Transfusion of red blood cells in patients with a prehospital Glasgow Coma Scale score of 8 or less and no evidence of shock is associated with worse outcomes

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BACKGROUND: Red blood cell transfusion practices vary, and the optimal hemoglobin for patients with traumatic brain injury has not been established.

METHODS: A retrospective review of data collected prospectively as part of a randomized, controlled trial involving emergency medical service agencies within the Resuscitation Outcomes Consortium was conducted. In patients with a Glasgow Coma Scale (GCS) score of 8 or less without evidence of shock (defined by a systolic blood pressure [SBP] < 70 or SBP of 70 to 90 with a heart rate ≥108), the association of red blood cell transfusion with 28-day survival, adult respiratory distress syndrome–free survival, Multiple Organ Dysfunction Score (MODs), and 6-month Extended Glasgow Outcome Scale (GOSE) score was modeled using multivariable logistic regression with robust SEs adjusting for age, sex, injury severity (Injury Severity Score [ISS]), initial GCS score, initial SBP, highest field heart rate, penetrating injury, fluid use, study site, and hemoglobin (Hgb) level.

RESULTS: A total of 1,158 patients had a mean age of 40, 76% were male, and 98% experienced blunt trauma. The initial mean GCS score was 5, and the initial mean SBP was 134. The mean head Abbreviated Injury Scale (AIS) score was 3.5. A categorical interaction of red blood cell transfusion stratified by initial Hgb showed that when the first Hgb was greater than 10 g/dL, volume of packed red blood cell was associated with a decreased 28-day survival (odds ratio, 0.83; 95% confidence interval [CI], 0.74–0.93; $p < 0.01$) and decreased adult respiratory distress syndrome–free survival (odds ratio, 0.82; 95% CI, 0.74–0.92; $p < 0.01$). When the initial Hgb was greater than 10, each unit of blood transfused increased the MODs by 0.45 (coefficient 95% CI, 0.19–0.70; $p < 0.01$).

CONCLUSION: In patients with a suspected traumatic brain injury and no evidence of shock, transfusion of red blood cells was associated with worse outcomes when the initial Hgb was greater than 10. (*J Trauma Acute Care Surg*. 2013;75: 8–14. Copyright © 2013 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level III.

KEY WORDS: Traumatic brain injury; transfusion; resuscitation.

An estimated 1.4 million people experience traumatic brain injuries (TBIs) each year in the United States, accounting for 50,000 deaths and leaving 80,000 to 90,000 patients with permanent disabilities.[1] It is well recognized that the primary injury to the brain occurs at the time of impact and that the focus of treatment for TBI is to prevent secondary injury. This is accomplished primarily by maintaining cerebral perfusion and reducing intracranial pressure.[2] The optimal resuscitation strategy to improve perfusion in patients with severe TBI has yet to be elucidated. Red blood cell transfusions are common in the management of severe TBI and have been estimated to occur in approximately 50% of TBI patients.[3] The principle goal of red blood cell (RBC) transfusion in the management of TBI is to maximize brain tissue oxygenation and thereby minimize secondary injury. However, recent clinical studies continue to demonstrate the deleterious effects of blood transfusion in severely injured patients.[4–6]

Current guidelines from the *Advanced Trauma Life Support (ATLS) Manual* advocate for early use of blood transfusion in patients with evidence of hemorrhagic shock.[7] The transfusion of blood products in patients with severe TBI without evidence of hemorrhagic shock however is outside the scope of the *ATLS Manual*. Brain Trauma Foundation guidelines for the management of patients with severe TBI also do not address the use of RBCs or other blood products for resuscitation in the absence of shock.[8]

Recently, a multicenter randomized controlled trial was completed to evaluate the early use of hypertonic fluids to restore cerebral perfusion and to reduce cerebral edema.

Importantly, this trial focused on patients with a prehospital Glasgow Coma Scale (GCS) score of less than or equal to 8 without hemodynamic compromise consistent with hemorrhagic shock. While this trial did not demonstrate superior 6-month neurologic outcomes or survival with the use of hypertonic fluids compared with normal saline, it represents the largest prospective randomized clinical trial involving prehospital and early resuscitation of patients with suspected severe TBI in the absence of hemorrhagic shock.[9] We sought to identify the association between RBC transfusion and outcomes using this patient cohort. We hypothesized that RBC transfusion would be associated with worse clinical outcomes.

PATIENTS AND METHODS

We performed a retrospective review of data collected prospectively as part of a multicenter, double-blind, randomized, controlled trial. The study was conducted by the Resuscitation Outcomes Consortium (ROC), a multicenter clinical trial network including 11 regional clinical centers in the United States and Canada. The trial involved 114 emergency medical services agencies within the catchment area served by the ROC. This three-group trial compared a 250-mL bolus of 7.5% saline (hypertonic saline) versus 7.5% saline per 6% dextran 70 (hypertonic saline/dextran) versus 0.9% saline (normal saline) as the initial resuscitation fluid administered to injured patients with suspected severe TBI in the out-of-hospital setting.[9]

Patient Population

Patients were included in the TBI cohort of the trial based on the following: blunt mechanism of injury, 15 years or older, and a prehospital GCS score of 8 or less without evidence of hemorrhagic shock. Hemorrhagic shock was defined by a prehospital systolic blood pressure (SBP) of 70 mm Hg or less or of 71 mm Hg to 90 mm Hg with a concomitant heart rate (HR) of 108 beats per minute or greater. Exclusion criteria included known or suspected pregnancy, younger than 15 years, out-of-hospital cardiopulmonary resuscitation, administration of more than 2,000 mL of crystalloid or any amount of colloid or blood products before enrollment, severe hypothermia (<28°C), drowning, asphyxia caused by hanging, burns involving more than 20% of total body surface area, isolated penetrating head injury, inability to obtain intravenous access, more than 4 hours between receipt of dispatch call to study intervention, prisoner

status, and interfacility transfer. For this analysis, we excluded those subjects who died in the field or were dead on arrival to the emergency department (ED) and those who were missing key covariates.

Clinical Data Collection

Detailed prehospital and hospital data were prospectively collected through Day 28 on all patients enrolled in the trial. Injury severity was determined using the Injury Severity Score (ISS) based on the Abbreviated Injury Score (AIS) 98.[10] The primary exposure of interest was the number of units of packed RBCs (pRBCs) transfused in the 24 hours following initial 911 call.

Outcome Measures

The primary outcome for this analysis was 28-day survival. Secondary outcomes included 24-hour survival, adult respiratory distress syndrome (ARDS)–free survival through 28 days, Multiple Organ Dysfunction score (MODs), and neurologic status 6 months after injury based on the Extended Glasgow Outcome Scale (GOSE) score.[11] The GOSE score was dichotomized to good outcome (moderate disability or good recovery), which was defined as GOSE score of greater than 4 versus poor outcome (severe disability, vegetative state, or dead) GOSE score of 4 or less. The definition for ARDS was based on the report of the American-European consensus conference on ARDS.[12] The Marshall criteria for the diagnosis of MODs was subject to patients having the required physiologic measurements available during their intensive care unit stay.[13]

Data Analysis

To evaluate the association of RBC transfusion with dichotomous outcomes, multivariable logistic regression with robust SEs was used, adjusting for age, sex, ISS, missing ISS, initial GCS score, initial SBP, highest field HR, penetrating injury, parent study intervention, fluid use, and study site. In addition, sensitivity models that also included initial hemoglobin and looked at categorical classification of volume of pRBC were performed. Data are presented as odds ratio (OR) with 95% confidence intervals (CIs). With the use of the same covariates, the association of RBC transfusion with the MODs was modeled using linear regression with robust SEs.

The 6-month GOSE scores were missing in 13% of subjects who survived to hospital discharge. To minimize the risk of bias from these missing data, this outcome was analyzed using multiple hot deck imputations, as was performed in the primary results paper.[9,14] The imputation model was based on data from all TBI patients discharged alive from the hospital, using either 1-month or discharge GOSE score, length of hospitalization, and treatment arm. Twenty imputations were used in the analysis. SAS software version 9.3 (SAS Institute Inc., Cary, NC) was used for the statistical analysis.

RESULTS

Of the 1,282 patients enrolled in the ROC interventional trial, 1,186 patients were included in this analysis. Patients declared dead in the field (n = 4) or on arrival to the ED (n = 3) and those missing 28-day vital status (n = 75) or other key covariates (n = 14) were excluded from the analysis. The majority of the analysis cohort were young (average age, 39.4 years), male (75.8%), and sustained a blunt mechanism of injury (98.5%). Patient and injury characteristics are outlined in Table 1.

Admission physiology and initial laboratory values are included in Table 2. The mean SBP on admission was approximately 140 mm Hg, with a mean HR of 98 beats per minute. Mean initial international normalized ratio was 1.3, partial thromboplastin time was 31.6, and platelet count was 234. The mean volume of fluid transfused in the prehospital setting was 0.9 L (range, 0.03–5.65 L). In the first 24 hours after arrival to the ED, the mean volume of fluid administered was 6.2 L (range, 0–42 L), and 333 (28%) received pRBC transfusions. Of those who received pRBCs, the mean (SD) number of units was 5.2 (6.1).

The results of the multivariable logistic regression are given in Table 3. Death occurred within 24 hours of ED admittance in 157 subjects (13%), and 302 (26%) died within 28 days. The OR for 28-day survival and 24-hour survival decreased significantly as patient age increased. Sex was not statistically significant in predicting 28-day survival. As the ISS increased, there was a decrease in the odds of both 28-day and 24-hour survival. Furthermore, increasing GCS score was associated with increases in both 28-day and 24-hour survival.

Neither volume of prehospital crystalloid received nor the type of fluid used was statistically significantly associated with mortality. An increase in volume of blood transfused was associated with significant decreases in both 28-day and 24-hour survival. Sensitivity models using categorical classification of RBC gave consistent results. Likewise, there was

TABLE 1. Demographic, Injury Severity, and Out-of-Hospital Care Characteristics

Patient Characteristics	n = 1,186
Age, mean (SD), y	39.4 (18.7)
Sex	
Male, n (%)	899 (75.8)
Female, n (%)	287 (24.2)
Mechanism of injury	
Blunt injury, n (%)	1,168 (98.5)
Penetrating injury, n (%)	21 (1.8)
Initial vital signs	
Initial SBP,[1] mean (SD)	134.2 (31.9)
Initial SBP not detectable, n (%)	11 (0.9)
Initial respiratory rate, mean (SD)	16.8 (7.9)
Initial GCS score, mean (SD)	5.2 (2.6)
Highest field HR, mean (SD)	104.9 (25.5)
ISS	
ISS, mean (SD)	27.0 (15.6)
Head AIS score, mean (SD)	3.5 (1.8)
Face AIS score, mean (SD)	0.7 (1.0)
Chest AIS score, mean (SD)	1.6 (1.8)
Abdomen AIS score, mean (SD)	0.7 (1.2)
Extremity AIS score, mean (SD)	1.0 (1.3)
External AIS score, mean (SD)	0.7 (0.6)

TABLE 2. Admission Physiology and Laboratory Values

Physiology and Laboratory Values	
Vital signs	
SBP, mean (SD)	139.3 (32.8)
Admission HR, mean (SD)	98.0 (25.1)
First temperature, mean (SD)	35.9 (1.3)
Arterial blood gas	
pH, mean (SD)	7.3 (0.1)
Pco_2, mean (SD)	43.1 (11.2)
Pao_2, mean (SD)	261.7 (154.2)
Lactate, mean (SD)	3.6 (2.6)
Coagulation studies	
International normalized ratio, mean (SD)	1.3 (0.8)
Partial thromboplastin time, mean (SD)	31.6 (22.5)
Platelet count, mean (SD)	233.6 (72.9)
Fibrinogen, mean (SD)	215.4 (100.5)

a decreased 28-day survival with increasing volume of fresh frozen plasma (FFP) administration. Volume of platelet transfusion had no significant effect on mortality.

Results of the multivariable logistic regression evaluating ARDS-free survival are shown in Table 4. ARDS was noted in 79 patients (7%) before Day 28, 14 of whom also died before 28 days. Increasing age, higher ISS, and decreasing GCS score were associated with decreased ARDS-free survival. The volume of crystalloid administered was not associated with a change in ARDS-free survival. However, the volume of FFP transfused was associated with a statistically significant decrease in ARDS-free survival. Volume of pRBCs transfused did not affect ARDS-free survival.

A categorical interaction of RBC transfusion stratified by the initial ED hemoglobin level is shown in Table 5. When the initial hemoglobin is greater than 10 g/dL, transfusion was associated with a decrease in 28-day survival, ARDS-free survival and the 6-month GOSE score. This association was not seen when the hemoglobin was 10 g/dL or less. A test for an interaction between initial hemoglobin and the effect of RBC transfusion was statistically significant for the 28-day survival and ARDS-free survival end points ($p < 0.01$), but not 6-month GOSE score ($p = 0.41$).

Table 6 represents a linear regression to evaluate the effects of RBC transfusion on the MODs. This shows that for each unit of pRBC transfused, the MODs is increased by an

TABLE 3. Multivariable Logistic Regression Evaluating 24-Hour and 28-Day Survival

	24-h Survival		28-d Survival	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, y		<0.01		<0.01
<20	Reference		Reference	
20–39	0.66 (0.24–1.78)		0.48 (0.21–1.11)	
40–60	0.38 (0.14–1.02)		0.32 (0.14–0.74)	
61–75	0.18 (0.06–0.51)		0.18 (0.07–0.45)	
>75	0.06 (0.02–0.16)		0.04 (0.01–0.11)	
Male	0.57 (0.33–0.97)	0.04	0.94 (0.61–1.43)	0.77
ISS	0.97 (0.95–0.98)	<0.01	0.96 (0.95–0.97)	<0.01
ISS missing	0.07 (0.02–0.21)	<0.01	0.09 (0.03,0.25)	<0.01
Initial GCS score	1.42 (1.25–1.61)	<0.01	1.42 (1.27–1.58)	<0.01
Initial SBP		0.29		<0.01
≤110	Reference		Reference	
111–150	1.03 (0.60–1.77)		0.86 (0.55–1.36)	
>150	0.72 (0.40–1.27)		0.30 (0.18–0.50)	
Highest field HR		0.03		<0.01
≤90	Reference		Reference	
91–110	1.26 (0.72–2.21)		2.85 (1.78–4.57)	
>110	0.61 (0.37–1.01)		1.53 (1.02–2.32)	
Penetrating injury	0.33 (0.10–1.12)	0.07	0.20 (0.08–0.51)	<0.01
Study arm		0.59		0.69
Normal saline	Reference		Reference	
Hypertonic saline + dextran	1.06 (0.61–1.84)		1.13 (0.74–1.73)	
Hypertonic saline	1.29 (0.78–2.14)		1.19 (0.79–1.81)	
First ED hemoglobin, g/dL	1.24 (1.11–1.39)	<0.01	1.17 (1.07–1.28)	<0.01
Prehospital crystalloid, L	1.22 (0.85–1.77)	0.28	0.99 (0.74–1.32)	0.93
ED/hospital crystalloid, 0–24 h, L	1.12 (1.02–1.23)	0.02	1.05 (0.98–1.11)	0.17
RBC, 0–24 h, U	0.89 (0.79–0.99)	0.03	0.92 (0.85–1.00)	0.04
FFP, 0–24 h, U	0.95 (0.84–1.08)	0.44	0.88 (0.79–0.99)	0.04
Platelets, 0–24 h, U	1.46 (0.85–2.51)	0.17	1.00 (0.82–1.23)	0.97

TABLE 4. Multivariable Logistic Regression Evaluating ARDS-Free Survival

ARDS-Free Survival	OR (95% CI)	*p*
Age, y		<0.01
<20	Reference	
20–39	0.38 (0.18–0.78)	
40–60	0.21 (0.10–0.45)	
61–75	0.15 (0.07–0.36)	
>75	0.04 (0.01–0.10)	
Male	0.83 (0.55–1.23)	0.35
ISS	0.95 (0.94–0.96)	<0.01
ISS missing	0.05 (0.02–0.14)	<0.01
Initial GCS	1.32 (1.21–1.44)	<0.01
Initial SBP		<0.01
≤110	Reference	
111–150	1.15 (0.76–1.73)	
>150	0.47 (0.30–0.75)	
Highest field HR		<0.01
≤90	Reference	
91–110	2.66 (1.74–4.08)	
>110	1.45 (0.99–2.13)	
Penetrating injury	0.24 (0.10–0.58)	<0.01
Study arm		0.61
Normal saline	Reference	
Hypertonic saline + dextran	1.11 (0.75–1.65)	
Hypertonic saline	1.22 (0.82–1.81)	
First ED hemoglobin, g/dL	1.15 (1.05–1.25)	<0.01
Prehospital crystalloid, L	1.09 (0.83–1.45)	0.53
ED/hospital crystalloid, 0–24 h, L	1.02 (0.96–1.07)	0.58
RBC, 0–24 h, U	0.93 (0.86–1.01)	0.10
FFP, 0–24 h, U	0.87 (0.78–0.96)	<0.01
Platelets, 0–24 h, U	1.07 (0.89–1.28)	0.49

estimated 0.45 in the highest initial hemoglobin group. Again, the test for interaction between initial hemoglobin and the effect of RBC transfusion was significant ($p < 0.01$).

DISCUSSION

The goal of transfusion in patients with severe TBI is to maximize brain tissue oxygenation and thereby minimize secondary injury. Anemia has been recognized as a contributor to secondary injury and has been associated with increased mortality and poor neurologic outcomes.[15–17] While the definition of anemia in clinical studies varies, one of the first studies in 1978 by Miller et al.[15] defined anemia as a hematocrit level less than 30 and demonstrated an association of anemia with increased mortality in patients with TBI. Recently, the potential benefits of RBC transfusion have been questioned as blood transfusion in trauma patients has been shown to be associated with increased infection,[18,19] multiorgan failure,[6] and death.[4,20] While multiple studies have demonstrated an increase in brain tissue oxygenation with transfusion of pRBCs, this response can be variable with 21% to 46% of patients actually experiencing a decrease in brain tissue oxygenation.[21,22] Furthermore, this increase in tissue oxygenation is transient and returns to baseline by 24 hours.[22] Transfusion of older blood has also been shown to decrease brain tissue oxygenation.[23] A thorough review by Sena et al.[3] outlines the arguments for and against a liberal transfusion strategy in the setting of TBI. Currently, however, there is no consensus as to what the optimum hemoglobin level should be after TBI or what clinical indications should trigger the need for transfusion.[24] In a survey of physicians at US trauma centers, transfusion practices vary widely among neurosurgeons, trauma surgeons, and nonsurgeon intensivists.[25]

TABLE 6. Adjusted Association of RBC Transfusion with MODs

	MODs	
Initial Hemoglobin	Coefficient (95% CI)	*p*
		<0.01
<7	−0.05 (−0.51 to 0.42)	
7–10	−0.07 (−0.28 to 0.14)	
>10	0.45 (0.19 to 0.70)	

The study "Out-of-hospital hypertonic resuscitation following severe TBI: a randomized controlled trial" represents the largest randomized clinical trial of prehospital hypertonic resuscitation following severe TBI.[9] Importantly, this trial focused on patients with severe TBI in the absence of hemorrhagic shock. In our retrospective study of those patients, volume of RBCs transfused was independently associated with a statistically significant decrease in both 24-hour and 28-day survival. In a sensitivity analysis, we stratified the patients by initial ED hemoglobin and found that in patients with an initial hemoglobin level of 10 or higher, transfusion of RBCs in the first 24 hours of their hospital stay was associated with a decreased 28-day survival, a decreased ARDS-free survival, and worse 6-month neurologic outcome based on the GOSE score. Furthermore, for each unit of RBC transfused, the MODs was increased by 0.45 in those with an initial hemoglobin of 10 g/dL or higher. Therefore, our data suggest that transfusion of RBCs in this patient population leads to worse outcomes.

We identified several limitations to this study. The first is use of the prehospital GCS score as a marker of severe TBI.

TABLE 5. Adjusted Association of Red Cell Transfusion and Outcomes by Initial Hgb Level

Initial Hemoglobin	28-d Survival		ARDS-Free Survival		6-mo GOSE Score > 4	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
		<0.01		<0.01		0.41
<7	0.95 (0.78–1.16)		0.98 (0.79–1.22)		0.88 (0.57–1.34)	
7–10	0.99 (0.91–1.09)		1.00 (0.92–1.09)		0.92 (0.84–1.02)	
>10	0.83 (0.74–0.93)		0.82 (0.74–0.92)		0.82 (0.71–0.94)	

While our intention is to evaluate the effect of RBC transfusion on patients with severe TBI, prehospital GCS score does not accurately predict the presence of TBI.[26] Of the 1,282 patients enrolled in the controlled trial, 375 (29%) were found to not have an anatomic finding of TBI based on a Marshall score of 1 on the initial head computed tomography.[9] Second, we were unable to elucidate what triggered the decision for transfusion in these patients. We were limited to an initial hemoglobin level and cannot be certain of the hemoglobin level at the time of transfusion. Blood transfusion could be a marker of developing hypotension or delayed hemorrhage and therefore be selective for a group with worse outcomes regardless of fluid management. Furthermore, we were unable to identify which patients may have been on anticoagulation, which may have been a confounding factor for patients receiving FFP. Lastly, as noted in the initial study, TBI management in the hospital was not controlled and varied based on the preferences of the providers.

In summary, transfusion of RBCs in patients with a prehospital GCS score of 8 or less and no evidence of hemorrhagic shock was associated with a decreased 24-hour and 28-day survival. Furthermore, if the initial hemoglobin was greater than 10, transfusion of RBCs was associated with worse outcomes, including decreased ARDS-free survival, decreased 6-month neurologic outcome, and increased multiorgan dysfunction. Minimizing RBC transfusion in this patient population may improve survival. Further research is required to define the optimal hemoglobin and optimal fluid resuscitation strategy for patients with severe TBI in the absence of hemorrhagic shock.

AUTHORSHIP

J.E., S.B., M.A.S. designed the study. The ROC contributed to the data collection. S.B., J.E., M.A.S. contributed to the statistical analysis and interpretation. All authors contributed to preparation of the manuscript and final revision.

DISCLOSURE

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EDITORIAL CRITIQUE

The Resuscitation Outcomes Consortium (ROC) has provided an intriguing prospective cohort study based on the largest RCT examining hypertonic saline resuscitation post-TBI (Bulger EM, et. al. Out-of-hospital hypertonic resuscitation following severe traumatic brain injury: a randomized controlled trial. *JAMA*, 2010, *304*(13), 1455–1464).

In this study examining subjects without shock, it is striking that 333 subjects were transfused, which represents a rate of nearly 30%, and if they were transfused, they received a mean of 5 units of pRBCs. This confounder is dissectible among the 11 ROC centers, where on average a 30-subject review per site, could answer why this occurred.

Given this is a cohort study not limited by the original RCT enrollment criteria, misclassification errors, or intention-to-treat analysis, there should be caution regarding the chosen population for this analysis. It would have been reasonable to exclude the 21 penetrating injuries that could have an adverse effect on transfusion and survival, especially if those penetrating injuries were also head injuries. Also, as the investigators discuss, we know from the mTBI research that lack of intracranial hemorrhage does not mean lack of TBI, but the original RCT quantified the Marshall head CT classification for every subject. So, it is unclear why this covariate was not included to balance the analysis, or why the Marshall head CT Class I patients (no intracranial hemorrhage) were not eliminated. For reference, there were 375 subjects with a Marshall Class I CT classification in the original RCT.

The ROC investigators should be congratulated for using valuable RCT data in efforts to identify the association between red cell transfusion and outcomes after severe TBI, defined using the Glasgow Coma Scale surrogate. The heterogeneity of TBI severity continues to limit our advances in neurotrauma care. Future prospective work examining our neurotrauma practices continues to be essential.

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