# Fresh whole blood use by forward surgical teams in Afghanistan is associated with improved survival compared to component therapy without platelets

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**BACKGROUND:** In Afghanistan, a substantial portion of resuscitative combat surgery is performed by US Army forward surgical teams (FSTs). Red blood cells (RBCs) and fresh frozen plasma (FFP) are available at these facilities, but platelets are not. FST personnel frequently encounter high-acuity patient scenarios without the ability to transfuse platelets. An analysis of the use of fresh whole blood (FWB) at FSTs therefore allows for an evaluation of outcomes associated with this practice.

**STUDY DESIGN AND METHODS:** A retrospective analysis was performed in prospectively collected data from all transfused patients at six FSTs from December 2005 to December 2010. Univariate analysis was performed, followed by two separate propensity score analyses. In-hospital mortality was predicted with the use of a conditional logistic regression model that incorporated these propensity scores. Subset analysis included evaluation of patients who received uncrossmatched Type O FWB compared with those who received type-specific FWB.

**RESULTS:** A total of 488 patients received a blood transfusion. There were no significant differences in age, sex, or Glasgow Coma Scale in those who received or did not receive FWB. Injury Severity Scores were higher in patients transfused FWB. In our adjusted analyses, patients who received RBCs and FFP with FWB had improved survival compared with those who received RBCs and FFP without FWB. Of 94 FWB recipients, 46 FWB recipients (49%) were given uncrossmatched Type O FWB, while 48 recipients (51%) received type-specific FWB. There was no significant difference in mortality between patients that received uncrossmatched Type O and type-specific FWB.

**CONCLUSIONS:** The use of FWB in austere combat environments appears to be safe and is independently associated with improved survival to discharge when compared with resuscitation with RBCs and FFP alone. Mortality was similar for patients transfused uncrossmatched Type O compared with ABO type-specific FWB in an austere setting.

## INTRODUCTION

With the end of combat operations in Iraq, attention to Afghanistan has returned. There, a substantial portion of resuscitative surgery has been performed by 20 personnel US Army forward surgical teams (FSTs) or similar units. Many of these teams have been split to more widely disseminate surgical care platforms.[1] FSTs doctrinally carry only 20 units of red blood cells (RBCs), but currently in Afghanistan they are augmented with fresh frozen plasma (FFP) and some with cryoprecipitate. Platelets (PLTs) are not available.[1-4] The concept of damage control resuscitation with the use of RBCs, FFP, and PLTs in balanced ratios that approximate those of whole blood has been supported by several recent publications in the military and civilian trauma literature.[5-11] Although these studies are retrospective in nature, the military has adopted a clinical practice guideline recommending 1:1:1 unit ratios of these blood components. In addition, current theater clinical practice guidelines recommend the use of fresh whole blood (FWB) be reserved for "casualties who are anticipated to require massive transfusion (10 or more units of packed RBCs in 24 hr), for those with clinically significant

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shock or coagulopathy (e.g., bleeding with associated metabolic acidosis, thrombocytopenia, or international normalized ratio >1.5) when optimal component therapy (e.g., apheresis PLTs and FFP) is unavailable or stored component therapy is not adequately resuscitating a patient with immediately life-threatening injuries."[12] Due to the austerity of their environment, FST personnel frequently encounter high-acuity patient scenarios without the ability to transfuse PLTs. The use of FWB in these locations therefore generates an opportunity to evaluate outcomes associated with whole blood transfusions. Current US military doctrine states that FWB must be type specific when transfused. In some remote settings where donors are limited, this is not possible, and uncrossmatched Type O FWB is transfused as a last resort. The objective of this study is to examine the association of FWB use versus use of component therapy (RBCs and FFP) only, with in-hospital mortality in combat casualties admitted to FSTs. Furthermore, we examine the association between receipts of ABO type-specific FWB versus uncrossmatched Type O FWB on in-hospital mortality.

## METHODS

The Institutional Review Board of the US Army Medical Research and Materiel Command approved the retrospective analysis of all admission performance improvement data of a convenience sample of six FSTs from December 2005 to December 2010. These units were chosen because they developed a comprehensive performance improvement plan that included collection of data regarding blood transfusion. The data were prospectively collected by the individual FST units during the 5-year study period. Blood product utilization, mechanism of injury, type of injuries, number and type of surgical procedures performed, and ultimate patient outcome were recorded. Demographic data including patient status, sex, and age were also collected. Physiologic variables including temperature, systolic blood pressure (SBP), respiratory rate, and Glasgow Coma Scale (GCS) at the time of initial patient presentation were collected. Mechanism of injury was also collected and categorized into four broad areas: gunshot wound, blast injury, motor vehicle crash, and burn. An Abbreviated Injury Score and Injury Severity Score (ISS) were calculated for each transfused patient with the use of the Military Abbreviated Injury Score 2005 (revised 2007). The primary endpoint was mortality determined at inpatient discharge from a Level V military facility for US forces or discharge to a local national facility for Afghanis. Other data collected included the number of blood products transfused, activated recombinant factor VIIa (rFVIIa) usage, patient age, and temperature on presentation. Patients determined to have died within 1 hour of presentation were eliminated from the study in an attempt to mitigate survivor bias. Afghani patients with penetrating head injuries with initial GCS of ≤7 were eliminated as they were often treated expectantly. Statistical analysis was performed by an independent statistician. Univariate analysis was performed with the use of SAS 9.1 (SAS Institute, Inc., Cary, NC). Two separate propensity score analyses were performed utilizing STATA 11.2 (StataCorp LP, College Station, TX). Variables that were associated with the use of FWB in the univariate analysis were used to calculate propensity scores. SBP at arrival to FST, arrival temperature, use of rFVIIa, total RBCs, and total FFP administered were used to calculate the propensity score that was the probability of receiving FWB. The balancing property of the propensity scores was tested and propensity scores were determined to be balanced in the FWB and non-FWB groups. The propensity scores were used in the logistic regression model predicting death, adjusting for the ISSs and the Glasgow Coma Scores. The propensity score was included as a continuous variable in the first model. In the second analysis, propensity scores were used to create strata or groups. Subjects were grouped into six strata based on similarity of propensity score and therefore have similar risk profile, without regard to outcome or receipt of FWB. Following stratification, death in each group was predicted with the use of a conditional logistic regression. Conditional logistic regression approach combines within-stratum effects with between-stratum effects to estimate the overall FWB effect on death.

## RESULTS

A total of 488 patients met inclusion criteria. They received 2612 units of RBCs, 1566 units of FFP, and 416 units of FWB. A total of 394 patients received blood transfusion without receiving FWB and 94 patients received blood transfusions that included FWB. Table 1 indicates that ISSs and respiratory rate were significantly higher in patients receiving FWB, while arrival SBP and temperature were significantly lower. There was no significant difference in age, sex, or GCS in those who received or did not receive FWB.

Predictably, patients receiving FWB also required significantly more units of RBCs and FFP. These patients also were more likely to receive rFVIIa and massive blood transfusion (MBT) defined as 10 or more units of RBCs or the equivalent combination of RBCs and FWB in the first 24 hours (Table 2). There was no statistical difference in in-hospital mortality between study groups. In patients who received FWB, the unadjusted mortality rate was 5.3% (5/94) for those transfused FWB and 8.8% (35/394) for patients who did not receive FWB. Mechanism of injury was similar between patients who received component therapy with FWB and those who received only RBCs and FFP (Table 3).

**TABLE 1. Admission vital sign and laboratory data by fresh whole blood (FWB) use**

| | No FWB (n = 394) | FWB (n = 94) | p Value |
|---|---|---|---|
| Age (years) | 25.6 ± 11.5; 25 (20, 30); 371 | 28.1 ± 9.7; 25 (22, 30); 81 | 0.08 |
| US and/or coalition | 53 (13.5) | 14 (14.9) | 0.715 |
| Non-US and/or coalition | 341 (86.5) | 80 (85.1) | 0.715 |
| Male sex | 375 (95.2) | 90 (95.7) | 1.00 |
| GCS | 13.8 ± 2.7; 15 (14, 15); 394 | 13.2 ± 3.4; 15 (14, 15); 93 | 0.11 |
| ISS | 19.6 ± 9.3; 16.5 (16, 25); 394 | 22.4 ± 8.9; 20 (16, 26); 94 | 0.008 |
| Arrival SBP (mmHg) | 110.5 ± 27.1; 110 (95, 128); 388 | 99.9 ± 30.1; 97 (80, 123); 94 | <0.001 |
| Arrival RR | 22 ± 8.2; 21 (16, 26); 383 | 25.2 ± 9.7; 25 (18, 30); 94 | 0.005 |
| Arrival temperature (°C) | 36.4 ± 0.8; 36.6 (36.2, 37.0); 373 | 36.1 ± 1.2; 36.2 (35.6, 36.8); 83 | 0.005 |

Continuous variables reported as mean ± SD; median (LowerQ, UpperQ); n.
Categorical variables reported as n (%).
GCS = Glasgow Coma Scale; ISS = Injury Severity Score; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation.

**TABLE 2. Blood products use by fresh whole blood (FWB)**

| | No FWB (n = 394) | FWB (n = 94) | p Value |
|---|---|---|---|
| FWB (U) | 0 | 4.4 ± 4; 3 (2,6) | <0.001 |
| Total RBCs (U) | 4.7 ± 3.7; 4 (2, 6) | 12.7 ± 9.4; 10 (6, 16) | <0.001 |
| Total plasma (U) | 2.6 ± 2.7; 2 (0, 4) | 10 ± 7.1; 8 (5, 12) | <0.001 |
| Total blood products (U) | 7.3 ± 5.8; 6 (3, 10) | 18.3 ± 13.1; 14 (10, 24) | <0.001 |
| Factor VII given | 23 (5.8) | 24 (25.5) | <0.001 |
| Massive transfusion | 46 (11.6) | 49 (52.1) | <0.001 |

Continuous variables reported as mean ± SD; median (LowerQ, UpperQ).
Categorical variables reported as n (%).
RBCs = red blood cells; SD = standard deviation.

**TABLE 3. Univariate comparison of mechanism of injury**

| Variable | FWB (n = 94) | No FWB (n = 394) | p Value |
|---|---|---|---|
| Gunshot wound | 48.9% | 46.7% | 0.696 |
| Blast | 43.6% | 46.7% | 0.590 |
| Burns | 0% | 1.3% | 0.272 |
| Motor vehicle collision | 0% | 3.0% | 0.087 |
| Other | 6.4% | 3.0% | 0.123 |

FWB = fresh whole blood.

Lower GCS, higher ISS, lower arrival SBP, and lower arrival patient temperature were associated with death (Table 4). Also, higher total RBC transfusion and higher total blood product transfusion were associated with death. Interestingly, total FFP and FWB transfused were not associated with death. Consistent with previous reports, patient mortality was associated with MBT and rFVIIa use (Table 5). Two separate propensity score analyses were performed with the use of a continuous variable and then stratification method. With the use of continuous variable logistic regression analysis, patients who received RBCs and FFP with FWB had significantly improved survival compared with those who received RBCs and FFP without FWB, odds ratio (OR) (95% confidence interval [CI]) 0.096 (0.02-0.53). Higher ISS and lower GCS were associated with increased mortality (Table 6). With the use of a stratified propensity score analysis, FWB use was also associated with improved survival OR (95% CI), 0.11 (0.02-0.78). Higher ISS and lower GCS were also associated with increased mortality (Table 7). A subset analysis was performed for patients who only received MBT. Ninety-four patients received MBT, with 49 transfused FWB, RBCs, and FFP and 45 patients received only RBCs and FFP. The mortality rate in those patients who received MBT with RBCs, FFP, and FWB was 8.16% and those who received MBT with RBCs and FFP alone had a mortality of 26.67% (p = 0.025). Another subset analysis was performed in patients who received FWB (n = 94) according to receipt of ABO type-specific FWB (51%) or uncrossmatched Type O FWB (49%). There was no statistical difference in in-hospital mortality for patients who received type-specific FWB (6.1%) compared with those who received uncrossmatched Type O FWB (6.7%) with three deaths in each group. Data were not available to report the ABO type of recipients who received uncrossmatched Type O FWB. No transfusion reactions were noted in patients who received FWB.

## DISCUSSION

This is the first study to compare transfusion of RBCs and FFP with FWB to patients who received only RBCs and FFP at Level II or forward surgical facilities. Our results indicate that, in a far forward setting during military operations, transfusion of RBCs, FFP, and FWB is independently associated with improved in-hospital survival compared with RBCs and FFP alone. As a result, not only does it appear to be safe to transfuse FWB in this setting when PLTs are not available but it may also improve outcomes compared with the use of RBCs and FFP alone.

The coagulopathy associated with hemorrhaging trauma patients has been long recognized.[13,14] In Vietnam, this clinical manifestation was sometimes referred to as oozing syndrome, tomato juice syndrome, and red ink

**TABLE 4. Admission vitals, patient demographics, and laboratory data by death status**

| | Alive (n = 448) | Dead (n = 40) | p Value |
|---|---|---|---|
| Age (years) | 25.9 ± 11; 25 (20, 30); 417 | 28.3 ± 13.5; 25 (21, 31); 35 | 0.23 |
| Male sex | 426 (95.1) | 39 (97.5) | 0.71 |
| US and/or coalition | 64 (14.3) | 3 (7.5) | 0.232 |
| Non-US and/or coalition | 384 (85.7) | 37 (92.5) | 0.232 |
| GCS | 14.1 ± 2.3; 15 (14, 15); 447 | 9.4 ± 4.7; 9.5 (5.5, 15); 40 | <0.001 |
| ISS | 19.4 ± 8.6; 16 (16, 25); 448 | 28. ± 12.1; 25 (19, 32); 40 | <0.001 |
| Arrival SBP (mmHg) | 109.9 ± 26.8; 110 (93, 128); 443 | 91.3 ± 35; 84 (78, 109); 39 | 0.002 |
| Arrival RR | 22.5 ± 8.4; 22 (16, 28); 438 | 24.1 ± 11; 24 (17, 32); 39 | 0.41 |
| Arrival temp (°C) | 36.4 ± 0.9; 36.6 (36.1, 37.0); 420 | 35.8 ± 1.1; 35.8 (35.3, 36.4); 36 | <0.001 |

Continuous variables reported as mean ± SD; median (LowerQ, UpperQ); n.
Categorical variables reported as n (%).
GCS = Glasgow Coma Scale; ISS = Injury Severity Score; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation.

**TABLE 5. Blood products use by death status**

| | Alive (n = 448) | Dead (n = 40) | p Value |
|---|---|---|---|
| FWB patient status | 89 (19.9) | 5 (12.5) | 0.250 |
| FWB (U) | 0.8 ± 2.2; 0 (0, 0); 448 | 1.4 ± 4.7; 0 (0, 0); 40 | 0.43 |
| Total RBCs (U) | 5.8 ± 5.5; 4 (2, 8); 448 | 10.5 ± 10.4; 8 (4, 13); 40 | 0.008 |
| Total plasma (U) | 3.9 ± 4.5; 3 (0, 6); 448 | 6.1 ± 7.9; 4 (1.5, 6); 40 | 0.09 |
| Total blood products (U) | 8.9 ± 8; 7 (3, 12); 448 | 15.1 ± 14.2; 10 (6, 19) 42 | 0.01 |
| Factor VII given | 39 (8.7) | 8 (20) | 0.04 |
| Massive transfusion | 79 (17.6) | 16 (40) | 0.002 |

Continuous variables reported as mean ± SD; median (LowerQ, UpperQ); n.
Categorical variables reported as n (%).
FWB = fresh whole blood; RBCs = red blood cells; SD = standard deviation.

**TABLE 6. Propensity score used as continuous variable in logistic regression predicting effect of FWB on death**

| | Odds ratio | 95% CI | p Value |
|---|---|---|---|
| FWB use | 0.096 | 0.02,0.53 | 0.008 |
| Injury Severity Score | 1.07 | 1.03,1.11 | <0.001 |
| Glasgow Coma Score | 0.72 | 0.65,0.79 | <0.001 |
| Propensity score | 9.72 | 1.45,64.97 | 0.019 |

Arrival systolic blood pressure, arrival temperature, use of factor VIIa, total red blood cells, and total plasma administered were used to calculate propensity score.
CI = confidence interval; FWB = fresh whole blood.

**TABLE 7. Stratified propensity score analysis predicting the effect of the use of FWB on death**

| | Odds ratio | 95% CI | p Value |
|---|---|---|---|
| FWB use | 0.11 | 0.02, 0.78 | 0.03 |
| Injury Severity Score | 1.06 | 1.01, 1.11 | 0.01 |
| Glasgow Coma Score | 0.71 | 0.63, 0.79 | <0.001 |

CI = confidence interval; FWB = fresh whole blood.

syndrome.[15] This coagulopathic bleeding is associated with the lethal triad of trauma, which also includes acidosis and hypothermia. However, coagulopathy is also recognized to occur early in trauma patients and is exacerbated by blood loss, acidosis, hypothermia, consumption, fibrinolysis, and dilution.[9,10,16-20] As many as one-third of combat trauma patients who require transfusion are coagulopathic at their initial presentation to a surgical facility.[14]

Recognizing the frequent futility of correcting coagulopathy and shock secondary to severe nonsurgical bleeding with traditional resuscitative methods after it occurs, the concept of hemostatic or damage control resuscitation with all the components of whole blood has evolved. The initial military research effort evaluated FFP transfused concurrent with RBCs and which ratio of RBC:FFP was associated with increased survival.[5,20,21] The conclusions of these studies were that transfusion of FFP concurrently with RBCs in patients requiring large volumes of blood was associated with improved survival and the RBC:FFP recommended ratio was 1:1. As a result of these studies, damage control resuscitation with the use of a 1:1 ratio of RBC and FFP was adopted by all surgical units including FSTs and combat support hospitals (CSHs) in Iraq and Afghanistan. This was relatively easily done as FFP can be frozen and stored for up to 1 year and was already available in both theaters. PLTs were not available in theater until late 2004 and then only at the larger combat support hospitals.[3]

Largely due to the sporadic and inconsistent availability of RBCs and FFP early in the war, FWB was frequently used as a source of RBCs, FFP, and PLTs. Anecdotal reports suggested that FWB was an excellent resuscitation fluid

and an early retrospective study by Spinella and colleagues suggested that FWB combined with RBCs and FFP may be superior to traditional component therapy consisting of RBCs, FFP, and apheresis PLTs.[23] However, a subsequent retrospective review by Perkins and colleagues compared MBT patients who received either apheresis PLTs or FWB and found that adjusted survival approached significance ($p = 0.06$) at 24 hours with no difference at 30 days, and a higher unadjusted incidence of ARDS in the FWB group was noted.[22] Based largely on these studies, a theater practice guideline was published, which recommended the use of FWB for circumstances when PLTs were not available. However, when component therapy provided inadequate resuscitation, the clinical practice guideline supported the use of FWB at the discretion of the surgeon.[23]

Afghanistan is a mature theater and apheresis PLTs are now available at CSHs, also referred to by North Atlantic Treaty Organization (NATO) forces as Role III facilities.[2] However, in Afghanistan, FSTs provide initial surgery to the combat injured in the majority of locations. The FST was designed to provide a surgical capability to a maneuvering combat brigade and the ability to do this successfully has been well reported in the literature.[24-28] In an attempt to provide surgical capability to as many locations as possible the 20 personnel FSTs have been split. This practice although initially questioned has been shown to be successful with excellent outcomes achieved by appropriately trained teams.[1,28] PLTs are not available at either full or split FSTs. This is problematic as the main purpose of the FST is to provide damage control surgery and resuscitation. Under these circumstances, FWB is commonly used due to its PLT constituent and almost always in conjunction with RBCs and FFP. There are additional theoretical benefits of FWB compared with components, which include fresh RBCs that may have increased efficacy at delivering oxygen as well as reduced harmful storage lesion effects. In addition, FWB is a more concentrated product (less anticoagulants and additives) than whole blood reconstituted from stored components.

Of the 488 patients in this study who received blood transfusion, 94 received FWB (19.26%). Patients who received FWB on average received 4.43 units of FWB, 8.27 units of RBCs, 5.59 units of FFP, and a mean of 18.27 units of total blood products. This shows that in large part patients who received FWB received it in the context of large volume if not MBT resuscitation.

In this study, patients transfused before the fall of 2008 usually received uncrossmatched Type O. It is likely that many of the patients who received Type O blood in this setting were Type O patients. During this period, in the forward setting, where there was no capacity to perform ABO typing of donors, it was not possible to determine how many casualties who received transfusion uncrossmatched Type O blood received Type ABO-specific blood. After this time, the theater policy mandated only transfusing type-specific FWB, and FSTs were augmented with type and cross capability. This study showed no difference in mortality between patients receiving uncrossmatched FWB compared with when type-specific FWB was intentionally transfused. The safety of transfusing uncrossmatched or Type O FWB in dire circumstances when type-specific FWB cannot be provided requires further study. The current US military policy prohibiting this practice may be increasing the risk of mortality for patients unnecessarily. No data exist that the authors are aware of that indicate that the use of Type O FWB as a last resort when ABO type-specific blood is not available is associated with increased risk of poor outcomes. While no transfusion reactions were noted in FWB recipients, the signs and symptoms of a transfusion reaction can easily be missed during massive hemorrhage and MBT. The additive risk introduced by the transfusion of Type O blood with incompatible plasma ABO antibodies is a severe intravascular hemolytic transfusion reaction (IHTR). In contrast to other transfusion reactions, IHTR constitutes an acute clinically recognizable entity characterized by physical discomfort, chest and/or abdominal pain, fever, hypotension, dyspnea, and appearance at the beginning of the transfusion. Depending on the transfused volume, later symptoms may include macroscopic hematuria, disseminated intravascular coagulation, and circulatory failure. In spite of the wide use of Type O whole blood during World War II, no reports of IHTR were observed until 1944 when a few were reported.[29] The reactions were not fatal but led to a US policy of screening the Type O donors for ABO plasma antibodies and excluding those with high titers from serving as "universal donors."[30] During the later Korean and Vietnam Wars, 52,000 and 230,300 transfusions were reported without any IHTR caused by a compatible transfusion. There were however some IHTRs as a result of incompatible blood transfusions due to administrative errors.[31]

Until very recently, there was no doctrinal capability to type and crossmatched blood at an FST and the complexity of managing a blood bank capable of typing and crossmatching blood was beyond the reasonable expectations of these small teams, especially in the early days of combat operations.[4,32] This practice is currently prohibited by the current US Army FWB clinical practice guideline in favor of type and crossmatched blood, despite no data indicating that the practice is associated with worse outcomes.[1,4,35-37]

Our study has limitations inherent to retrospective analyses. A convenience sample may introduce sampling bias. More importantly, our results may be affected by survival bias as it takes a mean of 30-45 minutes to receive the first unit of FWB. In this study, we eliminated patients who died within the first hour of treatment at the FST, which minimizes survival bias. The majority of those who died did so after transfer; however, due to the transfer of

Afghani patients to local facilities, determining the cause of death was not always possible, which makes it difficult to draw any conclusions on the long-term effects of FWB transfusion.

## CONCLUSIONS

The use of FWB in austere combat environments appears to be safe and is independently associated with improved survival when compared with resuscitation with RBCs and FFP alone. Mortality was similar for patients transfused uncrossmatched Type O FWB compared with ABO type-specific FWB in an austere setting. Further studies evaluating outcomes related to the use of uncrossmatched Type O FWB in these settings are warranted.

### CONFLICT OF INTEREST

The opinions or assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.

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