

Warm Fresh Whole Blood Is Independently Associated With Improved Survival for Patients With Combat-Related Traumatic Injuries

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Background: Increased understanding of the pathophysiology of the acute coagulopathy of trauma has led many to question the current transfusion approach to hemorrhagic shock. We hypothesized that warm fresh whole blood (WFWB) transfusion would be associated with improved survival in patients with trauma compared with those transfused only stored component therapy (CT).

Methods: We retrospectively studied US Military combat casualty patients transfused ≥ 1 unit of red blood cells (RBCs). The following two groups of patients were compared: (1) WFWB, who were transfused WFWB, RBCs, and plasma but not apheresis

platelets and (2) CT, who were transfused RBC, plasma, and apheresis platelets but not WFWB. The primary outcomes were 24-hour and 30-day survival.

Results: Of 354 patients analyzed there were 100 in the WFWB and 254 in the CT group. Patients in both groups had similar severity of injury determined by admission eye, verbal, and motor Glasgow Coma Score, base deficit, international normalized ratio, hemoglobin, systolic blood pressure, and injury severity score. Both 24-hour and 30-day survival were higher in the WFWB cohort compared with CT patients, 96 of 100 (96%) versus 223 of 254 (88%), ($p = 0.018$) and 95% to 82%, ($p = 0.002$), respec-

tively. An increased amount (825 mL) of additives and anticoagulants were administered to the CT compared with the WFWB group, ($p < 0.001$). Upon multivariate logistic regression the use of WFWB and the volume of WFWB transfused was independently associated with improved 30-day survival.

Conclusions: In patients with trauma with hemorrhagic shock, resuscitation strategies that include WFWB may improve 30-day survival, and may be a result of less anticoagulants and additives with WFWB use in this population.

Key words: Whole blood, Transfusion, Mortality, Survival, Combat.

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Traumatic injury is the leading cause of death for patients between the ages of 1 to 40 years.¹ Approximately 150,000 people die per year in the United States from traumatic injuries.² US Military reports estimate that 15% to 20% of traumatic deaths are preventable, and 66% to 80% of these deaths occur from hemorrhage.^{3,4} Rural civilian data indicates that approximately 10% of deaths are preventable.^{5,6} If 10% to 20% of 150,000 US civilian traumatic deaths are preventable, and 66% to 80% of these preventable deaths are due to uncontrolled bleeding this translates to between 10,000 and 24,000 potentially preventable hemorrhagic trauma deaths per year in the United States. Hemorrhagic deaths typically occur

within the first 24 hours of admission.^{7–9} Early identification and prevention of patients who are at risk of developing coagulopathy and subsequent strategies to control coagulopathic bleeding may therefore improve survival.^{10–13}

The transfusion approach to hemorrhagic injuries has evolved or continually progressed since it developed in the early 1900s. The evolution has included whole blood, modified whole blood to the current use of component therapy (CT).^{14,15} After the development of whole blood fractionation, CT now predominates as the primary transfusion approach secondary to concerns for resource utilization and safety.^{16–18} This change occurred without evidence comparing the benefits or risks between these products specifically for patients with traumatic hemorrhagic shock.^{16–18} Classic transfusion guidelines regarding indications for blood components are based on expert opinion, experiments in euvolemic patients requiring elective surgery, and modified whole blood that is no longer commonly available.^{16–18} In addition, the storage age of red blood cells (RBCs) has progressively increased over time to a current limit of 42 days^{14,15} without prospective study evaluating the clinical effect of increased RBC storage length in critically ill patients.

Recently, there has been a change in opinion by some in the trauma community regarding the transfusion approach to hemorrhagic shock. The concept of hemostatic or damage control resuscitation as the optimal approach for the treatment of patients with severe life-threatening hemorrhagic traumatic

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injuries is gaining wide acceptance.¹⁹ This approach advocates for the rapid control of surgical bleeding, transfusion of RBCs, plasma, and platelets in a 1:1:1 ratio; preference for the use of fresh RBCs; limitation of excessive crystalloid use; and prevention of acidosis and hypothermia.^{20–25} The use of warm fresh whole blood (WFWB) has also been utilized in US Military facilities out of necessity at combat hospitals in Afghanistan and Iraq to support the application of damage control resuscitation principles.^{18,26–28} A recent review describes over 6000 units of WFWB that has been transfused in recent combat operations.²⁹ The recent large scale use of WFWB by the US Military has rekindled interest of its use for patients at high risk of death from hemorrhage to include civilian disaster emergencies.²⁹

Theoretically, WFWB may be advantageous for patients in hemorrhagic shock over CT due to improved function of RBCs, plasma, and platelets, and avoidance of the adverse effects of the storage lesion when older RBCs are transfused. Interestingly, comparisons between patients transfused WFWB to those receiving only stored CT for traumatic hemorrhagic shock has not been evaluated. We hypothesized that WFWB transfusion would improve both short-term (24 hour) and 30-day survival when compared with patients transfused only stored CT in this population.

METHODS

This retrospective study was approved by the Institutional Review Board at Brooke Army Medical Center, San Antonio, TX. US Military patients were identified from a transfusion database maintained at the US Army Institute of Surgical Research. The database includes patients injured in both Afghanistan and Iraq and transfused at least one unit of RBCs between January 2004 and October 2007 at either a level II or a level III hospital. The following two groups of patients were compared: (1) WFWB, who were transfused WFWB, RBCs, and plasma but not apheresis platelets (aPLT) and (2) CT, who were transfused RBC, plasma, and aPLT but not WFWB. Patients were excluded if they received both WFWB and aPLTs or if they were transfused neither WFWB nor aPLTs. The primary outcomes were 24-hour and 30-day survival. All blood product amounts were measured at 24 hours from admission. The following terms are used in the article to describe different products. Stored RBCs are red cells that are stored in AS-5 solution that are shipped from the United States. The stored RBCs transfused to patients in this study were neither leukoreduced before storage nor were they at the time of transfusion. Total RBC units were calculated by adding RBC units and one unit of RBCs from each WFWB unit transfused. Plasma indicates both fresh-frozen plasma and thawed plasma. Apheresis platelets were collected at combat support hospitals and were stored up to 7 days. The total plasma to RBC ratio was calculated by also including a unit of plasma and RBCs from each unit of WFWB transfused, (plasma + WFWB/RBC + WFWB). The total platelet to RBC ratio was calculated by incorporating six units of

platelets for each unit of apheresis platelet unit transfused or one unit of platelets for each unit of WFWB (WFWB + 6[aPLT]/[WFWB + RBC]). Massive transfusion was defined as 10 or more total RBC units within the first 24 hours of admission. Volumes of each blood product were determined using standard volumes of each product transfused: RBC 360 mL, FFP 270 mL, aPLT 300 mL, and WFWB 450 mL. Anticoagulant or additive solutions within blood products transfused to both groups were determined by adding the following standard amounts for each product: RBC 120 mL, plasma 50 mL, aPLTs 35 mL, and WFWB 63 mL. Actual volume of blood products transfused was calculated by subtracting anticoagulant/additive from the volume of total blood products. Additional variables included in our analysis was patient age, admission vital signs, and laboratory values to include individual eye, verbal and motor Glasgow Coma Score (GCS), temperature (T), systolic blood pressure, heart rate, hemoglobin, base deficit, International Normalized Ratio, and injury severity score (ISS). The ISS was calculated by trained staff at the US Army Institute of Surgical Research according to the methods described by the Association for the Advancement of Automotive Medicine Abbreviated Injury Scale, 1998 Revision.³⁰

To determine whether changes in capabilities of combat support hospitals over time influenced our results we measured 30-day survival for both study groups before and after 1 December 2006. This arbitrary cut off date was chosen to allow for equal amounts of patients who received CT to be represented in the groups compared. Adverse events such as deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebral stroke, acute respiratory distress syndrome, and renal failure were recorded if these events were documented in the patients' charts. Strict definitions were neither utilized for each of these adverse events nor there was prospective screening for any of these events. The term traumatic hemorrhagic shock in this article is arbitrarily defined by the authors as patients with a base deficit of three or higher secondary to bleeding from traumatic injuries. A base deficit of three is abnormal and very likely represents lactic acidosis, anaerobic metabolism, or mild shock when it is measured upon admission in healthy patients who have not received a large amount of fluid resuscitation and present with traumatic injuries. As a result, the term shock as we liberally define it, for the purposes of describing the patients only in this study, ranges from mild to severe or compensated to uncompensated hemorrhagic shock.

Statistical Analysis

Median (interquartile range) was used to describe all data. Wilcoxon's rank-sum, χ^2 , and Fisher's exact tests were used for statistical comparisons as appropriate. GCS values for eye, verbal, and motors were categorized into normal or abnormal responses when included into the multivariate regression model. Normal values for GCS eye, verbal, and motor were defined as 4, 5, and 6, respectively. All variables

on univariate analysis with 30-day survival with a *p* value of <0.1 were considered for inclusion in a multivariate logistic regression analysis with backwards stepwise method to determine independent associations with 30-day survival. Only variables that were independently associated with 30-day survival are reported, and those that were not significant are not described as a result of using a backwards stepwise elimination method. Statistical analysis was performed with (SPSS, 15.0, Chicago, IL).

RESULTS

In the database, 968 patients were transfused ≥1 U RBC and 354 (37%) met criteria for inclusion into our analysis. There were 100 of 354 (28%) patients in the WFVB group and 254 of 354 (72%) in the CT group. For both groups median (interquartile range) ISS was 18 (10–26) and 30-day survival was 304 of 354 (86%). Patients receiving WFVB (*n* = 100) compared with CT (*n* = 254) had similar severity of injury determined by admission base deficit 6 (4–10) to 6 (3–11), International Normalized Ratio 1.4 (1.1–1.6) to 1.4 (1.2–1.8), and ISS 18 (10–26) to 18 (10–26), respectively, (*p* > 0.05), in addition to similar admission hemoglobin and systolic blood pressure (Table 1). The only difference between the study groups for admission vital signs and laboratory results was that the WFVB group did have decreased admission temperature compared with the CT group, 97.6 (96.4–98.2) versus 98.5 (97.4–99.5) and *p* ≤ 0.001.

In the WFVB group, the median percentage of total volume of WFVB transfused per total blood products was 2.25 of 7.4 (L), (30%). The individual amounts of each blood product transfused at 24 hours were each different, which is expected because groups were determined by the blood products transfused (Table 2). The transfusion approach was similar with respect to the total RBCs transfused, 16 (11–22) versus 16 (10–22) (*p* = 0.44), percentage of patients receiving recombinant activated factor VII, 42 versus 40%, (*p* = 0.72), and the median ratios of plasma to RBCs transfused between WFVB and CT study groups, 0.73 (0.53–1) versus

Table 1 Comparison of Variables Between WFVB and CT Groups

Variable	WFVB (<i>n</i> = 100)	CT (<i>n</i> = 254)	<i>p</i> Value
Age (yr)	24 (21–29)	23 (21–28)	0.16
Temperature (F)	97.6 (96.4–98.2)	98.5 (97.4–99.5)	<0.001
Heart rate (bpm)	112 (95–136)	115 (91–138)	0.88
SBP (mm Hg)	110 (80–122)	109 (80–130)	0.67
GCS eye	4 (2–4)	4 (1–4)	0.32
GCS verbal	5 (1–5)	5 (1–5)	0.53
GCS motor	6 (3–6)	6 (1–6)	0.19
Hemoglobin (g/dL)	11.6 (10–14)	11.8 (9.8–13.4)	0.44
Base deficit	6 (4–10)	6 (3–11)	0.77
INR	1.4 (1.1–1.6)	1.4 (1.2–1.8)	0.83
ISS	18 (10–26)	18 (10–26)	0.74

Data presented as Median (IQR) or as percentages
SBP, systolic blood pressure; INR, International Normalized Ratio.

Table 2 Comparison of Individual Blood Products, Volumes and Ratios Between WFVB and CT Groups

Variable	WFVB (<i>n</i> = 100)	CT (<i>n</i> = 254)	<i>p</i> Value
Stored RBC (U)	9 (7–14)	16 (10–22)	<0.001
Plasma (U)	4 (3–8)	10 (6–16)	<0.001
Apheresis platelets (U)	0	2 (1–4)	<0.001
WFVB (U)	5 (3–9)	0 (0–0)	<0.001
Cryoprecipitate (U)	0 (0–0)	0 (0–1)	0.007
Total RBC (U)	16 (11–22)	16 (10–22)	0.44
Total blood volume (L)	7.4 (5.4–10.4)	9.3 (6.2–13.3)	0.006
Anticoagulant/additives (L)	1.7 (1.3–2.5)	2.5 (1.6–3.6)	<0.001
Actual blood volume (L)	5.7 (4.1–8.)	6.8 (4.5–10)	0.03
PLT:RBC ratio	0.33 (0.2–0.5)	0.86 (0.6–1.3)	0.001
Plasma:RBC ratio	0.74 (0.55–0.9)	0.73 (0.53–1)	0.73
Massive transfusion (%)	89/100 (89%)	198/254 (78%)	0.017
rFVIIa use (%)	42/100 (42%)	101/353 (40%)	0.72

Data presented as Median (IQR) or as percentages.
rFVIIa, recombinant factor VIIa.

Table 3 Comparison of Variables for Survivors and Nonsurvivors at 30 d

Variable	Dead (<i>n</i> = 50)	Alive (<i>n</i> = 304)	<i>p</i> Value
Age (yr)	23.5 (21–29.3)	23 (21–27)	0.85
Temperature (F)	97.5 (94.2–99.3)	98.1 (97.3–99.2)	0.17
Heart rate (bpm)	108 (60–135)	106 (87–129)	0.21
SBP (mm Hg)	102 (53–133)	110 (83–129)	0.16
Hemoglobin (g/dL)	9.7 (7.4–12.4)	11.9 (10.1–13.5)	0.001
GCS eye	1 (1–3)	4 (3–4)	<0.001
GCS verbal	1 (1–4)	5 (1–5)	<0.001
GCS motor	1 (1–4)	6 (4–6)	<0.001
Base deficit	14 (6–20)	5 (3–9)	<0.001
INR	1.8 (1.3–2.7)	1.4 (1.1–1.6)	<0.001
ISS	25 (18–33)	17 (10–25)	<0.001

Data presented as Median (IQR) or as percentages.
SBP, systolic blood pressure; INR, International Normalized Ratio.

0.74 (0.55–0.9), (*p* = 0.73), respectively, (Table 2). Differences in transfusion approach between the groups were the median ratio of platelets to RBCs was decreased in the WFVB compared with the CT group 0.33 (0.2–0.5) versus 0.86 (0.6–1.3), respectively, (*p* = 0.001), and the incidence of massive transfusion was increased in the WFVB group compared with the CT group, 89% versus 78%, respectively, (*p* = 0.017; Table 2). Total, actual, and anticoagulant or additive volumes were all increased in the CT compared with the WFVB group. The net median increase of anticoagulants and additives administered to the CT group was 825 mL in the first 24 hours of admission (Table 2).

Variables that were associated with 30-day survival are described in Tables 3 and 4. In addition to the typical admission vital signs and laboratory values that are associated with survival, our results indicate that the amount of WFVB, plasma: RBC ratio, and less anticoagulant and additive volume were each associated with increased survival on univariate analysis. The patient group transfused WFVB had im-

Table 4 Univariate Comparison of Blood Products, Agents and Ratios for Survivors and Nonsurvivors at 30 d

Variable	Dead (n = 50)	Alive (n = 304)	p Value
Stored RBC (U)	19 (11–24)	12 (8–19)	0.001
Plasma (U)	10 (5–16)	9 (5–14)	0.46
Apheresis platelets (U)	2 (1–4)	1 (0–3)	0.01
WFWB (U)	0 (0–0)	0 (0–3)	0.002
Cryoprecipitate (U)	0 (0–1)	0 (0–1)	0.74
Massive transfusion %	43/50 (86%)	244/304 (80%)	0.44
rFVIIa use (%)	29/50 (58%)	114/304 (38%)	0.007
Plasma:RBC	0.58 (0.4–0.89)	0.75 (0.56–0.95)	0.003
Platelet:RBC	0.69 (0.4–1.1)	0.66 (0.44–1.1)	0.92
Actual blood volume (L)	7.2 (4.8–10.7)	6.3 (4.8–9.1)	0.1
Anticoagulant/additive volume (L)	2.9 (1.7–3.9)	2.2 (1.4–3.2)	0.03

Data presented as Median (IQR) or as percentages. rFVIIa, Recombinant Factor VIIa.

Table 5 Comparison of Survival Outcomes and Adverse Events Between Study Groups

Variable	WFWB (n = 100)	CT (n = 254)	p Value
24 h survival	96/100 (96%)	223/254 (88%)	0.018
30 d survival	95/100 (95%)	209/254 (82%)	0.002
Deep vein thrombosis	15/100 (15%)	21/254 (8%)	0.06
Pulmonary embolism	7/100 (7%)	11/254 (4%)	0.3
Myocardial infarction	1/100 (1%)	0 (0%)	0.28
Cerebral stroke	0 (0%)	5/254 (2%)	0.33
ARDS	7/100 (7%)	7/254 (3%)	0.08
Renal failure	8/100 (8%)	7/254 (3%)	0.04

ARDS, Acute Respiratory Distress Syndrome.

proved 24 hour, 96 of 100 (96%) versus 223 of 254 (88%), ($p = 0.018$), and 30-day survival 95 of 100 (95%) to 209 of 254 (82%), ($p = 0.002$), compared with the CT group, respectively, (Table 5). The Kaplan-Meier Curve for 30-day survival also indicates that 30-day survival was increased for patients in the WFWB group ($p = 0.002$; Fig. 1). Comparison of all adverse events recorded indicated that renal failure was more frequent in the WFWB compared with the CT group, 8% versus 3%, respectively, ($p = 0.04$). An increased incidence of deep vein thrombosis and acute respiratory distress syndrome approached significance (Table 5).

Multivariate logistic regression revealed that the group of patients transfused WFWB, (OR 12.4 [1.8–80], [$p = 0.01$]) and an increased plasma: RBC ratio (OR 11.7 [2.6–52], $p = 0.001$) were both independently associated with improved 30-day survival, (Table 6). The multivariate logistic regression analysis utilizing individual blood product amounts indicated that each unit of WFWB (OR 2.15 [1.21–3.8], [$p = 0.016$]) and plasma (OR 1.09 [1.02–1.18], [$p = 0.019$]) was independently associated with improved 30-day survival and each unit of RBCs (OR [0.91], [$p = 0.003$]) was independently associated with decreased 30-day survival.

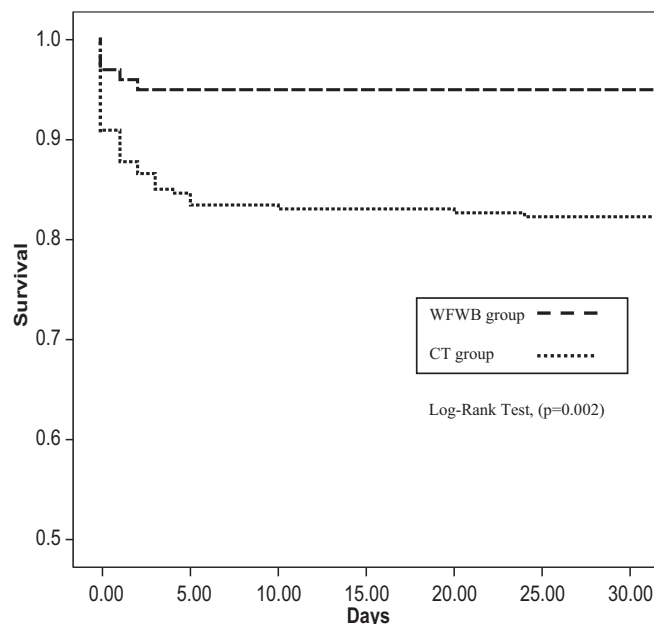


Fig. 1. Kaplan-Meier curve of 30-day survival according to study group.

Table 6 Multivariate Logistic Regression With Treatment Groups for 30-d Survival

Variables	OR (95.0% C.I.)	p Value
WFWB group	12.4 (1.8–80)	0.01
Plasma:RBC ratio	11.7 (2.6–52)	0.001
ISS	0.94 (0.91–0.97)	0.001
GCS eyes (normal)	4.1 (1.5–10.8)	0.004
Base deficit	0.88 (0.82–0.95)	<0.001

AUC (95% CI) for the logistic regression was 0.9 (0.85–0.95).

Table 7 Multivariate Logistic Regression Results With Blood Product Amount for 30-d Survival

Variables	OR (95.0% C.I.)	p Value
WFWB (U)	2.15 (1.21–3.8)	0.016
RBC (U)	0.91 (0.85–0.97)	0.003
Plasma (U)	1.09 (1.02–1.18)	0.019
Base deficit	0.91 (0.84–0.97)	0.002
GCS eyes (normal)	3.8 (1.4–10.2)	0.009
ISS	0.94 (0.91–0.98)	0.001

AUC (95% CI) for the logistic regression was 0.9 (0.86–0.95).

The amount of apheresis platelets was not independently associated with 30-day survival after adjusting for confounding variables in our best-fit model (Table 7).

To determine whether changes in capabilities of combat support hospitals over time influenced our results we measured 30-day survival for both study groups before and after December 1, 2006. Before this date survival in the WFWB and CT groups were 67 of 71 (94.4%) versus 102 of 126 (81%), respectively, ($p = 0.01$). After December 1, 2006

survival in the WFVB and CT groups were 28 of 29 (96.6%) versus 107 of 128 (83.6%), respectively, ($p = 0.08$).

DISCUSSION

This large retrospective study is unique in that it is the first to report improved 24-hour and 30-day survival for patients transfused WFVB with traumatic hemorrhagic shock when compared with patients transfused CT with similar severity of injury. A 13% increase in 30-day survival was measured with the use of WFVB in combat casualties transfused one or more units of RBCs compared with the CT group. It is also the first to indicate that the volume of WFVB transfused is independently associated with improved 30-day survival. The main difference between the groups that may have contributed to our results was that the patients in the CT group received an increased amount of anticoagulants and additives, and an increased amount of stored RBCs in the first 24 hours. In a subset analysis, our data indicates that as time progressed and capabilities improved at combat support hospitals that the relationship between improved survival and WFVB use remained and was not influenced by this factor.

Our results confirm previous studies that indicate that increased ratios of plasma to RBCs and increased volume of plasma are independently associated with improved survival in patients with acute coagulopathy of trauma.^{22,31-34} The findings in our report also compliment previously reported data that the amount of RBCs transfused is independently associated with decreased survival in critically ill patients. The potential mechanisms to explain the adverse effects with the transfusion of stored RBCs of advanced storage age have been summarized in multiple review articles.³⁵⁻³⁸ In addition, our results are the second to establish that in the same cohort opposite independent effects on survival can be measured by different blood products (RBCs were decreased compared with WFVB and plasma being increased). These results further support the claim that it is possible to adequately adjust for injury severity and obtain accurate results regarding the independent effects of individual blood products.³²

The difference in total platelet ratios compared between groups is difficult to interpret since the ratios were calculated according to the amount of platelet units in either WFVB or apheresis platelets compared with one unit of random donor platelets as is described in the methods. The fact that the function of any fresh component with its corresponding stored component is different makes any comparison of volume of that component difficult to analyze and interpret. Despite these limitations, the WFVB group of patients received a decreased ratio of PLT: RBCs, and therefore did not seem to have received a superior transfusion approach that would confound our results. According to our calculation of the total PLT: RBC ratio, patients in the WFVB group received a suboptimal transfusion strategy compared with the CT group. A recent study in patients with trauma indicates that an increased platelet to RBC ratio of above 1:2 was associated with improved 30-day survival,³¹ and an unpub-

lished report (presented at ATACCC 2008) by Perkins also indicates that patients transfused increased ratios of PLT: RBC with combat-related injuries is also independently associated with improved survival.

There are no previous reports in the literature comparing outcomes for patients transfused WFVB in any population because it is almost exclusively used in combat operations. Whole blood stored cold for less than 48 hours has been compared with CT in neonatal cardiac surgery populations with conflicting results which may be a result of methodological differences and inclusion criteria between these studies.^{39,40}

In this retrospective study from many combat support hospitals, we were not able to collect data that would allow us to precisely determine the mechanisms in which WFVB might improve survival. The patients included in our study who received more than one unit of RBCs ranged from presenting in compensated to uncompensated hemorrhagic shock according to admission vital signs and laboratory values. It is our belief that WFVB is more efficient than stored CT at correcting coagulopathy and shock in this population and also minimizes the adverse effects of the transfusion of the storage lesion of older RBCs.³⁵⁻³⁸ There are multiple previously published reports that review the mechanisms in which WFVB would improve survival compared with stored CT for patients in hemorrhagic shock. Fresh whole blood or fresh RBCs improves cardiac output, microcirculatory hemodynamics, and oxygen consumption compared with older stored whole blood or RBCs.⁴¹⁻⁴⁵ Each of these findings support improved function of RBCs when transfused fresh which improves their ability to prevent or correct shock or oxygen debt in critically ill patients. WFVB is also a more concentrated and functional product when compared with stored components reconstituted in a 1:1:1 ratio to reflect whole blood.⁴⁶ When components are reconstituted after the addition of anti-coagulants and additive solutions a cold and dilute anemic and hypocoagulable product is produced. For patients with the acute coagulopathy of trauma, WFVB transfusion may correct coagulopathy more efficiently than stored components as a result of the increased function and concentration of platelets and plasma when compared with stored components.⁴⁶⁻⁴⁸

An additional potential mechanism of the increased mortality measured in the CT group was the increased volume of anticoagulants and additives transfused to this group. The additional median 825 mL of anticoagulants and additives in the first 24 hours of admission may have increased the risk of both dilutional coagulopathy and significant anticoagulation in patients at high risk of death from hemorrhage. As future studies are designed it is important that the amount of anticoagulants and additives be measured and their clinical effects determined. With increased amounts of component products transfused the amount of anticoagulants and additives will increase and may potentially adversely affect patients in hemorrhagic shock. Based on the standard amounts

of anticoagulants listed in the "Methods" section one unit of reconstituted whole blood from one unit each of stored RBCs, plasma, and apheresis platelets will contain 279 mL of anticoagulants and additives compared with only 63 to 70 mL in one unit of whole blood. It is also interesting to note that the CT group received an increased volume of total and actual blood products in the first 24 hours despite decreased time alive during that time period. These results may have also been influenced by the increased amount of anticoagulants and additives transfused to the CT group, which potentiated bleeding and required more total and actual volume of blood products. Another perspective may be that the more concentrated and functionally efficient WFWB product reversed the acute coagulopathy of trauma better than CT, which resulted in improved survival and permitted decreased use of total blood products.

A third potential mechanism that can explain our results is that WFWB transfusion may improve outcomes in critically ill patients by minimizing the transfusion of RBCs of advanced storage age. Because of logistical constraints in Combat Support Hospitals in Iraq the median storage age of RBCs transfused is 33 days.³⁷ This is not too dissimilar to the average storage age of 21 days reported in the United States.⁴⁹ The adverse effects of the transfusion of RBCs of advanced storage age have been thoroughly reviewed and include inflammatory injury, impaired vasoregulation, and immune modulation, as well as decreased RBC deformability and increased RBC adhesion and aggregation.³⁷ These effects predominantly occur after 14 to 21 days of storage.^{36,37} Retrospective studies also indicate increased risk of sepsis, multiorgan failure, and death associated with the transfusion of RBCs of advanced storage age (Spinella, submitted).⁵⁰⁻⁵² The use of WFWB was associated with a significant decrease in the use or need to transfuse stored RBCs of advanced age, which may have contributed to the improved survival measured in this group.

The clinical effects of transfusing functional white blood cells are unknown in this population. There is the potential that the transfusion of increased amounts of WBCs may promote inflammatory injury. Transfusion-associated microchimerism (TA-MC) has been reported to be associated with the transfusion of viable white blood cells in RBC units of decreased storage age in patients with trauma.⁵³ The clinical significance of this phenomenon has not been clearly defined.⁵³ The development of transfusion-associated graft versus host disease or any other immunologic disorder has not been reported in patients with trauma as a result of TA-MC. Transfusion reactions were similar in a recent report comparing combat casualty patients transfused WFWB to those who were not.³⁷ In addition, the use of prestorage leukoreduced RBCs in patients with trauma has not been demonstrated to improve outcomes.^{54,55} Contrary to the concern that the transfusion of fresh WBCs may be detrimental, it may also be possible that the transfusion of functional WBCs from a healthy volunteer may actually improve mod-

ulation of the inflammatory system that is both overactive and underactive after traumatic injury.⁵⁶ Our results that WFWB was associated with increased incidence of renal failure and approached significance with deep vein thrombosis and acute respiratory distress syndrome could potentially be a result of increased inflammation secondary to the transfusion of large amounts of WBCs. Alternatively, because patients in the WFWB group were alive longer than in the CT group, this increased the opportunity for WFWB patients to develop these complications. These complications were also not prospectively screened for, which make the results more difficult to interpret. Lastly, this association between WFWB and renal failure was not adjusted for confounding variables. We did not perform multivariate logistic regression analysis to determine whether any of these complications were independently associated with the use or the amount of WFWB transfused. A larger data set with increased complications would be required for this analysis.

Additional risks associated with the transfusion of WFWB and apheresis platelets collected at combat hospitals are increased risk of transfusion transmitted infectious diseases. We have reported increased risk of hepatitis C and HTLV in donor samples transfused to combat casualties from over 6000 units of WFWB since 2003.²⁹ The risk of transfusion transmitted diseases (TTD's) with apheresis platelets collected at combat hospitals has not been documented but is possible since methods to formally test each platelet donor is not possible at combat hospitals. The process of screening, collecting, and transfusing WFWB in combat operations has been well described.^{18,28} Current methods used to minimize the risk of TTD's for both WFWB and field collected apheresis platelets include donor screening surveys, rapid screening tests of donated products for HIV, HCV and Hepatitis B, and pre-donation screening of potential donors (when possible) for routinely tested TTD's. In addition all US Military personnel are tested for HIV and immunized against Hepatitis B prior to deployment.

The assessment of the risks and benefits of the transfusion of both WFWB and stored CT (especially when RBCs of advanced storage age are transfused) need to be balanced with the high risk of mortality for patients with traumatic hemorrhagic shock. This balance is likely altered by the severity of injury or degree of critical illness of the patient. Storage lesion effects of RBC are less likely to have clinical effects in noncritically ill patients. In patients who do not have life-threatening bleeding or who are in shock the risks of WFWB may outweigh any potential benefits. Conversely, for patients with traumatic hemorrhagic shock it is our opinion that the survival benefits of WFWB outweigh its risks in combat settings especially when the alternative CT approach includes the use of old RBCs which have also been demonstrated to have adverse clinical effects to include and independent association with increased multiorgan failure and death in patients with trauma.^{51,52}

As a result of the potential survival benefits of WFWB, we also believe that efforts should continue to improve the safety of the volunteer whole blood donor pool which should include HIV, hepatitis B and C screening for all US Military personnel just before deployment. In addition, the development and deployment of rapid immuno-chromatographic screening tests for all other routinely tested transfusion transmitted infectious diseases is needed to diminish the risk of infection in recipients of WFWB and apheresis platelets. Risk of infectious disease transmission is present for both products because they are both collected at combat hospitals and cannot be formally tested for all transfusion transmitted diseases before transfusion. Future developments and refinements of rapid viral inactivation of blood products also has significant potential to eliminate the infectious risk of transfusing blood products and needs to be aggressively pursued.

Upon initial reflection it may seem that WFWB may not be feasible in large civilian trauma centers. With increased investment in blood bank personnel the availability of WFWB in trauma centers with adjacent blood collection centers is possible.

The recent development of infectious disease screening tests that only require 5 hours, and literature that indicates that WFWB can be maintained at room temperature for 72 hours while retaining its coagulation function improve the feasibility of WFWB availability at large civilian trauma centers.⁵⁷ Fresh whole blood stored warm up to 24 hours and fully tested for all routine infectious agents is available in this manner nationwide in Israel (U. Martinowitz, personal communication). In fact, a large randomized prospective study is about to start in the United States, which will compare survival for patients with traumatic injuries who are transfused whole blood or CT.

The limitations of our study are primarily due to its 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 WFWB, patients in this group did not exclusively receive whole blood, and we were forced to compare patients who received WFWB with RBCs and plasma to a cohort who only received CT therapy (RBCs, plasma, platelets). When the estimated volumes of each product as described in the methods are used, WFWB was approximately 30% of the total volume of the blood products transfused in the WFWB group. It would have been preferable to also include data on the amount of crystalloid and colloid fluids administered as well as individual abbreviated injury severity scores to compare between both groups, but this data were not recorded in the database. Comparison of abbreviated injury severity scores would have allowed us to determine whether anatomic injury for instance to the thorax or head was more severe in one group compared with the other. Although, total ISS and each GCS category indicated that both groups compared had equal overall anatomic severity of injury and level of consciousness on admission. Lastly, a significant limitation of our study is that we

were not able to determine the precise mechanism for improved survival with WFWB.

Strengths of this study are that it was multicenter, including patients from all seven combat support hospitals in both Iraq and Afghanistan. Also, we only included US patients, which allowed for 100% follow-up on outcomes. Most importantly the groups compared were similar in indicators of severity of injury to include admission vital signs, GCS sub-categories, laboratory values, ISS, total RBC, and actual blood volumes. The survival benefit measured was consistent for patients during early and late time periods of the study.

CONCLUSION

In patients with trauma who present with hemorrhagic shock, resuscitation strategies that include WFWB and an increased ratio of plasma: RBCs may improve 30-day survival. Prospective trials comparing the use of WFWB to the use of full CT are needed.

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