Controversy exists about the optimal perioperative fluid management in patients undergoing major surgery. Prevention of fluid overload intraoperatively has been associated with less postoperative complications.\(^1\) In addition, the transfusion of packed red blood cells (PRBCs) is associated with increased morbidity and mortality after cardiac surgery.\(^2\) Thus, avoiding transfusion might also be important to improve outcome of patients undergoing cardiac procedures.

Crystalloids, in the form of Ringer’s lactate (RL), and colloids such as hydroxyethyl starches and 5% human serum albumin (HA) are commonly used for intraoperative fluid management during heart surgery. The latter two have a more profound volume expansion effect than crystalloids and would therefore be more suitable for a restrictive fluid therapy.\(^3\) However, hydroxyethyl starch solutions have been shown to impair coagulation\(^4\)\(^5\) and renal function.\(^6\)\(^7\)\(^8\)\(^9\)\(^10\) Six per cent hydroxyethyl starch 130/0.4 (Voluven\(^{10}\)) (HES) is a newer generation tetra-starch formulation with a lower molecular weight, which might affect coagulation to a lesser degree than hydroxyethyl starch solutions with higher molecular weight.\(^12\)\(^13\)\(^14\)\(^15\) However, a recent meta-analysis stated that insufficient data are available for the effect of HES on the bleeding tendency in cardiac patients.\(^16\) In comparison with HES, HA has been used since the 1970s during cardiac surgery mainly for two reasons: first, HA is able to coat the fluid pathway surface and thereby reduces platelet activation and consumption.

**Editor’s key points**

- The perioperative use of colloid solutions has potential benefits in cardiac surgical patients, but may affect coagulation.
- In this randomized study of 240 patients, the use of high volumes of colloid (50 ml kg\(^{-1}\) day\(^{-1}\)) had no effect on the primary outcome measure, blood loss from chest drains.
- However, blood transfusion requirements were lower when a crystalloids-only fluids regimen was used.
- The infusion of high volumes of colloids caused more haemodilution and had greater adverse effects on coagulation.

**Background.** Infusion of 5% human albumin (HA) and 6% hydroxyethyl starch 130/0.4 (HES) during cardiac surgery expand circulating volume to a greater extent than crystalloids and would be suitable for a restrictive fluid therapy regimen. However, HA and HES may affect blood coagulation and could contribute to increased transfusion requirements.

**Methods.** We randomly assigned 240 patients undergoing elective cardiac surgery to receive up to 50 ml kg\(^{-1}\) day\(^{-1}\) of either HA, HES, or Ringer’s lactate (RL) as the main infusion fluid perioperatively. Study solutions were supplied in identical bottles dressed in opaque covers. The primary outcome was chest tube drainage over 24 h. Blood transfusions, thromboelastometry variables, perioperative fluid balance, renal function, mortality, intensive care unit, and hospital stay were also assessed.

**Results.** The median cumulative blood loss was not different between the groups (HA: 835, HES: 700, and RL: 670 ml). However, 35% of RL patients required blood products, compared with 62% (HA) and 64% (HES group; \(P=0.0003\)). Significantly, more study solution had to be administered in the RL group compared with the colloid groups. Total perioperative fluid balance was least positive in the HA group [6.2 (2.5) litre] compared with the HES [7.4 (3.0) litre] and RL [8.3 (2.8) litre] groups \(P<0.0001\). Both colloids affected clot formation and clot strength and caused slight increases in serum creatinine.

**Conclusions.** Despite equal blood loss from chest drains, both colloids interfered with blood coagulation and produced greater haemodilution, which was associated with more transfusion of blood products compared with crystalloid use only.

**Keywords:** blood loss; coagulation; colloids; fluid regime; Ringer’s lactate; rotation thromboelastometry; transfusion

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with concomitant release of inflammatory mediators. Secondly, HA prevents a substantial decrease in colloid oncotic pressure. Likewise, RL has also been used for many years during heart surgery, either as the sole replacement fluid or in combination with HA or HES. Since large volumes are generally administered throughout the procedure, even RL might influence coagulation via dilution of coagulation factors.

We hypothesized that 6% HES 130/0.4 would increase blood loss from the chest drains. Thus, the main objective of our study was to compare external blood loss from chest drains between groups receiving HA 5%, 6% HES 130/0.4, or RL as the main infusion during cardiac surgery. Blood transfusions, total perioperative fluid balance, thromboelastometry variables, course of serum creatinine and platelet count, intubation time, intensive care unit (ICU), and hospital stay were also assessed.

**Methods**

**Participants**

This randomized, double-blind, single-centre trial, which was conducted over the course of four consecutive years at our department was approved by the institutional review board and reported to the national regulatory authority (Gov Identifier: NCT 01174719). All 240 patients provided written informed consent before inclusion. Inclusion criteria were: patients undergoing elective cardiovascular surgery (i.e. coronary artery bypass grafting (CABG), valve repair or replacement, and surgery of the ascending aorta) on cardiopulmonary bypass (CPB). Exclusion criteria were known allergy to hydroxyethyl starch or albumin, preoperative anaemia, emergencies, treatment with acetylsalicylic acid <3 days before surgery, GPIIbIIIa antagonists use <7 days before surgery, coagulation disorders (i.e. INR >1.2, activated partial thromboplastin time (aPTT) >40 s, platelet count <100 g litre⁻¹), BMI >40 kg m⁻², left ventricular ejection fraction <20%, renal dysfunction defined as serum creatinine >1.5 mg dl⁻¹, proven heparin-induced thrombocytopenia, and danaparoid or lepirudin treatment during the month before the operation.

**Randomization, fluid regimen, and blinding**

Eligible patients were randomized into three groups comprising 80 patients each with the following fluid regimens:

- **HA group:** 5% albumin up to 50 ml kg⁻¹ day⁻¹, additional RL as required;
- **HES group:** 6% HES 130/0.4 up to 50 ml kg⁻¹ day⁻¹, additional RL as required;
- **RL group:** RL up to 50 ml kg⁻¹ day⁻¹, additional RL as required.

An independent IT specialist was in charge of randomization, which was performed using a random number generator. The local pharmacy prepared the study solutions that were supplied in identical 250 ml bottles. Blinding was performed with the help of opaque covers that were placed around the bottles and the infusion sets.

**Procedures**

Anaesthesia was induced with midazolam (0.1 mg kg⁻¹), propofol (1.0–1.5 mg kg⁻¹), fentanyl (3–10 µg kg⁻¹), and cisatracurium (0.2 mg kg⁻¹) and maintained with sevoflurane (target BIS value 40–50), and fentanyl (0.05–0.1 µg kg⁻¹ min⁻¹). Fluid administration was started with 250–500 ml of the study solution during induction of anaesthesia. The CPB circuit was primed with 1500 ml study solution together with 5000 IE heparin, and 100 ml mannitol 20%. Patients received either aprotinin (10⁶ IU after anaesthesia induction plus 10⁶ IU added to the CPB prime) or tranexamic acid (either 1.0 or 1.5 g after anaesthesia induction plus the same dosage in the CPB prime according to the patient’s body weight and renal function). Tranexamic acid was used as antifibrinolytic after November 2007 when sale of aprotinin was suspended by Bayer. After anticoagulation with heparin (300 IE kg⁻¹) and achieving an activated clotting time (ACT) >400 s, CPB was performed using non-pulsatile flow at 2.5 litre min⁻¹ m⁻², a non-heparin-coated circuit, and a membrane oxygenator (Quadrox™, Maquet, Hirrlingen, Germany, or Dideco Compactflow™, Mirandola, Italy). Mild-to-moderate hypothermia was induced (30–34 °C) and norepinephrine was given if necessary to maintain a mean arterial pressure > 60 mm Hg. Buckberg cardioplegic solution was used for myocardial preservation. Additional RL was added to the extracorporeal circuit when filling of the CPB reservoir was insufficient. During and after weaning from CPB, transoesophageal echocardiography was used to monitor myocardial performance and the impact of fluid loading and inotropic support on ventricular function. Further fluid management and also vasoressors and/or inotropic use was at the discretion of the attending consultant and not controlled by protocol. All study cases were performed by experienced cardiac anaesthesia fellows supervised by senior cardiac anaesthesiologists. Intraoperative fluid therapy with study solution was restricted to two-thirds of the maximally allowed daily dose (i.e. 33.3 ml kg⁻¹). It was assumed that anaesthesia and surgery would require a greater fluid load than the immediate postoperative period. Additional fluid requirements were met with RL in order to avoid accidental overdosage of either of the two colloids. The last third of the study solution (i.e. 16.7 ml kg⁻¹) was kept for the initial volume replacement in the ICU that also guaranteed that the total permitted dose would not be administered within a short period of time.

Rotation thromboelastometry (ROTEM® Pentapharm CO, Munich, Germany) ex vivo coagulation variables were examined using predefined tests: INTEM (ellagic acid activated intrinsic pathway) and FIBTEM (with platelet inhibitor cytochalasin D, evaluating the contribution of fibrinogen to clot formation). The samples were analysed within 120 s after blood was drawn from the central venous catheter and coagulation was initiated with activators using a semi-automated electronic pipette system according to the manufacturer’s instructions. Coagulation was allowed to proceed for 50 min. Automatic ROTEM variables were: clotting time (CT), clot formation time (CFT), α-angle, maximum clot firmness (MCF), and clot lysis.

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Fluid therapy and transfusion in cardiac surgery

These variables have been validated using standard coagulation tests. RÖTEM quality control measures were undertaken weekly by our laboratory staff. Reference ranges for RÖTEM thromboelastometry variables were taken from a multi-centre investigation. 24

Blood transfusion was performed according to STS-SCA transfusion guidelines. Transfusion triggers for the transfusion of PRBCs were: haemoglobin (Hb) concentrations of ≤7.0 g dl⁻¹ during and ≤8.0–9.0 g dl⁻¹ after CPB.

Administration of fresh-frozen plasma, platelets, and coagulation factors was based predominantly on RÖTEM variables and the pre- and postoperative coagulation profile of each patient. After appropriate reversal of residual heparin, fresh-frozen plasma and factor concentrates were given in the presence of prolonged CT and CFT INT and normal ACT. Fibrinogen was given when MCFFIB was <8 mm, and platelets were transfused when MCFFIB was >8 mm. In the ICU, Normo-test >1.5, aPTT >60 s, fibrinogen concentration <1 g litre⁻¹, and platelet count <50 × 10⁹ litre⁻¹ prompted transfusion of fresh-frozen plasma, platelets, or both.

Outcome variables

The primary outcome variables were clinical bleeding based on chest tube drainage over the first 24 h after CPB. Secondary outcomes were transfusion of PRBCs, fresh-frozen plasma, platelets, fibrinogen, factor concentrate, changes in Hb, thromboelastometry variables, and the total amount of study solution, total amount of administered fluid, fluid balance, intubation time, and length of hospital stay. Furthermore, the units of PRBC transfused within the second and the sixth postoperative day (POD), and also the course of Hb, platelets, and creatinine until POD 6 were compared between the groups. A creatinine was calculated as maximal creatinine value within 48 h minus baseline creatinine. Since aprotinine was replaced by tranexamic acid during the investigation period, we also compared utilization of these agents between the groups. A creatinine was calculated as maximal creatinine value within 48 h minus baseline creatinine. Since aprotinine was replaced by tranexamic acid during the investigation period, we also compared utilization of these agents between the groups. Since aprotinine was replaced by tranexamic acid during the investigation period, we also compared utilization of these agents between the groups.

Analyses of variance models were used for comparison of the log-transformed cumulative blood loss over 24 h after surgery, the infused study medication, and the cumulative postoperative fluid balance over 24 h between the three groups. Repeated-measures analyses of covariance (ANCOVA) models were used to test for differences in the log-transformed MCFFIB and CFT INT values between study groups, considering baseline values as covariates and time (arrival at the ICU vs 24 h after surgery) as repeated factor. Repeated-measure ANCOVA was also used for comparison of Hb, platelets, and creatinine levels between the groups, additionally considering values during surgery in the model. For all pair-wise comparisons between the study groups, the Tukey post hoc test was used to adjust for multiple comparisons. The non-parametric Kruskal–Wallis test was used to test for differences in non-study fluids, cumulative dose of study fluid expressed as ml kg⁻¹ day⁻¹, crystalloid to colloid ratio, intubation time, urine output, and Δ creatinine values between the groups. The χ² test was used to compare frequencies of patients receiving PRBC, FFP, platelets, fibrinogen, and factor concentrates between study groups. All P-values are reported as results of two-sided tests and values of <0.05 were considered statistically significant.

Results

A total of 240 patients randomized into three groups were included in the study. Patients’ characteristics and intra- and postoperative data are shown in Table 1. Four patients were excluded for the following reasons: one patient from the HA group developed urticaria after induction of anaesthesia and the study was terminated as a possible allergic reaction to the study solution could not be ruled out. Another three patients, two from the HA group and one from the RL group, were either haemodynamically unstable or became hypoxaemic after CPB and required either support with an intraaortic balloon pump or ECMO. Minor violations of the study protocol occurred in two patients. One patient mistakenly received 1000 ml Voluven® and another patient 600 ml of HA during the ICU stay within the study period, without being excluded from the study. Unblinding revealed that both patients were in the HES group. However, in the first patient, the cumulative amount of colloids (HES as study solution and additional Voluven®) did not exceed 50 ml kg⁻¹ day⁻¹. In the second patient, the sum of the administered study solution and the given HA was also within the tolerable range of 50 ml kg⁻¹ day⁻¹. Owing to inappropriate filling of an HA bottle with HES by our pharmacy, the HES group comprised 81 patients and the HA group only 79; of whom, three patients had to be excluded as mentioned above. The recruitment profile is depicted as a CONSORT flow diagram in Figure 1.

Although there was a trend towards lower blood loss over chest tubes in the RL group, the primary study endpoint, namely chest tube drainage over 24 h after surgery, was not significantly different between the groups (P=0.085; Table 2). There was, however, a significant group difference in the quantity of blood transfusion (P=0.0004). Patients in the RL group

Statistical analysis

The sample size calculation was based on data from our institutional data bank, where the actual blood loss from 99 CABG patients was found to be 714 ml with a standard deviation (sd) of 370 ml. The study was powered to detect a difference in blood loss of 185 ml (i.e. half sd) between the active control group was required. Consequently, a sample size of 80 patients per group only 79; of whom, three patients had to be excluded as mentioned above. The recruitment profile is depicted as a CONSORT flow diagram in Figure 1.

Although there was a trend towards lower blood loss over chest tubes in the RL group, the primary study endpoint, namely chest tube drainage over 24 h after surgery, was not significantly different between the groups (P=0.085; Table 2). There was, however, a significant group difference in the quantity of blood transfusion (P=0.0004). Patients in the RL group
received fewer PRBCs compared with HA ($P=0.0015$) and HES patients ($P=0.0002$). In addition, the percentage of patients receiving either PRBCs or any blood product was significantly lower in the RL group. In contrast, there was no difference for both variables when HA and HES patients were compared (Table 2). Most units of PRBC were given perioperatively during the first 24 h. There were no significant group differences in the number of PRBC units transfused within PODs 2–6 [HA: 2.04 (0.45); HES: 2.14 (0.79); RL: 2.15 (0.91) $P=0.544$]. Most PRBC units transfused during this period were ordered between POD 3 and 5. No significant inter-group differences were noted for transfused FFP and platelets. A greater percentage of patients in both colloid groups received fibrinogen. Regarding the amount of coagulation factor concentrates, no significant differences were found between the three groups.

Changes in Hb levels over time and between the groups were significantly different (Fig. 2). During surgery, Hb significantly declined from baseline in all groups. However, patients in the RL group showed the least decline during surgery ($P<0.0001$) and at arrival in the ICU ($P<0.0001$). Twenty-four hours after surgery, patients in the HA group presented with the lowest Hb values compared with the HES ($P<0.0001$) and the RL group ($P<0.0001$). No difference was observed between HES and RL patients at this time point. Likewise, no difference was noted in Hb values among the three groups on POD 6 [HA: 10.1 (1.3), HES: 10.3 (1.1) RL: 10.2 (1.1)]. Similar changes were found for platelet count until POD 6 (Fig. 3B).

**Table 1 Patients’ characteristics and perioperative data.** HA, 5% human serum albumin; HES, 6% hydroxyethyl starch 130/0.4; RL, Ringer’s lactate; ESL, logistic EuroSCORE; BMI, body mass index; LVEF, left ventricular ejection fraction; CABG, coronary artery bypass grafting; VR, valve replacement or reconstruction; Combined procedure: valve and CABG surgery, or double valve replacement or valve replacement with composite graft; CPB, cardiopulmonary bypass; ACC, aortic cross-clamp; ICU, intensive care unit; vasopressors use is defined according to SOFA score; RRT, renal replacement therapy. Values are either: numbers (n), percentages (%), means (SD), medians (25/75 percentile), or medians (lowest–highest value). *$P<0.05$ compared with colloid groups.

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>HA (n = 76)</th>
<th>HES (n = 81)</th>
<th>RL (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female (n)</td>
<td>53/23</td>
<td>52/29</td>
<td>61/18</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66 (23–85)</td>
<td>67 (28–87)</td>
<td>67 (24–87)</td>
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<tr>
<td>BMI (kg m$^{-2}$)</td>
<td>27 (4)</td>
<td>27 (4)</td>
<td>27 (4)</td>
</tr>
<tr>
<td>ELS</td>
<td>5 (6)</td>
<td>6 (6)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>&gt; 50</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>30–50</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td></td>
<td>&lt; 30</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>Type of surgery (%)</td>
<td>CABG</td>
<td>37</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>VR</td>
<td>29</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Combined</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>Anæsthesia</td>
<td>333 (74)</td>
<td>328 (76)</td>
</tr>
<tr>
<td></td>
<td>CPB</td>
<td>107 (32)</td>
<td>99 (42)</td>
</tr>
<tr>
<td></td>
<td>ACC</td>
<td>70 (23)</td>
<td>64 (29)</td>
</tr>
<tr>
<td>Use of antifibrinolics (n)</td>
<td>Aprotinin</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Tranexamic acid</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Use of vasopressors (%)</td>
<td>Low</td>
<td>70</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Postoperative data</td>
<td>Time to extubation (min)</td>
<td>580 (455/735)</td>
<td>562 (485/824)</td>
</tr>
<tr>
<td></td>
<td>ICU stay (day)</td>
<td>1 (1/16)</td>
<td>1 (1/48)</td>
</tr>
<tr>
<td></td>
<td>Hospital stay (day)</td>
<td>14 (7/66)</td>
<td>14 (8/55)</td>
</tr>
<tr>
<td></td>
<td>$\Delta$ Creatinine$_{0-48\text{h}}$ (mg dl$^{-1}$)</td>
<td>0.06 (−0.02/0.15)</td>
<td>0.02 (−0.05/0.11)</td>
</tr>
<tr>
<td></td>
<td>RRT (n)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Mortality 90 day (n)</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
significantly lower at this time point when compared with the HES ($P=0.027$) and the RL group ($P<0.001$). No statistically significant difference was found between the RL and the HES groups ($P=0.083$). CFT$_{\text{int}}$ values increased intraoperatively. They were significantly different ($P<0.0001$) between the groups on ICU arrival with the highest values being detected in the HES group and the lowest in the RL group. Twenty-four hours after surgery, the HA group showed significantly prolonged CFT$_{\text{int}}$ than patients of the RL ($P<0.0001$) and the HES groups ($P=0.004$). No significant difference was found between the HES and the RL groups at this time ($P=0.193$).

We recorded statistically significant group differences regarding the total amount of infused study solution ($P=0.0024$). We observed no difference between the colloid groups but significant differences between HA and RL ($P=0.0051$), and also HES and RL, respectively ($P=0.0016$; Table 4). Similarly, the fluid balance was significantly different between the groups ($P<0.0001$). The HES group had a more positive total fluid balance than the HA group ($P=0.0116$), and the RL group an increased fluid balance compared with both HES ($P=0.0262$) and HA ($P<0.0001$). The crystalloid to colloid ratio was lower in the HA relative to the HES group ($P=0.028$). There were no group differences regarding urine output ($P=0.952$, Table 4). Serum creatinine levels were significantly higher in the HA group immediately after surgery when compared with the HES and RL groups and remained elevated.

Fig 1 Consort 2010 flow diagram.
in relation to the RL group 24 h after surgery (Fig. 3A). Creatin- 

e only increased in the colloid groups (Table 1).

Ten patients, seven in the HES and three in the HA group, 

required reexploration for bleeding, either on the day of 

surgery or on POD 1. One patient in the HES and one in the 

HA group, and also two patients of the RL group had reopera-

tions after POD 5. Three patients died within 90 days, one in 

the HES group (1.2%) and two in the HA group (2.5%) (Table 1).

Usage of the two different antifibrinolytic agents was not 

significantly different between the groups (P = 0.982; Table 1).

Discussion

This is the first randomized controlled trial that directly com- 

pares the new-generation 6% hydroxyethyl starch 130/0.4 

(Voluvren®) (HES) and HA against RL for fluid management 

during cardiac surgery. Two hundred and forty patients were 

included and randomized in three groups with 80 patients 

per group. We used large volumes of fluid, as 50 ml kg⁻¹ 

day⁻¹ is the upper recommended daily limit for HES. We delib-

erately chose this dosage to maximize the chance of demon-

strating a significant effect. We found that fluid therapy with 

neither study solution caused increased external blood loss 

via chest tubes after operation. However, transfusion of PRBC 

and transfusion of any blood product during the first 24 h of 

the study were increased in both colloid groups, both intra-

operatively and after operation.
Our results are in line with published studies and meta-analyses comparing crystalloids and colloids for cardiac surgery. Colloids at all times produced a less positive fluid balance yet postoperative bleeding often did not differ between crystalloids and colloids. Studies comparing albumin with non-protein colloids during cardiac surgery were in the majority in favour of albumin regarding transfusion requirements and mortality. However, in those studies, older generation starches were used which consisted of high molecular weight molecules with high molar substitution and the new-generation HES 130/0.4 6% was not included. In contrast, perioperative volume replacement with up to 50 ml kg⁻¹ HES or 50 ml kg⁻¹ 4% human serum albumin in children undergoing congenital heart surgery resulted in fewer allogeneic blood transfusions in the HES group compared with the albumin group (median: 18 vs 29 ml kg⁻¹). This was explained by a more profound haemodilution induced by 4% albumin. Both colloids were, however, not compared against a crystalloid solution.

In a recent meta-analysis by Navickis and colleagues, it was concluded that hydroxyethyl starches were associated with increased blood loss, reoperation for bleeding, and blood product transfusion in relation to albumin after adult cardiac surgery. However, insufficient data still are available for HES. Previous trials investigating blood loss and transfusion requirements in adult cardiac surgery patients to date either compared HES with hydroxyethyl starch 200/0.5 or HES with crystalloids. In two smaller studies (n=15 per group), Schramko and colleagues compared HES with Ringer’s acetate and 4% gelatine and with hydroxyethyl starch 200/0.5 and 4% albumin, respectively. The latter, however, had no study arm with a crystalloid solution as an active control. No difference in blood loss and transfusion...
requirement was found between HES and hydroxyethyl starch 200/0.5 given at a median dose of 33 ml kg⁻¹. After dual antiplatelet therapy, Lee and colleagues also could not find a difference in perioperative blood loss between crystalloids and HES when administered up to 30 ml kg⁻¹. Furthermore, Tiryakioglu and colleagues did not observe a negative effect on chest tube drainage and need for transfusion when 1500 ml HES was used for CPB prime instead of Ringer. Although the novel HES preparation was reported to have only a minimal effect on haemostasis,¹³ HES impaired fibrin formation and clot strength after cardiac surgery following a total dose of 15 and 28 ml kg⁻¹ but did not negatively affect blood loss.³⁴ Similarly, in the study by Choi and colleagues,³⁸ both 500 ml HES and 500 ml HA in the pump prime negatively affected blood coagulation in patients undergoing mitral valve surgery. In contrast to data published by Schramko and colleagues,³⁴ both colloids (i.e. HA as well) equally prolonged fibrin formation and fibrin build-up, depressed the 𝛼-angle, depressed the maximal amplitude, and shear elastic modulus. Presumably, the HES and HA groups therefore also showed no difference in intra- and postoperative blood loss, in the amount of co-administered colloids and crystalloids, in urine output, and in the amount of transfused units of PRBC, FFP, and platelets. Again, both colloids were not compared against a crystalloid solution.

In contrast, patients in this trial received up to 50 ml kg⁻¹ study solution. Therefore, dilution of coagulation factors and also platelets and platelet dysfunction should even be more pronounced. This could account for the increased CFTINT in both colloid groups and the decreased MCFFib in the HES group on arrival in the ICU. A slight increase in CFTINT was also noticed in the RL group. The median CFTINT values returned to normal in all groups after 24 h. Changes of CFTINT and MCFFib were most distinct in the HES group, whereas in the RL group, changes were least. We chose these two ROTEM variables as they were most affected after infusion of HES—even at smaller doses.³⁷ All patients in our study routinely received antifibrinolytic drugs and hyperfibrinolysis was not observed in any patient. Whereas enhancement of fibrinolysis,³¹³ depletion of circulating coagulation factors⁴⁰ and reduced platelet count can be detected by ROTEM, impairment of platelet function due to CPB,⁴¹ and the administration of HES¹⁴ ⁴² and HA¹⁸ might be better tracked by specific platelet function tests.⁴¹ As we did not perform such tests, we cannot comment on the impact of both colloids on platelet function in the present trial.

Nevertheless, the difference in transfusion requirements in our study can be explained either by the negative impact of the two colloids on blood coagulation but also by the more profound haemodiluting effect, which decreased Hb levels earlier below 7.0 and below 8–9 g dl⁻¹, which were our triggers to give PRBC during and after CPB, respectively. This would explain the fact that more units of PRBC were transfused in the HES and HA groups, both intraoperatively and immediately after operation. In contrast, fluid management with RL in this study was associated with the lowest rate for transfusion of blood products, but also with a more positive fluid balance. Albumin, HES, and RL are not considered equipotent intravascular volume expanders, but their relative potencies are variable.

Crystalloids are generally considered to be less potent volume expanders than colloids, which initially increase plasma oncotic pressure, preload, and cardiac output. Albumin had a plasma volume expanding potency that is 40% higher than that of saline.⁴³ In relation to HA, the volume expansion effect of HES seems to be rather small.¹⁰ ¹¹ Accordingly, fluid balance in this study was highest in the RL group and lowest in the HA group, whereas fluid balance in the HES group was intermediate. This is also reflected by the crystalloid to colloid ratio that was lower in the HA group in relation to HES. The volume expansion effect was mainly pronounced intraoperatively, where more non-study fluids had to be given in the RL group, particularly to maintain adequate filling of the CPB reservoir. Vasopressor use was not different between our groups, which is in line with previous studies that compared HES with control fluids.¹¹ ⁴⁴ ⁴⁵

As has been shown previously, perioperative transfusion of PRBCs and the necessity for reexplorations are strongly associated with increased mortality, and also pulmonary and infectious complications.² Although mortality was low in our trial, which was not powered to detect group differences in mortality, the three patients who died within 90 days had been allocated to the HES and the HA groups, respectively. Similarly, reoperations due to bleeding complications were numerically higher in the two colloid groups.

This study has several limitations. It was conducted as a double-blind, randomized, controlled trial to detect significant group differences in external blood loss via the inserted chest tubes. It was not powered to detect differences in major complications (e.g. re-exploration, renal replacement therapy), and mortality. Much larger trials would have been needed to answer those questions. However, the observed positive Δ creatinine values in both colloid groups indicate that these patients were at increased risk for renal replacement therapy and greater mortality.²⁷ Furthermore, group differences in transfusion of any blood product and PRBC were highly significant, which signifies that the trial was sufficiently powered to detect such differences. Although there was no strict protocol for volume substitution when compared with vasopressor use, fluid administration in all groups was guided by the results from the transoesophageal echo exam and by clinical experience of a senior staff anaesthesiologist who had profound knowledge in transoesophageal echocardiography. The incidence of pruritus, a patient-relevant safety outcome variable, whose pathogenetic mechanism is tissue storage of starch molecules,⁴⁶ was not recorded. In a previous study that specifically addressed this issue, we found that 4.6% of patients treated with HES were affected.⁴⁷ However, several weeks may elapse after exposure to hydroxyethyl starches until onset of pruritus, which complicates proper assessment of groups at risk.

We conclude that all three fluid therapies did not affect our main outcome variable, namely chest tube drainage over 24 h after cardiac surgery with CPB. However, the transfusion rate of PRBCs or of any blood product was higher in both colloid groups, since the transfusion trigger was reached earlier due to more profound haemodilution in conjunction with a negative impact of HES and HA on blood coagulation. In addition, as Δ
creatinine increase solely occurred in these two groups, patients treated with these agents may also face an increased likelihood for kidney injury. Consequently, the use of large amounts of HES and HA in elective cardiovascular surgery, as it was the case in this trial, might be harmful, since it appears to be associated with an increased risk for blood transfusion and the need for renal replacement therapy.

Authors’ contributions

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Declaration of interest
None declared.

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