Recombinant factor VIIa fails to correct coagulopathy induced by haemodilution with colloid

Editor—In recent years, numerous single case reports and a few series of retrospective cohorts of patients have been published dealing with serious bleeding and massive transfusion demands in whom recombinant activated factor VII concentrate (rFVIIa) has been tried as salvage therapy. In the absence of controlled clinical studies, practice has arisen in many places where rFVIIa has been adopted as part of the haemostasis armamentarium for treatment of uncontrollable bleeding after trauma and surgery.

We presented data recently in the *British Journal of Anaesthesia* that illustrate a hypocoagulable state of blood after exposure to haemodilution with various colloid plasma expanders, and our experiments point to a relatively beneficial change in the dynamic whole blood clotting profile if such blood is substituted with fibrinogen concentrate. More recently, Brummel-Ziedins and colleagues have supplemented our findings by demonstrating that haemodilution with colloids causes diminished platelet

![Diagram](image_url)

**Fig 1** Continuous clot formation velocity profiles of whole blood subjected to haemodilution with colloid HES 130/0.4, or isotonic saline and patterns of haemostatic response to *ex vivo* addition of rFVIIa. Panels (A) and (B) reflect the initiation phase of coagulation. Panels (C) and (D) illustrate the propagation phase of clot formation. CT [clotting time (s)]: time duration until the initial formation of a fibrin clot; MaxVel [maximum velocity (mm 100 s⁻¹)]: the peak value of the velocity of clot generation.
activation, compromised fibrin polymerization and reduced whole blood thrombin generation capacity.\textsuperscript{2} We have undertaken additional experimental work in our laboratory to address the question of whether colloid-induced coagulopathy could possibly be reversed with the aid of rFVIIa by testing \textit{ex vivo} two dose levels of rFVIIa and a buffer control for their possible influence on coagulopathy induced by various levels of haemodilution with HES 130/0.4. Without haemodilution, rFVIIa, at the two dose-levels tested, normalized the prolonged clotting time in experiments with saline and HES 130/0.4. However, following haemodilution with colloid to a level of 25\% or more, rFVIIa does not appear to improve the diminished maximum coagulation velocity of whole blood clot formation (Fig. 1).

Recently, a randomized clinical trial on 300 trauma patients demonstrated that rFVIIa administered to bluntly traumatized patients significantly reduced the transfusion requirements as compared with placebo.\textsuperscript{3} Trauma patients with shock often receive volume substitution initially with quite large amounts of plasma expanders to maintain sufficient blood pressure. In view of this, our new data contribute to understanding the limited effect on haemostasis if rFVIIa is administered after large volumes of colloidal HES 130/0.4. The critical issue here is the lack of improvement of the velocity of clot formation. Our original paper\textsuperscript{1} shows that addition of fibrinogen increases the velocity of clot formation. In view of this, severe bleeding occurring shortly after volume substitution with HES may be managed better with fibrinogen before rFVIIa.

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What does cerebral oximetry measure?

Editor—We feel that the recent paper by Yoshitani and colleagues\textsuperscript{1} raises important issues. They demonstrated that, in patients undergoing elective hip arthroplasty, normovolaemic haemodilution caused no change in jugular bulb saturations ($S_{\text{O}_2}$) but decreased cerebral saturations ($S_{\text{C}_2}$) when measured with a cerebral oximeter (INVOS 4100S). Two explanations were offered for the unexpected disparity in readings. First, they postulated that subtle changes in regional $S_{\text{C}_2}$ might not be revealed with the global measure provided by $S_{\text{O}_2}$. Second, they proposed that changes in near infrared path length induced by haemodilution could affect the $S_{\text{C}_2}$ readings.

We feel the interpretation of the results deserves a more detailed appraisal. The INVOS 4100S gives a single readout for regional cerebral oxygen saturations using an algorithm based upon the Beer–Lambert law. In this study, both subject groups showed no change in $S_{\text{O}_2}$ but a decrease in $S_{\text{C}_2}$. The disparity in readings could be consistent with a systematic error. We suspect the algorithm incorporated within the INVOS 4100S may not take into account the fall in haemoglobin concentration. The fall in oxygenation index has actually been found to correlate with blood loss in healthy volunteers.\textsuperscript{2}

Cerebral oximetry does not take into account changes in the relative proportions of blood in the arterial or venous part of a capillary bed. The proportion of arterial blood in the cerebral capillaries had been estimated at 28\%.\textsuperscript{3} Hypoxia can induce changes in the cerebral arterial to venous volume ratio\textsuperscript{4} and it would not be unreasonable to assume that other factors may also affect the cerebral arterial to venous volume ratio. A change in the relative proportions of arterial and venous blood in the cerebral capillaries may alter cerebral oximetry readings without a ‘real’ effect on cerebral tissue oxygenation.

We have previously expressed concerns\textsuperscript{5} about the interpretation of cerebral oximetry in a clinical setting, and Yoshitani’s paper has raised the most important issue concerning the effect of haemodilution upon the readings. A change in $S_{\text{C}_2}$ could be attributable to many factors. In the clinical setting, changes in $S_{\text{C}_2}$ should be interpreted with caution, particularly when there is significant blood loss.

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Editor—We wish to thank Pattinson and colleagues for their comments on our recent article and are pleased to take this opportunity to reply. We demonstrated that there was a discrepancy between $S_{\text{O}_2}$ and $S_{\text{C}_2}$ values during normovolaemic haemodilution\textsuperscript{1} and two possible explanations were offered (as above). Pattinson and colleagues\textsuperscript{5} have suggested that our results deserve a more detailed appraisal and that various factors may have an effect on $S_{\text{C}_2}$ values. Validation of near infrared spectroscopy measurements has not been established.

In our study, we demonstrated that there was a significant correlation between haemoglobin concentrations and $S_{\text{C}_2}$ values. The results indicated haemoglobin concentration had a significant effect on $S_{\text{C}_2}$ values. Kurth and Uber\textsuperscript{6} suggested that there was a significant negative correlation between haemoglobin concentrations and optical path length in an experimental model. We believe that optical path length had a strong effect on $S_{\text{C}_2}$ values. As suggested above, the algorithm incorporated in the INVOS 4100S might not take into account the fall in haemoglobin concentration. The algorithm is not open for scrutiny (Somanetics, Troy, MI, USA). If a modified Beer–Lambert law, in which optical path length should be constant, was incorporated in INVOS 4100S, prolongation of optical path length would cause enhancement of changes in $S_{\text{C}_2}$. Therefore, if optical path length became longer with haemodilution, there would be an overestimation of changes in $S_{\text{C}_2}$.

Previous studies have demonstrated that various factors, such as haemoglobin concentrations, extracranial blood flow and changes in cerebral arterial to venous blood volume ratio had an effect on near infrared spectroscopy measurements.\textsuperscript{7–9} However, it was difficult to evaluate the degree of effects of such factors on $S_{\text{C}_2}$ values. We have only investigated the effect of haemoglobin concentration...