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Time course of haemostatic effects of fibrinogen concentrate administration in aortic surgery

C. Solomon[1,6]*, C. Hagl[2,4] and N. Rahe-Meyer[3,5]

[1] Department of Anaesthesiology and Intensive Care Medicine, SALK University Hospital, Salzburg, Austria
[2] Clinic for Cardiothoracic, Transplant and Vascular Surgery and [3] Department of Anesthesiology and Intensive Care Medicine, Hannover Medical School, Hannover, Germany
[4] Cardiac Surgery Clinic, University Clinic Grosshadern, Munich, Germany
[5] Department of Anesthesiology and Intensive Care Medicine, Franziskus Hospital, Bielefeld, Germany
[6] Present address: CSL Behring, Marburg, Germany

* Corresponding author. E-mail: solomon.cristina@googlemail.com

Editor's key points

- Fibrinogen concentrate can reduce bleeding and transfusion in aortic surgery, but there are concerns regarding its thrombogenicity.
- In a *post hoc* analysis of a prior randomized clinical trial, fibrinogen concentrate increased plasma fibrinogen and clotting activity.
- These effects were short-lived and were not associated with significant alterations in haemostatic parameters, which should be confirmed in larger multicentre studies.

Background. There is currently a contrast between the demonstrated benefits of fibrinogen concentrate in correcting bleeding and reducing transfusion, and its perceived thrombogenic potential. This analysis evaluates the effects of fibrinogen concentrate on coagulation up to 12 days after administration during aortic surgery.

Methods. We performed a *post hoc* analysis of a prospective, randomized, double-blind, controlled trial of fibrinogen concentrate as first-line haemostatic therapy in aortic surgery. After cardiopulmonary bypass (CPB) and protamine administration, subjects with coagulopathic bleeding received fibrinogen concentrate or placebo. The placebo group received allogeneic blood products, including fresh-frozen plasma (FFP; $n=32$); the fibrinogen concentrate group received fibrinogen concentrate alone (FC; $n=14$), or fibrinogen concentrate followed by allogeneic blood products (FC+FFP; $n=15$). Plasma fibrinogen, fibrin-based clotting (ROTEM®-based FIBTEM assay), and peri- and postoperative haematological and coagulation parameters were compared.

Results. Plasma fibrinogen and FIBTEM maximum clot firmness (MCF) decreased ~50% during CPB but were corrected by FC or FC+FFP. At last suture, the highest values for plasma fibrinogen (360 mg dl^{-1}) and FIBTEM MCF (22 mm) were within normal ranges—below the acute phase increases observed after surgery. In patients receiving only FFP as a source of fibrinogen, these parameters recovered marginally by last suture ($P<0.001$ *vs* FC and FC+FFP). All groups displayed comparable haemostasis at 24 h post-surgery. Fibrinogen concentrate did not cause alterations of other haemostasis parameters.

Conclusions. Fibrinogen concentrate provided specific, significant, short-lived increases in plasma fibrinogen and fibrin-based clot firmness after aortic surgery.

Keywords: blood coagulation tests; cardiopulmonary bypass; fibrin; fibrinogen; plasma

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There is a contrast between the demonstrated benefits of fibrinogen concentrate in correcting bleeding and reducing transfusion,[1] and its perceived thrombogenic potential, reported either as an independent association between plasma fibrinogen and cardiovascular disease[2 3] or as thromboembolic complications in afibrinogenaemia after fibrinogen supplementation.[4 5] Given the latter, one might expect increased risk for thrombogenic complications after fibrinogen supplementation in perioperative bleeding, although current data do not support this. One explanation is that, paradoxically, afibrinogenaemia is itself a risk factor for thromboembolic complications, possibly through von Willebrand factor-induced platelet aggregation, increased thrombin generation, or the absence of fibrin's antithrombin I function.[6]

Further confusion arises from plasma fibrinogen concentration being variously described as a marker,[2] predictor,[3] and mediator of coronary conditions.[7] As an acute-phase reactant, fibrinogen levels increase substantially after tissue injury, inflammation, infection, and atrial fibrillation.[2] Sustained plasma fibrinogen elevation has also been reported after aortic surgery.[8] It is important to distinguish between elevated plasma fibrinogen during an acute-phase response

and that due to targeted fibrinogen supplementation. Thus, a crucial question is: how does a fibrinogen concentrate bolus impact the coagulation system after surgery, compared with standard therapy using fresh-frozen plasma (FFP)?

We performed a randomized, double-blind, placebo-controlled study of fibrinogen concentrate as first-line haemostatic therapy in aortic surgery. Efficacy analysis showed that fibrinogen concentrate reduced perioperative transfusion compared with placebo.[9] All placebo group subjects received allogeneic blood products, including FFP as a source of fibrinogen. In the fibrinogen concentrate group, some subjects received fibrinogen concentrate as a sole source of fibrinogen, while others received fibrinogen concentrate and allogeneic blood products. Here, we provide a *post hoc* analysis of coagulation and haematological parameters recorded intraoperatively and after surgery. We aimed to determine whether fibrinogen concentrate induces large, long-lived increases in fibrinogen concentration and fibrin-based clotting, and also derangement of other coagulation parameters, compared with treatment with allogeneic blood components including FFP.

Methods

Study design and patient population

This single-centre, prospective, randomized, double-blind, parallel-group, placebo-controlled study was conducted at Hannover Medical School, Germany. It was approved by the local Ethics Committee and German Regulatory Authorities and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. The study was assigned Local Ethics Committee reference code 4891M-mono, EudraCT trial number 2007-004612-31, and clinicaltrials.gov identifier number NCT00701142. Details of study rationale, design, and patient selection have been published.[9]

Briefly, patients $\geq$18 yr old, undergoing elective aortic-replacement surgery involving cardiopulmonary bypass (CPB), were screened for eligibility (June 2008 to April 2010). Based on a power calculation for analysis of transfusion requirements, 60 subjects were planned; 80 patients were screened and randomized to the fibrinogen concentrate or placebo groups. An unblinded pharmacist bound by confidentiality agreement performed the randomization and prepared study medications. Randomization numbers were assigned sequentially, in a 1:1 ratio, block size of 4, stratified by surgery type. After signed consent was obtained, 61 subjects were included. Aortic valve operations with root/ascending aorta replacement, with or without aortic arch replacement, and thoracoabdominal replacements were included. Exclusion criteria included: patients with congenital or acquired (pre-surgery) coagulation disorders, previous surgery at the same site, stroke or myocardial infarction $\leq$2 months before surgery, and use of aspirin, clopidogrel, or vitamin K antagonists 2–5 days pre-surgery.

Procedures and groups

Details of surgical methods, measurement of coagulopathic bleeding, and the therapy algorithm have been published.[9] Subjects randomized to receive fibrinogen concentrate (Haemocomplettan® P/RiaSTAP™, CSL Behring, Marburg, Germany) or placebo (0.9% saline) were administered individualized doses based on thromboelastometric measurement of fibrin-based clot firmness using the ROTEM®-based FIBTEM test. Medication was administered only if coagulopathic bleeding (defined as 5 min bleeding mass of 60–250 g) was observed immediately after CPB removal, protamine reversal of heparin, and surgical control of focal bleeding. Anaesthesiologists and surgical staff were blinded to study medication (fibrinogen concentrate or placebo), which was delivered in opaque syringes. The content of each syringe (either 50 ml of 0.9% saline as placebo or 1 g fibrinogen concentrate dissolved in 50 ml water for injection) was administered in less than 20 s. The median total dose was 8 g (minimum 3 g, maximum 14 g). If coagulopathic bleeding continued after administration of study medication, a transfusion algorithm was initiated. If platelet count was $<$100 000 μl^{-1}, 2 units of apheresis platelet concentrate were administered; if platelet count was $\geq$100 000 μl^{-1}, 4 units of FFP were administered. If a second transfusion cycle was needed, subjects received whichever of the two treatments they had not been given initially. Subsequently, treatment was with 1 unit of platelet concentrate and 2 units of FFP until the 5 min bleeding mass was $<$60 g.

Bleeding was arrested in 14 of 29 subjects who received fibrinogen concentrate; no further haemostatic therapy was administered ('FC' group). Coagulopathic bleeding continued in 15 of 29 subjects post-fibrinogen concentrate; FFP, platelet concentrate, or both were administered according to the treatment algorithm ('FC+FFP' group). This *post hoc* subdivision allowed assessment of differential responses after treatment using fibrinogen concentrate $\pm$ FFP. All 32 placebo group subjects continued bleeding post-infusion and subsequently received FFP, with or without platelets, according to the treatment algorithm ('FFP' group).

Haematology and coagulation monitoring assays

Blood samples were drawn pre-study medication (before induction of anaesthesia, 20 min before removal of CPB, and after removal from CPB/administration of protamine) and post-study medication [after last suture, at 24 h (day 1), 48 h (day 2), and 8–12 days (day 10) after surgery]. Assays were performed at the study centre's laboratory by an unblinded technician bound by confidentiality agreement.

Laboratory coagulation tests

Tests were performed using a Sysmex® CA-7000 device (device and reagents obtained from Siemens Healthcare Diagnostics GmbH, Erlangen, Germany). Three millilitres of citrated blood were centrifuged; 1.5 ml of resulting plasma was used to determine plasma fibrinogen levels via the Clauss assay (Dade Thrombin Reagent). Remaining plasma was used to measure antithrombin (Innovance® Antithrombin Kit), factor II (FII; measured using FII-deficient plasma with Thromborel® S reagent), FV (FV-deficient plasma with