Editorial

Platelets from the refrigerator: a better way to stop bleeding?

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Platelet transfusions have become a mainstay of transfusion practice around the world and the growth of platelet transfusions in China has been significant in recent times. Historically, platelets were prepared from donations of whole blood using sets of plastic bags that allow preparation of a red cell concentrate, a plasma component, and a whole-blood derived platelet (WBDP) from a donation of whole blood. These platelets can be prepared by a two-step centrifugation process or by a method using pooled buffy coats from whole blood collections. In China, since many whole blood donations are still low volume of 200–300 mL compared to the common 500 mL donations in Western countries, the preparation of WBDP is less practical and might require pooling of platelets prepared from as many as twelve whole blood donations to prepare an adequate dose for an adult patient. Apheresis technologies for platelet collection have expanded rapidly in the Western world due to concerns about bacterial contamination which would limit donor exposures for patients and the undesirable requirement of pooling multiple bags of WBDP. Similarly, in China, there has been rapid growth in platelet collection by apheresis to meet growing needs in patient care (1).

Although most blood components are stored at 4 ℃ (4C), platelets collected by apheresis or separated from whole blood are routinely stored at room temperature (RT), based upon early studies that demonstrated that platelets survive for longer times in the patient's circulation when transfused after storage at RT (2). Most of the demand for platelet transfusions has historically been to maintain a platelet threshold sufficient to prevent bleeding in thrombocytopenic patients with hematologic malignancies. For this reason, platelets have been stored at RT for the purpose of hemorrhage prophylaxis for many years and represent the current standard of care in most of the world. At the time of the initial studies of platelet storage methodologies in the 1970's, however, it was recognized that platelets stored at 4C had better hemostatic function than platelets stored at RT and 4C platelets could correct the bleeding time, a useful method of hemostatic assessment, in subjects more rapidly than RT platelets. It was also known that the RT stored platelets underwent an *in vivo* correction so that they would work to provide hemostasis but with some delay. This promise of greater and more immediate hemostatic effectiveness was recognized by many investigators, but it was believed that hemostatic function of RT platelets would be restored *in vivo* in sufficient time in clinical practice to arrest bleeding in thrombocytopenic patients (3). The prevailing view of community blood centers and hospital transfusion services also maintained that a single method of platelet storage would be preferred and that split inventories of platelets stored at RT for prophylaxis and at 4C for acute hemorrhage would be overly complicated and medically unnecessary. Computer systems to handle the complexities of dual inventories were not commonly available at these earlier times. For these reasons, most of the world moved to platelet storage at RT which remains the current practice

Although platelets stored at RT have served patients well for many years, there are recognized limitations for their utility. The early generation of platelet storage bags did not allow gas transfer very efficiently so that the platelets would become more acidotic and undergo irreversible shape change from disc to spheres and no longer be functional (4). Platelet storage was therefore limited to three days in early bags, making supplies erratic particularly in holiday periods. Improved bags with enhanced gas transport capability gradually became available for practice, permitting five days of storage, which has been extended to seven days in some settings. These short storage periods, however, still make platelet supply inadequate in remote locations where

military or civilian trauma often occurs and platelets may not be routinely available.

Another complication of platelet RT storage is the problem of septic platelet transfusion reactions (SPTR) (5). These serious reactions, frequently resulting in patient death, occur with current practices that allow platelets to be stored at RT for five days in the US and up to seven days in other countries. Bacteria can be introduced from the donor skin during venipuncture despite attempts at skin sterilization, or from donors with asymptomatic transient bacteremia. Bacterial culture was introduced in the US and other countries in 2004 after the AABB recommended that blood centers perform culture of platelet components. Although the incidence of SPTR was reduced by two/thirds, reactions still persisted (6). Bacterial culture caused additional problems of delayed platelet delivery so the available shelf life in the blood center or hospital was effectively reduced to an inadequate three days. More recently, point of care testing, the use of pathogen inactivation, or additional surveillance cultures have been shown to reduce or eliminate the problem but with additional expense (7,8). A return to platelet storage at 4C would avoid this persistent problem.

Although the majority of platelets are given prophylactically to patients with hematologic malignancies to avoid bleeding problems that can occur during prolonged periods of thrombocytopenia, a significant number of platelets are given to patients with surgical interventions or treatment for trauma where the importance of immediate efficacy to stop hemorrhage is now been recognized. 4C platelets do not persist in the circulation as well as RT platelets (2), but the importance of their homing to sites of hemorrhage for rapid restoration of hemostatic competence suggests that their reduced *in vivo* survival is a worthy price to pay for enhanced efficacy.

The wisdom of having only RT platelets and whether they adequately meet the needs of thrombocytopenic patients with acute hemorrhage is now being called into question. For example, some patients develop refractory bleeding after cardiac surgery despite multiple transfusions of RT stored platelets (9). In a recent study of platelet transfusion therapy in patients receiving antiplatelet therapy with acute cerebral hemorrhage, platelet transfusions stored at RT were ineffective (10). Clinical experience of trauma surgeons with massive transfusion protocols where many platelet transfusions are administered also suggests that platelets with hemostatic readiness better than RT platelets may be critical.

A number of investigators have begun a series of studies that suggest a return to 4C platelets may be a prudent transfusion strategy, at least for acutely bleeding patients. Much of this work has been led by studies from the US military under the direction of Andrew Cap. The notable shortcomings of RT platelet storage make many of these studies very compelling reading (11,12). These papers describe a body of work from these investigators and others that demonstrate that 4C platelets have more rapid function and superior clot formation properties compared to RT platelets. They also demonstrate that the platelets are hemostatically effective *in vitro* and do not appear to be overly prothrombotic which could cause a plethora of thrombotic events. Additionally, studies have shown that 4C platelets, particularly when stored with platelet additive solutions, will reduced the aggregation caused by fibrinogen binding and permit storage for as long as two weeks.

Although clinical data in patients to demonstrate that 4C platelets are superior to RT platelets in reducing hemorrhage are limited, a number of trials are anticipated to verify the suggested advantages and if positive, would lead to necessary changes in platelet transfusion provision and therapy. Studies have been performed in Norway in cardiac surgery comparing 4C and RT platelets demonstrating that chest tube drainage was reduced with 4C platelets (13). It is anticipated that larger clinical studies will soon be available to determine if the predicted benefits of 4C platelet storage will be verified in patient care settings.

If clinical trials demonstrate that 4C platelets are better for acute hemorrhage, the question of whether blood providers will need to offer a split inventory of RT platelets for hematologic patients for prophylaxis while providing 4C platelets for acute hemorrhage would need to be addressed. Would converting all platelet storage to 4C be a reasonable option? It certainly would eliminate the problem of bacterial contamination and expensive solutions to this transfusion complication. On the other hand, the *in vivo* survival of 4C platelets is much shorter than RT platelets, which would suggest that hematologic patients would need more frequent platelet transfusions with the incumbent risks of alloimmunization and disease transmission. As a counter argument to this issue, however, recent trials have shown only marginal benefit of prophylactic platelet transfusions in some patients with hematologic malignancies (14); although patients with acute leukemia clearly benefit from prophylactic platelet transfusions, patients with lymphoma or undergoing autologous stem cell transplants might forego prophylactic platelet support. In those patients with unusual breakthrough bleeding events with or without

previous prophylaxis, transfusion of 4C platelets with more rapid enhanced hemostatic function rather than RT platelets would seem to have therapeutic advantages for an episode of acute hemorrhage.

In a parallel discussion, it is now being increasingly recognized that whole blood may be the best therapy for patients undergoing massive transfusion therapies. For the past fifty years, transfusion therapy in the developed world has relied upon the production of blood components from whole blood and discouraged the use of whole blood as unnecessary or wasteful. Transfusion medicine educators have often cited the following reasons for this widespread practice: (I) components avoid circulatory overload, (II) components could limit the accumulation of harmful metabolic materials that develop with blood storage, (III) components can concentrate required blood or plasma elements to produce effective levels, (IV) components could minimize disease transmission, and (V) perhaps most importantly, components would maximize the use of donated blood which is of critical importance in China with its frequent blood shortages . Although the overall wisdom of this approach seemed reasonable and responsive to the needs of all patients, several medical assumptions were also made to justify this approach as reasonable for trauma victims or massively bleeding surgical patients: (I) volume expansion with saline or other volume expanders with subsequent use of red cell concentrates (RBC) was the best practice, and (II) platelets stored at room temperature provided adequate hemostasis rapidly. It is now becoming evident from military and trauma studies that both of these previous assumptions are not true. The blood banking community also opined that whole blood did not contain adequate quantities of functional platelets and that coagulation factors declined in whole blood, making whole blood an incomplete product. It is now clear that whole blood contains plenty of platelets and coagulation factors and that WB contains adequate platelets and coagulation factors to function very well to quash hemorrhage in bleeding patients.

Whole blood can be stored for 35 days and there is no convincing evidence that red cells stored for up to 35 days are harmful to patients (15). Whole blood has an adequate amount of platelets and their storage at 4C will provide hemostatic effectiveness adequate for at least 10–14 days (3); it will be incumbent on providers to develop methods to recover RBC from WB not used in trauma, or for the transfusion community to develop reasonable guidelines to suggests the longer use of whole blood to provide RBC and coagulation support with the addition of supplemental platelets. This limitation of platelet storage in whole blood does not diminish the fact that provision of whole blood stored at 4C is another way to take advantage of the enhanced hemostatic properties of 4C platelets. Additionally, compared to current 1:1:1 massive transfusion protocols, donor exposure will be reduced from the typical cooler with six red cells, six FFP units, and an apheresis platelet (13 products) to six donor products (16).

While we await the results of clinical trials to answer the question of whether the 1970's movement to only RT platelets was the right decision, there is a current need to provide blood centers and hospital transfusion services with enhanced computer systems to permit more individualized transfusion practices. Patients who are alloimmunized, previously identified as subject to transfusion reactions, or who have other unique transfusion requirements are becoming more common in current medical practice. If both RT and 4C platelets are needed but for different clinical purposes, we will require systems to allow clinicians to order specific components for their patients and for blood providers to address these needs without delays or errors. New formulations of blood components have complicated transfusion practice, so investment in blood banking infrastructure and transfusion medicine education will be prudent investments for the future. On the other hand, a return to blood products that were previously available but now discouraged (4C platelets and whole blood) may be the best course to pursue.

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