Fibrinogen—is it a universal haemostatic agent?

D. Bolliger1,* and K. A. Tanaka2

1Department of Anaesthesia, Surgical Intensive Care, Prehospital Emergency Medicine and Pain Therapy, University Hospital Basel, Basel, Switzerland, and 2Department of Anesthesiology, Division of Cardiac Anesthesiology, University of Maryland, Baltimore, MD, USA

*Corresponding author. E-mail: daniel.bolliger@usb.ch

Fibrinogen is a crucial haemostatic factor in sustaining platelet aggregation via glycoprotein (GP) IIb/IIIa receptors during primary haemostasis. Platelet-bound fibrinogen is subsequently cleaved to fibrin monomers by thrombin, and fibrin monomers are polymerized by thrombin-activated factor XIII, resulting in secondary haemostasis. Very low fibrinogen concentrations with normal platelet count have been linked to an unstable clot formation.1, 2 Conversely, high fibrinogen concentrations are often expensive, and perioperative transfusion of allogeneic platelets has been associated with an increased risk of stroke, allergic reaction, pathogen transmission and immunodulation.3 There has been increasing interest in platelet alternatives in perioperative haemostasis, amongst them is the infusion of fibrinogen concentrate (FC).1, 4–6 9–11 The latter has been claimed by some authors as a “universal haemostatic agent”.12 13

In a recent issue of the British Journal of Anaesthesia, Schenk and colleagues14 compared the effects of ex vivo spiking with FC, and in vivo platelet transfusion on viscoelastic clot strength, using rotational thromboelastometry (ROTEM®; TEM International, Munich, Germany). Their hypothesis and aims are based on the assumption that enhanced fibrin polymerization proportionally increases clot strength, even in the presence of thrombocytopenia and/or platelet dysfunction.3–6 15 The platelet transfusion was deemed necessary by the physician in charge as

References

Funding

This report is independent research supported by the National Institute for Health Research (NIHR Post Doctoral Fellowship, Dr Whitney Scott, PDF-2015-08-059). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health.

doi:10.1093/bja/aew332

a treatment of coagulopathic bleeding in the enrolled patients. Most of cases were related to bleeding after cardiopulmonary bypass. Blood samples before platelet transfusion were spiked with fibrinogen ex vivo at the final concentrations between 88 and 704 mg dl⁻¹, corresponding to the FC dose of 50 to 400 mg kg⁻¹ or 4 to 32 g in an 80-kg patient. It was concluded that ex vivo FC doses of 100 to 200 mg kg⁻¹ resulted in similar thromboelastometric changes as the in vivo transfusion of 1 to 2 units of platelet concentrates.

Several findings of this study merit further considerations:

I. Indication of platelet transfusion was clinically determined as a treatment for microvascular bleeding, and the mean platelet count was 88 x 10⁹ l⁻¹ before transfusion. Thirty percent of their patients had been treated with one of P2Y₁₂ inhibitors before surgery. Despite there is a wide variability in the practice of platelet transfusion, these data would rather support the use of platelet concentrate. The efficacy of platelet transfusion has been questioned and is mostly guessed from an increase in platelet count or by reduced bleeding tendency. Schenk and colleagues documented a dose-dependent increase in platelet count after platelet transfusion. More GPIIb/IIIa receptors become available with a higher platelet count, which increases fibrin interactions, and viscoelastic clot strength. The effects of P2Y₁₂ inhibitors are not reflected on thromboelastometry, because thrombin-induced platelet activation sustains the active state of GPIIb/IIIa receptors. A previous published comparative study of ex vivo FC supplementation (100–400 mg kg⁻¹), and in vivo platelet transfusion in thrombocytopenia as a result of bone marrow failure, also demonstrated the similar viscoelastic effects on thromboelastometry (ROTEM®; TEM International, Munich, Germany). However, clinical implication of FC in that study was highly questionable because the fibrinogen concentration was 4.5 g l⁻¹, while platelet count was 17 x 10⁹ l⁻¹ at baseline. Clinical platelet transfusion is obviously aimed to increase platelet accumulations at the site of vascular injury, but ROTEM® is not designed to evaluate such effects.

II. In vitro addition of fibrinogen to thrombocytopenic blood increases viscoelastic clot strength in a concentration-dependent manner on ROTEM®. Fries and colleagues also demonstrated the haemostatic efficacy of FC in vivo in a porcine model of thrombocytopenia (30 x 10⁹ l⁻¹), by comparing FC (250 mg kg⁻¹) vs homologous platelet transfusion. In clinical practice, the first-line use of FC as a haemostatic intervention remains controversial in the surgical setting. There have been three recent studies which tested the effect of FC, as a first-line therapy to reduce allogeneic blood usage including platelets. In a small prospective randomized study including 20 patients who underwent valvular heart surgery, the administration of 4 g of FC resulted in similar postoperative bleeding volumes, and erythrocyte transfusion compared with the transfusion of 1 unit of apheresis platelets. Ranucci and colleagues conducted a prospective randomized placebo-controlled study of FC, which showed that a high normal fibrinogen concentration maintained by FC supplementation (median, 4 g), was effective in reducing the transfusion of erythrocytes, plasma, and platelets in complex cardiac surgery. In contrast, Rahe-Meyer and colleagues recently published the result of REPLACE study, reporting that FC (mean, 6.29 g) was not more effective than a placebo in complex aortic replacement surgery and was associated with increased platelet transfusion. The latter two studies differed in the durations of cardiopulmonary bypass (median, 105–110 min vs. >180 min), and thus a more extensive haemodilution is likely in the REPLACE study. The median FIBTEM-MCF achieved in FC group was 30 mm in the presence of thrombocytopenia (<100 x 10⁹ l⁻¹) in 48.7% of the patients. Schenk and colleagues showed that fibrinogen supplemented at 100–400 mg kg⁻¹ resulted in the mean FIBTEM-MCF values of 15–25 mm, which were below those achieved in the REPLACE study. It is thus difficult to simply link higher fibrinogen concentrations or viscoelastic clot strength to clinical efficacy of FC. It remains controversial to target very high fibrinogen concentrations using FIBTEM-MCF. Indeed, Ranucci and colleagues speculated that increasing FIBTEM-MCF above 14 mm, was not associated with further conservation of allogeneic blood products, based on the secondary analysis of their prospective FC intervention data.

III. Viscoelastic clot strength was used as a surrogate of potential haemostatic efficacy, but caution should be exercised in the interpretation. The low-shear environment (0.1 s⁻¹) of thromboelastometry, preferentially shows fibrin polymerization over platelet activity under high-shear conditions. Anaemia appears to differently affect thromboelastometry and in vivo coagulation. Viscoelastic clot strength tends to increase in the presence of anaemia, and while anaemia seems to exacerbate microvascular bleeding via reduced platelet margination to vessel walls during blood flow. The effect of fibrinogen on viscoelastic clot strength may be overestimated in vitro, especially under anaemic state, and can, therefore, not be directly compared with in vivo platelet activity. On viscoelastic coagulation assays, fibrin itself can generate viscoelasticity without platelets, and thus increased clot strength does not guarantee improved interactions between aggregating platelets and fibrinogen. Further, ROTEM® is rather insensitive to impaired platelet function as a result of intake of P2Y₁₂ receptor antagonists and shows usually normal findings in patients with dual platelet inhibitors. Indeed, ex vivo addition of FC (100 mg kg⁻¹) to the whole blood obtained from patients receiving P2Y₁₂ receptor antagonist therapy showed improved clot strength on thromboelastometry, but platelet aggregation induced by either adenosine 5'-diphosphate or thrombin receptor agonist peptide was not improved.

In summary, the work of Schenk and colleagues suggests an interesting alternative to platelet transfusion. Further testing of prophylactic or therapeutic fibrinogen administration as a haemostatic therapy to reduce platelet transfusion in thrombocytopenic patients seems to worth the effort. However, haemostatic reactions in vivo are inherently complex, and therefore, only limited information can be obtained from a single coagulation test such as ROTEM®. Further, primary fibrinogen replacement might not work well for severe dilutional coagulopathy, or P2Y₁₂ receptor antagonist-induced thrombocytopenia. In the light of recently published studies, aiming at extremely high concentrations of fibrinogen (>2.8 g L⁻¹) is questionable, and its indication should be limited to bleeding patients with hypofibrinogenemia until future evidence supports otherwise.

Declaration of interest
None declared.
References

17. Sarode R. How do I transfuse platelets (PLTs) to reverse anti-PLT drug effect? Transfusion 2012; 52: 695–701