Prothrombin complex concentrates in cardiac surgery: where are we?

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Purpose of review
Major bleeding in cardiac surgery is commonly encountered, and, until recently, most frequently managed with fresh frozen plasma (FFP). However, a Cochrane review found this practice to be associated with a significant increase in red blood cell (RBC) transfusions and costs. These findings have led to off-label uses of prothrombin complex concentrates (PCCs) in cardiac surgery. The purpose of this review is to compare and contrast the use of FFP and PCC, review the components, limitations and risks of different types of PCCs, and discuss the latest evidence for the use of PCC versus FFP in cardiac surgery.

Recent findings
A recent review and meta-analysis suggests that PCC administration in cardiac surgery is more effective than FFP in reducing RBC transfusions and costs.

Summary
The current data supports the use of 4F-PCC instead of FFP as the primary hemostatic agent in cases of major bleeding in cardiac surgery. The use of PCCs is associated with reduced rates of RBC transfusions while maintaining a favorable safety profile. Clear advantages of PCC over FFP include its smaller volume, higher concentration of coagulation factors and shorter acquisition and administration times.

Keywords
cardiac surgery, coagulopathy, hemostasis, major bleeding, prothrombin complex concentrates

INTRODUCTION

Major bleeding in cardiac surgery has an incidence of 2–15% and is associated with significant morbidity and mortality [1–3]. The cause of bleeding may be surgical and/or coagulopathic (Fig. 1) [4]. The incidence of coagulopathy after cardiopulmonary bypass has been reported to be approximately 11% but remains variable [1,4].

Administration of clotting factors as a management strategy for obtaining hemostasis in the presence of major bleeding is common. Fresh frozen plasma (FFP) is a common option to achieve hemostasis, employed in approximately 20–30% of cases [5]. Nevertheless, a Cochrane review found that FFP administration was associated with a significant increase in RBC transfusions and concluded there was not enough evidence to support the prophylactic administration of FFP to patients without coagulopathy undergoing elective cardiac surgery [6]. Further, the review reported that there was insufficient evidence regarding the use of FFP for treatment of patients with coagulopathies or those who are undergoing emergency surgery. These findings, alongside FFP's limitations as discussed below, have fueled research on the utility, effectiveness, and safety of prothrombin complex concentrates (PCC) in cardiac surgery. A recent review and meta-analysis by Roman *et al.* suggested that PCC administration in cardiac surgery is more effective than FFP in reducing perioperative RBC transfusions, with a 10% overall decrease in the rate of RBC transfusion [odds ratio (OR) 2.22; 95% confidence interval (CI) 1.45–3.40] [7]. Concomitantly, the authors highlighted that the fluid overload associated with the administration of FFP transfused led to increased hospital mortality, nonhome discharge, and ICU admittance. This combination of factors resulted in PCCs being more cost-effective than FFP.

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KEY POINTS

- 4F-PCC reverses coagulopathy quicker and with less bleeding than FFP.
- Clear advantages of PCC over FFP include its smaller volume, higher concentration of coagulation factors and shorter acquisition and administration times.
- 4F-PCC administration in cardiac surgery should be weight-based.
- 4F-PCC administration is well tolerated but may be associated with an increased risk of thromboembolism and acute kidney injury.
- Larger randomized trials are needed to substantiate PCC use guidelines in cardiac surgery.

In this review, we compare and contrast FFP and PCC, review the components, limitations and risks of different types of PCCs, and discuss the latest evidence for the use of PCC versus FFP in cardiac surgery.

FRESH FROZEN PLASMA VERSUS PROTHROMBIN COMPLEX CONCENTRATES

Although FFP and PCC are both components of blood that are administered intravenously, there are stark differences between the two products (Table 1). FFP has a wider variety of coagulation factors than PCC [5]. The use of FFP is limited by procurement time, risk of volume overload and potential for transfusion reactions [8]. PCCs, on the other hand, are stored at room temperature, administered in smaller volumes and are more rapidly infused when compared with FFP [9]. PCCs are constituted primarily of high concentrations of coagulation factors II, VII, IX, and X. The absence of substantial quantities of fibrinogen may lead to increased cryoprecipitate or fibrinogen concentrate utilization in patients treated with PCC when compared FFP but is not associated with an increased number of RBC transfusions ($n = 119$ with PCC and $n = 416$ with FFP, 67.2 versus 87.5%, adjusted OR 0.319, 95% CI 0.136–0.752) [10].

PROTHROMBIN COMPLEX CONCENTRATE PREPARATION AND DOSING

PCCs are derived from large pools of human plasma and are concentrated with coagulation factors II, IX, and X, with or without significant levels of factor VII [11]. PCCs were initially developed as a source of factor IX for the management of patients with hemophilia B, thus their dosing is expressed in units of factor IX [12]. They have a final overall clotting factor concentration approximately 25 times higher than normal FFP [13]. Several formulations of PCCs exist and are available in both nonactivated and activated forms [12]. Three-factor PCC (3F-PCC) and four-factor PCC (4F-PCC) are nonactivated formulations, meaning they contain a small amount of unfractionated heparin and/or antithrombin to prevent clotting factor activation [14]. Activated PCCs contain primarily activated factor VII. The major difference between 3F-PCC and 4F-PCC is that 3F-PCC does not contain a significant amount of factor VII, proteins C and S, whereas 4F-PCC does. Given the additional coagulation factors, 4F-PCC is the preferred method for the urgent reversal of acquired coagulation factor deficiency induced by vitamin K antagonists (VKA) as it has been found to lead to a more significant reduction in INR compared with 3F-PCC in VKA-associated bleeding and in trauma patients [12,15,16]. Urgent reversal of VKA is the only FDA-approved indication for 4F-PCC, whereas 3F-PCC are approved for the prevention and control of bleeding in patients with Factor IX deficiency because of hemophilia B. Other uses of these products are off-label.

HEMOSTATIC ASSESSMENT

Prior to utilization of hemostatic agents, assessment of the cause of major bleeding is critical. Assays

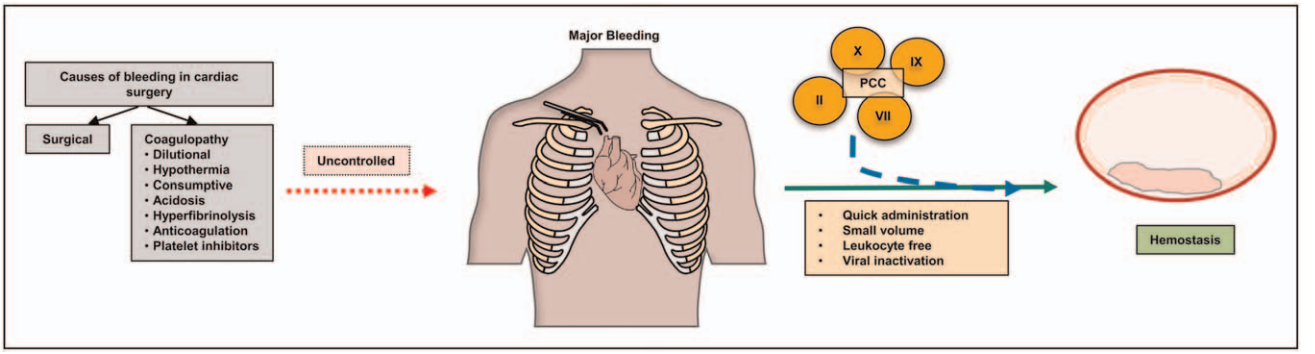

FIGURE 1. Mechanism of major bleeding in cardiac surgery.

Table 1. Fresh frozen plasma versus prothrombin complex concentrates

	Fresh frozen plasma	Prothrombin complex concentrates
Preparation	Human plasma	Human plasma
Components	All clotting factors, fibrinogen, plasma proteins, electrolytes, proteins C, S, antithrombin, tissue factor inhibitor and added anticoagulants	Factors II, VII, IX, X, proteins C and S Heparin
Storage	Frozen	Room temperature
Advantages	Wider variety of factors	Virally inactivated 25× more concentrated Shorter procurement and administration time More cost-effective
Disadvantages	Long procurement time Larger volume Longer administration time Risk of transfusion reaction Can transmit disease	Increased risk of thromboembolism and kidney injury Contraindicated in patients with HIT

HIT, heparin-induced thrombocytopenia.

performed on plasma alone including the activated partial thromboplastin time (aPTT), prothrombin time (PT) and international normalized ratio (INR) have long turn-around times and do not reliably correlate with clinically relevant coagulopathies. The use of real-time monitoring with viscoelastic hemostatic assays like thromboelastography (TEG) and rotational thromboelastometry (ROTEM) is increasingly common, with trials demonstrating decreased blood product utilization in viscoelastic assay-guided resuscitation [1,4,17]. These viscoelastic assays are performed on whole blood, can be performed during cardiopulmonary bypass and report to the endpoints of fibrin polymerization and platelet–fibrin interaction that are not reflected in either PT or aPTT [1].

PROTHROMBIN COMPLEX CONCENTRATES AND FRESH FROZEN PLASMA IN CARDIAC SURGERY

Several randomized controlled trials (RCT) comparing PCCs and FFP in bleeding cardiac patients have been performed (Table 2). A small RCT comparing PCCs and FFP in patients undergoing heart surgery with cardiopulmonary bypass by Demeyere *et al.* [18] showed that PCCs reversed coagulopathy quicker and with less bleeding than FFP (7/16 patients with PCC versus 0/15 patients with FFP, $P = 0.007$). The use of PCCs in isolated coronary artery bypass grafting (CABG) may reduce the need for RBC transfusion ($n = 119$ with PCC and $n = 416$ with FFP, 67.2 versus 87.5%, adjusted OR 0.319, 95% CI 0.136–0.752) [10]. In a parallel-group randomized pilot study to determine the proportion of patients who received PCC and then required FFP, Karkouti *et al.* [19▪▪] analyzed data from 101 patients who required coagulation factor replacement for bleeding during cardiac surgery. Differences in the RBC transfusions during the first 24 h after surgery were not statistically significant and adverse event profiles were similar ($n = 54$ with PCC, 47 with FFP, 95% CI 0.47–0.99, $P = 0.05$). Nevertheless, they found that patients treated with PCC had a 42% lower exposure to allogeneic blood components (95% CI 0.23–0.55; $P < 0.001$), had less blood loss (at 12 h, $P < 0.001$; and 24 h, $P < 0.001$) and required fewer RBC transfusions than those treated with FFP (within 24 h after cardiopulmonary bypass, 95% CI 0.36–0.78, $P = 0.001$; within 24 h after start of intervention, 95% CI 0.28–0.76, $P = 0.003$; and within 7 days after cardiopulmonary bypass, 95% CI of 0.48–0.92, $P = 0.01$). The PROPHESY trial was a single-site pilot RCT to determine the recruitment rate for a larger trial comparing the impact of PCC and FFP on the hemostatic capacity of bleeding patients, and assess trial procedures, protocol compliance and safety outcomes [5]. Their protocol demonstrates the feasibility of a RCT in patients not taking VKA who develop bleeding while undergoing cardiac surgery and list a number of learning points for future studies [5]. Overall, they found higher doses of PCC and FFP achieved better hemostatic correction compared with lower doses without any safety concerns [20▪▪]. To our knowledge, no study has looked at the efficacy of 4F-PCC in coagulopathy following mechanical heart valve implantation. However, Fariborz Farsad *et al.* compared the efficacy of 3F-PCC and FFP in adult patients with mechanical heart valves who were undergoing warfarin therapy and required reversal, and found that PCCs were more effective than FFP in correcting the INR at 16 and 48 h post infusion (PCC group, $n = 25$ versus FFP group, $n = 25$, $P = 0.01$) [21]. Limited data exists in pediatric cardiac surgery, with few small studies [22]. However, a contemporary

Table 2. Published studies comparing prothrombin complex concentrates and fresh frozen plasma in cardiac surgery

Reference	Method	Intervention	PCC *n*	Type of cardiac surgery	Main outcome/measures
[10]	Comparative analysis	4F-PCC versus FFP	119	Isolated CABG	PCC may reduce the need of blood transfusion
[18]	RCT	4F-PCC versus FFP	20	Mixed	PCC reverses coagulopathy quicker and with less bleeding than FFP
[19▪▪]	RCT	4F-PCC versus FFP	54	Mixed	Patients treated with PCC had a 42% lower exposure to allogeneic blood components, had less blood loss and required fewer red blood cell transfusions than those treated with FFP group
[20▪▪]	RCT	4F-PCC versus FFP	25	Mixed	Higher doses of PCC and FFP achieved a better overall hemostatic correction compared with lower doses without any safety concerns
[21]	RCT	3F-PCC versus FFP	25	Mechanical heart valves	PCCs are more effective than FFP in correcting the INR

3F-PCC, 3-factor prothrombin complex concentrates; 4F-PCC, 4-factor prothrombin complex concentrates; CABG, coronary artery bypass grafting; FFP, fresh frozen plasma; RCT, randomized control trial.

clinical trial of PCCs in pediatric cardiac surgery is ongoing (NCT05020483).

Given emerging practice patterns, the Transfusion and Haemostasis Subcommittee of the European Association of Cardiothoracic Anaesthesiology published a consensus statement on the use of 4F-PCC for cardiac and noncardiac surgical patients [23▪▪]. For the acute reversal of VKA therapy, hemostatic resuscitation, and reversal of direct oral anticoagulants when no specific antidote is available, they recommended the administration of an initial bolus of 25 IU/kg of 4F-PCC. In patients with a high risk for thromboembolic complications, such as those undergoing cardiac surgery, an initial dose of 12.5 IU/kg could be considered. A second dose may be indicated if coagulopathy persists and coagulation factor administration is indicated based on viscoelastic hemostatic assays.

With the multiple options for resuscitation of bleeding patients, use of a hemostatic checklist has promise for daily practice. Ali *et al.* developed a hemostatic checklist for use prior to insertion of sternal wires and chest closure, to decrease the risk of major postoperative bleeding requiring re-exploration. The checklist is divided into two sections: surgical sites and coagulation status [24▪]. The checklist can be completed in approximately 1 min if no bleeding is identified and was associated with decreased rates of postoperative bleeding and re-exploration rates and a total cost savings of approximately $5 000 000 over a 2-year period.

SPECIAL CONSIDERATIONS IN CARDIAC SURGERY

VKA like warfarin continue to be the first-line therapy for patients with mechanical heart valves and mechanical cardiovascular support, such as left ventricular assist devices (LVADs) [9]. Preoperative INR should be determined as reversal of VKA may be required in emergency invasive procedures or cases where severe bleeding is anticipated. Although vitamin K supplementation in these scenarios is often used to counteract the effect of VKA, this approach may take 12–24 h to normalize INR and depends on route of administration [25]. Immediate reversal may be achieved by replacing deficient clotting factors. In a recent review and meta-analysis, Brekelmans *et al.* [26] found that 4F-PCC was a more rapid and effective option to normalize INR in patients with VKA-associated bleeding than in the FFP group. A small RCT comparing PCC and FFP for the urgent reversal of warfarin in patients with mechanical heart valves found a similar result [21]. However, Brekelmans *et al.* [26], found mortality rates in patients receiving PCCs were comparable to that of patients receiving FFP.

LIMITATIONS AND RISKS

The use of PCC has limitations. It is absolutely contraindicated in patients with known anaphylactic/anaphylactoid reactions, patients with disseminated intravascular coagulation and patients with known heparin-induced thrombocytopenia [14].

Thromboembolism

The concentration of procoagulant factors contained in PCC raises concerns regarding the risk of thromboembolic events. A large, 15-year pharmacovigilance study found the risk of thromboembolic events to be as low as 1 in 31 000 but was variable and dependent on patient comorbidities

[27]. Two recent systematic review and meta-analyses examining the effects of 4F-PCC in reversal of VKA-associated bleeding showed that 4F-PCC did not increase the risk of thromboembolic complications and mortality [26,28]. In cardiac patients, no additional risks of thromboemobolic events were observed, with the authors speculating that the addition of anticoagulant proteins C and S in contemporary PCC formulations decreases risks of thromboembolism compared with historical formulations [7]. Studies performed since these reviews were performed support these conclusions and report low rates of thromboembolic complications [5,19▪▪,23▪▪,29].

Acute kidney injury

Trials have intermittently raised concerns regarding acute kidney injury (AKI) in patients receiving PCC. A retrospective study of 3454 patients undergoing cardiac surgery with decreased postoperative blood loss and RBC transfusion requirements but a higher risk of postoperative AKI [30]. A comparative analysis of 416 patients who received FFP and 119 who received PCC with or without FFP after isolated CABG showed that the use of PCC increased the risk of acute kidney injury (41.4 versus 28.2%, adjusted OR 2.300, 95% CI of 1.203–4.400) but not acute kidney injury stage 3 when compared with FFP (6 versus 8%, OR 0.850, 95% CI 0.258–2.796) [10]. Meanwhile, a nonsignificant trend towards increased risk of renal replacement therapy was found in the review and meta-analysis by Roman *et al.* [7]. The mechanism of AKI in patients receiving PCC is unclear, as thromboembolic risk was not observed in the trials [30]. Instead, it is hypothesized that the smaller volume administered with PCC may result in a more hypovolemic fluid balance, thereby increasing AKI risk [31].

CONCLUSION

In conclusion, the current data, though limited, supports the use of 4F-PCC instead of FFP as the primary hemostatic agent in cases of major bleeding in cardiac surgery. The use of PCCs is associated with reduced rates of RBC transfusions while maintaining a favorable safety profile. Clear advantages of PCC over FFP include its smaller volume, higher concentration of coagulation factors and shorter acquisition and administration times. A timely and systematic assessment of bleeding with point-of-care viscoelastic hemostatic assays is of utmost importance in guiding and targeting the choice of agents. If warranted, 4F-PCC administration should be weight-based with dosing based on patient comorbidities that may increase the risk for complications, such as chronic kidney disease and thrombogenic disorders like cancer. Implementation of a hemostatic checklist may be clinically useful in guiding therapy and may lessen overall financial costs. Nevertheless, larger randomized trials are needed to substantiate PCC use guidelines in cardiac surgery.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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