Effects of artificial colloids on haemostasis

Artificial colloids are used in situations with a high risk of bleeding such as trauma or during surgery. Although more efficacious than crystalloids, colloids can be associated with derangements of the haemostatic system and may also interfere with normal haemostasis via a number of different mechanisms.

Artificial colloids such as gelatins and hydroxyethyl starch preparations are frequently used in blood loss replacement to restore intravascular volume and avoid the risk associated with transfusion of allogenic blood products (Stoelting, 1991). The vascular membrane is freely permeable to crystalloids and therefore even a massive crystalloid resuscitation is less likely to achieve adequate restoration of microcirculatory blood flow than a colloidal-based volume replacement strategy (Funk and Baldinger, 1995). Although artificial colloids correct hypovolaemia more effectively than crystalloids, they have been associated with interferences of the haemostatic system (*Table 1*), which may be a consequence of not only the dilution of coagulation factors but also direct impairment of the coagulation system (Petroianu et al, 2000). This review focuses on the antihaemostatic effects of hydroxyethyl starch and gelatins on platelet function and blood coagulation.

Hydroxyethyl starches

Hydroxyethyl starches are polymers of glucose units derived from amylopectin and modified by substituting hydroxyethyl for hydroxyl groups on glucose molecules. Considerable insight into the influence of hydroxyethyl starch on blood coagulation comes from Treib et al (1995, 1996), who concluded that the negative effects on haemostasis depended on the in-vivo molecular weight and the rate of enzymatic degradation. Hydroxyethyl starch 130/0.4 is a newly developed third-generation hydroxyethyl starch solution, which has a smaller and more narrowly distributed molecular weight, a lower molar substitution ratio, a larger C2/C6 ratio, and seems to impair the coagulation system less than higher molecular weight hydroxyethyl starch solutions (Jamnicki et al, 1998; Gallandat Huet et al, 2000; Langeron et al, 2001). Kasper et al (2003) reported that the use of large-dose hydroxyethyl starch 130/0.4 of up to 50 ml/kg resulted in comparable blood losses and transfusion requirements to hydroxyethyl starch 200/0.5 at the recommended dose of 33 ml/kg in coronary artery bypass surgery patients. It seemed to be at least as safe as gelatin preparations (Haisch et al, 2001; Van der Linden et al, 2005) with regard to the use of allogeneic blood and blood products, or the standard coagulation variables and thrombelastograph measurements.

A study by Chong Sung et al (2006), using 6% hydroxyethyl starch 130/0.4 solution (10 ml/kg) for fluid replacement in 42 children aged between 6 months and 10 years who were undergoing cardiac surgery, showed no major differences in postoperative blood loss, transfusion requirement and activated partial thromboplastin time values compared to those treated with fresh frozen plasma during the first 24 hours. In these studies, however, some patients from both groups received fresh frozen plasma or platelets, which may have blurred potential differences. In contrast, a meta-analysis showed increased blood loss in children and adults receiving hydroxyethyl starch during cardiac surgery as compared to those treated with albumin (Wilkes et al, 2001), and some authors recommend caution in administering hydroxyethyl starch (Veldeman and Fischer, 2004; Wiedermann, 2004).

Numerous studies have compared different colloidal solutions using thrombelastograph or other viscoelastic measurements of clot formation, but most have shown that coagulation is more severely impaired by hydroxyethyl starch preparations than gelatins or albumin, especially when haemodilution becomes profound (Egli et al, 1997; Fries et al, 2002; Nielsen, 2005). Hydroxyethyl starch solution caused a von Willebrand disease type 1-like syndrome characterized by diminished coagulation factor VIII:C levels (Stump et al, 1985; Treib et al, 1995), which decreased more than might be expected from plasma dilution alone. The pathogenic mechanism is not completely elucidated, but the most frequently quoted hypothesis refers to accelerated elimination of the coagulation factor VIII/von Willebrand factor complexes after they bind with hydroxyethyl starch molecules (Treib et al, 1995), which may delay generation of sufficient thrombin to convert fibrinogen to fibrin (Collins et al, 2006). Furthermore, von Willebrand factor-mediated rolling and adhesion of platelets to subendothelial collagen could be diminished by the reduction in coagulation factor VIII/von Willebrand factor complexes (Treib et al, 1995).

Infusion of hydroxyethyl starch causes an efflux of coagulation factors from the vascular to the interstitial space, reducing blood coagulation capacities (Lucas et al, 1988), and also a decreased interaction of activated factor XIII with fibrin polymer (Nielsen, 2005, 2006a). The latter effect causes slowly growing and weaker clot formation which are subject to faster fibrinolysis (Nielsen, 2006b).

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Table 1. Characteristics of the available colloids and their effects on coagulation

Product		Commercial name	Concentration (%)	Oncotic pressure (mmHg)	Initial volume expansion (%)	Maximal dose (ml/kg/24 hr)	Effect on haemostasis
Natural colloid		Albumin	4	20–29	80		None
Artificial colloid	Fluid gelatin	Gelofusine	4	42	90		None–weak
	HES 200/0.5*	Hesteril	6	30–37	100	33	Weak
	HES 130/0.4*	Voluven	6	36	130	50	None–weak

HES = hydroxyethyl starch. * the first number is the mean molecular weight in kilodaltons and the second is the molar substitution ratio of hydroxyethyl starch substitution

On the other hand, platelet volume decreases after infusion of hydroxyethyl starch, presumably because of a shrinkage of platelets by the increased plasma colloid osmotic pressure (Stump et al, 1985). Hydroxyethyl starch may also induce cellular abnormalities with a decreased agonist-induced expression and activation of platelet surface GPIIb-IIIa by blocking the access of ligands to surface receptors or by inhibition of the conformational change of GPIIb-IIIa (Franz et al, 2001; Deusch et al, 2003; Thaler et al, 2005). Reduced availability of activated GPIIb-IIIa in turn impairs platelet adhesion to surface-bound fibrinogen and, most importantly, soluble fibrinogen ligand binding between neighbouring platelets, causing platelet aggregation. By adhesion and aggregation, platelets form a maze in which plasma can clot without thrombin being washed away. Activated platelets also provide the surface on which thrombin generation can take place (Monroe et al, 2002). Hence, it remains to be determined whether hydroxyethyl starch impairs platelet procoagulant activity by modifying the binding of constituents of the prothrombinase and tenase complex to the negatively charged phospholipids exposed on activated platelets, and subsequent thrombin generation (Deusch et al, 2003).

Gelatins

There are two distinct forms of gelatin solutions: succinylated gelatins and polygelines, both of which have an oncotic power close to that of plasma (Van der Linden and Schmartz, 1992). The daily dose of gelatin solutions is not limited, in contrast to other synthetic colloids.

Gelatins were not considered to have a significant negative influence on haemostatic competence other than by dilution (Karoutsos et al, 1999), but in-vivo and in-vitro studies have questioned this. In a study with healthy volunteers, infusion of 1 litre of gelatin resulted in a 1.7-fold increase in bleeding time, a substantial decrease in von Willebrand factor and ristocetin cofactor, and a significant impairment of ristocetin-induced platelet aggregation. The mechanism appears to be related to binding of von Willebrand factor to gelatin at its collagen binding sites, resulting in accelerated clearance of von Willebrand factor–gelatin complexes. Gelatin also binds with fibronectin (Engvall et al, 1978) and decreases plasma fibronectin concentration (Brodin et al, 1984), which forms covalent cross linkages and non-covalent associations with fibrin. These gelatin-based products may become incorporated into developing clots, thus disturbing clot architecture and mechanics (Egli et al, 1997; Niemi et al, 2006) by interfering with polymerization of fibrin monomers and growth of the clot's macromolecular structure (Mardel et al, 1998; Evans et al, 2003).

Furthermore, in a gelatin-diluted porcine model, Fries et al (2005) demonstrated that the administration of fibrinogen was not only able to restore the impaired clot firmness and clot formation time, but also able to reduce blood loss, even in the case of uncontrolled haemorrhage after liver laceration. Nevertheless, while fibrin polymerization itself is related both to thrombin generation and to the quantity and property of fibrinogen, it remains to be determined whether gelatin impairs thrombin formation and how it interferes with the reticular fibrin network. As gelatin appears to inhibit platelet aggregation induced by activators of the platelet receptor GPIIb-IIIa (Evans et al, 1998), it also remains to be determined whether the impairment of platelet procoagulant activity by denatured collagen is another potential mechanism of gelatin-induced impairment of haemostasis.

The clinical relevance of the impairment of haemostasis after gelatin infusion is uncertain. Only one study observed an increase in perioperative blood loss after cardiac surgery with gelatins compared to human albumin (Tabuchi et al, 1995). In this particular study, patients in the gelatin group received more than 3500 ml of gelatin. However, other studies comparing gelatin with hydroxyethyl starch or hydroxyethyl starch and albumin found no difference or, in some cases, an improvement in postoperative blood loss when gelatin was given (Boldt et al, 1993; Haisch et al, 2001; Van der Linden et al, 2005).

Conclusions

Hydroxyethyl starch and gelatin have negative influences on the coagulation system in addition to the dilutional effect. Depending on the type of compound, these effects relate to primary haemostasis, but may have repercussions on the coagulation cascade. In addition to a decrease in von Willebrand factor, with or without an associated reduction in factor VIII plasma levels and a resulting effect on thrombin generation, every colloid solution may also interfere with normal haemostasis in a particular way: hydroxyethyl starch inhibits platelet function, whereas

gelatin disturbs clot architecture and mechanics. In most cases, the clinical consequences of these effects are limited. The situation may be different if a large amount of either solution is given to patients presenting with haemostatic disorders, although marked differences between hydroxyethyl starch and gelatin may exist. **BJHM**

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KEY POINTS

- Colloid solutions are widely used for intravascular volume expansion in various clinical situations.
- Hydroxyethyl starch and gelatin are frequently used colloid solutions.
- Interference of colloids with the haemostatic system has become an increasing concern.
- The effect of colloids on haemostasis relates to primary haemostasis, but may have repercussions for the coagulation cascade.
- Hydroxyethyl starch and gelatin may interfere with normal haemostasis in a specific way.