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A Comparison of Prothrombin Complex Concentrate and Recombinant Activated Factor VII for the Management of Bleeding With Cardiac Surgery

Alyson Katz, PharmD, BCCCP[1], Tania Ahuja, PharmD, AACC, BCCP, BCPS, CACP[1], Serena Arnouk, PharmD, BCCCP[1], Tyler C. Lewis, PharmD, BCCCP[1], Kassandra Marsh, PharmD, BCIDP[1], John Papadopoulos, BS, PharmD, BCCCP[1], and Cristian Merchan, PharmD, BCCCP[1]

Abstract

Bleeding following cardiac surgery that warrants transfusion of blood products is associated with significant complications, including increased mortality at 1 year following surgery. Factor concentrates, such as prothrombin complex concentrate (PCC), or recombinant activated factor VII (rFVIIa) have been used off-label for bleeding in cardiac surgery that is refractory to conventional therapy. The objective of this retrospective study is to assess the hemostatic effectiveness of 4-factor PCC or rFVIIa for bleeding after a broad range of cardiac surgeries. Patients were included if they were at least 18 years of age and had undergone cardiac surgery with bleeding requiring intervention with 4-factor PCC or rFVIIa. There were no differences observed in the number of packed red blood cells (4-factor PCC: 2 units vs. rFVIIa: 2 units), fresh frozen plasma (0 units vs. 1 unit) or platelet (2 units vs. 2 units) transfusions following the administration of 4-factor PCC or rFVIIa. The patients in the rFVIIa group, required more cryoprecipitate than those in the 4-factor PCC group (4-factor PCC: 2 units (range 0-6) vs. rFVIIa: 2 units (range 0-8), $p = 0.03$). There were no differences in secondary outcomes of chest tube output at 2, 6, 12 and 24 hours, nor was there a difference in reexploration rates or the median length of stay in the intensive care unit. Thromboembolic complications at 30 days were similar between the two groups (4-factor PCC: 13% vs. rFVIIa 26%, $p = 0.08$). The total median dose requirement for 4-factor PCC was 1000 units (15 units/kg) and 2 mg (20 mcg/kg) for rFVIIa. The results demonstrate feasibility of utilizing the minimum amount of drug in order to achieve a desired effect. Both 4-factor PCC and rFVIIa appear to be safe and effective options for the management of bleeding associated with cardiac surgery.

Keywords

bleeding, cardiac surgery, critical care, safety

Introduction

Postoperative bleeding is a relatively common occurrence following cardiac surgery and is associated with significant morbidity and mortality.[1] The initial resuscitation after massive bleeding commences with packed red blood cells (pRBC) in order to sustain oxygen carrying capacity.[2] In addition, fresh frozen plasma (FFP) is often used as a means of supplementing coagulation factors.[3] This management of postoperative hemorrhage carries inherent risks of transfusion-related reactions, volume overload, and death at 1 year following surgery.[4,5]

Factor concentrates such as prothrombin complex concentrates (PCCs) or recombinant activated factor VII (rFVIIa) have been used off-label for bleeding in cardiac surgery that is refractory to conventional hemostatic therapy.[6] Compared to FFP, hemostatic agents such as PCC and rFVIIa, can rapidly be administered, do not require cross matching, have minimal risk of infection and are not associated acute lung injury.[2] Furthermore, given the smaller volume of administration, these agents

[1] Department of Pharmacy, NYU Langone Health, New York, NY, USA

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Corresponding Author:
Alyson Katz, PharmD, BCCCP, Medical Intensive Care Unit, Department of Pharmacy, NYU Langone Health, 545 First Avenue, New York, NY 10016, USA.
Email: alyson.katz@nyulangone.org

are unlikely to cause significant dilution of plasma constituents or circulatory overload.[2] Goal-directed use of coagulation factor concentrates may be desirable for minimizing patient exposure to allogenic blood products, while also augmenting the speed of intervention.[1,2,5]

Recently, studies have shown that concentrated factors may attenuate bleeding following cardiac surgery, as compared to placebo or FFP.[1,6-8] Both PCC and rFVIIa achieved hemostasis in 36%-75% of patients undergoing cardiac procedures and significantly decreased chest tube output when compared to FFP alone.[9,10] Only one prior study has compared the two agents head to head and found no difference in chest tube output at 24 hours following cardiac surgery.[1] As compared to rFVIIa, 4-factor PCC has a longer duration of activity, lower thrombotic risk and lower overall cost, which may be beneficial in cardiac surgery patients who experience acute blood loss.[1,11,12]

At our institution, both rFVIIa and 4-factor PCC have been used to manage significant bleeding during cardiac surgery. The purpose of this retrospective analysis is to assess the hemostatic effectiveness of 4-factor PCC compared to rFVIIa for bleeding after a broad-range of cardiac surgeries.

Materials and Methods

Study Design and Participants

This is a single-center, retrospective, Institutional Review Board-approved analysis of patients undergoing cardiac surgery between October 2015 and August 2019. Informed consent was waived due to the observational nature of the study. Patients were included if they were at least 18 years of age and had undergone cardiac surgery with bleeding perioperatively that required intervention with either 4-factor PCC (Kcentra®) or rFVIIa (Novoseven®). Patients were excluded if they received either agent for any indication other than mediastinal bleeding or if they had received both 4-factor PCC and rFVIIa.

Data collection was obtained through a retrospective review of the electronic health record, including patient demographics, past medical history, type of cardiac surgery performed, emergent versus elective nature, duration of cardiopulmonary bypass (CPB), and duration of aortic cross clamp. Surgery time was calculated from anesthesia start time to anesthesia stop time as documented in the patient medical record. Antithrombotic therapies prior to surgery and intraoperative doses of parenteral heparin and protamine reversal were documented. Historically, 4-factor PCC and rFVIIa products were stored, prepared and dispensed from the pharmacy. However, more recently, our institution has changed this practice, such that both 4-factor PCC and rFVIIa are now located in automated dispensing cabinets for immediate access by the surgical team without pharmacist review. The dose of 4-factor PCC or rFVIIa were determined by the operating surgeon, but institution-wide guidance was available if needed. All doses were categorized based on location of administration as either intra-operative or post-operative administration. The first dose of 4-factor PCC or rFVIIa was considered time zero. The total number of individual blood products transfused, as well as the sum of the number of units of pRBC, FFP, platelets, and cryoprecipitate 24 hours before and after time zero were collected. For the purpose of this analysis, 1 bag of cryoprecipitate (consisting of 5 units at our institution) counted as 1 additional blood product transfused. Repeat doses of 4-factor PCC or rFVIIa after time zero were also captured for 24 hours post-cardiac surgery. Laboratory values, including but not limited to hemoglobin, hematocrit, platelets, creatinine, and international normalized ratio (INR) were collected preceding and following administration of 4-factor PCC or rFVIIa. Total estimated blood loss documented during surgery and the chest tube output was also collected, as well as the administration of peri-operative blood products and hemostatic agents such as desmopressin (DDAVP), tranexamic acid (TXA) and aminocaproic acid, all of which were given at the discretion of the cardiac surgery team.

Outcomes

The primary outcome was the number of units of pRBC transfused 24 hours following 4-factor PCC or rFVIIa administration. Key secondary outcomes included the chest tube output at 2, 6, 12 and 24 hours following 4-factor PCC or rFVIIa administration. For those patients who received the hemostatic agent in the operating room, chest tube output was collected from the time of surgery completion. If given post-operatively, chest tube output calculation began at the time of dose administration. Other secondary outcomes included return to the operating room for surgical re-exploration, intensive care unit (ICU) length of stay, hospital length of stay, and in-hospital mortality.

Safety outcomes included thromboembolic events collected within 30 days following cardiac surgery. Thromboembolic events were defined as any venous thromboembolism (VTE) diagnosed by imaging or documentation of new stroke, myocardial infarction or limb ischemia.

Statistics

Continuous variables were expressed as median values and interquartile range unless otherwise noted. Categorical data was analyzed using a chi-squared or Fisher's Exact test, as appropriate. Continuous variables were compared using a Mann-Whitney *U* test. Chest tube output was calculated as mean + standard error of mean and compared using an Independent (2-tailed) Samples test. A p value of ≤ 0.05 was considered statistically significant. A univariate analysis was performed to determine factors that were significantly associated with in-hospital mortality. All variables found to be significantly associated with mortality on univariate analysis, based on a p value of ≤ 0.05, were entered into a multivariable regression analysis. Data analysis was performed using IBM SPSS Statistic Software (Chicago, IL, version 25).

Results

During the study time period, there were a total of 316 cardiac surgery patients that received 4-factor PCC and 102 patients

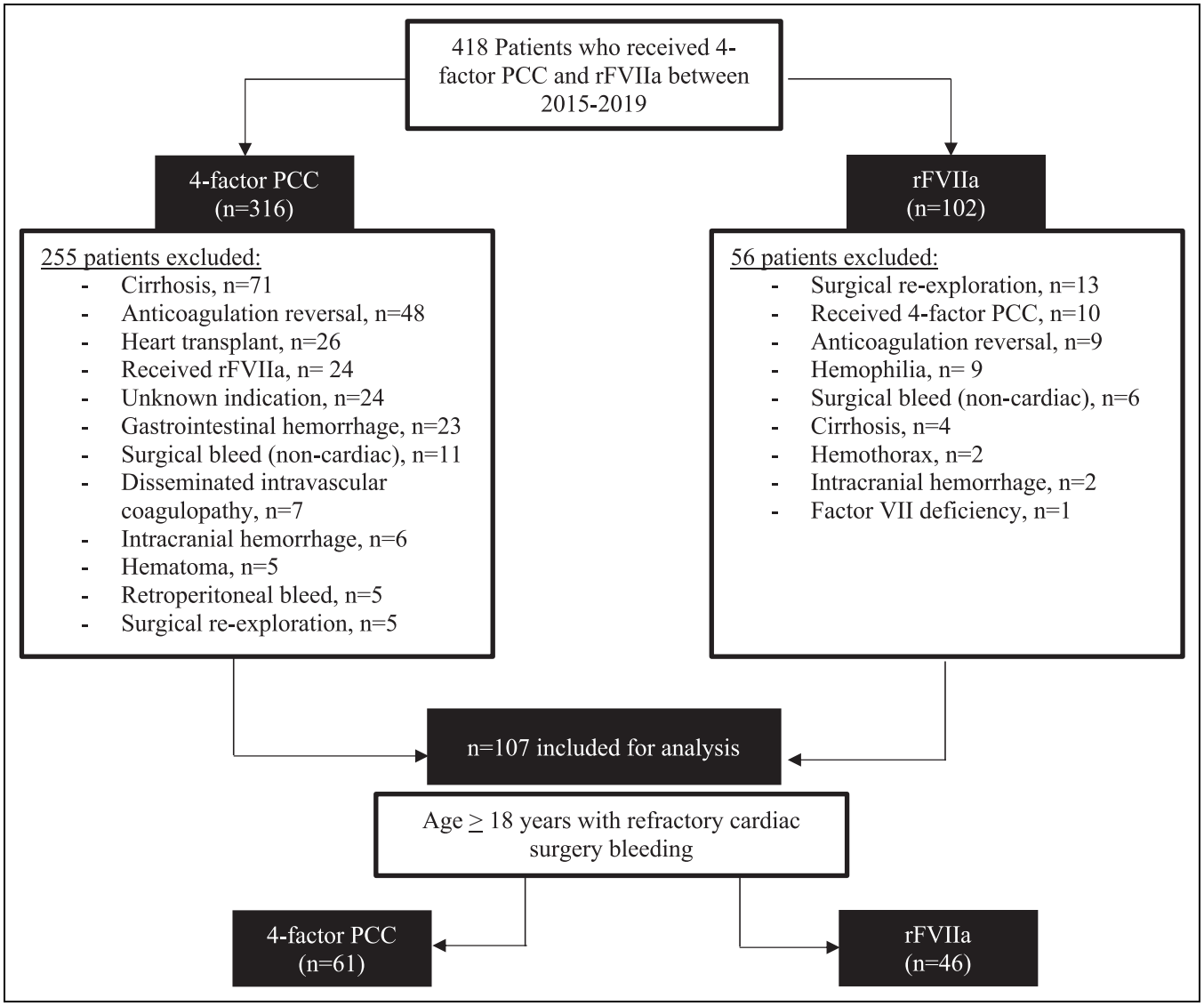


Figure 1. Flow diagram for study inclusion.

that received rFVIIa. From the 418 cardiac surgery patients screened, a total of 107 patients met inclusion and required hemostatic rescue for bleeding associated with cardiac surgery. Reasons for exclusion are listed in Figure 1. From these 107 patients, 61 (57%) received 4-factor PCC and 46 (43%) received rFVIIa. The preoperative demographics of patients from the cohort are displayed in Table 1. The patients were primarily male with a median age of 66 years old (range 29-88). The most common comorbidities were valvular disease (72%), coronary artery disease (59%), Chronic heart failure (34%) and atrial fibrillation (31%). More patients in the rFVIIa group had hypertension at baseline (80.4% vs. 55% $p = 0.007$).

The most common type of cardiac surgery in the total cohort was a single valve procedure (46%) followed by a multivalve procedure (16%). More patients in the 4-factor PCC group underwent an aortic procedure (ie. aortic arch replacement, aortic root replacement or aortic aneurysm) as compared to patients that received rFVIIa (n = 13, 21.3% vs. n = 2, 4.3%, $p = 0.01$) (Table 2). There were 45 (73.8%) and 39 (84.8%) patients in the 4-factor PCC and rFVIIa group, respectively, that presented for an elective surgery ($p = 0.17$). The CPB time was (180 min (IQR 122-233) in the 4-factor PCC group vs. 136 min (IQR 113-168) in the rFVIIa group; $p = 0.01$) and aortic cross clamp time was (122 min (IQR 81-159) vs. 97 min (IQR 70-122); $p = 0.04$), respectively. The median time of surgery was 7.9 hours (6.7-10) in the 4-F PCC group and 7.4 hours (5.8-8.8) in the rFVIIa group ($p = 0.04$). Patients in the 4-factor PCC group had lower hemoglobin (10.6 vs. 14 g/dL, $p = 0.001$) prior to cardiac surgery.

During the procedure, all patients received heparin and 88.5% of patients in the 4-factor PCC group and 91.3% in the rFVIIa group were reversed with protamine ($p = 0.75$). An

Table 1. Preoperative Demographics and Perioperative Features Baseline Characteristics.

	4-factor PCC (n = 61)	rFVIIa (n = 46)	P value
Age, years	65 (57-73)	69 (58-78)	0.06
Male gender, n (%)	40 (66)	37 (80)	0.09
Actual weight, kg	74.5 (60.6-87.1)	74 (65-85)	0.76
BMI, kg/m^2	25.2 (22.5-29.1)	25 (23-28)	1.00
Re-do sternotomy, n (%)	14 (23)	4 (9)	0.05
Hgb at admission	10.6 (8.7-12.7)	13 (10.6-13.8)	0.001
HCT at admission	33.1 (27-39.2)	39.5 (33.1-42.6)	0.001
Past medical history, n (%)			
Valvular heart disease	45 (73)	32 (70)	0.63
Coronary artery disease	41 (67)	23 (50)	0.07
Hypertension	34 (55)	37 (80)	0.007
Chronic heart failure	19 (31)	17 (37)	0.53
Atrial fibrillation	19 (31)	14 (30)	0.93
Renal disease	10 (16)	3 (7)	0.12
Myocardial infarction	9 (15)	4 (9)	0.34
Implantable cardiac device	9 (15)	0 (0)	0.01
Malignancy	9 (15)	4 (9)	0.34
Percutaneous coronary intervention	8 (13)	1 (2)	0.08
Bleeding in past 6 months	7 (11)	1 (2)	0.13
Ischemic stroke	6 (10)	1 (2)	0.23
Endocarditis	5 (8)	4 (9)	1.00
Cardiomyopathy	5 (8)	1 (2)	0.23
Deep vein thrombosis	4 (7)	0 (0)	0.13
Hemodialysis	3 (5)	1 (2)	0.63
Hemorrhagic stroke	2 (3)	1 (2)	1.00
Transient ischemic attack	1 (2)	0 (0)	1.00
Cirrhosis	1 (2)	0 (0)	1.00
Coagulopathy	1 (2)	0 (0)	1.00
Preoperative antithrombotics			
P2Y12 rec. antagonist (<5 days)	3 (5)	3 (7)	1.00
Aspirin (<7 days)	17 (28)	19 (41)	0.15
Warfarin (within 7 days)	5 (8)	10 (22)	0.05
INR at admission	1.4 (1.2-2.6)	2.1 (1.2-2.5)	0.72
DOAC (within 3 days)	2 (2.2)[a]	0 (0)	0.51

*All values listed in median (IQR), unless otherwise noted.
BMI: body mass index; Hgb: hemoglobin; HCT: hematocrit; INR: international normalized ratio.

antifibrinolytic agent was administered as a continuous infusion during the surgery to 87% of patients in the 4-factor PCC group and to 63% of patients in the rFVIIa group during the surgery (p = 0.004). Fifty-three (87%) patients in the 4-factor PCC group received cell saver at a median of 570 mL (IQR 400-780) and 35 patients (76.1%) in the rFVIIa group received cell saver at a median of 540 mL (400-770). The median estimated blood loss documented during cardiac surgery was 500 mL in both groups (p = 0.88). Patients in the rFVIIa group had a lower median platelet count (173 vs 160 $*10^3$ cells/mcL, p = 0.04) prior to administration.

Outcomes

Following the administration of the studied hemostatic agent, 70.5% of patients in the 4-factor PCC group required a median of 2 units (range 0-18) of pRBC and 78.3% of patients in the rFVIIa group required a median of 2 units (range 0-10) of pRBC, p = 0.58 (Figure 2). All other blood product data is listed in Table 3. There were no differences in the amount of product or number of patients requiring FFP or platelets. The patients in the rFVIIa group required more cryoprecipitate both prior to [2 units (range 0-5) vs. 2 units (range 0-6), p = 0.04] and following [2 units (range 0-6) vs. 2 units (range 0-8), p = 0.03] the dose. There was also no difference in the total sum of blood products administered following the dose of the hemostatic agent (5 units vs 7.5 units, p = 0.35). The median initial dose of 4-factor PCC was 700 units (IQR 500-1000 units) and 2 mg (IQR 1-2 mg) for rFVIIa. Most patients (95%) received the dose of 4-factor PCC in the operating room, as compared to only 50% of patients in the rFVIIa group. The median time to first dose was 6.32 hours (IQR 5.15-7.48) in the 4-factor PCC group and 8 hours (IQR 6.48-10.8) in the rFVIIa group (p < 0.001). A repeat dose of 4-factor PCC was administered in 30 patients (49.2%) as compared to 11 patients (24%) in the rFVIIa group(p = 0.008). The median time to receiving

Table 2. Cardiac Surgery Characteristics.

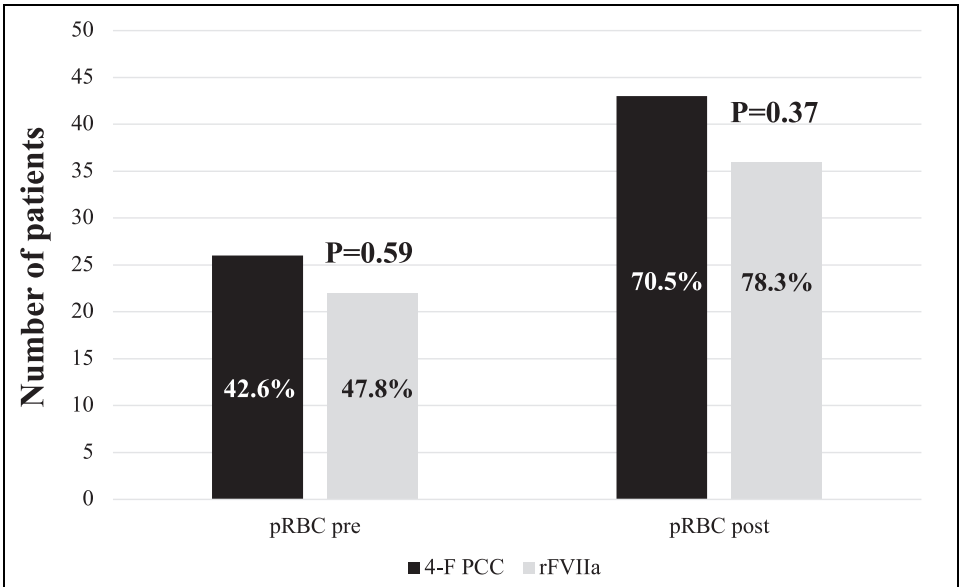
	4-factor PCC (n = 61)	rFVIIa (n = 46)	P value
Type of Surgery			
CABG	3 (5)	4 (9)	0.46
Multivalve procedure	10 (16)	7 (15)	0.87
Single valve procedure	28 (46)	20 (44)	0.80
CABG + valve	7 (12)	7 (15)	0.57
Aortic procedure[a]	13 (21)	2 (4)	0.012
Aortic dissection	7 (12)	5 (11)	0.92
VSD repair	2 (3)	1 (2)	1.00
Elective surgery	45 (74)	39 (85)	0.17
Emergent surgery	16 (26)	7 (15)	0.17
Operative data			
CPB time, min	180 (122-233)	136 (113-168)	0.01
Aortic cross-clamp time, min	122 (81-159)	97 (70-122)	0.04
Length of surgery, hours	7.9 (6.7-10)	7.4 (5.8-8.8)	0.04
Total dose of Heparin (units, median (IQR))[b]	30,000 (25,180-35,000)	30,000 (35,000-36,000)	0.88
Reversal with Protamine	54 (89)	42 (9)	0.75
Total dose of protamine, mg, median (IQR)	300 (250-353)	300 (250-400)	0.74
Antifibrinolytic, n (%)	53 (87)	29 (63)	0.004
DDAVP	2 (2)	0 (0)	0.52
Cell saver, n (%)	53 (87)	35 (76)	0.15
Cell saver volume, mL	570 (400-780)	540 (400-770)	0.79
Estimated blood loss, mL, median (IQR)	500 (300-700)	500 (200-1000)	0.88
Number of chest tubes, median (IQR)	3 (2-4)	3 (2-4)	0.31
Blood products prior to factor concentrate administration			
Packed red blood cells			
Pre, n (%)	26 (42.6)	22 (47.8)	0.59
Dose, units	0 (0-11)	0 (0-12)	0.38
Platelets			
Pre, n (%)	45 (73.8)	27 (58.7)	0.10
Dose, units	1 (0-8)	1 (5)	0.09
Fresh Frozen Plasma			
Pre, n (%)	13 (21.3)	15 (32.6)	0.18
Dose, units	0 (0-5)	0 (0-10)	0.44
Cryoprecipitate			
Pre, n (%)	43 (70.5)	30 (65)	0.56
Dose, units	2 (0-5)	2 (0-6)	0.04
Products required pre dose, n(%)[c]	53 (86.9)	39 (84.8)	0.75
Products required pre dose, units, median (IQR)[c]	4 (2-6)	6 (2.5-10.5)	0.35

*All values listed as n (%), unless otherwise noted.
[a]Aortic procedures: aortic arch replacement, aortic root replacement, aortic aneurysm.
[b]All patients received heparin.
[c]Product combination: pRBC + FFP+ Cryo + Platelets.
CABG: coronary artery bypass graft; VSD: ventricular septal defects; CPB: cardiopulmonary bypass.

a second dose of 4-factor PCC and rFVIIa was 30 minutes (IQR 14-43) vs. 39 minutes (IQR 19-90) from the initial dose, respectively. The median repeat dose of 4-factor PCC was 500U (IQR 500-1000U) and of rFVIIa was 1 mg (IQR 1-3 mg).

Secondary Outcomes

There was no difference in chest tube output at 2, 6, 12 and 24 hours, as displayed in Table 4. Thirteen (21%) patients in the 4-factor PCC group and 9 (19.6%) patients in the rFVIIa group returned to the operating room for either surgical exploration or cardiac tamponade (p = 0.67). The median length of ICU stay was 8 days in both groups. There were no differences in thromboembolic complication rates between the two groups at 30 days (n = 8, 13% vs. n = 12, 26%, p = 0.08), as listed in Table 5. A higher mortality rate was observed in patients who received 4-factor PCC (23% vs. 4.5%, p = 0.01). A univariate analysis was performed to assess factors associated with mortality. The following characteristics were associated with mortality: history of percutaneous coronary intervention (PCI) (OR 5.2 [95% CI 1.24-22.04], p = 0.02), cardiomyopathy (OR 13.53 [95% CI 2.25-81.45], p < 0.001), renal failure (OR 6.46 [1.83-22.77], p < 0.001), malignancy (OR 4.27 [1.19-15.22], p = 0.02), presence of an ICD (OR 5.23



	4- factor PCC (n=61)	rFVIIa (n=46)	P value
pRBC pre, units	0 (0-11)	0 (0-12)	0.38
pRBC post, units	2 (0-18)	2 (0-10)	0.58

All values listed in median (range), unless otherwise noted

Figure 2. Primary outcome: pRBC transfusions post hemostatic agent.

Table 3. Blood Products.

	4-factor PCC (n = 61)	rFVIIa (n = 46)	P value
Platelets			
Post, n(%)	48 (78.7)	33 (71.7)	0.41
Dose, units	2 (0-8)	2 (0-6)	0.80
Fresh frozen plasma			
Post, n(%)	24 (39.3)	26 (56.5)	0.08
Dose, units	0 (0-9)	1 (0-9)	0.88
Cryoprecipitate			
Post, n(%)	43 (70.5)	34 (73.9)	0.69
Dose, units	2 (0-6)	2 (0-8)	0.03
Products required post dose, n(%)[a]	55 (90.2)	40 (87)	0.60
Products required post dose, units[a] median (IQR)	5 (2-8)	7.5 (4-12.25)	0.35
Hemostatic agent			
Dose of hemostatic agent[b] median, (IQR)	700 (500-1000)	2 (1-2)	–
Administration location, ICU, n(%)	6 (10)	23 (50)	<0.001
Time to first dose, hours	6.32 (5.2-7.5)	8 (6.5-10.8)	0.001
Patients requiring repeat doses, n (%)	30 (49.2)	11 (24)	0.008
Repeat dose, (mcg/units), median (IQR)	500 (500-1000)	1 (1-3)	–
Time to first repeat dose, (min), Median (IQR)	30 (15-43)	39 (19-90)	0.22
Number of repeat doses	1 (0-4)	0 (0-3)	0.85
Total dose received, median (IQR)	1000 (1000-1500)	2 (1-3)	
Total dose received (weight based), median (IQR)	15units/kg (10-20)	20 mcg/kg (20-32.5)	

*All values listed as median (range), unless otherwise noted.
[a]Product combination: pRBC + FFP+ Cryo + Platelets.
[b]Refers to first dose given.

Table 4. Secondary Outcomes.

	4-factor PCC (n = 61)	rFVIIa (n = 46)	P value
Chest tube output[a], mL			
2 hours	273. 76+ 32.21	313.42 + 30. 81	0.38
6 hours	526.06 + 57.87	547.89 + 45.47	0.77
12 hours	742.62 + 69.00	838.50 + 73.37	0.34
24 hours	1164.76 + 85.53	1345.86 + 121.15	0.23
Return to operating room, n (%)	13 (21)	9 (19.6)	0.67
Surgical exploration	9 (69)	8 (17.4)	0.54
Cardiac tamponade	4 (6.5)	1 (2.2)	0.23
Time since surgery, hours	21 (7.2-66.7)	16.8 (7.2-45.6)	0.60
ICU Length of stay, days, median (IQR)	8 (6-13)	8 (6-15)	0.33
Hospital Length of stay, days, median (IQR)	10 (7-17)	11 (7-15)	0.59
Mortality in-hospital, n (%)	14 (23)	2 (4.5)	0.01

*All values listed as mean + SEM, unless otherwise noted.
[a]Cumulative chest tube output at each time point.

Table 5. Complications.

	4-factor PCC (n = 61)	rFVIIa (n = 46)	P value
Thromboembolic event at 30 days	8 (13)	12 (26)	0.08
DVT	1 (1.6)	3 (6.5)	0.31
Myocardial infarction	0 (0)	3 (3.4)	0.25
Ischemic stroke	6 (9.8)	4 (8.7)	1.00
Transient ischemic attack	0 (0)	2 (4.3)	0.11
Limb ischemia	1 (1.1)	0 (0)	0.43
Anticoagulation at time of complication	4 (6.6)	2 (4.3)	0.69

*All values listed in n(%), unless otherwise noted.

[1.24-22.04], p = 0.01), emergent surgery (OR 3.2 [1.07-9.79], p = 0.05), return to operating room (OR 3.5 [1.14-10.65], p = 0.04) and receipt of 4-factor PCC (OR 4.2 [1.14-15.8], p = 0.02). After multivariable regression analysis, only the following remained to be associated with increased mortality: past medical history of cardiomyopathy (OR 29.58 [1.42-613.23], p = 0.03) malignancy (OR 18.6 [2.1-163.11], p = 0.008), and emergent surgery (OR 13.78 [1.75-108.14], p = 0.013).

Discussion

We compared the hemostatic effectiveness and safety of 4-factor PCC to rFVIIa in the management of bleeding associated with cardiac surgery. We found no differences observed in the number of pRBCs transfused following the administration of 4-factor PCC or rFVIIa. Also, total blood product utilization was similar among patients who received 4-factor PCC or rFVIIa at a median of 5 and 7.5 units, respectively. We did observe more cryoprecipitate use in the group that received rFVIIa, which may be explained by the fact that this group was less likely to receive an antifibrinolytic agent. We observed no difference in the amount of FFP or platelets required in the two groups.

Both 4-factor PCC and rFVIIa have been used off-label for refractory bleeding from cardiac surgery and have demonstrated hemostatic effectiveness, as measured by a reduction in blood transfusion requirements.[1] In one retrospective review, chest tube output decreased by 50% when a 3-factor, non-activated PCC was used to manage postoperative bleeding when compared to rFVIIa.[3] In another retrospective, propensity-matched cohort, patients who underwent cardiac surgery with CPB, had significantly less chest tube output, and FFP or platelet transfusion requirements if they were in the group that received 3-factor PCC as compared to patients who received rFVIIa.[6] These studies demonstrate that 3-factor PCC may be utilized for bleeding after cardiac surgery, and provide a therapeutic advantage as determined by beneficial clinical outcomes and lower costs. More recently, a retrospective analysis that compared 25 U/kg of 4-factor PCC to 45 mcg/kg rFVIIa found no difference in chest tube output 24 hours postoperatively between the two groups (2669.6 mL vs. 3156.5 mL, p = 0.937), respectively; results that are similar to our current findings. [1] However, unlike our study, the patients that received rFVIIa in the above study, required more units of FFP (2.4 units vs 4.2 units, p = 0.016) and had a longer hospital length of stay (11.7 days vs. 15.9 days, p = 0.048).[1] Compared to our study population, fewer patients received more than 1 dose of a hemostatic agent, which may be due to higher initial dosing regimens. The authors concluded that 4-factor PCC may be an equally efficacious alternative to rFVIIa for significant bleeding during cardiac surgery.[1]

Weight-based dosing is recommended for both products, when used for bleeding in cardiac surgery, and the doses vary in the literature from 15 to 180 mcg/kg for rFVIIa and 15 to 40 IU/kg for 4-factor PCC.[1,3,12,13,14] The majority of studies that assessed an initial and repeated dose of 4-factor PCC or rFVIIa, observed that the administered dose of the hemostatic agent was a last resort and after blood product resuscitation. In our cohort, 49.2% and 24% of patients in the 4-factor PCC and rFVIIa groups, respectively, required repeat doses. The median time to a repeat dose was approximately 30 minutes, suggesting that the intention may have been to pre-emptively provide a low initial dose with a plan to re-dose if the desired level of hemostasis was not achieved. The total median dose requirement for 4-factor PCC was 1000 units (15U/kg) and 2 mg (20 mcg/kg) for rFVIIa. Our reported weight-based dosing falls in line with the lower end of reported dosing schemes, and we found no difference in blood product utilization, chest tube output, or the need to return to the operating room.

In our cohort, the incidence of serious adverse events was very low. We found no significant difference in venous or arterial thromboembolic events. Although this study was not powered to assess mortality, patients who received 4-factor PCC had a higher mortality rate, which may be attributed to patient and surgery characteristics as found on multivariable regression analysis. While a history of cardiomyopathy, malignancy, or need for emergent surgery were independent predictors of mortality, receipt of 4-factor PCC was not.

Limitations

Our analysis had several limitations. This was a retrospective, single-center analysis with an overall small sample size of patients. The hemostatic agent selected was not standardized, but rather was at the discretion of the cardiac surgeon. Furthermore, the hemostatic agent chosen was left to the discretion of the cardiac surgeon in the OR or surgical team once in the ICU. There was no standard protocol for resuscitation and lab values were not always checked prior to blood product administration. Another limitation of our study is the difference in patient demographics between the groups and the differences in cardiac procedures, which may be attributed to the non-randomized, retrospective nature of the study. Data for hourly chest tube output was only available post-operatively, and thus may have underestimated total blood loss. Lastly, the timing of cell saver administration in relation to the hemostatic agent was unclear, making it difficult to interpret whether cell saver may have had a marked effect.

Conclusion

Both 4-factor PCC and rFVIIa are pharmacotherapeutic options for patients experiencing bleeding during or after cardiac surgery. Our results demonstrate the feasibility of utilizing the minimum amount of drug in order to achieve a desired effect. Given the ease of accessibility of these agents when stocked in OR automated dispensing cabinets, redosing can be administered in a timely fashion. Future prospective research comparing 4-factor PCC to rFVIIa is warranted.

Authors' Note

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ORCID iD

Alyson Katz, PharmD, BCCCP https://orcid.org/0000-0002-7177-4631

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