

Reconstructing Deconstructed Blood for Trauma

I hear the train a comin'¹

—Johnny Cash, *Folsom Prison Blues*, 1956

MILITARY medicine has been, and continues to be, at the forefront of many important medical developments and innovations, especially in the area of the care of traumatic injury. The advances made for combat casualty care have had important and lasting impacts on the care of civilian trauma. Included in these have been the treatment of hemorrhagic shock, fluid resuscitation, and transfusion of blood and blood components. In this issue of *ANESTHESIOLOGY*, Ho *et al.*² examine the evidence for the increased use of plasma in treating major hemorrhage, a practice that began in the U.S. military and that has been embraced in U.S. civilian practice, as well.

The ability to separate whole blood into components began with Cohn's separation of plasma into fractions ("fractionation") and his suggestion that they be "explored . . . to determine their possible value in therapy."³ This eventually created an entire fractionation industry with the ability to isolate various "fractions" with significant therapeutic efficacy for specific disorders. The development of the plastic storage bag and other technological advances, such as component-specific storage/preservation, contributed importantly to the development of component therapy, as well.⁴ Thus, clinicians have been able to provide patients with the specific components required, without simultaneously transfusing components that are per-



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ceived as not needed, while furnishing them for patients who do need them. Although this strategy has been successful for those circumstances of a deficiency of one specific component, the overall efficacy of this strategy for patients needing more than one, or all components of blood, is questionable and untested. The almost ubiquitous separation of all blood collected in the United States, Canada, and Europe into red cells and plasma (for freezing or further fractionation) proceeded well beyond Cohn's original suggestion, abetted by the development of regional blood centers, rather than individual hospitals, as the major collectors of blood. The few who objected cited the additional cost and effort to transfuse both plasma and packed red cells (PRBC) for those in need of whole blood, especially for massive hemorrhage,^{5,6} implying that collection agencies were motivated by aims other than clinical care.⁵ However, the need for whole blood was challenged as unsupported by some at

the American Red Cross,⁷ the largest collector of donated blood in the United States. Patients who bleed sufficient quantities of whole blood require all components contained therein. For the past several decades this has required separate transfusion of PRBCs, plasma, and platelets. Several medical specialty societies, the American Society of Anesthesiologists included, have recommended that plasma be transfused only when there are clinical data/diagnoses to support the need for augmentation of coagulation factors.^{8,9}

Based on database analyses of the combat injured,¹⁰ the U.S. military recommends greater use of plasma¹¹ than has been recommended previously.⁹ Consequently, in military in-theater practice the ratio of transfused PRBCs to fresh frozen plasma (FFP) has approached their recommended 1:1

Photograph: J. P. Rathmell.

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◆ This Editorial View accompanies the following article: Ho AMH, Dion PW, Yeung JHH, Holcomb JB, Critchley LAH, Ng CSH, Karmakar MK, Cheung CW, Rainer TR: Prevalence of survivor bias in observational studies on fresh frozen plasma: Erythrocyte ratios in trauma requiring massive transfusion. *ANESTHESIOLOGY* 2012; 116:716–28.

ratio.* Similar database analyses of civilian trauma have generally provided data similar to that from the military, impelling many U.S. trauma centers to follow and continue to use this transfusion paradigm.¹² However, one may wish to take note of another retrospective database analysis from a single civilian trauma center, of an association of improvement in mortality with earlier blood component administration and increased platelet use, without a change in the actual PRBC:FFP ratio of 1.8 (although the target ratio was 1.5).¹³

Ho *et al.*,² in assessing the evidence for this change in practice, correctly note limitations of the analyses. In addition to those that generally apply to all retrospective database analyses, an important issue is that cause-and-effect may be even more muddled than is usual for database analyses, in that survivors may have had greater opportunity to receive more FFP than did those who did not survive (so-called “survivor bias”). This may be counter to the conclusion offered by some authors: that survival was improved by the transfusion of increased volume of FFP. The recently completed U.S. Department of Defense-sponsored PROMMTT prospective observational study performed at 10 major U.S. trauma centers will produce a wealth of data regarding current transfusion practice for major trauma, including timing of transfusion of blood components and outcome (John Holcomb, M.D., Professor, Department of Surgery, University of Texas Health Science Center, Houston, Texas, verbal communication, August 2011). Ten of the 14 retrospective analyses that did not have positive “survival bias” as judged by Ho *et al.* (including three of four judged as biased against the 1:1 practice) found a beneficial association of improved survival with a 1:1 transfusion ratio. Although this may be suggestive, it is not without the bias of retrospective analyses of databases and the fundamental inability of such analyses to establish cause and effect (despite statistical techniques that attempt to reduce bias). It does what such analyses can do: provide a plausible hypothesis for testing. A large civilian multi-center trial funded by the National Institutes of Health (Bethesda, Maryland) and U.S. Department of Defense, intended to compare the transfusion ratio of 1:1 for PRBC to FFP to another ratio, is being planned (“PROPPR”) but has not yet been initiated as of the date of this writing (August 2011). This trial is powered for a mortality endpoint; it may also yield valid information regarding hemostasis and mor-

bidity for the 1:1 paradigm *versus* another. An additional important consideration is that platelet preparations contain plasma. While some database analyses have not considered this, the PROPPR trial will control for platelet transfusion: both treatment arms will also be transfused one unit of platelets for each unit of PRBCs (or 1 plateletpheresis unit per 6 units of PRBCs). The success of the trial will be dependent upon successful implementation of the transfusion strategy to reduce the substantial variation of clinical transfusion practice in trauma (even when a specific PRBC:FFP ratio was sought at a single trauma center¹³) in order to avoid overlap of the two groups so that there will be adequate group separation to enable a valid test of the hypothesis. There is an additional issue that although critical, is not addressed by Ho *et al.*, presumably because most reports do not contain the necessary information: what is the appropriate endpoint for which to assess a therapy (such as the RBC:FFP ratio) that is proposed to improve hemostasis for trauma? For many years the U.S. Food and Drug Administration has used 28- or 30-day mortality as the acceptable regulatory endpoint, with the thesis that an endpoint must be “durable.” I have previously expressed the view that mortality is too coarse a measure and that an appropriate clinical trial endpoint should be more closely related to the pharmacodynamic and pharmacokinetic properties of the article that is being tested. Mortality at 28 or 30 days does not satisfy either of these requirements for either PRBC:FFP ratio or whole blood use in the first few hours after trauma. Recently, at an NIH/FDA/DOD sponsored workshop, all but one of the panelists addressing this issue agreed that an endpoint between 6 and 24 h is more appropriate.† The PROPPR trial will include 24-h mortality as a coprimary efficacy endpoint along with 28-day mortality.

Whatever the results of the PROPPR trial, it will not be the end of the line. The logical question that should arise is that if a ratio of transfused red cells to plasma of 1:1 is beneficial, then why not transfuse whole blood, thus reducing substantially recipient exposures to donors? There is evidence that trauma patients are at greater risk of immunomodulation as evidenced by donor leukocyte engraftment^{14,15} that is not altered by leukoreduction of donor red cell units.^{16,17} Transfusion of whole blood would reduce recipient exposure not only to donors of plasma, but potentially also to platelets, an indispensable element for hemostasis. Notably, the rate of development of transfusion-related acute lung injury and deaths therefore is greater after transfusion of plasma-containing components (platelets or FFP) than after PRBCs.‡ The original concept of the “coagulation cascade”¹⁸ did much to advance our understanding of hemostasis and treatment of its disorders, but it included only the coagulation factors in plasma. We now have a better understanding of the critical role in hemostasis of tissue factor-bearing cells and of platelets. Both provide, among other things, the surface for conversion of several zymogens to active coagulation factors.^{19,20} Furthermore, the platelet surface is necessary²¹ for

* Rentas FJ: Armed Services Blood Program Update. Society of Armed Forces Medical Laboratory Scientists Annual Meeting 2010. safmls.org/2010/2010%20Presentations/W%2021/ASBPO%20Update.pdf. Accessed July 6, 2011.

† Center for Biologics Evaluation and Research USFDA: Product development program for interventions in patients with severe bleeding due to trauma or other causes. December 9, 2010 (day 1). 2010: 308–354. <http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm241912.htm>. Accessed July 30, 2011.

‡ US FDA: Fatalities Reported to FDA following Blood Collection and Transfusion: Annual Summary for Fiscal Year 2010. <http://www.fda.gov/biologicsbloodvaccines/safetyavailability/reportaproblem/transfusiondonationfatalities/ucm254802.htm>. Accessed July 30, 2011.

the crucial generation of thrombin (“thrombin burst”) that is critical for the conversion of fibrinogen to fibrin,^{19,22} to produce fibrin that is of the proper structure and is resistant to fibrinolysis,^{23–25} and for the full activation of thrombin-activatable fibrinolysis inhibitor.²⁶ Platelets as a component of whole blood that is not stored, but used immediately, are hemostatic.²⁷ Platelets stored at 22°C (the current standard) for 24 h have reduced (approximately 40–50%^{28,29}) recovery after transfusion that decreases with further storage,^{28,30} but maintain the normal *in vivo* half-life of several days. These platelets have impaired function³¹ that requires several hours *in vivo* for restoration.^{32,33} Platelets stored at 4°C have substantially reduced *in vivo* recovery and circulating half-life^{28,31} but are activated with preserved function and superior function compared with those stored at 22°C^{31,33} and even to fresh platelets.³¹ This has led to the suggestion that 22°C-stored platelets be used for prophylaxis, while 4°C-stored (and apparently activated) platelets be used for immediate hemostasis.³⁰ However, one small randomized trial in cardiac surgery suggested that 1 unit of whole blood stored for 24 h at 4°C may have fewer hemostatic effects than 1 unit of fresh whole blood because of decreased platelet aggregability.³⁴ Thus, the storage duration and temperature of blood is of importance when considering its use for trauma. Fortunately, *in vitro* characterization of coagulation function of whole blood stored at 0°C or 22°C for varying durations is underway (Heather Pidcock, personal communication, 2011) and hopefully to be followed by *in vivo* testing. As they have for red cell storage, the blood banking community and regulatory authorities have focused on platelet *in vivo* recovery and survival, rather than function, as criteria for preservation and approval. Perhaps current testing will have the possibility of modifying that approach.

In the United States wide use of whole blood for trauma has not been possible, owing to the near complete lack of supply of whole blood by blood collection agencies to blood banks and then to clinicians, except at very, very few institutions, such as at the NIH Clinical Center into the 1980s (Harvey G. Klein, M.D., Chief, Department of Transfusion Medicine, National Institutes of Health, Bethesda, Maryland, written and verbal communication, July 2011) and San Francisco General Hospital in the 1980s (where a retrospective data analysis noted coagulopathies after massive transfusion of red blood cells without concomitant transfusion of plasma or platelets³⁵). Although that approach appeared to make clinical sense, it is no longer practiced at San Francisco General Hospital, and has not been adopted by other institutions, owing to logistics, inadequate data, and a reluctance to alter standard blood banking practices. It is regrettable that we missed the obvious opportunity to conduct the needed clinical trial at San Francisco General Hospital at that time. The U.S. military has been transfusing whole blood for

some traumatic injuries in-theater during all major conflicts from World War I through the recent combat in Iraq and Afghanistan.³⁶ Similar to the experience with increased use of FFP, one database analysis suggested increased survival with the use of whole blood,³⁷ while another retrospective examination of its use in massive transfusion found a nearly significant increase in survival at 24 h ($P = 0.06$), but not at 30 days. However, there was substantial loss of patients to follow-up at the later time, and a lesser overall use of whole blood than was reported in the earlier experience, despite the whole blood group having had more severe injuries (as determined by their injury severity score and trauma-injury severity score) and more severe physiologic derangement on admission (as documented by arterial pH, base-deficit, and platelet count).³⁸ Here too, “survivor bias” may have influenced the results owing to the additional time required to provide fresh blood after it is ordered. An alternate possibility is that whole blood transfusion allowed some patients with more severe injuries to survive beyond the initial 24 h (when they might not have survived without whole blood), only to succumb later owing to their more severe injuries and associated complications (perhaps a “survivors’ curse”). Thus, similar to the issue of the PRBC:FFP ratio, a prospective clinical trial is required to test these hypotheses. Two trials in adult cardiac surgery have been reported, but both were small and transfused a small volume of whole blood rather than having used it for all transfusion requirements. One reported a decrease in postoperative blood loss after approximately 2 units of fresh autologous blood (collected intraoperatively), but not PRBC transfusion,³⁹ and the other reported that 1 unit of fresh whole blood restored the bleeding time to normal, but was underpowered to show the difference in blood loss as statistically significant.⁴⁰ At least one clinical trial for the use of whole blood in trauma is in progress, (Bryan Cotton, M.D., M.P.H., Associate Professor, Department of Surgery, University of Texas Health Science Center, Houston, Texas, verbal and written communication, August 2011) powered to detect a decrease of transfusion of blood components (total sample size of 132),§ but not morbidity or mortality (Bryan Cotton, verbal and written communication, August 2011). Another trial is in the early conceptual stage. Nonetheless, practice may move in that direction.

Johnny Cash heard the train coming (note the trauma described in the second verse)¹; others (Bryan Cotton, verbal and written communication, August 2011),³⁶ and I can see it, as well. The blood banking community is likely to get on board only if they are convinced by data, surgeons, anesthesiologists, intensivists, and other clinicians caring for trauma patients.

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