helped review the related literature, draft the manuscript, and read and approve the final manuscript.

Name: Dawei Liu, PhD.
Contribution: This author helped revise the text, contribute to the critical review of the manuscript, and read and approve the final manuscript.

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Contribution: This author helped review the related literature, revise the text, and read and approve the final manuscript.

This manuscript was handled by: Alexander Zarbock, MD.

REFERENCES


23. Doshi P. Data too important to share: do those who control the data control the message? BMJ. 2016;2:352.


ENARRATIVE REVIEW ARTICLE


