Effects of a new modified, balanced hydroxyethyl starch preparation (Hextend®) on measures of coagulation

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Background. Hydroxyethyl starch (HES) may affect blood coagulation. We studied the effects of a modified, balanced, high-molecular weight [mean molecular weight (MW) 550 kDa], high-substituted [degree of substitution (DS) 0.7] HES preparation (Hextend®) on coagulation in patients undergoing major abdominal surgery.

Methods. Patients were allocated randomly to receive Hextend® (n=21), lactated Ringer's solution (RL, n=21) or 6% HES with a low MW (130 kDa) and a low DS (0.4) (n=21). The infusion was started after induction of anaesthesia and continued until the second postoperative day to maintain central venous pressure between 8 and 12 mm Hg. Activated thrombelastography (TEG) was used to assess coagulation. Different activators were used (extrinsic and intrinsic activation of TEG) and aprotinin was added to assess hyperfibrinolytic activity (ApTEG). We measured onset of coagulation [coagulation time (CT=reaction time, r)], the kinetics of clot formation [clot formation time (CFT=coagulation time, k)] and maximum clot firmness (MCF=maximal amplitude, MA). Measurements were performed after induction of anaesthesia, at the end of surgery, 5 h after surgery and on the mornings of the first and second days after surgery.

Results. Significantly more HES 130/0.4 [2590 (SD 260) ml] than Hextend® [1970 (310) ml] was given. Blood loss was greatest in the Hextend® group and did not differ between RL- and HES 130/0.4-treated patients. Baseline TEG data were similar and within the normal range. CT and CFT were greater in the Hextend® group immediately after surgery, 5 h after surgery and on the first day than in the two other groups. ApTEG MCF also changed significantly in the Hextend® patients, indicating more pronounced fibrinolysis. Volume replacement using RL caused moderate hypercoagulability, shown by a decrease in CT.

Conclusion. A modified, balanced high-molecular weight HES with a high degree of substitution (Hextend®) adversely affected measures of coagulation in patients undergoing major abdominal surgery, whereas a preparation with a low MW and low DS affected these measures of haemostasis less. Large amounts of RL decreased the coagulation time.

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Volume loss from the circulation may be caused by changes in the endothelial barrier and diffuse capillary leakage, in addition to blood loss. Adequate volume replacement appears to be a cornerstone for managing patients undergoing major surgery. Hypovolaemia is an important avoidable cause of organ dysfunction and death. In addition to crystalloids [e.g. saline solution, Ringer lactate (RL)] and the natural colloid human albumin, synthetic colloids such as dextrans, gelatins and hydroxyethyl starch (HES) can be used to treat volume deficit.

Coagulation is often impaired when blood loss occurs during surgery. Haemodilution caused by fluid replacement impairs coagulation by reducing the concentration of clotting factors. The type of fluid used may also affect coagulation. Coagulation changes occur after the use of HES, but different HES preparations can have different...
effects on haemostasis.\textsuperscript{5} HES with a high molecular weight (MW) and a high degree of substitution (DS) (hetastarch; MW 450 kDa, DS 0.7) reduced concentrations of VIIIIR:Ag and VIIIIR:RCO more than HES with lower MW and a lower DS [low-molecular weight (LMW) HES; MW 200–260 kDa, DS 0.5].\textsuperscript{6} Abnormal platelet function occurs more often after high-molecular weight (HMW) HES.\textsuperscript{7} Reports of HES reducing blood coagulation and increasing bleeding generally relate to giving HMW HES and HES with a high degree of substitution (DS 0.7).\textsuperscript{8} Consequently, an HES preparation with a lower MW (130 kDa) and a lower DS (0.4) has been developed to reduce the impairment of coagulation.\textsuperscript{9 10} Another way to reduce this effect is by modifying the HMW HES preparation. Hextend\textsuperscript{8} is a modified, physiologically balanced 6% hetastarch solution (molar substitution 0.7; average MW approximately 670 kDa, mean MW 550 kDa) containing balanced electrolytes (Na\textsuperscript{+} 143 mmol litre\textsuperscript{-1}, Cl\textsuperscript{−} 124 mmol litre\textsuperscript{-1}, lactate 28 mmol litre\textsuperscript{-1}, Ca\textsuperscript{2+} 2.5 mmol litre\textsuperscript{-1}, K\textsuperscript{+} 3 mmol litre\textsuperscript{-1}, Mg\textsuperscript{2+} 0.45 mmol litre\textsuperscript{-1}, glucose 5 mmol litre\textsuperscript{-1}).\textsuperscript{11} This HES preparation impairs coagulation less than the standard Hextend\textsuperscript{8} is a modi®ed, physio-

The patients were allocated prospectively to one of the following groups using a sealed envelope system: group I (n=21), volume therapy with Hextend\textsuperscript{8} (BioTime, Berkeley, CA, USA); group II (n=21), volume therapy with RL (B. Braun, Melsungen, Germany; Na\textsuperscript{+} 130 mmol litre\textsuperscript{-1}, K\textsuperscript{+} 5.4 mmol litre\textsuperscript{-1}, Cl\textsuperscript{−} 112 mmol litre\textsuperscript{-1}, Ca\textsuperscript{2+} 1.8 mmol litre\textsuperscript{-1}, lactate 27 mmol litre\textsuperscript{-1}); group III (n=21), treatment with 6% HES 130/0.4 (Fresenius, Bad Homburg, Germany).

Volume replacement was started after induction of anaesthesia (after baseline data had been obtained) and continued for 48 h until the morning of the second postoperative day. Volume was infused to keep central venous pressure (CVP) between 8 and 12 mm Hg. Red blood cells were transfused when haemoglobin was <8 g dl\textsuperscript{-1}, and fresh frozen plasma was given if coagulation measures were abnormal (aPPT >60 s, prothrombin time <50%, fibrinogen <2 g litre\textsuperscript{-1}) and bleeding occurred. We gave RL 500 ml h\textsuperscript{-1} to all patients during surgery. Additional RL was given to replace fluid losses from sweating and gastric tubes and RL was used as a solvent for drugs. When mean arterial pressure (MAP) was <50 mm Hg despite adequate filling pressure volume (CVP >10 mm Hg), epinephrine was given. Norepinephrine was added if volume therapy and dopamine did not keep MAP >50 mm Hg.

Premedication consisted of oral midazolam 1 h before surgery. Epidural anaesthesia was used in all patients. General anaesthesia was induced with thiopental 5 mg kg\textsuperscript{-1} and fentanyl 3 μg kg\textsuperscript{-1} and neuromuscular block was achieved with vecuronium 0.1 mg kg\textsuperscript{-1}. Anaesthesia was maintained with fentanyl, desflurane and vecuronium, titrated according to the patients’ needs. In all patients, mechanical ventilation was with 50% air in oxygen to keep arterial oxygen saturation >95% and end-expiratory carbon dioxide between 35 and 40 mm Hg. ECG, arterial blood pressure and CVP were monitored continuously. Fluid warmers and blankets were used during surgery to maintain body temperature.

| Table 1 Patient details. Data are mean (SD) except for age [mean (range)]. PRBC=packed red blood cells; FFP=fresh frozen plasma. *P<0.05 compared with the other groups |
|-----------------|-----------------|-----------------|
|                | Hextend\textsuperscript{8} (n=21) | Ringer lactate (n=21) | HES 130/0.4 (n=21) |
| Age (yr)       | 62 (45–74)      | 61 (48–78)      | 60 (48–77)     |
| Sex (F/M)      | 14/7            | 12/9            | 10/11          |
| Height (cm)    | 171 (9)         | 174 (11)        | 173 (12)       |
| Weight (kg)    | 74 (11)         | 76 (12)         | 72 (11)        |
| ASA (II/III)   | 10/11           | 11/9            | 12/9           |
| Duration of (min) | Surgery 196 (78) | 202 (62)        | 189 (70)       |
|                | Anaesthesia 299 (79) | 310 (63)        | 293 (62)       |
| Type of surgery (number of patients) |       |       |       |
| Colon          | 10              | 9               | 8              |
| Gastrectomy    | 4               | 5               | 6              |
| Whipple operation | 2             | 2               | 1              |
| Oesophagus     | 2               | 3               | 3              |
| Pancreas resection | 3            | 2               | 3              |
| Allogeneic blood/blood products |       |       |       |
| PRBC           | Number of patients 8 | 6               | 5              |
|                | Units/group 29* | 18              | 16             |
| FFP            | Number of patients 5 | 5               | 4              |
|                | Units/group 27* | 16              | 14             |
| Catecholamines (number of patients) |       |       |       |
| Epinephrine    | 2               | 2               | 1              |
| Norepinephrine | 1               | –               | –              |
| Survivors      | 7 days          | All             | All            |
|                | 30 days         | All             | All            |
After surgery, mechanical ventilation was continued as necessary until the patient was ready for tracheal extubation (stable circulation, spontaneous breathing with adequate blood gases and oesophageal temperature >36°C). The patients were managed by anaesthetists who were not involved in the study and were masked to the volume therapy.

**Coagulation measurements**

Standard coagulation variables [antithrombin III (AT III), fibrinogen, platelet count, aPTT] were measured from arterial blood samples using routine laboratory methods. Another 5 ml of citrated blood was taken for activated TEG using a four-channel TEG analyser (roTEG®; Nobis Diagnostics, Endingen, Germany). This modification of the conventional TEG system uses a different transducer that makes it less susceptible to mechanical stress, movement and vibration. The method is based on optical detection of the movement of a disposable plastic sensor attached to a short axle mounted on a ball-bearing. The sensor is inserted into the clotting blood. TEG monitoring provides continuous assessment of clot firmness, to measure the onset of coagulation [coagulation time (CT); standard TEG: reaction time (r)], the kinetics of clot formation [clot formation time (CFT); standard TEG: coagulation time (k)] and maximum clot firmness (MCF) (standard TEG: maximal amplitude (MA)).

TEG measurements were made within 10 min after blood sampling using a semi-automated pipetting system after adding different activators to the blood sample (activated TEG). To assess intrinsic TEG (InTEG), clot formation was measured in the presence of inhibition of fibrinolytic activity by aprotinin (aprotinin solution equivalent to 10 000 kallikrein inhibitor units ml⁻¹). Comparison of this result with the ExTEG value gives a measure of fibrinolytic activity.

All measurements were made by the same person. Measurements were made after induction of anaesthesia and before surgery, immediately after surgery, 5 h after surgery and on the mornings of the first and second days after surgery. The patient outcomes were followed-up for 30 days after surgery.

**Statistics**

A power analysis was done before the study started to determine the necessary number of patients in each group. The data used were from a previous TEG study on the effects of HES 130/0.4. A 50% increase in reaction time (r) after treatment was taken to be the minimum clinically important difference we wished to detect. For an alpha error of 0.05 (two-sided) and type II error of 0.2, a total of 21 patients was required in each group.
patients per group was found to be necessary. Data are presented as mean (SD) unless otherwise indicated. Statistical analysis was done with software package SPSS/PC+ (version 4.0 SPSS, Chicago, IL, USA). Fisher’s exact test was used for categorical data. A non-parametric test (Wilcoxon rank sum test) was used for variables that were not normally distributed (detected with the Kolmogorov-Smirnov test; e.g. use of blood products). Continuous, normally distributed data were compared using paired and unpaired Student’s t-test or analysis of variance for repeated measures (ANOVA, followed by Scheffe’s test). Bonferroni correction was applied when multiple comparisons were made. Continuous, non-normally distributed data were compared using the Wilcoxon test. Correlation analysis was used to correlate blood loss and data from TEG. \( P<0.05 \) was considered significant.

### Results
Patient details and the type of surgery are given in Table 1. There were no obvious differences between the groups. Significantly more blood and blood products were given to the Hextend\textsuperscript{®}-treated patients than to the two other groups (Table 1). Significantly more HES 130/0.4 [2590 (260) ml] than Hextend\textsuperscript{®} [1970 (310) ml] was given in the study period (Table 2). Blood loss was greatest in the Hextend\textsuperscript{®} group, but did not differ between RL- and HES 130/0.4-treated patients (Table 2). There was no significant correlation between blood loss and TEG measurements. Cardiovascular measurements and haemoglobin changes were similar in all groups (Tables 3 and 4). Standard coagulation tests showed no significant differences between the groups, except for small differences in fibrinogen (RL, significant difference) and AT III concentrations on the first and second days (Table 4).

TEG data were similar and within the normal range in all three groups at baseline (Figs 1–3). Using ExTEG and InTEG, CT and CFT were prolonged most in the Hextend\textsuperscript{®}-treated patients and were greater than in the two other groups immediately after surgery, 5 h after surgery and on the first day (Figs 1 and 2). On the second day, CT and CFT in the Hextend\textsuperscript{®} group were still greater than baseline but were not different from values for the other two groups. Changes in ExTEG-MCF/ApTEG-MCF were significantly more pronounced in the Hextend\textsuperscript{®} patients than in the other two groups, indicating more fibrinolysis (Figs 1 and 3).

Volume therapy with RL caused shortening of the CT (ExTEG, InTEG) at the end of surgery and 5 h after surgery (Figs 1 and 2), indicating moderate hypercoagulability. This returned to normal later in the study period (first and second days) (Figs 1 and 2).

### Discussion
The use of HES as a plasma substitute is sometimes restricted primarily because of reports of altered coagulation.\textsuperscript{2,3,8} HMW HES and highly substituted hydroxyethyl starch preparations can impair blood clotting and increase postoperative bleeding.\textsuperscript{8,16} A modified HMW HES (Hextend\textsuperscript{®}) and a new LMW/low-substituted HES (6% HES 130/0.4) have been developed to prevent these adverse effects.

We used TEG to assess the effects of the different plasma substitutes, as measuring plasma concentrations of coagulation proteins and other markers of coagulation appears to be a very simplistic approach for complete assessment of the complex changes that can occur in haemostasis.\textsuperscript{17} TEG data were similar and within the normal range in all three groups at baseline (Figs 1–3). Using ExTEG and InTEG, CT and CFT were prolonged most in the Hextend\textsuperscript{®}-treated patients and were greater than in the two other groups immediately after surgery, 5 h after surgery and on the first day (Figs 1 and 2). On the second day, CT and CFT in the Hextend\textsuperscript{®} group were still greater than baseline but were not different from values for the other two groups. Changes in ExTEG-MCF/ApTEG-MCF were significantly more pronounced in the Hextend\textsuperscript{®} patients than in the other two groups, indicating more fibrinolysis (Figs 1 and 3).
appears to be a more complete means of following the dynamic process of coagulation compared with conventional tests of haemostasis.\textsuperscript{18, 19} TEG monitors the kinetics of the complete haemostatic process, whereas with plasma coagulation tests only the speed of fibrin formation is assessed. TEG examines the interplay of the protein coagulation cascade, fibrinogen, and platelet function. TEG measurements can assist management of coagulation during and after surgery, and reduce blood loss and use of blood and blood products.\textsuperscript{18, 20, 21} We used modified, activated TEG instead of conventional (`non-activated') TEG because different features of the coagulation process can be detected sooner and better by activated TEG.\textsuperscript{22, 23}

We found that Hextend\textsuperscript{\textregistered} had the most adverse effects on activated TEG monitoring, whereas HES with a low MW and low DS affected coagulation less and RL caused a small increase in coagulation. Our results contradict other \textit{in vitro} and \textit{in vivo} studies, which did not show that Hextend\textsuperscript{\textregistered} had adverse effects on coagulation, except those expected as a result of haemodilution.\textsuperscript{11, 12} An \textit{in vitro} study with different dilutions of plasma with Hextend\textsuperscript{\textregistered} (up to 25\% plasma/75\% Hextend\textsuperscript{\textregistered}) found no adverse effect on coagulation,\textsuperscript{12} with possibly a protective effect on factors sensitive to prothrombin time (I, II, VII, X), on functional fibrinogen, and on factors of factor VIII macromolecular complex components (FVIII:C, VIII:vWF, VIII:vWF multimers), and no evidence of disseminated intravascular coagulation or procoagulant activation. The value of \textit{in vitro} coagulation studies is not clear, because in such studies the effects of surgery on the coagulation process are absent. Even after minor surgery (mammoplasty), a hypercoagulable state was seen, whereas after complex, lengthy surgery hypocoagulability may also be present.\textsuperscript{24}

HMW HES (hetastarch) can affect coagulation by adverse effects on both von Willebrand factor and platelet aggregation.\textsuperscript{8} Most reports of impaired haemostasis with

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure1}
\caption{Mean (SD) coagulation time [CT (onset of coagulation); normally <50 s; standard TEG: reaction time (r)], clot formation time [CFT (kinetics of clot formation), normally <180 s; standard TEG: coagulation time (k)], and maximum clot firmness [MCF; normally 53–74 mm; standard TEG: maximum amplitude (MA)] using (extrinsic) activation by tissue thromboplastin (extrinsic TEG). *P<0.05 compared with the other groups. †P<0.05 compared with baseline data. Filled squares, Hextend\textsuperscript{\textregistered}; filled triangles, HES 130/0.4; open circles, Ringer lactate. Horizontal dotted lines show the normal range.}
\end{figure}

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2}
\caption{Mean (SD) coagulation time [CT (onset of coagulation); normally <160 s], clot formation time (CFT; kinetics of clot formation, normally <180 s) and maximum clot firmness (MCF, normally 53–74 mm) using activation by surface activator [activation of the intrinsic system (intrinsic TEG)]. *P<0.05 compared with the other groups. †P<0.05 compared with baseline data. Symbols as in Fig. 1. Horizontal dotted lines show the normal range.}
\end{figure}
HES are associated with this first-generation HMW HES. A study of patients undergoing major surgery compared Hextend with standard HMW HES (hetastarch), and found no differences in perioperative blood transfusion and estimated blood loss. Onset of clot formation (r ± CT) was slower in the patients treated with hetastarch compared with those given Hextend, and other TEG variables showed no differences between the two groups. Why the modified, ‘balanced’ Hextend solution is almost free of this side-effect on coagulation is not clear. The authors speculated that the addition of Ca²⁺, lactated buffer and physiological concentrations of glucose and lower Cl⁻ concentrations gave Hextend a favourable side-effect profile. Our study using TEG monitoring in patients found no benefit of Hextend administration either in onset of coagulation (r – CT) or in the kinetics of clot formation (k – CFT). The difference of ExTEG MCF and ApTEG MCF (TEG measured in the presence of an inhibitor of fibrinolysis) showed reduced MCF [standard TEG: maximal amplitude (MA)] with Hextend compared with the new HES 130/0.4.

The shorter coagulation time in our RL-treated patients supports previous studies. In in vitro and in vivo TEG studies, Ruttman and colleagues showed that haemodilution per se increased the coagulability of whole blood (decrease in r and k; increase in MA) most likely due to induction of thrombin formation. This hypercoagulability was greater in saline- than in gelatin-diluted samples. In an in vitro TEG study, only extreme haemodilution with RL (10:10) increased the k and MA values, whereas the r value remained unchanged. Ng and Lo also reported increased coagulability when surgical blood loss was replaced with crystalloids. Monkhouse showed that diluting plasma with saline increases the thrombin activity two- to three-fold. This increase in thrombin activity in diluted samples was assumed to result from decreased antithrombin action rather than any real increase in thrombin generation. Similar changes in thrombin generation occur in vivo after giving large amounts of saline solution for acute haemorrhage. This crystalloid-induced increase in coagulability could predispose patients to deep vein thrombosis.

The new LMW low-substituted HES (HES 130/0.4) has better physicochemical properties compared with other HES solutions and its effect on coagulation also appears to be favourable. Konrad and colleagues used an in vitro haemodilution model and SONOCLOT analysis to measure the effects of this HES preparation on haemostasis: HES 130/0.4 affected clot maturation significantly less than other HES preparations and it had less effect on other aspects of clot formation and retraction. Clinical studies with HES 130/0.4 in orthopaedic and cardiac patients reported beneficial effects on bleeding tendency and the use of blood and blood products.

In summary, modification of an HMW starch did not eliminate adverse effects on coagulation when assessed by activated TEG. Reducing the molecular weight and the degree of substitution (HES 130/0.4) caused less impairment of haemostasis. Volume replacement only with crystalloids (RL) in patients undergoing major abdominal surgery was associated with moderate, short-lasting hypercoagulability.

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