**Purpose of review**
Infusion therapy is essential in intravascular hypovolaemia and extravascular fluid deficits. Crystalloidal fluids and colloidal volume replacement affect blood coagulation when infused intravenously. The question remains if this side-effect of infusion therapy is clinically relevant in patients with and without bleeding manifestations, and if fluid-induced coagulopathy is a risk factor for anaemia, blood transfusion, and mortality, and a driver for resource use and costs.

**Recent findings**
Pathomechanisms of dilutional coagulopathy and evidence for its clinical relevance in perioperative and critically ill patients are reviewed. Furthermore, the article discusses medicolegal aspects.

**Summary**
The dose-dependent risk of dilutional coagulopathy differs between colloids (dextran > hetastarch > pentastarch > tetrastarch, gelatins > albumin). Risk awareness includes monitoring for early signs of side-effects. With rotational thromboelastometry/thrombelastography, the deterioration not only in clot strength but also in clot formation and in platelet interaction can be assessed. Fibrinogen concentrate administration may be considered in severe bleeding as well as relevant dilutional coagulopathy. Targeted doses of gelatins and tetrastarches seem to have no proven adverse effect on anaemia and allogeneic blood transfusions. Further studies are needed.

**Keywords**
blood loss, blood transfusion, dilutional coagulopathy, hydroxyethyl starch

**INTRODUCTION**
Perioperative bleeding in trauma and surgery may be due to ruptured or cut vessels – often referred to as surgical bleeding – and/or may be induced by deteriorations in haemostatic competence – often referred to as coagulopathic bleeding. Perioperative acquired coagulopathy is complex and has been recently reviewed [1]. Changes in the blood coagulation system in the perioperative period include, for example, hyperfibrinolysis, coagulopathy due to blood loss, consumption, dilution, hypothermia, acidosis, hypocalcaemia, and anticoagulation. These coagulopathic changes in massive bleeding may result in a defect in clot firmness due to fibrinogen deficiency (being an early phenomenon) and thrombocytopenia, impaired clot stability due to hyperfibrinolysis and factor XIII deficiency (being a late phenomenon), and prolonged clot generation due to various coagulation factor deficiencies (Table 1).

Haemostatic strategies to stop severe bleeding in elective surgery and in peripartum haemorrhage have been summarized in the respective evidence-based guidelines from the European Society of Anaesthesiology [2]. The European Trauma guidelines describe the management of trauma-induced coagulopathy [3]. A prerequisite for targeted bleeding control is a sensitive and rapid identification of the actual cause(s) of bleeding. Viscoelastic point-of-care testing such as rotational thromboelastometry (ROTEM) or thrombelastography (TEG) may guide a timely, rational, and individualized therapy including, for example, administration of antihyperfibrinolytic drugs and/or potent coagulation factor concentrates (Table 1) [1–3]. Practicability and cost-effectiveness support this monitoring-guided concept [4*].

Obviously, patients with surgical and coagulopathic bleeding are susceptible for additional hits on the clotting system. For example, coagulopathic bleeding may be aggravated by inherited bleeding

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diathesis or preexisting antithrombotic (anticoagulant, antiplatelet) medication [2,3]. Intravenous infusions of fluids not containing coagulation factors and cellular procoagulant surfaces may also impair coagulation by unspecific dilution of the coagulation potential, and by specific anticoagulant side-effects.

Pathomechanisms of specific anticoagulant side-effects include acquired von Willebrand syndrome, factor VIII decrease, impaired thrombin generation, impaired thrombin–fibrinogen interactions, impaired factor XIII–fibrin polymer interaction, enhanced fibrinolytic response, reduced glycoprotein IIb–IIIa availability, decreased platelet aggregability and adhesion.

Impairment in fibrin polymerization is suggested to be the most outcome-relevant side-effect of colloids on coagulation, but is transient in nature and can – at least partially – be reversed by fibrinogen concentrate administration.

If colloids are infused restrictively and according to individualized preload and/or microcirculatory targets, dose-dependent side-effects on clot strength are suggested to be minimal and not requiring reversal.

**KEY POINTS**

- Intravenous infusions of fluids not containing coagulation factors and cellular procoagulant surfaces impairs coagulation by unspecific dilution of the coagulation potential, and by specific anticoagulant side-effects.
- Pathomechanisms of specific anticoagulant side-effects include acquired von Willebrand syndrome, factor VIII decrease, impaired thrombin generation, impaired thrombin–fibrinogen interactions, impaired factor XIII–fibrin polymer interaction, enhanced fibrinolytic response, reduced glycoprotein IIb–IIIa availability, decreased platelet aggregability and adhesion.
- Impairment in fibrin polymerization is suggested to be the most outcome-relevant side-effect of colloids on coagulation, but is transient in nature and can – at least partially – be reversed by fibrinogen concentrate administration.
- If colloids are infused restrictively and according to individualized preload and/or microcirculatory targets, dose-dependent side-effects on clot strength are suggested to be minimal and not requiring reversal.

**DILUTIONAL COAGULOPATHY**

Crystalloids and colloids have clearly different anticoagulant side-effects. First, the unspecific dilutional effect on coagulation is determined by the fluid’s volume efficacy, with colloids having a higher efficacy compared with crystalloids [5]. CRYSTMAS (Effects of Voluven on Hemodynamics and Tolerability of Enteral Nutrition in Patients With Severe Sepsis), FIRST (Fluids In Resuscitation of Severe Trauma), CRYSTAL (Efficacy and Safety of Colloids Versus CRYSTALoids for Fluid Resuscitation in Critically Ill Patients), and CHEST (Crystalloid versus HydroxyEthyl Starch Trial) report reduced volume requirements in the colloid groups indicating superior volume efficacy over the comparator [6–9] even though preload-based management targets have generally not been employed.

Second, specific anticoagulant side-effects have been reviewed previously, with dose-dependent differences in the risk of dilutional coagulopathy among the colloids (dextran > hetastarch > pentastarch > tetrastarch, gelatine > albumin) [10,11]. Interestingly, also the transfusion of packed red blood cell concentrates with or without mixing it with plasma [fresh frozen plasma (FFP)] and reconstitution of whole blood results in haemodilution and may induce dilutional coagulopathy [12]. Table 2 summarizes specific anticoagulant effects of colloids.

**Table 1. Vicious cycle of coagulopathy in major bleeding (from [1])**

<table>
<thead>
<tr>
<th>Coagulation defect</th>
<th>Clot firmness ↓</th>
<th>Clot generation ↓</th>
<th>Clot stability ↓</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common pathomechanisms</td>
<td>Fibrinogen deficiency, thrombocytopenia</td>
<td>Coagulation factor deficiencies, hyperfibrinolysis</td>
<td>Hyperfibrinolysis, factor XIII deficiency</td>
</tr>
<tr>
<td>Indicative ROTEM parameters and tests</td>
<td>A 10 (MCF) in FIBTEM and EXTEM</td>
<td>CT in EXTEM and INTEM</td>
<td>ML in EXTEM</td>
</tr>
<tr>
<td>Therapeutic correction</td>
<td>Fibrinogen concentrate (alternative: cryoprecipitate), platelet concentrate</td>
<td>PCC (alternative: plasma, rFVIIa), TXA (alternative: EACA)</td>
<td>TXA (alternative: EACA), factor XIII concentrate</td>
</tr>
</tbody>
</table>

A 10, amplitude after 10 min; CT, clotting time; EACA, epsilon aminocaproic acid; EXTEM, test assessing global coagulability induced by tissue factor; FIBTEM, test sensitive for fibrin polymerization; MCF, maximum clot firmness; ML, maximum lysis; PCC, prothrombin complex concentrate; rFVIIa, recombinant factor VIIa; ROTEM, rotational thromboelastometry; TXA, tranexamic acid.

**Transient decrease in factor VIII and acquired von Willebrand syndrome**

In contrast to slowly degradable hydroxyethyl starch (HES; heta, hexa, and pentastarch), rapidly degradable HES solutions (tetrastarch) had no effect on factor VIII and von Willebrand factor (vWF) levels even at high doses of up to 50–70 ml/kg [13]. There is a physiologic increase in these acute-phase parameters in the postoperative period that has been found to be diminished only after slowly degradable HES. The pathogenetic mechanism responsible for the adverse effects on plasmatic coagulation is not yet understood. Association with larger HES molecules may accelerate elimination of the factor VIII/vWF complex [10,11]. Pathophysiologic consequences of the transient decrease in factor VIII and acquired...
von Willebrand syndrome are, for example, decreased ristocetin cofactor activity and increased activated partial thromboplastin time.

**Antiplatelet effects of colloids: extracellular coating**

Physicochemical differences among colloids and HES generations were found to be important for the platelet-inhibiting properties, with slowly degradable HES solutions exerting more pronounced effects than rapidly degradable HES [11]. The pathogenetic mechanism behind is the extracellular coating of the platelet surface with colloidal macromolecules [14] and, thereby, an inhibition in the conformational changes and/or interaction of glycoproteins IIb–IIIa and Ib with their ligands, such as fibrinogen. It remains to be determined whether extracellular coating impairs platelet procoagulant activity by modifying the binding of constituents of the prothrombinase and tenase complex to the negatively charged phospholipids exposed at activated platelets. Pathophysiological consequences of the mild colloidal antiplatelet effect is a prolongation in Platelet Function Analyzer-100 (PFA-100) closure times, decrease in platelet aggregation and adhesion, as well as deterioration in clot formation time in the ROTEM or angle α in the TEG.

**No major effects of colloids on fibrinolysis**

As reviewed previously [10,11], clots get more susceptible for fibrinolytic breakdown in the presence of HES and albumin in in-vitro experiments, but induction of hyperfibrinolysis after in-vivo colloid infusions has not yet been reported. The clinical importance of a profibrinolytic side-effect of colloids remains unclear.

**No major effect on the acceleration of clotting**

Mild-to-moderate haemodilution has been reported to accelerate the onset of clotting. This phenomenon may either be an in-vitro artefact, or HES may indeed serve as an additional surface able to activate coagulation factors, thus accelerating the conversion of fibrinogen to fibrin. In contrast to crystalloid-induced hypercoagulability, an imbalance between thrombin generation and antithrombin concentration is not suggested to be involved in HES-induced hypercoagulability [15].

**No major effects of hyperchloraemic metabolic acidosis on coagulation**

Profound acidosis may affect coagulation by pH-dependent structural changes in factor IX, impaired factor Xa and thrombin generation, impaired fibrinogen breakdown, and protein C consumption. Buffered plasma-adapted composition of the crystalloid carrier solution of colloids up to 20 ml/kg increases chloride levels but appears to have only little impact on platelet aggregation and ROTEM kinetics [16].

**Impaired fibrin polymerization and decrease in fibrinogen levels**

Historically, the effects of colloids on coagulation factor VIII and vWF have been identified early after licensing of slowly degradable HES solutions, whereas the effects on platelets and fibrin have not been detected before point-of-care coagulation tests became available. At present, impairment in fibrin polymerization is suggested to be the most outcome-relevant side-effect of colloids on coagulation. Sensitive parameter for monitoring decreased fibrin polymerization is the maximum clot firmness (MCF) in the ROTEM, especially in the test sensitive for fibrin polymerization (FIBTEM). Similar decreases in the maximum amplitude in the functional fibrinogen assay in the TEG are expected but have not been demonstrated so far. In-vitro experiments have major limitations in assessing the effects of colloids on coagulation [17]. However, in-vitro trials repeatedly confirmed a decrease in MCF (in INTEM and EXTEM tests) at 10–30% dilution with HES [18,19]. The carrier solution of HES (electrolyte balanced vs. nonbalanced) had no effect on ROTEM parameters [16,20]. In-vivo infusion series showed a decrease in clot kinetics and clot strength after HES infusion vs. Ringer’s acetate after stroke volume-directed administration in neurosurgical patients [21,22]. This decrease was found to be only transient in major abdominal surgery at doses up to 15 ml/kg HES; after 24 h of infusion, no significant differences could be detected anymore [23]. Confirming the transient nature of fibrin polymerization impairment, also in complex
cardiac surgery, ROTEM data were comparable at the first postoperative day in the groups receiving HES vs. lactated Ringer’s solution [24] or HES vs. albumin [25] for the pump prime. HES and albumin up to 50 ml/kg similarly affected clot formation and clot strength in cardiac surgery [26]. Tetrastarch and gelatine similarly affected ROTEM parameters at pump prime doses [27]. Preloading with tetrastarch or gelatine was associated with a mild hypocoagulable effect in healthy parturients presenting for elective caesarean section; however, all TEG parameters in both the groups remained within or very close to the normal range after preloading [28].

Animal experiments showed consistent results: progressive haemodilution in horses induced changes in TEG, which were, however, up to 40 ml/kg always within the normal range [29]. In a burn injury model in pigs, fibrinogen levels were significantly lower in HES vs. gelatine vs. plasma-resuscitated animals only 8 h postinjury; at the following time points, there were no differences [30]. In piglets, 20 ml/kg infused under pressure in 2 min induced immediate responses after 1 min: impairment of fibrin polymerization was more pronounced after HES vs. albumin vs. saline 0.9% [31]. But also albumin is not free of side-effects on fibrin polymerization: at large degrees of haemodilution, adverse effects are in excess of what can be explained by haemodilution alone and fibrinogen activity is more impaired after albumin vs. saline 0.9% [32]. In small infants, clot firmness decreased significantly but remained within the normal range after both albumin and gelatine [33]. The authors concluded that from a haemostatic point of view, it might be preferable to use gelatine solution as an alternative to albumin.

Fibrinogen levels decrease less after HES exposure compared with indicative ROTEM parameters [34,35]. Fibrin-based clot elasticity parameters measured by free oscillation rheometry were decreased in blood samples incubated with HES and gelatine but had limited comparability with the ROTEM [34].

**REVERSAL OF COLLOID-INDUCED COAGULOPATHY**

Unfortunately, there is no drug in our critical care repertoire that has no potential risks or side-effects. Risk awareness, coadministering prophylaxis, and targeted symptomatic treatment of side-effects are routine strategies. Some medications combine in one pill, for example the active painkiller with an adjuvant substance against the common side-effect of obstipation (e.g. oxycodon along with naloxone in Targin, Mundipharma GmbH, Vienna, Austria). Such a pharmacological approach appears to be acceptable if efficacy, safety, and galenic compatibility of the active compound and the adjuvant are proven, and if no alternatives without this side-effects exist.

If colloids are infused restrictively and according to individualized preload and/or microcirculatory targets (and if colloids are not abused for general fluid substitution) [36], dose-dependent side-effects on clot strength are suggested to be minimal and – most likely – not requiring reversal. Nevertheless, it is intriguing to consider prescribing colloids – in order to use their superiority in volume efficacy over crystalloids – together with fibrinogen concentrate – in order to reverse detected colloid-induced reductions in clot strength. Feasibility studies in in-vivo animal experiments indicate that fibrinogen concentrate can rapidly reverse MCF to baseline values [37**]. In vitro, however, HES-induced FIBTEM reductions could be reversed completely in some experiments by fibrinogen concentrate or cryoprecipitate [36] but not in others [35,37**]. HES-induced MCF reductions responded less to fibrinogen concentrate compared with gelatin or albumin (also at hypothermia), and the combination with factor XIII concentrate improved reversal [35,38,39]. These experimental findings suggest the use of fibrinogen concentrate after resuscitation with albumin and gelatins [39,40]. ROTEM parameters cannot be improved in vitro with factor XIII concentrate alone in any tested diluent [40].

No clinical and histopathological signs for thromboembolic events could be detected, suggesting safety of factor concentrates for reversal [37**]. Similarly, thrombin generation potential was not increased by fibrinogen concentrate addition in contrast to cryoprecipitate and plasma, suggesting thrombogenic risks of a reversal approach based on allogeneic blood products [41].

**CLINICAL RELEVANCE OF COLLOID-INDUCED COAGULOPATHY**

The question arises whether derangements in laboratory parameters translate into clinically relevant bleeding manifestations, burdens, and harm, and if fluid-induced coagulopathy is an independent risk factor for anaemia, blood transfusion, and mortality, as well as a driver for resource use and costs. These aspects of patient safety and healthcare economics get more attention as the WHO supports the multimodal therapeutic concept of patient blood management (PBM) [42]. Inherent side-effects of fluids on dilution-dependent anaemia and dilutional coagulopathy may counterbalance the role of fluids in PBM (to increase the tolerance to anaemia)
and, therefore, need careful consideration. PBM requires clinicians worldwide to apply a restrictive transfusion behaviour and use physiological triggers for transfusion of packed red blood cell instead of haemoglobin triggers.

Outcome studies found controversial results. A meta-analysis published in 2013 detected no adverse effects of tetrastarch in the surgical population. In 38 trials (3280 patients), no increase in blood loss was found; in 20 trials (2151 patients), no increase in allogeneic blood transfusions was found, and there was no signal for increased mortality [43]. More recent evidence confirmed no increase in blood loss and transfusion requirements after HES exposure in major abdominal surgery [23] and cardiac surgery [25,27,44]. In neurosurgery, blood loss was not increased in patients receiving HES [21,22]. Some studies, however, demonstrated increased transfusion requirements despite similar blood loss or intact coagulation in cardiac surgery [24,26]. The explanation may be the use of haemoglobin levels as transfusion triggers instead of physiological transfusion triggers; because of the higher volume efficacy, haemoglobin drops more after colloids compared with crystalloids. Reduced transfusion requirements, mortality, length of stay, and infections were observed in orthopaedic patients [45]. However, some authors reported increased blood loss [46,47]. Even an increased mortality has been reported in those patients developing HES-induced clot strength reductions [48]. Reduction in thromboelastographic maximum amplitude within the normal range was an independent predictor for mortality. Albumin administration seemed beneficial in an animal experiment in terms of reducing blood loss and improving survival [49].

Also in the critically ill and septic population, studies reported controversial results; mean increases of 18 ml FFP in HES-treated patients appear not clinically meaningful, despite being statistically significant [9]. No increase towards hypercoagulability in the TEG in septic patients receiving tetrastarch was hypothesized to be predictive for death and bleeding [50]. Some trials showed no effects of HES on blood loss [6], whereas others found an increase in major bleeding events and transfusion rates [48,50]. However, in the latter studies, indication and dosing of the tetrastarch has been criticized; not the drug per se but rather the way it had been used [51,52] was considered harmful. Post-hoc analyses and meta-analyses aggregate methodological concerns and hide them behind the claim of high-quality evidence-based medicine. Although waiting for refined trials considering denominators of quality of critical care, we have to acknowledge the alarming signs in the existing trials indicating deleterious effects of HES: patient safety management warrants the avoidance of HES in critical illness.

SOCIETAL PERSPECTIVE

After the statement of the European Medicines Agency [53], HES is less prescribed in Europe because of medicolegal considerations. The European Medicines Agency supported us to think twice before infusing any fluid intravenously and acknowledge that fluids are drugs. Interestingly, also other colloids are increasingly being avoided although the evidence for safety problems for albumin or gelatin is scarce. In the statement of the Co-Ordination Group for Mutual Recognition and Decentralized Procedures – Human (CMDh), healthcare professionals are informed to consider the following:

HES solutions should only be used for the treatment of hypovolaemia due to blood loss when crystalloids alone are not considered sufficient.

With this article, the authorities reinforce applying individualized medicine and using, for example, preload monitoring to assess hypovolaemia. This is a step forward from conventional pressure-based management strategies. Blood loss is defined as a prerequisite for colloidal HES infusion; replacement of extracellular water losses is clearly not listed as an indication for a colloidal infusion. The wording in this article leaves room for individual decision making because the lack of efficacy of crystalloids does not need to be proven in the individual patient but only anticipated by the attending clinician before choosing a more potent colloid.

HES solutions are contraindicated in severe coagulopathy. HES solutions should be discontinued at the first signs of coagulopathy. Blood coagulation parameters should be monitored carefully in case of repeated administration.

The CMDh group requires clinicians to monitor the actual coagulation potential repeatedly, without defining the appropriate methodology for laboratory testing, grades, and pathomechanisms. From a practical viewpoint, ‘severe coagulopathy’ will most likely prolong activated partial thromboplastin time and INR above 1.5 times normal. Global coagulation tests, however, are inappropriate for assessing pathomechanisms of perioperative bleeding [2] and ‘first signs’ of dilutional coagulopathy. The CMDh statement may suggest stopping HES infusion at the latest if clot strength in the FIBTEM decreases.
Towards hospital–internal trigger values for fibrinogen substitution. Even this sensitive viscoelastic parameter may deteriorate because of other pathomechanisms during perioperative bleeding; irrespective of HES, the avoidance of an additional hit is rational. HES infusion may be continued in the presence of bleeding, hypovolaemia, and haemodynamic instability, once clot strength has been corrected, for example, by fibrinogen substitution [54].

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as: & of special interest & of outstanding interest


This review condenses the increasing evidence for the cost-effectiveness of individualized management of coagulopathic bleeding.

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