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Influence of Two Colloidal Extracorporeal Primes on Coagulation of Cardiac Surgical Patients: A Prospectively Randomized Open-Label Pilot Trial

Irene Bethlehem;* Korry Wierda;* Cornelis Visser;* Lilian Jekel;†
Matty Koopmans;‡ Michael A. Kuiper‡

*Departments of *Extracorporeal Circulation, †Cardiothoracic Surgery, and ‡Intensive Care, Medical Centre Leeuwarden, Leeuwarden, The Netherlands*

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Abstract: The search for the ideal priming fluid continues as more evidence is discovered about side effects of volume expanders. With the availability of modern, balanced hydroxyethyl starch (HES) solutions with less side effects than former HES solutions, we considered to replace our gelatin- (modified gelatin) based extracorporeal circuit prime for a HES (130/.42) prime. Therefore, we studied the influence of two colloidal priming fluids on postoperative coagulation in patients undergoing cardiac surgery. The primary endpoint was to compare clot formation time between the HES group and the gelatin group with rotational thromboelastometry (ROTEM). Additionally we compared colloid osmotic pressure and fluid balance of both groups. Forty patients, undergoing elective first time coronary artery bypass grafting or single-valve surgery, were included in this prospectively randomized open-label pilot study. Laboratory data and ROTEM data were collected and analyzed for differences between the two groups. ROTEM data show significantly more prolongation in Extem clot formation time and significant more decrease in Extem alpha in the HES group. Fibtem maximum clot firmness was significantly smaller in the HES group; this was consistent with fibrinogen concentration measurement, which decreased more in the HES group than in the gelatin group and recovered more over time in the gelatin group. We found no significant difference in colloid osmotic pressure between the groups. In this trial, HES (130/.42) impairs coagulation significantly more compared with gelatin. These differences in influence on coagulation did not lead to a difference in blood loss or fluid balance, so clinical relevance could not be proven.
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A variety of crystalloid and colloid fluids are used for extracorporeal circuit priming. The discussion continues whether to use crystalloids or colloids as volume replacement, but also which colloid to use. Colloids have a better volume-stabilizing effect than crystalloids, maintain colloid osmotic pressure, and thus avoid interstitial fluid accumulation (1,2). Human albumin solution is also used as priming fluid and is the most important natural protein maintaining colloid osmotic pressure and transporter of hormones, enzymes, toxins, and medication. However, disadvantages of albumin are the costs and risk of infection. Artificial colloids also have disadvantages. An allergic reaction can occur and there is concern about the influence on clot formation and renal function (2–8). Although many studies in the literature show different results, there is consensus that especially high-molecular-weight hydroxyethyl starch (HES) with a high-substitution degree has a negative influence on coagulation (4,9). Most colloids are dissolved in saline solution and can cause abnormal high chloride concentrations. Recently there has been more interest in so-called "balanced solutions." A balanced fluid replacement benefits acid-base status by avoiding hyperchloremic acidosis. The modern, balanced HES solutions show less accumulation, less alteration of pharmacokinetics, and thus less influence on kidney function and coagulation (9–11).

Colloids used in priming solutions in The Netherlands are modified gelatins, low- and medium-weight HES, and albumin. Crystalloid primes are also used. In our hospital

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Address correspondence to: Irene Bethlehem, EKP, Department of Extracorporeal Circulation, Heart Centre, Medical Centre Leeuwarden, H. Dunantweg 2, 8901 BR, Leeuwarden, The Netherlands. E-mail: irene.bethlehem@znb.nl
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modified gelatin (Gelofusine; B. Braun Melsungen AG, Melsungen, Germany) is used as main component of the priming solution. It is not a balanced solution and gelatins can cause an allergic reaction (incidence .07–.015%). We are interested in the possibility of using balanced HES (Tetraspan 130/.42; Fresenius Kabi, Schelle, Belgium) as extracorporeal circuit priming to improve patient outcome and reduce allergic reactions.

Before introducing a balanced HES (130/.42) as prime for the extracorporeal circuit, we tested the hypothesis that HES (130/.42) has the same effects on coagulation as does gelatin (modified gelatin).

Additionally, we compared colloid osmotic pressure (COP) and fluid balance of both groups, because HES has a higher COP and has a longer intravascular activity.

MATERIALS AND METHODS

After approval of the hospital medical ethics committee and individual written informed consent, 40 patients, undergoing elective first-time coronary artery bypass grafting or single-valve surgery were included. Patients were prospectively randomized into one of the two groups, the gelatin group or the HES group, during 2010 and 2011.

Exclusion criteria were serum creatinine concentration >120 μmol/L, coagulation disorders (activated partial thromboplastin time >40 seconds and/or thrombocyte concentration $<100/10^{-9}$/L), the use of thrombocyte aggregation inhibitors, other than acetylsalicylic acid, shorter than 5 days before surgery, age younger than 35 or older than 85 years, and a body surface area <1.75 cm^2.

Anesthesia was induced with weight-related doses of sufentanil (Janssen-Cilag BV, Tilburg, The Netherlands), midazolam (Roche Nederland BV, Woerden, The Netherlands), rocuronium (Sandoz BV, Almere, The Netherlands), dexamethason (Apotheek UMCG, Groningen, The Netherlands), cephazolin (EuroCept BV, Kortenhoef, The Netherlands), and clonidine (Boehringer Ingelheim BV, Alkmaar, The Netherlands). Anesthesia was maintained with propofol and sufentanil. Patients were ventilated according to the open lung concept (total volume [TV] 3–5 mL/kg; positive end-expiratory pressure level of 8–12 cm H_2O; inspiration:expiration ratio 50/50, pressure controled ventilation [PCV]; frequency [fr] 20–40/min).

After induction, baseline activated clotting time (ACT; Medtronic, Minneapolis, MN) was measured. Patients were infused with lactated Ringer's solution (Baxter, Utrecht, The Netherlands) and the study colloid.

Before initiation of cardiopulmonary bypass (CPB), patients received 300 IU/kg heparin (B. Braun Melsungen AG). The ACT was measured every 30 minutes and kept above 480 seconds during CPB. During CPB, the hematocrit was kept above 20%. If hematocrit was below 20%, hemofiltration (Terumo Cardiovascular Systems Corporation, Ann Arbor, MI) was applied or packed red blood cells were given. During the procedure, mild hypothermia (32–34°C) was performed and a flow rate of 2.4–2.6 L/min/m^2 was applied. During aortic clamp time, pulsatile flow was performed if possible. Myocardial protection was performed using blood cardioplegia, so-called "mini cardioplegia" or the Calafiore technique.

The dose of protamine (MedaPharma, Amstelveen, The Netherlands) administration for neutralization of the heparin effect was 1:1.33. Heparin reversal was confirmed with ACT returning to baseline. During the procedure, intraoperative blood loss was salvaged with the Continuous Auto Transfusion System (CATS; Fresenius Kabi). After termination of CPB, blood from the CPB circuit was salvaged with the CATS and retransfused.

Cardiopulmonary Bypass

The CPB hardware consisted of a HL-30 heart–lung machine (MAQUET Cardiopulmonary AG, Hirrlingen, Germany) and HCU-30 heater–cooler (MAQUET Cardiopulmonary AG) and inline blood analysis monitor (CDI 500; Terumo Cardiovascular Systems Corporation). The CPB circuit consisted of a Rotaflow centrifugal pump (MAQUET Cardiopulmonary AG), a Quadrox-D membrane oxygenator (MAQUET Cardiopulmonary AG), a Quart arterial filter (MAQUET Cardiopulmonary AG), a JVR 1900 collapsible venous reservoir (MAQUET Cardiopulmonary AG), and a BCR 3500 cardiotomy reservoir (MAQUET Cardiopulmonary AG). The components are Bioline-coated (MAQUET Cardiopulmonary AG), except for the venous reservoir, which has a Safeline coating (MAQUET Cardiopulmonary AG).

In the gelatin group the priming of the CPB circuit consisted of 1300 mL modified gelatin, 20 mL potassium chloride (MedaPharma) 7.45%, and 10 mL calcium chloride (B. Braun Melsungen AG) 2.25 μmol/mL.

In the HES group, the CPB circuit was primed with 1300 mL balanced 6% HES 130/.42 (containing Na^+ 140 mmol/L, CL^- 118 mml/L, K^+ 4 mmol/L, Ca^{2+} 2.5 mmol/L, Mg^{++} 1 mmol/L, $acetate^-$ 24 mmol/L, and $malate^{2-}$ 5 mmol/L.

Two hundred milliliters mannitol 20% (Medtronic), 50 mL NaHCO3 8.4% (Fresenius Kabi), and 2 g tranexamic acid (Pfizer bv, Capelle aan de IJssel, The Netherlands) were added to the prime in both groups.

Data Collection

Arterial blood was drawn in blood collection tubes (BD Vacutainer, Plymouth, UK) containing the appropriate anticoagulant and analyzed for hemoglobin, hematocrit, platelet count (CellDyn Sapphire; Abbott Diagnostics, Chicago, IL), COP (Osmomat 050; Gonotec Gmbh, Berlin, Germany), fibrinogen (Modular P800; Roche,

Table 1. Sample protocol.

	T0	T1	T2	T3
Hemoglobin (mmol/L)	X			X
Hematocrit (%)	X			X
Colloid osmotic pressure	X	X	X	X
Platelet count (*10^9/L)	X	X	X	X
Fibrinogen (g/L)	X	X	X	X
APTT (seconds)	X			X
PT (seconds)	X			X
ROTEM analysis	X		X	X

APTT, activated partial thrombin time; PT, prothrombin time; ROTEM, rotational thromboelastometry.

Basel, Switzerland), protrombin time, and activated partial thrombin time (ACL top; Instrumentation Laboratory, Brussels, Belgium).

Samples were drawn at four moments (Table 1): before anesthetic induction (T0); during CPB, after removal of the aortic clamp (T1); post-CPB, 30 minutes after protamine gift (T2); and 1 hour after arrival in the intensive care unit (T3).

Thromboelastometry

A four-channel thromboelastometry analyzer (ROTEM; Pentapharm, Munich, Germany) was used to measure rotation thromboelastometry (ROTEM).

A perfusionist performed the ROTEM measurement within 1 hour after the arterial sample was drawn. ROTEM measures the formation, stabilization, and eventual lysis of the clot (12). Addition of specific reagents allows assessment of intrinsic pathway (Intem), extrinsic pathway (Extem), qualitative assessment of fibrinogen status (Fibtem), and analysis without heparin influence: assessment of clot formation in heparinized patients and specific detection of heparin (Heptem).

Statistical Analysis

Results are shown as mean with standard deviation if groups are normally distributed or as median with interquartile range if groups are not normally distributed.

Shapiro-Wilkinson test was used to test if groups were normally distributed.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL) software for Windows, Version 16.0. Differences between groups are tested with unpaired *t* test or Mann-Whitney *U* test, as appropriate. We could not calculate sample size because it is our first study in this topic but according to the referred literature, 20 patients per group would be sufficient.

RESULTS

Forty patients were included and gave their written consent. Table 2 shows demographic and operative data.

Table 2. Demographic data.*

	Gelatin	HES
No.	20	20
Age (years)	64 ± 10	65 ± 7
BSA (m^2)	2.06 ± .20	2.02 ± .15
Male/female	16/4	18/2
CPB time (minutes)	107 ± 38	107 ± 30
Aorta clamp time (minutes)	79 ± 35	75 ± 27
CABG	16	18
MVS	3	1
AVR	1	1

*Data are expressed as mean ± standard deviation. or as number. Significant difference between groups shown as * if $p < .05$ (SPSS, unpaired *t* test).
HES, hydroxyethyl starch; BSA, body surface area; CPB, cardiopulmonary bypass; CABG, coronary artery bypass grafting; MVS, mitral valve surgery; AVR, aortic valve replacement.

These data show no significant differences between these groups.

Only between-group differences were tested.

Baseline laboratory data were significantly different between the groups for hemoglobin and hematocrit ($p = .013$ and $p = .019$ *t* test); values were lower in the gelatin group. Four patients in the gelatin group received packed cells during operation against none in the HES group. One patient, in both groups, needed fibrinogen concentrate (Haemocomplettan P; CSL Behring GmbH, Marburg, Germany) and one unit of platelets.

Fluid balance showed no significant difference (Table 3), although the amount of crystalloid solution transfused and blood loss in operation room seemed higher in the gelatin group ($p = .075$, unpaired *t* test and $p = .121$ Mann-Whitney test). The amount of colloids transfused was similar in both groups.

Table 3. Total amount of fluids in/out during the study period.*

	Gelatin	HES
Crystalloid (mL)	2450 (1405–3595)	1975 (850–4425)
Colloid (mL)	1900 (1300–3083)	2000 (1325–2500)
Colloid/kg (mL)	21 (14–44)	23 (13–36)
Urine output (mL)	775 (327–2194)	892 (353–1583)
Blood loss in OR (mL)	455 (119–1485)	350 (141–797)
Blood loss ICU (mL)	140 (27–542)	185 (42–595)
Transfused packed cells from cell saver during surgery (mL)	275 (0–709)	295 (132–633)
Fluid balance (mL)	2180 (1202–3528)	2315 (861–4196)
Transfused units	6 (4)	0
• RBC (no. of patients)	2 (1)	3 (1)
• Hemocompletion (no. of patients)	1 (1)	1 (1)
• Platelets (no. of patients)		

*Data are expressed as median (range, 5 and 95 percentile) or as number. Significant difference between groups shown as * if $p < .05$ (SPSS, unpaired *t* test or Mann-Whitney test, as appropriate).
HES, hydroxyethyl starch; OR, operating room; ICU, intensive care unit; RBC, red blood cells.

Table 4. Laboratory data.*

	T0		T1		T2		T3	
	Gelatin	HES	Gelatin	HES	Gelatin	HES	Gelatin	HES
Hemoglobin (mmol/L)	8.1 ± 1.1‡	8.8 ± .6					6.2 ± .9†	6.2 ± .6
Hematocrit (%)	38 ± 5‡	41 ± 3					29 ± 4	29 ± 3
COP (kPa)	3.0 ± .3	3.1 ± .3	2.4 ± .3	2.5 ± .3	2.3 ± .4	2.5 ± .3	2.6 ± .4	2.7 ± .3
Platelet count ($\times 10^9$/L)	255 ± 70	247 ± 88	213 ± 70	199 ± 64	145 ± 58	135 ± 60	172 ± 59	156 ± 64
Fibrinogen (g/L)	3.8 ± 1.1	3.8 ± .7	2.2 ± .7†‡	1.9 ± .5	1.9 ±.6	1.7 ± .5	2.3 ± .8†‡	1.8 ± .4
APTT (seconds)	31 ± 4	30 ± 2					29 ± 3	29 ± 3
PT (seconds)	1.08 ± .08	1.09 ± .07					1.35 ± .09	1.32 ± .11

*Data are expressed as mean ± standard deviation. Only between-group differences tested.
†Significant difference over time; T0–T1and T2–T3 between groups $p < .05$.
‡Significant difference in results, $p < .05$ (SPSS unpaired t test or Mann-Whitney test, as appropriate).
HES, hydroxyethyl starch; COP, colloid osmotic pressure; APTT, activated partial thrombin time; PT, prothrombin time.

Table 5. ROTEM data.*

		T0		T2		T3	
		Gelatin	HES	Gelatin	HES	Gelatin	HES
Intem	CT	153 ± 41	155 ± 23	230 ± 146	182 ± 26	189 ± 47	194 ± 34
	CFT	66 ± 15	63 ± 14	128 ± 48	140 ± 46	109 ± 38	124 ± 42
	Alpha	77 ± 3	77 ± 3	67 ± 7	65 ± 7	70 ± 6	67 ± 6
	MCF	64 ± 5	64 ± 5	50 ± 12	53 ± 6	56 ± 6	55 ± 6
Extem	CT	58 ± 18	66 ± 35	89 ± 17	94 ± 21	77 ± 19	90 ± 23
	CFT	85 ± 21	83 ± 27	139 ± 49†	162 ± 46	117 ± 35‡	147 ± 49
	Alpha	73 ± 4	75 ± 5	64 ± 7†	60 ± 6	68 ± 6‡	63 ± 8
	MCF	63 ± 6	63 ± 6	54 ± 7	52 ± 6	57 ± 6	53 ± 6
Fibtem	CT	55 ± 20	54 ± 16	74 ± 19	82 ± 29	66 ± 16	78 ± 26
	MCF	19 ± 6	19 ± 7	12 ± 5‡	8 ± 3	12 ± 4‡	8 ± 4
Heptem	CT			184 ± 27	192 ± 30	178 ± 36	190 ± 33
	CFT			145 ± 64	154 ± 55	120 ± 38	134 ± 50
	Alpha			65 ± 8	62 ± 8	67 ± 6	66 ± 7
	MCF			51 ± 7	51 ± 6	54 ± 6	53 ± 7

*Data are expressed as mean ± standard deviation.
†Significant difference over time; T0–T2 and T2–T3 between groups, $p < .05$.
‡Significant difference in results, $p < .05$ (SPSS unpaired t test or Mann-Whitney test, as appropriate).
ROTEM, rotational thromboelastometry; HES, hydroxyethyl starch; CT, clotting time; CFT, clot formation time; MCF, maximum clot firmness.

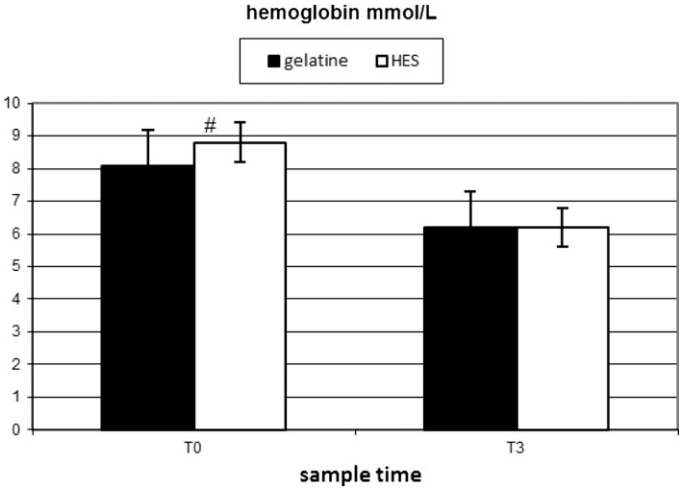

Figure 1. Hemoglobin concentrations at T0 and T3. #Significant difference between the groups, $p < .05$; *significant difference over time from T0–T1 and T2–T3; $p < .05$.

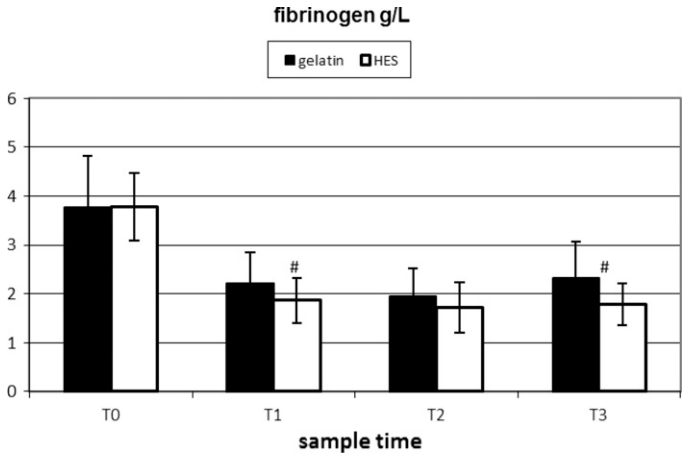

Figure 2. Fibrinogen concentrations at T0–T3. #Significant difference between the groups, $p < .05$; *significant difference over time from T0–T1 and T2–T3; $p < .05$.

The laboratory and ROTEM data were compared in two ways; decrease or increase over time between groups was compared and the absolute results between groups were compared (Tables 4 and 5).

Decrease of hemoglobin concentration, between T0 and T3, was higher in the HES group (Figure 1) (p = .034 unpaired t test).

Between T0 and T1 fibrinogen concentration decreased more in the HES group than in the gelatin group (p = .005 unpaired t test) and between T2 and T3 fibrinogen concentration recovered significantly more in the gelatin group (p = .012 unpaired t test).

This significant difference also appeared in absolute fibrinogen measurement at T1 (p = .049 Mann-Whitney test) and T3 (p = .003 Mann-Whitney test); fibrinogen concentration was lower in the HES group (Figure 2).

Other laboratory data showed no significant difference.

At T0, T2, and T3, ROTEM analysis was performed. At baseline, T0, no significant differences in Intem, Extem, and Fibtem were detected.

When differences over time between the groups were compared, we saw between T0 and T2 more prolongation in Extem clot formation time (CFT) (Figure 3) (p = .012 Mann-Whitney test) and a greater decrease in Extem alpha (p = .004 Mann-Whitney test) in the HES group Figure 4. Decrease in clot strength of Fibtem maximum clot firmness (MCF) between T0 and T2 seemed more in the HES group but was not significant (p = .072 Mann-Whitney test).

At T2 Fibtem MCF (p = .003 Mann-Whitney test) was significant lower in the HES group. This was still so at T3 where the Extem CFT was more prolonged (p = .033 unpaired t test), Extem alpha was smaller (p = .023 unpaired t test), and Fibtem MCF was less strong (p = .002 Mann-Whitney test) in the HES group (Figure 5).

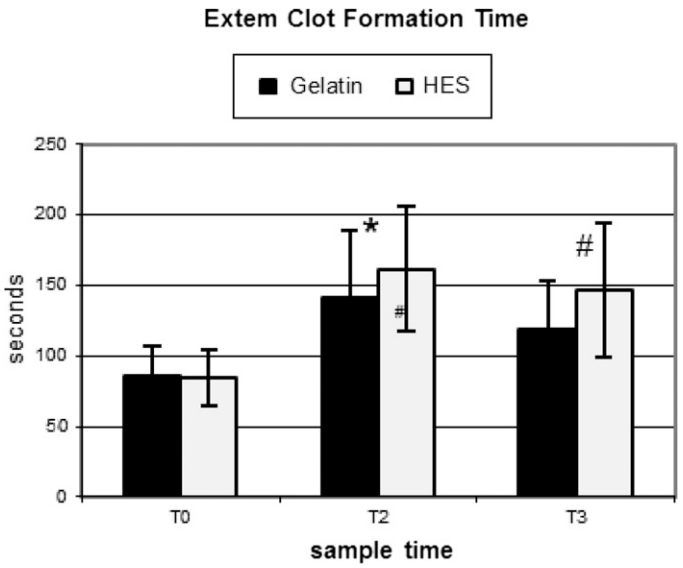

Figure 3. Changes in Extem-CFT (normal range, 34–159 seconds). #Significant difference in results, $p < .05$; *significant difference over time; T0–T2 and T2–T3 between groups, $p < .05$ (SPSS unpaired t test or Mann-Whitney test, as appropriate).

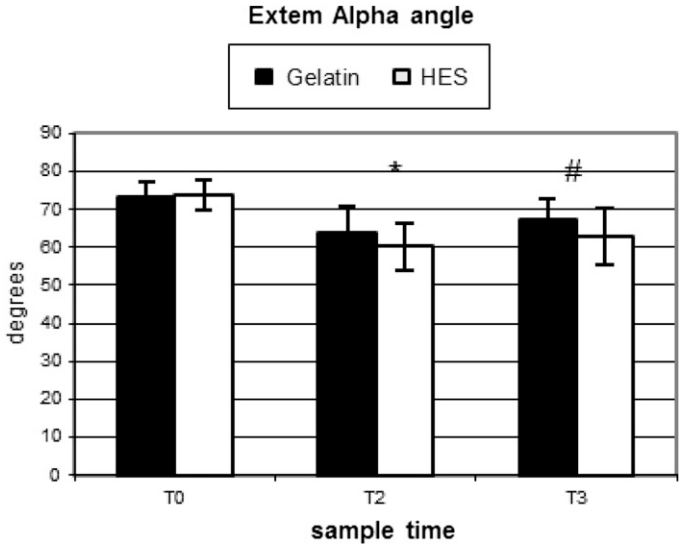

Figure 4. Changes in Extem alpha angle (normal range, 63–83°). #Significant difference in results, $p < .05$; *significant difference over time; T0–T2 and T2–T3 between groups, $p < .05$. (SPSS unpaired t test or Mann-Whitney test, as appropriate).

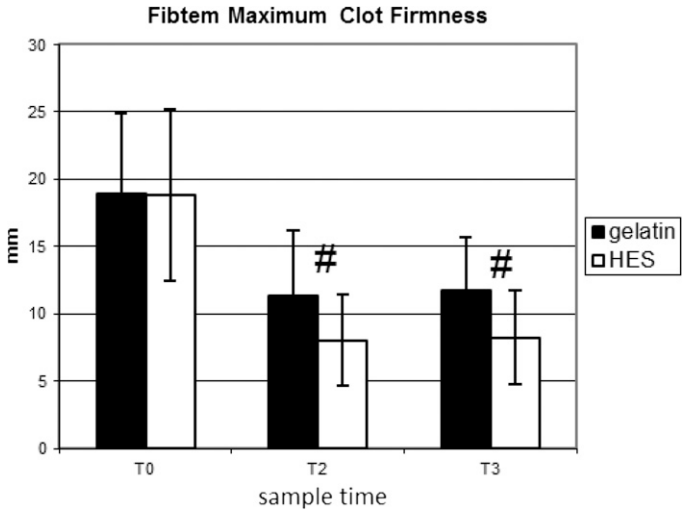

Figure 5. Changes in Fibtem-MCF (normal range, 9–25 mm). #Significant difference in results, $p < .05$ (SPSS unpaired t test or Mann-Whitney test, as appropriate).

DISCUSSION

Patients in the gelatin group had a significantly lower baseline hemoglobin concentration. This resulted in transfusion of packed cells in four patients in the gelatin group during operation against none in the HES group. Two

patients needed packed cells in the prime as a result of low preoperative hemoglobin; the other two needed packed cells after surgery as a result of blood loss and hemodilution. This also explains why hemoglobin in the HES group decreases more than in the gelatin group. Any influence of the transfused packed cells on hemostasis in the gelatin group cannot be ruled out because it is known that erythrocytes also play a part in the hemostatic status.

Postbypass, one patient in both groups needed fibrinogen concentrate (Haemocomplettan P; CSL Behring Gmbh) and one unit of platelets. Both patients had low fibrinogen concentration (<1.4 g/L) and low platelet count (<100.10) (9). Data of patients who received a transfusion were not excluded from the study. Although the results of the transfused patients caused a greater standard deviation, significant differences in coagulation parameters between the groups remained the same.

The use of colloids in patients undergoing cardiac surgery is generally accepted, although concern remains about side effects. Van Zundert et al. (1) described in a review article effects of different colloidal fluids on hemodynamics and pharmacologic properties and Lehman et al. (10) compared two HES solutions for pharmacokinetics. They concluded that the newer HES solutions with lower molecular weight (<200 Daltons) and low molar substitution (<.5) are the best choice as colloidal volume replacement because their lasting volume effect (3–4 hours) without accumulation and reduce side effects.

The mechanism of impaired blood coagulation by colloids has been described in several studies (6,7).

Different mechanisms of impairment are described; Niemi et al (3) and Kuitunen et al. (4) conclude impairment of coagulation caused by disturbed formation of fibrinogen by HES, but Fenger-Ériksen et al. (6) concluded in their study that dilution is the main determinant in coagulopathy and addition of exogenous fibrinogen corrected the coagulopathy completely.

In an overview of effects of plasma expanders on coagulation. Levi and colleagues confirm impairment by colloids and significant differences between various plasma replacement fluids. Clinical relevant effects on bleeding are mostly present if large amounts are infused (>1.5 L) or a pre-existent hemostatic disorder is present. Another review on efficacy of HES and its side effects (11) concluded that tetra starches have minimal effects on coagulation and are considered saved, but it should be noted that information from withdrawn publications was included in these reviews.

Our study was limited by the relative small patient groups and was not double-blind. Influence of practitioner on given amount of study colloid cannot be ruled out but there was no significant difference in administered study colloid and administration of fluids and blood components is protocolled. In this trial, the influence of HES on coagulation shows consistent results; absolute fibrinogen concentration and Fibtem (qualitative assessment of fibrinogen status) predict the same effect on coagulation in a different way. Our results are also consistent with the literature. Other publications on colloid-induced hypocoagulation in patients undergoing cardiac surgery found similar results; slower clot formation (increased ExtCFT) and a weaker clot (decreased fibMCF) in HES groups (different HES solutions) compared with gelatin and albumin (3,4). Schramko and colleagues (8) found prolonged CFT and decreased clot strength compared with Ringer's acetate but no difference between the colloids used, HES (130/.4) and gelatin. Care must be taken with interpretation of study results because of the variety of colloids and methods used. Results can also be different between patient groups; the cardiac patient is already hemostatically challenged, whereas healthy volunteers (9,10) are not.

This trial used a considerable amount of colloid and measured clot formation up to 1 hour of stay in the intensive care unit. Results show more influence of HES on several points in the coagulation process compared with gelatin but did not lead to a significant greater blood loss in the first hour after the operation. There was no difference in COP and fluid balance during the study. Influences on kidney function and acid-base status have to be investigated in a future study.

We conclude that in this prospective, randomized open-label pilot trial, HES (130/.42) impairs coagulation more than modified gelatin. Fibrinogen concentration, Extem CFT, Extem alpha, and Fibtem MCF were significantly different between the groups with the HES group demonstrating the most change. We found no significant difference in COP results between the groups.

These results did not lead to a difference in blood loss or fluid balance, so clinical relevance could not be found. Based on our results we have not changed the CPB prime at our institution. The (dis)advantages of balanced HES have to be studied further.

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