Warming Up to Cold-stored Platelets

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Platelets are critical in stopping hemorrhage as they treat the underlying coagulopathy and improve patient outcomes. However, maintaining an adequate platelet supply is challenging, particularly in austere settings. Thus, additional products such as cold-stored platelets are needed. In this issue, Strandenes *et al.*[1] describe the completion of a pilot trial that demonstrates the feasibility of conducting a larger randomized controlled trial to assess the safety and efficacy of cold-stored compared to room temperature (standard) platelets in patients undergoing complex cardiothoracic surgery. This pilot trial has an unusual two-stage design. In stage I, 50 adult patients undergoing complex cardiac surgery at high risk of hemorrhage were randomized to receive either cold-stored (n = 25) or standard (n = 25) platelets. Both products were agitated (as standard with room temperature platelets but not required to preserve function in cold-stored platelets[2]) and were stored up to 7 days. Patients were transfused based on the clinical judgement of the surgeon and/or anesthesiologist, who remained blinded. Stage II was a single-arm prospective observational study where an additional 15 patients were transfused with up to 2 cold-stored platelet units without agitiation stored for 8 to 14 days. If additional platelets were needed, patients received standard platelets.

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Platelet availability is hindered by the need for bacterial screening and the product's short shelf-life. Unlike red blood cells and plasma, which are stored refrigerated and/or frozen, platelets are stored at room temperature where bacteria can grow, potentially causing septic transfusion reactions. To decrease this risk, platelet shelf-life is limited to 5 or 7 days depending on product testing (often resulting in hospital availability for less than 3 days and high product wastage). In addition, the Food and Drug Administration and other regulatory agencies have recommended mitigation steps, including pathogen inactivation and bacterial screening.[3] There is concern that implementation of the new Food and Drug Administration guidance could decrease the availability of platelets for transfusion in the United States; this decrease in availability could put patients at risk.[4]

To overcome these problems, alternative products are needed. These alternatives include lyophilized platelets and cryopreserved platelets in addition to cold-stored platelets. All three products have potential to mitigate septic reactions and extend product shelf-life and are in clinical trials. Lyophilized and cryopreserved platelets are in earlier-phase clinical trials than cold-stored platelets but have extended shelf-life of years rather than days, potentially diminishing the future need for cold-stored platelets.

Cold-stored platelets are not new. Platelets were cold-stored until a study showed that they had increased clearance and reduced survival *in vivo* compared to standard platelets.[5] Since the main indication for a platelet transfusion is to prevent bleeding in thrombocytopenic hematology patients, the reduced half-life of cold-stored platelets was seen as a significant detriment. However, for bleeding patients, especially trauma patients, the platelets need to be transfused early in resuscitation and do not need extended posttransfusion survival.[6]

Literature from *in vitro* and preclinical studies demonstrated that cold-stored platelets might be an attractive alternative for therapeutic *versus* prophylactic indications. When platelets are exposed to the cold, they undergo morphologic and molecular changes that create a hemostatically primed state.[2] Cold-stored platelets also maintain shear- and agonist-induced aggregation responses,[2] display

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adhesion and aggregation under flow conditions that are comparable to fresh platelets,[7] and form stronger clots than standard platelets.[8]

In vivo testing in the 1970s showed that cold-stored platelets performed better than standard platelets to reduce the bleeding time in aspirin-treated healthy volunteers.[9] A second study in 1973 found that cold-stored platelets used in bleeding thrombocytopenic patients performed better than standard platelets by shortening bleeding time and hemostatic effect.[10] This study by Strandenes *et al.*[1] represents the first modern clinical trial. Evaluation of the clinical efficacy and safety is critical.

The Strandenes study[1] achieved its main aim of feasibility. The primary endpoint was chest drain output, and the secondary endpoints included platelet function measured by multiple electrode impedance aggregometry, total blood usage, immediate and long-term (28 days) adverse events, length of stay in intensive care, and mortality. Intention-to-treat and *post hoc* analysis from stage I found no significant difference in the primary outcome, in the secondary outcomes, and in the stage II comparison to stage I standard platelet transfusions. However, the pilot highlights the needs for future study design considerations. First, the randomization scheme was problematic. Due to technical difficulties with cold-stored platelet manufacturing, the authors randomized in week-long blocks so that the number and timing of cold-stored platelet manufacturing could be better controlled and wastage minimized. This led to early randomization, before enrollment. When enrollment and randomization are not tightly linked, a study is less likely to achieve a balance between intervention and control groups. Since patients who need a platelet transfusion are inherently different from those who do not, there is a greater probability that the randomization will create skewed cohorts. The risk for imbalance is notable in this study, since more than half of the randomized subjects (65 of 120) were not transfused nor included.

Second, the primary endpoint of chest drain volume is not optimal. The best primary outcome provides a direct measure of the intervention's effect. However, as the authors note, chest drain volume is influenced by many factors, most importantly surgical hemostasis. This problem is not unique to this study as platelet effects on bleeding always have confounders. However, the authors chose to circumvent the worst confounders—heavily bleeding patients—by excluding these patients in a *post hoc* analysis. While *post hoc* analysis can add useful information, it also introduces bias. The reason for randomization is to compensate for the heterogeneity inherent in any study population, and an intention-to-treat analysis benefits from this balance. Thus, excluding patients who have excess chest drain output breaks the randomization and potentially skews the results. Finally, the authors compare nonconcurrent data when they juxtapose chest drain output from patients transfused with standard platelets in stage I, with chest drain output from patients given extended storage cold-stored platelets from stage II. The two cohorts are not balanced, randomized study arms, and therefore the comparison may be invalid.

Despite these flaws, the authors have done well, laying the foundation for a larger randomized controlled trial to assess product safety and efficacy. While other trials of cold-stored platelets are planned or ongoing, cold-stored platelets are available. The Food and Drug Administration has approved cold-stored platelets with a 14-day shelf-life in the military, and South Texas Blood and Tissue Center received product license when standard platelets are unavailable. Other blood collection agencies also await Food and Drug Administration guidance to enable them to also supply this product. Additionally, cold-stored platelets are in refrigerated low-titer group O whole blood that is being used in prehospital and early hospital transfusion in massive hemorrhaging trauma patients.[11] Importantly, although there is interest in cold-stored platelets, their safety and efficacy remain unknown. In conclusion, this product and alternative platelet products are critical to the surgical and trauma community to assist with controlling massive hemorrhage and treating trauma-induced coagulopathy.

Competing Interests

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

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