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Whole Blood: The Future of Traumatic Hemorrhagic Shock Resuscitation

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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. It's development as an effective and safe therapeutic method required the solution of a number of special problems including: 1) identification of agglutination and hemolysis from mixture of incompatible bloods with the identification of blood groups in 1900 (1,2); 2) blood coagulation in storage addressed by the successful use of sodium citrate in 1914 (3); 3) 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 4) 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 US 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 units of stored whole blood was shipped to military hospital with peak in March of 1945,>2000 units per day. (7)

After World War II, the development of whole blood fractionation techniques promoted the concept that blood could be use more effectively if separated into packed red blood cells (PRBC), 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 units transfused) and most recently in Iraq and Afghanistan (> 6,000 units transfused). (8,9)

During this transition from whole blood to component therapy in the 1940s-1980's, there were few studies comparing the benefits and risks in different populations to support its acceptance. Additionally, 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 RBC remains since 1940s that the RBC membrane still be intact in 70% of cells 24 hours after transfusion. (9) Numerous studies in critically ill, surgery and trauma have demonstrated that stored RBC may increase morbidity and mortality due 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) traditionally noted as > 10 units PRBC in 24 hours but more recently described as >3-4 units PRBC/hr or initial resuscitation intensity of > 4 units within 30 minutes which better characterizes early mortality. (20) MT occurs in only 3-5% of civilian trauma but is more than doubled (10%) in the military combat trauma. (21,22) Many advocate that the most appropriate resuscitation in this population is whole blood, which address 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 to 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, 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 PRBC:FFP:PLT) however provides a more anemic, thrombocytopenic and coagulopathic product as compared to whole blood based on calculations. (Table I) (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 (TEG) 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 cold-stored whole blood may be a suitable blood product for trauma resuscitation in hemorrhagic shock, in particular those at risk for massive transfusion. At the 2013 Remote Damage Control and Resuscitation Symposium held in Bergan, 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 O whole blood during emergent utilization, role of leukocyte depletion and the development of a consensus trial. Summary of the presentations are presented within in this manuscript.

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 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 450-500 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, both for whole blood, red cell- and platelet concentrates but in the late 1990 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 purpose of this paper, 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 non-hemolytic transfusion reaction

Febrile non-hemolytic 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 above 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 hours after donation. There is no reason to think that leukocyte-reduced whole blood should give more febrile reactions since 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, nausea and vomiting. As the symptoms are related to the donor plasma, the number of donor exposure maybe significantly decreased by use of whole blood compared to 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 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 titre" O donors are used for whole blood transfusions and group O red cell 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 below 1/100 for IgM and 1/400 for IgG type antibodies as an acceptable low level.

Transfusion related lung injury (TRALI)

In many western countries, TRALI is now the most common transfusion-related cause of death. TRALI can be defined as acute lung injury (ALI) that occurs during transfusion or within six hours of transfusion, if the reaction is not explained by other ALI risk factors. The aetiology 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 (TA-GvHD)

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. Since 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 -1%.

Transfusion-transmitted infection (TTI)

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 limited number rapid testing methods for infectious markers compared to 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 hemolysing. The ABO blood group substances also exists as free molecules in the plasma and forms soluble ABO-immuncomplexes, thereby lowering the risk for intravascular hemolysis.

Most vaccines derived from bacteria or viruses has been shown to have the ability to booster the formation of A- and B-antibodies (29).

Since a PRBC unit contains less than 10mL of plasma, type O packed red cells can be used tor transfusion regardless of the ABO blood group of the recipient. In the case of whole blood or apheresis platelets each unit usually contains about 2-300 mL of plasma, which may result in a clinically relevant direct intravascular hemolysis of the transfused red cells 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 foetus. Rh-antibodies do not activate complement and therefore causes only an extravascular hemolysis. This means that even if Rh-positive red cells are transfused to an immunized Rh-negative recipient there will only be 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 red cells to women in fertile age must only be performed 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 PRBC, only plasma and platelet transfusions carry the risk for adverse reactions from transfused ABO-incompatible antibodies in civilian medical care. The clinical effects of ABO-incompatible platelets are rare but may result in acute haemolytic reactions or lower platelet counts. However, there is presently little 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 1h-4 days) and late effects (Table II). The risks and an evaluation of the therapeutic risks versus benefit of the transfusion is 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 are in almost all published reports related to the amount of antibodies transfused, i.e. 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 labelled 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 addressed.

The late effect of microchimerism is mainly observed in massively transfused trauma patients who have been shown to have circulating donor white cells in about 50%. In veterans from the Vietnam War these cells have been persistent for more than 50 years (34). Leucocyte reduction of the transfused units has no effect on the incidence of microchimerism. So far in spite of 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 (32) it is the authors' opinion that units of whole blood containing ABO-incompatible plasma can be used for life saving emergency

transfusions and that this is a relatively safe procedure particularly if the donor is "low titer". Currently the American Association of Blood Banks (AABB) standard 5.14.1 states "Recipients shall receive ABO-specific Whole Blood or ABO group compatible Red Blood Cell components". (36) The AABB also states that if plasma incompatible blood is transfused that 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 cells if removed by filtration, 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 is preserved for at least ten 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 ten days. One goal is to store whole blood for clinical use in ten days, and after that period produce high quality red cell concentrates from the stored whole blood units.

Concerning the quality of reconstituted whole blood, there are many papers 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 leucocyte reduced whole blood. “Transfusion packs” may be composed of red cell concentrates for 1-42 days, platelet concentrates stored for 1-7 days, and the plasma may be fresh frozen or thawed. We have conducted a study (Hervig et al, Blood transfusion, in press) where we have investigated effects of red cell 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 red cell 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 that ultimately require massive transfusion (MT) it is essential that massive transfusion 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 massive transfusion 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 (<90mmHg) as one of the primary predictors of large volume transfusion requirements. The ABC scoring system consists of 4 non-weighted parameters and include hypotension (<90mmHg), penetrating mechanism, positive focused assessment sonography of trauma, and a heart rate >120 bpm. (45) This score had an area under the curve of 0.84 via receiver operation characteristic curve analysis and is devoid of any laboratory measurements or

requirements. An ABC score of >= 2 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 massive transfusion including the use of tissue oxygenation (StO2). In one large study, a multicenter trial of 383 severely injured patients, StO2 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) Additionally, data from this study showed that StO2 was the only parameter that could provide early (at one, two, and three hours after arrival) prediction of bad outcomes in patients requiring massive transfusion (10 units of PRBC in 24 hours). These results demonstrate that StO2 is a sensitive predictor of a poor outcome resulting from clinically significant hypo perfusion. (47) An example of the ability of StO2 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 hours of arrival in the ED, 88% had a minimum StO2below 70% in the first hour of arrival in the ED, and of those who did not require a transfusion, only 22% had StO2 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 > 800,000 units of Type O whole blood used by the US military during WWII and > 300,000 units low titer Type O whole blood used in Vietnam, there is little 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 massive transfusion. (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 FWB as a resuscitative fluid and demonstrated conflicting results on 24-hour 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 only received 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.

More recently a prospective randomized controlled pilot trial of modified whole blood versus component therapy was performed in severely injuries 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 unit PRBC + 1 U FFP). Each group also received 1 unit of PLTs for every 6 units of modified whole blood or 6 units of PRBC/FFP. The authors were able to demonstrate that patients without severe brain injuries who were randomized to modify whole blood demonstrated a significant decreased in 24-hour 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 due to protocol requirement of 1 unit of platelets (20°C) to be transfused with every 6 units of cold stored whole blood. This modification was necessary due to the funding agency's institutional review board requirement that every PRBC and whole blood unit be leukoreduced resulting in platelets being cleared by the filtration process. Additionally there were concerns about platelet non-functional status due to platelet aggregation at 1-6°C for up to 5 days.

As previously discussed in this paper, the most recent evidence by Pidcoke et al 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 gold 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 the recent results of the Cotton et al trial.

Component vs. Whole Blood in Trauma Trial (COW BITT)

There is little 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 store whole blood (which is an FDA approved blood product) can improve outcomes and not increase the risk of adverse events compared to the use of blood components in a 1:1:1 unit ratio.

We purpose a 4-year (3-year clinical enrollment data with 6 months pre/post site training and data analysis), multicenter, prospective randomized trial utilizing level-1 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 PRBC:FFP:PLT of 1:1:1. The trial tentatively has been as the named the Component vs. Whole Blood in Trauma Trial (COW BITT).

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

Objective of the trial:

1. Evaluate whether LTLR Type O whole blood as compared to component blood transfusion will result in a lower incidence of mortality in patients at risk for massive transfusion from traumatic hemorrhagic bleeding.
2. Determine whether LTLR Type O whole blood (up to 10 units) as compared to standard component blood reduces the multiple system organ dysfunction (MSOD) rate, acute lung injury, nosocomial infection, shock parameters, early resuscitation and transfusion need, and thrombosis/embolic events.

3. Determine whether LTLR Type O whole blood (up to 10 units) as compared to standard component blood effects measures of oxygenation and coagulation profile such as tissue saturation of oxygen, lactate, thromboelastography, PT/PTT, platelet count, and fibrinogen

To minimize differences inherent to multicenter trials, standard operating procedures (SOP) for resuscitation and transfusion will be employed and monitored over the initial 24 hours and throughout a patients' admission. SOPs for patients who are at risk of massive transfusion (MT) will target blood transfusion of RBC:FFP:PLT of 1:1:1 for the control arm and those in the whole blood arm who exceed 10 unit LTLR Type O whole blood. Once 48 hours has passed without on-going blood transfusion requirements, 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 Hgb 7.0 in the ICU, non-bleeding 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 to estimate baseline mortality and effect size for the study. In hemorrhagic shock patients enrolled in the Glue Grant, patients who require at least 3-4 units of blood within the first 6 hours of injury had in-hospital approximately 22% mortality. This is similar and in conjunction with prior published literature in hemorrhagic shock patient. (53-57) Based upon 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 mortality) by reducing transfusion requirements, reducing the need for massive transfusion (> 10

units of blood in 24 hours post injury). Again, using the Glue Grant dataset, for those patients who required between < 10 units of PRBC over the initial 24 hours 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% to 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 alpha 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 are been little 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 vs. component therapy is needed to evaluate whether whole blood can truly improve outcomes with adverse effects.

References

1. Landsteiner K. Zur Kentniss der antifermentativen lytischen und agglutinierenden Wirkungen des Blutserums und der Lymphe. Zentralbl. Bakt. 28: 357-362, 23 Mar. 1900

2. Ottenberg, R. Reminiscences of the History of Blood Transfusion. J. Mt. Sinai Hosp. 4: 264-271, November-December 1937

3. Lewisohn R. The Development of the Technique of Blood Transfusion Since 1907; With Special Reference to Contributions by Members of the Staff of the Mount Sinai Hospital. J. Mt. Sinai Hosp. 10: 605-622, January-February 1944.

4. Lindeman E: Simple Syringe Transfusion with Special Cannulas. A New Method Applicable to Infants and Adults. Preliminary Report. Am. J. Dis. Child. 6: 28-32, July 1913

5. Starr D, Blood. New York, Harper Collins 2002; Robertson OH) Transfusion with preserved red blood cells. Brit Med J. 1918; 1:691-695.

6. Kendrick DB. Blood program in World War II. Washington DC, Office of the Surgeon General, 1964.

7. Hess JR, Thomas MJ. Blood use in War and disaster: lessons from the past century, Transfusion. 2003; 43:1622-1633.

8. Alexander JM, Sarode R, McIntire DD. Whole blood in the management of hypovolemia due to obstetric hemorrhage. Obst Gyn. 2009; 113:1320-1326.

9. Spinella PC. Warm fresh whole blood transfusion for severe hemorrhage: US military and potential civilian applications. Crit Care Med. 2008; 36:S340-345

10. Ho J, Sibbald WJ, Chin-Yee. Effects of storage on efficacy of red cell transfusion: when is it not safe? Crit Care Med. 2003; 31(S): S687-697.

11. Tinmouth A, Fergusson D, Yee IC et al. Clinical consequences of red cell storage in the critically ill. Transfusion. 2006; 46:2014-2027.

12. Barsran S, Frumento RJ, Cohen A et al. The association between duration of storage of transfused red blood cells and morbidity and mortality after reoperative cardiac surgery. Anesth Analg. 2006; 103:15-20.

13. Malone DL, Dunne J, Tracy JK, et al. Blood transfusion, independent of shock severity, is associated with worse outcomes in trauma. J Trauma. 2003; 54:898-907.

14. Purdy FR, Tweeddale MG, Merrick PM. Association of mortality with age of blood transfused in septic ICU patients. Can J Anaesth. 1997; 44:1256-1261.

15. Spinella PC, Perkins JG, Grathwohl KW, et al. Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. J Trauma. 2008; 64:S69-78.

16. Zallen G, Offner PJ, Moore EE et al. Age of transfused blood is an independent risk factor for postinjury multiple organ failure. Am J Surg. 1999; 178:570-572.

17. Robinson WP, Ahn J, Stiffler A et al. Blood transfusion is an independent predictor of increased mortality in nonoperatively managed blunt hepatic and splenic injuries. J Trauma. 2005; 58:437-445.

18. Vincent JL, Barron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. JAMA 2002; 288:1499-1507.

19. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirement in Critical Care Investigators, Canadian Critical Care Trials Group. N Engl J Med.1999; 340: 409-417.

20. Rahbar E, Fox EE, del Junco DJ, et al. Early resuscitation intensity as a surrogate for bleeding severity and early mortality in the PROMMTT study. J Trauma. 2013;75:S16-23.

21. Borgman M, Spinella PC, Perkins JG, et al. Blood products replacement affects survival in patients receiving massive transfusion at a combat support hospital. J Trauma. 2007; 63:805-813.

22. Schreiber MA, Perkins J, Kiraly L, et al. Early predictors of massive transfusion in combat causalities. J Am Coll Surg. 2007; 205:541-545.

23. Spinella PC, Perkins JG, Grathwohl KW et al. Warm fresh whole blood is independently associated with improved survival for patients with combated related trauma injuries. J Trauma. 2009; 66:S69-76.

24. Armand R, Hess JT. Treating coagulopathy in trauma patients. Transfus Med Rev. 2003; 17:233-31.

25. McMullin NR, Holcomb JB, Sondeen J. Hemostatic Resuscitation. New York, Springer, 2006

26. Pidcoke HF, McFaul SJ, Ramasubramanian AK et al. Primary hemostatic capacity of whole blood: a comprehensive analysis of pathogen reduction and refrigeration effects over time. This data indicate that platelet and coagulation function in cold-stored whole

blood may be sufficient to provide hemostatic resuscitation. Transfusion. 2013; 53:137S-149S.

27. Tormey CA, Sweeney JD, Champion MH, et al. Analysis of transfusion reactions associated with pre-storage-pooled platelet components. Transfusion. 2009; 49:1242-7.

28. Bolton-Maggs PH, Cohen H. Serious Hazards of Transfusion (SHOT) haemovigilance and progress is improving transfusion safety. Br J Haematol. 2013 Sep 14.

29. Berséus O, Boman K, Nessen S C, Westerberg L A. Risks of hemolysis due to anti-A and anti-B caused by the transfusion of blood or blood components containing ABO-incompatible plasma. Transfusion. 2013; 53: 114S-123S.

30. Eder AF, Dy BA, Perez JM, et al. The residual risk of transfusion-related acute lung injury at the American Red Cross (2008-2011): limitations of a predominantly male-donor plasma mitigation strategy. Transfusion. 2013 Jul;53(7):1442-9.

31. Gilstad C, Roschewski M, Wells J, Delmas A, Lackey J, Uribe P, et al. Fatal transfusion-associated graft-versus-host disease with concomitant immune hemolysis in a group A combat trauma patient resuscitated with group O fresh whole blood. Transfusion. 2012; 52(5):930-5.

32. Daniels G, Bromilow I. Essential Guide to Blood Groups. 1st ed. Blackwell Publishing Ltd, 2007.

33. Dunbar NM, Ornstein DL, Durmont LJ. ABO incompatible platelets: risks versus benefits. Curr Opin Hematol. 2012. 19:475-9.

34. Utter GH. The microcherism puzzle. Ed. Transfuson. 2012; 52: 926-28

35. Bloch EM, Jackman RP, Lee TH, Busch MP. Transfusion-associated microchimerism: The hybrid within. Transfus Med Rev. 2013; 27: 10-20.

36. Standards for Blood Banks and Transfusion Services. AABB. 2012.

37. Synder EL, Whitley P, Kingsbury T, et al. In vitro and in vivo evaluation of a whole blood platelet-sparing leukoreduction filtration system. Transfusion. 2010. 50:2145-51.

38. van der Meer PF, Cancelas JA, Cardigan R, et al. Evaluation of overnight hold of whole blood at room temperature before component processing: effect of red blood cell (RBC) additive solutions on in vitro RBC measures. Transfusion. 2011 Jan;51 Suppl 1:15S-24S.

39. van der Meer PF, Cancelas JA, Vassallo RR, et al. Evaluation of the overnight hold of whole blood at room temperature, before component processing: platelets (PLTs) from PLT-rich plasma. Transfusion. 2011 Jan;51 Suppl 1:45S-9S.

40. Yucel, N., et al., Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. J Trauma. 2006; 60(6): p. 1228-36; discussion 1236-7.

41. Larson, C.R., et al., Association of shock, coagulopathy, and initial vital signs with massive transfusion in combat casualties. J Trauma, 2010; 69 Suppl 1: p. S26-32.

42. Schreiber, M.A., et al., Early predictors of massive transfusion in combat casualties. J Am Coll Surg. 2007; 205(4): p. 541-5

43. McLaughlin, D.F., et al., A predictive model for massive transfusion in combat casualty patients. J Trauma. 2008; 64(2 Suppl): p. S57-63; discussion S63.

44. Dutton, R.P., R. Lefering, and M. Lynn, Database predictors of transfusion and mortality. J Trauma. 2006; 60(6 Suppl): p. S70-7.

45. Nunez TC, Voskresensky IV, Dossett LA et al. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? J Trauma. 2009; 66:346-52

46. Cohn SM, Nathens AB, Moore FA, Rhee P, Puyana JC, Moore EE, Beilman GJ. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. J Trauma. 2007; 62(1):44 –55.

47. Moore FA, Nelson T, McKinley BA, Moore EE, Nathens AB, Rhee P, Puyana JC, Beilman GJ, Cohn SM. Massive transfusion in trauma patients: tissue hemoglobin oxygen saturation predicts poor outcome. J Trauma. 2008; 64(4):1010 –1023

48. Smith J, Bricker S, Putman B. Tissue oxygen saturation predicts the need for early blood transfusion in trauma patients. Am Surg. 2008; 74:1006-11.

49. Ho KM, Leonard AD. Lack of effect of unrefrigerated young whole blood transfusion on patient outcomes after massive transfusion in a civilian setting. Transfusion. 2011; 51:1669-75.

50. Perkins JG, Cap AP, Spinella PC, et al. Comparison of platelet transfusion as fresh whole blood versus apheresis platelets for massively transfused combat trauma patients. Transfusion. 2011; 51:242-53.

51. Bryan A Cotton, Jeannette Podbielski, Elizabeth Camp et al. A Randomized Controlled Trial of Modified Whole Blood Versus Component Therapy in Severely Injured Patients Requiring Transfusions. Presented 133rd Annual Academic Surgical Association,

Indianapolis, IN, Apr 4-6, 2013.

52. (http://www.nationaltraumainstitute.org/research/2011studies/cryer.html).
53. Zink, K.A., et al., A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg. 2009; 197(5): p. 565-70; discussion 570.
54. Gonzalez, E.A., et al., Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma. 2007; 62(1): p. 112-9.
55. Heckbert, S.R., et al., Outcome after hemorrhagic shock in trauma patients. J Trauma. 1998; 45(3): p. 545-9.
56. Cales, R.H., Trauma mortality in Orange County: the effect of implementation of a regional trauma system. Ann Emerg Med. 1984; 13(1): p. 1-10.
57. Teixeira, P.G., et al., Impact of plasma transfusion in massively transfused trauma patients. J Trauma. 2009; 66(3): p. 693-7.

Table I. 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**
Hemocrit	**29%**	**33-43%**
Platelet count	**88k**	**130-350k**
Coagulation Factor Activity	**65%**	**86%**

*** Assumptions - PRBC Hct 55%, Platelets $5.5x10^{10}$, FFP 80% coagulation factors**

Table II. Immediate, Delayed and Late Complications of ABO-incompatible Plasma

Immediate adverse effects of the transfusion of ABO-incompatible plasma

- Formation of A-/B-immuncomplexes
- Agglutination and hemolysis of the red cells
- Activating mononuclear cytotoxic cells
- Formation and release of acute phase reactants (ie complement factors, cytokines)
- Activation and aggregation of platelets
- Activation of the coagulation system (DIC?)

Delayed adverse effects of the transfusion of ABO-incompatible plasma

- Febrile reactions
- Increased osmotic fragility of the red cells
- Persistent heme-induced activation of the inflammatory response
- Persistent thrombocytopenia
- Coagulopathies and increased fibrinolysis
- Part in the pathogenesis of transfusion related acute lung injury (TRALI)
- Immunomodulation in the recipient (ie 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 cells

Table III. Inclusion and Exclusion Criteria for Component vs. 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. StO2 <= 65%

Exclusion Criteria:

1. Blood transfusion prior to arrival to ED of participating research center
2. Age > 90 or < 18 years of age
3. Inability to obtain intravenous or interosseous access
4. Isolated fall from standing injury mechanism
5. Documented cervical cord injury with motor deficit
6. Known prisoner
7. Known pregnancy
8. Traumatic arrest with > 5 minutes of CPR without return of vital signs
9. Penetrating cranial injury
10. Traumatic brain injury with brain matter exposed
11. Isolated drowning or hanging victims
12. Isolated burns > estimated 20% total body surface area

Referral Hospital In-patient admission