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Increased Mortality in Adult Trauma Patients Transfused with Blood Components Compared with Whole Blood

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Abstract

Hemorrhage is a preventable cause of death among trauma patients, and management often includes transfusion, either whole blood or a combination of blood components (packed red blood cells, platelets, fresh frozen plasma). We used the 2009 National Trauma Data Bank to evaluate the relationship between transfusion type and mortality in adult major trauma patients ($n = 1745$). Logistic regression analysis identified three independent predictors of mortality: Injury Severity Score, emergency transfer time, and type of blood transfusion, whole blood or components. Transfusion of whole blood was associated with reduced mortality; thus, may provide superior survival outcomes in this population.

Keywords

blood transfusion; trauma; hemorrhage; mortality

INTRODUCTION

Trauma is the leading cause of death for individuals aged 1–44 years.¹ Exsanguination is the primary cause of preventable death;^{2–5} traumatic hemorrhage accounts for 35% of pre-hospital deaths, and more than 40% of deaths that occur within the first 24 hours after injury.⁵ Transfusion of whole blood or blood components is the primary means of managing hemorrhagic shock that results from traumatic injury, in conjunction with effective control of bleeding. Yet, there is a lack of evidence to support the most appropriate type of trauma resuscitation transfusion, whole blood or blood components, which includes packed red blood cells (PRBCs), platelets (PLTs), and fresh frozen plasma (FFP).

Approximately 5 million individuals receive blood or component transfusions in the United States each year, with nearly 24 million units transfused annually.^{6,7} An average transfusion of PRBCs requires approximately three pints of donated blood, and a single trauma patient may require up to 100 units of PRBCs during resuscitation.⁶ In 2011, whole blood transfusions accounted for only 0.15% of total transfusions; thus, blood components are the

primary choice for transfusion.⁸ In addition, 10.2% of all PRBC transfusions and 4.4% of all PLT transfusions were used by the Trauma/Emergency Department (ED) services.⁸ The average cost of a unit of PRBCs was \$225.42 and a unit of apheresis PLTs was \$535.17.⁸ Thus, transfusion consumes increasingly scarce financial resources and requires the continuing generosity of millions of donors annually.

An association between blood transfusion and greater mortality has been previously reported.^{9,10} Kapan and colleagues found that in patients who required damage control surgery for trauma, transfusion volume was an independent predictor of mortality; those who died received 3 more units of blood than those who survived, in spite of similar injury severity score (ISS).¹¹ Cripps and colleagues found that in trauma patients who required activation of the massive transfusion protocol, those who died received 8 more units of PRBCs, and the ratio of PRBCs to FFP was also significantly greater (1.47/1.94).¹² However, those who died had a significantly higher admission ISS and a lower Glasgow coma score; thus, those who died were more severely injured. In a recent review of trauma transfusion practices over 6 years, Kutcher and colleagues identified a decrease in the volume of crystalloids infused, in conjunction with an attempt to emulate whole blood, using the combination of PRBCs, FFP and platelet infusion; each reduction of 0.1 in the ratio of PRBC/FFP was associated with a 6% reduction in mortality.¹³ Thus, there is evidence to support the importance of not only the volume of transfusion, but also the type of blood transfused in trauma patient outcomes.

Researchers recently suggested that the transition from transfusion of whole blood to blood components during trauma resuscitation occurred without sufficient evidence to support this ubiquitous change in practice.¹⁴ The transition to component transfusion occurred as longer storage times were achieved, and was intended to enhance the efficient use of a scarce resource, blood. Spinella and colleagues advocated for the use of whole blood transfusion after observing that transfusion of warm, fresh whole blood for treatment of hemorrhagic shock was associated with improved survival at both 24 hours (whole blood - 96%, components - 88%, $p = 0.018$) and 30 days (whole blood - 95% components - 82%, $p = 0.002$), when compared to those transfused with multiple blood components.¹⁵ Improved survival with whole blood transfusion was attributed to lack of anticoagulants and additives that are inherent to stored blood components.¹⁵ Similarly, Nessen and colleagues found that infusion of fresh whole blood was an independent predictor of survival in those injured in combat (~ 90% reduction in likelihood of mortality), when compared with those who received multiple blood components, in spite of higher ISS, and lower admission blood pressure and core body temperature.¹⁶

Although management of hemorrhage focuses on control of blood loss and replacement of circulating volume, best practices related to transfusion have yet to be established. Thus, the aim of this study was to examine the association of type of blood transfusion, whole blood or blood components, with mortality in adult major trauma patients. We hypothesized that those who received whole blood would have a decreased likelihood of mortality compared to those who were transfused a combination of blood components in the management of their hemorrhage after trauma.

METHODS

We performed a secondary data analysis of the 2009 National Trauma Data Bank (NTDB) data set.¹⁷ Five hundred sixty-seven facilities from across the United States voluntarily submitted data from all trauma patient admissions in 2009 to form the database (n = 627,664).¹⁸ All data were de-identified prior to distribution of the data set.

Sample

We included those patients who were aged 18-45 years, had ISS greater than 25 indicating critical injury, were admitted to the hospital after care in the ED, and who received blood transfusion, either whole blood or blood components, as part of their emergency care. Patients were excluded from the analyses when they were dead on arrival to the emergency department, or were discharged to home after ED care and not admitted to the hospital.

Measures

Sociodemographic Variables—Sociodemographic variables included in the analyses were age, gender, and ethnicity. Due to small numbers of minorities in the database, ethnicity was classified as Caucasian or other. Older age (≥ 55 years of age) is a risk factor for mortality in trauma victims because of pre-existing comorbidities, and decreased physiological response to injury.¹⁹ Thus, we excluded those over age 45 years of age. We controlled gender in our analyses, as there is evidence to support gender differences in trauma survival and recovery, although this issue continues to be debated.²⁰⁻²⁴

Injury Severity—The ISS is a measure of trauma severity.²⁵ Scores are based on the extent of physiologic damage in the three most severely injured areas of the body (head/neck, face, chest, abdominal/pelvic, extremities/pelvic girdle, external) using the Abbreviated Injury Scale.²⁵ These scores are then squared and summed to achieve the ISS. Totals for the ISS range from zero to 75, with higher scores indicating more severe injury. A typical cutpoint used in the literature to identify more severely injured patients is an ISS of 15 or greater, with a score of 25 indicating a critical state of injury.²⁶⁻³⁰ The NTDB reports three versions of the ISS: the raw score reported by the hospital attending physicians, the score calculated in the database from the reported AIS scores, and the score that is calculated from International Classification of Diseases, Ninth Revision (ICD-9) codes.³¹

For this analysis, the ISS calculated from the ICD-9 codes was used as this was deemed the most valid for comparison purposes. The ISS is positively, although not linearly, correlated to mortality. Although higher ISS scores translate to higher likelihood of mortality for the trauma patient, given the scoring system of the ISS based on AIS scores, it is possible to have greater mortality rates for lower ISS scores (i.e. higher mortality for patients with an ISS of 16 versus 17) due to the physiologic location of the injury.^{25,32} The ISS has equivocal evidence to support the reliability and validity^{33,34} of the measure, and there are few evaluations of the psychometric properties. However, this measure continues to be widely used in trauma practice, and it is an accepted standard for injury severity measurement.^{32,35}

Emergency Medical System (EMS) Transfer Time—EMS transfer time was defined as the time from dispatch of emergency medical services to the time the patient arrived at the ED measured in minutes. We controlled the EMS transfer time because there is evidence that prolonged time to definitive treatment is associated with greater blood loss, hypothermia, and acidosis, thereby increasing risk for mortality.³⁶

Transfer from Another Facility—Patients were dichotomized into those admitted directly to the ED from EMS transfer and those transferred to a trauma center ED from another clinical facility. We controlled for this variables, as this may produce delay in definitive treatment.³⁷

Blood Product Administration—Blood products were categorized as administration of PRBCs and PLTs in combination, or whole blood transfusion (WBT). Data were not available for transfusion of fresh frozen plasma; thus, this component was not included in this analysis.

Mortality—Mortality was defined as death during the hospital stay for trauma, and was determined and reported by the attending physician.

Statistical Analyses

Sample characteristics were analyzed using descriptive statistics, independent t-tests and χ^2 as appropriate to describe the entire sample, and to compare those receiving blood components (PRBCs, PLTs, PRBCs/PLTs) with those who received whole blood, respectively. We used logistic regression to test the hypothesis that those transfused with whole blood would have a decreased likelihood of mortality compared to patients transfused with blood components after controlling for age, gender, and ISS. Demographic variables age, gender, and ISS were entered into the first regression block; EMS transfer time and transfer of the patient from another facility were entered into the second block. The blood product transfusion type, whole blood or components, was entered into the third block. An alpha level of 0.05 was set a priori to determine significance, and all analyses were performed using PASW, release 20.0 (SPSS, Inc., Chicago, IL).

RESULTS

Characteristics of the Participants

Participants (n = 1745) included in this analysis were primarily male (72%), Caucasians (63%), aged 29 ± 8 years with an Injury Severity Score of 35 ± 13 indicating critical injury (Table 1).²⁶⁻²⁹ Heart rate (HR) and systolic blood pressure (SBP) were available from both the EMS and emergency department records. Participants had a mean EMS HR of 99 ± 26 and a mean emergency department HR of 101 ± 26 . Mean EMS SBP for the sample was 122 ± 28 , with a mean emergency department SBP of 127 ± 30 . The average EMS transfer time for these patients was 19 ± 16 minutes, with a median time of 14 minutes. Only 21% of patients were transferred from another facility. Twenty-six percent of these patients died during hospitalization for their traumatic injuries. Ninety-five percent of participants

received blood components (n = 1,662); only 5% received whole blood (n = 83); this demonstrated the ubiquitous nature of component transfusion.

Those receiving whole blood and those receiving blood components were compared with independent t-tests or χ^2 analyses based on the level of measurement (Table 1). Patients who received whole blood were 2 years younger than those who received components (whole blood - 27 ± 8 years, components - 29 ± 8 years, $p = 0.01$), and the proportion of females who received blood components was significantly greater than the proportion who received whole blood (components - 29%, whole blood - 17%, $p = 0.02$). While a statistically significant difference in mean SBP was detected among the transfusion groups when measured in the emergency department, this difference was not clinically significant (whole blood - 112 ± 29 mmHg, components - 120 ± 32 mmHg, $p = 0.036$). There were no other differences between the groups.

Mortality Predictors

We used logistic regression to determine independent predictors of mortality (Table 2). The model fit was evaluated using the Omnibus Tests of Model Coefficients and the Hosmer-Lemeshow test; these analyses determined that we identified a significant model ($p < 0.001$) with acceptable model fit ($p = 0.318$), respectively. Data were entered into the regression in blocks to control potential confounding variables and evaluate their relationship to mortality.

The regression revealed three independent predictors of mortality: the ISS, EMS transfer time and type of transfusion, whole blood or components (Table 2). With each one-unit increase in ISS, patients were 14% more likely to die (OR 1.014, 95% CI 1.005 – 1.024, $p = 0.004$), and for each minute increase in EMS time, patients experienced a 1.2% decrease in likelihood of mortality (OR 0.987, 95% CI 0.975 – 0.999, $p = 0.035$). After controlling for age, gender, EMS transfer time and transfer from another facility, those patients who were transfused with blood components were 3.2 times more likely to die when compared with those who received whole blood (OR 3.164, 95% CI 1.314 – 7.618, $p = 0.010$). Thus, our hypothesis was supported by the analysis.

DISCUSSION

We found that in this large sample of adult trauma patients, the type of transfusion, whole blood or blood component, was an independent predictor of mortality; those patients who received blood component transfusion were 3 times more likely to die when compared with those who received whole blood transfusion, even though ISS was identical. Other independent predictors of mortality were the ISS and the EMS transfer time. Mortality risk increased 14% for each one unit increase in ISS, and decreased by 1% for each additional minute of EMS transfer time.

Similar to our finding, other investigators have found that transfusion of whole blood produced superior survival compared to component transfusion. Combat patients who received whole blood had twice the likelihood of 30-day survival compared to those receiving blood components (OR 2.15, 95% CI 1.21-3.8, $p = 0.016$). Seghatchian and Samama concluded that fresh whole blood was superior to stored component transfusion

with a 1:1:1 ratio (PRBCs:FFP:PLTs) in the prevention of coagulopathy in trauma patients, and Makley and colleagues found that transfusion of whole blood averted an inflammatory response produced by crystalloid resuscitation in animals after trauma.^{38,39} In contrast, Ho and Leonard found no difference in 30-day mortality in patients who received whole blood compared with components for massive transfusion, defined as ≥ 10 units; however, only one fourth of these patients were treated for traumatic injuries, patients were older than ours (mean age 52 ± 20 years), and diagnoses included gastrointestinal bleeding, cardiothoracic surgery and other types of surgery.⁴⁰ Thus, preexisting comorbidities may have produced a confounding effect on mortality.

There is evidence that the age of blood components may have a significant effect on survival after transfusion. Current blood bank practices include the rotation of older PRBCs to trauma centers with high patient volume to reduce waste, as these centers are more likely to transfuse these components before they reach expiration and must be discarded.⁴¹ Although the storage life of PRBCs is 42 days, there are predictable and identifiable morphological, biochemical, and functional alterations that occur and produce a “storage lesion”; the older the age of stored components, the greater the changes.

Morphological alterations found with storage lesion include change from the normal smooth, deformable disc-shape erythrocytes that easily bend to flow through the microcirculation, to a spherocytocyte, a sphere-shaped cell with protrusions, which is rigid and more likely to adhere to the endothelium of the microcirculation.^{42,43} Release of submicron-sized fragments of the cellular membrane and hemoglobin, known as microparticles, is also a component of the storage lesion.⁴⁴ These microparticles stimulate inflammation, have procoagulant activity, and contain hemoglobin, which is a scavenger of nitric oxide, an endothelium-derived relaxing factor.

Biochemical alterations found with the storage lesion are associated with continued cellular metabolism after donation, and include reduction in 2,3 diphosphoglycerate (2,3 DPG),⁴⁵ which is important in the release of oxygen from the hemoglobin molecule, decreased cellular pH,⁴⁶ increased lactate⁴⁶ and intracellular potassium,⁴⁷ increased release of ubiquitin, an immune modulating protein,⁴⁸ and collection of lipids, cytokines and free iron released from hemolyzed cells.⁴⁶ The global consequences of the storage lesion after transfusion are rapid destruction of spherocytocytes, reduced microcirculatory blood flow, altered coagulation, reduction in tissue oxygen delivery, ineffective endothelial vasoregulation,⁴⁵ impaired immune response, and systemic inflammation.

There are also significant differences in 24-hour survival of erythrocytes after transfusion; packed cells stored for 25-35 days demonstrated double the degree of hemolysis when compared with those stored for less than 10 days (11% versus 22%, $p = 0.05$).⁴⁹ Unfortunately, we were unable to determine whether the storage lesion in the infused PRBCs was an independent predictor of mortality, as age of the transfused products was not available in the data set. This is an important focus for continued research.

We also found that the ISS was an independent predictor of mortality. This is not surprising, and provides additional evidence for the construct validity of the ISS. Numerous other

investigators have also found the ISS to be a predictor not only for mortality, but also adverse outcomes and complications in the trauma population.⁵⁰⁻⁵⁶ Dutton, Lefering, and Lynn found higher ISS to be predictive of both an increased risk for transfusion and an increased volume of transfused blood or blood components.⁵⁷ Similar findings were reported in a systematic review performed, indicating injury severity as an important predictor of the need for transfusion in the trauma population.⁵⁸ As those included in our analysis had the statistically same ISS, the need for transfusion should have been statistically equivalent based on this evidence.

The third independent predictor of mortality was the EMS transfer time with each additional minute of transfer time associated with a 1% decrease in mortality likelihood. The impact of transport time on the likelihood of mortality is equivocal, with data supporting increased and decreased likelihood, as well as no impact on mortality. Longer transport times are often associated with pre-hospital interventions. Recent evidence from the Prospective Observational Multicenter Massive Transfusion (PROMMT) group identified a 16% reduction in the likelihood of mortality in trauma patients who received intravenous fluid administration⁵⁹; Bernard and colleagues found that rapid sequence intubation in the pre-hospital setting was associated with improved functional outcome in adults patients with severe traumatic brain injury.⁶⁰ Thus, pre-hospital interventions that require time have been shown to improve survival. We consider this to be a viable hypothesis for our finding.

In contrast, Gonzalez and colleagues found that longer EMS transport times were associated with higher mortality in rural trauma patients.³⁶ Johnson and colleagues identified a significant survival benefit in those trauma patients transported by private vehicle compared with EMS transport after controlling for ISS; thus, shorter transport time predicted greater likelihood of survival.⁶¹ However, McCoy and colleagues found no association between transport time and mortality in nearly 20,000 patients with blunt and penetrating trauma⁶², and The Resuscitation Outcomes Consortium Investigators also found no association between EMS activation time, on-scene, transport or total EMS time and mortality.⁶³ Thus, this variable is more complex than just the time in minutes and requires more systematic investigation, with consideration of the pre-hospital care administered.

Our study was limited in several ways. First, the NTDB dataset provided retrospective data and contains limited variables for analysis. For example, transfusion of blood components or whole blood is available as a dichotomous yes-no variable, but quantification of the units of each component or units of whole blood transfused was not available. Furthermore, while EMS and ED heart rate and systolic blood pressure were available for analysis, these variables are not supported by prior research evidence as independent predictors of transfusion requirement or as adequate indicators of hemorrhage status; thus, they were not included in the regression.^{64,65} In addition, the validity of the data could not be evaluated and the accuracy of data entry is uncertain. Errors in the database are possible because of the multiple hospitals, institutions, and data entry personnel who contributed to the database. We studied only a subset of younger patients in our analyses; thus, older patients may have different responses.

CONCLUSION

We found that transfusion of whole blood rather than blood components produced superior survival in adult trauma patients from the NTDB. The inclusion of a geographically diverse sample increases the generalizability of our findings. The current practice of ubiquitous component administration in the trauma population requires further study to ensure that optimal trauma outcomes are achieved in those who receive transfusion. Our findings also support the construct validity of the ISS, a common instrument, used in clinical practice and research to quantify severity of injury. Unfortunately, our transport time finding adds to the ambiguity about mortality and pre-hospital care, and demonstrates the need for further systematic evaluation of this complex issue.

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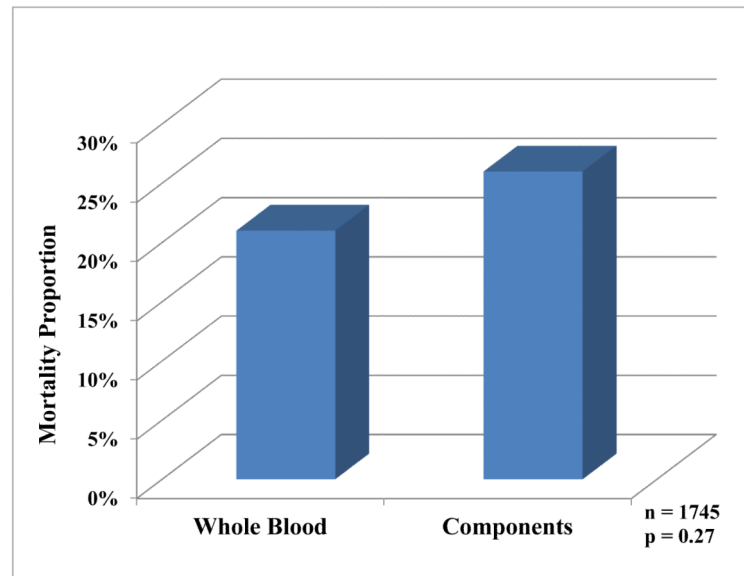


Figure 1. Patient Mortality by Transfusion Type
Proportions compared with Chi Square analysis

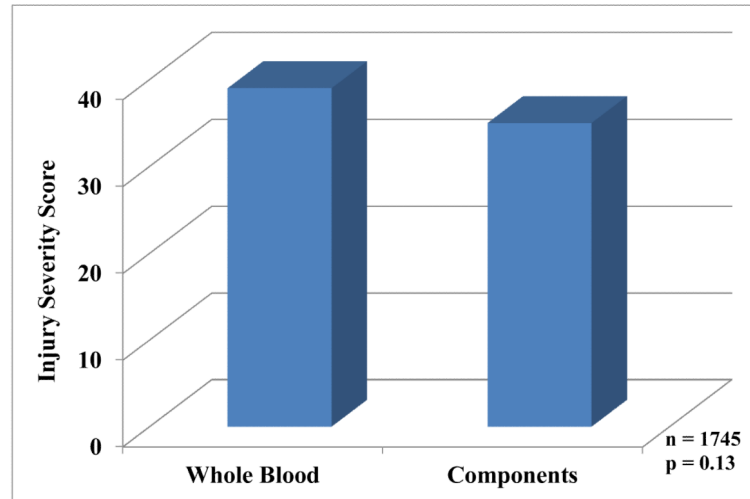


Figure 2. Mean Injury Severity Score by Transfusion Type
Scores compared using independent t tests

Table 1

Characteristics of the Participants (n = 1745)

Variable	Total Sample n = 1745	Whole blood n = 83	Blood components n = 1662	P value
Age in years	29 ± 8	27 ± 8	29 ± 8	0.01
Gender Male	1253 (72%)	69 (83%)	1184 (71%)	0.02
Ethnicity Caucasian	1105 (63%)	47 (57%)	1058 (64%)	0.20
Heart Rate (bpm)*				
EMS**	99 ± 26	98 ± 30	103 ± 27	0.23
Emergency Dept.	101 ± 26	105 ± 24	107 ± 29	0.67
Systolic Blood Pressure (mmHg)***				
EMS	122 ± 28	115 ± 31	114 ± 30	0.79
Emergency Dept.	127 ± 30	112 ± 29	120 ± 32	0.04
Injury Severity Score	35 ± 13	39 ± 17	35 ± 13	0.13
EMS Transfer Time in minutes	19 ± 16	15 ± 11	19 ± 16	0.15
Transferred from Other Facility (Yes)	367 (21%)	15 (18%)	352 (21%)	0.50
Mortality	446 (26%)	17 (21%)	429 (26%)	0.27

Values are mean ± standard deviation or frequency (proportion)

Groups compared using independent t tests for continuous variables and Chi square or Fishers Exact test for categorical variables

* Beats per minute

** Emergency Medical Services

*** Millimeters of mercury

Table 2

Independent Predictors of Mortality In Adult Trauma Patients (n = 1745)

Variable (Reference group)	β	Exp β	95% CI	P value
Age	-.009	.991	.975 – 1.008	0.32
Gender (Female)	-.274	.760	.554 – 1.044	0.09
Injury Severity Score	.014	1.014	1.005 – 1.024	0.004
EMS* Time	-.013	.987	.975 – 0.999	0.035
Transfer (No)	-.124	.883	.569 – 1.370	0.58
Blood Product (Whole)	1.152	3.164	1.314 – 7.618	0.01

Logistic regression analysis

For categorical variables, reference group in parentheses

* Emergency Medical Services