Blood products for resuscitation: moving forward by going backward

For the past 30 years, transfusion therapy in the developed world has relied on the manufacture of blood components from whole blood (WB). This trend has been paralleled by the availability of increasingly complex laboratory testing that could differentiate bleeding due to factor deficiency from bleeding due to platelet (PLT) deficiency or dysfunction. Transfusion medicine educators have often cited the following benefits to component therapy as opposed to WB therapy: 1) components replace the needed elements of blood (as determined by coagulation testing) while potentially avoiding circulatory overload associated with transfusion of "unneeded" components; 2) assuming deep inventory, components allow for the transfusion of universally ABO-compatible red blood cells (RBCs), plasma, and PLTs; 3) components could limit the accumulation of harmful metabolic materials that develop with blood storage; 4) components could minimize donor exposures and resulting disease transmission; and 5) perhaps most importantly, components would maximize the use of donated blood by improving the shelf life of RBCs (via storage in additive solution [AS]) and plasma (which can be frozen for long periods of time). Although the overall wisdom of component therapy seemed reasonable and responsive to the needs of all patients, several medical assumptions were also made to justify this approach as reasonable for victims of trauma or massively bleeding surgical patients requiring resuscitation: 1) volume expansion with saline or other volume expanders with subsequent use of RBCs was the best practice and 2) PLTs stored at room temperature provided adequate hemostasis rapidly. The blood banking community also opined that WB did not contain adequate quantities of functional PLTs and that coagulation factors declined in WB, making WB an incomplete product. It is now clear that WB contains plenty of PLTs and that they function very well to quash hemorrhage in bleeding patients; perhaps the statements about WB's PLT inadequacies are an early example of "alternate facts."

Observational studies from recent military experiences and clinical trials for civilian trauma victims have now produced evidence that volume expanders such as saline can contribute to an irreversible coagulopathy and that early resuscitation with plasma is the preferred approach.[1] This recognition has led to a change in practice whereby resuscitation is supported by massive transfusion protocols (MTPs) where plasma, PLTs, and RBCs are generally given in a 1:1:1 ratio with periodic supplementation of cryoprecipitate for fibrinogen replacement.[2] Such protocols have been implemented widely in trauma centers, as well as some community hospitals, but product availability limits their application to major hubs and blood storage limitations (5-7 days for PLTs and thawing time for plasma) makes the current paradigm of MTP resuscitation less available on the battlefield or remote civilian sites. Consideration should also be given to the fact that the typical MTP blood cooler usually contains 6 units of RBCs, 6 units of plasma, and one dose of PLTs, which exposes the adult recipient to 13 to 17 different donors with each cooler, plus five to 10 additional donors from periodic cryoprecipitate infusion, which is generally recommended after one to two cycles of MTP. Pediatric MTP donor exposures are proportionally smaller, but are still on the order of three to nine donors per cycle, plus cryoprecipitate. Since the patient's blood type is usually unknown and reliable pretransfusion testing would delay urgent resuscitation needs, MTP coolers often contain group O RBCs and group AB plasma, which is difficult to supply since only 3% of blood donors are AB and many female donors are excluded from the plasma supply due to transfusion-related acute lung injury (TRALI) mitigation efforts. In an effort to diminish reliance on AB plasma, many sites have recently started using group A plasma in MTP coolers. The use of WB in trauma resuscitations appears to offer several advantages to our current practices, which require intensive utilization of limited resources and expose recipients to large numbers of blood doors.[3]

The provision of WB for resuscitation by community blood centers is currently limited and a number of issues need to be addressed to facilitate its wider availability. If WB is only used for trauma with emphasis on the prehospital phase, the ebb and flow of supply and demand would inevitably lead to a frustrating cycle of frequent outdating and waste during periods of low demand juxtaposed against insufficient supply during acute times of need. However, because the hemostatic effect of PLTs stored in WB is adequate for only 10-14 days,[4] it will be important to develop methods to recover RBCs from WB not used in the first few weeks of storage or, alternatively for the transfusion community to develop reasonable guidelines to allow the use of WB for hemoglobin and coagulation factor support with appropriate PLT supplementation as needed.

Whole blood can be stored for 35 days and there is no convincing evidence that RBCs stored for up to 35 days

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(and beyond in AS) are harmful to patients.[5] This suggests that WB could be used for many applications besides acute trauma. In fact, approximately 20% of RBCs at our hospital are transfused to patients receiving a 1:1 ratio of RBCs to plasma; these patients would likely be better supported by WB, and the use of WB for routine transfusion applications would help to ensure a relatively stable demand for the product. If the demand for WB could be relatively stable, fresh WB required for trauma would be less of a boutique item for blood centers, increasing its availability.

Another major problem requiring considerable attention and delaying the more widespread use of WB is ABO and D compatibility. Trauma needs can be met by group O WB with low anti-A titers.[3] The acceptable anti-A or anti-A,B titer, how it should be measured, and its consistency over time in blood donors are issues that need to be resolved by researchers in the transfusion medicine community. In conjunction with our surgical colleagues, we will also need to address whether D + WB is acceptable for all resuscitations and whether concerns regarding leukoreduction and TRALI mitigation are more important than dramatically increased donor exposures and imperfect "reconstituted" ratios of RBCs:plasma:PLTs for these patients. If we expand WB utilization as suggested above to civilian uses with high-volume surgical cases, the availability of group-specific WB should also increase to handle situations where emergent transfusions with WB containing out of group plasma are not required. At our hospital, we are currently phasing in the use of WB for the quasi-emergent indications of scheduled manual WB exchanges and pediatric cardiac surgery.

The increased interest in WB and the understanding that the chilled PLTs it contains are functional has also energized a movement to bring 4 °C PLTs into clinical practice.[6] Blood providers, understanding that the majority of PLTs are transfused to patients with hematologic malignancies, moved exclusively to room temperature–stored PLTs because of their longer in vivo survival and the need to maintain PLT increments to prevent bleeding in these patients. It was reasoned that 22 °C PLTs would recover adequate hemostatic function to support acutely bleeding patients and that a single inventory of PLTs would lessen inventory shortages for blood centers and hospitals.[7] Although this approach seemed reasonable for many years, we now realize that activated, 4 °C PLTs plug the site of injury more rapidly in bleeding patients, making moot their long-term survival. There is evolving clinical evidence to prove that acute bleeding can be diminished more effectively with cold-stored PLTs. Another potential advantage is the evolving evidence that these PLTs can be stored for as long as 2 weeks, which would make them more available at distant sites, including forward military hospitals.[8] Finally, 4 °C storage would dramatically curtail the current concerns about bacterial contamination in 22 °C PLTs.

If clinical trials demonstrate that 4 °C PLTs are more effective than 22 °C PLTs at controlling acute hemorrhage, the question of split inventories of 22 °C PLTs for hematologic patients and 4 °C PLTs for acute hemorrhage will require attention. The in vivo survival of 4 °C PLTs is much shorter than that of 22 °C PLTs, which might require that hematologic patients transfused with 4 °C PLTs would need more frequent PLT transfusions with the risk of alloimmunization and disease transmission. On the other hand, recent trials have shown limited benefit of prophylactic PLT transfusions;[9] in cancer patients with bleeding despite optimal prophylaxis, transfusion of 4 °C PLTs with more rapid hemostatic effect would probably be the best option.

The transfusion medicine community is facing important and growing challenges.[10] Patient blood management has reduced the inappropriate demand for some blood components, especially RBCs, with the unintended consequence of economic instability for blood providers who relied on a steady or increasing demand for components to balance their budgets. Cost containment in hospitals and inadequate reimbursement for blood therapies are persistent challenges to the current model of blood center economics. At the same time, regulatory requirements are increasingly stringent and meeting them is time-consuming. All of these challenges complicate the availability of WB. We cannot, however, allow these concerns distract us from our mission to provide the best possible therapies for acutely bleeding patients. Moving backward—that is, returning to WB and cold-stored PLTs—appears to be a promising way to move the science of transfusion medicine forward and meet the needs of patients in both military and civilian settings.

CONFLICT OF INTEREST

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EDITORIAL

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