Warm fresh whole blood transfusion for severe hemorrhage: U.S. military and potential civilian applications

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Objective: **The objective of this study was to review the history and current literature regarding the benefits and risks of warm fresh whole blood transfusion to include recent U.S. Army research from Afghanistan and Iraq. We also discuss current indications for its use as well as potential civilian applications for large-scale disasters.**

Background: **The use of warm fresh whole blood currently only persists in emergency life-threatening scenarios when tested stored blood components are not available. Recent combat operations in Afghanistan and Iraq have redirected attention on the benefits and risks of warm fresh whole blood for life-threatening injuries in casualties.**

Main Results: **Between March 2003 and July 2007, over 6000 units of warm fresh whole blood have been transfused in Afghanistan and Iraq by U.S. medical providers to patients with life-threatening traumatic injuries with hemorrhage. Preliminary results in approximately 500 patients with massive transfusion indicate that the amount of fresh warm whole blood transfused is independently associated with improved 48-hr and 30-day survival and the amount of stored red blood cells is independently associated with decreased 48-hr and 30-day survival for patients with traumatic injuries that require massive transfusion. Risks of warm fresh whole blood transfusion include the transmission of infectious agents and the potential for microchimerism.**

Conclusions: **For patients with life-threatening hemorrhage at risk for massive transfusion, if complete component therapy is not available or not adequately correcting coagulopathy, the risk: benefit ratio of warm fresh whole blood transfusion favors its use. In addition, recent evidence suggests that there is potential for warm fresh whole blood to be more efficacious than stored component therapy that includes stored red blood cells in critically ill patients requiring massive transfusion. Efforts must continue to improve the safety of warm fresh whole blood transfusion for patients when it is required in emergency situations. U.S. civilian disaster agencies are preparing guidelines for its use in massive casualty scenarios and prospective, randomized trials are about to start to determine whether stored warm fresh (<24 hrs) whole blood improves outcomes compared with standard stored component therapy. (Crit Care Med 2008; 36[Suppl.]: S340–S345)**

KEY WORDS: whole blood; trauma; mortality; hemorrhage; coagulopathy; combat

The first warm whole blood transfusion in a human occurred in 1667 by Dr. Jean-Baptiste Denis in France (1). He directly transfused a cupful of blood from the femoral artery of a lamb through a silver tube inserted into a vein of a man theorizing that the gentleness of the lamb's blood would cure his maddening illness. Multiple transfusions were performed because the transfusion of the lamb's blood improved his psychosis dramatically. He developed symptoms of febrile acute hemolysis with each transfusion and died suddenly before his last transfusion. Interestingly, this man in retrospect may have had general paresis neurosyphilis and his febrile reactions to the transfusions may have actually improved his condition, because high temperatures are now known to kill *Treponema* organisms. On investigation, this patient's death was not related to the transfusion of lamb's blood, but actually resulted from arsenic poisoning by his wife. Because transfusion reactions continued to occur, the French and English governments, as well as the Pope, banned the practice of transfusion (1). The practice of transfusing humans did not occur again until 1818 when Dr Blundell in London began transfusing blood for hemorrhagic conditions from the artery of the donor to the vein of the recipient through injection kits. Over an 11-yr period, Blundell transfused ten patients, five of whom survived. Despite the discovery of blood types by Karl Landsteiner in 1900 and the subsequent development of crossmatching techniques by Dr Ottenberg in 1912, the routine blood typing before transfusion did not occur until the mid-1920s (1). During this time, multiple methods of transfusion to include direct anastomosis of artery to vein in addition to the use of metal devices were used. Direct anastomosis was technically difficult and painful but prevented the very common complication of clotting, which occurred with metal devices. It was not until the development of citrate storage solutions by Dr. Richard Lewisohn in 1914 that the process of collecting blood and transfusing it to recipients became much easier and started to increase in significant frequency (1).

History of Warm Fresh Whole Blood Transfusion

With the development of storage solutions by Peyton Rous in 1915 and 1916, the ability to resuscitate combat casualties with hemorrhagic lesions became possible and was integrated into medical practice at British and American hospi-

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tals in World War I (2). Stored whole blood was primarily used in World War II and heroic efforts were made at supplying the troops with this lifesaving product. Roughly 500,000 units of stored whole blood were shipped to U.S. military hospitals in a 13-month period spanning 1945 (2). Despite the massive shipment of stored whole blood, it was not always available when needed and direct transfusions from one soldier to another was still frequently needed with warm fresh whole blood. This practice of primarily transfusing stored product and only resorting to the use of warm fresh whole blood started in both world wars and persists today in recent conflicts to include those in Somalia, Kosovo, Afghanistan, and Iraq (2–5).

A direct result of the necessity of requiring large amounts of blood products for combat casualties has led to the development of whole blood fractionation into individual components and storage solutions increasing the shelf life of blood components. Blood fractionation was developed to improve resource use of individual components of whole blood needed for combat casualties, and the storage process of blood products was advanced to allow for prolonged storage to ship blood products to distant regions such as Vietnam (1, 2). Interestingly, these developments that were inspired to improve care for combat casualties may now have more detrimental effects than the use of warm fresh whole blood in this very same population (6–9).

The Transition to Component Therapy and Its Consequences in Massive Transfusion

Whole blood fractionation into red blood cells (RBCs), plasma, and platelets was developed to more efficiently use the individual components of blood. The advantage of the availability of individual components is that it allows for replacement of specific deficiencies or requirements and has the additional benefit which improves resource utilization. The availability of donors has always been a concern and increased utilization of this limited product is very beneficial. As the fractionation processes developed between the 1940s to the 1980s, component therapy increased and the use of stored whole blood diminished. There are now few current indications or routine use of stored whole blood (5). Interestingly, during this transition from whole blood to component therapy, very few studies have attempted to compare the benefits or risks between them in different populations, nor have the storage solutions that have developed over time to improve shelf life of RBCs been evaluated for clinical benefits or risks to the recipient. In fact, the criteria for approving storage solutions that was determined in the 1940s still remains today. Current licensing requirements for stored RBCs primarily require that the RBC membrane still be intact in 70% of cells 24 hrs after transfusion (7). Storage solution requirements for licensing do not include any direct measurements of the RBCs' ability to deliver oxygen to microvascular tissue beds. In fact, the few studies of stored RBCs that directly measure oxygen consumption for subjects in oxygen debt or shock or evaluate microvascular circulation in both animals and humans indicate that oxygen consumption and microvascular flow remains the same or decreases after RBC transfusion (7, 8, 10–15). In addition, countless retrospective studies indicate after adjusting for severity of injury factors that the amount and storage age of RBCs is independently associated with increased morbidity and mortality (9, 16–22). One large prospective, randomized controlled trial also indicates that increased stored RBC transfusions are associated with increased in-hospital mortality in critically ill patients (23).

The transition to component therapy has improved the availability of multiple blood components to patients who may only require a specific product. As a result of blood being a limited resource, this is very important and has driven the transition away from whole blood products (4). For patients who only require specific components, the transfusion of individual products is the most logical and appropriate method. There is a small population of patients who require transfusion because of massive hemorrhage of whole blood. Approximately 3% to 8% of trauma patients who require transfusion at civilian and deployed military trauma centers receive massive transfusions (24–28). Many believe that replacing whole blood to patients who are bleeding large amounts of whole blood is the most appropriate approach to addressing the shock and coagulopathy that these patients rapidly develop (29–32). This concept has been termed *hemostatic resuscitation* and advocates for the use of component products in a similar ratio to whole blood for patients with massive hemorrhage (26, 33, 34). Even with this approach it has been noted that trying to reconstitute whole blood from components that have been placed in anticoagulant and preservative solutions would provide a significantly anemic, thrombocytopenic, and coagulopathic product compared with a whole blood product (35). If a unit of whole blood was reconstituted with one unit of RBCs (hematocrit of 55%), platelets (5.5×10^{10} platelets), and frozen plasma (80% coagulation factor activity), it would become 660 mL of cold fluid with a hematocrit of 29%, 88,000 platelets per microliter, and 65% coagulation factor activity. In contrast, a 500-mL unit of fresh whole blood in 70 mL of citrate phosphate dextrose anticoagulant solution has a hematocrit of 33% to 43%, 130,000 to 350,000 platelets per microliter, and 86% activity of clotting factors (35). Additionally, unlike the use of stored blood products, warm fresh whole blood is not cold and maintains significant platelet and coagulation factor function for up to 72 hrs (36). As a result, it appears illogical and potentially irrational to resuscitate patients requiring massive transfusion with a strategy that at best provides an anemic, thrombocytopenic, coagulopathic, and cold product to a patient population that is at increased risk of mortality with hypothermia, acidosis, anemia, and coagulopathy.

Current U.S. Military Indications and Practice of Warm Fresh Whole Blood Transfusion

Blood component availability is different at each level of military treatment facilities with RBCs only available at forward surgical facilities and RBCs, plasma, and cryoprecipitate available at all combat support hospitals. Just recently, in 2005, apheresis platelets were made available to some but not all of the combat support hospitals in Iraq and Afghanistan by pheresis of platelets from donors at these military hospitals. Because each blood component is not available at most U.S. military hospitals, and at times the existing supply of a product may get exhausted in periods of increased combat activity, the requirement of warm fresh whole blood is often required.

Current standard military indications for warm fresh whole blood transfusions are for patients with life-threatening injuries that require any blood component that is not immediately available (37). In

addition, U.S. Army military massive transfusion clinical practice guidelines also suggest the transfusion of warm fresh whole blood for patients who continue to have significant bleeding with life-threatening injuries after receiving stored RBCs, plasma, and platelets in a 1:1:1 ratio. Between March 2003 and July 2007, over 6000 units of warm fresh whole blood have been transfused in Afghanistan and Iraq according to the Armed Services Blood Program Organization (Table 1). All patients transfused warm fresh whole blood received a mean of 5.8 units with the maximum amount transfused to one patient of 48 units (Table 1). Approximately 4% of blood products transfused in both Afghanistan and Iraq have been warm fresh whole blood with 45% of recipients being non-U.S. patients (Tables 1 and 2). The amount of warm fresh whole blood being transfused in both Afghanistan and Iraq has in general been increasing each year from 2001 to 2007 (Fig. 1). In a review from one combat support hospital, patients who are transfused warm fresh whole blood are coagulopathic, acidemic, hypothermic, anemic, and in shock (38). In addition, warm fresh whole blood donated by U.S. military personnel at one combat support hospital was transfused in similar proportions and amounts to U.S., Iraqi, and enemy combatant patients (38).

Current efforts by the U.S. Army Institute of Surgical Research have focused on developing methods to identify those with severe injuries who are at risk for massive transfusion. The purpose is to rapidly identify those at risk of developing the coagulopathy of trauma and to immediately apply hemostatic resuscitation strategies on identification of this risk rather than to wait for coagulopathy and massive transfusion to occur. This is the damage control philosophy of "staying out of trouble instead of getting out of trouble" or being proactive instead of reactive. Recent research in both military and civilian patients in both primarily penetrating and blunt trauma populations indicates that the risk of massive transfusion can be predicted with approximately 80% accuracy (27, 39–41). Some models can accurately predict massive transfusion within 10 mins of admission (27, 40, 41), which is important because the majority of preventable trauma deaths are from hemorrhage (42, 43) and most deaths occur within 6 to 12 hrs from admission (44–46). The rapid treatment of the coagulopathy of trauma hemostatic resuscitation strategies in patients requiring massive transfusion has been associated with improved survival (19, 24, 47).

Current practice guidelines supported by U.S. military medical leaders is to transfuse stored blood components, if available, in a 1:1:1 ratio similar to whole blood for casualties with severe hemorrhagic lesions who are identified as at high risk for massive transfusion. If any of the components are not available, then warm fresh whole blood is to be used to supplement the unavailable component products; alternatively, if the 1:1:1 strategy of transfusing stored components is failing, the use of warm fresh whole blood is also supported. A detailed algorithm of one the U.S. Army's combat support hospitals massive transfusion program that used warm fresh whole blood has been described by Repine et al (5).

Before the decision is made to transfuse warm fresh whole blood, there needs to be coordination to develop a volunteer donor pool, screening for eligibility to donate, methods to improve the safety of transfusing warm fresh whole blood, and policies that ensure the safety of whole blood donors. Currently, the practice of coordinating warm fresh whole blood collection differs slightly from one medical facility to the next as a result of differences in the size of the donor pool and preferences of the medical providers at each facility. In general, the donor pool consists of hospital and other military personnel who are local to the hospital. Hospitals that anticipate a large need for warm fresh whole blood develop volun-

Table 1. Description of total number of units and average amount per patient transfused of each blood product

	Total Units	Total Patients	Average Units	Low	High
Warm fresh whole blood (U)	6,001	1,035	5.8	1	48[a]
Red blood cell (U)	85,429	14,706	5.8	1	143[a]
Apheresis platelet (U)	3,723	1,540	2.4	1	29[a]
Fresh frozen plasma (U)	41,666	6,469	6.4	1	98[a]
Cryoprecipitate (U)	11,465	1,034	11.1	1	114[a]

[a]denotes transfused to non-U.S. Patient.

Table 2. Distribution of each blood product transfused to U.S. and non-U.S. casualties

	Total	U.S. Only	Non-U.S.	U.S. Only	Non-U.S.
Number patients transfused	15,796	3,949	11,847	25.0%	75.0%
Warm fresh whole blood (U)	6,001	3,255	2,746	54.2%	45.8%
Red blood cells (U)	85,429	23,725	61,704	27.8%	72.2%
Apheresis platelet (U)	3,723	1,366	2,357	36.7%	63.3%
Fresh frozen plasma (U)	41,666	12,699	28,967	30.5%	69.5%
Cryoprecipitate (U)	11,465	4,478	6,987	39.1%	60.9%

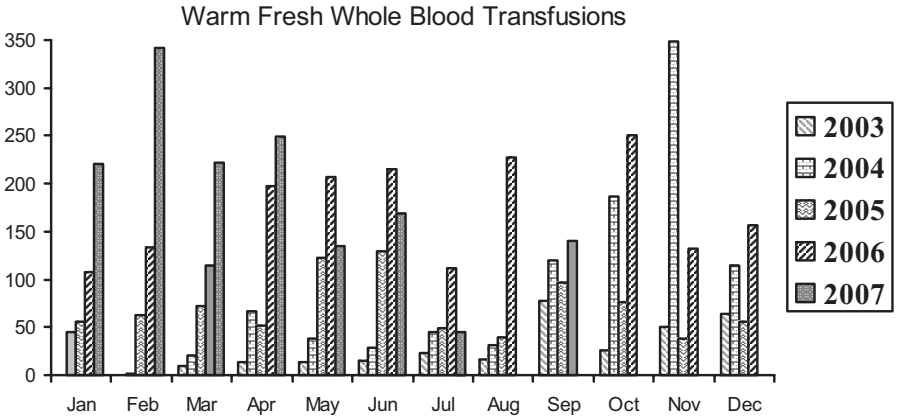

Figure 1. Number of units of warm fresh whole blood transfused per month in Iraq between March 2003 and July 2007.

teer donor lists by blood type and prescreen them for eligibility by questionnaire to streamline the collection process when needed. This questionnaire is reviewed again just before the donor's blood is collected to determine whether there have been any changes. If eligible, the donor is screened for anemia with the copper sulfate test and is crossmatched to the recipient. If all tests permit, 400- to 500-mL of the donors' warm fresh whole blood is collected into a CPDA bag (Teruflex Blood Bag System, Tokyo, Japan) and then transfused immediately to the casualty. Under optimal conditions of donor availability and adequate laboratory technician staffing, this entire process from the initiation of a whole blood drive to transfusion of the first unit takes approximately 20 to 30 mins. These units are transfused warm without leukoreduction or irradiation. To decrease the risk of infectious agent transmission, some hospitals with high-volume warm whole blood needs have prescreened their potential donor pool by sending specimens back to the United States for formal infectious disease screening of all routinely tested transfusion-transmitted diseases. This will not prevent transmission of agents that have been acquired after the donor has been tested, but will still decrease this risk. In addition, infectious disease transmission risk is decreased in military donors since all personnel are screened for human immunodeficiency virus (HIV) within 2 yrs before deployment, and recently, all new military recruits are immunized against hepatitis B. All healthcare providers are immunized for hepatitis B. Current discussions are underway regarding the benefit of screening all military personnel for hepatitis C before deployment. All donors who screen positive for transfusion-transmitted diseases are identified and formally evaluated. In addition, all recipients of warm fresh whole blood by policy are to be screened periodically for transfusion-transmitted diseases. The ability to perform crossmatching in remote locations may not be available and warm fresh whole blood is transfused based on blood types recorded on personal identification tags as a method of last resort.

Benefits and Risks of Warm Fresh Whole Blood

Whole blood is preferred by some providers because it provides replacement of each blood component in the same ratio that it is lost in patients with severe hemorrhage. Warm fresh whole blood has the additional advantage of not being affected by the storage process, which decreases the function of each of the components (14, 15, 48, 49). Critically ill patients in hemorrhagic shock should potentially receive increased benefit of treating both coagulopathy and shock with fully functional plasma, platelets, and RBCs compared with stored components.

Because warm fresh whole blood has only been used in emergency circumstances in both military and some civilian trauma centers, very little research has been published regarding its efficacy. Most published data have been on stored fresh whole blood, which has been defined as whole blood stored for less than 24 or 48 hrs. Transfusion of whole blood stored for less than 48 hrs has been recommended for first-line therapy in hemorrhagic shock by several authors (50–52). Stored whole blood is associated with decreased donor exposures, optimal resuscitation, and improved hemostasis compared with component therapy (20, 50, 53). Lavee et al. reported that one unit of stored fresh whole blood had the equivalent hemostatic effect of eight to ten platelet units (49). Unlike warm fresh whole blood, stored whole blood has detrimental effects such as decreased function of labile coagulation factors V and VIII within 12 to 18 hrs of storage at 4°C. In addition, platelet function is decreased within 5 hrs of storage at 4°C (48). Conversely, a recent report indicates that warm whole blood can be stored at room temperature and maintains its coagulation function for up to 72 hrs without the risk of bacterial growth (36).

Recent retrospective study results presented at the 2007 U.S. Military Combat Casualty Care conference (J. G. Perkins, unpublished data) indicate that in over 500 patients requiring massive transfusion, on multivariate regression analysis, the amounts of warm fresh whole blood and apheresis platelets were both independently associated with improved 48-hr and 30-day survival. In this same analysis, the amount of stored RBCs transfused was independently associated with decreased survival. This is the first data set to indicate that the use of warm fresh whole blood may improve survival in any population. Although the use of apheresis platelets was also associated with improved survival, the results that stored RBCs (mean storage age of 33 days) were independently associated with decreased survival suggests that preferential use of warm fresh whole blood instead of pure components (particularly when the stored RBCs are of advanced storage age) may improve outcomes. It is very difficult to analyze these data, because all patients who receive warm fresh whole blood have also received RBCs, plasma, and some apheresis platelets because it may take time for warm fresh whole blood to be collected and tested before transfusion. Only a prospective, randomized trial will be able to adequately answer this question. Currently, a large trauma center in the United States is about to start a prospective, randomized, controlled trial of warm fresh (<24 hrs) whole blood compared with component therapy for patients with severe traumatic injuries.

The risks of warm fresh whole blood transfusions compared with those of RBC transfusions have been recently reviewed (6). Transfusion reactions and transfusion-related acute lung injury occurred at similar rates. There was an increased risk of the transmission of hepatitis C for those who received warm fresh whole blood. In this review that evaluated over 2000 units of warm fresh whole blood transfused between 2003 and 2005, no patients contracted HIV. The risk of transmitting infectious agents with the use of warm fresh whole blood is increased despite efforts to decrease this risk by using rapid infectious disease testing kits for HIV and hepatitis B and C (Biokit, Biorapid, Barcelona, Spain). According to the Armed Services Blood Program Office as of September 2006, both hepatitis C- and B-positive units have been transfused to patients either resulting from lack of screening with the rapid tests or as a result of false-negative results from these rapid tests. Contrary to the sensitivity and specificity quoted by the manufacturer (98% to 99% for each test), an independent analysis by O'Connell at the U.S. Army Walter Reed Institute of Research indicates that the hepatitis B and C rapid testing kits had sensitivity and specificity of <30% for each. According the Armed Services Blood Program Office in over 2000 warm fresh whole blood transfusions, between March 2003 and September 2006, in which the rapid tests were used, they missed identifying one donor with hepatitis C and another with hepatitis B. In the past year, rapid testing kits for HIV have been replaced with the oraquick ad-

vance test (Orasure, Bethlehem, PA), which is U.S. Food and Drug Administration-approved to screen blood samples for HIV, and the biorapid kits for hepatitis B and C and HIV are no longer used.

An additional potential risk to recipients of warm fresh whole blood is the development of microchimerism. Previous studies in trauma patients indicate that microchimerism occurs at increased rates in trauma patients receiving younger products (54, 55). The transfusion of warm fresh whole blood may increase this risk, although this has not been confirmed. In addition, the long-term consequences of microchimerism in trauma patients have not been clearly defined.

Risks to donors in a warm fresh whole blood program in combat include anemia, which increases the risk of decreased donor performance. Despite copper sulfate test screening for anemia (<12.5 mg/dL), 14% of donors were anemic (<12.5 mg/dL) according to complete blood count results measured during the collection process (56). Methods to improve screening for anemia in donors who are required to return to combat are needed to minimize the risk of injury to donors. In addition, the consistent supplementation with iron to whole blood donor pools would also decrease the risk of anemia in donors.

The choice of whether to use warm fresh whole blood is simple when attempting to resuscitate a patient who is severely injured and requires blood component product replacement that is not available or when the use of standard components is not adequately correcting the coagulopathy in patients with life-threatening injuries. The risk of death in these patients is very high, approximately 30% to 50% with adequate or standard treatment. Many of these patients would die without its use. Therefore, the infectious and potential microchimerism risks must be taken to resuscitate these patients. Every effort must also be made to minimize these risks. The potential to screen all deploying military personnel for transfusion-transmitted diseases to determine whether they are eligible to donate and the increased access to plasma and platelets at smaller combat support hospitals are current strategies that are being considered to minimize the need to use warm fresh whole blood.

Military operations are not the only circumstance that warm fresh whole blood transfusion programs are necessary. Both Israel and Australia have contingency programs available for the use of fresh whole blood (52) (Uri Martinowitz, personal communication, 2005). In addition, U.S. emergency medical planners have acknowledged that although there has never been a disaster that has required a large amount of blood products before, they understand that the face of terrorism is constantly changing and there are feasible scenarios that would quickly exhaust the blood component supply of most major cities. As a result, government agencies are now working together to develop a cohesive plan to use warm fresh whole blood donated from prescreened donors as a last resort if stored components are exhausted in a mass casualty event. Hopefully, these plans will never need to be used. However, if they are, the ability to collect blood from prescreened donor pools and then rapidly transfuse it will save many lives. The transfusion of warm fresh whole blood is a simple process that can be executed effectively and safely with proper planning and education. Continued efforts to develop accurate rapid screening tests for transfusion-transmitted diseases are very important for both emergency screening of warm fresh whole blood and for use of routine blood products in Third World countries.

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