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Full Length Article

Rational and timely haemostatic interventions following cardiac surgery - coagulation factor concentrates or blood bank products

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ABSTRACT

Background: Cardiac surgery may cause a serious coagulopathy leading to increased risk of bleeding and transfusion demands. Blood bank products are commonly first line haemostatic intervention, but has been associated with hazardous side effect. Coagulation factor concentrates may be a more efficient, predictable, and potentially a safer treatment, although prospective clinical trials are needed to further explore these hypotheses. This study investigated the haemostatic potential of ex vivo supplementation of coagulation factor concentrates versus blood bank products on blood samples drawn from patients undergoing cardiac surgery.
Methods: 30 adults were prospectively enrolled (mean age = 63.9, females = 27%). Ex vivo haemostatic interventions (monotherapy or combinations) were performed in whole blood taken immediately after surgery and two hours postoperatively. Fresh-frozen plasma, platelets, cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate (PCC), and recombinant FVIIa (rFVIIa) were investigated. The haemostatic effect was evaluated using whole blood thromboelastometry parameters, as well as by thrombin generation.
Results: Immediately after surgery the compromised maximum clot firmness was corrected by monotherapy with fibrinogen or platelets or combination therapy with fibrinogen. At two hours postoperatively the coagulation profile was further deranged as illustrated by a prolonged clotting time, a reduced maximum velocity and further diminished maximum clot firmness. The thrombin lagtime was progressively prolonged and both peak thrombin and endogenous thrombin potential were compromised. No monotherapy effectively corrected all haemostatic abnormalities. The most effective combinations were: fibrinogen + rFVIIa or fibrinogen + PCC. Blood bank products were not as effective in the correction of the coagulopathy.
Conclusion: Coagulation factor concentrates appear to provide a more optimal haemostasis profile following cardiac surgery compared to blood bank products.

1. Introduction

Bleeding problems occurring during cardiac surgery are associated with increased morbidity and mortality [1,2]. Development of post cardiac coagulopathy is multifactorial, and haemostasis management is challenging. Current guidelines for management of bleeding recommend transfusion with human allogeneic blood products such as red blood cell concentrates, fresh frozen plasma, or platelets [3,4]. Unfortunately, transfusion of blood bank products is associated with serious side effects, such as increased mortality [5,6], nosocomial infections, multi organ failure, transfusion related acute lung injury and allergic or even anaphylactic reactions [7,8].

Cardiac surgery using extra corporeal circulation (ECC) induces a complex coagulopathy affecting several components of the coagulation system. Platelet counts and -functions are compromised and coagulation factors and natural anticoagulants are diminished due to haemodilution, loss, and consumption [9–11]. Fibrin polymerization is more impaired than total thrombin generation immediately after ECC [12], however two hours postoperative thrombin generation is also significantly impaired [13]. Approximately 12 h post-operatively the recorded abnormalities reverse to baseline [14]. Finally, acidosis, hypothermia and hyperfibrinolysis impair the function of the coagulation proteome and irreversibly reduce levels of fibrinogen and platelets [10,15].

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In addition to crude blood bank products, haemostatic remedies are available, including antifibrinolytics (tranexamic acid or aprotinin), fibrinogen (FIB), prothrombin complex concentrate (PCC) and recombinant factor VIIa (rFVIIa). A clinical trial of rFVIIa in cardiac surgery demonstrated a reduction in bleeding, transfusion requirement and need for re-exploration, however with an increased risk of thromboembolic complications [16]. So far, the potential efficacy and safety of PCC during cardiac surgery has not been investigated, however an emerging number of case reports and some retrospective studies have been published [17–20]. FIB has been shown to correct dilutional coagulopathy [21]. Retrospective studies and proof of principle clinical trials argue that FIB may be efficacious as first line treatment in management of critical bleeding during cardiac surgery [22–25].

It is a major concern that most blood bank products have not undergone mechanistic or experimental test of their haemostatic capacity and controlled prospective clinical trials are very sparse. It may be argued that both fresh frozen plasma and cryoprecipitate reveal limited and unpredictable haemostatic effect [26–28], and that the effect of platelets is highly dependent upon storage time of the product [29].

This present study investigated the haemostatic capacity of blood bank products as opposed to a panel of coagulation factor concentrates following cardiac surgery through ex vivo spiking experiments followed by global coagulation measurements using whole blood thromboelastometry profiles as well as thrombin generation characteristics. The following haemostatic agents were investigated: Fresh frozen plasma (FFP), platelets (PLT), cryoprecipitate (cryo), FIB, PCC and rFVIIa. We also addressed a rational timing of haemostatic interventions in relationship to the risk of development of post cardiac coagulopathy. We challenged the hypothesis that coagulation factor concentrates provide a significantly more potent haemostatic effect compared to FFP, cryo, or PLT following cardiac surgery.

2. Materials and methods

Blood samples were collected at three different time points: i) baseline = prior to surgery, ii) immediately after reversal of heparin (t = 0 h) and iii) two hours postoperatively (t = 2 h). Ex vivo interventions were performed at time points 0 h and 2 h.

2.1. Patients

Patients were recruited from the Department of Cardiothoracic and Vascular surgery, Aarhus University Hospital, Skejby, Denmark. All patients were adults (18 + years) and scheduled for elective surgery. Patients had discontinued platelet inhibitors five days prior to surgery, while any other anticoagulation treatment was withheld two days prior to surgery. Low molecular weight heparin could be continued until the day before surgery. Exclusion criteria were: previous heart surgery, hypothermia (<32 °C), known congenital bleeding disorders, endocarditis or anemia (defined as haemoglobin below 7.0 mmol/L). Patients with an abnormal pre-operative coagulation screen were not enrolled. Abnormal coagulation screen was concluded if the platelet count was below 150×10^9/L, fibrinogen concentration was below 1.87 g/L (5.5 μmol/L), INR was above 1.3 or aPTT above 45 s. The study was approved by the Danish Biomedical Ethics Committee (#M-2009-0078) and all patients provided informed consent. Patient demographics and perioperative characteristics are listed in Table 1.

Table 1
Demographics and perioperative data.

Female (n(%))	8 (27)
Age (mean (SD))	63.9 (±14)
Preoperative treatment aspirin (n(%))	19 (63)
Preoperative treatment clopidogrel (n(%))	2 (7)
Preoperative treatment with warfarin (n(%))	5 (17)
Euroscore (mean (SD))	4.1 (±3.8)
Ventricular function, ejection fraction > 50% (n(%))	26 (87%)
Renal insufficiency creatinine level > 130 mmol/L (n(%))	0 (0%)
Chronic obstructive pulmonary disease (n(%))	3 (10%)
Atrial flutter/fibrillation (n(%))	6 (20%)
Hypercholesterolemia (n(%))	21 (70%)
Surgical procedures:	
• Coronary artery bypass (n(%))	12 (40)
• Aortic valve replacement (n(%))	7 (23)
• Coronary artery bypass and aortic valve replacement (n%))	6 (20)
• Other (n(%))	5 (17)
Cardiopulmonary bypass time, min (mean (SD))	92 (±56)
Cross clamp time, min (mean (SD))	54 (±27)

2.2. Blood sampling

Preoperative blood samples were obtained from an antecubital vein, using a 21G butterfly needle, 3.2% citrate tubes (VenoSafe®, 3.4 ml, Terumo, Hatagaya, Japan) using minimal stasis. These were only used for the preoperative coagulation screen. All other blood specimens were withdrawn from a central venous line (BD Medical System, Becton Dickinson Critical Care System Ltd., Singapore) using the distal leg (all infusions were stopped and 10 ml of blood was discarded before the sample for analysis was taken). The blood sampling from the central venous line was performed consistently by only one person (author MT) in the entire project. This was done to avoid inter individual variance influencing results. Catheters were not flushed with heparin or used for heparin infusion.

After weaning off the ECC, blood samples were collected 5 min after heparin neutralisation by protamine sulphate. At the same time point an APTT measurement was done (Haemochron Junior®, ITC Medical, Edison, NJ).

2.3. Ex Vivo haemostatic interventions

The ex vivo haemostatic interventions were performed at two time points (0 h and 2 h). The interventions were:

- Monotherapy: FFP, PLT, cryo, FIB, PCC and rFVIIa
- Combination therapy: FFP + PLT, FFP + cryo, PCC + cryo, PCC + FIB, PCC + PLT, FIB + PLT and FIB + rFVIIa, double concentration of PCC + FIB and FIB + rFVIIa

Aliquots of 2000 μL whole blood were transferred to Eppendorf tubes and subsequently spiked with different haemostatic interventions.

Plasma and cryoprecipitate were obtained unfrozen from the local blood bank and stored at −80 degrees and thawed at 37 °C for 30 min prior to use. We randomly used plasma from two different donors while cryoprecipitate was produced from 2 pools. Freshly collected platelets were provided daily from the blood bank. Coagulation factor concentrates were purchased from respective manufacturers: Fibrinogen concentrate (Haemocomplettan®) and PCC (Beriplex®) from CSL Behring, Marburg, Germany, and rFVIIa (NovoSeven®) from Novo Nordisk A/S (Bagsværd, Denmark). All were reconstituted as recommended by the manufacturer and stored in small aliquots saved at −80 degrees until use. The dosages were according to package inserts while the dosage regime for blood bank products was calculated according to department guidelines and daily practice reflecting the recommendations by the Society of Thoracic Surgeons and The Society of Cardiovascular Anesthesiologists (3; 4). All medications and frozen blood products were thawed 30 min prior to use. Details on dosages are summarized in Table 2.

2.4. Medications

Unfractionated heparin (Heparin LEO®, Leo Pharma Nordic, Malmö, Sweden) was dosed using an initial bolus of 300 IU/kg followed by additional heparin to keep the target ACT above 400 s. Heparin was reversed