Platelet Additive Solution

For decades, platelets have been collected from whole blood or as a separate blood component by apheresis. Conventionally, these platelets are suspended in 100 percent plasma. However, interest is growing in using platelets stored in PAS whereby approximately 65 percent of plasma in a unit of platelets is replaced by an electrolyte-based chemical solution. PAS platelets offer two main advantages over conventional platelets: They are associated with fewer low-grade transfusion reactions and free up plasma for other purposes. Like conventional platelets, PAS platelets can survive in storage for five days and are viable when transfused.

PAS has been available in the United States for about four years. The InterSol Solution Platelet Additive Solution 3 (PAS-C) was approved by the U.S. Food and Drug Administration in 2009. It is designed to replace a proportion of the plasma used in the storage of Fenwal's AMICUS-derived, leukoreduced apheresis platelets. A similar product, Isoplate Solution Platelet Additive Solution F (PAS-F), was approved in 2013, and is intended for use with products collected using Terumo BCT's Trima Accel System.

Fewer Low-Grade Transfusion Reactions

According to Steven Kleinman, MD, clinical professor of pathology at the University of British Columbia and AABB's senior medical advisor, randomized controlled trials and observational studies have shown that PAS platelets are equivalent to platelets collected in standard plasma, with similar outcomes for clinical bleeding. "We are not increasing the hemostatic efficacy," said Kleinman. "The platelets don't work better, but they work as well."

PAS platelets offer two main advantages over conventional platelets: They are associated with fewer low-grade transfusion reactions and free up plasma for other purposes.

However, their use results in less low-grade transfusion reactions among recipients. "We now have evidence that reducing the amount of plasma lowers the rate of reactions to platelet transfusion, specifically allergic transfusion reactions and febrile nonhemolytic transfusion reactions," said Kleinman.

Claudia Cohn, MD, PhD, director of the blood bank laboratory at the University of Minnesota, has seen this benefit firsthand when her facility started using PAS platelets in 2011. As one of the largest centers for umbilical cord stem cell transplants, her facility uses about 1,000 units of platelets each month.

Her facility took part in a large multicenter study of PAS-C. The results showed a significant reduction in overall transfusion reactions, allergic transfusion reactions, and febrile nonhemolytic transfusion reactions among 14,000 transfusions at six study sites.

"Many transfusion reactions occur because of the plasma component in products. But, if you reduce the amount of plasma, you theoretically reduce the amount of transfusion reactions and that's just good for patients," said Cohn.

Advantages exist for lowering the rate of allergic transfusion reactions and febrile nonhemolytic transfusion reactions, even though these reactions are generally mild. In addition to being uncomfortable for patients, these events sometimes force clinical staff to stop the transfusion or prompt a work-up to ensure that the fever is not being caused by something more serious.

Plus, the potential added cost of PAS platelets would likely be offset by not having as many allergic transfusion reactions.

Similar Corrected Count Increment

Karen King, MD, medical director of hemapheresis and associate medical director of transfusion medicine at Johns Hopkins Hospital, brought PAS platelets to her institution in June 2012, where they were used interchangeably with conventional platelets. After six months, she and her colleagues determined in a retrospective review that PAS platelets were associated with nearly a 50 percent decrease in allergic transfusion reactions. They also looked at whether patient response to platelet transfusion — as measured by corrected count increment — was equal, better or worse.

"Whenever you manipulate platelets, you are concerned that you are losing platelets and decreasing viability, so that there may be some impact on the efficacy of the product once transfused," said King. "If you have a decreased corrected count increment, you'll have to use more platelet product, which could be detrimental to inventory issues and, of course, a huge cost increase."

Although King found that PAS platelets were associated with a statistically significant decrease in corrected count increments at 1 to 4 hours post transfusion, no significant difference was seen at 12 to 24 hours.

More Plasma for Other Purposes

Another potential advantage is that using PAS leaves more plasma available for other purposes, should centers decide to collect the additional plasma. For example, because only 100 ml of plasma is needed for a unit of PAS platelets (compared with 300 ml of plasma for conventional platelets), the 200 ml of plasma that are no longer necessary could be used for another transfusion or to make other products, such as coagulation factor concentrate.

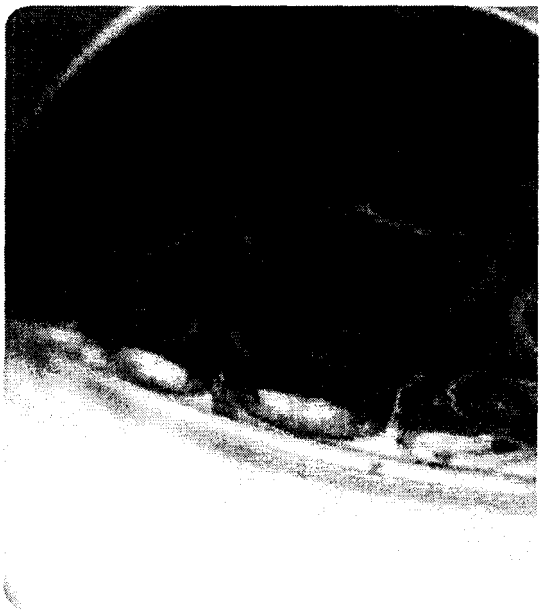
Research in Progress

The conceivable advantages and disadvantages of PAS platelets may not be fully known yet. One unresolved question is whether using PAS platelets might reduce the risk for transfusion-related acute lung injury, or TRALI, which is thought to be caused by antibodies present in the plasma. Theoretically, if TRALI is related to the strength of antibodies in the plasma and the amount of plasma that is transfused, then reducing their volume by two-thirds might lower risk for the complication. But it is unclear if that reduction is sufficient and there is no direct observational data on this hypothesis. Along these lines, Cohn is hoping to conduct a study to see if levels of bioactive lipids, which are present in the plasma fraction and may be related to TRALI, are lower in PAS platelets than conventional platelets.

In addition, King and colleagues are interested to find out if PAS platelets are equivalent to concentrated platelets for the prevention of allergic transfusion reactions. Concentrating platelets is associated with platelet loss due to the manipulation, decreased corrected count increments and additional labor. "If we could stop concentrating products for the prevention of allergic transfusion reactions, it would be a significant cost savings in terms of labor, it would improve laboratory efficiency, and it would be better for patient corrected count increments," King said.

King and Cohn also would like to determine if PAS platelets have lower titers for ABO antibody by virtue of having less plasma.

Lastly, according to Kleinman, research also is underway on a PAS that requires only 5 to 10 percent plasma.



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Thromboelastographic Goal-Directed Blood Component Therapy for Severe Hemorrhage

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Point-of-Care, Goal-Directed Blood Component Therapy: Defining the Need

Hemostasis is a complex physiologic process involving many constituents that act in symphony to form a clot. Conventional coagulation tests, such as prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen concentration, and platelet count, measure only a fraction of this process. Moreover, these tests sometimes lack accuracy in trauma settings, which has led to investigations of point-of-care viscoelastic tests (VETs), such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM).[1] The use of VETs has been shown to optimize (and often reduce) blood use when treating severely bleeding trauma patients who require damage control resuscitation (DCR).[1-4]

DCR, which in part aims to reproduce whole blood resuscitation via the use of approximately 1:1:1 ratios of red blood cells (RBCs), plasma, and platelets, has become the standard of care for the transfusion management of patients with severe hemorrhage.[1-6] This approach, however, comes with a potential cost: the use (at least, up-front) of greater quantities of plasma and platelets. This is just one more reason why the application of VETs during severe hemorrhage has become an important topic of discussion.[1-6]

The following section focuses on the use of TEG during the management of severe bleeding, though very similar principles and practical considerations also apply to the use of ROTEM.

VET-Guided Reduction in Blood Product Usage and the Mechanics of TEG

Data from European and US combat and civilian trauma studies have demonstrated the utility of VETs in assisting clinicians with their efforts to provide blood component therapy (BCT) in a goal-directed fashion that often enhances patient outcomes while sparing blood products.[1-4,7]

Key Points about TEG and ROTEM

- Describe the body's ability to form a clot with tracings that demonstrate adequacy of coagulation factors, fibrinogen/fibrin, clot strength, initial platelet function and fibrinolysis
- More useful than conventional coagulation tests because they offer nearer to real-time assessments for guiding blood component therapy and can be used as a tool to assist with the management of massive transfusions
- Can alleviate the strain on the blood bank in damage control resuscitation by more accurately guiding the delivery of required blood products

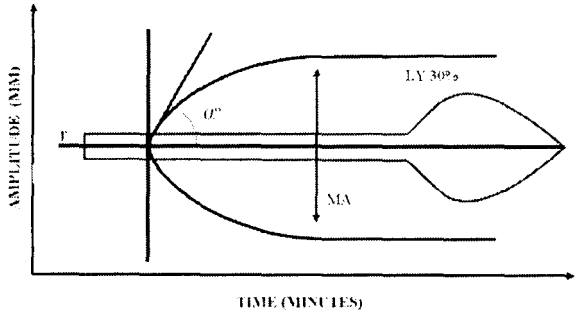
TEG assesses the degree of hemostatic integrity and measures the ability of whole blood samples to form a clot. Specifically, TEG depicts the following four stages of clot formation: (1) initiation, (2) amplification, (3) propagation, and (4) termination through fibrinolysis. This is accomplished by placing a 0.36 mL aliquot of citrated whole blood sample into a Kaolin coated ("standard") TEG cup that has been pre-warmed to 37°C. A pin, attached by a wire to a transducer, is then suspended into the sample. The cup rotates around the pin within the TEG autoanalyzer at an angle of 4.45 degrees every 10 seconds. As the clot forms, the pin and the cup are ultimately joined by the formation of the fibrin and platelet clot. This causes the pin and the cup to rotate together, with the resultant change in tension detected by the transducer. A graphical output is then plotted as a

change in tension (measured in millimeters on the y axis) versus time (measured in minutes on the x-axis).[2,3,7,8]

The four key parameters of the TEG tracing are the: (1) r value (reaction time to clot formation), (2) α (alpha) angle – rate of clot formation, (3) MA (maximum amplitude – maximum strength of clot), and (4) LY30 (percent clot lysis 30 minutes after the MA).[2,3,8] Together, these create an image that somewhat resembles a shovel (see Figure 1). The "handle" of the shovel, represented by r, is the interval that begins with initiation of the reaction and ends when the clot first manifests. The r value reflects the PT/INR and aPTT, or enzymatic phase, of coagulation. The α angle, which defines the curve of the shovel's blade, is equal to the slope of the curve and corresponds to fibrin and fibrinogen activity. The MA indicates the ability of the fibrin/platelet clot to contract and reflects clot strength. Finally, the subsequent tapering of the curve toward the baseline represents the effect of fibrinolysis on the clot. This percentage reduction of the MA, when measured at 30 minutes, is called the LY30.[2,3,8]

We have developed a helpful analogy for understanding the TEG whereby we associate shovels with grave digging. It should be the goal of healthcare providers to prevent the patient's tracing from taking on the appearance of a perfect shovel (i.e., one that could be used to "dig the patient's grave"). Rather, the ideal shovel (TEG tracing) should appear *non-functional*, with a tiny handle and an overly wide blade, correlating to a short r, a large α angle and MA, and a small LY30 that does not taper too rapidly. Refer to Figure 1.

Figure 1. Normal TEG tracing (in black) resembles a wide flat



(non-functional) shovel with a short handle. The superimposed "shovel" (in red) demonstrates a tracing with a prolonged r, flat α angle, small MA, and increased LY 30, indicative of a systemic coagulopathy with fibrinolysis.

Recommendations Based on Abnormal TEG Tracing[1,7]	
Significant Finding on "Standard" TEG Tracing	**Potential Therapeutic Intervention**
Prolonged r-value (> 7 minutes)	Plasma and/or prothrombin complex concentrate
Low or flat α angle (< 45°)	Cryoprecipitate
Narrow MA (< 48 mm)	Platelets +/- DDAVP +/- Cryoprecipitate
Increased LY30 (> 7.5%)	Anti-fibrinolytic agent

Evidence of the Efficacy of VET-guided BCT for Trauma Resuscitation

The use of VETs can be especially helpful when managing the transfusion needs of massively bleeding trauma patients (defined as adult patients who require ≥ 10 units of RBCs within 6 or 24 hours[4-9]), as it allows clinicians to determine more exactly who will require BCT support above and beyond the aforementioned ratios of RBCs/plasma/platelets. It also can assist with the diagnosis of disseminated intravascular coagulation. Large clinical trials have been designed and are underway to determine the ideal physiologic ratios of blood products guided by VETs that can be given to the trauma population.[9]

A limiting factor in the performance of VETs is the lack of universal standardization and quality assurance (QA) protocols. Participation of the entire trauma team in their hospital's transfusion committee QA programs, along with the designation of well trained and committed operators, will ensure proper utilization of VETs in the setting of severe hemorrhage.[1,-4,6-8]

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