

Low- and Medium-molecular-weight Hydroxyethyl Starches

Comparison of Their Effect on Blood Coagulation

Marina Jamnicki, M.D., Thomas Bombeli, M.D.,† Burkhardt Seifert, Ph.D.,‡ Andreas Zollinger, M.D.,§ Vladimir Camenzind, M.D.,‖ Thomas Pasch, M.D.,# Donat R. Spahn, M.D.***

Background: **High-molecular-weight hydroxyethyl starch (HES) compromises blood coagulation more than medium-molecular-weight HES. The authors compared medium molecular weight HES (200 kd [HES200]) and low-molecular-weight HES (70 kd [HES70]).**

Methods: **In a prospective, double-blind, randomized-sequence crossover study, 22 male volunteers received 15 ml/kg HES200 and HES70. Blood samples were taken before and 5 min, 30 min, 1 h, 2 h, 4 h, 8 h, and 24 h after infusion. The following parameters were analyzed at all time points: prothrombin time, activated partial thromboplastin time, fibrinogen, factor VIII, antigenetic and functional von Willebrand factor, platelets, Thrombelastograph® analysis parameters (reaction time, coagulation time, maximum amplitude, angle α, and clot lysis 30 and 60 min after maximum amplitude), ionized calcium, hematocrit, HES plasma concentration, molecular weight (weight average and number average), molar substitution, and polydispersity (weight average/number average). Repeated-measures analysis of variance ($P < 0.05$) was used to compare the response of the aforementioned parameters to the infusion of HES70 and HES200.**

Results: **Both HES solutions had a significant impact on all parameters. A slightly greater compromise with HES200 was found in activated partial thromboplastin time ($P = 0.010$), factor VIII ($P = 0.009$), antigenetic von Willebrand factor ($P = 0.041$), functional von Willebrand factor ($P = 0.026$), maximum amplitude ($P = 0.008$), and angle α ($P = 0.003$). No difference was established with the other parameters. HES concentration ($P < 0.001$), weight average ($P < 0.001$), number average ($P < 0.001$), and polydispersity ($P < 0.001$) were higher with HES200. There was no difference with molar substitution ($P = 0.091$).**

Conclusions: **Low-molecular-weight hydroxyethyl starch (70 kd) compromises blood coagulation slightly less than HES200, but it is unclear whether this is clinically relevant. (Key words: Colloids; hemodilution; Thrombelastograph® analysis.)**

WITH the urge to reduce allogeneic blood transfusions[1,2] and the suggestion to use albumin only in controlled studies,[3] artificial colloids have become increasingly popular. Hydroxyethyl starch (HES) is one of the most frequently used colloids but compromises blood coagulation.[4–6] The extent of this impairment depends mainly on the chemical properties of the HES used, especially on its molecular weight.[7] A difference has been shown between high- and medium-molecular-weight HES (450 kd *vs.* 264 kd),[7] but it is not yet clear whether this finding can be extended toward low-molecular-weight HES (70 kd [HES70]). The aim of the present study was to compare the influence on blood coagulation of a medium-molecular-weight HES (200 kd [HES200]) with the influence of a low-molecular-weight HES (HES70).

Materials and Methods

After obtaining approval from the Anesthesia and Surgery Ethics Committee of the University Hospital Zurich and written informed consent, 22 healthy, young (age, 21–34 yr), male volunteers were enrolled into this double-blind, prospective, randomized-sequence crossover study. A financial reward was offered to each volunteer. Exclusion criteria were a known HES allergy; hypervolemia; known cardiovascular, lung, or liver diseases; known metabolic disorders; history of bleeding diathesis; hypertension (diastolic blood pressure > 100 mmHg); known alcohol, drug, or nicotine abuse; treatment with heparin or acetylsalicylic acid within 5 days before the study; treatment with nonsteroidal antirheumatics within 24 h before the study; and simultaneous or previous (< 3 months) participation in any other clinical trial.

All volunteers received 15 ml/kg HES200 (weight-average mean molecular weight [Mw], 200 kd; molar substitution, 0.50 [0.45–0.55], C2/C6 ratio, 4.6) and HES70 (Mw, 70 kd; molar substitution, 0.5 [0.5–0.55], C2/C6 ratio, 3.1) (B. Braun Melsungen AG, Melsungen, Germany). The C2/C6 ratio describes the ratio of hydroxethyl groups substituted at the C2 and C6 positions of the glucose molecule. The washout period between infusions was at least 4 weeks. The sequence of HES infusions was randomized. After insertion of a 16-gauge cannula during local anesthesia into an antecubital vein, a first blood sample was taken before infusion (after discarding the first 10 ml). Over 30 min, the volunteers received 15 ml/kg either HES70 or HES200. Blood samples (after discarding the first 10 ml) were then taken

* Resident, ‖ Research Associate, # Professor and Chairman, ** Professor, Institute of Anesthesiology, † Assistant Professor, Department of Internal Medicine, University Hospital. ‡ Associate Professor, Department of Biostatistics, University of Zurich, Zurich, Switzerland. § Associate Professor and Head, Institute of Anesthesiology, City Hospital Triemli, Zurich, Switzerland.

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Address reprint requests to Dr. Spahn: Institut für Anästhesiologie, Universitätsspital Zürich, Rämistrasse 100, CH-8091 Zürich, Switzerland. Address electronic mail to: donat.spahn@ifa.usz.ch.

5 min, 0.5 h, 1 h, 2 h, 4 h, 8 h, and 24 h after the infusion. Native blood (without citrate) was sampled. The intravenous catheter was filled with 0.9% saline, and no heparin was used. The catheter was removed after 8 h. A venipuncture with an 18-gauge butterfly needle was performed after 24 h for blood sampling.

In each blood sample, blood coagulation was assessed using Thrombelastograph® analysis (TEG®) and conventional coagulation tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, factor VIII, antigenetic and functional von Willebrand factor (vWF), and platelet counts. Laboratory methods used were Thromborel S reagents for PT, Pathromtin SL for aPTT, and Multifibren U for fibrinogen measurement in a Behring Coagulation System Photometer (Behring Diagnostics GmbH, Marburg, Germany). Factor VIII was assessed functionally using factor VIII–deficient plasma (Helena Haemostasis Systems Ltd, Sunderland, Tyne and Wear, United Kingdom), functional vWF (Ristocetin cofactor assay) was measured in a turbidimeter (Labor, DiaLine, Itingen, Switzerland) using Ristocetin (Socochim, Lausanne, Switzerland), and antigenetic vWF was measured by an enzyme-linked immunosorbent assay (Asserachrom vWF; Diagnostica Stago, Asnières-sur-Seine, France). A computerized Thrombelastograph Coagulation Analyzer (CTEG #3000; Haemoscope, Morton Grove, IL) with celite activation was used, and the blood was processed within 3–4 min after collection.[8] TEG® tracings were analyzed in terms of reaction time, coagulation time, maximum amplitude (MA), angle α, and clot lysis 30 and 60 min after reaching MA.[8] Ionized calcium was also measured. Hemoglobin and hematocrit were measured to assess the level of hemodilution.

Hydroxyethyl starch degradation was assessed by measuring its concentration (milligrams/milliliter), molecular weight (Mw [kilodaltons] and number average molecular weight [kilodaltons]), molar substitution, and polydispersity (Mw/number average) in all blood samples between 5 min and 24 h. Molecular weight was determined using gel permeation chromatography coupled with multiangle laser light scatter (Wyatt Technology, Woldert, Germany). HES concentration was measured using a refractic index detector with online multiangle laser light scatter detector (Wyatt Technology). Molar substitution defined as the amount of mol hydroxyethyl groups per mol anhydro glucose units was determined according to Lee and Carter.[9] Thereby, hydroxyethyl groups of HES in the samples were cleaved by heating with hydroiodic acid and formed ethyl iodide, which was analyzed by gas chromatography (Gas Chromatograph PE Autosystem; Perking Elmer, Rotkreuz, Austria). For the calculation of molar substitution, HES concentration of the samples was directly deduced from the refractic index signal obtained by gel permeation chromatography–multiangle laser light scatter.

To elucidate the unexpected shortening of reaction time after infusions of both HES solutions, we performed an additional series of *in vitro* dilution with veronal acetate buffer, HES70, and HES200 using pooled standard human plasma (Dade Behring, Marburg, Germany). The plasma was initially diluted 1:1 with acetate buffer at a pH of 7.4 to increase sensitivity of the subsequent progressive dilution with acetate buffer, HES70, and HES200 (6.25–25%). PT was measured to assess onset of coagulation and was determined with recombinant thromboplastin (Innvoin; Dade Behring, Marburg, Germany) according to the manufacturer's instructions using an automated coagulometer (BCS, Behring, Marburg, Germany).

To put into perspective the difference between HES70 and HES200, a subsequent *in vitro* study was performed comparing 15% hemodilution with 5% albumin, HES70, and HES200 using unused blood from 20 unrelated donors enrolled in another study, and blood coagulation was again assessed using TEG®.

Statistical Analysis

In one volunteer it was impossible to obtain blood samples after 0.5 h of the first infusion, even after repeated venipunctures. All other volunteers completed the study according to the protocol; therefore, 21 complete sets of data were analyzed. Statistical analysis was performed using repeated-measures analysis of variance ($P < 0.05$). Data presented are mean ± SD.

Results

Hemoglobin concentration decreased from 13.7 ± 0.9 g/dl to 11.8 ± 0.8 g/dl 5 min after infusion (table 1). Hemoglobin concentration then recovered to reach baseline values at 24 h. There was a significant change over time (P_{time}) but no difference regarding the hemodi-

Table 1. Changes in Hemoglobin and Ionized Calcium Concentrations over Time

	0	5 min	0.5 h	1 h	2 h	4 h	8 h	24 h	P_{time}	P_{HES}
Hb HES70	13.6 ± 0.8	11.7 ± 0.7	12.0 ± 0.6	12.3 ± 0.7	12.7 ± 0.8	12.9 ± 0.7	13.3 ± 0.8	13.8 ± 0.9	< 0.001	0.128
Hb HES200	13.7 ± 0.9	11.8 ± 0.8	12.0 ± 0.8	12.2 ± 0.8	12.5 ± 0.8	12.8 ± 0.8	13.1 ± 0.8	13.8 ± 0.8	< 0.001	0.128
Ca HES70	1.15 ± 0.03	1.10 ± 0.02	1.11 ± 0.03	1.11 ± 0.03	1.13 ± 0.03	1.14 ± 0.03	1.15 ± 0.03	1.17 ± 0.03	< 0.001	0.733
Ca HES200	1.16 ± 0.03	1.11 ± 0.03	1.12 ± 0.03	1.12 ± 0.03	1.14 ± 0.03	1.14 ± 0.03	1.14 ± 0.03	1.17 ± 0.04	< 0.001	0.733

0 = Before hydroxyethyl starch (HES) infusion; P_{time} = *P* value for the effect of time, *i.e.*, change over time; P_{HES} = *P* value for the effect of HES 70 *versus* the effect of HES 200; Hb = hemoglobin (g/dl); Ca = ionized calcium (mM).

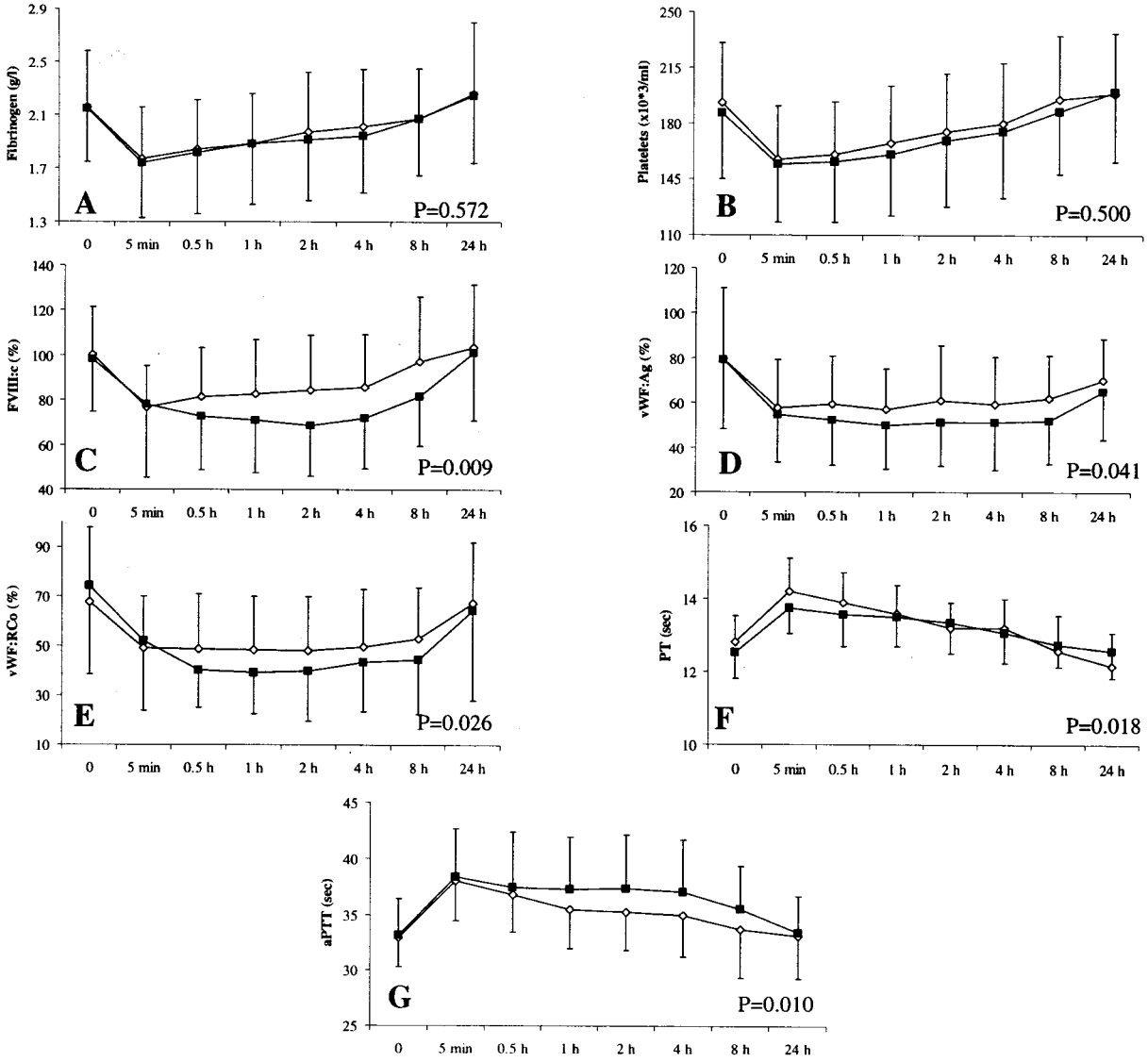

Fig. 1. Coagulation tests after hemodilution with hydroxyethyl starch (HES) 70 (diamonds) and HES200 (squares) before (0) and up to 24 h after HES infusion. (*A*) Fibrinogen; (*B*) platelets; (*C*) factor VIII (FVIII); (*D*) antigenetic von Willebrand factor (vWF:Ag); (*E*) functional von Willebrand factor (vWF:Rco); (*F*) prothrombin time (PT); (*G*) activated partial thromboplastin time (aPTT). *P* values (P_{HES}) indicate the difference between HES70 and HES200.

lutional effect between the two HES solutions (P_{HES}; table 1). Ionized calcium also decreased minimally after both HES infusions and reached baseline values at 24 h without a difference between the two HES solutions.

Conventional Coagulation Tests

All conventional coagulation tests were altered because of both HES infusions ($P_{time} < 0.001$) and recovered toward 24 h (fig. 1). No differences between HES groups were observed in fibrinogen concentration (fig. 1A) and platelet count (fig. 1B). A slightly more pronounced decrease was observed because of HES200 infusion in factor VIII concentration ($P_{HES} = 0.009$; fig. 1C), antigenetic vWF ($P_{HES} = 0.041$; fig. 1D), and vWF activity (Ristocetin cofactor; $P_{HES} = 0.026$; fig. 1E). The increase in PT was slightly more pronounced because of HES70 ($P_{HES} = 0.018$; fig. 1F), and aPTT was slightly more prolonged because of HES200 ($P_{HES} = 0.010$; fig. 1G).

Thrombelastograph® Analysis Parameters

Except for clot lysis, all TEG® parameters were affected by HES infusions ($P_{time} < 0.001$; fig. 2). A slightly more pronounced effect due to HES200 infusion was observed in maximum amplitude ($P_{HES} = 0.008$; fig. 2A) and angle α ($P_{HES} = 0.003$; fig. 2B), whereas the effect on reaction time (fig. 2C) and coagulation time (fig. 2D) was similar with both HES infusions.

In Vivo *Hydroxyethyl Starch Characteristics*

With the exception of molar substitution, all *in vivo* HES characteristics changed over 24 h ($P_{time} < 0.001$; fig. 3). HES plasma concentration was lower after HES70

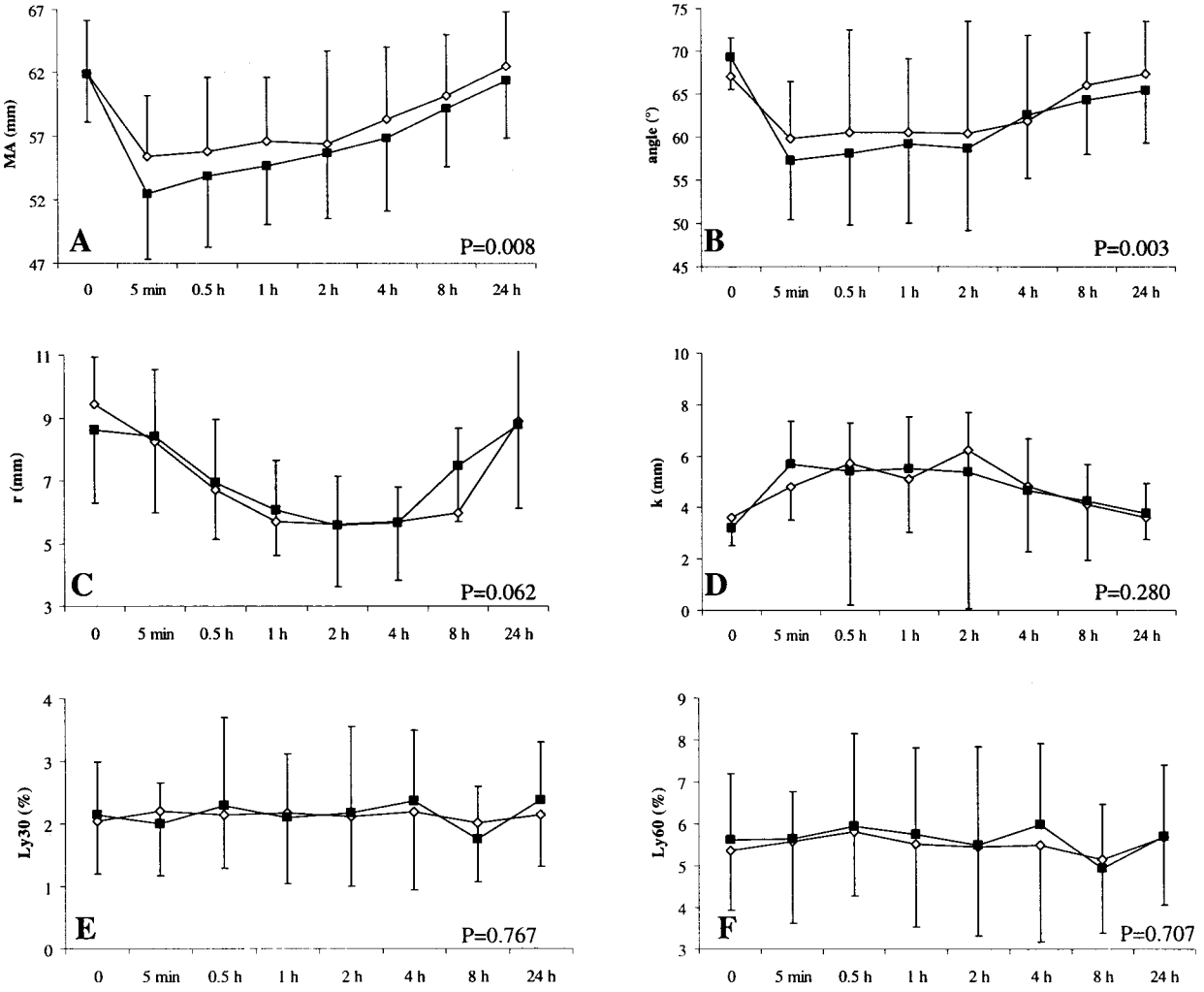

Fig. 2. Thrombelastograph® analysis parameters after hemodilution with hydroxyethyl starch (HES) 70 (diamonds) and HES200 (squares) before (0) and up to 24 h after HES infusion. (*A*) Maximum amplitude (MA); (*B*) angle α; (*C*) reaction time (r); (*D*) coagulation time (k); (*E*) clot lysis after 30 min (Ly30); and (*F*) clot lysis after 60 min (Ly60). *P* values indicate the difference between HES70 and HES200 (P_{HES}).

infusion ($P_{HES} < 0.001$; fig. 3A). Mw remained relatively stable after HES70 infusion but decreased over the course of 24 h after HES200 infusion ($P_{HES} < 0.001$; fig. 3B). Number average molecular weight increased particularly after HES70 infusion ($P_{HES} < 0.001$; fig. 3C), and HES polydispersity decreased particularly after HES200 infusion ($P_{HES} < 0.001$; fig. 3E).

In the additional series comparing dilution with acetate buffer, HES70, and HES200, PT was increasingly prolonged with progressive acetate buffer dilution (fig. 4). With HES70 and HES200, this prolongation was less than with acetate buffer ($P < 0.001$). *In vitro* 15% hemodilution with albumin resulted in a decrease in MA and reaction time, but angle α, coagulation time, and clot lysis were unaffected (table 2). *In vitro* 15% hemodilution with HES70 and HES200 resulted in a decrease in MA, angle α, and reaction time (nonsignificant for HES70), and an increase in coagulation time. Clot lysis was unaffected (table 2). The changes caused by HES70 and HES200 hemodilution were more pronounced than with albumin hemodilution. The difference between HES70 and HES200 was 15–52% of the difference between albumin hemodilution and hemodilution with HES70 and HES200, which describes the additional effect of the HES solutions on blood coagulation exceeding the effect of albumin hemodilution.

Discussion

The present study demonstrates that HES70 affects blood coagulation slightly less than HES200. Minimally smaller changes were found caused by HES70 than HES200 infusion in TEG® parameters, conventional plasmatic coagulation tests, and coagulation factor concentrations.

Decreases in MA and angle α with an increase in coagulation time (fig. 2) indicate a compromised blood coagulation by the infusion of HES200 as well as HES70.

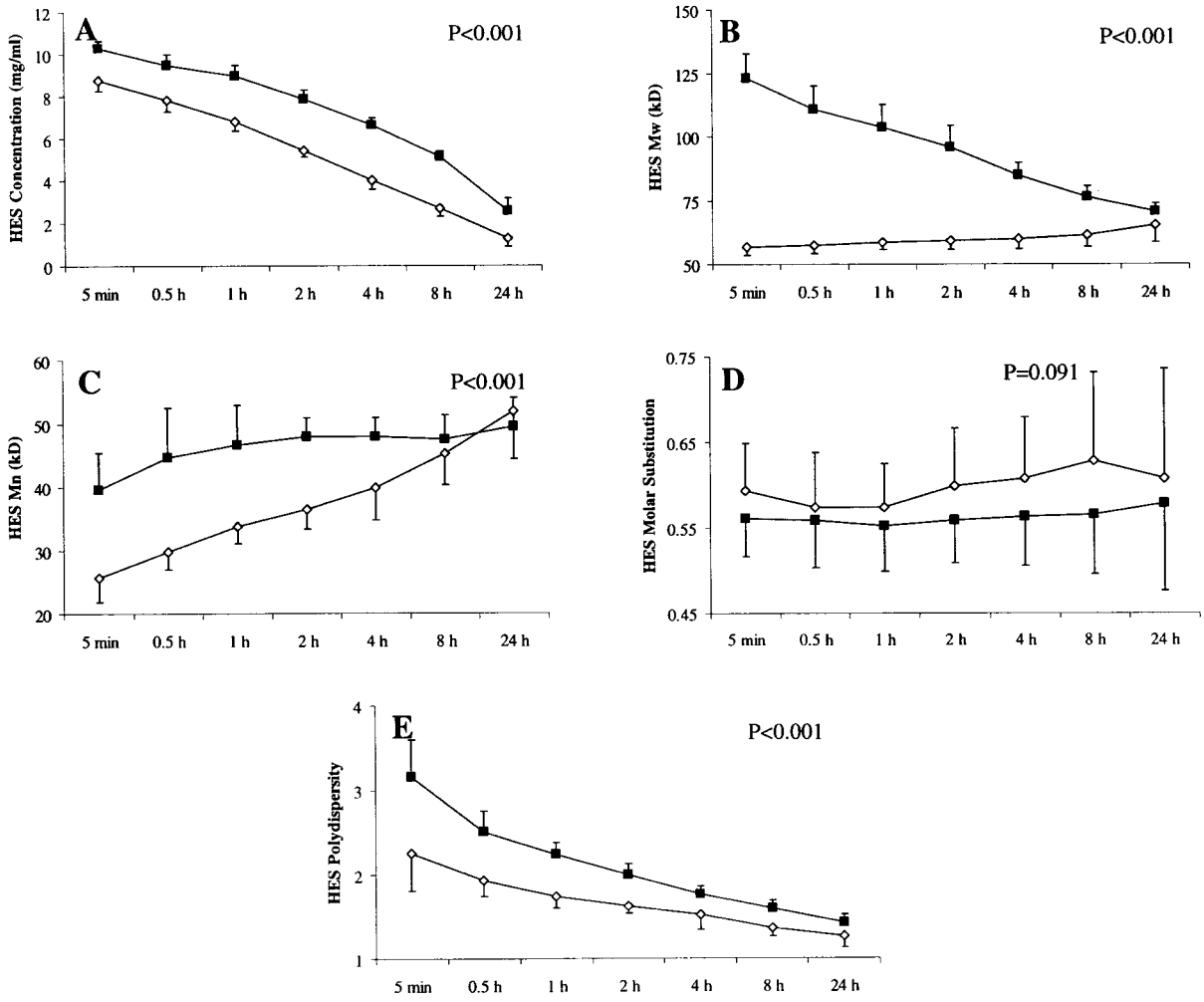

Fig. 3. Chemical characteristics of hydroxyethyl starch (HES) 70 (diamonds) and HES200 (squares) up to 24 h after HES infusion. (*A*) Concentration (milligrams/milliliter); (*B*) weight average molecular weight (Mw); (*C*) number average molecular weight (Mn); (*D*) molar substitution (MS); (*E*) polydispersity (Mw/Mn). *P* values indicate the difference between HES70 and HES200 (P_{HES}).

The decrease in MA and angle α was less with HES70. Both TEG® parameters are significantly influenced by platelet count and function. Because there was no difference in platelet count between the HES solutions (fig. 1B), the difference is likely to be related to the less pronounced decrease in vWF and its platelet-linking properties after infusion of HES70 (figs. 1D and 1E). A decrease in vWF has been found previously after high- and medium-molecular-weight HES infusions.[7] The decrease in vWF was less after infusion of medium-molecular-weight HES than after high-molecular-weight HES.[7] We have now demonstrated that the decrease in vWF is even less after low-molecular-weight HES infusion (figs. 1D and 1E).

This study did not include standard platelet aggregation tests because TEG® has been found to be particularly sensitive in detecting platelet-related changes in blood coagulation caused by HES infusion.[10]

The dilutional effect caused by a top load infusion of 15 ml/kg HES is greater for plasma constituents than for hemoglobin contained in erythrocytes. In our young athletic volunteers, one may assume a blood volume of 75–80 ml/kg. A hemoglobin of approximately 13.6 g/dl (table 1) results in a hematocrit of approximately 40%. This leaves a plasma volume of 60% of 75–80 ml/kg, *i.e.*

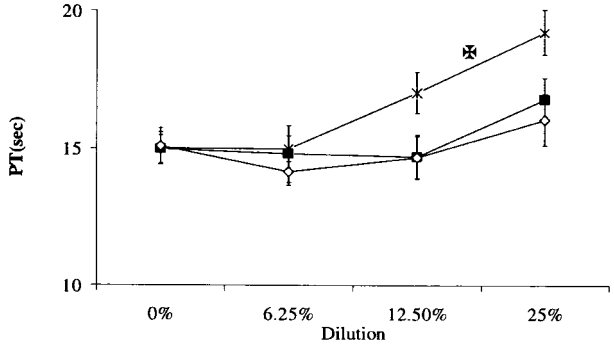

Fig. 4. Prothrombin time (PT) of pooled standard human plasma diluted with veronal acetate buffer (X), HES70 (diamonds), and HES200 (squares). †Dilution with veronal acetate buffer is significantly different from dilution with HES70 and HES200 ($P < 0.001$).

Table 2. TEG® Parameters at Baseline and after 15% *In Vitro* Hemodilution with Albumin, HES70, and HES200

	Baseline	15% Hemodilution with Albumin	15% Hemodilution with HES70	15% Hemodilution with HES200
Maximum amplitude (mm)	60.4 ± 4.3	55.0 ± 4.4*	52.1 ± 3.9*†	51.5 ± 4.6*†
Angle α (°)	69.8 ± 3.9	70.7 ± 4.2	65.8 ± 4.4*†‡	63.6 ± 4.6*†
Reaction time (mm)	8.0 ± 1.5	6.7 ± 1.8*	7.5 ± 1.1†	7.1 ± 1.2*
Coagulation time (mm)	3.2 ± 0.7	3.3 ± 0.9	4.1 ± 0.9*†‡	4.5 ± 1.1*†
Lysis 30 (%)	2.9 ± 1.4	2.5 ± 1.1	3.1 ± 1.0	2.7 ± 0.9
Lysis 60 (%)	6.5 ± 1.9	5.8 ± 1.3	6.9 ± 1.4†	6.7 ± 1.3†

Values are given as mean ± SD.

* Significantly different from baseline values ($P < 0.017$). † HES significantly different from albumin ($P < 0.025$). ‡ HES70 significantly different from HES200 ($P < 0.017$).

HES = hydroxyethyl starch.

45–48 ml/kg. With a top load infusion of 15 ml/kg HES, the maximum initial plasma volume expansion is 15 ml/kg, resulting in a theoretical dilution of plasma constituents by 24–25%. Some of this extra volume may have already been excreted or distributed in an extravascular compartment during the 30-min HES infusion. Instead of the theoretical hemoglobin dilution of 16–17%, only 14% was measured (table 1). One might thus hypothesize that the plasma volume expansion was only 12.5 ml/kg rather than 15 ml/kg. Assuming such a 12.5-ml/kg plasma volume expansion, a dilution of plasma constituents of approximately 20% is expected. We indeed observed an initial decrease of fibrinogen of 18% and 19% caused by HES70 and HES200 infusion. This represents pure passive dilution. However, the vWF decreased by 29% because of HES70 and by 47% because of HES200 infusion. We believe that this indicates that there are other mechanisms than pure passive dilution to explain the decrease in vWF caused by HES infusions. In addition, the time course is different between the hemoglobin and fibrinogen decrease and the decrease in vWF. Hemoglobin and fibrinogen concentrations decreased to a minimum immediately after HES infusions (5 min), but vWF reached its minimum only after 1–2 h. Again, this may be indicative of additional mechanisms explaining the decrease in vWF.

Although observed previously,[11] there is no generally accepted explanation for this phenomenon. In analogy to the acquired von Willebrand syndrome, antibody-mediated hypotheses have been postulated,[12] and proteolytic vWF,[7] a decreased vWF release, or enhanced elimination have been discussed.[13] Antibody-mediated mechanisms may be important in the acquired von Willebrand syndrome. However, because of the very rare occurrence of preformed HES antibodies, this is unlikely of relevance for the decrease in vWF after HES infusion.[14] Increased proteolytic degradation is also unlikely because vWF multimer analyses demonstrated that small and large vWF multimers decrease similarly because of HES infusion.[15] In addition, a decrease in vWF release is unlikely to explain the initial rapid decrease in vWF after HES infusion considering the vWF half-life is approximately 8 h. Therefore, the most likely reason for the overproportional decrease in vWF is an enhanced elimination. However, the mechanisms thereof have not been studied so far. It is conceivable that certain HES molecules may form complexes with the vWF to be cleared from the circulation. In the first hours after infusion, we observed a relatively large difference in molecular weight between HES200 and HES70 (figs. 3B and 3C). In addition, the maximum difference in vWF occurred during this period (figs. 1D and 1E). One might therefore speculate that the larger HES molecules are particularly involved in the mechanisms resulting in enhanced vWF elimination.

Surprisingly, reaction time decreased after infusion of both HES solutions (fig. 2C), indicating an accelerated onset of blood coagulation. To test this observation, we performed *in vitro* dilution of pooled standard human plasma with acetate buffer, HES70, and HES200 and measured PT. PT was chosen because it is, similar to reaction time, a relatively short coagulation time largely independent of factor VIII and vWF. With progressive *in vitro* dilution, PT increased markedly with acetate buffer. However, this increase was not or only minimally observed with HES70 and HES200, indicating that both HES solutions may exert an accelerating effect on blood coagulation relative to acetate buffer (fig. 4). It is possible that HES may serve as an additional surface able to activate coagulation factors.

The results of conventional coagulation assays (fig. 1) are consistent with TEG® findings (fig. 2), again demonstrating a slightly lesser blood coagulation compromising effect of HES70. Fibrinogen decreased after HES infusion to a similar degree as hemoglobin (fig. 1A and table 1). As a result, PT values increased (fig. 1F). Factor VIII also decreased after HES infusion, whereby the decrease was exaggerated after HES200, resulting in a slightly more pronounced increase in aPTT (fig. 1G). After both HES infusions, factor VIII decreased beyond a purely dilutional effect, but the decrease after HES70 infusion was less than after HES200 (fig. 1C). The mechanisms explaining the decrease in factor VIII beyond the dilutional effect have not been studied so far. As with vWF, en-

hanced elimination may be a key factor. Again, larger HES molecules may be particularly involved because we observed a significant difference between the *in vivo* molecular weight after HES70 and HES200 infusions during this period (fig. 3).

The difference between HES70 and HES200 on blood coagulation may appear small. However, the difference between HES70 and HES200 was 15–52% of the difference between *in vitro* hemodilution with albumin and hemodilution with HES70 or HES200 at 15% hemodilution. With progressive hemodilution (30%, 60%) the difference between TEG® parameters between albumin and HES200 hemodilution is known to increase.[8] Therefore, also the difference between HES70 and HES200 may increase with progressive hemodilution. Future studies are necessary to assess whether there is a clinically relevant difference between HES70 and HES200 regarding their effect on blood coagulation.

The finding that HES200 compromises blood coagulation more than albumin is in keeping with previous findings.[8] However, it differs from the observation of similarly compromised blood coagulation after HES200 and albumin infusions (1,500 ml) in patients undergoing major orthopedic surgery.[16] Major surgery in itself activates blood coagulation[17] and may thereby partially compensate the blood coagulation–compromising effect of HES200.

Thrombelastograph® analysis and conventional blood coagulation assays indicate that HES70 compromises blood coagulation slightly less than HES200. Future studies are necessary to assess whether this is of clinical relevance. Having a colloid with minimal blood coagulation–compromising properties would be beneficial for surgery with major blood loss and advanced normovolemic hemodilution. Should even artificial oxygen carriers become clinically available in the future,[18,19] blood coagulation might become the limiting factor in our attempts to avoid transfusion of allogeneic blood and blood products.

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