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REVIEW ARTICLE

Colloid solutions: a clinical update

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Abstract Albumin, dextran, gelatin, and hydroxyethyl starch (HES) solutions are colloids that efficiently expand the circulating blood volume. The administration of colloids restores the intravascular volume with minimal risk of tissue edema in comparison with crystalloid solutions alone. However, colloids are always given for surgical and critically ill patients. The type of the colloid, volumes applied, aggressiveness of fluid resuscitation, and the volume status at the initial phase of administration determine their clinical responses. The outcome after fluid resuscitation with various colloids in critically ill patients seems to be comparable according to systematic reviews. A randomized, adequately powered clinical trial comparing modern nonprotein colloid to albumin is still lacking. Rapidly degradable HES solutions have good hemodynamic effects, and the risk of adverse renal and coagulation effects, as well as allergic reactions, is minimal. The current investigation has also shown the beneficial effect of HES solution (especially HES 130/0.4) on inflammatory response, postoperative nausea and vomiting, and postoperative outcome. The indication of colloids with an assessment of the degree of hypovolemia and safety profiles should thus be taken into consideration before colloid administration.

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Introduction

According to a systematic review, there is no evidence that any one colloid solution is more efficacious or safer than any other [1]. However, in addition to the type of colloid, the dosing and aggressiveness of colloid administration have important roles in clinical effect. Nonprotein colloids, i.e., hydroxyethyl starches (HES), dextrans, and gelatins, together with the natural colloid albumin, are all of biological origin. Slowly degradable HES is the nonprotein colloid most often used in the United States, whereas rapidly degradable HES is most often used in Europe. However, gelatin, dextran, or albumin solutions are also given to critically ill patients [2].

Perioperative fluid optimization has been under discussion during the past few years. Ideally, the goal of fluid administration is to allow adequate tissue perfusion without inducing interstitial edema. Based on the current concept of fluid challenge, circulating plasma deficit may be replaced with an iso-oncotic colloid solution [3, 4]. In critically ill patients or in patients undergoing surgery, colloids are usually given in combination with crystalloids. Therefore, a comparison of the administration of colloids with a crystalloid-based treatment regimen during hypovolemia may not be justified for assessing the possible effects of colloids on morbidity or mortality [5].

The endpoints of fluid therapy should be easily feasible for the clinician. One certain endpoint is the optimization of the hemodynamic response. It is believed that colloids have superior capacity to crystalloids for achieving optimal hemodynamics. However, intravascular volume overload,

kidney dysfunction, coagulopathy, extravasation across leaky capillary membranes, and anaphylactic reaction may occur with the administration of any colloid. In this review, we focus on the characteristics of intravenous colloids, colloid choice for hypovolemia, and the safety profile of colloids.

Characteristics of intravenous colloids

Albumin

Albumin is a colloid solution with a homogeneous molecular weight of 69 kDa (Table 1a). Albumin is slightly hypo-oncotic as a 4% solution, iso-oncotic as a 5% solution, and hyper-oncotic as a 20% solution. The solvent is physiological (normal) saline. Albumin has no recommended limit of maximum dose. Iso-oncotic albumin infusion results in plasma volume expansion equal to the volume infused [6]. Hyper-oncotic albumin solution has been given mainly as a volume expander for large-volume paracentesis of ascites [7]. The transfer of infection is not totally excluded, although the method of preparation of the albumin solution minimizes the risk. There are no clinical reports of viral infections transferred by an albumin infusion [8]. Albumin may induce hypersensitivity reactions, and the incidence of anaphylactic reaction is higher than with HES preparations [9]. Twenty-five percent, but not 5%, recombinant albumin is now under clinical trial, and is expected to be used clinically in the near future.

Dextran

Dextran solution is a glucose polymer available with molecular weight of 70 kDa (6% iso-oncotic solution) or 40 kDa (10% hyper-oncotic solution) (Table 1b). The increase in plasma volume is approximately 100% of the administered volume of 6% dextran 70 or 175% of the administered volume of 10% dextran 40 [10]. The plasma-expanding effect lasts 3–5 h.

The incidence of dextran-associated anaphylactic reactions is reported to be 0.273% [9]. However, the incidence of these reactions is lower than those occurring by the use of albumin after introduction of low molecular weight dextran (40 kDa dextran) [11]. Dextran also has dose-dependent negative effects on hemostasis [12]; it may accumulate in tissues and induce hyper-oncotic renal dysfunction [13]. Dextrans are seldom used today for plasma expansion [2]. In addition to their adverse side effects, the reason may be the availability of new rapidly degradable HES solutions with few side effects (as described below). Furthermore, low molecular weight heparins have replaced dextrans as thromboprophylactic agents. Dextran combined with hypertonic saline, with a volume effect of 400% of the administered volume, has been found to be indicated in the immediate treatment of traumatic hemorrhagic shock [14]. The maximum recommended dosage of dextran is 1.5 g/kg/day.

Gelatin

Gelatin solutions are urea- or succinylated cross-linked modifications of bovine collagen (Table 1c). The molecular weight of gelatin solution is relatively low, 30–35 kDa, in comparison with those of other colloids. The carrier consists of NaCl at 110 mmol/l. The immediate plasma expansion effect of gelatin is 80–100% of the administered volume under conditions of normovolemic hemodilution. The plasma-expanding effect lasts 1–2 h. Gelatin has no maximum limit of dose. Gelatin can induce hypersensitivity reactions more often than HES solutions [9]. Although the raw product is from a bovine source, gelatins are believed to be free of the risk of prion transmission [15]. Most of the gelatin is excreted via the kidneys, and no tissue accumulation has been reported.

Hydroxyethyl starch

Hydroxyethyl starch (HES) solutions are high polymeric glucose compounds obtained by hydrolysis and subsequent hydroxyethylation from the maize or potato starch amylopectin [16]. The in vitro molecular weight of HES varies from 70 to 670 kDa (Table 1d). The physicochemical characteristics of hydroxyethyl starches are determined by their concentration (6% or 10% solution), mean molecular weight, degree of substitution, and C2/C6 ratio [17, 18]. Thus, the characteristic of HES is expressed as HES mean molecular weight/degree of substitution/ with or without the C2/C6 ratio. The degree of substitution expresses the average number of hydroxyethyl groups per unit of glucose. The C2/C6 ratio refers to the preferential hydroxyethylation site at the carbon atoms of the glucose subunit. Good plasma-expanding capacity of a HES solution with relatively low molecular weight and degree of substitution (i.e., HES 130 kDa/0.38–0.45) is achieved by increasing the C2/C6 ratio (Table 1d). Usually the solvent of HES is normal saline, but presently, HES is also available as a balanced form with a lesser concentration of NaCl than normal saline and other presumably beneficial additives.

The classification of hydroxyethyl starches as rapidly or slowly degradable solutions is based on their physicochemical characteristics. In vivo, the HES molecules of 50–70 kDa are rapidly excreted via the kidneys, and the larger molecules are hydrolyzed by amylase to smaller

Table 1 Characteristics of colloid solutions

(a) Albumin solutions

	4% Albumin	20% Albumin
Mean MW (kDa)	69	69
Initial volume effect (%)	100	350
Duration of plasma expansion (h)	1–3	–
Maximum daily dose (ml/kg)	No limit	No limit
Solvents		
Na^+ (mmol/l)	145	145
Cl^- (mmol/l)	130	130

(b) Dextran solutions

	6% Dextran 70	10% Dextran 40
Mean MW (kDa)	70	40
Initial volume effect (%)	100	175
Duration of plasma expansion (h)	5	3–4
Maximum daily dose (g/kg)	1.5	1.5
Solvents		
Na^+ (mmol/l)	145	145
Cl^- (mmol/l)	145	145

(c) Gelatin solutions

	3.5% Urea-cross-linked gelatin	5.5% Cross-linked gelatin	4% Succinylated gelatin
Mean MW (kDa)	35	30	30
Initial volume effect (%)	80	80	80
Duration of plasma expansion (h)	1–3	1–3	1–3
Maximum daily dose (g/kg)	No limit	No limit	No limit
Solvents			
Na^+ (mmol/l)	110	110	110
Cl^- (mmol/l)	110	110	110

(d) Hydroxyethyl starch (HES) solutions

HES (Mean MW/DS)	70/0.5	70/0.5	130/0.4	130/0.4	200/0.5	200/0.62	670/0.75
Concentration (%)	6	6	6	6	6 10	6	6
Mean MW (kDa)	70	70	130	130	200	200	670
DS	0.5	0.5	0.38–0.45	0.38–0.45	0.45–0.55	0.60–0.66	0.75
C2/C6 ratio	4:1	4:1	9:1	9:1	6:1	9:1	4–5:1
Initial volume effect (%)							
6% product	100	100	100	100	100	145	100
10% product					145		
Duration of plasma expansion (h)	1–2	1–2	3–4	3–4	3–4	5–6	5–6
Maximum daily dose (ml/kg)							
6% product	20	20	50	50	33	20	20
10% product					20		
Solvents							
Na^+ (mmol/l)	154	106	154	140	154	154	143
Cl^- (mmol/l)	154	92	154	118	154	154	124
Others	0	[a]	0	[b]	0	0	[c]

Data were provided by the manufacturers. Initial volume effect and its duration are derived from defined experimental conditions and cannot be directly translated into other clinical situations

Mean MW, mean molecular weight; DS, degree of substitution; – , unknown

[a] This product also includes other solvents (K^+, 4.0 mEq/l; Ca^{2+}, 2.7 mEq/l; lactate, 20 mEq/l; glucose, 1%)

[b] This product also includes other solvents (K^+, 4.0 mEq/l; Ca^{2+}, 2.5 mEq/l; Mg^{2+}, 1.0 mEq/l; malate, 5 mmol/l)

[c] This product also includes other solvents (K^+, 3.0 mEq/l; Ca^{2+}, 5.0 mEq/l; Mg^{2+}, 0.9 mEq/l; glucose, 0.1%)

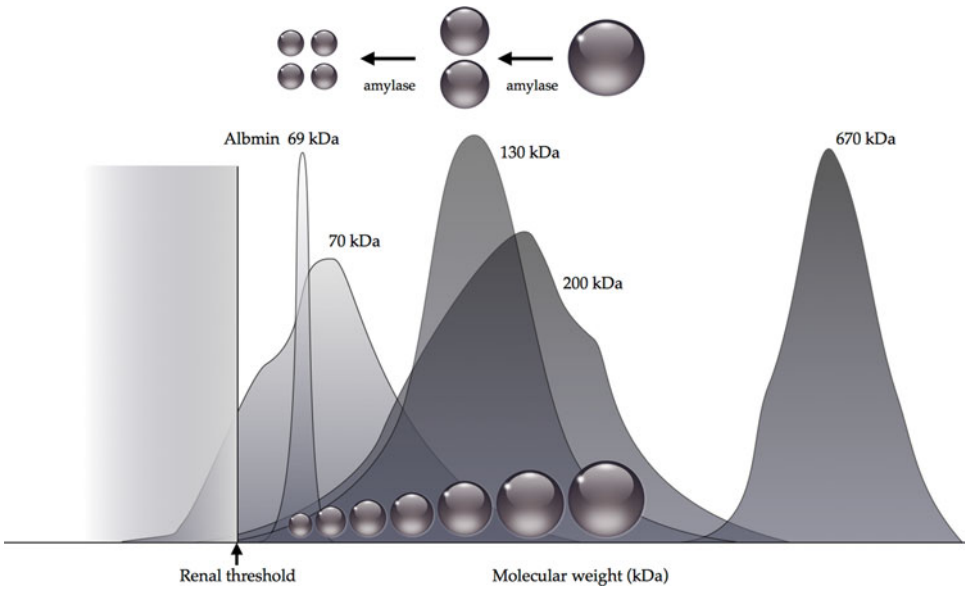

Fig. 1 The physicochemical characteristics of hydroxyethyl starch. The classification of hydroxyethyl starches as rapidly or slowly degradable solutions (Table 1d) is based on their physicochemical characteristics. In vivo, the hydroxyethyl starch molecules of 50–70 kDa are rapidly excreted via the kidneys, and the larger molecules are hydrolyzed by amylase to smaller ones that can be excreted via the kidneys

molecules that can be excreted via the kidneys [17] (Fig. 1). Slowly degradable HES solutions may accumulate in the reticuloendothelial system, whereas rapidly degradable HES, i.e., HES 130/0.4, does not accumulate, even after a repeated dosing regimen [19]. However, the accumulation of HES in the reticuloendothelial system does not seem to depress reticuloendothelial function [20]. Persistent itching, which is also a marker of accumulation of slowly degradable HES preparations, has not been found in patients treated with HES 130/0.4 [18, 21, 22].

The plasma-expanding effect of HES is condition sensitive [3]. In critically ill patients, the immediate plasma-expanding effects of 500 ml 6% HES 200/0.5 have been reported to vary among individuals from 27 to 840 ml [23]. Correspondingly, when HES 200/0.5 was administered to a presumably normovolemic patient preoperatively, the volume effect was approximately 40% of the administered volume, indicating that some HES was leaking outside the intravascular space [24]. In contrast, the immediate volume effect of 6% HES 200/0.5 or 6% HES 130/0.4 is 100% of the administered volume, lasting 3–4 h, as administered to hypovolemic patients under conditions of normovolemic hemodilution [25, 26]. Therefore, the assessment of the degree of hypovolemia is essential as HES or any other colloid is given.

The maximum doses of hydroxyethyl starches range from 20 to 50 ml/kg, depending on the type of HES. A prospective study showed that HES has a low risk of causing anaphylactic reactions (0.058%) compared with gelatins (0.345%) [9]. Hydroxyethyl starch is also available in combination with hypertonic saline, and this combination is indicated in the first-line treatment of hypovolemic shock in trauma patients.

Colloid choice for hypovolemia

Intravascular fluid administration is indicated in hypovolemia. Hypovolemia is associated with poor outcome after surgery, and mortality is increased by sepsis without fluid resuscitation [27, 28]. Early goal-directed therapy including fluid optimization has been proven to significantly improve the outcome of patients with severe sepsis and patients undergoing surgery [28–30].

Colloids are suggested to be indicated when circulation needs additional plasma volume or in the replacement of plasma loss [3]. Experimental models of colloid administration demonstrate the superiority of colloids in rapid resuscitation and restoration of tissue perfusion [31–33]. As expected clinically, colloids produce plasma volume expansion with 25–50% of the volume required for isotonic crystalloid solutions [34–38].

Some authors have suggested that the intensity and timing of the fluid administration might be more important during fluid resuscitation than the type of fluid itself [39]. However, from the clinical point of view, choosing the right kind of intravenous fluid is extremely important, because the efficacy of fluid administration is also significantly dependent on the type of intravenous fluid [3, 40–42]. This idea is supported by the findings in a study of penetrating torso injuries, which showed the adverse effects of excessively intensive fluid resuscitation as increased blood loss and mortality [43].

One clinically useful option in keeping the volume and composition of body fluids as normal as possible is to prevent subsequent hemodynamic compromise by fluid administration. The final aim is to restore adequate oxygen delivery, thus preventing organ failure [44]. The character

of the condition sensitivity of the plasma-expanding effects of colloids may also be translated into their hemodynamic responses. In experimental uncontrolled hemorrhage, the response of a colloid or crystalloid on hemodynamics was significantly related to the severity of the injury, i.e., the degree of hypovolemia and the rate of infusion [45].

Clinical trials of the hemodynamic responses of colloids have shown variable findings. The reason may be the differences in study designs, including variability in the timing and dosing of colloids, or in the degree of hypovolemia. The hemodynamic profiles of various colloids have been quite similar because the rate of colloid infusion has been relatively slow. The administration of HES (130, 200 kDa), gelatin, or albumin resulted in comparable hemodynamics during 20–48 h in patients undergoing cardiac or abdominal surgery [46–51]. Similar hemodynamics were also observed with HES 200 kDa or gelatin in patients with sepsis and during normovolemic hemodilution in patients who had undergone hip arthroplasty [52–54]. However, the 5-day hemodynamics in critically ill patients were more stable with HES (200 or 130 kDa) than with albumin [55–57]. The superior immediate effect of HES (200 or 130 kDa) on cardiac output after cardiac surgery compared with albumin and gelatin has recently been reported [58, 59]. The capacity of HES to prevent postoperative nausea and vomiting might also be related to its good maintenance of hemodynamics [60]. According to these studies, a rapidly degradable HES, such as HES 130/0.4, seems to be indicated whenever rapid favorable hemodynamic response is warranted when the circulation is assessed to need volume expansion.

Colloids are also needed for maintaining osmotic pressure during major blood loss. Dilution of serum proteins by the massive administration of crystalloids lowers colloid oncotic pressure (COP) with the risk of progressive expansion of the interstitial space. In some studies, the administration of colloids has resulted in less tissue edema [61–63]. Controversy still exists over whether the choice of fluid for restoration of circulating volume is able to limit the development of tissue edema. It has also been speculated that the weight gain related to perioperative crystalloid administration and increased mortality [64] might be reduced by the administration of colloids [3]. This idea is further supported by the fact that oncotic solutions achieve similar resuscitation goals with less than half the infusion volume of crystalloids [65–67].

Colloids have favorable effects on microcirculation, inflammation, and blood viscosity. Particularly, the rheological effects of dextran, i.e., a decrease in whole blood viscosity, are well known [68]. The capillary leakage can be prevented by administration of HES (pentastarch; HES 200/0.5) in patients with sepsis or trauma [69]. It has also been shown experimentally that pulmonary capillary leakage is prevented to a greater extent by HES than by gelatin [70]. Improvement of microcirculation [71] and decrease of plasma viscosity by HES but not by gelatin [72] may also be translated into good tissue oxygenation not seen during the administration of Ringer's lactate alone [73, 74] (Fig. 2).

The "balanced concept" of HES means that the electrolytes in HES products consist of modified Ringer's solution composition but not only NaCl as normal saline. This concept was first introduced with slowly degradable HES (Hextend; HES 670/0.7) solution and recently with rapidly degradable HES (HES 130/0.4). Hydroxyethyl starch was modified to contain less sodium chloride (i.e., Na^+, 140 mmol/l; Cl^-, 118 mmol/l) than normal saline with additives such as K^+, 4.0 mmol/l, Ca^{2+}, 2.5 mmol/l, Mg^{2+}, 1.0 mmol/l, acetate, 24 mmol/l, and malate, 5 mmol/l. A balanced slowly degradable HES solution has less effect on coagulation than the HES in normal saline, but the difference is clinically insignificant [75]. More importantly, the clinical effect of a balanced HES solution is seen in acid–base equilibrium. Balanced rapidly degradable HES 130/0.4 solution induced no disturbances in the acid–base balance, whereas the HES in normal saline showed on average postoperative base-excess decrease of 5 mEq/l in patients who had undergone major noncardiac surgery [76]. Correspondingly, base excess was unchanged with balanced HES 130/0.4 but reduced with the HES in normal solution in elderly patients who had undergone cardiac surgery [77]. Furthermore, less inflammatory endothelial activation and

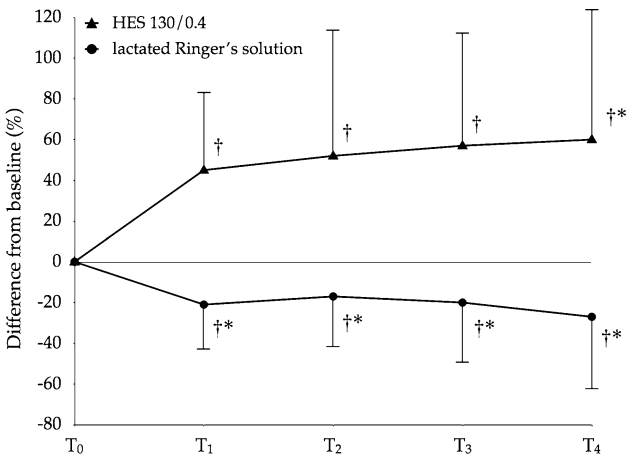

Fig. 2 Differences (in percentage from baseline) of tissue oxygen tension in the two volume groups. Data are presented as mean ± SD ($n = 21$ each). T_0 = baseline (before volume administration and before surgery), T_1 = 60 min later (during surgery), T_2 = 120 min after T_1 (during surgery), T_3 = at the end of surgery, T_4 = on the morning of the first postoperative day in the intensive care unit. *HES*, hydroxyethyl starch (molecular weight, 130 kDa; degree of substitution, 0.4). $^{\dagger}P < 0.05$ compared with baseline data, $^{*}P < 0.05$ compared with the other volume group. (Modified from Lang et al. [73], with permission)

alteration in kidney integrity were observed with the balanced form than with the HES in normal saline [77]. The balanced strategy of fluid administration seems not to harm a patient's homeostasis and is a promising strategy for correcting hypovolemia. Gelatin, dextran, or albumin solutions are not available in balanced forms. Acidifying an albumin infusion may be an appropriate action under some clinical conditions, such as after cardiac surgery [59].

The possible beneficial effects of colloids on patient outcome or mortality are not mentioned in systematic reviews [5, 78–80]. In trauma patients, the administration of colloids may even increase mortality [79]. However, the characteristics of colloid solutions as well as the fluid composition in controls vary widely in meta-analysis. The patient populations are not always comparable, and the aims of fluid challenge are not indicated. Furthermore, most of the included studies are too underpowered to detect any effect on mortality.

We also still lack an adequately powered study to find the possible effect of modern nonprotein colloid on morbidity and mortality in comparison with albumin. In smaller clinical trials, albumin infusion had no beneficial effects compared with HES or gelatin in critically ill patients [81, 82]. Hypoalbuminemia is associated with increased mortality, but there is no evidence that hypoalbuminemia is an indication for an albumin infusion [83]. Hypoalbuminemia in elderly patients who have undergone cardiac surgery does not improve with albumin infusion in comparison with HES 130/0.4 [84]. It seems also that the administration of albumin is not indicated in patients with burns [85], although it is still the most common colloid used in burn trauma, which usually involves hypoalbuminemia [86].

A previous suggestion of the increased mortality caused by albumin [87] in critically ill patients was not supported by the results of a randomized study with approximately 7,000 patients [88]. The 28-day mortality was 21% and did not differ according to the treatment assignment with either albumin or normal saline. The finding is also in accordance with recent meta-analysis concerning the effects of albumin in critically ill patients [78, 89, 90]. However, subgroup analysis of the Albumin Reviewers' study [90] suggests that albumin may be related to an unfavorable outcome in trauma patients: the relative risk (95% confidence interval) for death with albumin in trauma patients was 1.36 (0.99–1.86) and that for associated traumatic brain injury was 1.62 (1.12–2.34).

Albumin is also expensive compared to nonprotein colloids, although the exact magnitude of the costs of intravenous fluids in relationship to the total costs of intensive care is difficult to assess [91]. An appropriate indication for albumin might be the replacement of ascites fluid during drainage in patients with cirrhosis and spontaneous bacterial peritonitis [7, 92].

Unfortunately, based on these results of meta-analysis and previous investigations already described, the indication of colloid solution still remains unanswered for mortality outcome, especially in trauma patients.

Safety profile of colloids

Renal function

The reason for renal dysfunction in hypovolemic patients is multifactorial. The reported effects of colloids on renal function are variable but also related to the type of the colloid, according to recent studies [53, 93]. None of these randomized studies comparing various colloids were powered to reveal possible effects on renal replacement therapy or mortality, and no such differences have been observed.

There are several suggestions for the mechanism of renal dysfunction associated with colloids. The decrease of tubular flow during glomerular filtration of colloids (dextrans, 10% HES, or 20% or 25% albumin) may cause renal dysfunction [94]. Accumulation of small molecules in the tubuli may account for acute tubular toxicity. The elevated serum chloride concentrations associated with the carrier of colloid solution may also impair renal blood flow [95].

The slowly degradable HES solutions have been shown to be harmful to kidneys. Osmotic nephrosis-like lesions without any effect on kidney function have been seen in kidney transplant recipients after HES 200/0.62 was administered to brain-dead organ donors [96]. In another nonrandomized study, kidney recipients whose donors were given HES 200/0.62 ($n = 15$) had a higher creatinine concentration than recipients whose donors were given gelatin ($n = 12$) [97]. However, there were no differences in the number of renal replacement therapies for recipients when kidney donors were given HES 200/0.5 ($n = 20$), 450/0.7 ($n = 16$), or gelatin/albumin ($n = 73$) [98]. A recent study revealed that the third-generation HES 130/0.4 given to kidney donors seemed to be associated with a better effect on the renal function of recipients than that of HES 200/0.6 [99] (Fig. 3). In that particular study, lower serum creatinine concentrations were observed at 1 month and 1 year after the kidney transplantation, but the difference in delayed graft function was not statistically significant, although it was 11% lower in the HES 130/0.4 group.

In severe sepsis, HES 200/0.62 also showed a slightly worse renal profile than gelatine, and HES was an independent risk factor for acute renal failure [53]. However, no influence of renal failure on renal replacement therapy or mortality was observed. In addition, the serum creatinine concentration seemed to be higher in the HES 200/0.62 group before fluid resuscitation [141 μmol/l (median) in

the HES group and 110 μmol/l in the gelatin group]. The hyper-oncotic 10% HES 200/0.5 solution also increased the frequency of renal replacement therapy and mortality in a dose-dependent manner in patients with severe sepsis in comparison with modified Ringer's lactate (Fig. 4) [93]. The study has been criticized in terms of solely administering hyper-oncotic hyperchloremic solution in the HES group and including patients with serum creatinine concentration as high as 320 μmol/l. Furthermore, in the subgroup analysis, mortality was found to be even lower in the HES group (31%) than in the Ringer's lactate group (41%) because the dose was limited to less than 22 ml/kg.

A reasonable clinical finding about the risk factors for renal replacement therapy was shown in a cohort study of 3,000 critically ill patients [100]. This study found that sepsis, circulatory failure, hematological malignancy, or renal dysfunction before fluid resuscitation, but not the administration of various hydroxyethyl starches, were independent risk factors for renal replacement therapy.

The results of these studies of slowly degradable HES solutions such as HES 200/0.5 may not be directly applicable to the use of more rapidly degradable HES solutions such as HES 130/0.4. The use of HES 200/0.5 over 5 days in a study of critically ill patients in the intensive care unit was without negative effects on renal function compared to albumin [56]. In a study in elderly patients (>75 years old) undergoing major abdominal or cardiac surgery, administration of 6% HES 200/0.5 [101] or 130/0.4 [76, 84, 102] was not associated with changes in markers of renal dysfunction as compared with albumin or gelatin [102]. In fact, in studies of patients undergoing cardiac surgery [103] or elective aortic aneurysm surgery [104], renal profile according to sensitive kidney-specific markers or creatinine clearance in the group that received gelatin was slightly worse than in the HES 130/0.4 or 200/0.5 groups [103, 104]. Furthermore, HES 130/0.4 did not negatively influence kidney integrity compared with a human albumin-based volume-replacement strategy in patients who had undergone cardiac surgery [97] or aortic aneurysm surgery [105] with preoperative compromised kidney function. In

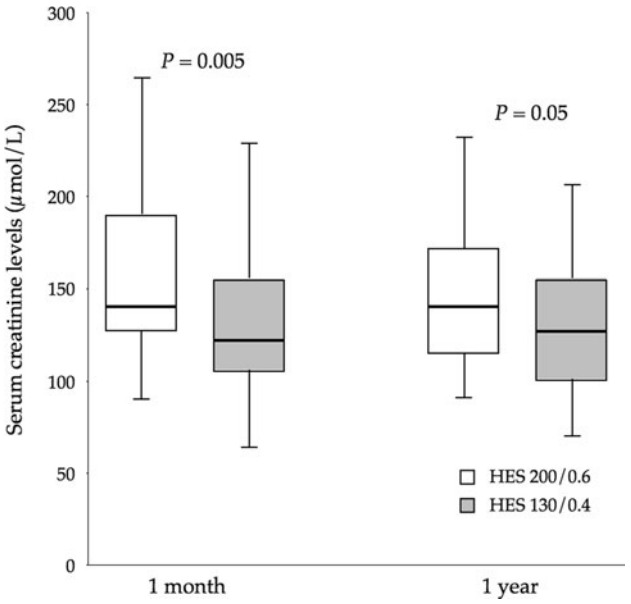

Fig. 3 Levels of serum creatinine measured in the recipients at 1 month and 1 year posttransplantation who received either hydroxyethyl starch (HES) 200/0.6 or 130/0.4 during the surgery. Data are presented as median (*thick line*) ± 25/75th percentile (*boxes*) ± 10/90th percentile (*bars*) ($n = 32$ each). The serum creatinine levels at 1 month were lower in the patients treated with HES 130/0.4 than in those treated with HES 200/0.6, and this difference was still observed 1 year after the transplantation. (Modified from Blasco et al. [99], with permission)

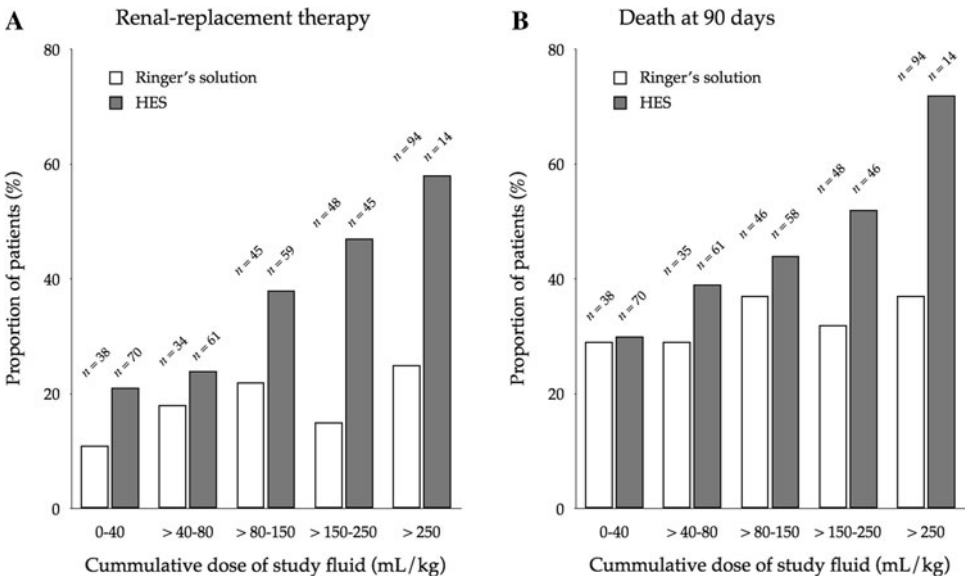

Fig. 4 Cumulative effect of volume resuscitation on the need for renal replacement therapy (**a**) and the rate of death at 90 days (**b**). *HES*, hydroxyethyl starch. The need for renal replacement therapy and 90-day mortality were significantly correlated with the cumulative dose of HES ($P < 0.001$ and $P = 0.001$, respectively) but not with the dose of Ringer's lactate ($P = 0.11$ and $P = 0.31$, respectively). (Modified from Brunkhorst et al. [93], with permission)

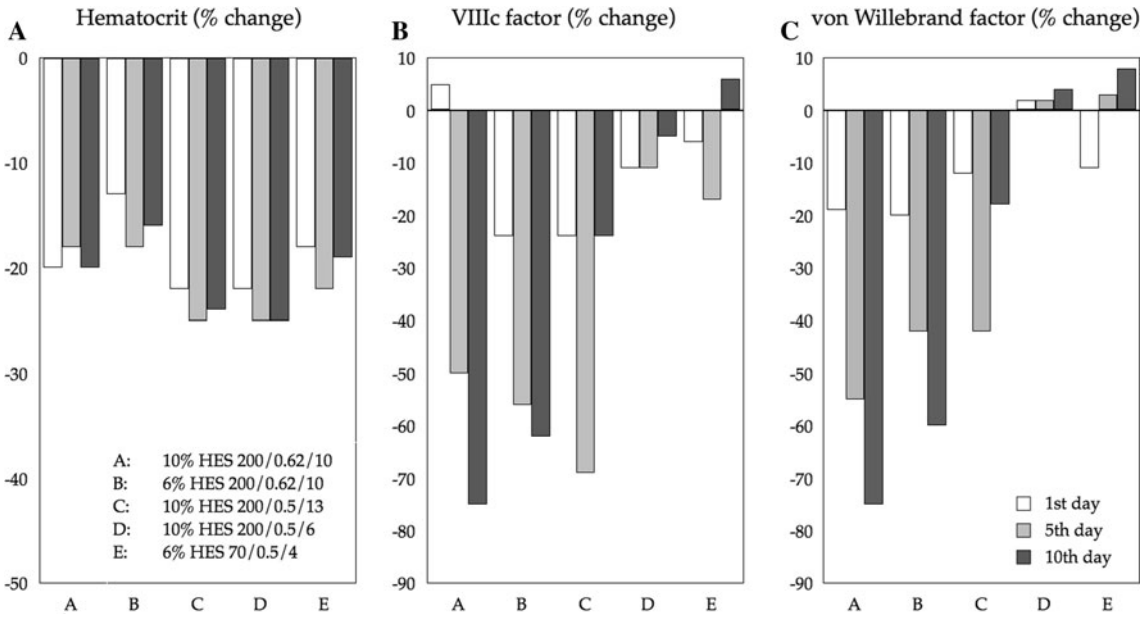

Fig. 5 Percent changes in hematocrit (**a**), coagulation factor VIIIc (**b**), and von Willebrand factor (**c**) during the course of a 10-day volume therapy. Data are presented as mean. VIIIc factor, coagulation factor VIIIc; von Willebrand factor, von Willebrand ristocetin cofactor. Although the hemodilutional effects of hydroxyethyl starch (*HES*) solutions did not differ among the products tested, the inhibitory effects of HES solutions on VIIIc and von Willebrand factors were significantly different among the types of HES solutions. (Modified from Treib et al. [109], with permission)

cases of severe renal dysfunction, a single bolus of 500 ml HES 130/0.4 did not impair creatinine clearance either [106].

Any hyper-oncotic colloid may have the potential to produce kidney dysfunction or renal failure because colloids may decrease glomerular filtration [13]. Because the results of colloids regarding renal damage are doubtful and highly probably related to the type and dose of the solution, colloids should always be carefully administered, especially to organ donors and patients with sepsis or renal dysfunction. The logical extrapolation of the results of rapidly degradable HES solutions in surgical patients to critically ill patients with sepsis requires confirmation in clinical trials. The safest colloid today in terms of kidney function seems to be a rapidly degradable HES, such as HES 130/0.4, or gelatin. Insufficiently treated hypovolemia may also induce renal dysfunction and treatment by the administration of crystalloids alone may not achieve restoration of blood volume. Other researchers failed to find any deterioration in renal function associated with the use of various HES preparations: 6% HES 200/0.5 and HES 70/0.5 [101], 6% HES 200/0.5, 6% HES 200/0.62, and 6% HES 670/0.75 [107], even when high doses were used [108].

Coagulation

All colloids induce dilution of red blood cells, platelets, and coagulation factors that may be clinically significant during extreme hemodilution [10]. Slowly degradable HES solutions and dextran especially decrease the activities of coagulation factor VIII and von Willebrand factor and impair clot strength and platelet function in addition to their hemodilutional effects [12, 109, 110] (Fig. 5). However, these detrimental effects of HES on hemostasis were not seen in similar magnitudes by all types of HES in another study [12]. Rapidly degradable HES solution, HES 130/0.4, has been given to patients with severe brain injuries without a negative effect on coagulation factor VIII or von Willebrand factor concentrations [108]. Similarly, in orthopedic patients, HES 130/0.4 did not affect coagulation factor VIII concentration [111].

In addition to laboratory knowledge about the mechanisms of colloid-induced coagulation disturbance, it is important to evaluate to what extent the shown defect could be translated into increased blood loss in clinical practice. Although albumin may have anticoagulant effects [112], there is no clinical evidence that albumin infusion could increase blood loss in patients undergoing surgery. Gelatin in vitro also decreases the clot strength, but to a lesser degree than rapidly degradable HES solution [113]. Gelatin has also been observed to interfere with platelet aggregation and to impair clot strength in patients undergoing cardiac surgery without an effect on blood loss [114–119].

Increased blood loss has been mainly reported after slowly degradable HES solution or dextran has been given to patients undergoing surgery. In orthopedic and

urological surgery, dextran infusions for thromboprophylaxis are associated with an increased postoperative blood loss and the requirement for allogeneic blood [120].

The administration of the slowly degradable HES hetastarch increased cumulative chest tube drainage by an average of 330 ml compared to drainage in patients not receiving hetastarch (HES 670/0.75) in a retrospective analysis of adults undergoing cardiac surgery [121]. It was also found that the hetastarch group received 100% more red blood cells than those not given hetastarch. In an analysis of 14 randomized studies, adult patients undergoing cardiac surgery who were administered HES 200 or 670 kDa had, on average, 96 ml more 24-h cumulative chest tube drainage after cardiopulmonary bypass than those administered albumin [122]. A balanced high molecular weight HES with high molar substitution (HES 670/0.75) given to patients undergoing major abdominal surgery also increased blood loss by an average of 520 ml in comparison to those patients given HES 130/0.4 [123]. In a pooled analysis of randomized trials, intraoperative blood loss could be reduced by an average of 404 ml, and postoperative blood loss could be reduced by an average of 272 ml, with HES 130/0.4 compared to HES 200/0.5 [124]. The volume of red blood cells transfused was also significantly lower, at 137 ml.

Summary

Albumin, dextran, gelatin, and HES solutions are colloids that efficiently expand the circulating blood volume. The administration of colloids restores the intravascular volume with minimal risk of tissue edema in comparison with crystalloid solutions alone. However, colloids are always given for surgical and critically ill patients. The type of the colloid, volumes applied, aggressiveness of fluid resuscitation, and the volume status at the initial phase of administration determine their clinical responses. A randomized, adequately powered clinical trial comparing modern nonprotein colloid to albumin is still lacking. Rapidly degradable HES solutions have good hemodynamic effects and the risk of adverse renal and coagulation effects, as well as allergic reactions, is minimal. The current investigation has also shown the beneficial effect of HES solution (especially HES 130/0.4) on the inflammatory response [125], postoperative nausea and vomiting [60], and postoperative outcome [126].

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