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Cryoprecipitate (Cryo) and Alternatives

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KEY POINTS

- Cryoprecipitated Antihemophilic Factor (cryoprecipitate) is primarily used for fibrinogen replacement.
- Clinical criteria and dosing for fibrinogen replacement therapy are hereby described.
- Healthcare providers should be familiar with the alternatives currently available for fibrinogen replacement.

CRYOPRECIPITATE

Since 2015, transfusions of cryoprecipitate (cryo) have increased nationally, correlating with an increase in distribution by blood centers.[1,2] As demand for cryoprecipitate in the U.S. threatened to outpace supply, blood centers and hospitals investigated available alternative products for fibrinogen replacement, all of which are derived from human plasma, but differ in manufacturing process, fibrinogen concentration, preparation process for transfusion, product expiration, and cost to transfuse (see Table 1). Cryoprecipitate contains factor VIII (FVIII), von Willebrand factor (vWF), factor XIII (FXIII), and fibrinogen. It is a cold insoluble precipitate manufactured from whole blood or apheresis plasma.[3] Fibrinogen plays a critical role in hemostasis and clot formation and maintaining a minimum fibrinogen level is important in bleeding patients.[3,4] Initially, cryoprecipitate was transfused for patients with FVIII and FXIII deficiencies and von Willebrand disease (vWD) as the primary source for these hemostatic factors. However, it is now contraindicated for these patients if recombinant factor concentrates (not manufactured from human plasma) are available.[3,4] Fibrinogen supplementation is now mostly indicated for bleeding or prevention of bleeding in patients with hypofibrinogenemia (see Table 2).[5] Recent studies have demonstrated a benefit of fibrinogen replacement in the setting of patients with major hemorrhage related coagulopathy.[5] This has led to studies assessing the benefit of fibrinogen replacement in clinical settings such as trauma, obstetrics, and cardiothoracic surgery, especially with use of the cardiopulmonary bypass pump, and likely has led to the increased use of these products in these settings.[6,7] Additionally, there has been increased adoption of viscoelastic testing, including thromboelastography (TEG) and rotational thromboelastometry (ROTEM), which is associated with an increased utilization of cryoprecipitate and fibrinogen concentrates.[8,9]

Cryoprecipitate may be produced from plasma frozen within eight hours of collection (FFP), plasma frozen within 24 hours of collection (PF24), or from plasma pathogen-reduced prior to freezing (PR-Cryo FC).To mitigate the decrease in the supply of cryoprecipitate manufactured from FFP, some blood centers have obtained U.S. Food and Drug Administration (FDA) approval to manufacture it from PF24.[10] Cryoprecipitate produced from either FFP or PF24 must meet FDA quality control (QC) requirements for potency that mandates a minimum of 80 international units of FVIII and 150 mg of fibrinogen, although the content of fibrinogen in each unit fluctuates due to donor variability and institution-specific practices and is typically higher than the minimum required with an average of 325mg/unit reported.[11]

Cryoprecipitate may also be pooled to facilitate transfusion of higher doses of fibrinogen from a single container from units that must meet these minimum QC requirements. The expiration of cryoprecipitate once thawed in a closed system for transfusion is six hours for a single unit or if pooled using a sterile connecting device, and four hours if pooled or if the units are thawed in an open system. This short time-to-transfuse can lead to a high wastage rate and often requires hospital transfusion service staff for on-demand thawing.[12]

PR-Cryo FC is prepared from single donor apheresis plasma or a pool of two whole blood-derived plasma units which are pathogen reduced utilizing the INTERCEPT ®Blood System (Cerus, Concord, Calif.) before freezing. An advantage over cryoprecipitate is that the product can be stored post-thaw for up to five days at room temperature allowing PR-Cryo FC to be prepared in advance and available for immediate, empirical use, minimizing wastage and shortening time to transfusion.[13] One study compared the hemostatic function of PR-Cryo FC to fibrinogen concentration by ROTEM and thrombin generation.[14] Storage out to 10 days at 20– 24°C did not diminish the hemostatic function of PR-Cryo FC and the study concluded that PR-Cryo FC provides similar and/or improved hemostatic rescue compared to fibrinogen concentration in dilutional coagulopathies, and this rescue ability is stable.[14] In actively hemorrhaging patients, where delays due to thawing may be associated with an increase in adverse outcomes including mortality, immediate availability of PR-Cryo FC has the potential to improve outcomes. A downside is the cost, which may be offset by the time limited "New Technology Add-On Payment" applicable to Medicare Fee for Service patients.[15]

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FIBRINOGEN CONCENTRATES

Fibrinogen Concentrates (FCs) are usually procured by the pharmacy and have the benefit over cryoprecipitate products of longer room temperature storage, greater dose predictability, higher concentration of fibrinogen per product volume, and rapid preparation of product at the patient's bedside. Although this product is made from thousands of pooled donations, it still appears to be safe from infection due to viral inactivation with solvent/detergent and filtration, or precipitation/adsorption methods which provide less infectious disease transmission risk than cryoprecipitate. FCs can be used for up to 24 hours after preparation/reconstitution providing a greater time for transfusion than with cryoprecipitate.[16] There are two FDA approved FCs available in the U.S., RiaSTAP (CSL Behring, King of Prussia, PA) and FIBRYGA (Octapharma USA, Paramus, NJ), both are only approved for congenital fibrinogen deficiency, including afibrinogenemia and hypofibrinogenemia, all other use is considered off-label.[17,18] Potential downsides are cost, the loss of potential concurrent hemostatic benefit of vWF, FXIII, and conflicting data on the benefit of FCs over cryoprecipitate in the cardiac surgery setting.[19]

CONCLUSION

Cryoprecipitate, produced from FFP or PF24, is still the primary source of fibrinogen replacement in the U.S. Other alternatives described in this ***Blood Bulletin*** are also available and gaining acceptance, including PR-Cryo FC and FCs, with cost as a main downside to these alternatives.

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Table 1: Fibrinogen Replacement Products

Product	Cryo (unit/pools)[11]	PR-Cryo FC[13]	RiaSTAP® (concentrated fibrinogen)[18]	Fibryga® (concentrated fibrinogen)[17]
Fibrinogen content	150 mg minimum per unit/ average 325 mg per unit	740-3700 mg	900-1300 mg (actual content listed on vial) per single dose vial	1 g per single dose vial
Product volume	Unit: ~15-20 ml "Pools" typically 4-5 units cryo/pool	60 ml	Reconstituted in 50 ml of sterile water	Reconstituted in 50 ml of sterile water
Time to prepare	Thaw: 10-20 minutes	Thaw: 10-20 minutes to prepare	Reconstitute: 5-10 minutes	Reconstitute: 5-10 minutes
Expiration	6 hours if single unit or pooled using a sterile connection device, 4 hours if pooled with open system	5 days from thaw	24 hours from thaw	24 hours from thaw
Approximate Acquisition Cost per Dose Adult Setting	~$60-80/unit or~$300-400 for a 5 unit cryo pool	*See reimbursement brochure (ref 16), generally >$ than equivalent cryo dose	$1,000/g in U.S. >$ cost than equivalent cryo dose	$1,000/g in U.S. >$ cost than equivalent cryo dose
Viral Screening and/or Inactivation	Nucleic Acid Test (NAT) for HIV, hepatitis B (HBV) and C (HCV), and other viruses	NAT for HIV, HBV and HCV, and other viruses amotosalen/UVA pathogen reduction	NAT for HIV, HBV and HCV, and other viruses heat & glycine precipitation for virus inactivation	NAT for HIV, HBV and HCV, and other viruses, solvent/detergent (S/D) step for virus inactivation, nanofiltration step for virus removal.

Table 2: Fibrinogen Replacement Indications & Cryoprecipitate Dosing

Indications for Fibrinogen Replacement [11]	Dosing of Cryoprecipitate[11]
• Life-threatening hemorrhage: 200 mg/dl • Active bleeding: 150 mg/dl • Prophylaxis for an invasive procedure: 100 mg/dl • Note: ABO compatible is preferred, but not required; Rh type need not be considered. ABO incompatible cryoprecipitate is not associated with clinically significant hemolysis.	• One single unit of cryoprecipitate contains an average of 325 mg of fibrinogen. • In a 70 kg patient the expected fibrinogen increase from a 5-unit pool is 35 mg/dl. • A typical adult dose of cryoprecipitate is two 5-unit pools or one pool of 10 units. • A pediatric dose of cryoprecipitate may be given in individual units. • General dosing recommendation: one unit per 7-10 kg body weight to raise plasma fibrinogen by approximately 50-75 mg/kg.

FIBRYGA and RiaStap Dosing: Dosing guidelines available in the package inserts.[17,18]

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