The association of prothrombin complex concentrates with postoperative outcomes in cardiac surgery: an observational substudy of the FIBRES randomized controlled trial

Association entre les concentrés de complexe prothrombinique et les issues postopératoires en chirurgie cardiaque : une sous-étude observationnelle de l'étude randomisée contrôlée FIBRES

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Abstract

Purpose The mainstay of therapy for coagulation factor deficiency in cardiac surgical patients is frozen plasma (FP); however, prothrombin complex concentrates (PCCs) may offer logistical and safety advantages. As there is limited comparative evidence, we conducted this study to explore the association of comparable PCC or FP doses with transfusion and outcomes.

Methods This was a post hoc analysis of a multicentre randomized trial comparing fibrinogen concentrate with cryoprecipitate (FIBRES trial) in bleeding cardiac surgical patients. This analysis included 415 patients who received only PCC (n = 72; 17%) or only FP (n = 343; 83%) for

factor replacement. The main outcomes of interest were red blood cell (RBC) and platelet transfusion within 24 hr of cardiopulmonary bypass. Secondary outcomes included postoperative adverse events. Associations were examined by hierarchical generalized estimating equation models adjusted for demographic and surgical characteristics.

Results The median [interquartile range (IQR)] PCC dose was 1,000 [1,000–2,000] units, while the median [IQR] FP dose was 4 [2–6] units. Each unit of FP was independently associated with increased adjusted odds of RBC (1.60; 95% confidence interval [CI], 1.36 to 1.87; P < 0.01) and platelet transfusion (1.40; 95% CI, 1.15 to 1.69; P < 0.01) while each 500 units of PCC was independently associated with reduced adjusted odds of RBC (0.67; 95% CI, 0.50 to 0.90; P < 0.01) and platelet transfusion (0.80; 95% CI, 0.70 to 0.92; P < 0.01). Adverse event rates were comparable.

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Conclusions *In cardiac surgical patients with post-cardiopulmonary bypass bleeding, PCC use was associated with lower RBC and platelet transfusion than FP use was. Prospective, randomized clinical trials comparing FP with PCC in this setting are warranted.*

Résumé

Objectif *Le pilier du traitement du déficit en facteur de coagulation chez les patients de chirurgie cardiaque est le plasma congelé (PC); cependant, les concentrés de complexe prothrombinique (CCP) peuvent offrir des avantages en matière de logistique et de sécurité. Comme il existe peu de données probantes comparatives, nous avons réalisé cette étude pour explorer l'association de doses comparables de CCP ou de PC avec la transfusion et les issues postopératoires.*

Méthode *Il s'agit d'une analyse post-hoc d'une étude randomisée multicentrique comparant le concentré de fibrinogène au cryoprécipité (étude FIBRES) chez des patients avec hémorragies en chirurgie cardiaque. Cette analyse a inclus 415 patients qui n'ont reçu que du CCP (n = 72; 17 %) ou du PC (n = 343; 83 %) pour le remplacement des facteurs. Les principaux critères d'évaluation étaient la transfusion d'érythrocytes et de plaquettes dans les 24 heures suivant la circulation extracorporelle (CEC). Les critères d'évaluation secondaires comprenaient les événements indésirables postopératoires. Les associations ont été examinées par des modèles d'équation d'estimation généralisée hiérarchiques ajustés en fonction des caractéristiques démographiques et chirurgicales.*

Résultats *La dose médiane de CCP [écart interquartile (ÉIQ)] était de 1000 [1000 à 2000] unités, tandis que la dose médiane [ÉIQ] de PC était de 4 [2-6] unités. Chaque unité de PC était indépendamment associée à une augmentation de la probabilité ajustée de transfusion d'érythrocytes (1,60; intervalle de confiance [IC] à 95 %, 1,36 à 1,87; P < 0,01) et de plaquettes (1,40; IC 95 %, 1,15 à 1,69; P < 0,01), alors que chaque 500 unités de CCP étaient indépendamment associées à une réduction de la probabilité ajustée de transfusion d'érythrocytes (0,67; IC 95 %, 0,50 à 0,90; P < 0,01) et de plaquettes (0,80; IC 95 %, 0,70 à 0,92; P < 0,01). Les taux d'événements indésirables étaient comparables.*

Conclusion *Chez les patients de chirurgie cardiaque présentant un saignement post-CEC, l'utilisation de CCP a été associée à un taux de transfusion plus faible d'érythrocytes et de plaquettes que lors de l'utilisation de PC. Des études cliniques randomisées prospectives comparant le PC au CCP dans ce type de contexte sont nécessaires.*

Cardiac surgery accounts for a significant proportion of all allogeneic blood components transfused in North America, with approximately 20–40% of patients undergoing coronary artery bypass grafting requiring transfusion.[1] Excessive bleeding and transfusions in the context of cardiac surgery are independently associated with adverse perioperative outcomes, including prolonged length of stay, increased costs, end organ complications, and mortality.[2] Indeed, there appears to be a dose–response relationship between the volume of blood components transfused and adverse outcomes.[2]

The causes of coagulopathy are multifactorial and include thrombocytopenia and platelet dysfunction, decreased fibrinogen concentration, impaired thrombin generation, and depletion of coagulation factors.[3,4] Regarding the latter, the average patient undergoing cardiac surgery with cardiopulmonary bypass (CPB) has a 40–50% drop in coagulation factor levels and a > 50% drop in thrombin generation capacity, suggesting that it is an important cause of coagulopathy.[5–7]

Frozen plasma (FP) is the treatment of choice in bleeding patients with coagulation factor deficiency and is administered to approximately 15% of all patients undergoing cardiac surgery in the United States.[8,9] Frozen plasma transfusion, however, may contribute to hemodilution and higher red blood cell (RBC) transfusion volume, and carries significant risks, including transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI), two of the most common causes of death from transfusion.[9]

In contrast, four-factor prothrombin complex concentrates (PCCs), which are derived from pooled plasma and contain the coagulation factors II, VII, IX, and X, may have safety advantages over FP as they undergo pathogen reduction and have a lower risk of causing TRALI. Moreover, they do not require ABO matching, are easily reconstituted, and are concentrated, allowing for rapid administration and reducing the risk of TACO. In many jurisdictions, PCCs are approved for the urgent reversal of vitamin K antagonists such as warfarin.[3] Their use is increasingly recognized by professional organizations as a viable treatment option for coagulation factor replacement in the setting of perioperative bleeding while acknowledging the limited safety data available.[10]

While randomized controlled trials are the ideal way to directly compare the safety and efficacy of these

hemostatic components, observational studies can provide important information. Prior observational studies have suggested that PCC use is associated with less transfusion but have generally not compared similar incremental doses of PCC and FP and have provided limited information on patient outcomes. Therefore, we conducted this post hoc analysis with the aim of evaluating the association between PCC or FP administration and blood component transfusion avoidance in a cohort of cardiac surgical patients experiencing clinically significant post-CPB bleeding, accounting for variable dosing and potential confounders. We also examined the association between PCC or FP and important perioperative safety outcomes, including renal and thromboembolic events.

Methods

Data source and population

This was a retrospective analysis of data obtained from the Fibrinogen Replacement in Surgery (FIBRES) randomized controlled trial.[11,12] From 10 February 2017 to 1 November 2018, FIBRES recruited 827 patients across 11 centres in Canada. The primary aim of FIBRES was to determine if fibrinogen concentrate was noninferior to cryoprecipitate for the treatment of bleeding related to acquired hypofibrinogenemia after cardiac surgery.[12] Research ethics board approval was obtained at each site prior to trial initiation, with ethics approval being obtained for this substudy from the University Health Network (2 June 2020; amendment 16-5636.15). Manuscript presentation is consistent with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.[13]

The FIBRES trial included adult patients undergoing CPB and requiring fibrinogen replacement for clinically significant post-bypass bleeding.[11] Patients were excluded if they had received fibrinogen concentrate or cryoprecipitate within 24 hr of surgery, if there was a history of severe allergic reaction to either product, if they refused blood components for religious or other reasons, if plasma fibrinogen was greater than 3.0 g·L^{-1} within 30 min of treatment order, and if there was known pregnancy.[11] The primary outcome of FIBRES was blood components administered during the immediate 24 hr post CPB, with trained blinded assessors prospectively collecting data relevant to outcomes for up to 28 days after surgery. All adverse events were classified using the Medical Dictionary for Regulatory Activities (version 21.1) system of nomenclature.[11] Of the 827 patients eligible for inclusion in FIBRES, 735 were randomized.

Only those receiving either PCC alone or FP alone were included in this substudy.[12]

Predictors and outcomes

The primary predictors of interest were dose of PCC or FP administered from the time of separation of CPB to 24 hr after. In addition to a dose-based comparison of PCC with FP, the two groups (patients receiving PCC compared with patients receiving FP) were compared. The main outcomes of interest were RBC and platelet transfusion within 24 hr of CPB. There are two types of platelets issued in Canada (75% standard buffy coat pools from four allogeneic donors and 25% apheresis units from a single allogeneic donor). Both types were counted as a four-unit transfusion.[12] Other measured outcomes included perioperative morbidity, defined as follows: 1) thromboembolic and ischemic events within 28 days of CPB—deep venous thrombosis, pulmonary embolism, peripheral ischemia, bowel ischemia, ischemic optic neuropathy, occlusion of grafts or arteries, myocardial infarction, stroke, transient cerebral ischemic events, and spinal cord ischemia and 2) renal adverse events within seven days—acute kidney injury (AKI) defined as stage 1 or higher as per the Kidney Disease: Improving Global Outcomes 2012 guideline, consistent with RIFLE classification "risk for AKI" or higher.[14,15] Preoperative estimated glomerular filtration rate was calculated using the CKD-Epi formula.[16] Intensive care unit (ICU) and hospital length of stay were compared between groups.

Statistical analysis

Continuous variables are reported as means and standard deviations (SDs) or medians and interquartile ranges [IQRs] where indicated. Categorical variables are reported as frequencies or percentages. Comorbidities, procedure types, demographic characteristics, and other important potential confounding variables were compared between patients who received PCC or FP using the Wilcoxon rank-sum test to compare medians, the Chi square test for contingency table data with cell counts equal to or greater than 5, or Fisher's exact test for contingency table data with cell counts less than 5. The association between dose of PCC and FP administered and units of RBC transfused was visually examined using boxplots.

For binary outcomes, we developed unadjusted and adjusted multivariable logistic regression models. For count data, we constructed unadjusted and adjusted negative binomial regression models. Clustering by centre was taken into account using mixed models that accounted for clustering. Models were examined to ensure model fit and assumptions were met. For each logistic

regression model, we used global measures of model fit based on information criterion statistics. Model discrimination was assessed using the C-statistic We assessed model calibration using the Hosmer–Lemeshow test by comparing the observed events within prespecified risk groupings (deciles of risk), with higher P values indicating better calibration. For multilevel models accounting for clustering by site, QIC statistics were examined.

We treated the PCC dose as a continuous variable to obtain a risk ratio for outcomes per clinically relevant dose of PCC administered (for example, for every 500 U of PCC administered). We built a second series of models where FP was treated as a continuous variable to obtain an adjusted risk ratio (aRR) per clinically relevant dose of FP administered (for example, per one unit of FP transfused), using the same rationale as above. In selecting comparator doses, we aimed to maintain uniformity with dosing guidelines for PCC in the context of licensed indications, such as for reversal of vitamin K antagonists, where for mild elevations in the international normalized ratio (INR), a dose of 25 IU·kg^{-1} is typically used.[17] Additionally, we compared the two groups (patients receiving PCC vs patients receiving FP) with each other in terms of transfusion and safety outcomes.

Important confounders were specified a $priori$ based on factors reported to impact postoperative events,[18,19] as well as the FIBRES study arm. Models were adjusted for preoperative creatinine clearance, hemoglobin level, body mass index, age, sex, presence of heart failure, critical preoperative status of the patient, surgical complexity (with complex surgery defined as procedures other than coronary artery bypass grafting only, single valve only, or repair of atrial septal defect only), and surgical urgency (elective or non-elective status). Models for length of stay outcomes were additionally adjusted for preoperative ICU or hospital admission, preoperative myocardial infarction, and chronic lung disease.[20] All clinically important variables showed no multi-collinearity and were entered into the multivariable regression models.

Special data handling methods were not employed for missing data, as generally there were minimal missing data in the FIBRES data set ($< 5\%$).[21] We used SAS University Edition (SAS Institute, Inc, Cary, NC, USA) for all statistical analyses. All reported P values are two-sided, and we considered values of $P < 0.05$ to be statistically significant.

Results

Baseline and demographic characteristics

Demographic and clinical data of patients receiving PCC or FP are presented in Table 1. Of the initial 735 patients included in the primary analysis set, 134 patients who received both PCC and FP and 186 patients who received neither were excluded. Thus, data from 415 patients were analyzed in this study, 72 (17%) of whom only received PCC and the remaining 343 (83%) only received FP for factor replacement. Two patients who received PCC were excluded because data on dosing were not available (Fig. 1).

Patients in the FP group were slightly older, heavier, more likely to be male, and more likely to undergo non-elective surgery. Nevertheless, critical preoperative status, surgical complexity, renal function, and other comorbidities were similar (Table 1). The proportion of patients assigned to either cryoprecipitate or fibrinogen concentrate as part of the original FIBRES study arm was not different ($P = 0.14$).

Prothrombin complex concentrate doses received before CPB end, such as for warfarin reversal, were not included in the analysis ($n = 25$). A total of 13 patients (18%) in the PCC group were on warfarin therapy prior to surgery (median [IQR] preoperative INR, 1.46 [1.05–2.14]) compared with 21 (6%) patients on warfarin in the FP group (mean [IQR] preoperative INR, 1.96 [1.5–2.37]). There was no statistically significant difference in the median preoperative INR between patients on warfarin compared with those who were not on warfarin ($P = 0.11$), or between the PCC and FP groups as a whole ($P = 0.70$). The proportion of patients on warfarin with a preoperative INR > 1.5 was similar between the PCC and FP groups, (PCC group, $n = 5$ [7%] vs FP group, $n = 22$ [6%]; $P = 0.87$) as was the proportion with a preoperative INR > 2.0 (PCC group, $n = 4$ [6%] vs FP group, $n = 10$ [3%]; $P = 0.28$).

Across all sites, the mean (SD) dose of PCC was 1,472 (622) IU and the median [IQR] dose was 1,000 [1,000–2,000] IU, while in patients receiving FP the mean (SD) dose was 5.3 (5.6) units with a median [IQR] of 4.0 [2.0–6.0] units. There were significant site differences in use of PCC and FP (Table 2, Chi square test, $P < 0.01$).

The total number of patients receiving RBC transfusion was 299 (87%) in the FP group and 44 (61%) in the PCC group (Chi square test, $P < 0.01$). The total number of patients receiving platelet transfusion was 320 (93%) in the FP group and 58 (81%) in the PCC group (Chi square, $P < 0.01$). No patients included in this substudy had a documented transfusion reaction. Boxplots of units of FP

Table 1 Demographic and clinical characteristics of the study population

Variable	Treatment group		P value
	FP only (N = 343)	PCC only (N = 72)	
Age (yr), median [IQR]	66 [57–73]	65 [42–72]	0.03*
Female, n/total N (%)	99/343 (29%)	30/72 (42%)	0.03*
Male (%)	244/343 (71%)	42/72 (58%)	
Body mass index (kg·m^2), median [IQR]	23 [20–26]	21 [18–25]	< 0.01*
Preoperative creatinine clearance (mL·min^{-1}), median [IQR]	71 [49–91]	73 [52–102]	0.49
Preoperative hemoglobin (g·L^{-1}), median [IQR]	133 [115–146]	134 [115–147]	0.70
Preoperative international normalized ratio, median [IQR]	1.0 [1.0–1.2]	1.0 [1.0–1.2]	0.70
Left ventricular ejection fraction, n/total N (%)			
> 50%	239/343 (74%)	48/72 (69%)	0.05*
31–50%	59/343 (18%)	9/72 (13%)	
21–30%	17/343 (5%)	9/72 (13%)	
< 21%	9/343 (3%)	4/72 (6%)	
Myocardial infarction, n/total N (%)	68/343 (20%)	7/72 (10%)	0.11
Diabetes mellitus, n/total N (%)	72/343 (21%)	12/72 (17%)	0.16
Chronic lung disease, n/total N (%)	45/343 (13%)	12/72 (17%)	0.43
Pulmonary hypertension, n/total N (%)	69/343 (20%)	20/72 (28%)	0.31
Cerebrovascular disease, n/total N (%)	38/343 (11%)	12/72 (17%)	0.19
Critical preoperative status, n/total N (%)	47/343 (14%)	12/72 (17%)	0.51
Urgent surgery, n/total N (%)	86/343 (25%)	9 /72 (13%)	0.01*
Emergent surgery, n/total N (%)	60/343 (18%)	8/72 (11%)	
Redo sternotomy, n/total N (%)	83/343 (24%)	20/72 (28%)	0.52
Complex surgery, n/total N (%)	260/343 (76%)	55/72 (76%)	0.92
Units of PCC, median [IQR]	0 [0–0]	1,000 [1,000–2,000]	< 0.01*
Units of FP, median [IQR]	4 [2–6]	0 [0–0]	< 0.01*
Units of red blood cells, median [IQR]	3 [2–5]	1 [0–2]	< 0.01*
Units of platelets, median [IQR]	2 [1–3]	2 [1–3]	< 0.01*

Creatinine clearance was calculated using the CKD-Epi formula.[14,15] Complex surgery was defined as procedures other than coronary artery bypass grafting only, single valve only, or repair of atrial septal defect only. Differences between medians were assessed using the Wilcoxon rank-sum test; Differences among counts were assessed using Fisher's exact test or the Chi square test. P values < 0.05 were considered significant and are marked with asterisks.

BMI = body mass index; FP = frozen plasma; IQR = interquartile range; PCC = prothrombin complex concentrates.

and PCC administered compared with units of RBC transfused suggest an association between FP administration and higher volume transfusion (Fig. 2).

Red blood cell transfusion within 24 hr of CPB

In unadjusted logistic regression analysis accounting for clustering by study site (Table 3), each 500 IU of PCC transfused were associated with RBC transfusion avoidance (odds ratio [OR], 0.72; 95% confidence interval [CI], 0.62 to 0.84; P < 0.01). Conversely, each unit of FP was associated with significantly increased risk of RBC transfusion (OR, 1.47; 95% CI, 1.26 to 1.71; P < 0.01). When important potential confounders were included in the model, the results were similar. Each 500 IU of PCC was still associated with RBC transfusion avoidance (aOR, 0.67; 95% CI, 0.50 to 0.90; P < 0.01), while each unit of FP was associated with increased RBC transfusion (aOR, 1.60; 95% CI, 1.36 to 1.87; P < 0.01) (Table 4). When patients were compared between groups, those who received PCC had a significantly decreased unadjusted (Table 5) and adjusted odds for RBC transfusion (aOR, 0.20; 95% CI, 0.07 to 0.56; P < 0.01 (Table 6).

Fig. 1 Patient flow in the FIBRES substudy. FIBRES - Effect of fibrinogen concentrate *vs* cryoprecipitate on blood component transfusion after cardiac surgery;[12] FP = frozen plasma; PCC = prothrombin complex concentrate.
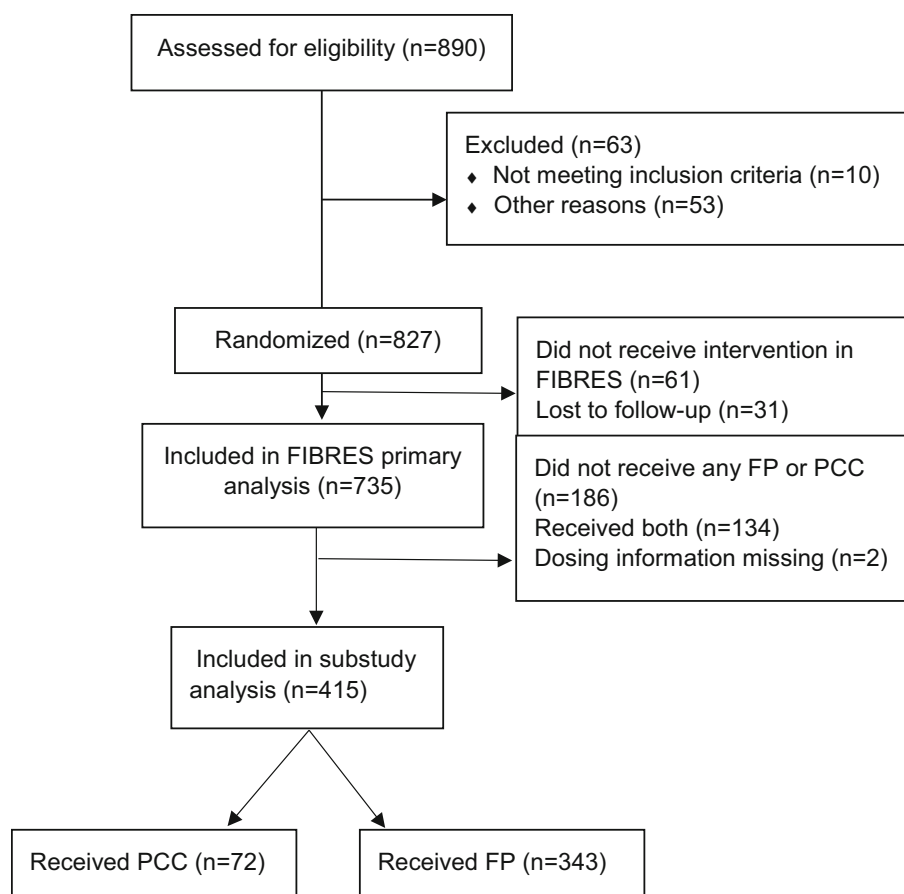

Table 2 Variability in PCC *vs* FP transfusion practices among centres

Study site identifier	Number of patients receiving PCC or FP by study site				Doses of PCC or FP by site		
	None	FP only	PCC only	FP and PCC	Mean (SD) dose of PCC*	Mean (SD) dose of FP*	Total number of patients at site
01	116 (32%)	111 (30%)	42 (11%)	98 (7%)	1,690 (653)	4.0 (2.7)	367 (50%)
02	16 (38%)	24 (57%)	1 (2%)	1 (2%)	1,000 (0)	3.8 (1.7)	42 (6%)
03	3 (10%)	28 (90%)	0 (0%)	0 (0%)		3.6 (2.3)	31 (4%)
04	3 (6%)	3 (6%)	26 (50%)	20 (39%)	1,192 (449)	4.0 (0.0)	52 (7%)
05	11 (28%)	27 (68%)	0 (0%)	2 (5%)		4.4 (2.1)	40 (5%)
06	2 (5%)	31 (80%)	1 (3%)	5 (13%)	1,000 (0)	5.6 (3.4)	39 (5%)
07	12 (29%)	29 (71%)	0 (0%)	0 (0%)		4.4 (3.1)	41 (6%)
08	13 (21%)	46 (75%)	0 (0%)	2 (3%)		11.2 (11.9)	61 (8%)
09	6 (17%)	23 (64%)	2 (6%)	5 (14%)	1,000 (0)	4.7 (2.9)	36 (5%)
11	2 (17%)	10 (83%)	0 (0%)	0 (0%)		5.0 (3.9)	12 (2%)
14	2 (14%)	11 (79%)	0 (0%)	1 (7%)		5.2 (3.8)	14 (2%)
Total	186 (25%)	343 (47%)	72 (10%)	134 (18%)	1,472 (622)	5.3 (5.5)	735 (100%)

Fisher's exact test, $P < 0.01$. *Mean doses with standard deviations (SD) are shown for patients who received only PCC alone or only FP alone, comprising the study population of interest.

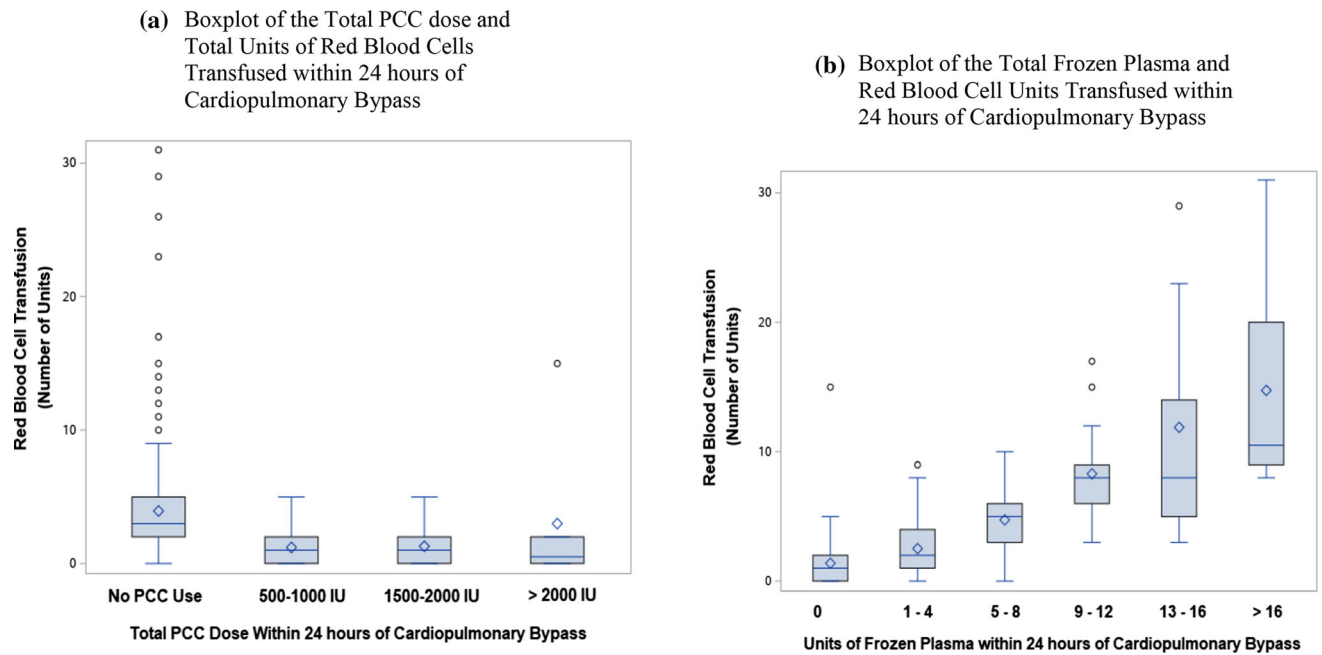FP = frozen plasma; PCC = prothrombin complex concentrates.

(a) Boxplot of the Total PCC dose and Total Units of Red Blood Cells Transfused within 24 hours of Cardiopulmonary Bypass

(b) Boxplot of the Total Frozen Plasma and Red Blood Cell Units Transfused within 24 hours of Cardiopulmonary Bypass

Fig. 2 Boxplot diagram illustrating the association between PCC or frozen plasma use and red blood cell transfusion within 24 hr of cardiopulmonary bypass. PCC = prothrombin complex concentrate.

Table 3 Unadjusted risk estimates for primary and secondary outcomes

Group	N (%) experiencing event	Predictor	Unadjusted risk estimate (95% CI)	P value
Any RBC transfusion within 24 hr of CPB			Odds ratio	
PCC	44 (61%)	per 500 units	0.72 (0.62 to 0.84)	< 0.01*
FP	299 (87%)	per unit	1.47 (1.26 to 1.71)	< 0.01*
Any platelet transfusion within 24 hr of CPB			Odds ratio	
PCC	58 (81%)	per 500 units	0.78 (0.68 to 0.89)	< 0.01*
FP	320 (93%)	per unit	1.44 (1.17 to 1.76)	< 0.01*
Acute kidney injury within 7 days of CPB			Odds ratio	
PCC	14 (19%)	per 500 units	0.99 (0.90 to 1.08)	0.78
FP	99 (29%)	per unit	1.14 (1.06 to 1.23)	< 0.01*
Thromboembolic events at 28 days post CPB			Risk ratio	
PCC	13 (18%)	per 500 units	1.01 (0.89 to 1.14)	0.89
FP	52 (15%)	per unit	0.95 (0.90 to 1.00)	0.04*
Hospital length of stay			Risk ratio	
PCC	9 [7–12] days	per 500 units	0.99 (0.92 to 1.07)	0.78
FP	10 [7–16] days	per unit	1.04 (1.03 to 1.05)	< 0.01*
Intensive care unit length of stay			Risk ratio	
PCC	4 [3–6] days	per 500 units	1.05 (0.99 to 1.11)	0.14
FP	4 [3–8] days	per unit	1.04 (1.03 to 1.05)	< 0.01*

Associations were examined by generalized estimating equation models for either count (Poisson) or binary (logistic) data, which were adjusted for preoperative creatinine clearance, hemoglobin level, body mass index, age, sex, presence of heart failure, study arm, critical preoperative status of the patient, and surgical complexity and urgency. Acute kidney injury (AKI) was defined as stage 1 or higher as per the Kidney Disease: Improving Global Outcomes 2012 guideline, which is consistent with RIFLE classification risk for AKI or higher.[14,15]

P values < 0.05 were considered significant and are marked with asterisks. For length of stay data, medians and interquartile ranges are shown.

CI = confidence interval; CPB = cardiopulmonary bypass; FP = frozen plasma; PCC = prothrombin complex concentrates; RBC = red blood cell.

Table 4 Adjusted risk estimates for primary and secondary outcomes

Group	Predictor	Adjusted risk estimate (95% CI)	P value
RBC transfusion within 24 hr of CPB		Odds ratio	
PCC	per 500 units	0.67 (0.50 to 0.90)	< 0.01*
FP	per unit	1.60 (1.36 to 1.88)	< 0.01*
Platelet transfusion within 24 hr of CPB		Odds ratio	
PCC	per 500 units	0.80 (0.70 to 0.92)	< 0.01*
FP	per unit	1.40 (1.15 to 1.69)	< 0.01*
Acute kidney injury within 7 days of CPB		Odds ratio	
PCC	per 500 units	1.00 (0.89 to 1.14)	0.94
FP	per unit	1.14 (1.04 to 1.25)	< 0.01*
Thromboembolic events at 28 days post CPB		Relative risk	
PCC	per 500 units	1.00 (0.87 to 1.16)	0.96
FP	per unit	0.96 (0.89 to 1.03)	0.22
Hospital length of stay		Relative risk	
PCC	per 500 units	0.99 (0.90 to 1.14)	0.86
FP	per unit	1.04 (1.03 to 1.05)	< 0.01*
Intensive care unit length of stay		Relative risk	
PCC	per 500 units	1.05 (0.97 to 1.14)	0.26
FP	per unit	1.04 (1.03 to 1.05)	< 0.01*

Associations were examined by generalized estimating equation models for either count (negative binomial or Poisson) or binary (logistic) data, which were adjusted for preoperative creatinine clearance, hemoglobin level, body mass index, age, sex, presence of heart failure, study arm, critical preoperative status of the patient, and surgical complexity and urgency. Length of stay models were additionally adjusted for preoperative myocardial infarction, chronic lung disease, and preoperative intensive care or hospital admission. Acute kidney injury was defined as stage 1 or higher as per the Kidney Disease: Improving Global Outcomes 2012 guideline, which is consistent with RIFLE classification "risk for AKI" or higher.[14,15]

P values < 0.05 were considered significant and are marked with asterisks.

CBP = cardiopulmonary bypass; CI = confidence interval; FP = frozen plasma; PCC = prothrombin complex concentrates; RBC = red blood cell.

Platelet transfusion within 24 hr of CPB

In unadjusted logistic regression analysis accounting for clustering by study site (Table 3), each 500 IU of PCC transfusion was associated with platelet transfusion avoidance (OR, 0.78; 95% CI, 0.68 to 0.89; P < 0.01). Each unit of FP was associated with a significantly increased risk of platelet transfusion (OR, 1.44; 95% CI, 1.17 to 1.76; P < 0.01). In the final adjusted model, the overall results were similar. Each 500 IU of PCC was associated with platelet transfusion avoidance (aOR, 0.80; 95% CI, 0.70 to 0.92; P < 0.01), while each unit of FP was associated with increased platelet transfusion (aOR, 1.40; 95% CI, 1.15 to 1.69; P < 0.01) (Table 4). When compared with the group receiving FP, patients receiving PCC had a significantly lower unadjusted (Table 5) and adjusted odds of platelet transfusion (aOR, 0.31; 95% CI, 0.18 to 0.53; P < 0.01) (Table 6).

Thromboembolic events within 28 days of CPB

A total of 65 (16%) patients experienced at least one thromboembolic complication. In the FP group, 52 (15%) patients had a thromboembolic event compared with 13 (18%) patients in the PCC group (Chi square test, P = 0.84). In the unadjusted model, each 500 IU of PCC was not associated with any increased risk of thromboembolic events (risk ratio [RR], 1.01; 95% CI, 0.89 to 1.14; P = 0.78). Similarly, in the unadjusted model, each unit of FP was not associated with any increase in thromboembolic events (RR, 0.95; 95% CI, 0.90 to 1.00; P = 0.04). In the adjusted model accounting for potential confounders, each 500 IU of PCC was still not associated with any increase in thromboembolism (aRR, 1.00; 95% CI, 0.87 to 1.16; P = 0.96). Results were similar for the final adjusted model for each unit of FP (aRR, 0.96; 95% CI, 0.89 to 1.03; P = 0.22) (Tables 3 and 4). When compared between groups, there was no significant difference in the risk of thromboembolic events between patients who received PCC compared with those who received FP (Table 5, Table 6).

Table 5 Unadjusted risk estimates for primary and secondary outcomes by exposure group

Group	Number (%) experiencing event	Predictor	Unadjusted risk estimate (95% CI)	*P* value
Any RBC transfusion within 24 hr of CPB			Odds ratio	
PCC	44 (61%)	Group of interest	0.26 (0.11 to 0.64)	< 0.01*
FP	299 (87%)	Reference		
Any platelet transfusion within 24 hr of CPB			Odds ratio	
PCC	58 (81%)	Group of interest	0.29 (0.16 to 0.54)	< 0.01*
FP	320 (93%)	Reference		
Acute kidney injury within 7 days of CPB			Odds ratio	
PCC	14 (19%)	Group of interest	0.79 (0.65 to 0.96)	0.02*
FP	99 (29%)	Reference		
Thromboembolic events at 28 days post CPB			Risk ratio	
PCC	13 (18%)	Group of interest	1.09 (0.72 to 1.65)	0.67
FP	52 (15%)	Reference		
Hospital length of stay			Risk ratio	
PCC	9 [7–12] days	Group of interest	0.85 (0.62 to 1.16)	0.31
FP	10 [7–16] days	Reference		
Intensive care unit length of stay			Risk ratio	
PCC	4 [3–6] days	Group of interest	0.95 (0.70 to 1.29)	0.72
FP	4 [3–8] days	Reference		

Associations were examined by generalized estimating equation models for either count (Poisson) or binary (logistic) data, which were adjusted for preoperative creatinine clearance, hemoglobin level, body mass index, age, sex, presence of heart failure, study arm, critical preoperative status of the patient, and surgical complexity and urgency. Acute kidney injury was defined as stage 1 or higher as per the Kidney Disease: Improving Global Outcomes 2012 guideline, which is consistent with RIFLE classification "risk for AKI" or higher.[14,15]

P values <0.05 were considered significant and are marked with asterisks. For length of stay data, medians and interquartile ranges are shown.

CBP = cardiopulmonary bypass; CI = confidence interval; FP = frozen plasma; PCC = prothrombin complex concentrates; RBC = red blood cell.

Acute kidney injury within seven days of CPB

There were a total of 113 (27%) acute renal events within seven days of CPB, with 14 (19%) in the PCC group and 99 (29%) in the FP group (Chi square test, *P* = 0.03). In unadjusted analysis, each 500 IU of PCC was not associated with increased odds of AKI within seven days of CPB (OR, 0.99; 95% CI, 0.90 to 1.08; *P* = 0.78). In the unadjusted model, each unit of FP was associated with increased odds of AKI (OR, 1.14; 95% CI, 1.06 to 1.23; *P* < 0.01). In the adjusted models, each 500 IU of PCC was not associated with an increased odds of AKI (aOR, 1.00; 95% CI, 0.89 to 1.14; *P* = 0.94). In the adjusted model, each unit of FP was again associated with an increased odds of AKI (aOR, 1.14; 95% CI, 1.04 to 1.25; *P* < 0.01) (Tables 3 and 4). Nevertheless, when compared between groups, there was no significant increase in the risk of AKI in patients who received FP compared with those who received PCC (Tables 5 and 6).

Intensive care unit and hospital length of stay

In unadjusted analysis, FP use was associated with a longer hospital and ICU stay (Table 3). In adjusted analysis, FP use was similarly associated with a slightly prolonged hospital and ICU length of stay (*P* < 0.01) compared with PCC use (Table 4). When examined between groups, there was no significant increase in the length of hospitalization or ICU stay in patients who received PCC compared with those who received FP (Table 5, Table 6).

We performed several sensitivity analyses and these results are presented in the Electronic Supplementary Material (eTables).

Discussion

In this study of adult cardiac surgery patients experiencing clinically significant post-CPB bleeding, PCC use was associated with increased RBC and platelet avoidance compared with FP use both in terms of magnitude of transfusion avoidance per dose, as well as when patients receiving either PCC or FP were compared directly with

Table 6 Adjusted risk estimates for primary and secondary outcomes by exposure group

Group	Predictor	Adjusted risk estimate (95% CI)	*P* value
RBC transfusion within 24 hr of CPB		Odds ratio	
PCC	Group of interest	0.20 (0.07 to 0.56)	< 0.01*
FP	Reference		
Platelet transfusion within 24 hr of CPB		Odds ratio	
PCC	Group of interest	0.31 (0.18 to 0.53)	< 0.01*
FP	Reference		
Acute kidney injury within 7 days of CPB		Odds ratio	
PCC	Group of interest	0.91 (0.68 to 1.21)	0.52
FP	Reference		
Thromboembolic events at 28 days post CPB		Relative risk	
PCC	Group of interest	0.96 (0.60 to 1.52)	0.85
FP	Reference		
Hospital length of stay		Relative risk	
PCC	Group of interest	0.84 (0.59 to 1.18)	0.31
FP	Reference		
Intensive care unit length of stay		Relative risk	
PCC	Group of interest	0.93 (0.64 to 1.36)	0.70
FP	Reference		

Associations were examined by generalized estimating equation models for either count (negative binomial or Poisson) or binary (logistic) data, which were adjusted for preoperative creatinine clearance, hemoglobin level, body mass index, age, sex, presence of heart failure, study arm, critical preoperative status of the patient, and surgical complexity and urgency. Length of stay models were additionally adjusted for preoperative myocardial infarction, chronic lung disease, and preoperative intensive care or hospital admission. Acute kidney injury was defined as stage 1 or higher as per the Kidney Disease: Improving Global Outcomes 2012 guideline, which is consistent with RIFLE classification "risk for AKI" or higher.[14,15]

P values < 0.05 were considered significant and are marked with asterisks.

CBP = cardiopulmonary bypass; CI = confidence interval; FP = frozen plasma; PCC = prothrombin complex concentrates; RBC = red blood cell.

each other. We observed no increase in important secondary safety endpoints with PCC use. This study also highlights important differences between institutions and clinicians in the utilization of PCC compared with FP, indicating clinical equipoise and a lack of consensus regarding the role of PCCs in this setting (Table 2).

The use of PCCs compared with FP has been previously shown by observational studies to be associated with transfusion avoidance both in cardiac surgery and trauma patients.[22–25] While our primary objective was to estimate efficacy between PCC and FP for outcomes related to transfusion avoidance, a novel aspect of our study was the additional inclusion of dose-effect in the analyses. This allows us to draw a more direct comparison between the hemostatic efficacy of the two components while adjusting for potential confounders. Despite the relatively small number of patients in our study receiving only PCC, we observed a clear association between the volume of FP transfused with the volume of RBCs transfused (Fig. 2). Hemodilution may be a significant contributor to the association of FP transfusion with increased RBC and platelet transfusion.[26] FP may also be favoured in the

context of large volume hemorrhage, while administration of PCC may occur in coagulopathy without large volume bleeding or where there is concern regarding fluid overload.[27] Additional studies are required to tease apart these differences (Fig. 3).

It is clear that PCC is used in the cardiac surgical population despite a lack of high-quality evidence, and at some centres PCC use is very common. This may be driven by viscoelastic testing-guided transfusion algorithms focusing on individual blood component replacement strategies, the logistical advantages of PCC, or presumed superiority based on observational studies.[28] The variability in practice pertaining to administration of PCC *vs* FP should be explored further, and extends to the doses utilized by clinicians. Currently there is no clear consensus on the optimal dose of PCC for coagulopathy related to cardiac surgery,[17,29,30] with doses in our study ranging from 500 to 2,000 IU for a single administration. Given the significant differences in transfusion avoidance in favour of the PCC group in this study, our results suggest a dose between 1,000 IU and 2,000 IU is likely to be effective. Recent pilot randomized controlled trials have used PCC
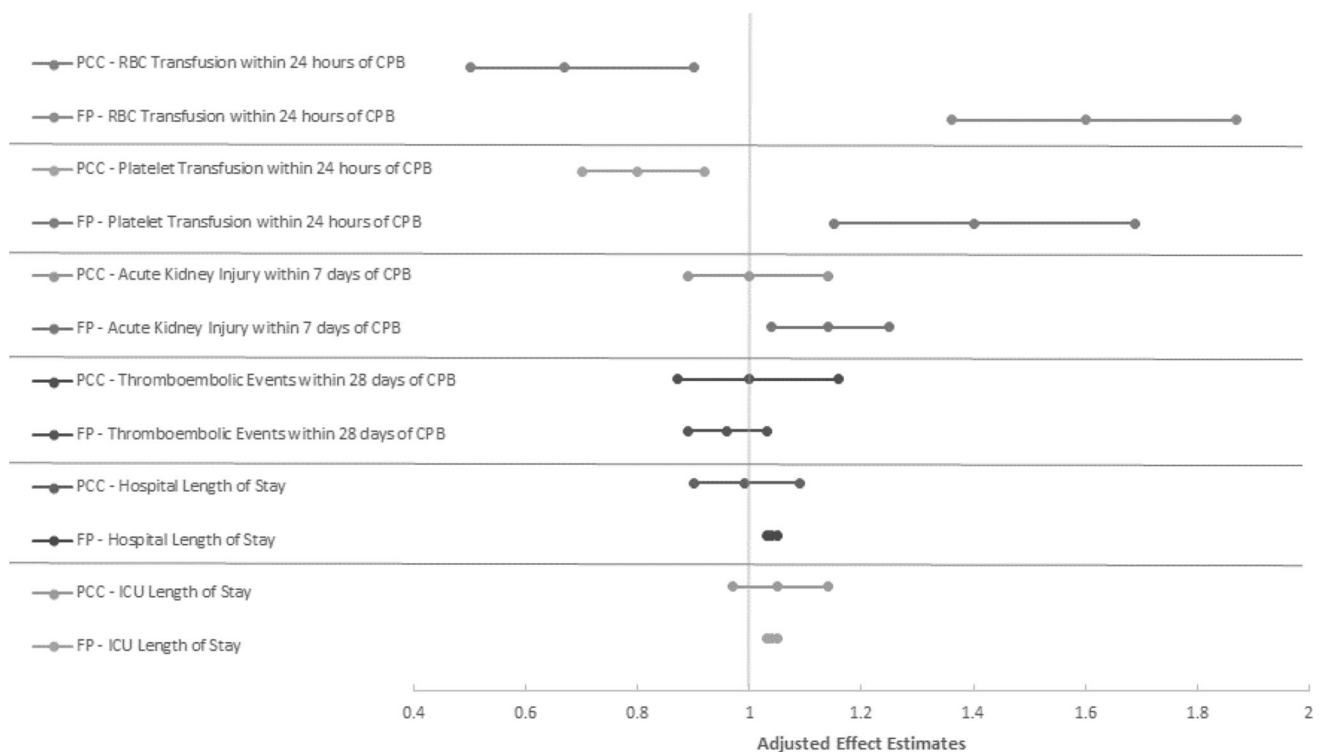
Fig. 3 The adjusted association of PCC (per 500 units) or FP (per unit) dose with postoperative outcomes. Effect point estimates with corresponding 95% confidence intervals are shown. CPB = cardiopulmonary bypass; FP = frozen plasma; ICU = intensive care unit; PCC = prothrombin complex concentrate; RBC = red blood cell.

doses of 15–25 IU·kg^{-1} (1,000–2,000 IU for an average sized patient), with observed hemostatic effects comparable with FP observed throughout this dose range, albeit in small numbers of patients.[29,30]

This study builds on existing evidence and re-examines the efficacy of PCCs, while adding to the sparse published data on the safety of PCCs in the context of bleeding after cardiac surgery. Previously published work has been limited by small sample sizes, making comparisons of rare outcomes between groups difficult because of insufficient power. Our study attempts to address these limitations by including only a higher risk cohort of patients with active bleeding, removing some elements of confounding related to the indication for PCC administration and improving the power of our study to detect a difference in adverse outcomes.[29] Additionally, safety data utilized in this study was prospectively collected, and included renal and thromboembolic outcomes, some of the most disputed and concerning outcomes in the literature.

Previously published work has suggested an increased risk of renal adverse events in patients receiving PCC compared with FP.[23,24] We did not observe an increase in the odds of AKI by seven days in patients receiving PCC. While restoring effective circulating volume is necessary for adequate organ perfusion, volume overload is an equally important consideration as it is associated with renal morbidity in patients undergoing cardiac surgery.[31] A high central venous pressure in the setting of impaired cardiac function adversely alters renal hemodynamics by decreasing renal perfusion pressure, and increases the risk of AKI.[31] This may in part account for the association we observed between FP administration and AKI.[32]

There are many remaining questions to answer, largely due to the inherent limitations of retrospective study design. While concern for residual confounding remains in the context of retrospective studies, our work adds to the evidence supporting that the use of PCCs in cardiac surgical patients is at least non-inferior and possibly superior in efficacy to the use of FP. Ongoing controversies and safety concerns regarding the role of PCCs in cardiac surgery can be addressed through the conduct of a randomized controlled trial.[33] The common use of PCC in cardiac surgical patients with highly variable dosing combined with a lack of high-quality evidence establishing superiority indicates that a well-designed clinical trial is warranted.

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