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In vivo investigation into the effects of haemodilution with hydroxyethyl starch (200/0.5) and normal saline on coagulation†

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Summary

We have investigated the effects of haemodilution with either saline or hydroxyethyl starch (200/0.5) (HES) on blood coagulation in healthy volunteers *in vivo*. Standard haematological tests (packed cell volume (PCV), platelets, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, antithrombin III, bleeding time and platelet aggregation), and thrombelastography (TEG) were performed before and after administration of either 0.9% saline 1000 ml or HES 1000 ml i.v. over a 30-min period. Dilution of PCV and platelet concentrations as a result of volume load were 9% in the saline group and 19% in the HES group. Reductions in fibrinogen (18.6% and 28.8%) and antithrombin III (25.5% and 37.8%) were significantly greater than could be explained by haemodilution alone in both groups. Indices of platelet aggregation were significantly enhanced by saline haemodilution, but not by HES, which inhibited epinephrine-induced aggregation and prolonged bleeding time. TEG in the saline group showed significantly shortened *r* and *k* times (24% and 26%, respectively), and increased α angle (24%) and maximum amplitude (MA, 6%). HES haemodilution decreased MA (11%) but did not affect other TEG variables. We conclude that haemodilution of normal blood exerted a procoagulant effect, possibly by enhancement of thrombin formation. Circulating concentrations of antithrombin III were depleted more than could be explained by haemodilution alone leading to a hypercoagulable state. This effect was offset by an antiplatelet action of HES, which was not seen with saline. The mechanism is unknown. (*Br. J. Anaesth*. 1998; **80**: 612–616)

Keywords: blood, coagulation; blood, haemodilution; blood, replacement; fluids, i.v.; measurement techniques, thrombelastography

The hydroxyethyl starches are a relatively new, effective group of compounds designed to provide plasma volume expansion but there has been concern about their effects on coagulation. Many of the studies which have examined the effects of colloids on coagulation have used a crystalloid control[1–4] or have failed to allow for crystalloid that the patient may have been given in addition to the colloid, for example in the cardiopulmonary bypass pump prime.[5,6] However, crystalloid solutions may also affect coagulation. In 1959 Tocantins, Carroll and Holburn[7] and Monkhouse[8] reported that moderate haemodilution with crystalloids could enhance coagulability. This was later confirmed by Janvrin, Davies and Greenhalgh[9] and Heather, Jennings and Greenhalgh,[10] and also by our own findings.[11] Popov-Cenic and colleagues[12] reported that enhanced coagulation, ascribed to premedication and anaesthesia *per se*, was offset by i.v. administration of hydroxyethyl starch. In 1975, Vinnazzer and Bergmann[13], in a double-blind study, compared standard tests of coagulation and thrombelastography before and after operation in two groups, one treated with hydroxyethyl starch and the other with isotonic saline in the perioperative period. Their findings showed a postoperative hypercoagulable state in the control (saline) group but non-significant changes in the test (hydroxyethyl starch) group. As their study was performed after operation, it did not demonstrate if these changes in coagulability were already present after infusion of the i.v. fluid, before any surgical stress response occurred which might have influenced coagulation variables further.

Thrombelastography (TEG) is a technique first developed by Hartert in 1948.[14] It had little clinical use for many years until it was re-evaluated in the surgical setting in 1974. Subsequently it was developed further and more recently has been applied and validated in both liver transplantation and cardiac surgery. The TEG pattern is divided into component variables. Reaction time (*r*) is the interval between the start of recording and the time at which the amplitude of the tracing is 2 mm. It reflects the function of the intrinsic clotting pathway. Coagulation time ($r+k$) is the time required for the amplitude to reach 20 mm and provides information not only on intrinsic factors but also on platelets and fibrinogen, which are also represented by the clot formation rate ($\alpha°$). Maximum amplitude (MA) is the greatest amplitude achieved on the TEG and is a measure of clot strength and elasticity, reflecting the properties of platelets and fibrinogen, and also factor XIII.[15]

We conducted an *in vivo* study in volunteers using commonly used tests of coagulation and TEG, to determine the effect of haemodilution with i.v. fluids

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Table 1 Haematological data before and after haemodilution with saline or hydroxyethyl starch (HES) (mean (SD)). PCV = Packed cell volume; PT = prothrombin time; aPTT = activated partial thromboplastin time; Anti. III = antithrombin III, as a percentage of laboratory normalized values. *$P<0.05$, ***$P<0.001$, within-group differences from baseline

	Saline			HES		
	Baseline ($n=20$)	After dilution ($n=20$)	Change	Baseline ($n=20$)	After dilution ($n=19$)	Change
PCV (%)	43.3 (4.7)	39.0 (3.9)***	−4.1 (1.8)	42.5 (3.2)	34.5 (3.3)***	−7.9 (2.1)
Platelets (10^9 litre^{-1})	208.0 (36.5)	188.8 (36.4)	−19.3 (11.4)	215.9 (45.9)	171.7 (33.5)***	−44.3 (22.1)
PT (s)	13.15 (1.07)	13.85 (1.06)***	0.69 (0.54)	13.09 (0.80)	14.55 (1.01)***	1.46 (0.70)
aPTT (s)	33.9 (2.7)	34.7 (2.9)*	0.74 (1.37)	33.2 (2.9)	36.6 (3.6)***	3.4 (2.1)
Fibrinogen (g litre^{-1})	2.65 (0.75)	2.14 (0.55)***	−0.52 (0.30)	2.68 (0.65)	1.90 (0.47)***	−0.78 (0.27)
Anti. III (%)	116.1 (33.7)	80.1 (15.9)***	37.7 (43.4)	108.8 (30.2)	62.8 (16.0)***	45.9 (36.2)

on coagulation. Standard tests of coagulation such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and bleeding time are generally more sensitive in hypocoagulable states than in enhanced coagulation states.[16] TEG provides a visual pattern of functional clotting status and is the most sensitive method of detecting an increase in coagulability.[17] Therefore, we used both methods to examine coagulation.

Subjects and methods

After obtaining approval from the Human Ethics Committee of the University of Cape Town and informed patient consent, we determined the effects on blood coagulation of infusion of 20% of blood volume using either 0.9% saline (saline) or hydroxyethyl starch (200/0.5) (HES) (HAES-steril, Fresenius AG, Germany) in healthy, ASA I volunteers, weighing 55–85 kg, with no pre-existing disease. There were 20 subjects in each group. A financial inducement was offered to each subject. All subjects were tested twice in a cross-over study, with at least 7 days between tests. A 20-gauge cannula was inserted into an antecubital fossa for blood sampling for standard haematological tests (full blood count (FBC), PT, aPTT, platelet aggregometry, and concentrations of fibrinogen and antithrombin III), bleeding time and TEG. Platelet aggregometry was performed on platelet-rich plasma in a platelet aggregometer (Chrono-log, Havertown, Pa). The change in optical density on addition of successive aggregating agents was recorded as a tracing on a chart recorder. Aggregating agents used were adenine diphosphate (ADP) 5, 10 and 100 μmol litre^{-1}, epinephrine 10 μmol litre^{-1} and ristocetin 1.2 mg ml^{-1}. Percentage aggregation was calculated from the recorded sigmoid curve.

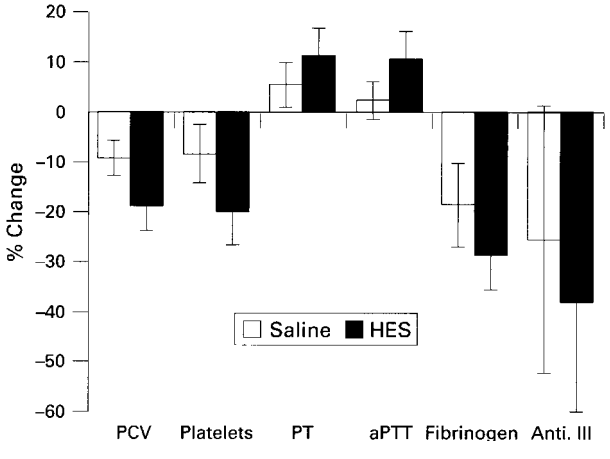

Figure 1 Percentage change from baseline values for haematological variables (mean (SD)) in the HES and control groups. PCV = Packed cell volume, PT = prothrombin time, aPTT = activated partial thromboplastin time and Anti. III = antithrombin III.

Subjects then received either 0.9% saline 1000 ml or colloid 1000 ml (HES) via the cannula. This was infused over 30 min. Provision was made to stop the infusion immediately and exclude any subject who experienced side effects. At the end of infusion, blood was sampled via the cannula, after discarding the first 5 ml, and coagulation studies and TEG were repeated. Disposal of contaminated waste was in accordance with accepted hospital norms.

A separate pilot study was conducted to exclude the method of sampling as a potential source of experimental error. In this study, we showed that sampling from the cannula following infusion of saline, after discarding the first 5 ml, produced the same TEG pattern as a sample obtained simultaneously from a vein on the opposite arm. Therefore, placement of the cannula and the sampling method had no effect on the TEG. We did not study possible effects of HES, but the volume of the cannula (<0.2 ml) and discarded blood (5 ml) implies that any contamination of the subsequent sample was very unlikely.

Table 2 Measures of platelet function (bleeding time and percentage aggregation) before and after haemodilution with saline or hydroxyethyl starch (HES) (mean (SD)). *$P<0.05$, ***$P<0.001$, within-group differences from baseline

	Saline			HES		
	Baseline ($n=20$)	After dilution ($n=20$)	Change	Baseline ($n=20$)	After dilution ($n=19$)	Change
Bleeding time (min)	3.35 (0.89)	3.45 (0.92)	0.1 (0.67)	3.34 (0.8)	4.42 (0.99)***	1.08 (0.45)
ADP 100 μmol litre^{-1}	76.6 (11.1)	79.8 (9.8)*	3.3 (6.1)	72.2 (7.4)	72.3 (10.8)	0.1 (7.1)
ADP 10 μmol litre^{-1}	69.3 (12.8)	72.0 (13.5)	2.5 (8.0)	63.4 (9.9)	62.9 (14.1)	0.6 (7.8)
ADP 5 μmol litre^{-1}	58.5 (17.9)	63.0 (18.5)	4.5 (11.2)	54.0 (13.9)	52.0 (17.3)	2.0 (9.4)
Epinephrine 10 μmol litre^{-1}	53.7 (27.8)	56.0 (31.4)	2.2 (23.9)	58.2 (25.0)	38.4 (29.7)***	19.8 (23.0)
Ristocetin 1.2 mg ml^{-1}	83.4 (8.9)	88.2 (9.9)*	4.7 (9.9)	80.6 (7.2)	82.0 (10.0)	1.5 (8.0)

Table 3 Thrombelastograph data before and after haemodilution with saline or hydroxyethyl starch (HES) (mean (SD)). ***$P<0.001$, within-group differences from baseline

	Saline			HES		
	Baseline ($n=20$)	After dilution ($n=20$)	Change	Baseline ($n=20$)	After dilution ($n=19$)	Change
r time (min)	13.4 (3.5)	10.2 (3.0)***	−3.2 (1.2)	13.1 (3.6)	11.7 (3.6)	−1.4 (4.7)
k time (min)	7.1 (1.8)	5.3 (1.6)***	−1.8 (1.2)	7.1 (2.0)	6.6 (2.2)	−0.5 (2.4)
Alpha angle (°)	37.0 (7.4)	45.7 (9.4)***	8.7 (5.5)	37.8 (7.6)	38.1 (9.4)	0.3 (8.6)
MA (mm)	50.0 (5.4)	53.2 (5.4)***	3.2 (2.4)	50.8 (8.6)	45.0 (6.6)***	−5.8 (6.5)

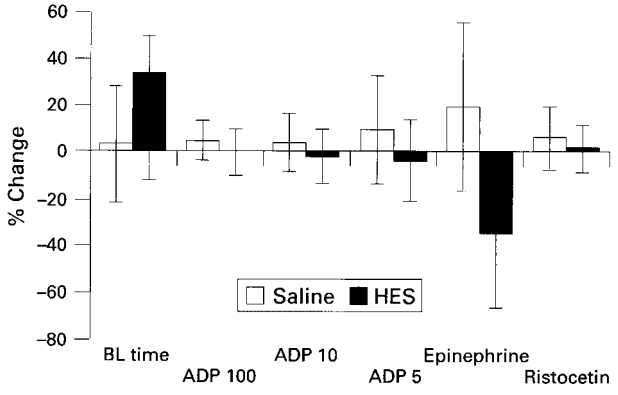

Figure 2 Percentage change from baseline values for measures of platelet function (mean (SD)) in the HES and control groups. BL time = Bleeding time, and ADP 100, 10 and 5 = adenosine diphosphate 100, 10 and 5 μmol litre^{-1}, respectively.

Data before and after infusion of fluid in each group were compared using paired *t* tests. Changes from values before infusion were calculated as numerical data and as percentage change from baseline.

Results

In one subject in the HES group it was impossible to obtain blood samples after infusion without repeat venepuncture, and in another subject there was a technical failure with the TEG, resulting in 18 complete sets of data in the HES group and 20 in the saline group.

Packed cell volume (PCV) was reduced by approximately 19% and 9% of baseline values after infusion of HES and saline, respectively (table 1, fig. 1). Reduction in platelet count was observed in both groups, although in the saline group this was not significantly different from baseline. There were significant increases in PT and aPTT in both groups, but values after dilution were within the normal range quoted by our laboratory for both tests. Concentrations of fibrinogen and antithrombin III decreased in both groups to a greater degree than could be explained by haemodilution alone, and the percentage change in these two variables was significantly greater than the percentage change in PCV ($P<0.001$). The percentage decrease in antithrombin III after haemodilution was not different between groups (fig. 1).

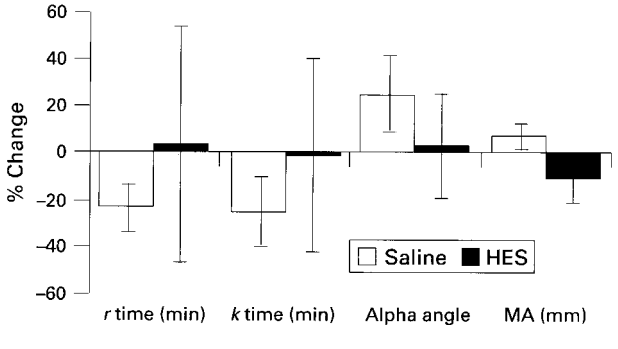

Figure 3 Percentage change from baseline values for TEG data (mean (SD)) in the HES and control groups.

Platelet aggregation, measured by stimulation with ADP 100 μmol litre^{-1} and ristocetin, increased significantly in the saline group. Epinephrine-stimulated platelet aggregation decreased significantly in the HES group (table 2, fig. 2). Bleeding time increased significantly in the HES group.

The TEG results showed significant reductions in *r* time, *k* time and MA, and a significant increase in α angle in the saline group, whereas the only change in the HES group was a significant reduction in MA (table 3, fig. 3).

Discussion

Our results demonstrated a predictable decrease (10% and 20%) in PCV and platelet count as a result of haemodilution in the two groups, the greatest decrease being in the colloid group, where presumably less immediate extravascular redistribution of fluid occurs. However, concentrations of antithrombin III decreased significantly to approximately 60% of pre-dilution values in both groups. Concentrations of antithrombin III after dilution were less than half pre-dilution values in some subjects. This suggests that these subjects may have been at a clinically significant increased risk of deep vein thrombosis (DVT) formation if they had been undergoing surgery. The decrease in antithrombin III concentration cannot be explained by dilutional factors alone, especially when considered in conjunction with our TEG results which showed significantly shortened *r* and *k* times in the saline group, suggesting enhanced activity of coagulation factors. Monkhouse[8] postulated an imbalance between the formation of thrombin and activity of antithrombins as being responsible for the enhanced coagulation demonstrated after haemodilution.

Our findings suggest that haemodilution *per se* may induce formation of thrombin, with subsequent consumption of both fibrinogen and antithrombin III. The enhanced platelet aggregation observed with some reagents in the crystalloid group after dilution also seems to suggest that i.v. crystalloid induces an increase in coagulability. The absence of a significant increase in platelet aggregation in the colloid (HES) group may be because of the known antiplatelet effect of HES,[18] possibly via a specific effect on von

Willebrand factor,[19] which may balance the hypercoagulability produced by haemodilution. This is supported by our finding of a probable consumption of antithrombin III, together with absence of enhancement of platelet aggregation (in fact, a decrease with one reagent) in this group. The increased α angle and MA in the saline group are in keeping with the enhanced coagulability and platelet aggregation seen in this group.

TEG measures whole blood coagulation, whereas PT and aPTT are measured on platelet-poor plasma. The slight prolongation of PT and aPTT in this study probably reflects dilution of coagulation factors in plasma, whereas shortening of *r* and *k* times could be explained by platelet activation or other cell-mediated effects not seen in studies on cell-depleted plasma.

Recent work has suggested that the procoagulant effect of crystalloid infusions may be clinically relevant during surgery. Ng and Lo[16] reported that during surgical blood loss with crystalloid volume replacement, increased whole blood coagulability was observed, which was related to the degree of haemodilution. Heather, Jennings and Greenhalgh[10] demonstrated that saline-induced enhanced coagulability could be used as a predictor of the risk of formation of DVT, which confirmed the suggestion by Janvrin, Davies and Greenhalgh[9] that there might be a relationship between haemodilution with crystalloid solution and the risk of DVT.

Our study has confirmed previous *in vitro* findings that haemodilution with crystalloid solutions increases the coagulability of blood.[11] The results also confirm the *in vitro* suggestion that hetastarch solutions may have a lesser effect, probably mediated via an antiplatelet action. Our finding of enhanced coagulability has recently been confirmed using 30% haemodilution with crystalloids, but not with colloids in an *in vitro* study.[20] In this study, using pH and calcium-corrected diluents, the authors demonstrated a reduction in *r* and *k* times, and an increase in alpha angle at 30% haemodilution with saline. They found no effect of gelatin on the TEG and showed an increase in *k* time, and decreases in alpha angle and MA with starch. These results are compatible with our findings, given the smaller dilutions used in our study.

The clinical implications of this finding are potentially important. Not only do our results suggest that infusion of crystalloid solutions may increase the risk of thrombotic complications in surgical patients, but they also cast doubt on studies of coagulation using crystalloid haemodilution as a control.[2–6 12]

TEG has been used widely to measure coagulation in clinical anaesthesia.[21] The global, yet overlapping, data that are provided by the TEG, allow more appropriate replacement therapy to be given, in addition to providing a useful test of liver function during the immediate period after cross-clamp in liver transplantation.[22 23] The relationship between TEG and standard laboratory tests of coagulation is positive, with the greatest correlation between *r* time and aPTT.[24–27]

Based on our findings we can speculate that infusion of i.v. fluid (1000 ml) could enhance the formation of thrombin and its consequent binding to antithrombin III, thus reducing concentrations of antithrombin III more than can be explained by haemodilution alone. Furthermore, platelet aggregation appears to be enhanced by infusion of saline, but not by HES. This may have clinical implications for the management of stroke, postoperative DVT, vascular surgery, trauma and coronary artery surgery, where current practice is to use large amounts of crystalloid solution for cardiopulmonary bypass pump prime for patients undergoing cardiac revascularization procedures, an effect which might have an adverse reaction on graft survival and postoperative morbidity and mortality.

This study was a preliminary attempt to investigate if our *in vitro* observations could be confirmed in an *in vivo* situation, but without the confounding factors of anaesthesia and surgery. It should be repeated using various i.v. solutions at different concentrations to determine the range of haemodilution that enhances coagulation before the dilutional effect becomes too great to sustain increased coagulation, and to investigate the degree to which different solutions may affect the formation of thrombin and platelet aggregation. A recent study has demonstrated that 50% haemodilution of blood with HES or with a modified gelatin solution *in vitro* produced shortening of *r* time, indicating enhanced initiation of coagulation even at extreme haemodilution; this effect was not seen with dextran 40 which inhibited all aspects of coagulation.[28]

The mechanism whereby this effect may occur is unknown. However, it is interesting to observe that there may have been a survival benefit for the evolution of such a mechanism. One may speculate that when internal haemodilution occurs after blood loss, enhanced coagulability may prevent further haemorrhage in the wild state, and this could offer a survival benefit.

We conclude that haemodilution *per se* induced a procoagulant state by an unknown mechanism, and that this may be clinically significant. When haemodilution was produced using hydroxyethyl starch, this procoagulant state was partially offset by an antiplatelet effect.

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