Pathophysiology and management of coagulation disorders in critical care medicine

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Chapter 8

Effects of Different Plasma Substitutes on Blood Coagulation. A comparative review

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Abstract

Objective: To compare the effects of different colloid plasma substitutes on blood coagulation and post-operative blood loss.

Data sources: Relevant studies were obtained from the medical literature.

Study selection: Articles were selected that provided data on the effects of colloids on hemostasis and post-operative blood loss in humans. Studies comparing different colloids were looked for using MEDLINE and by searching through the references of studies as they were collected.

Data synthesis: Articles were reviewed and relevant data were extracted and partly presented in comparative tables.

Conclusions: Dextran, gelatin and HES all can induce a specific decrease of von Willebrand factor and factor VIII:c. Blood coagulation is most impaired by dextran and high molecular weight HES, both associated with increased post-operative blood loss. The effects of HES on blood coagulation have been shown to depend on its molecular weight and rate of elimination. Detrimental effects have been shown for HMW-HES and after repeated administration also for MMW-HES with a high degree of substitution (HES 200/0.62) or MMW-HES with high C2/C6 hydroxyethylation ratio (HES 200/0.5/13). Rapidly degradable HES 200/0.5/6 and gelatin-based plasma expanders appear not to impair hemostasis. However, based on the reviewed literature, all artificial colloids could potentially induce increased bleeding tendency after infusion of very large volumes and especially when given to patients with even mild forms of von Willebrand disease. In those circumstances alternatives like plasma or albumin, although associated with other serious complications, could be considered.
Effects of plasma substitutes on blood coagulation

Introduction

Synthetic colloids are increasingly used as plasma substitutes in hypovolemic patients because they are readily available, carry no risk of transmitting viral or other plasma transfusion-related disease and are relatively inexpensive. As these colloids are frequently used in bleeding patients or in situations with a high risk of bleeding such as trauma or during surgery, there is some concern regarding the effects of colloids on blood coagulation and platelet function. In fact, all three distinct classes of artificial colloids (i.e. dextrans, hydroxyethyl starches and gelatins) have been associated with derangements of the hemostatic system, although the clinical significance of these derangements is a matter of debate. Most evidence points to an impairment of coagulation by plasma substitutes although some authors, referring to thromboelastography studies, have suggested that hemodilution per se results in a hypercoagulable state. These findings, however, have been disputed. In this review we will focus on the anti-hemostatic effects of artificial colloids and albumin on platelet function and blood coagulation.

Dextrans

Dextran s are polydisperse glucose polymers produced by bacteria growing in sucrose containing media. Commercially available dextran-based plasma substitutes have an average molecular weight of 40 or 70 kDa. Besides their plasma expanding properties they also exert an anticoagulant effect. Indeed, dextran have been shown to be effective in preventing post-operative venous thrombosis and pulmonary embolism. Dextran infusion induces a "von Willebrand syndrome" with decreased levels of von Willebrand factor (vWF) and associated factor VIII (VIII:c). The fall in vWF and factor VIII:c after dextran administration is more than can be explained by its dilutional effects. Von Willebrand factor is the ligand between the platelet surface receptor protein GPIIb and subendothelial collagen, thereby causing platelet adhesion to the vessel wall. Decreased levels of vWF therefore may lead to an impaired primary hemostasis. Indeed, prolonged bleeding times were observed after infusion of dextran in animals as well as in humans. The prolongation of bleeding time was totally reversed after increasing vWF levels by the intravenous administration of desmopressin (1-desamino-8-D-arginine vasopressin, DDAVP). Besides its effects on the factor VIII/vWF complex dextrans also
enhance fibrinolysis.\textsuperscript{15-17} Earlier reports have suggested that fibrinolysis is increased by formation of complexes that include dextran, fibrin, plasminogen activator and \(\alpha\)-2 antiplasmin. Within these complexes dextran appears to protect plasmin from the inhibitory effects of \(\alpha\)-2 antiplasmin. Indeed, clots formed in the presence of dextran are relatively bulky in size, exhibit less tensile strength, and seem more easily disrupted.\textsuperscript{18-20} Recently, it has been shown that fibrinolysis may rather be enhanced after dextran infusion by increased plasma concentrations of tissue type plasminogen activator (t-PA) and decreased concentrations of the physiological inhibitor of fibrinolysis plasminogen activator inhibitor –1 (PAI-1).\textsuperscript{17}

After its administration, the anti-hemostatic effects of dextran on factor VIII/vWF and fibrinolysis may result in an increased bleeding tendency. In clinical studies comparing dextran with unfractionated heparin, low molecular weight heparin or the heparinoid Orgaran as prophylaxis against venous thromboembolism, dextran infusion resulted in increased post-operative blood loss after transurethral prostatectomy\textsuperscript{21} or orthopaedic surgery\textsuperscript{22,23} and increased the need for blood transfusion after surgery for hip fracture.\textsuperscript{24} In a study comparing dextran with 4\% albumin solution as intraoperative infusion fluid in orthopaedic surgical patients who were also treated with LMWH thrombosis prophylaxis, patients treated with dextran needed more blood transfusions.\textsuperscript{25} There are no clinical studies comparing dextran with other synthetic colloid solutions with respect to bleeding complications.

**Gelatins**

Gelatins are polydisperse polypeptides produced by degradation of bovine collagen. Two separate forms are produced: succinylated (modified) gelatins, which have NH\textsubscript{3} groups replaced by COO- groups by reaction of the basic peptide with succinic acid anhydase, and polygelines, consisting of polypeptides crosslinked by urea-bonds. Although for a long time gelatins were considered not to influence blood coagulation other than by dilution,\textsuperscript{26} there is now increasing evidence that gelatins do influence platelet function and blood coagulation. *In vitro* blood coagulation in the presence of gelatin was studied using thromboelastography and scanning electron microscopy. Clots produced in the presence of gelatin had decreased weight and strength and loss of the normal reticular network of fibrin strands.\textsuperscript{27} Although these results could not be
confirmed in another study using thromboelastography, this study also showed a more modest increase in clot strength after dilution by gelatin as compared with saline dilution.\textsuperscript{28} Others have studied the effects of \textit{in vitro} dilution of blood on platelet aggregation. It was found that gelatin impaired aggregation induced by ristocetin and polybrene.\textsuperscript{29} Agglutination tests induced by ristocetin and polybrene are specific for binding of vWF to the platelet receptor Gp1b. These findings are supported by the observation that \textit{in vivo} administration of 1 liter of a gelatin-based plasma expander to healthy humans induced a von Willebrand like syndrome with lengthening of bleeding time, impaired ristocetin-induced platelet aggregation and decreased levels of plasma vWF. It was suggested that vWF binds to gelatin by means of its collagen binding site. Also a decrease in thrombin generation, as measured by thrombin-antithrombin complexes and prothrombin fragment F1+2, was observed after gelatin administration probably caused by hemodilution.\textsuperscript{30} The clinical relevance of the impairment of hemostasis after gelatin infusion is uncertain. Only one report suggests increased blood loss after cardiac surgery when gelatin instead of albumin was given peroperatively.\textsuperscript{29} However, other studies comparing gelatin with HES\textsuperscript{31} or HES and albumin\textsuperscript{32} found no difference or in some cases even an improvement\textsuperscript{33} in post-operative blood loss when gelatin was given.

\textbf{Hydroxyethyl starch}

Hydroxyethyl starch (HES) is generally considered as an effective and safe plasma substitute. However, bleeding complications have been reported after administration of HES in various clinical settings. High molecular weight HES (HMW-HES, Hetastarch, average MW 480,000 Da), which is the only HES solution that is approved in the United States as a plasma expander, has been associated with increased post-operative bleeding after neurosurgery\textsuperscript{34} and in patients undergoing cardiac surgery.\textsuperscript{32,35,36} Furthermore, many case reports have been published describing bleeding complications after HMW-HES in various clinical situations.\textsuperscript{37,38,39,41} It has been suggested, that not all HES solutions have negative effects on blood coagulation, but that these effects depend on the average molecular weight of the HES molecules and its kinetics of elimination.
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Pharmacokinetics of HES

Natural starches cannot be used as plasma substitutes because they are rapidly degraded by circulating amylase and they are insoluble at neutral pH. Hydroxyethyl starches are polymers of glucose units derived from amylopectin and modified by substituting hydroxyethyl for hydroxyl groups on glucose molecules. The substitution results in slower degradation and highly increased solubility. HES are very polydisperse solutions of molecules with a broad range of molecular weights from very small to several hundred thousand Dalton. After administration of HES, the low molecular weight fraction is rapidly lost by renal elimination and the large molecules are progressively hydrolyzed, resulting in an average \textit{in vivo} MW that is significantly lower than the average molecular weight of the infused fluid. The rate at which degradation of HES molecules occurs, depends on the degree of substitution (DS), that is the proportion of glucose units having a hydroxyethyl group substituted for a hydroxyl group. There are three possible sites for substitution leading to a maximum DS of three. Currently available HES solutions have a DS of 0.5 to 0.7. The rate of degradation and elimination is highest with low values for DS. Because substitution is possible at positions 2, 3 or 6 of the glucose unit, different patterns of substitution are possible. The substitution pattern is characterized by the C2/C6 hydroxyethylation ratio. Clearance of HES is slowest with high C2/C6 ratios. The characteristics of HES solutions are given by its initial molecular weight, the degree of substitution and the C2/C6 ratio. Thus, HES 200/0.5/6 has an initial average MW of 200,000 Dalton, with 50% of glucose units having a hydroxyethyl group and with a C2/C6 ratio of 6 (i.e. 6 times more substitutions at the C2 position as compared with the C6 position).

Effects on factor VIII and von Willebrand factor

Studies in healthy human volunteers have shown that circulating levels of factor VIII and vWF decreased significantly after infusion of 0.5-1L of HMW-HES\textsuperscript{43} or medium molecular weight HES (MMW-HES).\textsuperscript{44,45} Similar reductions in factor VIII and vWF have not only been found in healthy volunteers, but also in a number of clinical studies.\textsuperscript{37,46-51} Considerable insight in the influence of HES on blood coagulation come from observations by Treib et al. In several 10-days hemodilution experiments in patients, these authors found that a decrease in vWF and factor VIII was only observed when MMW-HES was given that was
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slowly degradable (i.e. with high degree of substitution and/or high C2/C6 ratio). Those infusions resulted in accumulation of HES molecules with higher molecular weights. It was concluded that the negative effects on hemostasis depended on the in vivo molecular weight,\textsuperscript{42,52,53} and that therapy with low-molecular weight HES 70/0.5/4 or easily degradable MMW-HES 200/0.5/6 did not influence blood coagulation.\textsuperscript{54} However, we recently observed a 33\% decrease in vWF and 28\% decrease in factor VIII after administration of 1 liter rapidly degradable HES 200/0.5/6 to healthy volunteers. These decreases were more than could be explained by HES-induced plasma dilution. In accordance with the diminished vWF levels, platelet adhesive function, measured by the platelet function analyzer PFA-100, was significantly prolonged after HES as compared to albumin 4\% which is compatible with an acquired von Willebrand's syndrome (E. de Jonge et al, unpublished observations). A possible explanation for these different findings in healthy volunteers as compared with the studies in patients could be that vWF is an acute phase protein, increasing during acute illness and thereby potentially masking a concomitant HES-induced decrease. Furthermore, relatively low quantities of HES were given during the hemodilution experiments by Treib et al. (1000 or 500 ml/day). In circumstances when large volumes of HES are given over a short time period (e.g. in bleeding patients with circulatory shock), HES could potentially induce a clinically relevant coagulation defect. Also, uncertainty exist about the clinical effect of the administration of HES on blood coagulation in patients with already low circulating levels of vWF.

Other markers of coagulation and fibrinolysis

Reductions in the concentrations of other plasma coagulation factors, that could be fully ascribed to plasma dilution after administration of HES, have been reported repeatedly.\textsuperscript{50,53,55,56} The prothrombin time only slightly prolongs after the administration of HES, probably due to dilution of plasma factors.\textsuperscript{2,43} The effects of HES on the activated partial thromboplastin time (aPTT) depends on its molecular weight and the kinetics of elimination. Significant prolongation of the aPTT up to 40\% has been described after repeated infusion of slowly degradable MMW-HES 200/0.62/10. In contrast only a minimal prolongation was found after the infusion of LMW-HES 70/0.5/4 or easily degradable MMW-HES 200/0.5/6.\textsuperscript{42,45} A significant prolongation of the aPTT has also been found
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after HMW-HES 480. The effects of HES on the aPTT can be readily explained by the specific decreases in factor VIII, potentially in combination with some dilution of other plasma factors. HMW-HES 480 has been associated with increased fibrinolysis. Hetastarch, but not MMW-HES, induced a significant decrease of urokinase-activated clot lysis time. However, fibrin monomers and fibrin degradation products were not increased.55:57 Infusion of 500 mL MMW-HES 200/0.5 in healthy volunteers did not result in changes in plasma levels of tissue-type plasminogen activator (t-PA), urokinase-plasminogen activator (u-PA), plasminogen activator inhibitor (PAI), plasmin-antiplasmin complexes (PAPc) or D-dimer when compared to infusion of albumin 5%. The effects of HES on coagulation and fibrinolysis also have been studied using thromboelastography yielding results that are pointing in the same direction. In vitro studies suggested prolonged clot formation time and increases in clot lysis after profound hemodilution with HES.58:59 Finally, HES might affect platelet function. Platelet volume decreases after infusion of HES, probably due to a shrinkage of platelets by the increased plasma colloid osmotic pressure.42 It has however not yet been established whether the decrease in platelet volume after HES administration affects platelet function and bleeding time. Prolonged bleeding times have been reported after HMW-HES57 and the infusion of MMW-HES has been associated with normal57 as well as prolonged bleeding times.2,33 In contrast, in another study comparing the influence of MMW-HES 200/0.5 and albumin on platelet aggregation no difference between the two colloids was observed.60

Albumin

Albumin is generally considered not to influence blood coagulation and is often used as control fluid in studies evaluating the effects of other colloids. Indeed, we recently found that infusion of 1L albumin 4% to healthy volunteers resulted in only slightly diminished levels of fibrinogen and factor V, VII, VIII:c and vWF. These decreases could be completely explained by dilution of plasmapfactors by the infused fluid (E. de Jonge, unpublished observations). However, it has been reported that albumin induces an impairment of platelet aggregation and prolongation of bleeding time which observations could be confirmed in our study.51,62 The mechanism by which platelet function is impaired is uncertain. We did not find any report on an increased bleeding tendency related to the infusion of albumin.
Pathogenesis of colloid-induced von Willebrand syndrome

The fact that all three classes of artificial colloids share the same vWF lowering property may suggest that some common pathophysiologic mechanism exists. This postulated common mechanism has not been fully elucidated yet. No change has been observed in the multimeric pattern of vWF after HES, dextran or gelatin infusion. It has been shown that the lowering effects of these colloids on vWF antigen can not be reproduced in vitro. Thus, it has been suggested that colloids bind to vWF leading to accelerated in vivo elimination. This mechanism has also been observed in patients with monoclonal gammopathy who have an acquired form of von Willebrand's disease and accelerated excretion of vWF-IgG paraprotein complex.

Comparison of the different colloids with respect to blood coagulation

Studies comparing different colloids in regard to laboratory markers of blood coagulation are summarized in table 1. Direct comparisons are difficult to make as all studies differ in the plasma substitutes used, the amount of colloid infused and the population studied. Furthermore, some studies looked at effects of short-term fluid therapy (e.g. only during surgery) whereas others considered 10-day hemodilution. Nevertheless, some general conclusions can be drawn. First, the effects of HES on coagulation appear to depend on its molecular weight as well as on the rate of in vivo degradation. High molecular weight HES undoubtedly affects blood coagulation even if given over a limited time period. Slowly degradable medium molecular weight HES (MMW-HES with high degree of substitution or high C2/C6 hydroxyethylation ratio) also impairs coagulation after repeated administration, probably due to accumulation of macromolecules. In contrast, most studies consider easily degradable MMW-HES (with low degree of substitution and low C2/C6 ratio) or LMW-HES to have minimal influence if any on blood coagulation when compared to albumin. The effects of modified gelatin solutions appeared to be similar to the effects of easily degradable MMW-HES and albumin. An overview of studies comparing different colloids regarding post-operative blood loss is given in table 2. One single study found increased post-operative blood loss after dextran as compared with albumin. Parallel to the observations on laboratory markers of coagulation, administration of HMW-HES may lead to increased blood loss. No study could find increased bleeding tendency after MMW-HES when compared to albumin, suggesting that MMW-HES can safely be given during surgery.
Table 1. Overview of studies comparing the effects of different plasma substitutes on laboratory markers of coagulation

<table>
<thead>
<tr>
<th>Colloids</th>
<th>N=</th>
<th>Population</th>
<th>Amount of colloid</th>
<th>Parameters studied</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Studies with HMW-HES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claes 1992*</td>
<td>40</td>
<td>Brain tumor surgery or hysterectomy</td>
<td>1000 ml</td>
<td>APTT, PT, TT, Fbg, VIII:c, vWF</td>
<td>Diminished increase of VIII:c and vWF after HMW-HES</td>
</tr>
<tr>
<td>Brutoco, 1996*</td>
<td>38</td>
<td>Cardiac surgery in children</td>
<td>Up to 30 ml/kg</td>
<td>PT, aPTT, TT, Fbg, Platelets</td>
<td>Increased PT in children who received &gt; 20 ml/kg HES</td>
</tr>
<tr>
<td><strong>Studies with MMW-HES and low degree of substitution</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beyer 1997*</td>
<td>46</td>
<td>Major orthopaedic hip surgery</td>
<td>≥ 2500 ml within 24 hr</td>
<td>PT, TT, Fbg, Platelets</td>
<td>No difference</td>
</tr>
<tr>
<td>Boldt 1996*</td>
<td>56</td>
<td>Trauma or surgical patients with sepsis</td>
<td>= 5 L HES or 3 L albumin in 5 days</td>
<td>Platelet aggregation induced by ADP, epinephrine and collagen, Platelets, AT III, Fbg, aPTT, PT</td>
<td>No difference</td>
</tr>
<tr>
<td>Boldt 1998*</td>
<td>300</td>
<td>Trauma and sepsis patients</td>
<td>= 5 L HES or 2 L albumin in 5 days</td>
<td>Fbg, aPTT, VIII:c, TAM, D-dimer, t-PA, u-PA, PAI, PAFe</td>
<td>No difference</td>
</tr>
<tr>
<td>Kapioti 1994*</td>
<td>10</td>
<td>Healthy volunteers, cross-over study</td>
<td>= 1800 ml</td>
<td>Fbg, aPTT, VIII:c, TAM, D-dimer, t-PA, u-PA, PAI, PAFe, PT, aPTT, Platelets, bleeding time, Fbg, Factor VII, VIII, IX</td>
<td>Decreased levels of VIII:c after HES</td>
</tr>
<tr>
<td>London 1989*</td>
<td>94</td>
<td>Cardiac surgery in children</td>
<td>= 75 gram in priming solution</td>
<td>PT, aPTT, Platelets, bleeding time, Fbg, Factor VII, VIII, IX</td>
<td>No difference</td>
</tr>
<tr>
<td>London, 1992*</td>
<td>60</td>
<td>CABG</td>
<td>= 1000 ml</td>
<td>PT, aPTT, Platelets, bleeding time, Fbg, Factor VII, VIII, IX</td>
<td>Increased aPTT after HES (only immediately at end of bypass)</td>
</tr>
<tr>
<td>Rackow 1989*</td>
<td>20</td>
<td>Sepsis</td>
<td>≥ 3000 ml gelatin and 20 ml/kg HES</td>
<td>Platelet aggregation induced by ristocetin and ADP, in vitro bleeding time, aPTT, PT, vWF</td>
<td>Decreased levels of vWF after MMW-HES and gelatin</td>
</tr>
<tr>
<td>Tignelaar 1997*</td>
<td>36</td>
<td>CABG</td>
<td>= 2500 ml</td>
<td>PT, aPTT, TT, Fbg, VIII:c, vWF</td>
<td>No difference</td>
</tr>
<tr>
<td>Vogt 1994*</td>
<td>41</td>
<td>Total hip replacement</td>
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<tr>
<td><strong>Studies with MMW-HES and high degree of substitution</strong></td>
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<tr>
<td>Treib 1996*</td>
<td>20</td>
<td>10-days hemodilution for cerebral circulatory disturbances</td>
<td>1000 ml/day on day 1-4, 500 ml/day on day 5-10</td>
<td>PT, aPTT, TT, Fbg, VIII:c, vWF</td>
<td>Progressive prolongation of aPTT and decreased levels of VIII:c and vWF after HES 200/0.62</td>
</tr>
</tbody>
</table>
### Table 1, continued

<table>
<thead>
<tr>
<th>Colloids</th>
<th>N=</th>
<th>Population</th>
<th>Amount of colloid</th>
<th>Parameters studied</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies with MMW-HES and high C2/C6 ratio</td>
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<tr>
<td>Treib 1995&lt;sup&gt;32&lt;/sup&gt;</td>
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<tr>
<td>10% HES</td>
<td>20</td>
<td>10-days hemodilution for cerebral circulatory disturbances</td>
<td>1000 ml/day on day 1-4, 500 ml/day on day 5-10</td>
<td>PT, aPTT, TT, Fbg, VIII:c, vWF</td>
<td>Increased aPTT and decreased levels of VIII:c and vWF after HES 200/0.5/13</td>
</tr>
<tr>
<td>HES 200/0.5/6</td>
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<tr>
<td>In Vitro studies</td>
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<tr>
<td>Egli 1997&lt;sup&gt;37&lt;/sup&gt;</td>
<td>96</td>
<td>In vitro experiments</td>
<td>30 or 60% dilution</td>
<td>Thromboelastography</td>
<td>Compromised coagulation parameters and increased clot lysis after HES, gelatin and albumin. Maximum effect found with HES.</td>
</tr>
<tr>
<td>6% HES 200/0.5, 4% modified gelatin, 5% albumin, 0.9% saline</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mardel 1996&lt;sup&gt;40&lt;/sup&gt;</td>
<td>20</td>
<td>In vitro experiments</td>
<td>15-75% dilution</td>
<td>Clot weights and elasticity by thromboelastography</td>
<td>Decreased clot weights and elasticity after dilution by polygeline and modified gelatin</td>
</tr>
<tr>
<td>3.5% polygeline, 4% modified gelatin, 0.9% saline</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortier 1997&lt;sup&gt;44&lt;/sup&gt;</td>
<td>11</td>
<td>In vitro experiments</td>
<td>50% dilution</td>
<td>Thromboelastography</td>
<td>Increased clot formation time and decreased maximum amplitude after HES. Dilution with dextran resulted in extremely compromised coagulation</td>
</tr>
<tr>
<td>6% HES 200/0.5, 4% modified gelatin, 10% dextran 40</td>
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</tr>
<tr>
<td>Jannicki 1998&lt;sup&gt;70&lt;/sup&gt;</td>
<td>80</td>
<td>In vitro experiments</td>
<td>30% and 60% dilution</td>
<td>Thromboelastography</td>
<td>Comparable decrease in coagulation parameters and increased clot lysis after both HES solutions</td>
</tr>
<tr>
<td>6% HES 130/0.4, 6% NaCl</td>
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<tr>
<td>HES 200/0.5, 0.9%</td>
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</table>

Studies comparing gelatin with albumin or MMW-HES did find no difference, except for one study that observed decreased blood loss after gelatin when compared to MMW-HES and one that found increased blood loss when compared to albumin, but only in a sub-group also treated with aprotinin.<sup>29,33</sup> Thus, it appears that dextran and HMW-HES can induce an increased bleeding tendency, whereas MMW-HES and gelatin are probably safe in this respect. There are, however, two major limitations to this conclusion. First, no studies have addressed the risk of bleeding after repeated administration of colloids. Theoretically, this could easily increase the risk of bleeding, especially with infusion of slowly degradable HES. Second, these conclusions are probably only valid in subjects with normal levels of vWF or even increased levels due to the acute phase response in acutely ill patients. All artificial colloids should be given cautiously to patients who are known with even mild forms of von Willebrand's disease. In those circumstances alternatives like plasma or albumin, although associated with other serious complications, could be considered.
Table 2. Overview of prospective randomized clinical trials comparing post-operative blood loss after different plasma substitutes.

<table>
<thead>
<tr>
<th>Colloids</th>
<th>N=</th>
<th>Population</th>
<th>Amount of colloid</th>
<th>Outcome</th>
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<tbody>
<tr>
<td><strong>Dextran vs. Albumin</strong></td>
<td></td>
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</tr>
<tr>
<td>Lisander, 1996</td>
<td>40</td>
<td>Revision hip arthroplasty</td>
<td>≈ 10 ml/kg</td>
<td>Increased blood loss and blood transfusion after dextran</td>
</tr>
<tr>
<td>Boldt 1993</td>
<td>60</td>
<td>CABG</td>
<td>1190 – 1450 ml</td>
<td></td>
</tr>
<tr>
<td>Mortelmans, 1995</td>
<td>42</td>
<td>Total hip replacement</td>
<td>≈ 2000 ml</td>
<td></td>
</tr>
<tr>
<td>Beyer 1997</td>
<td>46</td>
<td>Major orthopaedic hip surgery</td>
<td>≈ 2500 ml within first 24 hr</td>
<td></td>
</tr>
<tr>
<td>Tigchelaar, 1997</td>
<td>36</td>
<td>CABG</td>
<td>Maximum dose: 3000 ml gelatin and 20 ml/kg MMW-HES</td>
<td></td>
</tr>
<tr>
<td><strong>HES vs. Gelatin</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Boldt 1993</td>
<td>60</td>
<td>CABG</td>
<td>1190 – 1450 ml</td>
<td>Increased blood loss after HMW-HES. No difference between MMW-HES and gelatin</td>
</tr>
<tr>
<td>Brutocao, 1996</td>
<td>38</td>
<td>Cardiac surgery in children</td>
<td>Up to 30 ml/kg</td>
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<tr>
<td>Vogt 1996</td>
<td>41</td>
<td>Total hip replacement</td>
<td>≈ 2500 ml</td>
<td></td>
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<tr>
<td>London 1989</td>
<td>94</td>
<td>After cardiac surgery</td>
<td>≈ 1800 ml</td>
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<tr>
<td>London 1992</td>
<td>60</td>
<td>Cardiopulmonary bypass priming solution</td>
<td>75 gram</td>
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<td>Tigchelaar, 1997</td>
<td>36</td>
<td>CABG</td>
<td>Maximum dose: 3000 ml gelatin and 20 ml/kg MMW-HES</td>
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<tr>
<td>Rosencher, 1992</td>
<td>16</td>
<td>Total hip replacement</td>
<td>1500 – 2000 ml</td>
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<td><strong>Gelatin vs. Albumin</strong></td>
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<tr>
<td>Tabuchi 1995</td>
<td>60</td>
<td>CABG</td>
<td>2000 ml as priming solution for extracorporeal circuit</td>
<td>Increased blood loss after gelatin in sub-group also treated with aprotinin</td>
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<tr>
<td>Wahba, 1996</td>
<td>20</td>
<td>Cardiac surgery</td>
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References

41. Lockwood DN, Bullen C, Machin SJ. A severe coagulopathy following volume
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Chapter 8


