

Initial Experience of the Use of 3-Factor Prothrombin Complex Concentrate and Thromboembolic Complications After Cardiac Surgery



India Zweng, MD^a, Sean Galvin, MBBS, FCSANZ, FRACS^b,
Ray Robbins, PhD^c, Rinaldo Bellomo, MD, FRACP, FCICM, PGDipEcho^{d*},
Graeme K. Hart, MBBS, FCICM^e, Siven Seevanayagam, MD, FRACS^f,
George Matalanis, MD, FRACS^f

^aDepartment of Surgery, Austin Hospital, Melbourne, Vic, Australia

^bDepartment of Cardiothoracic Surgery, The Wellington Regional Hospital, Wellington, New Zealand

^cDepartment of Administrative Informatics, Austin Hospital, Heidelberg, Melbourne, Vic, Australia

^dDepartment of Epidemiology and Preventive Medicine, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Vic, Australia

^eDepartment of Intensive Care, Austin Hospital, Melbourne, Vic, Australia

^fDepartment of Cardiac Surgery, Austin Hospital, Melbourne, Vic, Australia

Received 10 July 2017; received in revised form 6 August 2018; accepted 30 August 2018; online published-ahead-of-print 14 September 2018

Background

3-factor prothrombin complex concentrate (3F-PCC) may provide a valuable treatment option for coagulopathy in cardiac surgery patients. However, it may expose patients to increased risk of thromboembolic events. Accordingly, we compared the incidence of thromboembolic events between patients exposed to 3F-PCC and those receiving conventional therapy.

Methods

Demographic, operative and postoperative data was obtained in a cohort of consecutive patients exposed to 3F-PCC and a contemporaneous control population. Propensity-score matching was performed for risk adjustment. Unadjusted and adjusted patient demographics and incidence of thromboembolism were compared.

Results

Patients receiving 3F-PCC (PCC) were younger (mean age PCC: 64 ± 14.2 vs. No PCC: 67.6 ± 11.6 , $p = 0.022$), and less likely to have diabetes or previous myocardial infarction. PCC patients experienced more prolonged aortic cross clamp times (mean time in minutes PCC: 119.9 ± 58.8 vs. No PCC: 92.3 ± 54), more complex cardiac surgeries and were more likely to have received more fresh frozen plasma (FFP), cryoprecipitate and red blood cells. Despite this, both unadjusted and adjusted 30-day mortality and

Introduction

Perioperative and postoperative bleeding are major problems following cardiac surgery. Such bleeding is

associated with increased morbidity and mortality [1]. Thus, achieving haemostasis is a major therapeutic priority [2]. Various agents are available for the promotion of coagulation [2]. These agents include fresh frozen plasma

*Corresponding author at: Department of Epidemiology and Preventive Medicine, Australian and New Zealand Intensive Care Research Centre, Monash University, Melbourne, Australia. Tel.: +61 3 94965992; Fax: +61 3 94963932., Emails: rinaldo.bellomo@monash.edu, rinaldo.bellomo@austin.org.au

readmission rates were similar between groups. There were 9 (9.2%) and 34 (6.8%) ($p = 0.40$) thromboembolic events in the unadjusted PCC and control groups respectively. Adjusted risk for thromboembolic event rates was also comparable (Odds ratio: 1.512, 95% Confidence Interval 0.401–5.7, $p = 0.541$).

Conclusions

3-factor prothrombin complex concentrate was administered to patients at greater risk of complications including bleeding. Our initial experience suggests that the use of PCC does not appear to increase thromboembolic risks compared to conventional treatment.

Keywords

Prothrombin complex concentrate • Thromboembolic complications • Cardiac surgery • Coagulopathy

(FFP), cryoprecipitate (CRYO), platelets, tranexamic acid, aprotinin, protamine, recombinant factor VIIa, and fibrinogen concentrate [2]. Each of these agents can help decrease bleeding but may carry certain risks. For example, FFP carries infectious and non-infectious risks including transfusion associated circulatory overload and allergic transfusion reactions [3–5] suggesting that other similar interventions may be safer.

3-factor prothrombin complex concentrate (PCC) is one possible additional treatment option, which may carry some advantages over FFP. PCC, marketed in Australia and New Zealand as Prothrombinex[®] (CSL-Behring, Melbourne, Vic, Australia) is a product containing the human plasma-derived vitamin-K dependent factors II, IX and X and only low levels of factor VII (so called 3-factor PCC). Other PCCs marketed in the world (so-called 4-factor PCC), however, also contain therapeutic levels of VII [4]. One of the advantages of PCC consists of it being a concentrated powder that is readily reconstituted in low volumes of fluid. In contrast to FFP administration, PCC provides a high amount of coagulation factors while minimising any circulatory volume overload, [3]. Moreover, unlike FFP, PCC does not require thawing, [5] is ABO neutral, and less likely to precipitate allergic transfusion reactions [3]. Finally, it can be reconstituted and administered much faster than FFP. Accordingly, off-label PCC use has been reported in some centres for the treatment of patients with bleeding post cardiopulmonary bypass (CPB) [2]. However, irrespective of whether PCC has efficacy in decreasing postoperative bleeding, there is little information regarding the safety of PCC in such patients. This is unfortunate, because there is concern that PCC may lead to a markedly increased risk of thromboembolic complications [3,4]. Accordingly, we conducted a retrospective observational study to investigate the rate of thromboembolic events in a centre where PCC has been and is used as rescue therapy for perioperative coagulopathic bleeding in patients receiving cardiac surgery with CPB.

Methods

Patient Characteristics

We analysed 592 patients who were admitted to the Austin Hospital for cardiac surgery and subsequently received resuscitation with blood products. Of these, 98 patients

had received 3-factor PCC (Prothrombinex[®], CSL-Behring) as part of their resuscitation regime, while 494 had only received clotting factors-based treatment for coagulopathy, such as CRYO, FFP or platelets. No specific exclusion criteria were applied.

Study Participants and Ethics Approval

From 3 January 2011 to 30 July 2013 data from all patients who 1) were admitted to the Austin Hospital for cardiac surgery and 2) subsequently received resuscitation with blood products, were analysed. Data were obtained from the Austin Hospital Blood Bank and cross-referenced with the Australian Society of Cardiothoracic Surgeons database for further demographic information and 30-day mortality and re-admission rates. The study was approved by the Austin Hospital Human Research Ethics Committee and, due to de-identification, anonymity and no patient risk, the need for consent for the use of electronic medical record data was waived.

Each patient was subsequently cross-referenced for complications, based on the international classification of disease, version 10 (ICD-10) coding, grouped to the Classification of Hospital Acquired Diagnoses (CHADx) as independently coded for by trained coders. The major CHADx category 5 was used as most relevant to our study, because it included all thrombotic complications such as thrombotic stroke, deep venous thrombosis, pulmonary embolism, and myocardial infarction.

Study Endpoints

The primary study endpoint was the occurrence of any thromboembolic event. Secondary study endpoints measured were 30-day mortality and 30-day hospital readmission, and the combined outcome of thromboembolic event, ICU readmission, and mortality.

Statistical Analysis

Data were analysed using IBM SPSS Statistics for Mac OS, version 22.0 (IBM Corp, Armonk, NY, USA). Categorical variables were compared using Fisher's Exact test. Continuous variables were expressed as the mean \pm the standard deviation.

Propensity score matching was performed for risk adjustment. The model included the maximum number of preoperative variables relevant to coagulopathy and thromboembolic events. Units of blood products were not able to be included in

the match as our dataset does not discriminate between products given before and after PCC, additionally the products are frequently given simultaneously based on the clinical scenario. The variables included were age, sex, EuroSCORE, smoking history, diabetes, hypertension, history of cerebrovascular disease, history of myocardial infarction, previous coronary artery bypass grafting (CABG), previous valvular surgery, cardiopulmonary bypass and aortic cross-clamp times. Logistic regression was used to generate the propensity score, using the treatment group as the dependent variable. The c-statistic was calculated to determine the adequacy of the propensity model. Patients were then matched one to one based on their generated propensity score using the 'greedy' matching method. A fixed caliper width of 0.02 was used.

Standardised differences were calculated for both the entire cohort and the propensity-matched cohort in order to aid visualisation of balance achieved between groups following matching. A standardised difference below 10% is generally reflective of extremely close matching; however we accepted slightly higher values owing to the sample size, as standardised differences tend to be elevated above 10% despite only small differences in absolute number between groups when the number of matched pairs is relatively small (<100 patients). These propensity-matched pairs were then further analysed. Categorical variables were compared using McNemar's test.

Multivariate logistic regression was performed for the propensity-matched pairs for the composite outcome of mortality within 30 days, readmission to intensive care unit (ICU) and thrombotic event. There was one instance in which a patient was both readmitted to ICU and suffered a thromboembolic event. The model was adjusted for age, sex, total units of red blood cells, and total units of cryoprecipitate, fresh frozen plasma, and platelets combined.

Multivariate logistic regression was also performed for the propensity-matched pairs for the single outcome of any thromboembolic event. This model was adjusted for age, sex, total units of red blood cells, and total units of cryoprecipitate, fresh frozen plasma, and platelets combined. Both models were additionally performed without age and sex as sensitivity analysis to test its robustness (see Appendix).

Results

The preoperative demographics of patients from the entire cohort are displayed in [Table 1](#). Patients who received PCC were more likely to be younger and less likely to have hypertension, diabetes or previous myocardial infarction. Patients receiving PCC were also more likely to have had longer cardiopulmonary bypass and aortic cross-clamp times and more likely to have undergone more complicated and prolonged operations, including aortic aneurysm repair with simultaneous David procedure or Bentall's procedure, aortic dissection repair, multi-valve replacement/repair, and atrial septal defect closure, CABGs, and a valve replacement in a single operation. The use of blood products in patients

treated with PCC compared with controls is also presented in [Table 1](#). Patients treated with PCC also received significantly more FFP, cryoprecipitate, platelets and red cell transfusion. Of the 98 PCC patients, 39 (40%) also received both FFP and cryoprecipitate; 27 (27.5%) also received cryoprecipitate; 4 (4%) also received FFP; while 28 (28.5%) received PCC alone. The amount of PCC given ranged from 500 to 9,000 international units (IU). The median dose received per patient was 1,500 IU (three vials) and the mean dose was 1,775.5 IU.

Propensity Matched Comparison

Propensity-score matching yielded 80 patient pairs (c-statistic: 0.724). Patient details following propensity-score matching are displayed in [Table 2](#). Following matching, there were no statistically significant differences between groups. Most variables had a standardised difference <20%, with half of the values <10%. Adjusted thrombotic complication rates, and 30-day mortality and readmission rates were comparable between the groups ([Table 3](#)). After propensity matching, patients treated with PCC still received significantly more transfusion of platelets.

Thromboembolic Complications and Other Outcomes

Unadjusted rates of thrombotic events, 30-day mortality and readmission were comparable between groups and are displayed in [Table 3](#). There were 43 thrombotic events that occurred in the entire cohort, 9 occurred in the PCC cohort, the remaining 34 occurred in those who did not receive PCC.

The thrombotic events among the PCC cohort consisted of the following events: five cerebral infarcts; one case of venous thrombosis; one acute myocardial infarct; one coronary thrombosis without infarction; and one transient ischaemic attack. The thrombotic events in the 34 who did not receive PCC included the following events: 17 were cerebral infarcts; seven cases of arterial thrombosis/embolism; five cases of venous thrombosis; three acute myocardial infarcts; and two coronary thromboses without infarction.

An analysis of the unmatched unadjusted data pertaining to treatment with 3F-PCC in the presence of coronary grafts was performed. There were 358/592 (60%) patients in the overall cohort who underwent CABG or CABG plus valvular surgery. Of these, 83 (23%) received PCC. Within this PCC treated group there were four cases of cerebral infarction, one case of coronary thrombosis and one case of clinically diagnosed AMI, a total of six events in 83 patients. Within the no 3F-PCC group, there were five cases of cerebral infarction, two cases of acute myocardial infarction (AMI), one case of trans-ischaemic attack (TIA), and three cases of arterial thrombosis/embolism, a total of 11 events in 275 patients ($p = 0.22$).

Multivariate logistic regression for the composite outcome showed an insignificant decrease in relative risk for the composite outcome of mortality, ICU readmission and thrombotic events among patients who had received PCC

Table 1 Preoperative demographics and perioperative features for entire cohort.

Absolute values (percentages)/mean \pm standard deviation				
Variable	PCC (n = 98)	No PCC (n = 494)	P-value	Standardised difference
Age	64.05 \pm 14.22	67.61 \pm 11.582	0.022	-27.5
Male	67 (68)	319 (65)	0.489	-8.0
Hypertension	66 (67)	416 (84)	<0.001	40.1
Diabetes	17 (17)	167 (34)	<0.001	38.4
Pre-op creatinine	77.51 \pm 163.03	99.69 \pm 86.8	0.053	-17.0
Previous AMI	26 (27)	231 (47)	<0.001	42.9
EuroSCORE	6.9 \pm 3.62	6.26 \pm 3.39	0.094	7.9
Smoking history	56 (57)	288 (58)	0.881	2.3
Previous CABG	5 (5)	14 (3)	0.223	-11.6
Previous valve	8 (8)	19 (4)	0.106	-18.2
Incidence CPB	98 (100)	453 (92)	0.001	-42.5
Aortic cross-clamp time	119.87 \pm 58.8	92.35 \pm 54	<0.001	48.7
Procedure				
CABG	31 (32)	254 (51)	-	41.0
CABG and valve	10 (10)	63 (13)	-	8.0
Valve	19 (19)	99 (20)	-	1.6
Other*	38 (39)	78 (16)	<0.001	-53.4
Aortic surgery	18 (47)	51 (65)	-	
Aneurysm	14 (78)	32 (63)	-	
with Bentall's procedure	5 (36)	6 (19)	-	
with David procedure	3 (21)	5 (16)	-	
Dissection	6 (33)	24 (47)	-	
ASD with CABG, valve or other	4 (10)	6 (8)	-	
Multi valve surgery	3 (8)	4 (5)	-	
CABG, valve and other	3 (8)	4 (5)	-	
Tumour resection	3 (8)	1 (1)	-	
Other combinations	7 (18)	12 (15)	-	
Platelets (ICU and OR units)			<0.001	
0 units	6 (6)	194 (39)		
1-2 units	62 (63)	237 (48)		
3-4 units	18 (18)	44 (9)		
>4 units	12 (12)	19 (4)		
FFP (ICU and OR units)			0.001	
0 units	55 (56)	386 (78)		
1-2 units	24 (24)	59 (12)		
3-4 units	13 (14)	27 (5)		
>4 units	6 (6)	22 (4)		
CRYO (ICU and OR units)			<0.001	
0 units	32 (33)	363 (73)		
1-2 units	3 (3)	15 (3)		
3-4 units	9 (9)	10 (2)		
>4 units	54 (55)	106 (21)		
RBCs (ICU and OR units)			<0.001	
0 units	12 (12)	86 (17)		
1-2 units	24 (24)	195 (39)		
3-4 units	18 (18)	108 (22)		
>4 units	44 (45)	105 (21)		

Abbreviations: AMI, acute myocardial infarction; CPB, cardio pulmonary bypass; CABG, coronary artery bypass grafting; ICU, intensive care unit; OR, operating room; FFP, fresh frozen plasma; CRYO, cryoprecipitate; RBC, red blood cell; PCC, prothrombin complex concentrate.

*Values expressed are as a percentage of the 'Other' category/category to which it belongs.

*Note: 7 patients in the entire cohort group underwent both aneurysm and dissection repair (2 in the PCC and 5 in the no PCC), thus the total value for dissection and aneurysm repair exceeds the absolute figure for aortic surgery.

Table 2 Demographics for propensity-matched pairs.

Absolute values (percentages)/mean \pm standard deviation				
Variable	PCC (n = 80)	No PCC (n = 80)	P-value	Standardised difference
Age	66.9 \pm 12.18	69.4 \pm 10.5	0.120	-24.7
Male	55(69)	46 (58)	0.190	-23.5
Hypertension	60 (75)	58 (73)	0.858	-5.7
Diabetes	17 (21)	21 (26)	0.578	11.8
Pre-op creatinine	103.1 \pm 49.8	101.2 \pm 58.1	0.830	3.4
Previous AMI	26 (33)	25 (31)	>0.99	-2.7
EuroSCORE	6.75 \pm 3.78	7.6 \pm 3.48	0.110	-25.3
Smoking history	48 (60)	45 (56)	0.749	-7.6
Previous CABG	3 (4)	3 (4)	>0.99	0.0
Previous valve	6 (8)	4 (5)	0.746	-10.3
Incidence CPB	80 (100)	80 (100)	-	-
Aortic cross-clamp time	106.31 \pm 47.3	101.3 \pm 53.3	0.531	9.9
Procedure				
CABG	31 (39)	31 (39)	-	0.0
CABG and valve	10 (12.5)	15 (19)	-	17.3
Valve	16 (20)	21 (26)	-	14.9
Other*	23 (29)	13 (16)	0.216	-30.3
Aortic surgery				
Aneurysm	6 (50)	3 (37.5)	-	-
with Bentall's procedure	5 (42)	1 (33)	-	-
with David procedure	0 (0)	2 (66)	-	-
Dissection	6 (50)	5 (62.5)	-	-
ASD with CABG, valve or other	5 (22)	1 (8)	-	-
Multi valve surgery	0 (0)	0 (0)	-	-
CABG, valve and other	2 (9)	1 (8)	-	-
Tumour resection	3 (13)	0 (0)	-	-
Other combinations	1 (4)	3 (23)	-	-
Platelets (ICU and OR units)			0.001	
O units	5 (6)	28 (35)		
1-2 units	49 (61)	36 (45)		
3-4 units	17 (21)	14 (17.5)		
>4 units	9 (11)	2 (2.5)		
FFP (ICU and OR units)			0.059	
O units	46 (57.5)	63 (79)		
1-2 units	20 (25)	11 (14)		
3-4 units	10 (12.5)	2 (2.5)		
>4 units	4 (5)	4 (5)		
CRYO (ICU and OR units)			0.061	
O units	27 (34)	51 (64)		
1-2 units	3 (4)	4 (5)		
3-4 units	8 (10)	2 (2.5)		
>4 units	42 (52.5)	23 (29)		
RBCs (ICU and OR units)			0.292	
O units	8 (10)	13 (16)		
1-2 units	19 (24)	25 (31)		
3-4 units	16 (20)	17 (21)		
>4 units	37 (46)	25 (31)		

Abbreviations: AMI: acute myocardial infarction; CPB: cardio pulmonary bypass; CABG: coronary artery bypass grafting; ICU: intensive care unit; OR: operating room; FFP: fresh frozen plasma; CRYO: cryoprecipitate; RBC, red blood cell; ASD, atrial septal defect; PCC, prothrombin complex concentrate

*Values expressed are as a percentage of the 'Other' category/category to which it belongs.

Table 3 Early postoperative outcome for entire cohort and propensity-matched pairs.

Early outcome entire cohort	Absolute values (percentages)		P-value
	PCC (n = 98)	No PCC (n = 494)	
30-day mortality	5 (5)	16 (3)	0.369
30-day readmission	13 (13)	56 (11)	0.605
Thrombotic complications	9 (9)	34 (7)	0.399
Early outcome propensity-matched pairs	PCC (n = 80)	No PCC (n = 80)	P-value
30-day mortality	5 (6)	3 (4)	0.727
30-day readmission	9 (11)	9 (11)	>0.99
Thrombotic complication	8 (10)	4 (5)	0.388

Abbreviation: PCC, prothrombin complex concentrate.

compared to those who had not (Odds Ratio: 0.86, 95% Confidence Interval 0.33–2.25, $p = 0.76$). Multivariate logistic regression for the single outcome of thromboembolic event showed an insignificant increase in relative risk among patients who had received PCC compared to those who had not (Odds ratio: 1.512, 95% Confidence Interval 0.401–5.7, $p = 0.541$).

Discussion

Key Findings

In this single centre study, we investigated thromboembolic events and patient outcomes in cardiac surgery patients who had received 3-factor PCC mostly in addition to conventional factors or conventional clotting products therapy for perioperative bleeding. Despite experiencing more prolonged cardiopulmonary bypass times and more complex cardiac procedures, both unadjusted and adjusted rates of thromboembolic events were comparable between groups. The early outcomes of 30-day mortality and 30-day readmission were also comparable on both unadjusted and adjusted comparison.

Relationship to Previous Findings

Randomised trials comparing safety and efficacy of administering 4-factor PCC in patients requiring reversal of oral anticoagulation prior to cardiopulmonary bypass or for major bleeding have demonstrated comparable complication rates to controls, including thromboembolic complications [6,7]. These trials have led to US Food and Drug Administration (FDA) approval of 4-factor PCC use for vitamin K antagonist reversal in patients with acute major bleeding and those requiring acute surgical intervention [5]. These randomised controlled trials, however, excluded patients who were deemed at high thromboembolic risk [5]. However, a further study evaluating thromboembolic complications with 4-factor PCC in unselected patients for reversal of vitamin K antagonists also supported the safety of PCC [5].

Despite the above findings, there is concern supported by case reports [8,9] regarding the overall safety of PCC and the

risk of PCC-induced thromboembolic complications in the unique population of patients receiving cardiac surgery. Yet, several reports indicate that PCC is currently being used in selected patients in different centres worldwide [10–14]. This is likely because of evidence that decreased thrombin generation is a major factor contributing to coagulopathy after cardiopulmonary bypass [11] and evidence that such deficit can be restored to normal values by the equivalent of 25 IU of PCC per kg [11]. These case series have reported low levels of thromboembolic events. A recent retrospective study reporting of 3-factor PCC found no increased risk of thromboembolic events compared to controls with PCC use in cardiac surgery. This study additionally reported decreased postoperative bleeding and requirement for red blood cell (RBC) transfusion [15]. However, with the exception of the above recent study, investigations have been small, with the largest including only 53 patients, have not systematically assessed patients for all types of thromboembolic complications, and have almost always used 4-factor PPC therapy (a potentially more thrombotic PCC than 3-factor PCC). In this regard, our study markedly increases the number of 3-factor PCC-treated patients reported in the literature.

Study Implications

Our finding that the unadjusted and adjusted risk of thromboembolic complications is not significantly greater than that seen with conventional blood product-based therapies supports the notion that, within the limitations of this study, there is no evidence of harm from use of 3-factor PCC. These findings mirror recent studies finding no increased risk of thromboembolic events with the use of 3-factor PCC [15].

The requirement for blood product administration has been shown to be associated with adverse events following cardiac surgery. This includes both all cause mortality, infection and the risk of stroke and myocardial infarction. This may be of particular concern in patients undergoing CABG in whom graft patency is of major concern. Whilst this study was not powered to look at the incidence of graft failure specifically in this group, it is reassuring to see that the use of 3F-PCC was not associated with an overall increased incidence of stroke,

myocardial infarction or other thromboembolic complications in patients undergoing CABG.

Moreover, the observation that, after adjustment for co-administration of clotting factors and platelets, the odds ratios for such complications are not significantly different to control patients provides further evidence of safety. Finally, the finding that, on multivariate logistic regression analysis, the point estimate for the odds ratio of risk for the composite outcome of mortality, ICU readmission and thrombotic complication is only 0.86 provides further reassurance. This study has implications for treatment of coagulopathy in cardiac surgery in both Australia and New Zealand and the wider international community. For example, 3-factor prothrombin complex concentrate preparations available in the United State include Profilnine SD (Grifols, Barcelona, Spain) and Bebulin VH (Baxter) [16,17].

Strengths and Limitations

Our study design encompasses propensity-score matching and multivariable modelling, allowing comparison of a treatment and control group with similar demographics and chronology from one single centre, thus attenuating the effect of selection and time-related bias associated with patient demographics, hospital protocol, and clinician preference. Finally, the detailed and independent assessment of the incidence of thromboembolic complications in our study has likely minimised the risk of ascertainment bias.

Our study also carries some limitations. First, it is retrospective in design and thus has limited ability to account for potentially important variables in the propensity model. Given that we did not have records of blood product administration divided into before and after PCC administration, we were unable to include this in our propensity score model. Additionally, the exact timing of administration of 3F-PCC was not recorded, thus we were unable to ascertain whether patients received 3F-PCC treatment in the operating theatre, ICU or both. We have included the maximum number of variables available to us in developing the model. Furthermore, propensity score matching inevitably leads to a loss of patients for comparison and thus delivers a smaller number for statistical analysis. Second, there was clear selection bias in choosing which patients should receive PCC making it impossible to fully discern whether the complications observed represented the effect of PCC or the effect of surgical complexity and prolonged CPB. In particular, despite the propensity match, patients who were bleeding more at the time of surgery or on return to ICU may have been more likely to receive the additional 3F-PCC, either from a decision by the surgeon, the anaesthetist, or the intensivist. This bias is also suggested by the fact that the 3F-PCC treated patients received significantly more transfusion of platelets. However, when using the composite outcome of mortality within 30 days, readmission to ICU and thrombotic events as the outcome, the multivariate logistic regression model (adjusted for age, sex, total units of red blood cells, and total units of cryoprecipitate, fresh frozen plasma, and platelets combined)

found a point estimate in favour of treatment with PCC (OR: 0.86). This finding provides a degree of reassurance in relation to major safety concerns.

Thirdly, we acknowledge that measurement of drain output pre and post administration of 3F-PCC would have been an ideal indicator for efficacy of treatment. Unfortunately, this information was not recorded, and, additionally, exact timing of 3F-PCC administration was not documented, meaning that this information was not obtained. Finally, this study has limited power to detect minor differences in thromboembolic complications. However, even if the true risk were considered to be twice the point estimate observed in this study on adjusted comparison (odds ratio of 1.512), more than 6,000 patients would have to be randomised in each group in a future trial comparing PCC with placebo for researchers to have an 80% power to detect it at an alpha of 0.05. It is extremely unlikely that such a comparative study would ever be done. Moreover, any consideration of such risk would have to be balanced with consideration of potentially improved overall clinical outcomes as suggested in our adjusted model. A prospective analysis encompassing monitoring of thromboembolic events would be of great value in providing further evidence of safety of 3F-PCC in cardiac surgery.

Conclusions

Our observational study suggests that 3-factor PCC is not associated with an increased risk of thromboembolic complications or unfavourable outcomes compared to conventional treatment. These findings imply that PCC may be an acceptable therapy for the management of severe perioperative bleeding in open heart surgery and suggest the need for additional studies to confirm or refute our findings.

Conflict of Interest

There is no conflict of interest to declare.

Funding Statement

There is no funding to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.hlc.2018.08.016>.

References

- [1] Petricevic M, Biocina B, Milicic D, Svetina L, Boban M, Lekic A, *et al.* Activated coagulation time vs. intrinsically activated modified rotational thromboelastometry in assessment of hemostatic disturbances

- and blood loss after protamine administration in elective cardiac surgery: analysis from the clinical trial (NCT01281397). *J Cardiothorac Surg* 2014;9(129).
- [2] Ireland AoAoGBa. GUIDELINES Blood transfusion and the anaesthetist: management of massive haemorrhage. *J Assoc Anaesth Great Britain and Ireland* 2010;65:1153–61.
- [3] Lin DM, Murphy LS, Tran MH. Use of prothrombin complex concentrates and fibrinogen concentrates in the perioperative setting: a systematic review. *Transfus Med Rev* 2013;27(2):91–104.
- [4] Tanaka KA, Mazzeffi M, Durila M. Role of prothrombin complex concentrate in perioperative coagulation therapy. *J Intensive Care* 2014;2(1):60.
- [5] Joseph R, Burner J, Yates S, Strickland A, Tharpe W, Sarode R. Thromboembolic outcomes after use of a four-factor prothrombin complex concentrate for vitamin K antagonist reversal in a real-world setting. *Transfusion (Paris)* 2015;00:1–9.
- [6] Demeyere R, Gillardin S, Arnout J, Strengers PF. Comparison of fresh frozen plasma and prothrombin complex concentrate for the reversal of oral anticoagulants in patients undergoing cardiopulmonary bypass surgery: a randomized study. *Int J Transfus Med* 2010;99:251–60.
- [7] Sarode R, Milling Jr TJ, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. *Circulation* 2013;128(11):1234–43.
- [8] White R, Rushbrook J, McCgoldrick J. The dangers of prothrombin complex concentrate administration after heart surgery. *Blood Coagul Fibrinolysis* 2008;19:609–10.
- [9] Koster A, Meyer-Jark T, Shirmer U, Sandica E. Fulminant intra-operative right heart and pulmonary artery thrombosis following prothrombin complex concentrate infusion after complex open heart surgery with cardiopulmonary bypass. *A Case Rep* 2014;15:89–91.
- [10] Fraser TA, Corke C, Mohajeri M, Stevenson L, Campbell PJ. A retrospective audit of the use of prothrombinex-HT for refractory bleeding following adult cardiac surgery. *Crit Care Resusc* 2006;8:141–5.
- [11] Percy CL, Hartmann R, Jones RM, Balachandran S, Mehta D, Dockal M, Scheiflinger F, O'Donnell VB, Hall JE, Collins PW. Correcting thrombin generation ex-vivo using different haemostatic agents following cardiac surgery requiring the use of cardiopulmonary bypass. *Blood Coagul Fibrinolysis* 2015;26:357–67.
- [12] Ortmann E, Besser MW, Sharples LD, Gerrard C, Berman M, Jenkins DP, Klein AA. An exploratory cohort study comparing prothrombin complex concentrate and fresh frozen plasma for the treatment of coagulopathy after complex cardiac surgery. *Anesth Analg* 2015;121:26–33.
- [13] Song HK, Tibayan FA, Kahl EA, Sera VA, Slater MS, Deloughery TG, Scanlan MM. Safety and efficacy of prothrombin complex concentrates for the treatment of coagulopathy after cardiac surgery. *J Thorac Cardiovasc Surg* 2014;147:1036–40.
- [14] Arnékián V, Camous J, Fattal S, Rézaiguia-Delclaux S, Nottin R, Stéphan F. Use of prothrombin complex concentrate for excessive bleeding after cardiac surgery. *Interact Cardiovasc Thorac Surg* 2012;15:382–9.
- [15] Cappabianca G, Mariscalco G, Biancari F, Maselli D, Papesso F, Cottini M, Crosta S, Banescu S, Ahmed AB, Beghi C. Safety and efficacy of prothrombin complex concentrate as first-line treatment in bleeding after cardiac surgery. *Crit Care* 2016;20:1172–6.
- [16] Holland L, Warkentin TE, Refaai M, Crowther MA, Johnston MA, Sarode R. Suboptimal effect of a three-factor prothrombin complex concentrate (Profilnine-SD) in correcting supratherapeutic international normalized ratio due to warfarin overdose. *Transfusion (Paris)* 2009;49:1171–7.
- [17] Sniecinski RM, Levy JH. Bleeding and management of coagulopathy. *J Thorac Cardiovasc Surg* 2011;142:662–7.