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WHOLE BLOOD: THE FUTURE OF TRAUMATIC HEMORRHAGIC SHOCK RESUSCITATION

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ABSTRACT—Toward the end of World War I and during World War II, whole-blood transfusions were the primary agent in the treatment of military traumatic hemorrhage. However, after World War II, the fractionation of whole blood into its components became widely accepted and replaced whole-blood transfusion to better accommodate specific blood deficiencies, logistics, and financial reasons. This transition occurred with very few clinical trials to determine which patient populations or scenarios would or would not benefit from the change. A smaller population of patients with trauma hemorrhage will require massive transfusion (>10 U packed red blood cells in 24 h) occurring in 3% to 5% of civilian and 10% of military traumas. Advocates for hemostatic resuscitation have turned toward a ratio-balanced component therapy using packed red blood cells–fresh frozen plasma–platelet concentration in a 1:1:1 ratio due to whole-blood limited availability. However, this "reconstituted" whole blood is associated with a significantly anemic, thrombocytopenic, and coagulopathic product compared with whole blood. In addition, several recent military studies suggest a survival advantage of early use of whole blood, but the safety concerns have limited is widespread civilian use. Based on extensive military experience as well as recent published literature, low-titer leukocyte reduced cold-store type O whole blood carries low adverse risks and maintains its hemostatic properties for up to 21 days. A prospective randomized trial comparing whole blood versus ratio balanced component therapy is proposed with rationale provided.

KEYWORDS—Whole blood, component blood therapy, leukocyte reduced blood, low-titer type O blood, randomized prospective trial

HISTORY OF MODERN BLOOD TRANSFUSION

By the early 20th century, blood transfusions were more often technically difficult (i.e., vein-vein or artery-vein direct transfusion) and carried greater risks than a major surgical operation. Its development as an effective and safe therapeutic method required the solution of a number of special problems including (*a*) identification of agglutination and hemolysis from mixture of incompatible bloods with the identification of blood groups in 1900 (1, 2); (*b*) blood coagulation in storage addressed by the successful use of sodium citrate in 1914 (3); (*c*) technical difficulties with direct vascular connection for blood transfusions, which became obsolete with the development of "syringe" technique and two-way stopcock by 1915 (4); and (*d*) the development of aseptic technique, which decreased infections. Toward the end of World War I, whole-blood transfusions were widely accepted as the primary resuscitation for hemorrhagic lesions (5). However, when the United States entered World War II, the military embraced freeze-dried plasma as the primary transfusion product for bleeding but soon noted that casualties resuscitated with plasma had worse than expected outcomes. This prompted the return of whole blood as the primary agent of choice for transfusion of casualties (6). By the end of the war, more than 500,000 U of stored whole blood was shipped to military hospital with peak in March 1945, more than 2,000 U per day (7).

After World War II, the development of whole-blood fractionation techniques promoted the concept that blood could be used more effectively if separated into packed red blood cells (PRBCs), platelet concentrations (PLT), and fresh frozen plasma (FFP) and cryoprecipitate. The availability of individual components had its advantage in replacement therapy for specific deficiencies as well as logistical, financial, and inventory management benefits. As the fractionation process developed after World War II, component therapy increased significantly and became the standard for civilian transfusion practices, but stored whole blood has remained an integral part of special civilian medical indications in cardiac surgery, obstetrics, and military blood management in Korea, Vietnam (>800,000 U transfused), and most recently in Iraq and Afghanistan (>6,000 U transfused) (8, 9).

During this transition from whole blood to component therapy in the 1940s to 1980s, there were few studies comparing the benefits and risks in different populations to support its acceptance. In addition, the storage solutions that had been developed to increase the shelf life of RBCs were not evaluated for risks and benefits to the recipient. The main requirement for stored RBCs remains since 1940s that the RBC membrane still be intact in 70% of cells 24 h after transfusion (9). Numerous studies in critically ill, surgery, and trauma have

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demonstrated that stored RBCs may increase morbidity and mortality due to the amount and age of stored RBCs (10–19).

For patients who require only specific components and particularly in low amounts, the concept of component therapy is an appropriate approach. However, there is a smaller population of traumatically injured patients who require transfusion of all blood components due to lost of whole blood. Massive transfusion (MT) was traditionally noted as more than 10 U PRBCs in 24 h but more recently described as more than 3 to 4 U PRBCs/h or initial resuscitation intensity of more than 4 U within 30 min, which better characterizes early mortality (20). Massive transfusion occurs in only 3% to 5% of civilian traumas but is more than doubled (10%) in the military combat traumas (21, 22). Many advocate that the most appropriate resuscitation in this population is whole blood, which addresses both hemorrhagic shock and coagulopathy. Whole blood provides a balanced amount of RBCs, plasma, and platelets, as well as an increased concentration of stored components and improved function compared with stored components (23, 24). This concept, known as hemostatic resuscitation, uses components in a similar ratio to whole blood (25). Although whole blood is an approved and regulated product by the US Food and Drug Administration and the American Association of Blood Banks (AABB), it is not routinely available and forces clinicians to pursue the use of ratio-balanced component therapy. This approach of balance-ratio component therapy (1:1:1 of PRBCs:FFP:PLT), however, provides a more anemic, thrombocytopenic, and coagulopathic product as compared with whole blood based on calculations. (Table 1) (23, 24) Although fresh warm whole blood would be an ideal hemostatic resuscitation product, concerns over infectious risks with current rapid testing methods render it impractical except for military austere environments. Recently, an extensive evaluation of cold-stored whole blood (4°C) has demonstrated that it maintains its hemostatic function based on thromboelastography parameters over 21 days, and refrigeration attenuates loss of platelet function over time (26).

Based on vast military and austere environment experience with whole blood, lack of evidence for component therapy in traumatic hemorrhage shock, and recent data specifically addressing hemostatic concerns of cold-stored whole blood, it appears that cold-stored whole blood may be a suitable blood product for trauma resuscitation in hemorrhagic shock, in particular those at risk for MT. At the 2013 Remote Damage Control and Resuscitation Symposium held in Bergen, Norway, feasibility of a prospective randomized controlled trial comparing cold-stored whole blood versus standard component therapy in trauma hemorrhagic shock was discussed concerning the safety of low-titer type O whole blood during emergent utilization, role of leukocyte depletion, and the development of a consensus trial. Summary of the presentations is presented in this article.

TABLE 1. **Comparison of "reconstituted" whole blood (1:1:1) to whole blood**

	"Reconstituted" whole blood (1:1:1)*	Whole blood
Total volume	660 mL	570 mL
Hematocrit	29%	33%–43%
Platelet count	88 k	130,000–350,000
Coagulation factor activity	65%	86%

*Assumptions: PRBC hematocrit 55%, PLTs 5.5 × 10^{10}, FFP 80% coagulation factors.

BLOOD SAFETY AND IMPLICATIONS OF LEUKODEPLETION

A key question is the definition of blood safety. In many countries, blood safety is ensured by a hemovigilance system. This is defined as "a set of surveillance procedures covering the whole transfusion chain (from the collection of blood and its components to the follow-up of recipients), intended to collect and assess information on unexpected or undesirable effects resulting from the therapeutic use of labile blood products, and to prevent their occurrence or recurrence." Although the military experience with whole-blood transfusion practice has been successful, there have been complications as vein thrombosis, renal failure, respiratory distress, and one case of transfusion-associated graft-versus-host disease. It has been speculated that these complications to some part may be related to the white blood cells in the whole-blood units. Correspondingly, there is a refreshed interest in leukocyte-reduced whole blood—produced by a method sparing the platelets. Leukocyte reduced whole blood is defined as 450 to 500 mL whole blood in 63 mL CPD-A, filtered to remove leukocytes to a residual content less than 10^6. Many filters have been developed for whole blood, red blood cell (RBC), and platelet concentrates, but in the late 1990s, many blood bank leaders were interested in filters sparing platelets as sufficient platelet function is essential in transfusion therapy of patients with massive bleedings. Thus, for the purpose of this article, leukocyte reduced whole blood is defined as leukocyte reduction with platelet-sparing filtration. As literature is sparse concerning clinical experience with leukodepleted whole blood containing platelets, these considerations are partly based on knowledge established from clinical use of conventional blood components.

Febrile nonhemolytic transfusion reaction

Febrile nonhemolytic transfusion reaction is defined as a type of transfusion reaction, which is associated with fever but not directly with hemolysis. Temperature elevation should be at least 1°C with a serious reaction defined as elevation greater than 2°C. Leukocyte reduction of whole blood by filtration is performed shortly after donation, whereas leukocyte reduction of cell concentrates is done up to 24 h after donation. There is no reason to think that leukocyte-reduced whole blood should give more febrile reactions because these reactions are linked to cytokines. A recent publication presenting data from a study with a platelet-removing whole-blood filter supports this, although one could argue that the platelet-derived cytokines could be the most important contributor (27).

Allergic reactions

The symptoms of an allergic transfusion reaction are usually mild and include urticarial, skin redness, and itching. Severe systemic reactions (anaphylaxis) may occur, including life-threatening respiratory distress and hypotension, dyspnea, and nausea and

vomiting. As the symptoms are related to the donor plasma, the number of donor exposures may be significantly decreased by use of whole blood compared with component therapy. On the other hand, use of pooled plasma instead of single-donor plasma seems to reduce allergic symptoms likely secondary to dilution effect as well as the addition of neutralizing antibodies.

Hemolytic transfusion reactions

Preformed antibodies in the patients cause hemolytic transfusion reactions. Acute reactions are most serious, especially due to immunoglobulin M (IgM)–type anti-A and anti-B, but delayed reactions may occur due to restimulation of an alloantibody (often a-Fy^a or anti-Jk^a) undetected at the time of transfusion. According to hemovigilance reports from many countries, "wrong" blood is the major cause for these severe transfusion reactions (28). The risks will be substantially reduced if only "low titer" type O donors are used for whole-blood transfusions and group O RBC and platelet donors and group AB plasma donors for reconstituted whole blood (29). Although there is no officially set standard for a "low titer," there is a general acceptance of an A- and B-antibody titer less than 1/100 for IgM and 1/400 for IgG-type antibodies as an acceptable low level.

Transfusion-related acute lung injury

In many western countries, transfusion-related acute lung injury (TRALI) is now the most common transfusion-related cause of death. Transfusion-related acute lung injury can be defined as acute lung injury (ALI) that occurs during transfusion or within 6 h of transfusion, if the reaction is not explained by other ALI risk factors. The etiology of TRALI is related to donor/blood unit factors as HLA antibodies and other antibodies in the patients and biologic response modifiers in the blood bags. Antibodies in the patient may also be involved, and yet to be described factors in the patient's illness may predispose to the condition. For both whole blood and reconstituted whole blood, the use of only male, not-transfused donors (whole blood, platelets, and plasma) seems to reduce the risk (30).

Transfusion-associated graft-versus-host disease

This is a rare transfusion reaction, but the mortality is around 90%. Immune-competent donor lymphocytes engraft in the recipient and cause rejection of the host, as the host is unable to mount a response due to HLA one-way compatibility or immunosuppression. The patient is usually dying of intractable diarrhea. This reaction may be prevented by irradiation or x-ray treatment of the units. Because this treatment is unavailable in remote locations, there is a risk related to "buddy" transfusion and in other circumstances where whole blood or cellular components are transfused without treatment. This is documented from a case history during US military operations (31). The risk in susceptible patients is estimated at 0.1% to 1%.

Transfusion-transmitted infection

The risk of infecting patients through transfusion has always been a major concern in transfusion practice. Although donor information and selection, donor questionnaire, extensive testing, and products pathogen reduction technologies are implemented, causing the residual risk to be in the 10^{-5}, this is still the major concern among the public and also among many health professionals.

Despite the low risk, documentation from recent military experience demonstrates that some patients are infected through transfusion. It is obvious that, in austere environments, blood donor selection cannot be performed as in a civilian blood bank. Currently, there are a limited number of rapid testing methods for infectious markers compared with the sophisticated test panels that may be used in a civilian blood center.

WHOLE BLOOD—IS ABO TYPE SPECIFIC NECESSARY?

The ABO blood group substances consist of carbohydrate chains and are shared with bacteria and plant seeds (32). As the antigenic substances are adsorbed from the intestinal bacteria, all individuals from 3 months of age carry preformed antibodies of IgM type against the other A/B blood groups in their plasma. These antibodies are complement activating and strongly hemolyzing. The ABO blood group substances also exist as free molecules in the plasma and forms soluble ABO immunocomplexes, thereby lowering the risk for intravascular hemolysis. Most vaccines derived from bacteria or viruses have been shown to have the ability to booster the formation of A and B antibodies (29).

Because a PRBC unit contains less than 10 mL of plasma, type O packed RBCs can be used for transfusion regardless of the ABO blood group of the recipient. In the case of whole blood or apheresis platelets, each unit usually contains about 2 to 300 mL of plasma, which may result in a clinically relevant direct intravascular hemolysis of the transfused RBCs depending on the amount of antibodies present.

The Rh blood group substances consist of protein chains bound to the cell membrane (32) and an immunization can only occur after a transfusion/injection of Rh-positive cells or a pregnancy with an Rh-positive fetus. Rh antibodies do not activate complement and therefore cause only an extravascular hemolysis. This means that even if Rh-positive RBCs are transfused to an immunized Rh-negative recipient there will be only a gradual slow hemolysis. The Rh antibodies can, however, pass the placenta barrier and induce a severe hemolysis in an Rh-positive fetus. Therefore, the transfusion of Rh-positive RBCs to women in fertile age must be performed only in an extreme medical urgency.

In the military forces especially in far-forward conditions, group O whole blood has been widely used as "universal blood" for emergency transfusions. Since the introduction of PRBCs, only plasma and platelet transfusions carry the risk for adverse reactions from transfused ABO-incompatible antibodies in civilian medical care. The clinical effects of ABvO-incompatible platelets are rare but may result in acute hemolytic reactions or lower platelet counts. However, there are presently few data and no consensus on the best approach for managing ABO compatibility in platelet transfusions (33).

The adverse effect in the recipient from the transfusion of ABO-incompatible plasma can be separated into immediate, delayed (within 1 h to 4 days) and late effects (Table 2). The risks and an evaluation of the therapeutic risks versus benefit

TABLE 2. **Immediate, delayed, and late complications of ABO-incompatible plasma**

Immediate adverse effects of the transfusion of ABO-incompatible plasma
• Formation of A/B immunocomplexes
• Agglutination and hemolysis of the RBCs
• Activating mononuclear cytotoxic cells
• Formation and release of acute phase reactants (i.e., complement factors, cytokines)
• Activation and aggregation of platelets
• Activation of the coagulation system (disseminated intravascular coagulation?)
Delayed adverse effects of the transfusion of ABO-incompatible plasma
• Febrile reactions
• Increased osmotic fragility of the RBCs
• Persistent heme-induced activation of the inflammatory response
• Persistent thrombocytopenia
• Coagulopathies and increased fibrinolysis
• Part in the pathogenesis of TRALI
• Immunomodulation in the recipient (i.e., increased risk for infections)
Late adverse effects of the transfusion of ABO-incompatible plasma
• Possibility of an increased incidence of microchimerism with circulating donor white blood cells

of the transfusion are discussed in a recent review covering published reports of complications in the transfusion of whole blood and platelet units containing ABO-incompatible antibodies (32).

The clinical significance of the immediate adverse effects of the transfusion of ABO-incompatible plasma is in almost all published reports related to the amount of antibodies transfused, that is, antibody titer and plasma volume. To minimize the risks, all plasma-containing blood component units should be collected from donors with a low titer of ABO antibodies.

Type O blood has been extensively used in military scenarios since the World War II, and there are very few reports of serious adverse effects (32). After the introduction of only low-titer type O whole-blood units, serious intravascular hemolysis has only been reported in connection with correctly labeled units being transfused to the wrong patient. Most of the delayed adverse effects of the transfusion of ABO-incompatible plasma can also be seen after a regular transfusion and should be observed, registered, and clinically vaddressed.

The late effect of microchimerism is mainly observed in massively transfused trauma patients who have been shown to have circulating donor white blood cells in about 50%. In veterans from the Vietnam War, these cells have been persistent for more than 50 years (34). Leukocyte reduction of the transfused units has no effect on the incidence of microchimerism. So far, despite extensive search, no couplings to any autoimmune or other immunological disorder have been found (35).

Based on all the published reports and articles cited in the study of Daniels and Bromilow (32), it is the authors' opinion that units of whole blood containing ABO-incompatible plasma can be used for lifesaving emergency transfusions and that this is a relatively safe procedure particularly if the donor is "low titer." Currently, the AABB standard 5.14.1 states "Recipients shall receive ABO-specific whole blood or ABO group–compatible RBC components" (36). The AABB also states that if plasma-incompatible blood is transfused the hospital must have a plan to monitor and mitigate possible consequences. Based on the AABB standard as well as the novel concept of using low-titer O-type whole blood for hemorrhagic shock in the civilian hospitals, the authors recommend a prospective randomized trial be performed to evaluate the risks and benefits.

STORAGE OF WHOLE BLOOD

As fresh whole blood contains all the constituents of the blood—except the white blood cells if removed by filtration—it is considered to be an excellent product. This is indicated *in vivo* by reports from both military and civilian use and *in vitro* from quality control records and publications related to use of platelet-sparing whole-blood filters (37).

The major challenges are therefore related to storage time and temperature. Cold storage is by *in vitro* testing superior to storage at ambient temperature, and data show that both platelet function in general and clot formation capability are preserved for at least 10 days. We (Hervig Lab) are presently conducting studies on platelet function and activation during storage, and we have found little platelet activation during storage for 10 days. One goal is to store whole blood for clinical use in 10 days and after that period produce high-quality RBC concentrates from the stored whole-blood units.

Concerning the quality of reconstituted whole blood, there are many articles dealing with quality control, storage, and transfusion of blood components (38, 39). However, there has been little focus on the effects of the different storage times that are involved in reconstituted leukocyte reduced whole blood. "Transfusion packs" may be composed of RBC concentrates for 1 to 42 days, platelet concentrates stored for 1 to 7 days, and the plasma may be fresh frozen or thawed. We have conducted a study which will be published soon in the journal *Blood Transfusion*, where we have investigated effects of RBC and platelet storage times on key platelet functions as aggregation response and thrombin formation after collagen stimulation. The experiments showed significant differences in responses depending on the age composition of the cellular components. It may seem that changes in the RBC membrane could be of importance, which also is indicated in published studies.

PREDICTING RISK OF MASSIVE TRANSFUSIONS

With the demonstrated benefit of targeting high plasma and platelet transfusion ratios in those patients who ultimately require MT, it is essential that MT can be predicted relatively early, soon after presentation to the trauma center in a large proportion of patients (40). There exists an increasing pool of literature suggesting that this can be done relatively easily soon after (or before) trauma center arrival. The majority of these MT scoring systems incorporate laboratory values in

addition to vital signs upon admission in both civilian and military settings (40–44). Consistently, these scoring systems include hypotension (<90 mmHg) as one of the primary predictors of large-volume transfusion requirements. The ABC (assessment of blood consumption) scoring system consists of four nonweighted parameters and includes hypotension (<90 mmHg), penetrating mechanism, positive focused assessment sonography of trauma, and a heart rate more than 120 beats/min (45). This score had an area under the curve of 0.84 via receiver operating characteristic curve analysis and is devoid of any laboratory measurements or requirements. An ABC score of 2 or greater was 75% sensitive and 86% specific for predicting MT, correctly classified 85%.

In addition to clinical scoring systems, there are objective laboratory measurements of predicting MT including the use of tissue oxygenation (StO_2). In one large study, a multicenter trial of 383 severely injured patients, StO_2 measured in the first hour after emergency department (ED) arrival predicted development of multiple organ dysfunction or death as well as or better than systolic blood pressure, serum lactate, and base deficit (46). In addition, data from this study showed that StO_2 was the only parameter that could provide early (at 1, 2, and 3 h after arrival) prediction of bad outcomes in patients requiring MT (10 U of PRBCs in 24 h). These results demonstrate that StO_2 is a sensitive predictor of a poor outcome resulting from clinically significant hypoperfusion (47). An example of the ability of StO_2 to specifically signal the need for transfusion comes from a recent clinical study involving 26 trauma patients at risk for hemorrhagic shock. Results from this study showed that of patients who required a transfusion within 24 h of arrival in the ED, 88% had a minimum StO_2 less than 70% in the first hour of arrival in the ED, and of those who did not require a transfusion, only 22% had StO_2 values that dropped below 70% for the first hour (48).

DOES WHOLE BLOOD IMPROVE OUTCOMES?

There have been limited studies and mixed results on the use of whole blood in traumatic hemorrhagic shock concerning transfusions requirements and outcomes. Despite the use of more than 800,000 U of type O whole blood used by the US military during World War II and more than 300,000 U low-titer type O whole blood used in Vietnam, there are few data on impact in its outcomes in hemorrhagic shock, either positive or negative. In one civilian study, a linked data cohort study was conducted on 353 consecutive patients requiring MT (49). Of the 353 patients, 77 received unrefrigerated whole-blood transfusions. The whole-blood transfusion group had a significantly better coagulation profile but failed to demonstrate a reduction in allogenic blood product transfusions or mortality. Two retrospective US military studies with adjusted analysis compared the use of components only versus components with fresh whole blood (FWB) as a resuscitative fluid and demonstrated conflicting results on 24-h and 30 day survival in combat casualties (23, 50). The limitations of these studies are primarily due to their retrospective nature. As a result, there is increased risk of selection bias and potentially the inability to measure and adjust for all potential confounding factors. In addition, because of the time required to initiate and collect FWB, patients in this group did not exclusively receive whole blood, thus comparing patients who received FWB with RBCs and plasma to a cohort who received only component therapy (RBCs, plasma, platelets). When the estimated volumes of each product as described in the methods are used, FWB was approximately 30% of the total volume of the blood products transfused in the FWB group in the study by Spinella (9).

More recently, a prospective randomized controlled pilot trial of modified whole blood versus component therapy was performed in severely injured patients (51). Modified whole blood was defined as leukodepleted cold-stored (4°C) whole blood. Patients were randomized to receive on arrival either modified whole blood (1 unit) or component therapy (1 U PRBCs + 1 U FFP). Each group also received 1 U of PLTs for every 6 U of modified whole blood or 6 U of PRBCs/FFP. The authors were able to demonstrate that patients without severe brain injuries who were randomized to modify whole blood demonstrated a significant decrease in 24-h blood transfusion volumes. Although the study demonstrated decreased blood transfusions volume with modified whole blood, the direct benefit of cold-stored whole blood on transfusion volumes is still unclear because of protocol requirement of 1 U of platelets (20°C) to be transfused with every 6 U of cold-stored whole blood. This modification was necessary because of the funding agency's institutional review board requirement that every PRBCs and whole-blood unit be leukoreduced resulting in platelets being cleared by the filtration process. In addition, there were concerns about platelet nonfunctional status due to platelet aggregation at 1°C to 6°C for up to 5 days.

As previously discussed in this article, the most recent evidence by Pidcoke et al. (26) demonstrates platelet function is actually preserved for up to 10 days in cold storage of 4°C, thus unnecessary to give warm platelets (20°C) in addition to cold-stored whole blood. It is also difficult to determine the total number of units of whole blood given to the modified whole-blood group, which may have significant implications on total transfusion volumes, coagulation, and complications either for or against cold-stored whole blood as an initial blood resuscitation product. Finally, the study was a pilot trial and not powered for mortality outcomes, which is often the criterion standard when comparing resuscitation method outcomes.

One other prospective randomized trial comparing whole blood to component therapy has been proposed and partially funded by the National Trauma Institute (52). Via personal communication with the principal investigator (G. Cryer), the clinical portion of the trial is on hold pending funding as well as modification of the clinical trial to consider use of platelet-sparing leukofiltrated whole blood based on recent results from other studies (51).

COMPONENT VERSUS WHOLE BLOOD IN TRAUMA TRIAL (COW BITT)

There are few and contradictory data regarding the potential benefits and risks of whole-blood use in traumatic hemorrhagic shock patients. The use of whole blood instead of component therapy may result in faster resolution of shock and

coagulopathy, decreased overall transfusion requirements, and decreased donor exposure to the recipient. This rapid treatment of shock and coagulopathy may result in improved patient outcomes by reducing the risk of organ failure and death, in addition to decreased complications, and decreased care costs. A randomization multicenter trial is required to determine if cold-stored whole blood (which is a Food and Drug Administration–approved blood product) can improve outcomes and not increase the risk of adverse events compared with the use of blood components in a 1:1:1 U ratio.

We propose a 4-year (3-year clinical enrollment data with 6 months' pre/post site training and data analysis), multicenter, prospective randomized trial utilizing level I trauma centers with excellent affiliations with local blood bank institutions to compare low-titer leukocyte reduced (LTLR) type O whole blood versus component blood therapy in a ratio of PRBCs: FFP:PLT of 1:1:1. The trial tentatively has been named the Component Versus Whole Blood in Trauma Trial (COW BITT).

Patients with blunt or penetrating injured patients presenting with hemorrhagic bleeding meeting the inclusion/exclusion criteria (Table 3) will be randomized.

Objectives of the trial are as follows:

a. Evaluate whether LTLR type O whole blood as compared with component blood transfusion will result in a lower incidence of mortality in patients at risk for MT from traumatic hemorrhagic bleeding.

TABLE 3. **Inclusion and exclusion criteria for component versus whole-blood trauma trial (COW PITT)**

Inclusion criteria
a. Air or ground medical transport to tertiary definitive care trauma center participating in trial
and
b. Suspected traumatic bleeding
and
c. ABC score ≥2
and
d. Sto_2 ≤65%
Exclusion criteria
a. Blood transfusion before arrival to ED of participating research center
b. Aged >90 or <18 y
c. Inability to obtain intravenous or interosseous access
d. Isolated fall from standing injury mechanism
e. Documented cervical cord injury with motor deficit
f. Known prisoner
g. Known pregnancy
h. Traumatic arrest with >5 min of cardiopulmonary resuscitation without return of vital signs
i. Penetrating cranial injury
j. Traumatic brain injury with brain matter exposed
k. Isolated drowning or hanging victims
l. Isolated burns more than estimated 20% total body surface area
m. Referral hospital inpatient admission

b. Determine whether LTLR type O whole blood (up to 10 U) as compared with standard component blood reduces the multiple system organ dysfunction rate, ALI, nosocomial infection, shock parameters, early resuscitation and transfusion need, and thrombosis/embolic events.

c. Determine whether LTLR type O whole blood (up to 10 U) as compared with standard component blood affects measures of oxygenation and coagulation profile such as tissue saturation of oxygen, lactate, thromboelastography, prothrombin time/partial thromboplastin time, platelet count, and fibrinogen.

To minimize differences inherent to multicenter trials, standard operating procedures for resuscitation and transfusion will be used and monitored over the initial 24 h and throughout a patients' admission. Standard operating procedures for patients who are at risk of MT will target blood transfusion of RBCs:FFP:PLT of 1:1:1 for the control arm and those in the whole-blood arm who exceed 10 U LTLR type O whole blood. Once 48 h has passed without ongoing blood transfusion requirments, standard transfusion practice guidelines in the ICU will be followed including standard restrictive transfusion guidelines for each respective institution in line with the TRICC trial recommendations (transfusion trigger of hemoglobin 7.0 in the ICU, nonbleeding patient) (19).

To appropriately power the study for 30-day mortality, unpublished prospective data from the Inflammation and the Host Response to Injury Large Scale Collaborative Program, (www.gluegrant.org) and additional published literature aid to estimate baseline mortality and effect size for the study. In hemorrhagic shock patients enrolled in the Glue Grant, patients who require at least 3 to 4 U of blood within the first 6 h of injury had approximately 22% in-hospital mortality. This is similar and in conjunction with prior published literature in hemorrhagic shock patients (53–57). Based on these, point estimates use a baseline mortality of 22% for our power calculations. By intervening early into the coagulopathy, which complicates significant traumatic injury and hemorrhagic shock, the intent of the trial would be to improve outcomes (30-day mortality) by reducing transfusion requirements, reducing the need for MT (>10 U of blood in 24 h after injury). Again, using the Glue Grant data set, for those patients who required less than 10 U of PRBCs over the initial 24 h following injury, the mortality rate was 8.3%. For our sample size estimation for the 30-day mortality outcome, we chose a difference of 14% (22%−8%) from a baseline mortality of 22% when comparing patients randomized to LTLR type O whole blood versus standard component therapy. The trial will be powered at 88% with a two-sided α level of 0.05 requiring a sample size of 150 patients per group.

SUMMARY

In civilian medicine, blood component therapy has reduced the utilization of whole blood to a minimum in countries that can afford blood component production. Thus, the focus on whole blood as a therapeutic blood component has been neglected except in austere environments or special situations. There have been few data to support the shift away from whole-blood resuscitation in traumatic hemorrhagic shock,

and recent data from wars in Iraq and Afghanistan support that whole blood in early resuscitation may impact mortality and morbidity. Moreover, the hemostatic effects of cold-store whole blood are maintained longer than previously thought. A multicenter prospective randomized trial comparing whole blood versus component therapy is needed to evaluate whether whole blood can truly improve outcomes with adverse effects.

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