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CORRESPONDENCE

The off-label utilization of prothrombin complex concentrate with cryoprecipitate as an alternative to plasma transfusion in bleeding patients with acute right ventricular failure

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To the Editor,

The coagulopathic patient with right ventricular failure presents a conundrum to the perioperative clinician. Because these patients are preload dependent, hemorrhage may rapidly result in cardiogenic shock and end-organ ischemia. Acute coagulation factor replacement to correct factor deficiencies and reverse bleeding entails the transfusion of a large volume of plasma (10-15 $mL \cdot kg^{-1}$), which will increase most coagulation factors by 20-30% so as to approach the 30-40% target levels considered adequate for hemostasis.[1] In turn, however, such large transfusion volumes can potentially decrease left ventricular preload and cardiac output through ventricular interdependence. Furthermore, when the surgical setting is cardiothoracic, volume overload may promote catastrophic wound or graft dehiscence. When confronted with such complex coagulopathic patients, we have administered the combination of prothrombin complex concentrates (PCCs) with cryoprecipitate as a lower-volume alternative to plasma transfusion.

The combination of 1,000 units of a four-factor prothrombin complex and 10 units of cryoprecipitate provides most coagulation factors in doses comparable with four units of plasma, but at less than 15% of the volume (Table).

We acknowledge that neither Factor V nor Factor XI is present in significant quantities in either PCCs or cryoprecipitate but propose that these shortfalls are unlikely to be clinically meaningful. The platelet transfusions that many hemorrhaging patients require (particularly in the setting of the acquired thrombasthenia of cardiopulmonary bypass circuits) likely provide an alternative source of Factor V, as 20% of circulating Factor V is contained within platelet alpha granules.[2] While Factor XI concentrates are available, they are not currently licensed in Canada and are therefore difficult to obtain. Furthermore, the significance of not replenishing Factor XI in a patient with global coagulopathy is unclear. In patients with congenital Factor XI deficiency, for example, there is a poor correlation between factor levels and bleeding tendency,[3] possibly reflecting the ability of tissue-factor(TF)/Factor VII to activate Factor IX, Factor XI's natural substrate. As one of the hemostatic mechanisms of Factor XI is the induction of thrombin activatable fibrinolysis inhibitor,[4] the co-administration of antifibrinolytic medications, such as tranexamic acid (considered a standard of care in patients undergoing cardiopulmonary bypass surgery), may also provide some compensation for relative Factor XI deficiency in hemorrhaging patients.[5] Given the above, with the long circulating half-life of Factor XI at 50 hr and its thrombogenicity when plasma levels exceed 70%, we do not endorse specific replacement in this setting.[5]

Our anecdotal experience regarding the hemostatic efficacy of PCCs when combined with cryoprecipitate suggests that the combination may be a useful alternative to plasma in patients with global coagulopathy who are unable to tolerate plasma transfusions, particularly if they are already being managed concurrently with platelet transfusions and

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Table The differences in calculated factor concentrations prothrombin complex concentrates (PCCs) and cryoprecipitate *vs* a standard dose of plasma

	Plasma*		PCCs + Cryoprecipitate*		
	Plasma (/mL dose)	Totals in An Average Adult Dose	PCCs -1,000 U (/mL dose)	Cryoprecipitate (/mL dose)	Total in an Average Adult Dose
Factor II (U)	0.95	851	26		1,040
Factor V (U)	1.06	950			0
Factor VII (U)	0.93	833	16.5		660
Factor VIII (U)	0.91	815		6.3	630
Factor IX (U)	0.87	780	25		1,000
Factor X (U)	1.07	959	33		1,320
Factor XI (U)	0.94	842			0
Fibrinogen (mg)	3.92	3,512		43.2	4,320
vWF (U)	1.26	1,129		8.1	810
Protein C (U)	1.07	959	22		880
Protein S (U)	1.09	977	22		880
Average Volume of an Adult Dose (mL)		1,000	40	100	140

*Factor concentrate values for frozen plasma were calculated by taking the average values described by Serrano *et al*.[6] for a buffy coat plasma production method. Factor concentrate values for PCCs were calculated by taking the average values outlined by the product monograph for Octaplex (Octapharma, Lachen).[7] Factor concentrate values for cryoprecipitate were calculated by taking the average values outlined by both Caudill *et al*.[8] and *Canadian Blood Services, Circular of Information*.[9] Total adult doses were calculated by taking the average volume of both plasma and cryoprecipitate using the *Canadian Blood Services Circular of Information*[9] and for PCCs utilizing a 1,000 U dose of Octaplex (Octapharma, Lachen) being 40 mL reconstituted with saline[7]

vWF = von Willebrand factor

antifibrinolytic therapy. In general, we have deployed the PCC/cryoprecipiate combination when the majority of the following patient variables have been present:

1. Patient is experiencing significant hemorrhage (e.g., bleeding > 150 mL·min^{-1}).
2. Surgical hemostasis has been obtained.
3. International normalized ratio is > 1.7 due to global coagulopathy (e.g., not attributable to anticoagulant medications or clotting factor inhibitors).
4. Other potential contributors to coagulopathy have been corrected (e.g., acidosis, hypothermia, thrombocytopenia, thrombasthenia— in settings where thrombasthenia is suspected but must be managed empirically, a minimum of two adult doses of platelets is suggested).
5. Appropriate antifibrinolytic doses have been used.
6. Evidence of impending right ventricular failure (e.g., right atrial pressure [RAP] > 8-10 mmHg, increasing RAP, right ventricular outflow tract obstruction on transesophageal echocardiography, etc.).

As PCCs are licensed for use only in patients with deficiencies of vitamin K-dependent clotting factors (e.g., as temporary reversal agents for warfarin), this off-label use is always preceded by a consultation between the attending physician and the blood transfusion service medical director at our institution. Physicians have reported both the correction of coagulation test times and reductions in bleeding, and in this context, we have yet to observe major adverse thrombotic events. In the majority of cases, platelet transfusions have usually been administered before consideration of the combination. Readers of the *Journal* may achieve similar effects when confronted with comparable challenging cases. Nonetheless, the formal examination of this regimen in controlled clinical research is suggested before the adoption of this transfusion measure as a standard of care.

Conflicts of interest None declared.

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