Intravascular volume therapy with hydroxyethyl starch (HES) solutions has become an established approach to correct absolute or relative hypovolaemia. Besides the desired volume efficacy, HES can alter blood coagulation, mainly platelet function and fibrinogen polymerization. Haemostasis can also be impaired by dilutional-hyperchloroaemic acidosis induced by the HES carrier solution. We hypothesized that a saline-based tetrastarch carrier solution impairs parameters of blood coagulation more compared with a balanced carrier solution.

**Methods.** The study was designed as a prospective, double-blinded, randomized, cross-over trial in healthy male volunteers. At intervals of at least 10 days, 13 subjects received 20 ml kg⁻¹ of balanced or saline-based tetrastarch over 2 h. Blood was subjected to blood gas analysis, assessment of platelet function (with multiple electrode aggregometry (MEA)), and clot formation (with rotational thrombelastometry).

**Results.** Maximum aggregation in response to adenosine diphosphate (ADP) decreased after saline-based HES infusion, but not after balanced solution-based HES infusion. ADP-induced platelet aggregation was significantly lower after saline-based HES compared with baseline (21%; \(P<0.025\)) and compared with balanced solution-based HES (17%; \(P<0.025\)). There were no significant changes in platelet aggregation induced by thrombin receptor-activating peptide and in any parameter of rotational thrombelastometry. Chloride concentrations were significantly higher after saline-based HES compared with balanced solution-based HES.

**Conclusions.** The carrier solution for HES up to 20 ml kg⁻¹ had little impact on platelet aggregation or clot formation as assessed by MEA and rotational thrombelastometry, respectively. Further clinical studies are required to verify this finding in patients and to correlate results of whole blood aggregometry and rotational thrombelastometry with perioperative bleeding and transfusion requirements.

**Keywords:** blood, coagulation; diagnostic techniques and procedures, platelet function test; diagnostic techniques and procedures, thrombelastography; hydroxyethyl starch; isotonic solutions

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after infusion of tetrastarch dissolved in two different carrier solutions.

**Methods**

Institutional review board approval was obtained before the study (registration no. 188/2007). The study was designed as a prospective, double-blinded, randomized, cross-over trial in 13 healthy male volunteers (performed May to November 2008). Inclusion criteria were male sex, age 18–65 yr, ASA classification I, and no bleeding history. After written informed consent, potential subjects underwent physical examination and blood analysis for platelet count, prothrombin time, activated partial thromboplastin time, fibrinogen, creatinine and blood urea nitrogen concentration, and blood type. Coagulation time and fibrinogen concentration were determined using an automated coagulation analyzer (STA-R Evolution, Stago, Asnieres, France). Exclusion criteria were BMI >25 kg m$^{-2}$, cardiac or renal insufficiency, known bleeding disorders, and/or blood type O. The latter were excluded because application of HES induces a more pronounced inhibition of blood coagulation in carriers of blood type O. Female volunteers were not considered because ovarian hormones have an impact on platelet function. Subjects were not allowed to take any medication 14 days before and during the study period.

After enrolment, volunteers were randomized to receive two different HES preparations (20 ml kg$^{-1}$) administered over 2 h at intervals of at least 10 days in order to avoid a potential confounding effect of the first infusion on the second. One solution was a non-balanced potato-derived tetrastarch 6% 130/0.42 C2/C6 ratio 6:1 in isotonic saline (sodium 154 mmol litre$^{-1}$, chloride 154 mmol litre$^{-1}$) (VenoFusionin\textsuperscript{®}, B. Braun, Maria Enzersdorf, Austria), and the other was a balanced potato-derived HES 6% 130/0.42 C2/C6 ratio 6:1 dissolved in Ringer’s acetate (sodium 130 mmol litre$^{-1}$, chloride 112.5 mmol litre$^{-1}$, potassium 5.5 mmol litre$^{-1}$, calcium 1 mmol litre$^{-1}$, magnesium 1 mmol litre$^{-1}$, and acetate 27 mmol litre$^{-1}$) (Vitafusal\textsuperscript{®}, Serumwerk Bernburg, Bernburg, Germany). Subjects and supervisors were blinded with regard to the test solution. Blood was drawn before infusion, after infusion of 10 ml kg$^{-1}$ test solution (at 1 h), and at the end of the infusion (at 2 h). For each blood collection, atraumatic venipuncture was carried out with minimum stasis using a 21 G butterfly needle. The first 4 ml was always discarded, and samples were subjected to blood gas analysis immediately after withdrawal. Platelet function analysis and viscoelastic coagulation testing were performed within 2 h.

**Blood gas analysis**

Blood was drawn into a Portex\textsuperscript{®} (Portex, Keene, NH, USA) blood gas sample syringe. Venous blood gas analysis was performed using a standard analyzer (Radiometer Copenhagen\textsuperscript{®}, Brønshøj, Denmark), and included determination of pH, base excess (BE), bicarbonate (HCO$_3^-$), haemoglobin, and electrolyte (sodium, chloride, and ionized calcium) concentrations.

**Multiple electrode aggregometry**

Blood was drawn into a 3.5 ml DTI-tube (direct thrombin inhibitor blood collection tube; Verum Diagnostica GmbH, Munich, Germany). Platelet function was determined implementing whole blood platelet aggregometry with Multiplate\textsuperscript{®} (Verum Diagnostica GmbH) as described.\textsuperscript{20} The impedance change due to platelet aggregation is transformed into arbitrary aggregation units (AU) by the system software and plotted against time. Platelet aggregation was determined in response to adenosine diphosphate (ADP, 6.5 μM) and thrombin receptor-activating peptide-6 (TRAP, 32 μM) using the commercially available test reagents, which permit the assessment of different pathways of platelet activation. Results shown are maximum platelet aggregation expressed in AU.

**Rotational thrombelastometry**

Blood was drawn into plastic tubes containing 3.8% trisodium citrate (Vacuette\textsuperscript{TM} tubes Greiner, Kremsmünster, Austria; 9:1 v/v). Global haemostatic assessment was performed using rotational thrombelastometry (ROTEM\textsuperscript{®}, TEM Innovations, Munich, Germany) as described.\textsuperscript{21} At each time point, two commercially available ROTEM\textsuperscript{®} tests were performed according to the manufacturer’s recommendations; tissue factor is the coagulation activator in EXTEM\textsuperscript{®} and ellagic acid activates coagulation in INTEM\textsuperscript{®}. Clotting time (CT), clot formation time (CFT), angle alpha ($\alpha$), maximum clot firmness (MCF), and lysis index were documented. All ROTEM analyses were performed for 60 min.

**Statistics**

A power analysis based on in vitro and ex vivo pilot experiments revealed that a sample size of 12 was required in order to detect a difference of 15% in ADP-induced platelet aggregation ($\beta=0.90$, $\alpha=0.05$). Data were tested for normal distribution using the Kolmogorov–Smirnov test. Analysis of variance was used to assess the effect of the formulation and the amount of the test infusion and their interaction. Two-sided paired Student’s t-test was used for post hoc comparisons between controls before test infusion and after 10 and 20 ml kg$^{-1}$ of infusion and also between the two test solutions. The level of significance was adjusted according to the Bonferroni–Holm correction. Corrected P-values of $<0.025$ were considered statistically significant. Values are given as mean (SD).

**Results**

Baseline characteristics of the 13 volunteer subjects are summarized in Table 1.

**Blood gas analysis**

There was a statistically significant decrease in haemoglobin concentration after 20 ml kg$^{-1}$ of both test infusions, with no differences between the balanced and saline-based solution (Table 2). Chloride concentrations increased significantly after 20 ml kg$^{-1}$ of tetrastarch infusion and were significantly
higher after saline-based HES infusion compared with balanced HES infusion. pH, BE, and HCO₃⁻ changed in opposite directions after saline-based and balanced HES infusion resulting in higher levels after balanced compared with saline-based infusions. There were no significant changes in calcium concentrations between the two solutions (Table 2).

**Multiple electrode aggregometry**

Maximum aggregation in response to ADP decreased after saline-based HES infusion but not after HES in balanced solution (Fig. 1). The decrease in ADP-induced platelet aggregation reached statistical significance after 20 ml kg⁻¹ of saline-based tetrastarch \(P<0.025\). Compared with baseline values, there was a 9% and 21% decrease in ADP-induced platelet aggregation after saline-based tetrastarch infusion of 10 and 20 ml kg⁻¹, respectively. ADP-induced platelet aggregation was significantly lower after 20 ml kg⁻¹ of saline-based HES compared with balanced HES infusion with a difference of 17%.

| Table 1 Characteristics of the study population. BMI, body mass index; BUN, blood urea nitrogen; INR, international normalised ratio; PT, prothrombin time; aPTT, activated partial thromboplastin time. Data are number with median (range) for age, or mean (sd). |
|---|---|
| n | 13 |
| Age (yr) | 23 (21-30) |
| BMI (kg m⁻²) | 22.0 (1.7) |
| Platelet count (g litre⁻¹) | 248 (57) |
| Creatinine (mg dl⁻¹) | 1.03 (0.11) |
| BUN (mg dl⁻¹) | 14.4 (3.1) |
| INR | 1.1 (0.1) |
| aPTT (s) | 36.8 (2.0) |
| Fibrinogen (mg dl⁻¹) | 225.1 (33.3) |
| Test infusion volume (ml) | 1426 (160) |

There were no significant changes after test infusions and between the two solutions with respect to TRAP-induced platelet aggregation (Fig. 1). The two other multiple electrode aggregometry (MEA) parameters (velocity of aggregation, area under the aggregation curve) showed the same pattern as maximum aggregation (data not shown). Time until MEA analyses was comparable for both solutions.

**Rotational thrombelastometry**

There were no significant differences between saline-based and balanced HES infusions in any of the ROTEM® parameters tested (Table 3). EXTEM® CT increased significantly during saline-based HES infusion compared with baseline but did not change after exposure to HES in balanced solution. In contrast, INTEM® CT increased significantly after infusion of 20 ml kg⁻¹ HES in balanced solution but not after saline-based HES.

The increase in EXTEM® CFT and INTEM® CFT and also the decrease in EXTEM® \(\alpha\) and INTEM® \(\alpha\) were statistically significant even after 10 ml kg⁻¹ of both test infusions. The decrease in EXTEM® MCF and INTEM® MCF was also statistically significant after 10 ml kg⁻¹ of both test infusions \(P<0.025\). No increased lysis index was observed before and after test infusions. Time until ROTEM® analyses was comparable for both solutions.

**Discussion**

This is the first ex vivo study of the effect of HES carrier solutions on coagulation parameters. The carrier solution of tetrastarch had minimal effects on platelet aggregation assessed by MEA and clot formation assessed by ROTEM® at the doses studied. There was no significant difference in viscoelastic parameters of ROTEM® analyses after test infusions of up to 20 ml kg⁻¹ of tetrastarch dissolved in isotonic saline or balanced solution. In whole blood MEA using the strong platelet agonist TRAP, there were no differences after progressive haemodilution. The only significant signal

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**Table 2 Blood gas analyses before and after test infusions. Hb, haemoglobin; BE, base excess; BW, bodyweight. Data are mean (sd). \(P<0.025\), *within test infusion group; †between test infusion groups**

<table>
<thead>
<tr>
<th>Carrier solution</th>
<th>Control</th>
<th>After 10 ml kg⁻¹ BW</th>
<th>After 20 ml kg⁻¹ BW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (g litre⁻¹)</td>
<td>Balanced</td>
<td>15.1 (0.8)</td>
<td>13.5 (0.7)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>15.5 (0.8)</td>
<td>13.6 (0.8)</td>
</tr>
<tr>
<td>pH</td>
<td>Balanced</td>
<td>7.35 (0.02)</td>
<td>7.36 (0.02)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>7.36 (0.04)</td>
<td>7.36 (0.04)</td>
</tr>
<tr>
<td>BE (mmol litre⁻¹)</td>
<td>Balanced</td>
<td>1.39 (1.81)</td>
<td>2.02 (1.54)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>2.28 (1.34)</td>
<td>1.84 (1.64)</td>
</tr>
<tr>
<td>HCO₃⁻ (mmol litre⁻¹)</td>
<td>Balanced</td>
<td>24.2 (1.19)</td>
<td>24.8 (1.09)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>24.9 (1.37)</td>
<td>24.7 (1.32)</td>
</tr>
<tr>
<td>Cl⁻ (mmol litre⁻¹)</td>
<td>Balanced</td>
<td>105.2 (2.6)</td>
<td>105.7 (2.7)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>104.8 (2.7)</td>
<td>107.5 (3.2)</td>
</tr>
<tr>
<td>Ca²⁺ (mmol litre⁻¹)</td>
<td>Balanced</td>
<td>1.19 (0.12)</td>
<td>1.21 (0.06)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>1.22 (0.06)</td>
<td>1.19 (0.06)</td>
</tr>
</tbody>
</table>
was obtained in the MEA tests using the weak platelet agonist ADP. In this ADP test, platelet aggregability was lower after saline-based HES infusion. Platelet counts after 20 ml kg$^{-1}$ test infusion remained above a methodological cut-off level of 100 G litre$^{-1}$ in our pilot experiments. The observed difference in ADP-induced MEA test results appears to represent a genuine effect of the saline carrier solution. Future studies correlating MEA values to clinical outcome are needed. Interestingly, in previous studies, blood loss and transfusion requirements were not different between patients exposed to balanced or saline-based colloid carrier solution. These trials only assessed conventional coagulation tests, and showed no relevant differences between the solutions. These previous studies, however, did not use coagulation parameters such as platelet aggregation and overall clot strength that are suggested to be important in dilutional coagulopathy and clinical bleeding. The present trial extends previous observations showing only negligible differences between balanced and non-balanced HES carrier solutions on platelet aggregation and clot strength.

Tetrastarch infusion can lead to dilutional coagulopathy. HES macromolecules can also have direct effects on haemostasis, with rapidly degradable HES such as tetrastarch having only minimal effects compared with slowly degradable HES such as penta-, hexa-, and hetastarch. Haemostatic side-effects of tetrastarch were dose-dependent in the current study. MEA parameters showed a dose-dependent trend towards reduced platelet reactivity. Time to initial fibrin strand formation and the time and slope of clot formation assessed with ROTEM were prolonged with increasing infusion volume. Also viscoelastic strength of the clot was weakened with increasing dose of tetrastarch. Reduced clot strength in the ROTEM test with inhibition of the platelet contribution, the FIBTEM test, has been interpreted as acquired fibrinogen deficiency responsible for increasing blood loss. We did not measure FIBTEM in this study, but it is important to consider that even after about 1.5 litre of tetrastarch infusion in our volunteers, the mean maximum clot strength of the more global EXTEM and INTEM tests remained well above trigger levels for therapeutic interventions defined experimentally in bleeding patients. Several authors have investigated urgent reversal of impaired clot

![Fig 1. Platelet aggregation by MEA in response to ADP and TRAP after infusion of balanced tetrastarch (blue bars) or saline-based tetrastarch (green stripped bars). AU, aggregation units; ADP, adenosine diphosphate; MEA, multiple electrode aggregometry; TRAP, thrombin receptor-activating peptide. Data are mean (so). P<0.025, *within test infusion group, #between test infusion groups.]

<table>
<thead>
<tr>
<th>Carrier solution</th>
<th>Control</th>
<th>After 10 ml kg$^{-1}$</th>
<th>After 20 ml kg$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTEM CT (s)</td>
<td>Balanced</td>
<td>94.5 (34.8)</td>
<td>102.0 (28.7)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>91.0 (17.9)</td>
<td>115.5 (30.4)*</td>
</tr>
<tr>
<td>EXTEM CFT (s)</td>
<td>Balanced</td>
<td>146.3 (36.3)</td>
<td>185.4 (47.1)*</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>135.6 (27.7)</td>
<td>167.8 (36.3)*</td>
</tr>
<tr>
<td>EXTEM MCF (mm)</td>
<td>Balanced</td>
<td>53.5 (4.1)</td>
<td>47.8 (3.8)*</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>53.3 (5.2)</td>
<td>48.9 (3.9)*</td>
</tr>
<tr>
<td>EXTEM $\alpha$ (°)</td>
<td>Balanced</td>
<td>62.4 (5.0)</td>
<td>56.5 (5.7)*</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>63.9 (4.6)</td>
<td>59.5 (5.0)*</td>
</tr>
<tr>
<td>INTEM CT (s)</td>
<td>Balanced</td>
<td>196.9 (35.4)</td>
<td>220.3 (72.1)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>209.2 (67.9)</td>
<td>217.9 (74.0)</td>
</tr>
<tr>
<td>INTEM CFT (s)</td>
<td>Balanced</td>
<td>103.4 (29.7)</td>
<td>157.7 (57.4)*</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>110.4 (32.0)</td>
<td>143.1 (23.3)*</td>
</tr>
<tr>
<td>INTEM MCF (mm)</td>
<td>Balanced</td>
<td>57.9 (4.8)</td>
<td>51.2 (4.0)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>57.5 (4.0)</td>
<td>51.7 (3.0)</td>
</tr>
<tr>
<td>INTEM $\alpha$ (°)</td>
<td>Balanced</td>
<td>72.0 (9.7)</td>
<td>61.8 (8.0)</td>
</tr>
<tr>
<td></td>
<td>Saline-based</td>
<td>69.3 (5.3)</td>
<td>63.6 (3.7)</td>
</tr>
</tbody>
</table>
strength after colloidal haemodilution including administra-
tion of fibrinogen concentrate.\textsuperscript{3, 28} Our results suggest that
infusion of up to 1.5 litre of tetrastarch does not lead to sig-
nificant coagulopathy, as defined by ROTEM\textsuperscript{R} parameters,
requiring factor concentrate supplementation. However,
factors confounding clot strength such as hypothermia or
severe blood loss can require prohaemostatic therapy in
surgical patients who also need colloidal fluid therapy of
<1.5 litre.

Of note, we observed no increased fibrinolysis even after
20 ml kg\textsuperscript{-1} tetrastarch. In vitro studies show decreased clot
stability in blood samples incubated with tissue plasminogen
activator simulating hyperfibrinolytic conditions.\textsuperscript{29, 30} It
appears that HES enhances the fibrinolytic response only in
this in vitro lysis provocation test, but has no profibrinolytic
effect in vivo.

In contrast to our previous study demonstrating an inhibi-
tory effect of slowly degradable tetrastarch on TRAP-induced
platelet function,\textsuperscript{6} we observed no inhibition by rapidly de-
gradable HES. In line with our previous studies demonstrat-
ing no inhibitory effect of rapidly degradable HES,\textsuperscript{5} these
findings imply that global platelet reactivity in response to
the strong agonist thrombin remains preserved after tetra-
starch but not after penta-, hexa-, and hetastarch infusion.
We used ADP as a model of a weak platelet agonist in the
present and previous studies, and observed inhibition of
ADP-induced platelet aggregability after both saline-based
hexastarch\textsuperscript{4} and saline-based tetrastarch infusion (Fig. 1).
The magnitude of inhibition by saline-based tetrastarch,
however, was less compared with pharmacological inhibition
by ADP-receptor antagonists as described for clopidogrel
responders.\textsuperscript{31} The underlying mechanism is unclear, but
since extracellular coating is considered the pathomech-
anism of HES-dependent platelet dysfunction,\textsuperscript{6} non-specific
binding to the platelet surface might be reduced in a
balanced buffered carrier milieu.

Homeostasis of calcium ions is relevant for coagulation
enzyme function. Systemic levels of ionized calcium
remained constant in our volunteers even after haemodilu-
tion with balanced tetrastarch containing calcium (Table 2).
It appears that with infusion volumes up to 20 ml kg\textsuperscript{-1},
administration of calcium ions cannot be responsible for
the observed differences between the saline-based and
balanced carrier solution. The decrease in haemoglobin
levels after HES infusion was similar (Table 2). Thus compar-
able volume efficacy cannot explain differences in
ADP-induced platelet aggregation.

This study confirms a trend towards dilutional-
hyperchloraemic acidosis by the use of saline-based carrier
infusion. After infusion of saline-based starch, pH and BE
decreased and chloride increased (Table 2). These changes
were statistically significant but small. Even if the clinical
relevance has been questioned,\textsuperscript{9} it remains unknown if
these additional derangements contribute to clinical symp-
toms in patients with severe acid-base disturbances.

This study has several limitations. First, only 20 ml kg\textsuperscript{-1}
tetrastarch was administered; higher infusion volumes of
up to the recommended maximum daily dose of 50 ml
kg\textsuperscript{-1} might induce more pronounced effects. Secondly, in
healthy volunteers without bleeding and fluid requirements,
colloidal infusion results in hypervolaemic haemodilution
which might alter endothelial response\textsuperscript{12} and haemostasis.
We chose a study design investigating volunteers because
we wanted to isolate potential effects of tetrastarch carrier
solutions (without confounding factors present in patients
undergoing surgery). However, our findings in volunteers
cannot directly be applied to patients in various clinical situa-
tions. Thirdly, with the test panel used, several haemostatic
functions remain obscure. MEA and viscoelastic testing
were used in the present study because they have been
found to be associated with clinical outcome.\textsuperscript{31, 33} However,
an increasing number of tests have become available for ex-
perimental and/or clinical use and permit visualization of
aspects of the complex coagulation system. Among them,
thrombin generation, platelet adhesion, secretion, and plate-
let procoagulant activity might contribute additional infor-
mation in studies further investigating the anticoagulant
effects of colloids. Fourthly, our results obtained after infu-
sion of potato-derived tetrastarch in a carrier balanced
with acetate cannot be extrapolated to tetrastarch dissolved
in a carrier solution buffered with lactate or malate or to
waxy maize-derived tetrastarch. We used potato-derived tet-
ratrastarch because at the time of the study this was the only
balanced tetrastarch commercially available.

In conclusion, the carrier solution of HES infusion up to 20
ml kg\textsuperscript{-1} had only little impact on platelet aggregation
assessed by MEA and clot formation assessed by ROTEM\textsuperscript{R}
in healthy volunteers. Further clinical studies are required
to verify this finding in patients, after infusion of higher
volumes up to the maximum daily doses, and to correlate
results of MEA and ROTEM\textsuperscript{R} with perioperative bleeding and
transfusion requirements.

**Declaration of interest**

S.K.-L. received speaker’s fees for lecturing and travel reim-
brursement from B. Braun, Fresenius Kabi, Verum Diagnostica,
and TEM Innovations. G.S. received speaker’s fees for lectur-
ing and travel reimbursement from Fresenius Kabi, Verum
Diagnostica, and TEM Innovations.

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