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Haemostatic efficacy of fibrinogen concentrate: is it the threshold or the timing of therapy?

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Fibrinogen is the key substrate of thrombin in haemostatic clot formation, and its plasma concentration is highly susceptible to blood loss and haemodiluton;[1–3] therefore, it has been recognized as a primary target of coagulation therapy in the management of perioperative major bleeding.[2–7] Human plasma-derived fibrinogen concentrate is convenient to use because it is lyophilized and quickly reconstituted for i.v. injection. In addition, it is simple to monitor the dose because fibrinogen concentrate increases plasma fibrinogen concentration in a dose-dependent manner[8] and increases fibrin-specific clot formation (FIBTEM) on thromboelastometry.[9 10] However, there is no consensus on the minimal fibrinogen concentration or FIBTEM value that is required for perioperative haemostasis,[11] and there are concerns regarding overuse and misuse.[12 13] The value of FIBTEM-based fibrinogen interventions has been evaluated previously in both prospective studies and retrospective analyses (Table 1).[14 17–19] However, it is yet unknown whether a low normal fibrinogen concentration (1.5 g litre^{-1}) is adequate for haemostasis in the perioperative setting or whether higher concentrations of fibrinogen might be required to reduce bleeding.

In this issue of the *British Journal of Anaesthesia*, Haas and colleagues[15] shed new light on the perioperative fibrinogen replacement strategy. The authors performed a well-designed randomized controlled study in paediatric patients undergoing craniosynostosis and scoliosis surgery. Patients were randomized to receive therapy with fibrinogen concentrate based on a high (13 mm) or low target value (8 mm) of FIBTEM maximal clot firmness (MCF). The authors found that intraoperative fibrinogen intervention using the higher threshold significantly reduced bleeding by ~67% and transfusion requirements by nearly 50% compared with the lower threshold value in craniosynostosis surgery. In scoliosis surgery, however, the extent of bleeding was similar between both groups, and only a trend for reduced transfusion with the higher threshold was found.

The two thresholds, 8 and 13 mm of FIBTEM MCF, used in this study represent the lower and upper target range in the European guidelines for the treatment of massive perioperative bleeding.[6] They are also likely to correspond to the minimal fibrinogen concentration (1.5 g litre^{-1}) recommended by the European guidelines[6] and the median concentration of fibrinogen (2.35 g litre^{-1}) for this age group.[20] Those who were randomized to the higher threshold received intervention early because their baseline FIBTEM MCF values were 10–11 mm (corresponding to plasma concentrations of about 1.8–2.0 g litre^{-1}).[21] It can be speculated that plasma fibrinogen concentrations were maintained at above 2.0 g litre^{-1} in the high-threshold group when intraoperative bleeding occurred. In the low-threshold group, however, plasma fibrinogen could be decreased to below 1.5 g litre^{-1} as bleeding continued. It is thus important to consider the timing of therapy in addition to the optimal threshold. Nakayama and colleagues[16] recently reported a prospective randomized study of conventional *vs* thromboelastometry-guided haemostatic intervention in paediatric cardiac surgery. In their study, the FIBTEM threshold was set rather low at 5 mm for

Table 1 Fibrin-specific clot formation thresholds used by published prospective randomized studies. $A_{10/15}$, amplitude after 10/15 min; ACT, activated clotting time; FC, fibrinogen concentrate; FFP, fresh frozen plasma; FIBTEM, fibrin-specific clot formation; MCF, maximal clot formation; NA, not available; RBC, red blood cell; ROTEM, rotational thromboelastometry

Author, yr	Study setting	Intervention and trigger values		Key findings	Fibrinogen concentrations after surgery
		Intervention group	Control group		
Girdauskas and colleagues, 2010[14]	56 adult patients undergoing complex cardiac surgery	FC administered if FIBTEM MCF<8 mm (*n*=27)	FC administered if plasma fibrinogen concentration <1.2 g litre^{-1} (*n*=29)	ROTEM-guided transfusion is associated with decreased use of allogeneic blood products	NA
Haas and colleagues, 2015[15]	49 paediatric patients undergoing craniosynostosis or scoliosis surgery	FC administered if FIBTEM MCF<13 mm (*n*=27)	FC administered if FIBTEM MCF<8 mm (*n*=22)	Higher trigger value reduced bleeding and RBC transfusion in craniosynostosis but not scoliosis surgery	NA
Nakayama and colleagues, 2014[16]	100 paediatric patients undergoing cardiac surgery	FFP administered if FIBTEM A_{10}<5 mm (*n*=50)	FFP administered if ACT≥150 s after protamine 0.5 mg kg^{-1} (*n*=50)	ROTEM-guided transfusion reduced bleeding and RBC transfusion	1.65 g litre^{-1} (intervention) *vs* 1.25 g litre^{-1} (control)
Rahe-Meyer and colleagues, 2013[7]	61 bleeding adult patients undergoing complex cardiac surgery	FC administered if FIBTEM MCF<22 mm (*n*=29)	NaCl 0.9% (placebo) administered if FIBTEM MCF<22 mm (*n*=32)	FC reduced the need for allogeneic blood products	2.60 g litre^{-1} (intervention) *vs* 1.89 g litre^{-1} (control)
Weber and colleagues, 2012[17]	100 bleeding adult patients undergoing cardiac surgery	FC administered if FIBTEM A_{10}≤10 mm (*n*=50)	FC administered if plasma fibrinogen concentration <1.5 g litre^{-1} (*n*=50)	ROTEM-guided transfusion reduced transfusion of allogeneic blood products and improved outcome	2.29 g litre^{-1} (intervention) *vs* 1.97 g litre^{-1} (control)

10 min amplitude (A_{10}), but the FIBTEM-based protocol resulted in early plasma transfusion compared with the conventional therapy. The reduced red blood cell transfusion and postoperative blood loss in the FIBTEM group are partly explained by the higher fibrinogen concentrations than those with the conventional therapy (1.65 *vs* 1.25 g litre^{-1}). Importantly, total amounts of plasma and platelet transfusion were not different between both groups.[16] Likewise, Haas and colleagues[15] found that total administered amounts of fibrinogen and factor XIII concentrate, and of plasma and platelet transfusion were comparable between their two groups. It is thus important to optimize the threshold and the timing of haemostatic intervention because they interact closely with each other.

There have been previous clinical studies that involved prophylactic administration of fibrinogen concentrate to maintain high normal fibrinogen concentrations for cardiac surgery[22] and for postpartum haemorrhage.[23] However, major concerns regarding the prophylactic substitution are that bleeding attributable to a surgical cause cannot be stopped by fibrinogen, and administered fibrinogen can quickly be lost in haemorrhage and haemodilution.[24] The efficacy of prophylactic fibrinogen substitution may be strongly influenced by the surgical technique, extent of vascular injury, and intraoperative blood loss. The study by Haas and colleagues[15] was, therefore, terminated prematurely because of the surgical staff change. A larger multicentre study should be considered to validate a FIBTEM MCF of 13 mm as a potential haemostatic target to reduce allogeneic blood exposure, postoperative intensive care stay, and other transfusion-related complications.

Besides the limitations of a small single-centre study, the study of Haas and colleagues[15] is underpowered for any safety analysis. Overdosing of fibrinogen concentrate might be associated with thromboembolic complications, especially in patients with cardiovascular diseases.[25 26] There is a paucity of data on the safety of any factor concentrate usage in paediatric acquired coagulopathy, but the thromboembolic risk of paediatric patients appears to be lower than that of adults.[27] In adult cardiac surgery, the administration of fibrinogen targeting a plasma concentration of ~2 g litre^{-1} (corresponding to a FIBTEM MCF of ~10 mm) was not associated with worse 30 day and 1 yr outcomes compared with patients without administration of fibrinogen concentrate.[4]

In summary, the work of Haas and colleagues[15] has provided further evidence that maintaining fibrinogen at above 2.0 g litre^{-1} might be more advantageous in reducing bleeding volumes and red blood cell transfusion than on-demand therapy after fibrinogen concentration reduces to below 1.5 g litre^{-1}. The extrapolation of their findings to general paediatric surgical populations should be done cautiously, because this was a single-centre study with a limited sample size in very specific surgical procedures. At present, a routine prophylactic administration of fibrinogen concentrate is not recommended, but a fibrinogen concentration below 2.0 g litre^{-1} or FIBTEM MCF below 10 mm seems to be an acceptable target to commence early haemostatic intervention in patients who are at increased risk for profuse bleeding in major surgery.

Declaration of interests

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Reliable critical care: making it easy to do the right thing

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Sir Muir Gray, Director of the NHS Chief Knowledge Office, hypothesized that 'The application of what we know will have a bigger impact than any drug or technology likely to be introduced in the next decade.' He recognized that blind investment in new drugs and technologies that provide only a modest improvement in efficacy may cost more lives than it saves, because this investment will consume scarce resources needed for improved delivery of care. Therefore, it can be argued from a health, economic, and moral standpoint that we should spend less on new technology and new drugs and more on improving systems for delivery of care[1] and turning knowledge into action.

Whilst few of us would disagree that robust evidence from clinical trials should be implemented to improve patient care, it has become apparent that a gap exists and that the translation of evidence into routine practice is not as widespread and easily done as one would have expected. Evidence suggests that it takes on average 17 years for research evidence to reach clinical practice.[2] This is a remarkably slow and inefficient process. Indeed, it took 13 years for cardiologists to recommend thrombolysis for the treatment of acute myocardial infarction after the publication of randomized controlled trials showed therapeutic benefit.[3] Furthermore, Lomas and colleagues[4] calculated a 5 year gap between publication of guidelines and changes to routine practice in Western health-care systems. Although the paucity of robust and high-quality evidence in critical care used to be cited as a reason for the lack of change in practice, critical care research in the last 10 years has been inundated with a number of practice-changing headlines, leaving clinicians with the responsibility of ensuring that these are incorporated into everyday practice to enable patients to receive safe, effective, and person-centred care.

In 2000, the acute respiratory distress syndrome (ARDS) network study demonstrated conclusively and unarguably that limiting tidal volume to <6 ml kg^{-1} predicted body weight (PBW) and end-inspiratory pressure to not more than 30 cm H_2O, compared with patients ventilated with higher tidal volumes (>12 ml kg^{-1} PBW), significantly reduces mortality in acute lung injury and ARDS, with a number needed to treat of 11 patients to save one life.[5] No special equipment or expertise was required to achieve this benefit. Despite the perceived relative simplicity of implementing low-tidal volume ventilation, a number of studies published in the last 10 years reveal a disappointing failure of clinicians to adopt and implement this piece of evidence.[6–8]

In a simple yet elegantly designed and conducted service evaluation study in this issue of the *BJA*, Bourdeaux and colleagues[9] have demonstrated how a large screen configured to display information routinely collected from a clinical information system resulted in a significant and sustained improvement in the use of evidence-based ventilation practice and reduced unwarranted tidal volume variation with improved reliability. In a mixed medical and surgical intesive care unit in a UK teaching hospital, two similar cohorts of patients on controlled mechanical