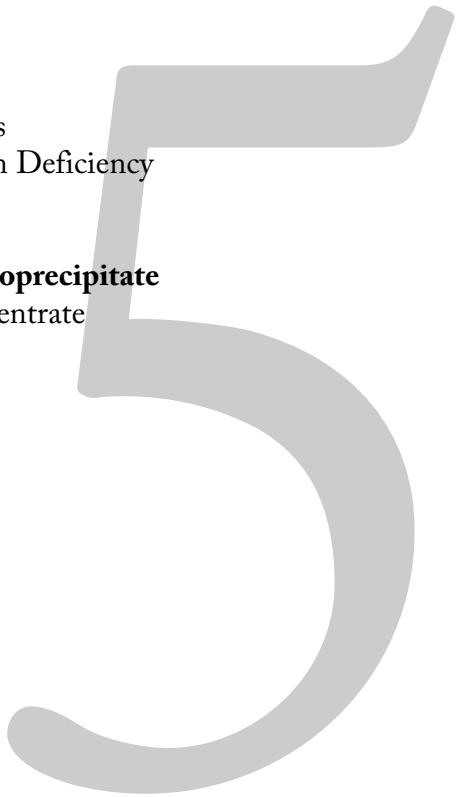
Chapter Preview



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5

Cryoprecipitate: Indications and Dosing

Jason E. Crane, DO, and Mona Papari, MD

THIS CHAPTER ADDRESSES the process of manufacturing and storage and the main clinical indications for cryoprecipitate. "Cryoprecipitate" is the most commonly used term for Cryoprecipitated Antihemophilic Factor (Cryoprecipitated AHF), also referred to as "cryo" in an abbreviated form.

Cryoprecipitated AHF was "discovered" when researchers tried to manufacture a better hemostatic alternative for hemophilia A patients, compared to transfusion of large volumes of Fresh Frozen Plasma (FFP). Although there were other earlier attempts at isolating Factor VIII by plasma fractionation and lyophilization, these attempts were limited by insufficient Factor VIII yield. It was not until 1964 when a method simple enough for manufacturing of "antihemophilic globulin" was identified. Knowing that the Factor VIII efficacy decreases at room temperature, Dr. Judith Pool noticed that there were only small amounts of Factor VIII in the supernatant from the not-fully thawed plasma and that the majority of Factor VIII was found in the insoluble fraction.[1-3] Following Dr. Pool's genial discovery, the manufacturing of cryoprecipitate was widely adopted by blood banks.

The contents of cryoprecipitate are regulated in the United States and Europe, and blood centers that manufacture cryoprecipitate have to perform quality control in order to prove that those requirements are being fulfilled. Generally, the current manufacturing methods produce cryoprecipitate with factor levels significantly higher than the minimum required levels (more than double), a fact that has allowed many blood centers to pool only 5 units instead of the previously customary 10 units.[4] All the manufacturing steps, as well as storage conditions, shelf life, and specific content of cryoprecipitate, are addressed in detail later in this chapter.

Although the indications for transfusion of cryoprecipitate are apparently well known by the ordering physicians, in reality cryoprecipitate might not be used for all medical conditions in which it would be beneficial, and calculation or

Jason E. Crane, DO, Medical Director, and Mona Papari, MD, Senior Chief Medical Officer, Vitalant, Rosemont, Illinois
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estimation of the correct dose is often based merely on educated guesses.

The main components of cryoprecipitate are fibrinogen, Factor VIII, von Willebrand factor (vWF), Factor XIII, and fibronectin, in a small volume of residual plasma. The clinical indications for transfusions are put forward mainly with the aim of replacing one of the aforementioned factors, with a strong predilection for fibrinogen replacement in the first-line indications, but also for replacement of Factor XIII when deficient. Replacement of the other components, namely Factor VIII and vWF, is no longer done routinely in clinical practice in the United States, but may be done as a secondary treatment option for hemophilia A, von Willebrand disease, and uremic bleeding syndrome (uremic coagulopathy), when other treatment options have failed or are not available. Use of recombinant or pathogen-reduced factor concentrates should always be the first consideration for treatment.

Massive transfusion has become one major indication for transfusion of cryoprecipitate, especially when associated with disseminated intravascular coagulation (DIC), such as in very large-volume obstetric hemorrhages, but also in bleeding circumstances of other etiologies. There are massive transfusion protocols (MTPs) that advocate use of cryoprecipitate in an equal ratio with the other blood components (1:1:1:1 ratio of plasma to red cells to platelets to cryoprecipitate); however, others choose to tailor the cryoprecipitate transfusion based on clinical and laboratory values, or based on rapid viscoelastic testing (VET) methods such as thromboelastography (TEG), rotational thromboelastometry (ROTEM), or Quantra, an ultrasound-based VET.[5-9]

The common indications for transfusion of cryoprecipitate, sometimes for less common medical conditions such as congenital fibrinogen deficiency, and the recommended dosage are detailed in this chapter. Also addressed is the use of cryoprecipitate for manufacturing of fibrin sealant, despite the fact that commercially available virally inactivated fibrin sealants are preferred and have largely replaced the cryoprecipitate-based sealants.

Manufacturing

Cryoprecipitate is manufactured from FFP (plasma frozen within 8 hours of collection) by thawing the FFP unit and centrifugation of the cold insoluble proteins; the resulting precipitate, suspended in approximately 15 mL of plasma, is refrozen and the remaining plasma, devoid of the coagulation factors present in cryoprecipitate, can be manufactured into Plasma Cryoprecipitate Reduced, also known as cryo-poor plasma (see Chapter 4). Cryoprecipitate may also be prepared from Plasma Frozen Within 24 Hours After Phlebotomy (PF24), regardless of whether plasma was separated from the whole blood collection and held at temperatures of at least –18 C or colder for 24 hours from collection, or plasma was separated from whole blood that was kept at room temperature for up to 24 hours and then placed at –18 C or colder.[10] FFP may be thawed either overnight in a 1-to-6-C refrigerator or in a waterbath maintained at that temperature.[11] Thawed cryoprecipitate may be used as single units, especially in pediatric transfusions, or be pooled in either an open or closed system, which is the preferred method for transfusion of adult patients.[4]

Cryoprecipitate may be stored for up to 1 year at –18 C. The expiration of the thawed cryoprecipitate is only 4 hours for units or pools thawed in an open system, and 6 hours for single units and pools using sterile connecting devices. Because of the short expiration time, most transfusion services avoid keeping thawed cryoprecipitate in their inventory, and only thaw it on demand, to decrease wastage. Such a strategy is not foolproof, as it might lead to delays in providing the blood component and not maintaining the desired ratio of components in MTPs, especially when VET methods are not employed.

The Food and Drug Administration (FDA) approved pathogen-reduced cryoprecipitate (Pathogen Reduced Cryoprecipitated Fibrinogen Complex, or informally, PR-Cryo) in the United States in November 2020. The only currently approved manufacturing method for PR-Cryo fibrinogen concentrate (FC) is from either a single donor apheresis plasma unit or from a pool of two whole-blood-derived plasma units that are pathogen reduced by the INTERCEPT Blood System

(Cerus) technology before freezing. INTERCEPT Fibrinogen Complex (IFC) may be pooled in different configurations in closed systems and stored for up to 12 months at ≤–18 C. The major advantage of this product is that it may be stored for up to 5 days at room temperature, between 20 and 24 C, after thawing, resulting in faster availability for transfusion, and less wastage. Of course, another advantage offered by pathogen inactivation is broad-spectrum protection against transfusion-transmitted infections (TTIs), as well as inactivation of leukocytes.

The fibrinogen content of PR-Cryo units varies depending on the pooling configuration; FC15 is the most commonly used method, and it is obtained by pooling 4 whole-blood-derived units. The fibrinogen content in FC15 is reported to be, on average, 1556 mg (with a range of 1209 to 1913) at thawing and 1435 mg (with a range of 1129 to 1760) at 5 days after thawing.[12]

For traditional cryoprecipitate, AABB standards require the method of production to yield at least 150 mg fibrinogen and 80 IU of Factor VIII per unit,[13] although in reality the yield is frequently significantly higher (most blood centers report more than double the amount of fibrinogen when performing quality control). Table 5-1 compares the storage conditions and fibrinogen content for cryoprecipitate and PR-Cryo.

Indications

Cryoprecipitate was originally developed to treat hemophilia A but is now frequently used to treat acquired coagulopathy, such as in trauma, obstetric hemorrhage, cardiothoracic surgery, and liver disease.[4] It should be noted that in liver disease, because multiple coagulation factors are often deficient, use of FFP may show better improvements in the coagulation profile than transfusing cryoprecipitate alone.[4] It is also useful in treating bleeding due to uremia.[14]

Trauma

Preventing coagulopathy in trauma has long been a focus of research. Since at least the Vietnam War, studies have documented a trauma-induced coagulopathy. In the study by Simmons, a disordered coagulation profile was noted initially after trauma (favoring hypercoagulable followed by hypocoagulable states), and a dilutional coagulopathy was demonstrated after massive transfusion.[15] In more recent studies, fibrinogen has been identified as the first coagulation factor to be depleted,[16] as consumption outpaces the ability to regenerate it.[17] Early use of cryoprecipitate in trauma to decrease mortality has been studied but not definitively shown,[18] although a large review published in 2018 includes a smaller number of patients studied relative to other blood products.[19] However, Curry and colleagues did demonstrate that early use of cryoprecipitate does increase the fibrinogen level.[18] Adding to these data, Dorken-Gallastegi and colleagues showed a significant 24-hour survival benefit if a ratio of 100 mL of cryoprecipitate per 7 to 8 units of Red Blood Cells (RBCs) is used.[20]

In CRYOSTAT-2, a randomized controlled trial (RCT) involving 26 UK and US hospitals, 771 patients were randomly assigned to standard of care, and 760 patients were randomly assigned to early cryoprecipitate plus standard of care. Ultimately the study found "the addition of early and empirical high-dose cryoprecipitate to standard of care did not improve all cause 28-day mortality."[21] However, a recent study by Meizoso et al, which entailed a review of 476 patients in a prospective observational database at a level I trauma center, did recommend early cryoprecipitate in trauma, noting there was not enough evidence to recommend FC over cryoprecipitate currently.[22] The most recent European guidelines on management of coagulopathy after trauma recommend use of cryoprecipitate or FC in the case of major bleeding accompanied by hypofibrinogenemia, noting that both have been found to improve the fibrinogen level.[23] Of note, in the FEISTY (Fibrinogen Early in Severe Trauma Study) trial, FC was able to replace fibrinogen faster than cryoprecipitate.[24]

Given the references to FC above, it is important to note that since the last edition (2019), newer studies seem to indicate greater interest in FC rather than cryoprecipitate. These will be discussed in further detail below in the section on alternatives.