In vivo effect of haemodilution with saline on coagulation

Editor—As the influence of i.v. fluids on the coagulation system is of importance and also sustains the discussion on optimal fluid therapy, we would like to comment on the results reported by Ng and colleagues and the suggestions presented in the accompanying editorial. The study design chosen by Ng and colleagues to investigate coagulation and haemodilution might eliminate the influence of tissue trauma provoked by surgery, but is not without the effect of any confounding variables.

First, the ratio of blood withdrawn:replacement with normal saline was 1:2, which suggests that the haemodiluted patients were hypovolaemic rather than haemodiluted. Second, all study subjects were patients with malignant disease, who are known to exhibit some state of hypercoagulability because of their underlying disease. Third, the shortening of the reaction time (r-time) by 30% and the coagulation time (k-time) by 36–45% was statistically different from the controls, but they also showed prolongation of the r- and k-times, although no intervention occurred. The question arises as to whether such changes are relevant in vivo, as they might be explained as an in vitro phenomenon attributable to sedimentation of red cells in the thrombelastograph (TEG) cup. Uraemic patients have been shown to have an increased bleeding time, but also exhibit thrombelastographic signs of hypercoagulability measured by shorter r- and k-times, increased α-angle and maximum amplitude compared to normal controls. Interestingly, the latter study showed a significant negative correlation between haematocrit and signs of hypercoagulability. Moreover, isolated reduction of the haematocrit from 40 to 10% also resulted in thrombelastographic signs of hypercoagulability. Reports of accelerated coagulation during haemodilution might therefore be influenced by changes in red cell sedimentation occurring with changing haematocrit. It is likely that this effect also depends on the physicochemical properties of the dilution fluid used and the time needed to process the coagulation measurements. Our in vitro and in vivo data on the influence of colloids and crystalloids on coagulation show an accelerated initiation of coagulation during moderate haemodilution with Ringer’s lactate and gelatin for the slow-reacting intrinsic TEG measurements only. In contrast to the data of Ng, our results for accelerated coagulation were always accompanied by a reduction in clot firmness. Furthermore, we were surprised that, in the study by Ng and colleagues, the α-angle increased by about 71% in the haemodiluted group at 30 min, although platelets and fibrinogen decreased markedly. Given a normal value of 60°, this would mean that the angle would have reached values well above 90°. Was this really observed? Analysis of our in vivo data for the α-angle showed no significant difference in the intraoperative response profile (area under the curve minus baseline, AU(CA−D)) of extrinsic TEG measurements between different fluid regimens (hydroxyethyl starch, modified gelatin 4% combined with a basal infusion of Ringer’s lactate, or Ringer’s lactate), and a significant difference in intrinsic TEG tracings between the two colloid groups only (Table 1).

Another question arises concerning measurements of concentrations of thrombin–antithrombin complexes (TAT). Why were concentrations of TAT much higher in the control group, and why did they also show a large standard deviation not observed in the haemodiluted group? Despite these inter-group discrepancies, the authors assumed that thrombin generation was increased in their haemodiluted patients as concentrations of TAT did not change during haemodilution, but showed an insignificant decrease in the controls.

A clinical study investigated coagulation after haemodilution with gelatin (in addition to a basal infusion of Ringer’s lactate), which has also been associated with signs of hypercoagulability. In this study, concentrations of TAT did not change significantly over several hours in haemodiluted or control patients. Yet 3 h after surgery, a significant increase was observed, but only in control patients. Furthermore, all measurements of activated coagulation and fibrinolysis showed no differences between groups.

In summary, there is very little evidence that administration of i.v. fluids leads to clinically detectable hypercoagulability. Data from one study conducted in 1980, investigating only 30 ‘wet’ and 30 ‘dry’ patients during abdominal surgery without perioperative thrombosis prophylaxis, are insufficient to associate i.v. fluid therapy with development of deep venous thrombosis. Some data indicate that the impairment of coagulation is the least when predominantly crystalloids are used. These effects are seen as an advantage for surgical patients with respect to preventing further blood loss and limiting the need for transfusion of blood products. Moreover, reports on disseminated intravascular coagulopathy after administration of crystalloids are lacking in the literature. In vivo, the response of the coagulation system is mainly governed by the extrinsic pathway. Therefore, the impact of TEG measurements which are obtained without extrinsic activation, thus depending on the reactions provoked by contact to foreign surfaces, remains to be determined.

Until it is proven clearly that hypercoagulability measured by TEG is not only an in vitro phenomenon but also relevant in vivo, it seems dangerous to recommend withholding i.v. fluids. Normovolaemia is essential for maintaining sufficient oxygen delivery to the tissues, and thus fluid therapy, not only influences coagulation, but also preserves organ function.

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Editor—Thank you for the opportunity to reply to the letter by Dr Innerhofer and colleagues commenting on our paper. We acknowledge Dr Innerhofer’s point that the clinical significance of the hypercoagulability caused by crystalloid infusion remains to be evaluated. However, we believe that, given the prospective, randomized and controlled design, it is safe to state that our study is without the effect of any confounding variables.

We cannot agree with Dr Innerhofer that, because replacement with saline was 1:2, patients in the haemodiluted group in our study were hypovolaemic. The usual 25–30% retention rule is oversimplified and refers to an equilibrium state only. The percentage retention of infused crystalloid in the intravascular compartment is dynamic. It depends upon the volume infused, the rate of infusion, and on when one is making the measurement. This has been discussed elegantly by Hahn and colleagues. As we were allowing only 10 min for the infused fluid to distribute in our study procedure, 1:2 is the ratio administered to achieve normovolaemia. In fact, if we assume normovolaemia then the drop in haemoglobin (Hb) concentration after removal of 10, 20

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Table 1 Extrinsically- and intrinsically-activated TEG measurements during knee replacement surgery in groups randomized to receive hydroxyethyl starch 6% (HES) 2000/5, modified gelatin 4% with Ringer’s lactate (GEL), or lactated Ringer’s solution (RL). Differences between groups were analysed by comparing the perioperative response profile (area under the curve, AUCA-D). Data are median (interquartile range): A, baseline; B, before tourniquet release; C, end of surgery; D, 2 h later. Statistically significant difference (AUCA-D, P<0.05): *GEL vs HES. No other statistically significant differences between HES, GEL and RL groups. Analysis of repeated measures ANOVA (all groups pooled) showed no significant time effect.

<table>
<thead>
<tr>
<th>α-angle (°)</th>
<th>RL (n=20)</th>
<th>GEL (n=20)</th>
<th>HES (n=20)</th>
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<tbody>
<tr>
<td>Extrinsic TEG</td>
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</tr>
<tr>
<td>A</td>
<td>71 (64/76)</td>
<td>71 (66/72)</td>
<td>67 (64/71)</td>
</tr>
<tr>
<td>B</td>
<td>72 (66/74)</td>
<td>71 (63/72)</td>
<td>69 (64/73)</td>
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<tr>
<td>C</td>
<td>71 (66/77)</td>
<td>69 (62/71)</td>
<td>65 (60/69)</td>
</tr>
<tr>
<td>D</td>
<td>72 (61/76)</td>
<td>70 (68/73)</td>
<td>62 (58/67)</td>
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<tr>
<td>AUCA-D</td>
<td>2.3 (−7.5/11.5)</td>
<td>−4.5 (−10/−0.5)</td>
<td>−5.8 (−17.3/2.8)</td>
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<td>Intrinsic TEG</td>
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<tr>
<td>AUCA-D</td>
<td>2.5 (−11/7.5)</td>
<td>2.5 (−6/7.5)*</td>
<td>−9.3 (−12.5/−0.5)</td>
</tr>
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and 30% of blood volume can be predicted by the exponential equations:10

\[ Hb_{10\%} = Hb_0 e^{-0.1} \]
\[ Hb_{20\%} = Hb_0 e^{-0.2} \]
\[ Hb_{30\%} = Hb_0 e^{-0.3} \]

where \( Hb_{10\%} \), \( Hb_{20\%} \) and \( Hb_{30\%} \) refers to the Hb concentration after removal of 10, 20 and 30% of blood volume and concomitant isovolaemic haemodilution. \( Hb_0 \) is the initial Hb concentration. In other words, the Hb concentration after removal of 10, 20 and 30% of blood volume should be 0.90 \( Hb_0 \), 0.82 \( Hb_0 \) and 0.74 \( Hb_0 \) respectively. In our study, the values were 0.90, 0.80 and 0.74 respectively, which confirmed almost exact isovolaemia.

Dr Innerhofer’s suggestion that the shortening of r- and k-times might be an artefact related to changes in red cell sedimentation is interesting, as they reported the effect may disappear when the TEG measurement was made more quickly. However, to accelerate measurement, the differences one would have to introduce are more than just the cell sedimentation rate. Certain components of the coagulation process would invariably be suppressed or enhanced. The differences in TEG variables one observes may not be attributable to differences in measurement time alone. The fact that an isolated reduction of haematocrit does not compromise in vitro blood coagulation: a randomized trial. Br J Anaesth 2002; 88: 475–80


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Lockey for their comments on our article. We agree totally with D. J. Lockey (1997) about the potential for hand-held devices to perform blood gas analysis in the pre-hospital setting. This is usually the case, but with the advent of hand-held devices that can perform blood gas analysis, it may be that in the few patients with conditions that require such analysis, it will be more practical.

As stated, the application of cricoid pressure with the classic LMA results in near complete airway obstruction, presumably of similar aetiology (i.e. forward displacement of the glottic inlet). As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions. As stated, the application of cricoid pressure with the classic LMA simulates the same conditions.

We agree with Helm and colleagues that capnography is a valuable monitoring method. CAPNOS can be used in the pre-hospital setting to confirm tracheal intubation and detect disconnection. It is similar to capnography in the hospital intensive care setting and can help in confirming proper ventilation, especially in patients with severe lung contusion. However, we agree that capnography can be difficult to interpret in hypovolaemic trauma patients or those with severe lung contusion.

With regard to 'adequate ventilation', capnography can be used as a monitoring method in the pre-hospital setting, especially in primary transfers as well as secondary transfers. Intensive Care Society, the Association of Anaesthetists, have produced guidelines for transfer of the critically ill. Both organizations advise the use of capnography. We see no reason why they should not be followed routinely in the pre-hospital setting. Both organizations advise the use of capnography. We see no reason why they should not be followed routinely in the pre-hospital setting.