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Clinical Investigation

CLINICAL INVESTIGATION

Use of prothrombin complex concentrate for management of coagulopathy after cardiac surgery: a propensity score matched comparison to plasma

J. Fitzgerald[1], M. Lenihan[1], J. Callum[2], S. A. McCluskey[1,3], C. Srinivas[1,3], A. van Rensburg[1,3] and K. Karkouti[1,3,*]

[1]Department of Anesthesia and Pain Management, Toronto General Hospital, University Health Network, University of Toronto, Toronto, ON, Canada, [2]Department of Clinical Pathology, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada and [3]Peter Munk Cardiac Centre, Toronto General Hospital, University Health Network, Toronto, ON, Canada

*Corresponding author. E-mail: keyvan.karkouti@uhn.ca

Abstract

Background: An important cause of coagulopathy in cardiac surgery is impaired thrombin generation. While plasma is often used to correct this element of the coagulopathy, studies *in vitro* suggest that prothrombin complex concentrates (PCCs) might be more effective. Comparative data, however, are scant.

Methods: We compared the outcomes of those who received only plasma with those who received PCCs (with or without plasma) for management of coagulopathy in patients who underwent cardiac surgery with cardiopulmonary bypass at a single institution from 2012 to 2016. Propensity score matching was used to obtain between-group balance. Primary outcome was avoidance of perioperative red cell transfusions. Other outcomes were incidence of massive transfusion (more than nine red cell units), refractory bleeding (requiring factor VIIa), and adverse events.

Results: Of 6362 patients, 1151 (18.2%) received plasma without any PCCs, and 204 (3.2%) received PCCs, either with (n=125) or without plasma (n=79). Overall, patient risk-profile was higher in the PCCs group. In a well-balanced propensity score match that included 117 patients per group, the odds ratio (OR) for red cell avoidance was 2.4-fold [95% confidence interval (CI) 1.2–4.8] higher in the PCCs group. Massive transfusion (OR 0.58; 95% CI 0.33–1.0) and refractory bleeding (OR 0.49; 95% CI 0.24–1.03) incidences were almost significantly lower in the PCCs group. The adverse event profiles were similar.

Conclusions: Our exploratory study suggests that the use of PCCs as part of a multifaceted coagulation management strategy may have blood-sparing effects. Their incorporation into clinical practice, however, must await determination of their risk-benefit profile via multicentre randomised trials.

Keywords: cardiac surgery; surgical blood loss, coagulopathy

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Editor's key points

- It is unclear whether prothrombin complex concentrates are as effective as frozen plasma to correct coagulopathy in cardiac surgery.
- This retrospective, propensity score matched study showed that the use of prothrombin complex concentrates was associated with a lower risk for red blood cell transfusion compared with frozen plasma treatment.
- The use of prothrombin complex concentrate was associated with a similar safety profile as for frozen plasma transfusion.
- Correction of coagulopathy by prothrombin complex concentrate may have blood-sparing effects when compared with frozen plasma transfusion; multicentre randomised controlled trials are required to confirm this benefit.

Cardiac surgery requiring the use of cardiopulmonary bypass (CPB) is frequently complicated by coagulopathy that can lead to excessive haemorrhage and blood transfusions, potentially worsening patients' prognosis.[1–3] As the causes of coagulopathy are often multifactorial, clinicians use an array of therapies to control the haemorrhage, including antifibrinolytics to inhibit fibrinolysis, platelet transfusions to treat thrombocytopenia and platelet dysfunction, cryoprecipitate or fibrinogen concentrate to increase fibrinogen concentrations, and frozen plasma or prothrombin complex concentrate (PCC) to replenish depleted clotting factors and to improve thrombin generation.[1,4]

Concerning the latter, impaired thrombin generation is increasingly recognised to be an important contributor to the coagulopathy of cardiac surgery.[5,6] While plasma may effectively restore thrombin generation and is an integral part of transfusion algorithms,[4,7] it has important shortcomings.[8] It requires ABO blood group compatibility matching and thawing, which can delay therapy. It can also lead to adverse events including allergic reactions, transfusion-related acute lung injury (TRALI), transfusion associated circulatory overload (TACO), transmission of infectious diseases, and thromboembolic events.[8,9] Moreover, as large volumes (10–15 ml kg^{-1}) of plasma are needed to effectively raise thrombin generation,[7] it can lead to substantial haemodilution resulting in additional red cell transfusions.

PCCs, which are purified products that are prepared from plasma and contain the procoagulant factors II, VII, IX, and X, the anticoagulant proteins C and S, and small amounts of heparin,[4] have several potential advantages to plasma. Unlike plasma, they do not require ABO compatibility matching or thawing, and have a substantially lower risk for TRALI and TACO.[9] Moreover, *in vitro* studies suggest that PCCs may be more effective than plasma in enhancing thrombin generation after cardiac surgery.[7] In contrast, as PCCs do not contain the full, balanced complement of procoagulants and anticoagulants that are present in plasma, they may be less effective or carry a higher risk for thrombotic events and acute kidney injury (AKI) than plasma for management of coagulopathy.[10,11]

Despite the potential advantages of PCCs over plasma, there are few direct comparisons between the two therapies for managing the coagulopathy of cardiac surgery. Nevertheless, at our institution, PCC is being increasingly used to supplement or supplant plasma in bleeding cardiac surgical patients, providing us with a cohort of patients who received PCC, plasma, or both during their surgery. Using this cohort, we conducted this retrospective observational study to compare the outcomes of patients who received only plasma with those who received PCCs with or without additional plasma as part of their coagulation management, using propensity score matching to control for important between-group imbalances. We hypothesised that the use of PCC would be associated with reduced transfusion needs and massive transfusion without increasing the risk of thromboembolic complications and AKI.

Methods

This was a retrospective observational study that included data collected on cardiac surgery patients operated from January 1, 2012 to December 30, 2016 at the Toronto General Hospital, a teaching hospital affiliated with the University of Toronto (Toronto, ON, Canada). A full range of adult cardiac surgical procedures are performed at this hospital. After approval from the institutional research ethics board, which waived the need for informed consent, patient data were obtained from institutional databases. We included all patients who underwent cardiac surgery with CPB, but excluded those in whom transfusion data were missing. For patients who had multiple operations requiring CPB during the study period, only data from their first surgery were used. Full-time research personnel blinded to the objectives of this study adjudicated all outcomes from patients' records.

Clinical practice

Clinical practice has been previously described.[12] CPB circuits were phosphorylcholine coated and the typical prime included 1000 ml of crystalloid (with mannitol and heparin added). Anticoagulation for CPB was achieved with a heparin bolus of 400 IU kg^{-1} with additional doses as required to maintain the activated clotting time >480 s. During CPB, shed pericardial blood was salvaged into the cardiotomy suction reservoir and re-infused via the CPB circuit for as long as patients were anticoagulated. Heparin was reversed with protamine (1 mg per 100 IU of the initial bolus of heparin). Cell salvage was available for all patients and was used to recover lost blood before and after anticoagulation at the discretion of the clinical team. Tranexamic acid (various dosing strategies but typical total dose was 50–100 mg kg^{-1}) was routinely administered to patients if there were no absolute contraindications. Institutional allogeneic red cell transfusion criteria included a haemoglobin <7 g dl^{-1} during CPB, <8 g dl^{-1} post-CPB, and <9 g dl^{-1} in unstable or bleeding patients. Autologous red cell pre-donation was not used.

Management of post-CPB coagulopathy was guided by a combination of whole-blood point-of-care assays (viscoelastic and platelet function measures, performed when temperature reached 36°C at the end of CPB) and standard laboratory assays (complete blood count, prothrombin time, international normalised ratio (INR), partial thromboplastin time, and fibrinogen concentration performed soon after protamine administration), as previously described.[13,14] Administration of plasma (usually 10–15 ml kg^{-1} in two to four unit increments) and PCC (Octaplex, Octapharma, Toronto, ON,