121st Blood Products Advisory Committee Meeting

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Topic I: Considerations for Cold Stored Platelets Intended for Transfusion

Issue: FDA is seeking advice from the Blood Products Advisory Committee (BPAC) to advance the safe, effective, and efficient development of cold stored platelets (CSP).

The Committee will hear presentations discussing available data on the characterization and functional testing of CSP, clinical studies evaluating the safety and efficacy of CSP, and the potential role of CSP in the clinical care of military and civilian patient populations. The Committee will consider the available evidence and provide advice on studies needed to support the use of CSP intended for transfusion and stored beyond 3 days.

I. Background:

A. Platelets for transfusion

Platelets have a critical role in normal hemostasis and control of bleeding. Platelet transfusions are used to prevent bleeding in patients with thrombocytopenia, to treat patients with dysfunctional platelets (e.g. congenital disorders or medication-induced dysfunction), or to treat active bleeding (e.g. in massive transfusion or surgical bleeding) [1]. Platelet components are prepared from whole blood collections or collected by apheresis, can be stored in 100% plasma or platelet additive solutions, and may undergo further modification such as pathogen reduction.

In the US, platelet components are generally stored at 20 to 24 degrees C (room temperature platelets, RTP) for 5-7 days, depending on the storage container and measures to control bacterial risk (21 CFR 610.53(b)). RTP storage requires continuous agitation to facilitate oxygen utilization and maintain optimal morphology, physiologic function, and pH during storage [2, 8] (21 CFR 640.25(a)). For RTP, the dating period is currently limited to 5 days unless dating is extended (up to 7 days) using an FDA cleared bacterial testing device labeled as a safety measure.

Most platelet transfusions in the United States are given prophylactically to reduce the risk of spontaneous bleeding in patients who are thrombocytopenic following chemotherapy or hematopoietic stem cell transplantation [2, 3]. While the role of RTP transfusion has been studied extensively in this clinical setting [4-7], only limited data

are available to support transfusing platelets to other patient populations for different clinical indications, such as perioperative or traumatic bleeding [2, 8-11].

B. Cold Stored Platelets

Although RTP have become the standard in clinical medicine, platelet products can also be stored at 1 to 6 degrees C (cold stored platelets, CSP) (21 CFR 640.24(d)). Historically, in the US, the storage period for CSP was limited to 72 hours from the time of collection of the source blood. Commonly used prior to 1970, CSP were mainly derived from whole blood collections at that time. In subsequent decades, platelet use shifted almost exclusively to RTP because of their higher recovery and longer survival in circulation compared to CSP [12-15]. A reluctance to maintain a dual inventory of platelet products with different storage requirements may have also contributed to the decline in use of CSP [16].

There has been renewed interest in the use of CSP, especially in settings of trauma and massive bleeding [17-21]. While platelets are a part of most Damage Control Resuscitation protocols [22], the limited shelf-life of RTP and their need for continuous agitation introduce challenges for their use in medical emergencies.

CSP offer the potential to overcome some of the logistical limitations of RTP, particularly by improving availability for pre-hospital transfusions during transportation, in austere environments and military settings. For example, agitation is optional for CSP under 21 CFR 640.25(a) because platelet metabolism is slowed under cold storage [23, 24]. There is also increasing interest in extending the storage time for CSP beyond 3 days. While the optimal storage conditions for CSP remain to be defined, results from *in vitro* characterization and limited clinical studies suggest that longer storage times may be possible, with maintenance or even improvement of hemostatic activity compared to RTP of similar storage duration (see section I.C. below), and this could potentially be of benefit for both military and civilian populations. Finally, cold storage can prevent bacterial growth of clinically relevant bacterial contaminants [25], potentially decreasing the risk of sepsis associated with RTP [26, 27].

C. *In vitro* characterization of CSP

Several *in vitro* laboratory measurements of stored platelet components have been used to predict *in vivo* clinical performance of RTP. Some laboratory tests (e.g. extent of shape change and hypotonic stress response) predict clinical performance *in vivo*, based on their correlation with circulatory recovery and survival, and corrected count increments in transfused subjects[28, 29]. Although no single test serves as an adequate direct surrogate for platelet effectiveness, these tests have provided tools to predict platelet quality and *in vivo* viability following various platelet collection, storage,

and modification (for example, following pathogen reduction) approaches. Table 1 shows common *in vitro* parameters used to evaluate platelets.

Platelet components undergo a series of physiologic and biochemical changes during storage. The observed deterioration in laboratory tests of platelet quality and function during storage is frequently referred to as a “storage lesion”. Studies generally demonstrate that longer storage duration of RTP is correlated with decreased corrected count increments and posttransfusion platelet recovery and survival [30-33].

Some aspects of the typical storage lesion are mitigated or slowed during storage in the cold compared to room temperature. For example, CSP have lower metabolic rates than RTP, maintaining pH greater than 6.2 during 21 days of storage[24]. However, CSP undergo a unique series of physiologic changes in response to the cold that have sometimes been referred to as a “cold storage lesion”. Originally described many decades ago[34, 35], *in vitro* studies have shown that the changes in CSP include increases in intracellular calcium, shape changes, clustering of GPIb on the platelet membrane, changes in membrane glycosylation including interaction with hepatic lectin receptors, and increases in externalized P-selectin and phosphatidyl serine[16, 23, 36-38]. CSP can demonstrate lower platelet counts and formation of aggregates during storage, particularly when stored in 100% plasma [39], and CSP exhibit decreased extent of shape change and hypotonic shock response compared to RTP[40]. The overall changes in CSP can result in decreased circulatory recovery and survival when compared to RTP (see section I.D.).

Table 1 *- Common in vitro tests used to evaluate platelets*

Category of Test	Types of Tests
Physical characteristics	Count Morphology Electron microscopy Microparticle quantitation Swirling
Biochemical/metabolic status	pH Lactate Glucose pO2 pCO2 ATP Mitochondrial function tests
Platelet activation and apoptosis	CD62 (P-selectin) Phosphatidyl serine exposure (Annexin V binding) CD63 GPIIb/IIIa activation (PAC-1 binding) PF4 secretion
Physiologic responses	Hypotonic stress response (HSR) Extent of shape change (ESC) Aggregometry Viscoelastic testing (e.g. thromboelastography, rotational thromboelastometry) Clot contraction Adhesion assays

While circulatory recovery and survival are impaired, the *in vitro* changes in CSP also indicate that CSP have an “activated” profile. CSP have demonstrated greater aggregation responses to agonists, higher clot strength in viscoelastic testing, and improved adhesion under flow compared to RTP of similar storage age [41-43]. However, it is unclear whether standard *in vitro* measurements of activation and metabolism correlate with *in vivo* transfusion outcomes other than circulatory recovery and survival.

When evaluating and comparing *in vitro* parameters in platelets, several variables in the manufacture of platelet components are usually considered. These include platelet type (whole-blood derived versus apheresis), apheresis collection platform, storage containers, storage medium (100% plasma versus platelet additive solutions), and further processing such as the use of pathogen reduction. Although some of the effects of these variables in CSP have been examined *in vitro* [39, 44-46] and in limited *in vivo*

studies in healthy volunteers[47], the effect of these variables on the clinical hemostatic efficacy of CSP remain largely unknown.

D. Clinical studies with CSP

While *in vitro* results suggest that CSP may have better preservation of hemostatic activity when compared to RTP of similar storage duration, there remains a paucity of well-controlled clinical studies examining their use. Some of the studies are outlined below.

CSP stored for up to 3 days

Studies published in the 1970s demonstrated that CSP prepared from whole blood showed improved pH, aggregability, and structure following up to 72 hours of storage, although their *in vivo* circulation and recovery were impaired compared to RTP (approximately 75% reduction in circulatory half-life and 30% reduction in recovery) [48]. In thrombocytopenic patients and in healthy volunteer subjects pre-treated with aspirin, some studies found that CSP demonstrated better correction of bleeding time [48, 49], while other studies did not [13].

CSP stored beyond 3 days

CSP stored up to 15 days in 100% plasma or up to 10 days in plasma with platelet additive solution (PAS) were recently examined in healthy volunteers [47]. This study demonstrated that the platelet components stored in 100% plasma contained fewer platelets but demonstrated higher recovery *in vivo* than platelet components stored in PAS. Platelets stored in 100% plasma showed 43% mean recovery after 3 days of storage, 24% mean recovery after 10 days of storage, and 11% mean recovery after 15 days of storage. After 10 days of storage, mean recoveries of platelets stored in two different formulations of PAS were 18% and 8%, respectively. *In vivo* assessment was limited to recovery and survival of the transfused platelets and did not assess hemostatic activity or efficacy in the transfused subjects.

Investigators in Norway recently conducted a two-armed randomized study in 41 patients undergoing complex cardiac surgery comparing CSP to conventional RTP, both stored for up to 7 days in PAS with continuous agitation [50]. Based on chest-tube output and platelet function testing in recipients, data suggest that CSP stored for up to 7 days maintain hemostatic activity, with similar safety outcomes such as mortality, rate of thromboembolic events, and length of ICU stay when compared to patients transfused with RTP. A single-arm extension of this study in 8 patients examined CSP stored 7-14 days without agitation, and found similar results.

Clinical experience outside of clinical trials

The U.S. Department of Defense has also reported on CSP use in the military [51]. In 2017, U.S. Central Command authorized an extension of cold storage for up to 10 days

in deployed settings. This program reported transfusing 34 patients with 3-day CSP in 100% plasma, 7 patients with 10-day CSP in 100% plasma, and 7 patients with 10-day CSP in PAS, with no reactions or negative outcomes noted.

Stubbs et al recently provided a preliminary report of their experience in clinical use of CSP in an academic US healthcare system under a variance to the regulations (see section I.E.) that allowed for 3 days of storage [52]. This group reported transfusing 21 units to 20 patients but noted that short shelf-life and aggregate formation led to high discard rates.

Future studies

Recently, Krachey et al described the design of a prospective, randomized clinical trial of CSP in cardiac surgery patients using Bayesian adaptive methods. This multi-site trial aims to determine the maximum duration of cold storage that maintains noninferiority compared to RTP using a defined hemostatic efficacy score as a primary endpoint [53]. Subjects would be randomized to receive RTP stored up to 5 days or CSP stored up to 5 days, 10 days, or 15 days, with longer durations of cold storage used only if shorter durations appear noninferior to standard storage. The committee will hear presentations on the planned design of this trial and proposals to use this trial to support FDA approval of CSP stored for longer durations.

E. Regulatory considerations for CSP

When platelets are stored at temperatures other than 20 to 24 degrees C, the dating period is specified by the instructions for use of the blood collection, processing, and storage system that are approved or cleared for such use by FDA (21 CFR 610.53(b)). While FDA regulations permit storage at 1 to 6 degrees C, commonly used blood collection, processing, and storage systems do not include cold storage of platelets in their instructions for use. In 2015, FDA granted an alternative procedure under 21 CFR 640.120 (a) (also called a variance) to a blood establishment allowing CSP to be stored at 1 to 6 degrees C in a collection system (instead of 20 to 24 degrees C as specified in the collection system instructions for use) without agitation for up to 3 days and for use in the resuscitation of actively bleeding patients [54]. More recently, to make platelets available in military settings where the logistical challenges limit use of RTP, FDA granted a variance that allows for CSP to be stored up to 14 days and used in the treatment of active bleeding when conventional platelets are unavailable or their use not practical [54]. Additional considerations, including supportive clinical studies, may be needed for the widespread use of cold stored platelets. Additional discussion is also needed in the context of their intended use.

Following *in vitro* testing of platelets to characterize their morphology, biochemistry, activation, and physiologic responses (see section I.C.), FDA's evaluation of the safety and effectiveness of platelet products, or devices used in the manufacture of platelet

products, has typically relied on measurement of *in vivo* recovery and survival of autologous radiolabeled platelets as a surrogate marker for hemostatic effectiveness. In the case of CSP, circulatory recovery and survival might not be an appropriate surrogate marker for hemostatic effectiveness, and the optimal designs of clinical studies to evaluate the hemostatic effectiveness of CSP have not been defined.

II. Discussion:

There is renewed interest in the use of cold stored platelets for transfusion that have been stored beyond 3 days. Based on supportive, albeit limited clinical evidence, some have proposed that the potential advantages of CSP warrant their use in settings of active bleeding, especially in military use and traumatic hemorrhage, where extended platelet dating would increase their availability. These arguments have also included considerations that CSP may be warranted for specific patient populations (e.g. treatment of acute hemorrhage)[19].

When evaluating the safety and efficacy of CSP stored for longer periods (i.e. beyond 3 days), several factors to consider include:

1. Available *in vitro* studies, including whether *in vitro* parameters or functional studies can predict the quality and hemostatic efficacy of CSP.

2. The possible effect of differences in platelet product manufacturing such as platelet collection platforms, storage media (plasma versus platelet additive solution), and pathogen reduction on CSP quality and hemostatic efficacy.

3. The design of clinical studies to evaluate the safety and efficacy of CSP.

4. The potential benefits of CSP weighed against potential risks, such as the clinical implications of reduced circulatory survival, and potential thrombogenicity associated with increased activation.

In its ongoing efforts to support the availability of safe and effective platelet products for transfusion, FDA is seeking the committee's advice and comments on the available data on CSP, including current knowledge gaps, and clinical studies that would be needed to support the general use of CSP beyond 3 days of storage.

III. Questions to the Committee:

1. Please comment on the available data on cold stored platelets, including discussion of knowledge gaps and potential need for preclinical or clinical studies, with respect to the following:
    a. Length of storage beyond 3 days
    b. Indications for use (such as treatment of active bleeding)
    c. Differences in collection platforms and storage media
    d. Pathogen reduction

2. Please comment on the design of any additional clinical studies needed to evaluate the safety and hemostatic efficacy of cold stored platelets to support their widespread use in the United States.

IV. References:

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