

Fibrinogen and Bleeding in Cardiac Surgery: Clinical Studies in Coronary Artery Bypass Patients

AKADEMISK AVHANDLING

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av

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Leg. Läkare

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Avhandlingen baseras på följande delarbeten

- I) Aljassim O, Karlsson M, Wiklund L, Jeppsson A, Olsson P, Berglin E.
Inflammatory response and platelet activation after off-pump coronary artery bypass surgery
Scand Cardiovasc J 2006; 40: 43-8
- II) Karlsson M, Ternström L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A.
Plasma fibrinogen level, bleeding, and transfusions after on-pump coronary artery bypass grafting surgery: a prospective observational study
Transfusion 2008; 48: 2152-8
- III) Karlsson M, Ternström L, Hyllner M, Baghaei F, Flinck A, Skrtic S, Jeppsson A.
Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomized pilot study
Thromb Haemost 2009; 102: 137-44
- IV) Karlsson M, Ternström L, Hyllner M, Baghaei F, Skrtic S, Jeppsson A.
Prophylactic fibrinogen infusion in cardiac surgery patients: effects on biomarkers of coagulation, fibrinolysis and platelet function
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Background: Cardiac surgery is accompanied by inflammatory activation and bleeding complications. Fibrinogen is a key factor in the coagulation cascade and can be used to treat ongoing bleeding, but is not well studied as prophylactic treatment to prevent bleeding in patients with normal plasma fibrinogen levels or as a predictive tool to identify patients with increased bleeding risk.

Aims: To investigate the association between biomarkers of inflammation and hemostasis after off pump coronary artery bypass grafting (OPCAB). Further, to study the relationship between plasma fibrinogen concentration and postoperative bleeding and transfusion after on pump coronary artery bypass grafting (CABG). To investigate if prophylactic fibrinogen infusion reduces bleeding and transfusions after CABG. Finally, to study the effect of fibrinogen infusion on markers of coagulation, fibrinolysis and platelet function.

Materials and methods: In study I, biomarkers of inflammation (IL-6, IL-8, PMN-elastase, C3a, sC5b-9) and hemostasis (platelet count, β -thromboglobulin, anti-thrombin, D-dimer and fibrinogen) were measured before and after surgery in 10 OPCAB patients. II: plasma fibrinogen was analyzed the day before surgery in 170 elective CABG patients and related to postoperative bleeding and transfusions. III: 20 patients were randomized to preoperative infusion of 2 grams (g) fibrinogen concentrate or placebo. Side effects, bleeding and transfusions were registered. IV: Biomarkers of coagulation, fibrinolysis and platelet activation in relation to fibrinogen treatment were analyzed in the same patients as in study III.

Results: I: Inflammatory markers did not change during surgery while β -thromboglobulin increased and anti-thrombin and fibrinogen decreased. There were significant correlations between several markers of inflammation and hemostasis. II: Postoperative bleeding volume correlated univariately with preoperative fibrinogen concentration ($r = -0.53$, $p < 0.001$). Fibrinogen was an independent predictor of postoperative bleeding volume and blood transfusions. III: Infusion of 2g fibrinogen increased plasma levels by 0.6 ± 0.2 g/l and reduced postoperative blood loss by 32%. There were no clinically detectable adverse events of fibrinogen infusion. IV: Fibrinogen infusion induced no or minimal changes in most investigated biomarkers, except D-dimer which was significantly higher 2h after surgery in the fibrinogen group.

Conclusions: There is evidence for an association between the inflammatory response and hemostasis after cardiac surgery. The preoperative fibrinogen concentration is a limiting factor for postoperative hemostasis. Preoperative measurement of fibrinogen provides information about bleeding volume and transfusion requirements after CABG. Prophylactic fibrinogen infusion significantly reduces postoperative bleeding without clinical adverse events. Infusion of 2g fibrinogen to cardiac surgery patients results in no or minimal changes in biomarkers reflecting coagulation and platelet function.

Key words: inflammatory response, CPB, fibrinogen, bleeding, CABG, hemostasis