Transfusion for remote damage control resuscitation

"Awake, arise or be forever fall'n"
—John Milton: Paradise Lost, Book I, Line 330[1]

This issue of **TRANSFUSION** is accompanied by a supplement, "Remote Damage Control Resuscitation," containing articles emanating from presentations of a very interesting conference that occurred in Bergen, Norway, in June 2012. Scanning the table of contents will provide the reader with an understanding of the wide-ranging nature of this symposium, from basic science through drug, biologic, and device development and their use in civilian and military practice. Prominent among the issues discussed was the use of blood, blood components, and hemostatic agents for resuscitation of trauma victims.

Care of trauma victims has undergone substantial innovation and progress in the past several years, propelled in large measure by the US military experience in Iraq and Afghanistan, following a long tradition of leadership of military medicine. This evolving use of transfusion therapy includes the use of blood and blood components in many ways that differs from that of usual civilian clinical practice.

Research and practice are moving damage control resuscitation from hospital-based to the prehospital environment, including remote locations, with transportation times from the latter to the former that can be substantial. As has occurred in the past, the advances pioneered by the military have been rapidly accepted by the US civilian trauma care sector. However, these advances in medical care are only possible when supported by a proper infrastructure. The US Army's Blood Program has accomplished what many would have thought not possible thanks to the efforts of many unsung heroes. The supplement will give the reader a clear vision that while practice has advanced substantially, further progress for both in-hospital and prehospital trauma resuscitation, in great measure, will require availability of blood and blood components more appropriate to trauma care and remote damage control resuscitation.

Blood banking practices in the US civilian community have developed in concert with the perceived needs of its "customer" base: patients with hematologic disorders, those with various "medical disorders," and for elective surgery, but not primarily for trauma care. Advances in technology, devices, storage media, and conditions have allowed blood banks to supply red blood cells (RBCs) stored for up to 42 days in the United States and 56 days in the EU as "packed" (and thus containing only a few milliliters of plasma), plasma generally as thawed from the frozen state (fresh-frozen plasma [FFP]), and platelets (PLTs) stored for up to 5 days at 22°C. These advances have served well those patients in need of the individual components. While RBCs, FFP, and PLTs as currently collected, stored, and administered meet the needs of most patients requiring one component, the efficacy of their combined use for those requiring two or three of these simultaneously is untested and questioned by many. It has become increasingly evident that while these components generally meet the needs of the above populations, they are less suitable for major trauma.[2]

Retrospective database analyses have pointed to improved patient outcome with an increased use of plasma with volumes approaching 1 unit per unit of RBCs transfused.[3,4] First noted in military practice,[4] similar findings have been reported from civilian databases.[3] Although not all reports are positive,[5,6] the practice is now well established in US civilian trauma centers.[7] A large multicenter trial is in progress to compare the clinical outcomes of transfusion of 1 unit of plasma per unit of RBCs with 1 unit of plasma per 2 units of RBCs; both study arms include transfusion of PLTs with RBCs and plasma.[8] However, both of these paradigms differ substantially from earlier practice; clinical trial design, which could have provided a comparison with more traditional transfusion practice, was limited by the change in thinking and practice that had already occurred. The US military already recommends greater use of plasma than previously.[9] Some institutions already provide some blood components in prehospital evacuation systems.

Nevertheless, practice and these studies essentially reconstruct blood that had been deconstructed to allow for individual component therapy.[2] The rationale for this approach has been examined recently elsewhere[2] and need not be repeated here with that level of detail, except to note the comment "that if a ratio of transfused red cells to plasma of 1:1 [with platelets] is beneficial, then why not transfuse whole blood?" thereby reducing recipient exposure to donors. Trauma patients are at greater risk of donor white blood cell engraftment (immunomodulation)[10,11] that is not eliminated by leukoreduction of transfused RBCs.[12,13] The availability of whole blood is rare, to the point of being nearly nonexistent for adults in the United States.

Stored RBCs have deficits that have been widely discussed. Among them are the so-called "storage lesions," that include decreased 2,3-phosphoglycerate concentration with resultant decreased hemoglobin (Hb) P50

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(increased Hb affinity for oxygen), decreased ATP concentration, decreased deformability, decreased intra- and extracellular pH, increased potassium, CO_2 concentrations, and microparticles in the supernatant fluid. Some of these deficits have caused some to question the immediate efficacy of RBC transfusion. However, testing of healthy volunteers demonstrating RBC transfusion reversal of anemia-induced cognitive function[14] and the clinical examples of many patients having survived intact the rapid transfusion of sufficient volumes of RBCs (multiple blood volumes) that virtually depleted the patient's native RBCs, testify to clinical efficacy. The other storage effects are potential issues of safety, but are not likely to differ importantly if RBCs are stored as packed or as whole blood. However, they are affected by storage temperature and duration.

Supply, storage, and cross-matching issues for augmenting oxygen delivery could be at least partially assisted by the use of Hb-based oxygen carriers. However, these compounds are not near approval in the United States.[15] At least one product is available within the "expanded use" program of the FDA,[16] but the nature of getting approval for each use individually makes it not applicable for use in acute trauma in either the prehospital or hospital environments.

However, the use of whole blood relates more to coagulation function than oxygen delivery, that is, the presence of coagulation factors in plasma and functional PLTs. Of special note in the supplement is the evaluation by Pidcoke and coworkers[17] of the hemostatic function of whole blood stored at 4 and 22°C, with and without the application of a pathogen reduction technology. This demonstration is a first, necessary step in creating a scientifically based foundation for the use of whole blood for major trauma. Hopefully, in vivo testing will ensue. A database analysis from Afghanistan, contained in the supplement, found an association of increased survival with the use of fresh whole blood compared to component therapy without PLTs.[18] A recently completed clinical trial of 115 patients (B.A. Cotton, personal communication, 2012) compared the use of stored whole blood plus PLTs with component therapy for trauma patients on arrival to the hospital.[19]

Furthermore, in ordinary circumstances, circulating blood has a substantial reserve of RBCs, coagulation factors, and PLTs. It appears that the reserves for these components are approximately equivalent, with inadequacy occurring at approximately one-third to one-half of the normal concentrations. For example, in normal, healthy adults, no systemic effects of inadequate oxygenation are detected at a Hb concentration of 5 g/dL,[20] but neurocognitive deficits occur at a Hb concentration of 6 g/dL.[21] Isolated decreased coagulation factor concentrations are thought to not adversely affect coagulation function until the concentrations decrease to approximately 30% of normal.[22] However, the concentrations required to achieve relatively normal hemostasis are not known for states of multiple deficiencies, such as trauma with massive hemorrhage and volume replacement.

Some of the recently performed transfusion medicine research tends to center on decreased component use, rather than improved outcome.[23] A lower dose of PLT transfusion to patients with hematologic disorders results in decreased number of transfused PLTs without a difference in spontaneous bleeding episodes.[24] However, the incidence of bleeding in all groups was still 70%, and there was a very strong continuous relationship between decreased PLT count (from $\geq 100 \times 10^9$/L to $\leq 5 \times 10^9$/L) and increased spontaneous bleeding.[24] These findings are supportive of the earlier observational findings of Gaydos and coworkers.[25] If the incidence of bleeding episodes in patients without trauma and tissue damage is increased at PLT concentrations below 100×10^9/L, then it is reasonable to consider that hemostasis for trauma requires PLT counts at or above this concentration. This thought is supported by two relatively small reports of massive transfusion after trauma, with clinically judged abnormal bleeding associated with PLT counts below approximately 100×10^9/L[26,27] that was controlled with transfusion of fresh whole blood[26] or PLTs.[27] Additionally, coagulation factors and PLTs are consumed appropriately with trauma and bleeding, and it is entirely possible that in this circumstance, both could be required at an earlier stage than are RBCs.

Furthermore, PLT storage conditions have been developed primarily for patients with hematologic malignancies. PLTs have reduced recovery when stored at 22°C for 24 hours[28,29] that is further reduced with longer storage.[28,30] Most importantly for hemostasis, 22°C-stored PLTs have decreased function[31] requiring several hours in vivo to recover.[32,33] In contrast, PLTs stored at 4°C have increased activation,[31,33] but with lesser recovery and survival,[28,31] likely owing to their activation. The former in vitro property is confirmed by Pidcoke and colleagues.[17] Similarly, pathogen reduction technology results in some PLT activation with some reduced recovery and survival. While two pathogen reduction technologies are licensed in Europe, neither has progressed to that point in the United States, owing to perceived pulmonary issues interpreted as possibly owing to PLT activation for one of the technologies.[34] There is some thought, first voiced by Valeri,[30] that somewhat-activated PLTs, which do not require hours in vivo to recover function, are to be preferred for treatment of active hemorrhage. In any case, the bulk of evidence-based PLT transfusion guidelines have been derived in relatively stable patients; these guidelines and our current products may not be optimal for a different context: patients with acute hemorrhage either induced by or resulting in thrombocytopenia.

Absence of support for the use of whole blood within the blood collection and banking community is

understandable. It incurs additional logistic burden and perhaps increased labor costs, as well, and limits the ability to produce individual components (although 88%[35] of PLTs for transfusion are now derived from apheresis, rather than whole blood donations). Our limited supply of healthy donors has made component therapy a prudent strategy for meeting the needs of multiple patients from an ever-diminishing donor base. Nevertheless, if shown to be beneficial, these are necessary costs to pay. Therefore, it is critical for blood centers to support clinical trials of whole blood or other modifications of current blood components to demonstrate whether the clinical demand and increased costs can be justified by substantial medical evidence.

The practical issues of providing whole blood for trauma victims are also substantial. Blood centers and transfusion services will not be able to provide whole blood that matches the ABO and Rh types of all recipients, so trauma resuscitation may need to make uncomfortable compromises regarding Rh sensitization and incomplete ABO testing for recipients.[36] As has been observed previously, clinical medicine does not include a condition of "no risk" and the best that we can do is to consider how to minimize risk while attempting to maximize benefits of various therapies.[36] We may need to accept point-of-care blood testing, perhaps performed in the field, from individuals with less training than the medical technologists who routinely perform these functions. We will need to reach consensus with trauma specialists about acceptable storage periods for whole blood and develop strategies in transfusion services allowing for conversion of some of the whole blood to RBCs if not needed for trauma or other instances of massive transfusion. These issues will require creative discussions so that whole blood advocates will understand the compromises from standard practices, transfusion specialists will accept the changes from current routines, and both parties will understand the cost issues that will need to be faced if these practices are proven to benefit patients.

The US Army has been using fresh whole blood from WWI through the current period of combat,[37] currently with reliance on previous testing of donors. Pathogen reduction will likely improve safety. Simultaneously, there are a number of efforts to enable supply of various plasma products and synthetic or semisynthetic PLTs for the prehospital environment. Lyophilized plasma has been used by the French,[38] German, and Dutch military for some time. These products are well suited to remote use and also can improve the problems of variabilities of volume and coagulation factor concentrations of single-donor FFP. Development of both freeze-dried and spray-dried plasma is proceeding in the United States, but face regulatory hurdles never encountered for approval of FFP.

Refocusing blood product research from the traditional regulatory-driven end points of recovery and survival to important, relevant, realistic clinical end points would assist in developing our understanding of the best strategy for therapy for specific patient populations.

John Milton recognized that important action requires enthusiasm and invigoration to replace complacency.[1] Trauma care specialists and industry are spearheading active research; it is time for the blood banking community to consider that currently provided products and our civilian-based hospital procedures do not suit the needs of all patients and join the quest.

CONFLICT OF INTEREST

RBW has a relationship with or consults for the following companies and organizations that have an interest in RBCs; and/or plasma and/or platelet transfusion: US Food and Drug Administration; US National Heart, Lung, and Blood Institute/National Institutes of Health; US Department of Defense; TerumoBCT; CSLBehring; OPK Biotech; and Sangart, Inc. The author was project/corp VP and Executive Scientific Advisor at Novo Nordisk A/S 2005-2007. PMN has a relationship with or consults for the following companies that have an interest in RBC and/or plasma and/or PLT transfusion: TerumoBCT, OPK Biotech, and Fenwal.

Richard B. Weiskopf, MD
e-mail: rbw@itsa.ucsf.edu; rbw@TheWeiskopfGroup.com
Department of Anesthesia
University of California
San Francisco, CA
Paul M. Ness, MD
Pathology, Medicine, and Oncology
Johns Hopkins School of Medicine
Baltimore, MD

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