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Perioperative administration of fibrinogen does not increase adverse cardiac and thromboembolic events after cardiac surgery

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Editor's key points

- Fibrinogen concentrate is increasingly used to decrease bleeding after cardiac surgery.
- However, it has the potential to increase thrombotic events and safety data are lacking.
- This retrospective analysis examined the effect of fibrinogen administration to a target of 2 g litre^{-1} in cardiac surgical patients.
- There was no increase in mortality or adverse outcomes, but more data are required.

Background. Although infusion of fibrinogen concentrate is increasingly used in bleeding patients after cardiac surgery, safety data are scarce. We aimed to evaluate the effect of perioperative administration of fibrinogen concentrate on postoperative morbidity and mortality in patients undergoing cardiac surgery.

Methods. During a 2 yr study period, 991 patients underwent cardiac surgery at a single university centre and were eligible for propensity score (PS) matching. We matched 190 patients with perioperative infusion of fibrinogen concentrate (median dose 2 g) with 190 controls without fibrinogen administration. After PS matching, crude outcome was analysed. Further, a multivariate logistic regression including additional risk factors for adverse outcome was performed. The primary endpoint was a composite of mortality and the occurrence of major cardiac and thromboembolic events within 1 yr. Secondary outcomes included mortality after 30 days and 1 yr and the composite of mortality and adverse events after 30 days.

Results. The administration of fibrinogen concentrate was not associated with an increased risk for mortality and thromboembolic or cardiac events within 1 yr after cardiac surgery [unadjusted hazard ratio (HR) 0.91; 95% confidence interval (CI) 0.55–1.49; P=0.697]. When using multivariate logistic regression model, the HR for adverse outcome in patients with administration of fibrinogen concentrate was 0.57 (95% CI 0.25–1.17; P=0.101). Similarly, the administration of fibrinogen concentrate did not adversely affect the secondary outcomes when applying unadjusted and multivariate regression analyses.

Conclusions. Our study strongly suggests that the administration of fibrinogen concentrates at low dose is not associated with thromboembolic complications or adverse outcomes after cardiac surgery.

Keywords: cardiac surgery; fibrinogen; thromboembolism; treatment outcome

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Fibrinogen plays a critical role in the coagulation process, and it is increasingly recognized as one of the primary haemostatic targets in perioperative bleeding after cardiac surgery.[1–4] Accordingly, several studies have found that higher pre- and postoperative fibrinogen concentrations were associated with lower bleeding volumes.[2 5–8] Therefore, perioperative preservation of fibrinogen and the infusion of fibrinogen concentrate in the case of bleeding and haemodilution associated with hypofibrinogenaemia might be a key step in perioperative haemostasis. Preliminary data suggest that the infusion of fibrinogen concentrate reduced postoperative bleeding volumes and transfusion requirements.[9–13] In contrast, a recent study including 84 patients undergoing cardiac surgery questioned the benefit in haemostasis resulting from the administration of fibrinogen concentrate or cryoprecipitate.[7]

In addition to the limited evidence regarding the appropriate indication, dosing, and efficacy of fibrinogen concentrate in the perioperative treatment of the bleeding patient undergoing cardiac surgery,[14–16] fibrinogen is a procoagulatory drug, which could potentially cause thromboembolic complications and impair patient outcome. High fibrinogen levels are recognized as a risk factor for increased mortality in non-surgical patients.[17 18] In surgical patients, a high preoperative fibrinogen level has been identified as risk factor for the

development of vein graft stenosis after peripheral vascular surgery[19] and has been associated with increased mortality after coronary surgery.[20]

At our institution, fibrinogen concentrate is regularly administered to bleeding patients after cardiac surgery. In this retrospective analysis of prospectively collected data, we aimed to evaluate the association between perioperative administration of fibrinogen concentrate to bleeding patients undergoing cardiac surgery and postoperative thromboembolic events and mortality after 30 days and 1 yr. We hypothesized that fibrinogen administration would increase neither postoperative thromboembolic and cardiac events nor short- and long-term mortality.

Methods

Study design

With the approval of the local ethics committee (amendment to EKBB 06/07, Ethikkommission beider Basel, Switzerland) and written informed consent from all patients, we performed a secondary retrospective analysis of prospectively collected data at the University Hospital Basel. The original study has recently been published.[21] We included all patients undergoing cardiac surgery between January 2008 and December 2009 with the exception of patients undergoing surgery of the ascending aorta (with or without hypothermic circulatory arrest) or pericardiectomy. All patients fulfilling inclusion and exclusion criteria were eligible for propensity score (PS) matching (Fig. 1).

Perioperative management

Patients were orally premedicated with midazolam (7.5 mg) or bromazepam (1.5–3 mg). Anaesthesia was induced by thiopental (3–4 mg kg^{-1}) or etomidate (0.2–0.3 mg kg^{-1}) and fentanyl (2–6 μg kg^{-1}). Anaesthesia was maintained by isoflurane and midazolam/fentanyl infusion or by isoflurane and propofol infusion. Neuromuscular block was induced and maintained by atracurium. For procedures requiring cardiopulmonary bypass (CPB), systemic full-dose heparin (350 units kg^{-1}) was administered as a bolus before cannulation with additional doses to maintain an activated clotting time (ACT) >480 s (ACT plus® System, Metronic, Münchenbuchsee, Switzerland). Tranexamic acid (30 mg kg^{-1}) was given immediately after the initial dose of heparin. CPB priming volume amounted to 2000 ml. Myocardial protection was achieved by intermittent anterograde blood or crystalloid cardioplegia. For coronary artery bypass grafting without CPB, heparin was initially administered at a dose of 300 units kg^{-1} with additional doses to maintain ACT >350 s. No tranexamic acid was given during off-pump procedures. Body temperature was maintained at >32°C during CPB and at >36°C during off-pump surgery. CPB weaning was managed with catecholamines at the discretion of the attending anaesthesiologist. Heparin reversal was achieved by protamine aiming for ACT values within ±10% of the value before surgery.

The following triggers for infusion of fibrinogen concentrate and transfusion of allogeneic blood products were used during the perioperative period: fibrinogen concentrate was administered to bleeding patients according to our ROTEM® algorithm (FIBTEM® maximal clot firmness <8 mm),[22] or fibrinogen plasma concentration <2 g litre^{-1}.[23] A minimum haemoglobin concentration of >65 g litre^{-1} was required during CPB. After CPB and in the intensive care unit (ICU), patients with a haemoglobin concentration of <70 g litre^{-1} were given red blood cell (RBC) transfusion; patients with a haemoglobin concentration of 70–100 g litre^{-1} were treated according to the discretion of the physician in charge when the following transfusion triggers occurred: persistent bleeding, haemodynamic instability, and signs of myocardial ischaemia. Patients with a haemoglobin concentration of >100 g litre^{-1} were not given RBC transfusion. Fresh-frozen plasma (FFP) and platelets were given to clinically bleeding patients according to our ROTEM® algorithm,[22] in the case of low platelet count (<50 000×10^9 litre^{-1}) or prolonged prothrombin time. However, in a small minority of patients with clinically massive bleeding or preoperative use of platelet aggregation inhibitors, procoagulatory products were transfused based on the judgement of the attending physician only.

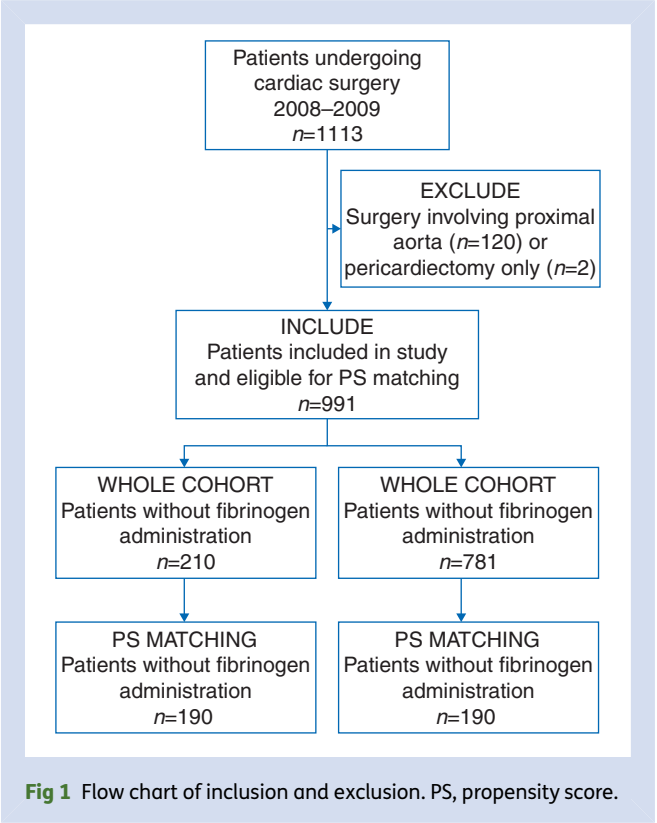

Fig 1 Flow chart of inclusion and exclusion. PS, propensity score.

Data collection and endpoint ascertainment

Trained research personnel prospectively collected detailed data on patient characteristic, surgical techniques, blood transfusion, pre- and postoperative laboratory testing, administration of coagulation factor concentrates, and in-hospital course and clinically important adverse events. Data on adverse events during hospitalization defined as thoracic re-exploration, acute (new-onset) renal impairment, severe brain injury,