Risks associated with fresh whole blood and red blood cell transfusions in a combat support hospital

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Objective: **Fresh whole blood (FWB) and red blood cells (RBCs) are transfused to injured casualties in combat support hospitals. We evaluated the risks of FWB and RBCs transfused to combat-related casualties.**

Design: **Retrospective chart review.**

Setting: **Deployed U.S. Army combat support hospitals.**

Subjects: **Donors of FWB and recipients of FWB and RBCs.**

Measurements and Results: **The storage age of RBCs at transfusion was measured as an indicator of overall risk associated with the storage lesion of RBCs between January 2004 and December 2004 at one combat support hospital. Between April 2004 and December 2004, FWB was prescreened only at one combat support hospital for human immunodeficiency virus, hepatitis C virus, and hepatitis B surface antigen before transfusion. To estimate the general incidence of infectious agent contamination in FWB units, samples collected between May 2003 and February 2006 were tested retrospectively for human immunodeficiency virus, hepatitis B surface antigen, hepatitis C virus, and human lymphotropic virus. Results were compared between FWB samples prescreened and not prescreened for infectious agents before transfusion. At one combat support hospital in 2004, 87 patients were transfused 545 units of FWB and 685 patients were transfused 5,294 units of RBCs with a mean age at transfusion of 33 days (±6 days). Retrospective testing of 2,831 samples from FWB donor units transfused in Iraq and Afghanistan between May 2003 and February 2006 indicated that three of 2,831 (0.11%) were positive for hepatitis C virus recombinant immunoblot assay, two of 2,831 (0.07%) were positive for human lymphotropic virus enzyme immunoassay, and none of 2,831 were positive for both human immunodeficiency virus 1/2 and hepatitis B surface antigen by Western blot and neutralization methods, respectively. The differences in the incidence of hepatitis C virus contamination of FWB donor units between those prescreened for hepatitis C virus (zero of 406; 0%) and not prescreened (three of 2,425; 0.12%) were not significant ($p = .48$).**

Conclusions: **The risk of infectious disease transmission with FWB transfusion can be minimized by rapid screening tests before transfusion. Because of the potential adverse outcomes of transfusing RBCs of increased storage age to combat-related trauma patients, the risks and benefits of FWB transfusions must be balanced with those of transfusing old RBCs in patients with life-threatening traumatic injuries. (Crit Care Med 2007; 35:2576–2581)**

Key Words: trauma; transfusion; hemorrhage; coagulopathy; war; whole blood

Between January 2004 and December 2004, 3,287 patients were treated at the 31st Combat Support Hospital (CSH) in Baghdad for traumatic injuries. Most often in the patients requiring transfusion, blood components—red blood cells (RBCs), fresh frozen plasma, and cryoprecipitate—were utilized to replace blood loss. These stored blood components are supplied by the Armed Services Blood Program from donations collected and processed in the United States and transported overseas to military medical facilities. Because of the time required to transport blood products and the short shelf life of 5 days, platelets were not available during the study period. Thus, in some instances fresh whole blood (FWB) was transfused as a source of fresh platelets, but also when RBCs or cryoprecipitate could not be processed rapidly enough for multiple casualties. At the CSH in Baghdad in 2004, with increased familiarity and anecdotal experience that patients improved with its use, FWB began to be transfused in preference to stored RBCs and fresh frozen plasma. The rationale was FWB would provide fresh (not stored) fully functional hemoglobin, coagulation factors, and platelets for patients at high risk of mortality from hemorrhagic shock; FWB may be more functional or efficient than stored blood components (1–4). U.S. military doctrine supports transfusion of fresh or stored whole blood for patients with life-threatening traumatic injuries (5). Indications for the use of FWB at our CSH included patients who were at risk for massive transfusion with life-threatening injuries; these have been previously pub-

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lished (1, 6). The potential benefits of utilizing whole blood or essentially reconstituting whole blood by using RBC, fresh frozen plasma, and platelet components in equal quantities or a 1:1:1 ratio (similar to whole blood) in patients with severe traumatic injuries has been discussed recently (7–12). Yet some physicians are reluctant to use this therapy because of potential or unknown risks. This report provides a broad assessment of some of the risks to recipients in the practice of FWB transfusion by examining the incidence of transfusion reactions and infectious agent transmission in FWB recipients. We also explore the risks associated with the age of stored blood components utilized in the combat zone, and discuss strategies to reduce risks and improve outcomes associated with both FWB and RBC transfusion.

METHODS

This retrospective protocol received Institutional Review Board approval through the Department of Clinical Investigation at Brooke Army Medical Center in San Antonio, TX. Transfusion reactions and the age of RBCs transfused at the Baghdad CSH were recorded from January 2004 to December 2004. Transfusion reactions were recorded in a database maintained by the CSH laboratory director. The rate of transfusion reactions in patients from the Baghdad CSH who received FWB and RBCs was then compared with the incidence in patients who received only RBCs. Febrile nonhemolytic transfusion reaction was defined as an increase in temperature of >1°C during or after the transfusion that could not be accounted for by another process. Transfusion-related acute lung injury was defined as the development of bilateral pulmonary infiltrates within 6 hrs of a transfusion, associated with increased oxygen requirement, decreased pulmonary compliance, fever, or hypotension. Acute intravascular hemolytic transfusion reactions were identified by the acute development of hemoglobinuria with any of the following symptoms: fever, hypotension, chills, hemoglobinemia, or vomiting. For all transfusion recipients, we also noted the total number of FWB and RBC units transfused, the age of RBCs at delivery to the CSH, and the age of RBCs at transfusion to recipients. Age of RBCs at delivery and transfusion were calculated from a database maintained by the laboratory director and the Armed Services Blood Program Office. All RBC units sent to the CSH had a shelf life of 42 days. Age at date of delivery was calculated as 42 days − (date of expiration − date of delivery). Age at transfusion was calculated as 42 days − (date of expiration − date of transfusion). Leukoreduction was not performed on RBCs before storage and was not performed before transfusion on FWB. Both RBCs and FWB were transfused with standard blood administration tubing without the utilization of leukopore filters.

To estimate the general incidence of infectious agent contamination in FWB units transfused, retrospective testing (confirmatory method) was performed on samples collected between May 2003 and February 2006 at many U.S. CSHs. Methods of testing for each organism were enzyme immunoassay screen followed by Western blot if reactive for human immunodeficiency virus (HIV) 1/2, enzyme immunoassay for human lymphotropic virus, enzyme immunoassay screen (if reactive followed by recombinant immunoblot assay) for hepatitis C virus (HCV), enzyme immunoassay screen (if reactive followed by neutralization) for hepatitis B surface antigen (HBsAg). Testing was performed at the Robertson Blood Center at Ft. Hood, TX. FWB was screened before transfusion for HIV, HBsAg, and HCV only at the CSH in Baghdad by utilizing a rapid immunochromatographic test (non–Food and Drug Administration approved; Biokit, Madrid, Spain) between April 2004 and December 2004. These rapid tests were purchased from and shipped to Baghdad from Spain. Not all units of FWB transfused at the Baghdad CSH in 2004 could be screened because of limited availability of testing kits. Because the rapid screening tests are not approved by the Food and Drug Administration, before 2006 they were not a standard item for CSH laboratories. The manufacturer reported sensitivities and specificities for each of these rapid tests are as follows: HIV 1 and 2 kit specificity 98.2%, sensitivity 98.5%; HCV kit specificity 98.7%, sensitivity 99.4%; HBsAg kit specificity >98%, sensitivity not reported by the manufacturer for this test.

Statistical Analysis. Parametric data are presented as mean (±SD). Student's *t*-test was used to compare means. Chi-square or Fisher's exact test was used for comparisons of categorical data as indicated. A z-test was used to compare proportions from independent samples. Significance for all comparisons was set at $p < .05$. Statistical analysis was performed with SPSS 13.0 (SPSS, Chicago, IL).

RESULTS

Between January 2004 and December 2004, 3,287 patients were admitted to the CSH in Baghdad for traumatic injuries. There were 685 (21%) patients admitted for traumatic injury who were transfused 5,294 units of stored RBCs with a mean of 7.7 units per patient. The mean storage age of RBCs at arrival to the CSH from the United States was 27 days (±5.2 days) and at transfusion was 33 days (±6 days) (Fig. 1). FWB units were typically transfused immediately after collection. Eighty-seven (2.6%) patients admitted for traumatic injury were transfused 545 units of FWB with a mean of six units (three liters) per patient. Eighty-four patients received both RBCs and FWB. The mean RBCs and FWB units transfused to these patients were 16 (±10) and 7 (±7), respectively. The percentage of RBCs and FWB transfused to these 84 patients was 1,337 of 1,875 units (71.3%) and 538 of 1,875 units (28.7%), respectively.

Transfusion Reactions. Between January 2004 and December 2004, 685 patients received 5,294 units of stored RBCs at the Baghdad CSH. In 682 of these patients, 87 also received 545 units of FWB. Transfusion reactions were recorded for two of 87 (2.3%) FWB recipients and 12 of 598 (2.0%) non–FWB transfusion recipients, ($p = .82$). Transfusion reactions for FWB recipients included one case of febrile nonhemolytic transfusion reaction and one case of transfusion-related acute lung injury. Transfusion reactions reported for non-FWB recipients included two cases of acute intravascular hemolytic reactions, one case of transfusion-related acute lung injury, and nine cases of febrile nonhemolytic transfusion reaction.

Infectious Disease Transmission. Retrospective testing of 2,831 samples from FWB donor units transfused in Iraq and Afghanistan between May 2003 and February 2006 indicated that three of 2,831 (0.11%) were positive for HCV recombinant immunoblot assay, two of 2,831 (0.07%) were positive for human lymphotropic virus enzyme immunoassay, and none of 2,831 were positive for both HIV 1/2 and HBsAg by Western blot and neutralization methods, respectively (Table 1). Of 2,831 samples tested, only the samples from the Baghdad CSH were screened for infectious diseases before transfusion. Of the 545 units of FWB collected at the Baghdad CSH, 460 donors were screened for HIV 1/2 and 408 donors were screened for both HCV and HBsAg. Units from two potential donors tested positive for HCV before transfusion; these units were discarded and were not sent back to the United States for retrospective testing. Of those that were screened before transfusion and were negative by screening, none were positive at formal testing back in the United States (Table 1). The difference in the incidence of HCV contamination of FWB donor units between those prescreened for HCV 0/406

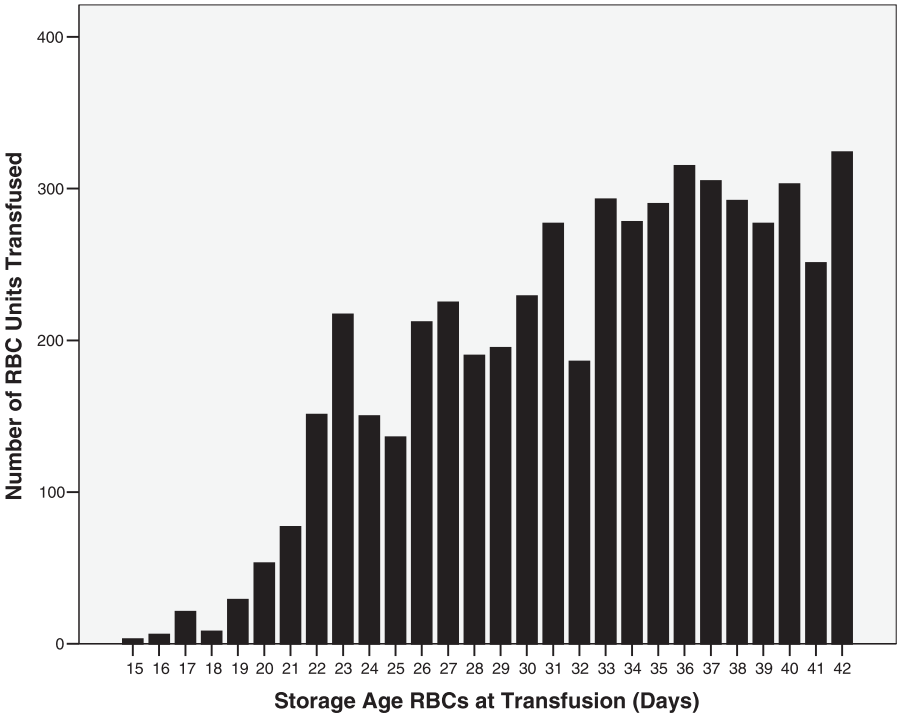

Figure 1. Age of stored red blood cells (*RBCs*) on day of transfusion, n = 5,294 RBC units, mean storage age ± SD = 33 ± 6 days.

Table 1. Comparison of incidence of confirmed positive samples from deployed and nondeployed donors

	Deployed Donors, Rapid-Screened Before Transfusion	Deployed Donors, Not Rapid-Screened Before Transfusion	Nondeployed Donors[a]
HIV (%)	0/460 (0)	0/2371 (0)	0/41,297 (0)
HCV (%)	0/406 (0)	3/2427 (0.12)	24/41,297 (0.06)
HBsAg (%)	0/406 (0)	0/2427 (0)	26/41,297 (0.06)
HTLV (%)	NA	2/2831 (0.07)	25/41,297 (0.06)

HIV, human immunodeficiency virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HTLV, human T-cell lymphotropic virus; NA, not available.

[a]Includes military and civilian donors from the Robertson Blood Collection Center, Ft. Hood, TX.

(0%) and not prescreened three of 2,425 (0.12%) was not significant ($p = .48$).

DISCUSSION

While many authors have discussed the potential clinical benefits of FWB transfusion (1–4, 13–18), to our knowledge this is the first study documenting risks to recipients of FWB. The incidence of transfusion reactions was equal between patients who received FWB compared with patients who received only RBCs and fresh frozen plasma, and the incidence of infectious disease transmission was higher with FWB than what is currently reported for component therapy products. The risk of infectious disease transmission with FWB can be decreased with the use of rapid screening tests before its transfusion.

Risk also exists with standard component therapy. The risk of increased morbidity and mortality associated with the transfusion of RBCs in critically ill patients has been reviewed by many (7, 9, 19–23). The optimal treatment of hemorrhagic shock in these critically injured patients requires a data-driven assessment of the potential benefits and risks of all available blood products (Table 2).

Transfusion Reaction Risk. It was not possible to accurately assess the risk of transfusion reaction for individual units of specific blood products in a population that received large amounts of FWB, RBC, and fresh frozen plasma, often simultaneously and in a short period of time. The low rate of transfusion reactions reported for both FWB and RBC transfusions may have been a result of under-reporting of febrile transfusion reactions due to the chaotic environment in busy CSHs. Transfusion-related acute lung injury was difficult to diagnose in our patients with multiple concomitant traumatic injuries that included a high incidence of traumatic pulmonary hemorrhage and contusion and acute respiratory distress syndrome. Despite the difficulties in associating transfusion reactions with specific blood products in this retrospective study, the use of FWB did not appear to increase the incidence of transfusion reactions.

Risk of Infection to FWB Recipients. Rapid screening before transfusion can minimize the risk of HIV, hepatitis B virus, and HCV, as was the case in our FWB transfusion program that utilized a non–Food and Drug Administration approved rapid screening method. Rapid screening tests can decrease the transmission of infectious agents and should be strongly considered as a standard part of any FWB transfusion program for life-threatening hemorrhage.

The manufacturer reports sensitivity and specificity for each of the rapid screening tests in the range of 98% to 99% for HIV, HCV, and HBsAg. Retrospective testing of donor units in the United States revealed no false negative results with rapid screening tests. According to the reported sensitivity and specificity of these rapid tests, it can be expected that approximately one to two of every 100 positive samples infected with HIV, HCV, or hepatitis B virus will not be detected. The incidence of infectious agents tested in donors was similar in the deployed setting compared with donors at military blood collection centers, except for HCV (Table 2). The confirmed incidence of HCV measured in those volunteering to donate from this deployed military population during this study was three of 2,831 (0.11%). In a similar military population, using the rapid screening test and based on this incidence of HCV, the risk of transfusing an HCV-contaminated unit would be one per 69,930 units transfused. The value of rapid screening for infectious agents was additionally highlighted by the fact that it prevented the transfusion of two units presumably contaminated with HCV.

Because active duty military personnel are tested for HIV before deploy-

Table 2. Comparison of risks and benefits of fresh whole blood (FWB) and stored red blood cells (RBCs) with >14 days of storage for critically ill patients

	FWB	RBCs With >14 Days of Storage
Transfusion reactions	Similar incidence of FNHTR and TRALI in FWB + and − patients	
Infectious disease transmission	Increased incidence compared to stored RBCs. Minimized with the use of rapid screening tests for certain infectious agents	Rare because of extensive testing before transfusion
Physiologic benefits	Improved microcirculatory hemodynamics [18, 24], cardiac output [16, 17, 25], and coagulation function [13, 14]	
Adverse effects on physiology, morbidity, and mortality		Increased inflammatory mediators [26, 27] Increased RBC aggregation [28] Increased free hemoglobin [29] Decreased 2, 3 DPG and tissue perfusion [30] Decreased oxygen consumption [31] Increased infections [32] TRALI [33, 34] Multiorgan failure [9] Death [19, 35]

FNHTR, febrile nonhemolytic transfusion reaction; TRALI, transfusion-related acute lung injury; FWB+, patients who received FWB, RBCs, and fresh frozen plasma; FWB−, patients who received RBCs and fresh frozen plasma; DPG, diphosphoglycerate.

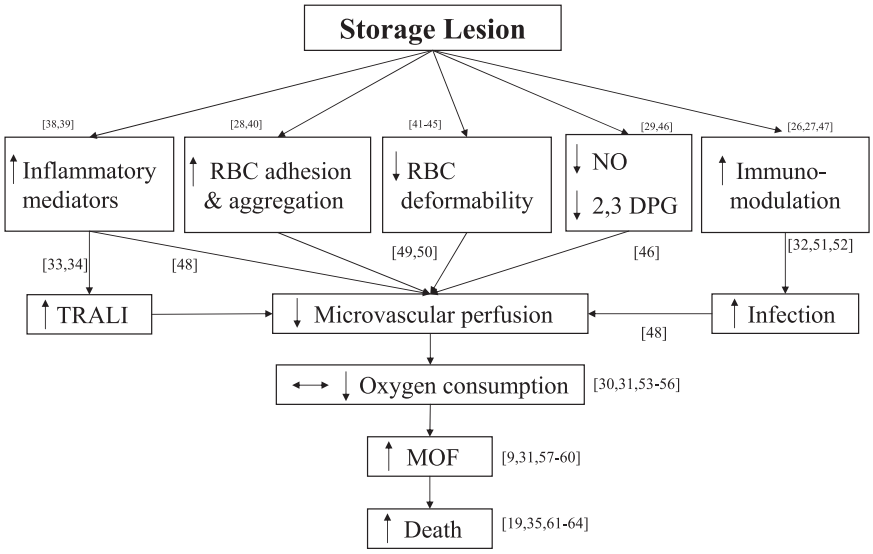

Figure 2. Effects of storage lesion associated with increased storage time and amount of red cell transfusions. *RBC*, red blood cell; *NO*, nitric oxide; *2,3 DPG*, 2,3 diphosphoglycerate; *TRALI*, transfusion-related acute lung injury; *MOF*, multiorgan failure.

ment, the risk of transmitting HIV is diminished compared with the general population. However, military populations are not routinely screened for HCV, hepatitis B virus, and human lymphotropic virus. Predeployment testing could lower the risk of transmitting these agents to recipients of FWB transfusions. Some CSHs currently predetermine and pretest the donor pool by sending samples of their blood to the United States for formal infectious agent testing before utilizing their blood for transfusion.

Stored RBC Risk. Recent reviews regarding the storage lesion associated with RBC transfusions have questioned their risk-benefit profile in critically ill patients (20–23, 36, 37). Figure 2 summarizes the potential adverse effects of transfusing a large amount of stored RBCs to critically ill patients and provides biological plausibility supporting the literature that indicates stored RBCs can have an adverse effect on outcome in critically ill patients. It is possible that the adverse effects reported with the use of stored RBCs are a consequence of transfusing RBCs with >14 days of storage in critically ill patients. Table 2 summarizes risks associated with the transfusion of RBCs with >14 days of storage. These risks are of concern because the average storage age of RBCs transfused in the United States is 21 days (65).

The reported adverse effects of transfusing a large amount of red cells stored for >14 days is of concern to the military physician during combat. Due to significant logistic constraints and difficulty in rapidly transporting blood products from distant collection sites, RBC units tend to be older when administered to casualties. The risk of transfusing large amounts of RBCs >14 days old to critically ill trauma patients has not been tested in a prospective, randomized, controlled trial. But the consistency and biological plausibility of animal and human laboratory data in addition to clinical studies (Fig. 2) support the concept that it is probable that the transfusion of large amounts of RBCs >14 days old is potentially harmful to critically ill patients (9, 19, 24, 28, 30, 32–35). Therefore, despite the fact that randomized, controlled trial data are not available, the transfusion of RBCs <14 days old has significant potential to improve outcomes for patients with severe traumatic injury.

Potential Benefits of FWB. The reported physiologic benefits of FWB are summarized in Table 2. Data on the use of FWB and stored component therapy in combat environments for life-threatening hemorrhage continues to be collected and will be analyzed to determine the effect on survival. Prospective randomized trials are needed to evaluate the efficacy and risks associated with FWB

compared with either stored whole blood or component therapy for patients with severe traumatic injuries. These studies need to account for the age of stored whole blood or red cells.

CONCLUSIONS

Transfusion reaction rates were similar between FWB recipients and patients who only received RBCs. The risk of infectious disease transmission is low and can be further reduced by rapid screening tests before transfusion. At CSHs, the small but real increased risk of infectious agent transmission associated with FWB must be balanced with the documented benefit of FWB and the potential for increased morbidity and mortality with the use of old RBCs.

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