haemostatic intervention by increasing fibrinogen plasma concentration after the removal of CPB and administration of protamine.

When a patient is bleeding, it is vital to obtain coagulation test results as soon as possible in order to avoid delays in the identification of coagulation abnormalities and facilitate early treatment and correction of bleeding. Unfortunately, standard laboratory coagulation tests often have long turnaround times, thereby delaying the identification and correction of coagulation problems.[5] For example, the turnaround time of fibrinogen concentration measurement by the Clauss assay has been reported as 30–60 min,[6 7] and longer times of around 88 min have also been published.[5] Additionally, delayed results may not accurately reflect the current haemostatic status of the patient. There is, therefore, an urgent need for an accurate, reliable, and fast method of measuring the patient's haemostatic status. Point-of-care testing (POCT), such as the ROTEM-based FIBTEM assay, can obtain results in 5–10 min;[5 8] however, although POCT is widely used after cardiovascular surgery, many institutions do not yet have the necessary equipment to carry out these tests. A recent study of 26 patients undergoing CPB described plasma fibrinogen values at 60 min on CPB of 209 mg dl^{-1}, comparable with those taken at the end of CPB, after administration of protamine (202 mg dl^{-1}).[3] Importantly, the mean CPB duration was 125 min. Therefore, the time point '60 min on CPB' also represents close to 1 h before the end of CPB in these patients, which may be a good time point for most standard laboratories to perform coagulation testing and obtain a first estimation of the coagulation status post-CPB. Many of the current publications on haemostatic therapy with fibrinogen concentrate after CPB use the FIBTEM parameters obtained on CPB, at removal of the aortic clamp (20–30 min before the end of CPB), as a dosing tool. To date, there are no data published on fibrinogen concentration values at the same time point, although clinicians may find such information very useful. Indeed, there is already an ongoing clinical trial of fibrinogen concentrate during elective complex cardiac surgery which is using Clauss assays taken during CPB to determine the dose of fibrinogen (ClinicalTrials.gov identifier NCT01124981).

With these considerations in mind, we would be interested to see further data from the study carried out by Solomon (if available). We note that blood samples were obtained from the patients both 20 min before removal of CPB and after removal from CPB/administration of protamine. The article also states that both Clauss assays and ROTEM-based FIBTEM assays were carried out on the samples, and that the dose of fibrinogen administered was based on the FIBTEM measurement taken before removal of CPB. It would be of great interest to investigate the possibility of using the fibrinogen measurements taken before the removal of CPB to determine fibrinogen dosing, and to establish whether or not this approach would have significantly affected the treatment these patients received. If no significant difference is observed, this could be of clinical importance for patients with extensive surgery and high risk of bleeding after CPB, for whom delays to treatment must be minimized.

Declaration of interest

None declared.

L. Ormonde
Lisbon, Potugal
E-mail: lpco@netcabo.pt

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doi:10.1093/bja/aeu172

Reply from the authors

Editor—We would like to thank Ormonde and colleagues, who requested further data on our study regarding the time course of haemostatic effects of fibrinogen concentration in patients undergoing aortic surgery with cardiopulmonary bypass (CPB),[1] for their interest in our work. We agree that carrying out fibrinogen concentration measurement during CPB could result in more timely identification of coagulation defects in clinics that do not use point-of-care coagulation testing.

The mean (SD) plasma fibrinogen levels observed in our study for all 61 patients (both those treated with fibrinogen concentrate and those treated with placebo) were similar at 20 min before the removal of CPB [1.66 (0.34) g $litre^{-1}$] and immediately after CPB removal [1.58 (0.34) g $litre^{-1}$], as were

the FIBTEM MCF measurements during and after CPB [9.70 (2.75) and 9.67 (2.90) mm, respectively]. We have examined whether or not Clauss assay measurements taken during CPB can be used to calculate fibrinogen doses similar to those administered during our study, which were calculated using FIBTEM measurements made during CPB using the formula: fibrinogen concentrate dose (g)=(target FIBTEM MCF − actual FIBTEM MCF) (mm) × [bodyweight (kg)/70] × 0.5 g mm^{-1}. The target FIBTEM MCF was 22 mm. The relationship between the Clauss assay measurement and the dose administered in the study was examined using linear regression, with the dose administered being the outcome variable.

We were able to generate the following equation for calculating the dose of fibrinogen using the Clauss assay measurement taken during CPB:

$$\text{Fibrinogen concentrate dose (g)} = [3.73 - \text{actual Clauss fibrinogen (g litre}^{-1})] \times 0.0424 \times \text{body weight (kg)}$$

As this equation was based on the dosage using FIBTEM values, we would expect the mean fibrinogen dose to be the same; this was confirmed as, using this equation, the mean (SD) fibrinogen dose for the patients included in our study would have been 7.7 (1.8) g, compared with the actually administered mean dose (based on FIBTEM measurement taken during CPB) of 7.7 (2.3) g.

However, although the average calculated dose is important, it is possible that the equation provides the correct dosing on average while potentially resulting in a different dose for some individual patients. To clarify this, we applied the Bland–Altman limits of agreement method to measure the size of differences between the fibrinogen dose based on the Clauss assay and the dose based on the FIBTEM measurement. The analyses suggested a mean difference between the dose calculations of 0.0 g. The Bland–Altman limits of agreements are from −2.3 to 2.3 g (equivalent to −29.9 to 29.9% of the mean dose), which is the interval into which 95% of all differences between the fibrinogen dose calculated using these two methods will lie. This analysis suggests a dose based on Clauss fibrinogen during CPB may differ from a FIBTEM calculated dose by up to 2.3 g. Clinical judgement is required as to whether this is an acceptable difference, and thus whether the equation is suitable or not.

Fibrinogen dose calculated using the Clauss assay equation given above was also compared with that calculated using the FIBTEM measurement taken immediately after removal of CPB (before administration of fibrinogen). The mean fibrinogen dose based on FIBTEM immediately after removal of CPB was 7.7 (2.3) g, with no statistical difference between this and the dose based on the Clauss measurement made during CPB (P=0.86). The Bland–Altman limits of agreement method was used to examine the agreement between individual observed and predicted values. This method gave the 95% limits of agreement interval as being from −2.5 to 2.6 g (equivalent to −32.5 to 33.8% of the mean dose). This analysis suggests that a dose based on Clauss fibrinogen during CPB may differ from a dose based on FIBTEM immediately after removal of CPB by up to 2.6 g.

The analyses presented here indicate that the Clauss measurements taken during CPB may be a suitable basis for calculating the fibrinogen dose in these patients, with derived doses largely similar to those calculated using FIBTEM measurements made either during or immediately after removal of CPB. Using the Clauss assay measurement taken during CPB to determine fibrinogen concentrate dosage may be one way to minimize treatment delay when other methods (such as the ROTEM-based FIBTEM test) are not available. It should be noted that although the Clauss assay is widely used to measure plasma fibrinogen concentration, limited agreement has been observed for the measurement obtained using different Clauss methods within the same laboratory, and for measurements between different laboratories.[2] This variability could impact on the triggers used to decide whether to administer haemostatic therapy to the patient. Furthermore, it must be kept in mind that the Clauss assay can be affected by the presence of heparin in the sample.[3] Commercially available reagents differ in their sensitivity to heparin with some stating that the assay may be affected by heparin levels >2 units ml^{-1}, while others contain heparin neutralizers and high concentrations of thrombin.[4] Shortly before the removal of CPB, levels of heparin >2 units ml^{-1} may be present;[5] therefore, clinicians must be informed whether the Clauss assay used in their unit is sensitive to heparin, and how this may affect the results of the Clauss fibrinogen measurement. In order to confirm the validity of using the Claus assay during CPB to determine fibrinogen concentrate dosage, we would suggest carrying out a more extensive study across a larger cohort of patients.

Declaration of interest

C.S. is an employee of CSL Behring, but was not an employee of CSL Behring while the study was being conducted, and has received speaker honoraria, research support, or both from Tem International and CSL Behring, and travel support from Haemoscope Ltd. N.R.-M. has participated in advisory boards and received speaker honoraria and research support from CSL Behring and Tem International.

C. Solomon*
N. Rahe-Meyer
Salzburg, Austria
**E-mail: solomon.cristina@googlemail.com*

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doi:10.1093/bja/aeu173

Saline and metronidazole

Editor— We read with interest the correspondence by Loader and Brooks[1] alerting the readers about the packaging similarities of paracetamol and metronidazole.

We would like to draw attention to a similar situation that arose in our hospital when metronidazole (Baxter, 500 mg in 100 ml) and sodium chloride 0.9% w/v (Baxter, 100 ml) were introduced at the same time without much staff consultation.

We raised an alert locally in our department as to the existence of the situation. We also ensured that the two products were separated and finally one of the products was replaced by a different manufacturer with a very different packaging.

We agree that the person administering the product should check the content before administration and holds a responsibility for the effects. This type of organizational circumstance which provides for human error to occur in a stressful situation could be avoided by a simple method of changing the packaging of one of the products. This aspect has been highlighted in a large-scale survey among anaesthesia practitioners.[2] The use of colour, graphics, and typography has been recommended by the safety agency in an effort to avoid errors.[3]

Declaration of interest

None declared.

G. Ramaswamy*
R. Naik
Enfield, UK
**E-mail: g.ramaswamy@nhs.net*

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doi:10.1093/bja/aeu177

Cerebral blood flow is determined by arterial pressure and not bypass flow rate

Editor—Moerman and colleagues[1] reported that in cardiac surgery patients, restoration of arterial pressure with i.v. phenylephrine during low-flow cardiopulmonary bypass decreased cerebral oxygen saturation. They conclude that this decrease in cerebral oxygen saturation may be due to decreased cerebral blood flow.

Nevertheless, they discuss the possibility that the decrease in cerebral oxygen saturation may result from measurement artifact due to cutaneous vasoconstriction by phenylephrine and the failure of cerebral oximeters to account for extra cranial contamination.[2] Indeed, laboratory and clinical studies of cerebral blood flow during cardiopulmonary bypass support the position that it is measurement artifact that explains their results.

In our baboon model, phenylephrine administered to increase arterial pressure during low-flow bypass markedly increased cerebral blood flow.[3] In both laboratory and clinical studies, when arterial pressure and cardiopulmonary bypass flow rate were varied, cerebral blood flow was dependent on mean arterial pressure and not bypass flow rate.[4 5] Additionally, measurements of cerebral metabolic rate for oxygen in these studies further support the conclusion that the small changes in cerebral oxygen saturation observed by Moerman and colleagues indicate extra cranial contamination and not decreased cerebral blood flow.

Declaration of interest

None declared.

A. E. Schwartz
New York, USA
E-mail: arthur.schwartz@mountsinai.org

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doi:10.1093/bja/aeu178

Do not attempt resuscitation decisions in the perioperative period

Editor—Many of the opinions expressed by Knipe and Hardman in their recent editorial[1] have previously been published as correspondence by Poplett and Smith with a comprehensive reply from ourselves[2] after publication of the Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines on 'Do Not Attempt Resuscitation (DNAR) Decisions in the