Supplemental Online Content

Smith MM, Schroeder DR, Nelson JA, et al. Prothrombin complex concentrate vs plasma for post–cardiopulmonary bypass coagulopathy and bleeding: a randomized clinical trial. *JAMA Surg*. Published online June 29, 2022. doi:10.1001/jamasurg.2022.2235

This supplemental material has been provided by the authors to give readers additional information about their work.

Appendix 1: Study Inclusion and Exclusion Criteria

Baseline Inclusion criteria were:

1. ≥ 18 years of age
2. Undergoing a cardiac surgical procedure utilizing cardiopulmonary bypass
3. Study staff availability

Baseline Exclusion criteria were:

1. Institutional research cessation policy in effect due to COVID 19
2. Enrollment in other/conflicting studies
3. Are unable to grant informed consent or comply with study procedure
4. History of hypercoagulable condition (e.g. Factor V Leiden, AT-3 deficiency, Prothrombin gene mutation, Anti-phospholipid antibody syndrome, etc.) or previous unprovoked thromboembolic complications
5. Coagulopathic conditions such as factor deficiencies, factor inhibitors, heparin induced thrombocytopenia, or use of intravenous anticoagulants other than heparin at the time of cardiovascular surgery
6. Thromboembolic event with past 3 months
7. Received oral therapy with ELIQUIS (apixaban) or Xarelto (rivaroxaban) within 3 days prior to planned surgical procedure
8. Received oral therapy with clopidogrel, prasugrel, or dabigatran within 5 days prior to planned surgical procedure
9. Are undergoing emergency open heart-surgery
10. Undergoing minimally invasive non-sternotomy heart surgery
11. Cardiopulmonary bypass time is expected to be <30 minutes
12. Are pregnant
13. Heparin allergy

Enrolled subjects must meet additional intraoperative criteria to receive study treatment:

Intraoperative Inclusion criteria were:

1. Have evidence of excessive microvascular bleeding in the surgical field as determined by the surgical team
2. Prothrombin time (PT) >16.6 sec/ International normalized ratio (INR >1.6) sec on initial post cardiopulmonary bypass labs

Intraoperative Exclusion criteria were:

1. Fibrinogen < 144 mg/dL on initial post cardiopulmonary bypass labs
2. Life threatening bleeding necessitating transfusion of hemostatic products (PCC or plasma) prior to the study intervention time point
3. Circumstances for which the safety of the patient could be jeopardized by continued adherence to the study protocol
4. Extracorporeal membrane oxygenation (ECMO) requirement intraoperative or postoperative

Appendix 2. Adverse Event Definitions:

- Thromboembolic events (new venous or arterial thrombosis diagnosed by Doppler ultrasound, stroke or transient ischemic attack, mesenteric ischemia requiring intervention, myocardial infarction requiring intervention, end organ ischemia secondary to thromboembolic phenomenon)
- Acute kidney injury (AKI) was defined by Acute Kidney Injury Network (AKI-N) criteria as on absolute rise in serum creatinine of ≥ 0.3mg/dL or 50% / 1.5 fold increase from baseline, within 48 hours of surgery.[16]
- Renal failure necessitating initiation of NEW renal replacement therapy.
- Acute Respiratory Distress Syndrome (ARDS) by Berlin definition.[17]
- Transfusion related complications:

a. TRALI (Transfusion related acute lung injury)[18], hemolytic reaction, anaphylactic/allergic reaction

Supplemental Table 1. Intraoperative Laboratory Values*

	Plasma (N=48)			PCC (N=51)		t-test	Estimated Treatment effect**		
Variable	N	Mean (SD)		N	Mean (SD)	p	Estimate	(95% CI)	p
Hemoglobin, g/dL									
Pre CPB	48	12.47 (1.55)		51	11.65 (1.58)	0.011			
Pre treatment	48	9.86 (1.27)		51	9.64 (1.26)	0.38			
Post treatment	47	9.81 (1.68)		51	10.51 (1.62)	0.040	0.81	(0.20, 1.43)	0.010
Platelet count, $\times 10^9$/L									
Pre CPB	48	205.13 (70.64)		51	199.57 (64.15)	0.68			
Pre treatment	48	111.31 (37.41)		48	107.40 (40.56)	0.62			
Post treatment	48	129.31 (33.62)		51	136.14 (40.35)	0.36	9.50	(-3.65, 22.65)	0.155
Fibrinogen									
Pre treatment	47	212.26 (51.25)		49	213.84 (54.12)	0.88			
Post treatment	47	218.74 (55.95)		50	208.56 (45.94)	0.33	-12.71	(-27.68, 2.26)	0.095
PT, seconds									
Pre treatment	48	19.17 (1.91)		50	19.27 (2.12)	0.81			
Post treatment	48	15.07 (1.86)		51	13.75 (1.34)	<0.001	-1.37	(-1.91, -0.84)	<0.001
INR									
Pre treatment	48	1.73 (0.18)		50	1.75 (0.19)	0.73			

	Plasma (N=48)			PCC (N=51)		t-test	Estimated Treatment effect**		
Variable	N	Mean (SD)		N	Mean (SD)	p	Estimate	(95% CI)	p
Post treatment	48	1.37 (0.14)		51	1.26 (0.15)	<0.001	-0.12	(-0.16, -0.07)	<0.001
aPTT, seconds									
Pre treatment	47	39.60 (12.86)		50	42.66 (16.25)	0.31			
Post treatment	48	35.33 (19.55)		51	34.98 (13.49)	0.92	-2.24	(-8.41, 3.94)	0.474

*Pre-treatment values were obtained post-CPB prior to receiving study drug. Post-treatment values were obtained approximately 10 minutes following the administration of the last unit of study drug.

**Estimated treatment effect from analysis of covariance with the post-treatment value included as the dependent variable, treatment (PCC vs FFP) included as the independent variable and the pre-treatment value included as the covariate.

Abbreviations: aPTT = activated partial thromboplastin time, CPB = cardiopulmonary bypass, INR = international normalized ratio, PT = prothrombin time

Supplemental Table 2. Intraoperative Transfusions and Estimated Blood Loss*

	Pre-Study Drug			Post-Study Drug			Total Intraoperative		
Characteristic	Plasma (N=48)	PCC (N=51)	p**	Plasma (N=48)	PCC (N=51)	p**	Plasma (N=48)	PCC (N=51)	p**
RBC, units			0.07			0.040			0.26
0	31 (65)	25 (49)		33 (69)	44 (86)		27 (56)	21 (41)	
1	6 (13)	7 (14)		10 (21)	4 (8)		5 (10)	8 (16)	
2	8 (17)	11 (22)		3 (6)	3 (6)		4 (8)	12 (24)	
3 or more	3 (6)	8 (16)		2 (4)	0 (0)		12 (25)	10 (20)	
Platelets, units			0.06			0.32			0.40
0	25 (52)	17 (33)		33 (69)	40 (78)		16 (33)	14 (27)	
1	17 (35)	23 (45)		12 (25)	7 (14)		12 (42)	21 (41)	
2	5 (10)	10 (20)		1 (2)	4 (8)		9 (19)	10 (20)	
3 or more	1 (2)	1 (2)		2 (4)	0 (0)		3 (6)	6 (12)	
Cryoprecipitate, units			0.17			0.30			0.20
0	44 (92)	42 (82)		44 (92)	43 (84)		40 (83)	37 (73)	
1	2 (4)	2 (4)		0 (0)	2 (4)		2 (4)	3 (6)	
2	1 (2)	7 (14)		3 (6)	6 (12)		4 (8)	8 (16)	
3 or more	1 (2)	0 (0)		1 (2)	0 (0)		2 (4)	3 (6)	

Plasma, units			1.00				0.35				0.35
0	0 (0)	0 (0)			44 (92)	49 (96)			44 (92)	49 (96)	
1	0 (0)	0 (0)			0 (0)	0 (0)			0 (0)	0 (0)	
2	0 (0)	0 (0)			3 (6)	2 (4)			3 (6)	2 (4)	
3 or more	0 (0)	0 (0)			1 (2)	0 (0)			1 (2)	0 (0)	
Cell Saver, mL									633 (484, 1018)	702 (472, 917)	0.70
EBL, mL									1266 (968, 2035)	1404 (944, 1834)	0.70

*Data are summarized using n (%) for the number of units transfused and median (25^{th}, 75^{th}) for cell saver and estimated blood loss.

**Rank sum test.

Abbreviations: EBL = estimated blood loss, mL = milliliters, PCC = prothrombin complex concentrate, RBC = red blood cells