Hydroxyethylstarch and gelatin solutions impair blood coagulation after cardiac surgery: a prospective randomized trial

A. Schramko1*, R. Suojaranta-Ylinen1, A. Kuitunen1, P. Raivio2, S. Kukkonen1 and T. Niemi1

1Department of Anaesthesiology and Intensive Care Medicine and 2Department of Cardiothoracic Surgery, Helsinki University Hospital, Meilahti Hospital, PO Box 340, Helsinki FI-00029 HUS, Finland

*Corresponding author. E-mail: alexey.schramko@hus.fi

Background. Colloids are often used after cardiac surgery as intravascular volume replacement therapy. Cardiac surgical patients have an increased risk of bleeding. Both hydroxyethylstarch (HES) and gelatin solutions impair haemostasis. We examined the impact and dose effect on coagulation of HES 130/0.4, gelatin, or Ringer’s acetate solutions after cardiac surgery.

Methods. Forty-five patients received three boluses (each 7 ml kg⁻¹) of either 6% HES 130/0.4, 4% gelatin, or Ringer’s acetate solution after elective cardiac surgery. The infusion of study solution was continued in the dose 7 ml kg⁻¹ over the following 12 h. The total dose of study solution was 28 ml kg⁻¹. Hypovolaemia was treated with Ringer’s acetate. Modified thromboelastometry was performed to detect coagulation disorders.

Results. Clot formation time was prolonged and clot strength decreased after infusion of 7, 14, and 21 ml kg⁻¹ of either colloid compared with the Ringer’s acetate group. After infusion of 14 and 21 ml kg⁻¹ of Ringer’s acetate, clot strength was slightly, but significantly, increased. On the first postoperative morning, clot strength was still decreased in the gelatin group in comparison with the Ringer’s acetate group. Neither HES nor gelatin induced fibrinolysis. Chest tube drainage was comparable between all groups.

Conclusions. Even a small dose of HES 130/0.4 or gelatin impaired clot strength after cardiac surgery in a dose-dependent fashion, but neither colloid increased blood loss.

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Colloids are used after cardiac surgery because of their ability to maintain intravascular volume and regional tissue perfusion more efficiently than crystalloids.1–3 Hydroxyethylstarch (HES) solutions modify blood coagulation in vivo and in vitro by prolonging coagulation time and decreasing clot strength.4,5 The use of rapidly degradable HES solutions (molar substitution ratio under 0.5) on bleeding is safe in comparison with slowly degradable HES solutions with high degrees of substitution.6,7 Despite its negative effect on laboratory parameters of blood coagulation, the modern ‘third generation’ HES 130/0.4 has not been associated with increased blood loss,5,8 and this solution has been recommended for fluid resuscitation.9

Previously, gelatin has been used in critically ill patients because of its minimal effect on renal function,10 but a recent study showed that gelatin impairs renal function more than the third-generation HES 130/0.4 solution.11 Gelatins also impair blood coagulation in vitro12 and influence platelet aggregation after cardiac surgery.13 Ringer’s solution does not disturb blood coagulation14 and has been used for fluid therapy in patients with coagulation disorders. No differences in mortality of critically ill patients have been demonstrated after the use of different colloid or crystalloid solutions.15

Cardiopulmonary bypass (CPB) causes powerful activation of the haemostatic system, and the risk of postoperative bleeding is increased.16 Previously, Wilkes and colleagues17 showed that the use of HES solutions (HES 450/0.7 and HES 200/0.5) after CPB predisposed patients to increased blood loss.

We recently showed that a relatively small dose of rapidly degradable HES solutions (HES 130/0.4 and 200/0.5) after...
ELECTIVE CARDIAC SURGERY IMPAIRED BLOOD COAGULATION WITHOUT ANY CLINICAL EFFECT ON BLOOD LOSS.\(^5\) IN OUR PREVIOUS STUDY,\(^5\) HES WAS GIVEN AS A SINGLE DOSE (15 ml kg\(^{-1}\)). CONSEQUENTLY, THE PRESENT RANDOMIZED SINGLE-BLINDED STUDY WAS DESIGNED TO EVALUATE THE EFFECT OF REPEATED DOSES OF HES 130/0.4 AND GELATIN ON BLOOD COAGULATION AND ON BLOOD LOSS AFTER CARDIAC SURGERY IN A CONTROLLED SETTING. RINGER’S ACETATE WAS USED AS A CONTROL. BLOOD COAGULATION WAS STUDIED USING MODIFIED THROMBOELASTOMETRY (ROTEM\(^6\)) USING FOUR DIFFERENT COAGULATION TESTS TO DETERMINE POSSIBLE MECHANISMS OF COAGULATION DISTURBANCES.

**Methods**

**Patients**

Forty-five patients undergoing elective primary cardiac surgery (between January 2007 and December 2008) were included in the study. The Ethics Committee for Surgery in the Hospital District of Helsinki and Uusimaa, and National Agency of Medicines in Finland, accepted the study protocol (EudraCT ref. no. 2006-003896-11). All patients gave written informed consent to participate in the study. Patients with a known preoperative coagulation disorder, renal or hepatic failure (creatinine > 120 \(\mu\)mol litre\(^{-1}\), alanine aminotransferase > 90 unit litre\(^{-1}\), or aspartate aminotransferase > 70 unit litre\(^{-1}\)), preoperative left ventricular ejection fraction < 40%, patients who had received warfarin, heparin, low-molecular-weight heparin, clopidogrel, or acetylsalicylic acid within the previous 5 days before the operation were excluded. Preoperative cardiac medication was continued until the morning of surgery, except for angiotensin-converting enzyme inhibitors and angiotensin II antagonists.

Patients were premedicated and treated during surgery according to the clinical protocol of the hospital as described earlier.\(^7\) CPB was performed using a non-pulsatile pump and a membrane oxygenator in a standard manner.\(^8\) Ringer’s acetate was given during surgery. Shed mediastinal blood was not retransfused in the postoperative manner.\(^5\) Ringer’s acetate was given during surgery. Shed mediastinal blood was not retransfused in the postoperative period. Tranexamic acid, \(\varepsilon\)-aminocaproic acid, aprotinin, and colloid solutions were not given during surgery.

**Study groups**

Immediately after admission to the intensive care unit (ICU), subjects were allocated in a random order (closed envelopes were prepared before the beginning of the study by a person who did not take part in the treatment of the study subjects) to receive one of the following solutions:

(i) 6% HES solution (Voluven\(^®\); 60 mg ml\(^{-1}\), average molecular weight 130 kDa, molar substitution ratio 0.4; Fresenius Kabi, Bad Homburg, Germany) (HES group, \(n=15\));

(ii) 4% gelatin solution (Gelofusine\(^®\); B. Braun Medical OY, Helsinki, Finland) (GEL group, \(n=15\));

(iii) Ringer’s acetate solution (Ringer-acetate\(^®\); Fresenius Kabi) (RIN group, \(n=15\)).

Three boluses (each 7 ml kg\(^{-1}\)) of the study solution were administered in order to keep the pulmonary capillary wedge pressure (PCWP) between 10 and 15 mm Hg and cardiac index over 2.0 litre min\(^{-1}\) m\(^{-2}\). Thereafter, a dose of 7 ml kg\(^{-1}\) of the study solution was slowly administered during the following 12 h. Subjects received a total dose of 28 ml kg\(^{-1}\) of the study solution within 16–20 h after surgery.

**Haemodynamic management and blood transfusion**

Epinephrine infusion was initiated (0.02–0.2 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) when the cardiac index remained < 2.0 litre kg\(^{-1}\) min\(^{-1}\), despite the aimed pulmonary artery wedge pressure between 10 and 15 mm Hg. Norepinephrine infusion (0.03–0.3 \(\mu\)g kg\(^{-1}\) min\(^{-1}\)) was started whenever mean systemic arterial pressure was below 70 mm Hg, despite the previously described PCWP and cardiac index. Additional infusions of Ringer’s acetate were administered, if the PCWP was below 10 mm Hg despite the infusion of the study solution.

In the ICU, haemoglobin concentration (Hb) was maintained above 8.0 g dl\(^{-1}\) with packed red blood cells. If postoperative blood loss exceeded 200 ml h\(^{-1}\), ACT (ACTII\(^®\), Medtronic Inc., Minneapolis, MN, USA), prothrombin time value (Nycostest PT\(^®\), Oslo, Norway), and platelet count (PC) were determined. If PC was below \(50 \times 10^9\) litre\(^{-1}\), 1 unit of 10 kg\(^{-1}\) platelet concentrate was given. If activated clotting time (ACT) was prolonged more than 10 s compared with the pre-bypass level, 25 mg of protamine was administered. If prothrombin time was > 30 s, 5 ml kg\(^{-1}\) of fresh-frozen plasma was transfused. If bleeding continued, 1 g of tranexamic acid was given.

**Thromboelastometry and laboratory analyses**

Thromboelastometry, haemodynamic, and laboratory measurements were performed upon arrival to ICU (Pre), after each bolus of the study infusion (7, 14, and 21 ml kg\(^{-1}\)), and on the first postoperative morning (1 POM).

Blood samples for thromboelastometry were collected via a non-heparinized radial artery catheter into polypropylene tubes (BD Vacutainer\(^®\), BD Diagnostics, Plymouth, UK) containing 3.2% buffered citrate. Modified thromboelastometry coagulation analysis (ROTEM\(^®\); Pentapharm CO, Munich, Germany) using four different ROTEM\(^®\) tests [intrinsic ROTEM (contact coagulation activator, InTEM\(^®\)); extrinsic ROTEM (tissue coagulation activator, ExTEM\(^®\)); fibrinogen ROTEM (FibTEM\(^®\)); aprotinin ROTEM (ApTEM\(^®\))] was performed by an investigator blinded to the study colloid. With the FibTEM\(^®\) test, platelet function is inhibited by cytochalasin D to prevent platelet aggregation. FibTEM\(^®\) measures the strength of the fibrin
component of the clot. ApTEM® identifies hyperfibrinolysis by addition of aprotinin to ExTEM®.18

Coagulation was initiated with activators using a semi-automated electronic pipette system according to the manufacturer’s instructions. Coagulation was allowed to proceed for 60 min. Automatic ROTEM® variables were: clotting time (CT, s), clot formation time (CFT, s), α-angle (α, degree), maximum clot firmness (MCF, mm), and clot lysis (%). The variables of thromboelastometry are validated with standard coagulation tests.19 The effect of platelets on clot strength was assessed by the difference between ExTEM® and FibTEM®-induced MCF: platelet MCF=ExTEM® MCF–FibTEM® MCF.20

Arterial blood samples were analysed for Hb (g litre⁻¹), haematocrit (Hct, %), and PC (10⁹ litre⁻¹) using Cell-Dyn 610 haematology analyzer (Sequila-Turner Corp., Mountain View, CA, USA). ACT was measured by ACT II® device (Medtronic Inc., Minneapolis, MN, USA).

Cumulative chest tube drainage, urine output, and the cumulative amount of transfused blood products and Ringer’s acetate solution were recorded after surgery, on arrival in the ICU, after each bolus of the study solution, and on the 1 POM.

Statistical analysis

The number of subjects needed for the study was based on an expected difference in MCF of the thromboelastometry tracing which has been shown to correlate with postoperative bleeding after cardiac surgery.21 On the basis of our previous study,20 it was estimated that 15 subjects per group were needed to detect a decrease of 15% in MCF with an α- and a β-error of 0.05 and 0.2, respectively. Since the data were normally distributed (Kolmogorov–Smirnov test), analysis of variance (ANOVA) was applied. After ANOVA, pairwise comparisons were performed by the Bonferroni test as indicated. t-test was used to compare paired differences within the groups. The results are reported as means and standard deviations (±s). Frequencies were tested by χ² test. P-values of <0.05 were considered to be statistically significant. All statistical measurements were performed with SPSS for Windows (version 16.0).

Results

Subjects in all three groups were comparable regarding patient characteristic and operative data (Table 1). Routine laboratory tests were within the normal range before operation (data not shown). Two subjects in the HES, four in the GEL, and three in the RIN groups received red blood cells, and one subject in the GEL and RIN groups received platelet concentrate intraoperatively (P<0.97 and 0.63 between all groups, respectively). Fresh-frozen plasma was not transfused intraoperatively (Table 2).

Baseline thromboelastometry was similar in the study groups (Table 3). Infusion of 7, 14, and 21 ml kg⁻¹ of colloid solutions decreased MCF and α-angle, and prolonged CFT using all ROTEM® tests. After infusion of 14 ml kg⁻¹ of Ringer’s solution, the MCF (using ExTEM® and FibTEM® tests) and α-angle were significantly increased and CFT decreased (using InTEM®) in comparison with Pre. Using the ApTEM® test, MCF was increased in the RIN group after infusion of 21 ml kg⁻¹ and on the 1 POM. Platelet MCF (ExTEM® MCF–FibTEM® MCF) remained unchanged during the study period in all groups (data not shown).

CFT was longer, and MCF and α-angle were lower after infusion of 7, 14, and 21 ml kg⁻¹ of both colloid solutions in comparison with the RIN group using InTEM® and ExTEM® tests. With FibTEM® (only MCF was measured) and ApTEM®, CFT was prolonged and MCF and α-angle decreased significantly in both colloid groups in comparison with the RIN group after doses of 14 and 21 ml kg⁻¹ of study solution. On the 1 POM, MCF and α-angle were still lower in the GEL group in comparison with the RIN group using the ExTEM®, FibTEM®, and ApTEM® tests. Using InTEM®, MCF in the GEL group was significantly lower than in the HES and RIN groups, but there was no difference between the HES and RIN groups.

CT was prolonged after infusion of 14 ml kg⁻¹ (using ExTEM®) of HES in comparison with the RIN group (P<0.02). Otherwise, CT was comparable between the groups (P>0.05).

There were no differences in lysis parameters (P>0.05) between groups before and after study solution infusions.

Table 1 Patient characteristic and operative data. Values are number of patients or mean (range). One-way ANOVA or χ² test as appropriate. AVR, aortic valve replacement; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; GEL, 4% gelatin; HES, hydroxyethylstarch 130/0.4; MVR, mitral valve repair; RIN, Ringer’s acetate

<table>
<thead>
<tr>
<th></th>
<th>HES</th>
<th>GEL</th>
<th>RIN</th>
<th>P all groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>10/5</td>
<td>9/6</td>
<td>10/5</td>
<td>0.91</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65 (46–84)</td>
<td>63 (50–78)</td>
<td>65 (50–77)</td>
<td>0.55</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77 (59–100)</td>
<td>76 (55–89)</td>
<td>72 (50–94)</td>
<td>0.56</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>1.9 (1.6–2.1)</td>
<td>1.9 (1.6–2.1)</td>
<td>1.8 (1.5–2.2)</td>
<td>0.65</td>
</tr>
<tr>
<td>CABG</td>
<td>10</td>
<td>8</td>
<td>7</td>
<td>0.53</td>
</tr>
<tr>
<td>AVR</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>0.14</td>
</tr>
<tr>
<td>MVR</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>0.21</td>
</tr>
<tr>
<td>AVR+CABG</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0.36</td>
</tr>
<tr>
<td>Duration of CPB (min)</td>
<td>91 (58–186)</td>
<td>98 (72–140)</td>
<td>80 (42–129)</td>
<td>0.22</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>65 (38–146)</td>
<td>72 (51–102)</td>
<td>59 (25–106)</td>
<td>0.35</td>
</tr>
</tbody>
</table>
After completion of 7, 14, and 21 ml kg⁻¹, was increased after completion of 7 and 21 ml kg⁻¹.

After operation, the chest tube drainage during 18 h after surgery were comparable in all three groups (Table 2). There were no statistically significant differences in the amount of administered packed red blood cell concentrates, fresh-frozen plasma, or platelet concentrates after operation (Table 2).

The doses of administered fluids, urine output intraoperatively and after operation, and the chest tube drainage during 18 h after surgery were comparable in all three groups (Table 2).

### Discussion

We demonstrated similar impairment of whole-blood coagulation by infusion of HES 130/0.4 or gelatin solutions after cardiac surgery in adults. We observed that maximum clot strength and α-angle were significantly lower, and CFT was longer after infusion of colloid...
solutions in comparison with Ringer’s acetate, and these changes were dose-dependent. Impairment of clot formation and strength was still seen on the 1 POM in the gelatin group, whereas in the HES group, it had recovered.

Our study showed that infusion of both HES 130/0.4 and gelatin solutions after cardiac surgery alter clot strength and fibrin build-up similarly. Several mechanisms have been suggested by which colloids impair blood coagulation. Large molecules of colloids interfere with fibrinogen, coagulation factor VIII, and von Willebrand factor more than predicted from haemodilution alone. In studies assessing whole-blood viscoelastic properties, HES and gelatin promote platelet dysfunction, disturb the reticular fibrin mesh, decrease clot firmness, and reduce functional clot quality. In such conditions, the resulting thrombus may be less stable and more susceptible to lysis. Also, haemodilution might reduce thrombin generation and fibrin clot formation independently of each other.

Impairment of blood coagulation was detected using both InTEM® and ExTEM® tests, which suggests that HES and gelatin solutions alter mainly the strength of the whole-blood clot (decreased MCF), but also to some extent fibrin formation (prolonged CFT). Similar findings have been reported previously. However, the exact mechanism remains unclear since we did not demonstrate impaired fibrin polymerization per se nor did we measure fibrinogen concentration. Reduced fibrinogen concentration could impair fibrin polymerization in conditions of haemodilution. Our finding of decreased maximum fibrin clot strength with the FibTEM® test (where the impact of platelets is eliminated from the clotting process) indicates a reduction in strength of the fibrin component of the clot. Since platelet contribution to clot strength (ExTEM®, MCF–FibTEM® MCF) was not altered by HES or gelatin, our observation suggests that the observed coagulation disorder after the infusion of colloid solutions is not mediated by platelets.

We observed a slight but significant increase in MCF and θ-angle after cumulative infusion of 14 (using ExTEM® and FibTEM®), 21, and 28 ml kg⁻¹ of Ringer’s acetate solution (using ApTEM® test). This finding reflects a relative procoagulant effect of Ringer’s acetate solution after cardiac surgery. Crystalloids have been shown to enhance blood coagulation, especially when rapid infusions of fluid have been used. Such infusions alter the balance between anticoagulants and the spontaneously activated fraction of procoagulants, which could result in an enhancement of clot formation.

The use of CPB induces haemodilution, platelet dysfunction, reduces the amount of coagulation factors, and promotes fibrinolysis. Open heart surgery and CPB cause tissue factor-mediated activation of the extrinsic coagulation pathway. Also, the intrinsic coagulation pathway is activated as a result of contact of blood with the non-biological surface of the CPB circuit. Therefore, coagulation after cardiac surgery is strongly altered, and the risk of bleeding is increased. For this reason, the choice of fluids for optimal volume replacement therapy is of critical importance.

Previously, clot lysis was seen only in extreme situations using thromboelastometry. It has been speculated that the blood clot could be vulnerable after HES haemodilution. We did not observe any fibrinolysis activity in our patients since clot strength remained unchanged with ApTEM® test when compared with ExTEM®. This finding does not support the routine use of antifibrinolytic agents in the postoperative period after elective cardiac surgery.

Both HES and gelatin solutions decreased Hb, Hct, and PC more than Ringer’s acetate, which is in accordance with previous studies, and might be explained by different volume effects of the study solutions given. Interestingly, Hb value normalized on the 1 POM in the HES group, but not in the gelatin group. Variance in the degree of haemodilution might affect the thromboelastometry results. In the present study, each patient received an equal amount of study solution after operation. However, in order to achieve and maintain predetermined goals of haemodynamics, the patients received additional infusions of Ringer’s acetate when necessary. The aim of the study was not to achieve a similar degree of haemodilution. Thus, the thromboelastometric results reflect actual alterations in blood coagulation. Haemodilution is an essential part of this clinical setting after cardiac surgery.

We demonstrated that HES 130/0.4 and gelatin impaired coagulation after cardiac surgery, but these disturbances did not cause detectable clinical changes, that is, the amount of postoperative blood loss or the amount of blood products transfused did not differ significantly between the groups. Even though the difference was not statistically significant, fewer red blood cells were transfused in the Ringer’s acetate group in comparison with the colloid groups. This difference might reflect the greater haemodilutional effect.

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### Table 4 Fluid balance on the 1 POM. Values are mean (sd). One-way ANOVA test. GEL, 4% gelatin; HES, hydroxyethylstarch 130/0.4; RIN, Ringer’s acetate

<table>
<thead>
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<th>P all groups</th>
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<tbody>
<tr>
<td>Intraoperative Ringer’s acetate (ml)</td>
<td>1743 (1014)</td>
<td>2031 (549)</td>
<td>1623 (565)</td>
<td>0.34</td>
</tr>
<tr>
<td>Postoperative Ringer’s acetate (ml per 18 h)</td>
<td>981 (788)</td>
<td>1704 (1077)</td>
<td>1301 (918)</td>
<td>0.15</td>
</tr>
<tr>
<td>Intraoperative urine output (ml)</td>
<td>761 (367)</td>
<td>1161 (692)</td>
<td>778 (510)</td>
<td>0.09</td>
</tr>
<tr>
<td>Postoperative urine output (ml per 18 h)</td>
<td>2884 (961)</td>
<td>2923 (1040)</td>
<td>2509 (753)</td>
<td>0.43</td>
</tr>
<tr>
<td>Chest tube drainage (ml)</td>
<td>951 (336)</td>
<td>1099 (420)</td>
<td>921 (367)</td>
<td>0.43</td>
</tr>
<tr>
<td>Prime fluid (ml)</td>
<td>2587 (633)</td>
<td>2820 (1605)</td>
<td>2606 (564)</td>
<td>0.80</td>
</tr>
<tr>
<td>Postoperative fluid balance (ml per 18 h)</td>
<td>638 (1447)</td>
<td>1488 (1755)</td>
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<td>0.31</td>
</tr>
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</tr>
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</table>
of colloids than crystalloids. In the present study, the use of HES 130/0.4 did not increase postoperative blood loss after cardiac surgery, while previously high-molecular-weight HES solutions have been shown to increase chest tube drainage even in smaller doses of under 20 ml kg\(^{-1}\).\(^{17}\) A recent study also demonstrated a favourable effect of HES 130/0.4 in comparison with HES 200/0.5 on postoperative blood loss after non-cardiac surgery.\(^{37}\)

Our study was limited by the relatively small patient population with different types of cardiac surgery. On the other hand, our patient population was fairly homogenous in comparison with patients treated in general ICUs. Additionally, this study was not powered to demonstrate any differences in the amount of blood products transfused.

We conclude that even a small dose (7 ml kg\(^{-1}\)) of modern rapidly degradable HES 130/0.4 or gelatin solution impairs clot formation and strength temporarily in cardiac surgical patients and this effect is more pronounced as the dose is increased. The clinical effect of this coagulation disturbance should be further studied in other patient groups with increased risk of bleeding.

**Conflict of interest**

None declared.

**Funding**

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