Warm Fresh Whole Blood and Thoracic Trauma in Iraq and Afghanistan

Ryan J. Keneally, Andrew M. Parsons, Peter B. Willett
Department of Anesthesiology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA

ABSTRACT

Background: Thoracic trauma occurred in 10% of the patients seen at US military treatment facilities in Iraq and Afghanistan and 52% of those patients were transfused. Among those transfused, 281 patients received warm fresh whole blood. A previous report documented improved survival with warm fresh whole blood in patients injured in combat without stratification by injury pattern. A later report described an increase in acute lung injuries after its administration. Survivorship and warm fresh whole blood have never been analyzed in a subpopulation at highest risk for lung injuries, such as patients with thoracic trauma. There may be a heterogeneous relationship between whole blood and survival based on likelihood of a concomitant pulmonary injury. In this report, the relationship between warm fresh whole blood and survivorship was analyzed among patients at highest risk for concomitant pulmonary injuries. Materials and Methods: Patients with thoracic trauma who received a transfusion were identified in the Joint Theater Trauma Registry. Gross mortality rates were compared between whole blood recipients and patients transfused with component therapy only. The association between each blood component and mortality was determined in a regression model. The overall mortality risk was compared between warm fresh whole blood recipients and non-recipients. Results: Patients transfused with warm fresh whole blood in addition to component therapy had a higher mortality rate than patients transfused only separated blood components (21.3% vs. 12.8%, P < 0.001). When controlling for covariates, transfusion of warm fresh whole blood in addition to component therapy was not associated with increased mortality risk compared with the transfusion of component therapy only (OR 1.247 [95% CI 0.760-2.048], P = 0.382). Conclusion: Patients with combat related thoracic trauma transfused with warm fresh whole blood were not at increased risk for mortality compared to those who received component therapy alone when controlling for covariates.

Key Words: Resuscitation, thoracic trauma, whole blood

INTRODUCTION

The US military has transfused warm fresh whole blood (WFWB) in forward deployed settings. The Department of Defense’s Joint Theater Trauma System (JTTS) issued a clinical practice guideline (CPG) on WFWB in 2006 that has been revised annually. The CPG states WFWB is approved for use in: “casualties who are anticipated to require massive transfusion (10 or more units pRBCs in 24 hours), for those with clinically significant shock or coagulopathy (e.g. bleeding with associated metabolic acidosis, thrombocytopenia or INR > 1.5), when optimal component therapy (e.g. apheresis platelets and FFP) are unavailable or stored component therapy is not adequately resuscitating a patient with immediately life-threatening injuries.” The CPG stated that when available, component therapy (CT) should be used preferentially due to infectious risks.

WFWB has some theoretical benefit compared with component therapy (CT). WFWB contains platelets and plasma in the normal physiologic ratio to red blood cells. Closely matched ratios have been associated with decreased mortality. These potential benefits seemed to be confirmed in a 2009 report by Spinella et al., of decreased mortality rates among patients transfused with WFWB and CT compared with CT alone.

WFWB also has some potential deleterious effects. Spinella et al., described a trend towards increased adult respiratory distress syndrome (ARDS) with WFWB (7% vs. 3%, P = 0.08). In a subsequent report by Chan, et al., WFWB was associated with a greater risk for acute lung injury (ALI) even when accounting...
for the trauma revised injury severity score (TRISS), mechanism of injury and crystalloid and plasma transfused. Chan, et al. did not, however, report increased risk for ARDS or impact upon mortality. Both Spinella et al., and Chan et al., evaluated general samples of trauma patients without the analysis of subpopulations. It seemed that despite possible overall benefit with WFWB, there might be deleterious pulmonary effects as well.

The potential deleterious effects of WFWB may have a different impact on certain subsets of the trauma population. Patients at greater risk for ALI/ARDS or at risk for greater mortality if ARDS developed may have increased mortality relative to other WFWB recipients. The subset of thoracic trauma patients was chosen for analysis as there is evidence that they are at increased risk for ALI/ARDS and this increases mortality. Patients sustaining any blunt thoracic trauma have a greater than 50% risk for a parenchymal injury, which increases risk for ALI. Patients sustaining significant thoracic trauma (abbreviated injury severity score [AIS] of the thorax ≥ 3) with or without a diagnosed pulmonary injury are at increased risk for ARDS. Patients with pulmonary trauma requiring a transfusion have increased risk for ARDS as well. ARDS increases mortality in patients with pulmonary and thoracic traumas. The authors theorized that WFWB would increase the incidence or severity of ALI/ARDS and it would lead to a detectable change in mortality compared to patients with combat related thoracic trauma (CRTT) who received CT alone.

MATERIALS AND METHODS

With approval from the Institutional Review Board of the Uniformed Services University, data was extracted from the Joint Theater Trauma Registry (JTTR). The JTTR is a database of patients seen at US military treatment facilities in Iraq and Afghanistan. Patients were identified by the International Classification of Diseases, Ninth Clinical Modification (ICD9) codes listed in Table 1 for thoracic trauma occurring from its inception in 2002 to March 2012. The dataset included US Service Members, NATO military members, non-NATO military members, and all civilians who presented for care at US medical treatment facilities. Data points collected on patients were: Other ICD 9 codes, mechanism of injury (MOI), date and location of injury, location of care, age, gender, NATO status, injury severity score (ISS), abbreviated injury scores for head and neck region (AIS HN), AIS thorax, AIS abdomen, AIS extremity, AIS skin, field intubation status, use of recombinant activated factor VII (rFVIIa), admission values for heart rate (HR), systolic blood pressure (SBP), international normalization ratio (INR), base excess (BE), hematocrit (HCT), arterial pH, arterial oxygen saturation, respiratory rate, Glasgow coma score (total and components), totals of crystalloids administered, packed red blood cells (pRBC), fresh frozen plasma (FFP), apheresis platelets (PLT), cryoprecipitate (cryo), and whole blood transfused (WB). Each unit of PLT and 10 units of cryo were considered one unit of total blood products. ISS, AIS and dominant MOI (penetrating, blunt or other) were designated by JTTR staff for classification.

Statistics

Survivors were compared to non-survivors using Student’s t-test or the Mann-Whitney rank sum test, as appropriate. Not all patient records contained all data points and the number of patients with each respective data point is listed in Table 1. Odd ratios for mortality were determined using logistic regression analysis. All variables listed above were considered and non-significant variables were removed in a backward stepwise fashion. Variables were considered significant and included in the final regression model when \( P < 0.05 \). Initial arterial pH value < 7.2 was added to the regression model despite a lack of statistical significance \( (P = 0.06) \) due to the clinical relevance combined with near statistical significance. Two regression models were constructed. The first regression model compared the gross mortality risk between groups using all significant variables including a combined total of all blood products transfused as a single independent variable, pH and a dichotomous variable added for the administration or lack of administration of WFWB. A second regression model was constructed to determine the change in mortality per unit for each type of blood product transfused. In the model, the total numbers of each type of blood product transfused were included as separate independent variables (i.e. units of pRBC, units of FFP, units of WFWB, etc.) to compare the change in mortality risk per unit of each type.

In order to determine the need for propensity matching a regression model was constructed with the transfusion of any WFWB as the dependent variable and all other variables mentioned above as potential independent variables, which were removed in a backward stepwise fashion. Only patient records with complete data points were used in each regression analysis.

RESULTS

The JTTR contained 3937 patients with an ICD 9 code for thoracic trauma that were transfused, of which 92% were male and 61.6% were members of NATO or allied militaries. The median age was 24 years old (inter quartile range [IQR] 21-30).
and patient age ranged from 1 to 77. The median total number of all units of blood transfused per patient was 10 (IQR 4-24). The mortality rate was 13.5%. There were 281 patients, who received WFWB. All patients receiving WFWB also received CT. There was a higher mortality rate among patients receiving WFWB (21.3% vs. 12.8%, P < 0.001) [Table 2]. The WFWB group received a higher median number of pRBC, FFP, PLT, cryo and total number of blood products and had a lower median pH.

To assess the association between WFWB and mortality, two regression models were constructed. Each model analyzed the same data set of only the complete records (n = 2090). The first regression model grossly compared the WFWB group and the CT group. In this model, ISS, AIS HN, BE, INR > 2, pH < 7.2, use of rFVIIa, NATO status, and the total number of all blood products transfused were selected as covariates and WFWB was added as a binary variable. In this model, each unit transfused increased mortality (OR 1.010 [1.006-1.014], P < 0.001). Transfusion of WFWB was not associated with a change in mortality (OR 1.247, 95% CI 0.760-2.048, P = 0.382).

The second regression model determined the ‘per unit change’ in mortality associated with WFWB. In this model ISS, AIS HN, BE, INR ≥ 2, pH < 7.2, use of rFVIIa, NATO status, and the total number of units of pRBCs, FFP and WFWB were used as independent variables. WFWB, FFP and pRBCs were associated each with a similar increase in mortality per unit transfused [Table 3].

Neither AIS chest ≥ 2 nor raw score of AIS chest were associated with a change in mortality when separately included in the initial regression model (OR 0.82 [0.50-1.35], P = 0.435 and OR 0.104 [0.91-1.18], P = 0.589, respectively) and neither was included in either of the final models. All regression models were also repeated using the portion of the population with AIS chest ≥ 2. The repeat regression analysis with the additional stratification did not change the results of any regression analysis. There was still no change in mortality risk with the use of any WFWB compared to component therapy alone and the change in mortality risk per unit for each unit of WFWB was not significantly different.

None of the models were formally adjusted for propensity matching. The only factor associated with the use of WFWB was the number of units of blood transfused (odds for receiving WFWB increased 1.024 per unit of blood transfused, 95% CI 1.022-1.029, P < 0.001) [Table 4]. Since this was already a variable in the regression models, no further propensity adjustment was made.

**DISCUSSION**

The CRTT patients receiving WFWB had a significantly higher mortality rate than those receiving CT alone. The groups were not exactly matched. The WFWB group had a lower median

| Table 2: Whole blood plus component therapy vs. component therapy only comparison |
|---------------------------------------------------------------|
| **Variable** | **WB (%)** | **CT (%)** | **P** |
|---------------------------------------------------------------|
| N               | 281       | 3656      | <0.001|
| Mortality rate  | 21.3      | 12.8      | <0.001|
| ISS             | 20 (13-29)| 18 (13-27)| 0.32 |
| Base Excess     | −3.00 (−7.00−1.00) | −6.00 (−7.00−1.00) | 0.57 |
| INR             | 3.00 (1.00-5.00) | 3.00 (1.20-5.00) | 0.44 |
| Hematocrit      | 35.70 (30.40-41.20) | 35.00 (30.40-41.30) | 0.66 |
| SBP             | 121 (109-136) | 123 (109-132) | 0.08 |
| HR              | 106 (88-122) | 108 (90-126) | 0.15 |
| pH              | 7.30 (7.27-7.36) [7.27] | 7.32 (7.24-7.37) [7.29] | <0.001|
| AIS HN          | 0 (0-2)   | 0 (0-2)   | 0.47  |
| pRBCs           | 14 (6-23) | 4 (2-20)  | <0.001|
| FFP             | 9 (4-20)  | 4 (1-8)   | <0.001|
| Cryo            | 1 (0-6)   | 0 (0-0)   | <0.001|
| Platelets       | 1 (0-4)   | 0 (0-1)   | <0.001|
| Total units     | 27 (17-37) | 3 (4-22)  | <0.001|
| Mortality       | 1.247 (0.750-2.048) | 0.382 |

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| Table 3: Mortality associated with blood components in combat related thoracic trauma patients |
|---------------------------------------------------------------|
| **Component** | **All transfused** | **AIS chest ≥ 2 only** |
|---------------------------------------------------------------|
|---------------------------------------------------------------|
| pRBC (per unit) | 1.050 | 1.021-1.079 | <0.001 |
| FFP (per unit)  | 1.044 | 1.015-1.074 | 0.003 |
| pPlatelets (per unit) | 0.996 | 0.910-1.013 | 0.134 |
| pCryo (per unit) | 1.030 | 0.927-1.144 | 0.581 |
| WFWB (per unit) | 1.062 | 1.019-1.106 | 0.004 |
| rFVIIa use (any) | 1.876 | 1.339-2.629 | <0.001 |
| ISS             | 1.011 | 1.002-1.020 | 0.012 |
| AIS HN          | 1.128 | 1.039-1.226 | 0.004 |
| BE              | 0.977 | 0.955-0.994 | 0.01 |
| INR2           | 1.687 | 1.25-1.928 | 0.003 |
| rFVIIa         | 1.876 | 1.339-2.629 | <0.001 |
| pH<7.2        | 1.311 | 0.99-1.75 | 0.06 |

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| Table 4: Odds for receiving WFWB |
|----------------------------------|
| **Variable** | **Odds for receiving WFWB** | **P** |
|----------------------------------|
|---------------------------------------------------------------|
|---------------------------------------------------------------|
| Total blood products (per unit) | 1.02 (1.02-1.03) | <0.001 |
| rFVIIa use                  | 1.12 (1.06-1.91) | 0.665  |
| BD                           | 1.01 (0.97-1.05) | 0.132  |
| pH <7.2                     | 1.15 (1.05-1.27) | 0.658  |
| INR 22                      | 0.45 (0.20-1.01) | 0.052  |
| AIS Head and Neck (per unit) | 0.99 (0.87-1.13) | 0.915  |
| AIS Thorax (per unit)        | 1.14 (0.95-1.37) | 0.151  |
| ISS (per unit)               | 0.99 (0.97-1.01) | 0.316  |
| NATO member                  | 1.31 (0.89-1.92) | 0.266  |
| Initial care at Level II facility | 0.75 (0.50-1.13) | 0.266  |
pH, received more blood products, and received more of each specific category of blood product than the CT group making a comparison of mortality rates difficult. The groups were compared to determine if there was a mortality risk difference between the two groups using a regression model controlling for covariates. The use WFWB was not associated with a change in mortality risk when controlling for covariates including the total number of blood products transfused. The gross comparison suggests that the difference in mortality rates between groups may have been the result of something other than the transfusion of WFWB. Additionally, the change in risk for mortality per unit of WFWB was determined as well as the risk per unit of component therapy. Each unit of WFWB transfused was associated with increased mortality risk. The change in mortality per unit of WFWB was of a similar magnitude and direction as the change associated with each unit of pRBC or FFP transfused. The lack of change in mortality risk when controlling for covariates and the similar change in mortality risk between each additional unit of WFWB, pRBC and FFP suggest that WFWB is not associated with a change in mortality compared with CT alone after CRTT.

The results suggest that the use of WFWB is not associated with a change in mortality compared with CT alone. The different mortality rates between populations may have been due to the need for larger amounts of blood or the clinical picture, which caused providers to select WFWB may have been a greater determinant of mortality. The classical markers of injury and shock may have failed to reveal a difference between groups that providers saw on a case-by-case basis. The only variable associated with WFWB administration in the CRTT data was the total number of blood products transfused. This association is logical, given the CPG approving its use when blood component supplies are exhausted. This observation supports the theory that the difference in mortality rates was related to volume of blood products transfused rather than the WFWB.

These results are in disagreement with a previous report on WFWB. Spinella et al., reported that among a sample of 354 combat related trauma patients, the 100 patients that were transfused with WFWB had lower 24 hour and 30 day mortality rates among WFWB recipients (4% vs. 12%, P = 0.018 and 5% vs. 18%, P = 0.002, respectively) and greater likelihood for survival (OR for survival 12.4, 95% CI 1.8-80, P = 0.01). Potential explanations for the discrepancy include different inclusion criteria and statistical methodology. Regarding inclusion criteria, Spinella et al.’s report analyzed a general group of combat related trauma patients and not only CRTT. Regarding statistical methodology, differences between groups limit the direct comparison of mortality rates. In the Spinella et al., report, the CT group received a larger volume transfusion than did the WFWB/CT group (9.3 L [6.2-13.3] vs. 7.4 L [5.4-10.4], P = 0.006), whereas the opposite occurred in the CRTT data. The higher survival rate in the WFWB group of the Spinella et al., report may be due to requiring nearly 2 liters less blood products and preservatives compared with the WFWB group. In the CRTT data, the higher mortality rate in the WFWB group may have been associated with receiving more blood products than the non-WFWB group. The unadjusted mortality rates are thus incomparable. The difference in adjusted mortality risk with the use of WFWB between studies may be due to differences in regression models. Spinella et al., did not include total volume of blood transfused in their model whereas the analysis of CRTT does control for total number of units of blood products. Spinella et al., also demonstrated increased survival per unit WFWB transfused (OR for survival 2.15 per unit, 95% CI 1.21-3.8, P = 0.016); whereas the CRTT data demonstrated increased mortality with each unit of WFWB. This disagreement may have also resulted from differing regression models and not considering the total resuscitation in the Spinella et al.,’s report. While these studies are not in agreement on the degree of benefit associated with the use of WFWB, they are reassuring in the implication that the “walking blood bank” is likely safe including in CRTT patients who may be at the greatest risk for ALI or ARDS after receiving WFWB. Neither study measured potential infectious risks of WB, but other reports have suggested the risk is minimal.

**LIMITATIONS**

This retrospective database analysis has several limitations. As is common in studies of this nature, the results demonstrate associations and not causality. The possible impact of ALI or ARDS in patients with CRTT receiving WFWB is unknown, as these diagnoses were not tracked. The mortality data only represent in-hospital deaths since the JTTR did not capture post discharge data. The laboratory value and vital sign data represent only admission data and not nadirs. Also, only 2090 of 3937 patients identified had complete data sets for the study variables.

**CONCLUSION**

CT and WFWB appear associated with equal mortality risk in CRTT patients. There was a higher mortality rate among patients who received WFWB but they received higher median amounts of blood. Presumably, the need for more blood was the reason for the difference in mortality. These results modulate the optimism generated by the report on WFWB by Spinella et al. They reported lower mortality rates among WFWB recipients and a decreased risk for mortality with WFWB. The results of this study and their disagreement with Spinella et al.’s report suggest that the relationship should be analyzed prospectively based on injury patterns. There may be a heterogeneity of effect from WFWB in trauma patients with different injury patterns or the earlier report may have been flawed by not including volume of resuscitation in the regression analysis. The results presented also refute the pessimistic view of WFWB generated by the Chan et al. Despite an apparent increased risk for ALI with WFWB, there may not be a mortality difference after WFWB in what should be the highest risk subset of patients. This report along with the other two retrospective studies suggests a prospective trial is indicated. The trial must
be designed to answer the following questions: First, is there a mortality difference with the use of WFWB? Second, what is the incidence of ALI/ARDS after WFWB compared with CT alone in all trauma patients? Third, is there a synergistic relationship between thoracic trauma and WFWB in causing ALI/ARDS? Fourth, if a synergism exists does it lead to a change in mortality? Answering these questions are critical. The results may support the need to develop other alternatives to WFWB. Until further study, the use of WFWB according to the CPG should be continued for patients with CRTT, as there was no evidence of harm that resulted when compared with CT.

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