Whole Blood Resuscitation and Association with Survival in Injured Patients with an Elevated Probability of Mortality

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BACKGROUND: Low-titer group O whole blood (LTOWB) resuscitation is becoming common in both military and civilian settings and may represent the ideal resuscitation intervention. We sought to characterize the safety and efficacy of LTOWB resuscitation relative to blood component resuscitation.

STUDY DESIGN: A prospective, multicenter, observational cohort study was performed using 7 trauma centers. Injured patients at risk of massive transfusion who required both blood transfusion and hemorrhage control procedures were enrolled. The primary outcome was 4-hour mortality. Secondary outcomes included 24-hour and 28-day mortality, achievement of hemostasis, death from exsanguination, and the incidence of unexpected survivors.

RESULTS: A total of 1,051 patients in hemorrhagic shock met all enrollment criteria. The cohort was severely injured with >70% of patients requiring massive transfusion. After propensity adjustment, no significant 4-hour mortality difference across LTOWB and component patients was found (relative risk [RR] 0.90, 95% CI 0.59 to 1.39, p = 0.64). Similarly, no adjusted mortality differences were demonstrated at 24 hours or 28 days for the enrolled cohort. When patients with an elevated prehospital probability of mortality were analyzed, LTOWB resuscitation was independently associated with a 48% lower risk of 4-hour mortality (relative risk [RR] 0.52, 95% CI 0.32 to 0.87, p = 0.01) and a 30% lower risk of 28-day mortality (RR 0.70, 95% CI 0.51 to 0.96, p = 0.03).

CONCLUSIONS: Early LTOWB resuscitation is safe but not independently associated with survival for the overall enrolled population. When patients were selected with an elevated probability of mortality based on prehospital injury characteristics, LTOWB was independently associated with a lower risk of mortality starting at 4 hours after arrival through 28 days after injury. (J Am Coll Surg 2023;237:206–219.

Members of the SWAT study group who coauthored this article are listed in the Appendix.

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Abbreviations and Acronyms

COMPONENT	=	blood component resuscitation
ISS	=	Injury Severity Score
LTOWB	=	low-titer group O whole blood
RR	=	relative risk
TBI	=	traumatic brain injury

Hemorrhage remains the leading cause of potentially preventable death after injury.[1,2] Despite major improvements in trauma resuscitation during the past 2 decades, patients continue to suffer high mortality due to uncontrolled hemorrhage in the first few hours after arrival.[1,3,4] Interventions that provide outcome benefits that can be initiated early after injury have the potential to reduce morbidity and mortality and are essential to improving the care of the severely injured patient.[5-7]

Low-titer group O whole blood (LTOWB) resuscitation is increasingly common in both military and civilian settings and may represent the ideal early resuscitation intervention after injury. Recent studies demonstrate the safety of uncrossmatched LTOWB.[6,8-11] Although early LTOWB resuscitation has increasingly been shown to be associated with improved outcomes, current high-level prospective, multicenter evidence supporting its pragmatic use is limited, specifically in the polytrauma patient with shock and concomitant traumatic brain injury (TBI).[8,9,12] It may be in these complex injured patients where the character of early resuscitation matters most and where outcome benefits may be most evident.[13-18]

We sought to characterize the safety and efficacy of LTOWB in patients with hemorrhagic shock with and without concomitant TBI treated with early LTOWB resuscitation relative to patients who receive blood component resuscitation (COMPONENT) as their standard care. We hypothesized that LTOWB resuscitation would be associated with both survival and improved hemostasis.

METHODS

A prospective, multicenter, observational cohort study, with a planned enrollment time period of 3.5 years, was performed using 7 busy, level 1, trauma centers participating in the Linking Investigations in Trauma and Emergency Services (LITES, https://www.litesnetwork.org) clinical trials network. The cohort study was conducted and reported in accordance with the STROBE guidelines for observational studies.[19] Ethical approval for the study was obtained using single IRB approval from the University of Pittsburgh and the Human Research Protection Office of the Department of Defense. The single IRB approved a waiver/alteration of the consent process and waiver of Health Insurance Portability and Accountability Act authorization spanning 36 hours.

Participating trauma centers were originally surveyed for the use of cold stored LTOWB in the early phase of injury as part of their standard care for patients in hemorrhagic shock. At study initiation, three of the original 7 participating trauma centers had existing early, in-hospital, cold-stored LTOWB resuscitation programs employed in their emergency department/trauma bay setting. Characteristics of each LTOWB program, including leukoreduction, titer levels used, and specific indications for LTOWB transfusion (eg childbearing age status), were at the discretion of each site's local resuscitation protocol. A single LTOWB trauma center site also had the capability to provide LTOWB during the prehospital phase of care. The remaining COMPONENT sites used ratio-based blood component resuscitation strategies for hemorrhagic shock and similarly followed their respective local resuscitation protocols. Inclusion criteria for the cohort study were injured patients at risk of massive transfusion who met Assessment of Blood Consumption criteria[20,21] (two or more of the following): hypotension (systolic blood pressure ≤ 90 mmHg); penetrating mechanism of injury; positive Focused Assessment for the Sonography of Trauma examination; heart rate ≥ 120; and who within 60 minutes of arrival required both blood/blood component transfusion and hemorrhage control procedures in the operating room or interventional radiology suite. Patients with qualifying vital signs and/or blood product transfusion that occurred in the prehospital phase of care also met inclusion criteria. A Focused Assessment for the Sonography of Trauma examination that was deferred due to the expedient transport to the operating

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room was considered as meeting one of the Assessment of Blood Consumption criteria.[20] The presence of TBI for the study was designated by positive CT scan brain imaging after enrollment criteria were met. Exclusion criteria included age less than 15 years, penetrating brain injury, >5 minutes of consecutive CPR, death before initiation of transfer to the operating room/interventional radiology for hemorrhage control procedures, known prisoners, and known pregnancy.

Data were collected via a research electronic data capture (REDCap) online data repository for all participating sites, and all analyses were performed using SAS version 9.4. Measures included patient demographics, injury characteristics, prehospital and in-hospital vital signs, resuscitation interventions, transfusion volume totals, mortality outcomes, and laboratory assessments. Additional outcomes, including Rotterdam CT scores were collected for the TBI subgroup.[22,23]

The primary objectives of the study were to compare patient-level outcomes across early LTOWB and COMPONENT resuscitation groups. A LTOWB patient had to have received at least a single unit of LTOWB during the prehospital or early in-hospital phase of care. COMPONENT patients received only component blood products during their early resuscitation. Transfusion volume of any resuscitation type was based on patient need and the local site-specific transfusion practice. The prespecified primary outcome for the trial was 4-hour mortality. Secondary outcomes of interest included 24-hour mortality, 28-day mortality, achievement of hemostasis, adjudicated death from exsanguination/hemorrhage, and the incidence of unexpected survivors based on a prehospital probability of mortality >50% at 28 days.[17,24-26] Unexpected survivor characterization was a post hoc subgroup analysis. Laboratory assessment of coagulation status and 4-hour and 24-hour transfusion requirements were also compared. Additionally, we assessed the incidence of multiple organ dysfunction, nosocomial infection, venous thromboembolism, deep venous thrombosis, pulmonary embolus, and laboratory markers of hemolysis for verification of safety. The presence of TBI was a prespecified subgroup for mortality outcomes. Rotterdam scores[23] were determined by a single blinded neuroradiologist for all initial head CT scans and repeat head CT imaging when performed. Achievement of hemostasis was determined by reaching a nadir transfusion requirement of a single unit of whole blood or component red blood cells within a 60-minute period during the first 4 hours from arrival. Patients who did not achieve hemostasis or died within this 4-hour time frame were designated as not achieving hemostasis. Four-hour and 24-hour transfusion requirements were compared using units of product. Total transfusion volume requirements were compared by summing total volume in milliliters of transfusion across LTOWB and COMPONENT groups. The volume of each component transfused was estimated (red cell unit, 330 mL; plasma unit, 270 mL; single apheresis platelet unit, 250 mL) and the volume of a unit of LTOWB was estimated to equal to 500 mL.[9] Massive transfusion was defined as the need for at least 3 units or more of any red blood cell–containing product (COMPONENT red blood cells or LTOWB) within a 60-minute time period during the first 4 hours from arrival.[27-30] Causes of death due to exsanguination/hemorrhage were adjudicated by the enrolling site principal investigator.

All outcome models estimate a relative risk ratio by fitting a generalized linear model with a Poisson distribution, a log link function, and a robust variance adjustment.[31] For the 4-hour mortality primary outcome across COMPONENT and LTOWB patients, an adjusted relative risk ratio was estimated using an inverse probability of treatment weight derived from a generalized boosted regression where treatment was regressed on a set of prehospital patient confounders, including vital signs, interventions/procedures, and measures of injury severity. For all other adjusted outcome comparisons, relative risk ratios were estimated controlling for age, sex, mechanism of injury (blunt vs penetrating), head Abbreviated Injury Score, Injury Severity Score (ISS), prehospital systolic blood pressure, and the need for prehospital blood product transfusion. The prehospital probability of mortality was estimated using logistic regression models using all relevant prehospital vital signs, prehospital interventions/procedures, and injury severity characteristics and was assessed using receiver operating characteristic curve analysis. Data from COMPONENT patients were used to fit the model, and the results were then applied across the entire enrolled cohort. Tests of association included Student's *t*-test when continuous measures were normally distributed, Mann-Whitney U when they were skewed, and chi-square when measures were categorical.

RESULTS

Over the planned 3.5-year enrollment period, 1,051 patients in hemorrhagic shock met all inclusion criteria and no exclusion criteria and were enrolled in the prospective cohort study (42 months; March 2018 to August 2021; Fig. 1). As early whole blood resuscitation

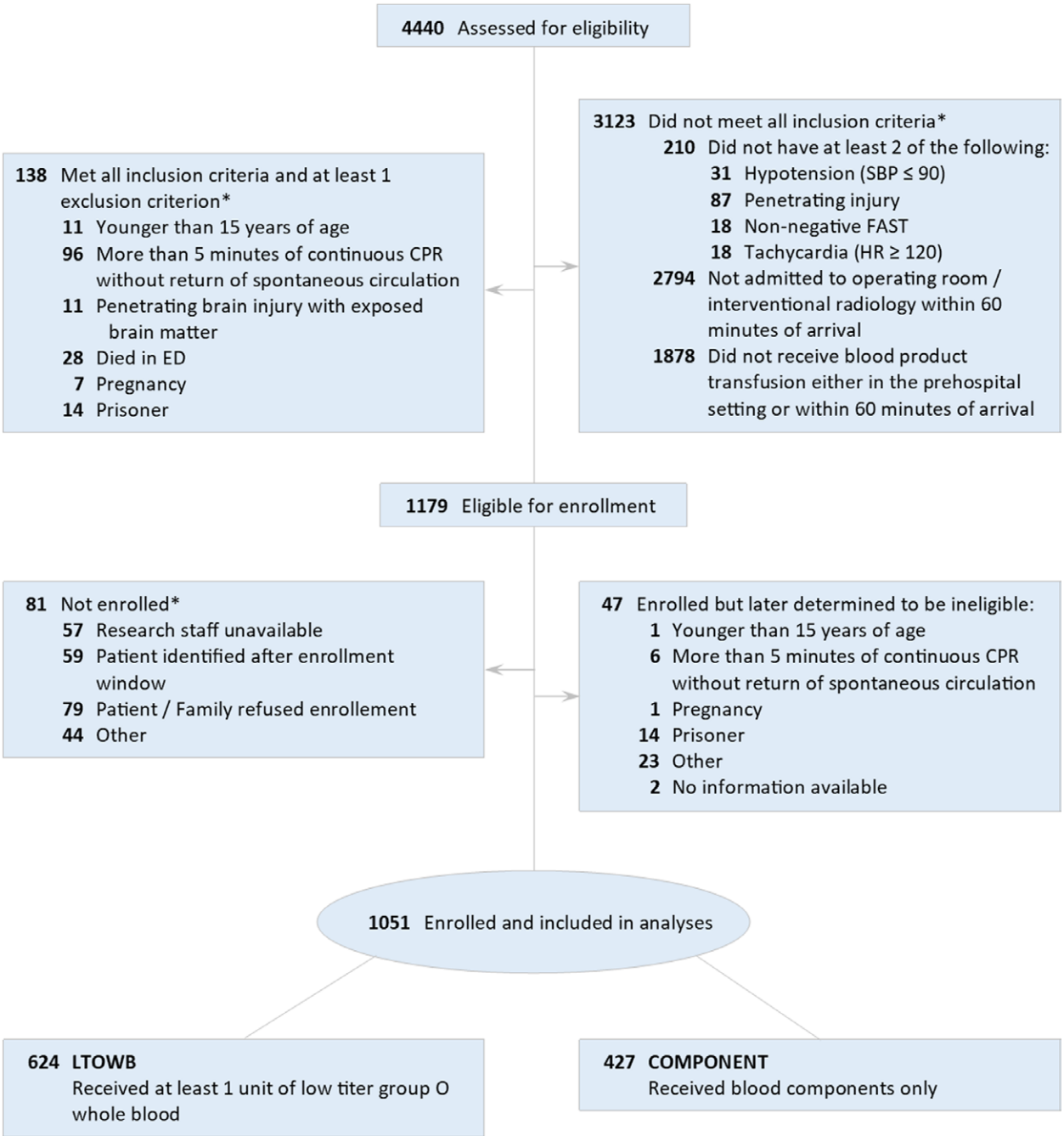

Figure 1. CONSORT diagram for enrollment. ED, emergency department; FAST, Focused Assessment with Sonography in Trauma; HR, heart rate; LTOWB, low-titer group O whole blood; SBP, systolic blood pressure.

became more accessible across the country, sites initially surveyed as COMPONENT sites initiated whole blood programs and became LTOWB-capable sites. More than 60% of patients had sustained a penetrating mechanism of injury (gunshot wound or stabbing). The enrolled study population was severely injured with a median injury ISS of 22 (interquartile range 13 to 30), and a 4-hour and a 28-day mortality rate of 8% and 17%, respectively. More than 70% of enrolled patients required massive transfusion.[28] The enrolled cohort of patients had an incidence of radiographically documented TBI of 13.3%.

The prospective observational eligibility criteria attempted to select patients in hemorrhagic shock but did not stipulate any specific blood product resuscitation regimen. Enrolled patients at their respective trauma centers followed their standard resuscitation protocols. Only 66.3% of enrolled patients at LTOWB sites received LTOWB during their resuscitation. In those patients who received LTOWB, the median number of LTOWB units transfused was 2.0 interquartile range [1.0 to 3.5]. Of the subgroup of enrolled patients with TBI, 75% of patients at LTOWB sites received LTOWB resuscitation, with a median of 2.0 interquartile range [0.0 to 4.0] of LTOWB units being transfused.

When enrolled patients were compared by the early resuscitation regimen they received (LTOWB vs COMPONENT resuscitation), LTOWB and COMPONENT patients were similar in age, mechanisms of injury, and the need for prehospital blood transfusion. LTOWB and COMPONENT patients had similar ISS scores, but LTOWB patients were more likely to have an ISS >15. LTWOB patients were more likely male, were more commonly transferred from the scene of injury, had lower systolic blood pressures, had lower Glasgow Coma Scale scores, and were more likely to have concomitant TBI (Table 1).

When the primary 4-hour mortality outcome was compared across LTOWB and COMPONENT patients (Table 2), unadjusted mortality rates were similar (8.2% vs 7.5%, p = 0.71) After propensity adjustment, no significant 4-hour mortality difference across LTOWB and COMPONENT patients was found (RR 0.90, 95% CI 0.59 to 1.39, p = 0.64). Similarly, when 4-hour mortality was compared across the TBI subgroup, no significant mortality differences were found. When 24-hour mortality and 28-day mortality were compared, no unadjusted or adjusted mortality differences were demonstrated for the overall cohort or the TBI subgroup (Table 2).

When serial Rotterdam scores derived from head CT imaging of TBI patients were compared across LTOWB and COMPONENT patients, no significant differences were found in the scores derived from the initial head CT images or when subsequent head scan images (second) were compared. When the frequency of worsening head CT Rotterdam scores was compared across the groups, no significant differences were found (Table 3). International normalized ratio/prothrombin time at 4 hours and 24 hours were compared, there were no significant differences found between groups except a significantly lower median and lower percentage of abnormal clot lysis at 30 minutes (LY30) at the 24-hour period in LTOWB patients (Table 4).

Considering 4-hour and 24-hour blood transfusion requirements compared across LTOWB and COMPONENT patients, there were no significant differences found in plasma or platelet transfusion and an expected reciprocal difference in the transfusion of LTOWB and component red blood cells (Table 4). There were no significant differences in total units of blood product transfused across comparison groups. When total transfusion volumes across the 2 groups were compared based on estimated volumes for a component and whole blood unit, the LTWOB demonstrated significantly greater volumes overall at both 4 hours and 24 hours after arrival.

When we compared the rate of massive transfusion across LTOWB and COMPONENT patients, LTOWB patients had a significantly higher rate of massive transfusion by 4 hours from admission (74.4% vs 64.8%, p < 0.01). When we compared mortality due to adjudicated death from exsanguination, there was no significant difference found between LTOWB and COMPONENT groups (8.8% vs 7.7%, p = 0.53). When we compared the rate of achieving hemostasis by 4 hours, LTOWB and COMPONENT patients were similar (82.9% vs 86.3%, p = 0.14).

When outcomes for safety were compared across LTOWB and COMPONENT groups, there were no differences found for the incidence of venous thromboembolism, multiple organ dysfunction, or nosocomial infection (Table 5). There was a significantly higher median of ICU and ventilator–free days for COMPONENT patients. When laboratory measurements for hemolysis were compared at 24 hours, no significant differences in haptoglobin or lactate dehydrogenase were seen, but LTOWB patients had elevated total bilirubin levels relative to component patients. Importantly, no hemolytic or transfusion reactions were reported in either group of the trial.

To compare the rate of unexpected survivors across the enrolled cohort, we first determined the individual patient prehospital predicted risk of 28-day mortality, using prehospital vital signs, prehospital interventions/procedures, and injury severity characteristics, and assessed its predictive capabilities via receiver operating characteristic curve analysis. Our prehospital mortality model was an excellent predictor of mortality with an Area Under the Curve = 0.89 (Fig. 2). When we selected those patients with a probability of mortality >50% and looked at the incidence of 28-day mortality across the comparison groups, the LTOWB group had a significantly lower rate of mortality than the COMPONENT group (unadjusted 39.3% vs 72.5%, p < 0.01). When we further characterized this unexpected survivor cohort, after controlling for all relevant confounders,

Table 1. Demographic and Injury Characteristics by Resuscitation Type

Measure	LTOWB (n = 624)	COMPONENT (n = 427)	p Value
Age, y, median [IQR]	35.0 [26.0–51.0]	35.0 [25.0–47.0]	0.15
Sex, m, n (%)	546 (87.5)	297 (69.6)	<0.001
Race, n (%)			0.001
White	280 (44.9)	235 (55.0)	
Black	225 (36.1)	139 (32.6)	
Other	119 (19.1)	53 (12.4)	
Injury mechanism, n (%)			
Blunt	252 (40.5)	161 (37.7)	0.36
Fall	29 (4.7)	21 (4.9)	0.85
Machinery	2 (0.3)	1 (0.2)	0.79
MVC occupant ejected	14 (2.3)	15 (3.5)	0.22
MVC occupant not ejected	93 (15.0)	63 (14.8)	0.93
MVC motorcyclist	53 (8.5)	19 (4.4)	0.010
MVC cyclist	4 (0.6)	2 (0.5)	0.71
MVC pedestrian	26 (4.2)	23 (5.4)	0.36
MVC ATV	5 (0.8)	4 (0.9)	0.82
MVC not otherwise specified	6 (1.0)	3 (0.7)	0.65
Struck by or against	14 (2.3)	8 (1.9)	0.68
Other	16 (2.6)	8 (1.9)	0.46
Penetrating	386 (62.1)	271 (63.5)	0.64
Firearm	281 (45.2)	193 (45.2)	0.99
Impalement	6 (1.0)	2 (0.5)	0.36
Stabbing	71 (11.4)	52 (12.2)	0.71
Other	31 (5.0)	26 (6.1)	0.44
Transfer origin, n (%)			<0.001
Scene	526 (84.6)	323 (75.6)	
Outside ED	96 (15.4)	104 (24.4)	
ISS, median [IQR]	22.0 [14.0–33.0]	21.0 [10.0–34.0]	0.17
>15, n (%)	444 (72.8)	281 (66.7)	0.037
Traumatic brain injury (CT diagnosed), n (%)	99 (15.9)	44 (10.3)	0.010
Head AIS, median [IQR]	0.00 [0.00–2.00]	0.00 [0.00–0.00]	0.20
>2, n (%)	133 (21.8)	76 (18.1)	0.14
Chest AIS, median [IQR]	2.00 [0.00–3.00]	2.00 [0.00–3.00]	0.032
>2, n (%)	284 (46.6)	175 (41.6)	0.11
Abdomen AIS, median [IQR]	3.00 [0.00–4.00]	3.00 [0.00–4.00]	0.28
>2, n (%)	321 (52.6)	230 (54.6)	0.53
Extremity AIS, median [IQR]	2.00 [0.00–3.00]	2.00 [0.00–3.00]	0.66
>2, n (%)	220 (36.2)	151 (35.9)	0.92
Glasgow Coma Scale, median [IQR]	14.0 [3.00–15.0]	15.0 [7.00–15.0]	0.004
<9, n (%)	208 (35.4)	109 (26.0)	0.001
Systolic blood pressure, mmHg, median [IQR]	99.0 [80.0–120]	105 [82.0–122]	0.046
<90 mmHg, n (%)	176 (35.1)	126 (32.1)	0.36
Heart rate, bpm, median [IQR]	110 [88.0–130]	108 [88.0–126]	0.29
>100 bpm, n (%)	322 (58.7)	248 (61.4)	0.39
Shock index, median [IQR]	1.06 [0.81–1.37]	1.00 [0.79–1.31]	0.10

(*Continued*)

Table 1. Continued

Measure	LTOWB (n = 624)	COMPONENT (n = 427)	p Value
Received any prehospital blood product, n (%)	225 (36.2)	138 (32.3)	0.20
Red blood cells	128 (20.6)	122 (28.6)	0.003
Plasma	36 (5.8)	32 (7.5)	0.27
Platelets	12 (1.9)	16 (3.7)	0.07
Whole blood	118 (19.0)	0 (0.0)	
Received any prehospital tranexamic acid, n (%)	35 (5.6)	15 (3.5)	0.11
Received any prehospital crystalloid, n (%)	309 (49.7)	227 (53.2)	0.27
Prehospital/ED intubation, n (%)	225 (36.1)	131 (30.7)	0.07
Prehospital/ED CPR, n (%)	47 (7.5)	29 (6.8)	0.64
Prehospital pelvic binder, n (%)	47 (7.6)	31 (7.3)	0.86

AIS, Abbreviated Injury Scale; ATV, all-terrain vehicle; COMPONENT, blood component resuscitation; ED, emergency department; IQR, interquartile range; ISS, injury severity score; LTOWB, low-titer group O whole blood; MVC, motor vehicle collision.

Table 2. Primary and Secondary Outcomes by Resuscitation Type

Outcomes	LTOWB (n = 624)	COMPONENT (n = 427)	Unadjusted			Adjusted*		
			RR	95% CI	p Value	RR	95% CI	p Value
Primary								
4-h mortality†	50 (8.2)	32 (7.5)	1.09	(0.71–1.66)	0.70	0.90	(0.59–1.39)	0.64
TBI subgroup	6 (6.4)	2 (4.5)	1.40	(0.29–6.68)	0.67	0.61	(0.14–2.70)	0.51
Secondary								
24-h mortality	82 (13.4)	49 (11.5)	1.16	(0.83–1.62)	0.37	1.08	(0.77–1.52)	0.67
TBI subgroup	19 (20.2)	6 (13.6)	1.48	(0.64–3.45)	0.36	0.89	(0.41–1.96)	0.78
28-d mortality	110 (17.9)	66 (15.5)	1.16	(0.88–1.53)	0.30	1.10	(0.83–1.47)	0.51
TBI subgroup	25 (26.6)	11 (25.0)	1.06	(0.58–1.96)	0.84	0.84	(0.45–1.56)	0.57

*Adjusted for age, sex, injury type, head Abbreviated Injury Scale score, prehospital hypotension, receiving any prehospital blood product, and Injury Severity Score.
†The adjusted model is weighted by the inverse probability of treatment (propensity score).
COMPONENT, blood component resuscitation; LTOWB, low-titer group O whole blood; RR, relative risk; TBI, traumatic brain injury.

Table 3. Rotterdam CT Score Measures by Resuscitation Type

Measure	LTOWB (n = 98)	COMPONENT (n = 42)	p Value
Rotterdam score			
First CT scan, mean ± SD	2.34 ± 0.90	2.33 ± 1.05	0.82
Second CT scan, mean ± SD*	2.78 ± 1.50	2.74 ± 1.52	0.95
Difference, mean ± SD	0.44 ± 1.05	0.40 ± 1.04	0.87
Worsening, n (%)†	21 (21.4)	13 (31.0)	0.23

*19 patients died before they could be scanned for a second time. The scores for these patients have been set to 6.
†Because 71.4% of patients experienced no change in scores, this measure distinguishes those whose score became worse compared with those whose score remained unchanged or improved (n = 1).
COMPONENT, blood component resuscitation; LTOWB, low-titer group O whole blood.

regression analysis demonstrated LTOWB patients had >35% lower independent risk of 28-day mortality (RR 0.64, 95% CI 0.45 to 0.92, p = 0.02).

To further characterize the unexpected survivor relationship, we first tested to determine if there was an interaction between prehospital predicted mortality and any LTOWB benefit. We found that the prehospital probability of mortality of an individual patient significantly moderated the survival benefit attributable to LTOWB at 28 days. Based on these findings, we further explored this relationship and plotted the proportion of deaths at 4 hours and 28 days for LTOWB and COMPONENT patients by the predicted prehospital probability of mortality (Figs. 3A, 3B). These demonstrated a separation of LTOWB and COMPONENT patients as the probability of mortality increased. We then again performed our adjusted regression analyses for 4-hour mortality, 24-hour mortality, and 28-day mortality at increasing increments of prehospital predicted mortality probabilities (Table 6). These results demonstrated that, in those patients with a prehospital predicted mortality of 5% or greater, LTOWB was independently associated with >48% lower risk of 4-hour mortality (RR 0.52, 95% CI

Table 4. Coagulation Parameters and Transfusion Requirements by Resuscitation Type

Measure	LTOWB (n = 624)	COMPONENT (n = 427)	p Value
Coagulation parameter			
Within 4 h of arrival			
International normalized ratio, median [IQR]	1.21 [1.15–1.40]	1.26 [1.16–1.40]	0.20
Prothrombin time, sec, median [IQR]	350 [244–562]	342 [228–539]	0.44
Rapid thromboelastography*			
Kinetic time, min, median [IQR]	2.00 [1.50–2.70]	1.90 [1.50–2.50]	0.14
>2.5 min, n (%)	128 (30.0)	72 (24.2)	0.09
Alpha angle, degrees, median [IQR]	69.1 [63.4–73.0]	69.7 [64.3–73.5]	0.19
<60 degrees, n (%)	72 (16.7)	41 (13.8)	0.29
Maximum amplitude, mm, median [IQR]	56.9 [51.3–61.2]	57.6 [52.4–62.1]	0.13
<55 mm, n (%)	176 (40.5)	113 (37.9)	0.49
Clot lysis at 30 min, %, median [IQR]	0.00 [0.00–0.40]	0.00 [0.00–0.30]	0.42
>3%, n (%)	8 (2.0)	8 (2.9)	0.43
Activated clotting time, sec, median [IQR]	113 [105–128]	113 [105–128]	0.69
>128 sec, n (%)	69 (18.5)	48 (17.1)	0.63
Within 24 h of arrival			
International normalized ratio, median [IQR]	1.30 [1.20–1.40]	1.31 [1.20–1.50]	0.25
Prothrombin time, sec, median [IQR]	407 [281–619]	377 [270–584]	0.25
Rapid thromboelastography*			
Kinetic time, min, median [IQR]	1.30 [1.10–1.80]	1.30 [1.10–1.60]	0.19
>2.5 min, n (%)	28 (7.3)	12 (4.4)	0.12
Alpha angle, degrees, median [IQR]	74.2 [71.1–77.0]	74.6 [71.9–76.7]	0.39
<60 degrees, n (%)	11 (2.9)	3 (1.1)	0.12
Maximum amplitude, mm, median [IQR]	63.8 [59.3–68.1]	64.1 [60.3–67.9]	0.61
<55 mm, n (%)	39 (10.1)	18 (6.6)	0.12
Clot lysis at 30 min, %, median [IQR]	0.20 [0.00–0.80]	0.20 [0.00–1.30]	0.04
>3%, n (%)	7 (1.8)	12 (4.7)	0.03
Activated clotting time, sec, median [IQR]	113 [105–128]	113 [105–128]	0.97
>128 sec, n (%)	67 (18.5)	37 (14.4)	0.18
Transfusion requirement, median [IQR]			
Within 4 h of arrival			
Red blood cells, units	4.00 [1.00–10.0]	5.00 [2.00–11.0]	<0.001
Plasma, units	3.00 [0.00–9.00]	3.00 [1.00–8.00]	0.15
Platelets, units	0.00 [0.00–2.00]	0.00 [0.00–1.00]	0.56
Whole blood, units	2.00 [1.00–3.00]	—	—
Total, units	10.0 [4.00–23.0]	9.00 [4.00–19.0]	0.12
Total, mL†	3170 [1330–6880]	2695 [1210–5780]	<0.001
Within 24 h of arrival			
Red blood cells, units	5.00 [1.00–12.0]	5.00 [2.00–13.0]	<0.001
Plasma, units	4.00 [0.00–11.0]	4.00 [1.00–9.00]	0.36
Platelets, units	1.00 [0.00–2.00]	0.00 [0.00–2.00]	0.21
Whole blood, units	2.00 [1.00–3.00]	—	—
Total, units	12.0 [4.00–27.0]	10.0 [4.00–22.0]	0.07
Total, mL†	4105 [1765–9290]	2945 [1265–6935]	<0.001

*Values are missing for n = 152 (14.5%) LTOWB patients and n = 103 (9.8%) COMPONENT patients.
†Volume for each unit of red blood cells, plasma, platelets, and whole blood was estimated to be 330, 275, 250, and 500 mL, respectively.
COMPONENT, blood component resuscitation; IQR interquartile range; LTOWB low titer group O whole blood.

Table 5. Safety Outcome Measures by Resuscitation Type

Measure	LTOWB (n = 624)	COMPONENT (n = 427)	p Value
Outcomes			
Deep vein thrombosis, n (%)	49 (7.9)	22 (5.2)	0.09
Pulmonary embolism, n (%)	38 (6.1)	26 (6.1)	>0.99
Multiple organ failure, n (%)	90 (33.7)	48 (27.4)	0.16
Nosocomial infection, n (%)	155 (24.8)	95 (22.2)	0.33
ICU-free days, median [IQR]*	21.0 [0.00–25.0]	22.0 [4.00–26.0]	0.05
Ventilator free days, median [IQR]*	24.0 [5.50–26.0]	25.0 [13.0–27.0]	<0.01
Hemolysis laboratory markers within 24 h of arrival,† median [IQR]			
Total bilirubin, mg/dL	0.95 [0.60–1.50]	0.80 [0.60–1.30]	0.03
Haptoglobin, mg/dL	70.0 [42.0–109]	67.5 [38.2–113]	0.33
Lactate dehydrogenase, U/L	407 [281–619]	377 [270–584]	0.25

*Range is 0 to 28. Patients who died before day 28 are assigned a score of 0.
†Values missing for n = 160 (15.2%) LTOWB patients and n = 130 (12.4%) COMPONENT patients.
COMPONENT, blood component resuscitation; IQR, interquartile range; LTOWB, low-titer group O whole blood.

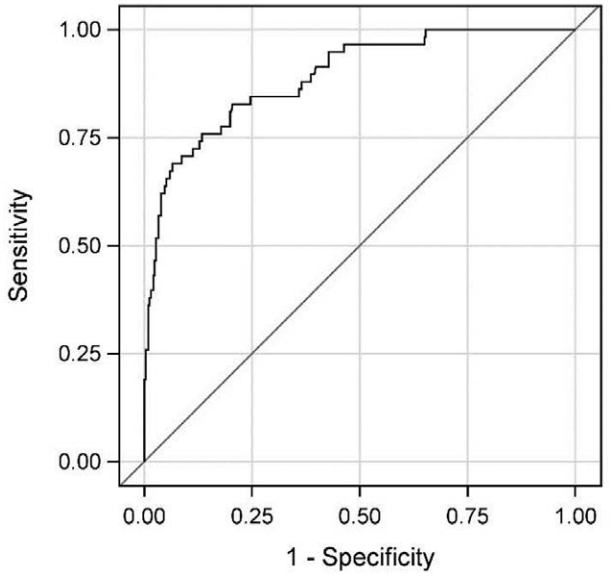

Figure 2. Receiver operating characteristic (ROC) curve for prehospital probability of mortality regression model. Area under the curve = 0.8912.

0.32 to 0.87, p = 0.01). In those patients with a prehospital predicted mortality of 10% or greater, LTOWB was independently associated with >33% lower risk of 24-hour mortality (RR 0.67, 95% CI 0.47 to 0.97, p = 0.03). In those patients with a prehospital predicted mortality of 20% or greater, LTOWB was independently associated with a 30% lower risk of 28-day mortality (RR 0.70, 95% CI 0.51 to 0.96, p = 0.03).

Finally, due to the relatively low volume of LTOWB an individual patient received, we wanted to determine if there was a dose-response relationship regarding the quantity of LTOWB that was transfused. When we included the ratio of total LTOWB transfused relative to the total component product received in 24 hours in our regression models and further adjusted for the need for massive transfusion, this ratio was an independent predictor of survival in the LTOWB group of patients at 28 days (RR 0.60, 95% CI 0.42 to 0.85, p < 0.01). This demonstrates that, as the proportion of LTOWB increases during the early resuscitation period, irrespective of large volume transfusion, the independent risk of mortality decreases.

DISCUSSION

Despite major changes regarding when and how injured patients are resuscitated during the past 2 decades, mortality from hemorrhage continues to occur within hours of arrival at definitive trauma centers across the country.[2-4] The tenets of "damage control resuscitation" improve outcomes after injury through balanced blood component resuscitation, minimization of crystalloid resuscitation, prevention of coagulopathy, and potential mitigation of downstream effects of shock and endothelial injury.[1,32,33] Whole blood resuscitation, considered the definitive damage control resuscitation blood product, has been increasingly used in the civilian setting during the past 8 years, and low-titer anti-A and anti-B group O whole blood is considered the standard care at more than 80 high-volume trauma centers across the country.[6,8,9,34,35]

The documentation of outcome benefits attributable to whole blood resuscitation have lagged behind these resuscitation practice changes, and the specific injured patient cohorts who may benefit most from whole blood

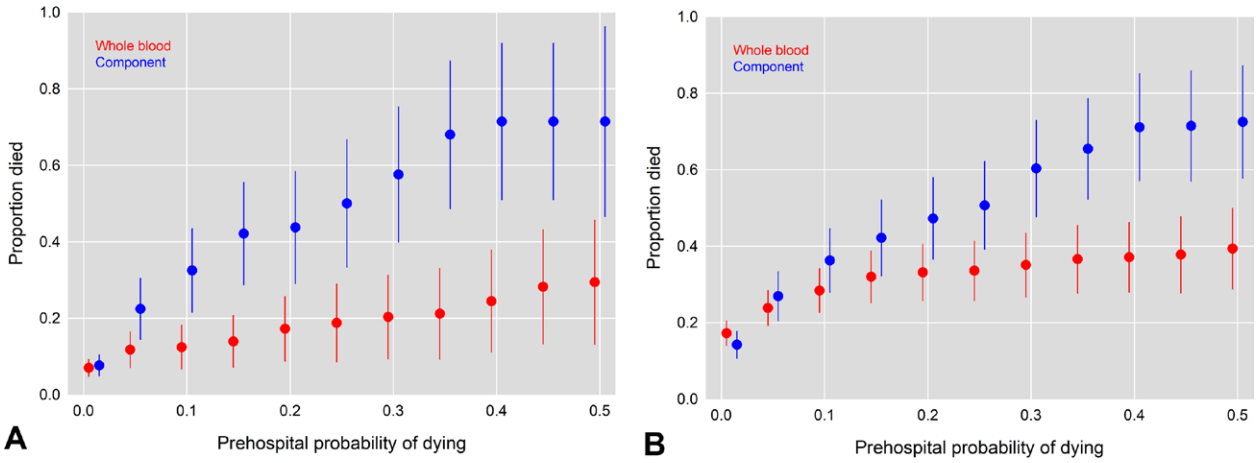

Figure 3. Proportion of 4-hour (A) and 28-day (B) deaths across low-titer group O whole blood and blood component resuscitation groups plotted against the prehospital probability of mortality.

Table 6. Mortality Outcomes by Time, Prehospital Probability of Death, and Resuscitation Type

			Model results†		
Mortality/probability*	**LTOWB**	**COMPONENT**	**RR**	**95% CI**	**p Value**
Hour 4, n/N (%)					
>0.05	24/204 (11.8)	26/116 (22.4)	0.52	(0.32–0.87)	0.01
>0.10	18/145 (12.4)	25/77 (32.5)	0.38	(0.22–0.67)	<0.01
>0.20	15/87 (17.2)	21/48 (43.8)	0.39	(0.21–0.71)	<0.01
>0.35	11/52 (21.2)	17/25 (68.0)	0.26	(0.14–0.46)	<0.001
>0.50	10/34 (29.4)	10/14 (71.4)	0.35	(0.19–0.66)	<0.01
Hour 24, n/N (%)					
>0.05	56/257 (21.8)	37/143 (25.9)	0.84	(0.59–1.20)	0.35
>0.10	49/181 (27.1)	35/87 (40.2)	0.67	(0.47–0.97)	0.03
>0.20	36/112 (32.1)	32/58 (55.2)	0.52	(0.35–0.76)	<0.01
>0.35	24/68 (35.3)	26/42 (61.9)	0.51	(0.33–0.80)	<0.01
>0.50	18/43 (41.9)	19/28 (67.9)	0.57	(0.35–0.93)	0.02
Day 28, n/N (%)					
>0.05	85/357 (23.8)	53/197 (26.9)	0.93	(0.69–1.25)	0.63
>0.10	72/254 (28.3)	50/138 (36.2)	0.80	(0.59–1.09)	0.16
>0.20	56/169 (33.1)	43/91 (47.3)	0.70	(0.51–0.96)	0.03
>0.35	45/123 (36.6)	36/55 (65.5)	0.62	(0.45–0.86)	<0.01
>0.50	35/89 (39.3)	29/40 (72.5)	0.64	(0.45–0.93)	0.017

*Prehospital probability of mortality was estimated by regressing mortality on demographics, injury type, Abbreviated Injury Scores, prehospital vital signs, prehospital medication, prehospital procedures, and receiving prehospital blood products on component-only patients. Parameter estimates were then applied to LTOWB patients for comparison.
†Adjusted for age, sex, injury type, head Abbreviated Injury Scale score, prehospital hypotension, receiving any prehospital blood product, and Injury Severity Score.
c, concordance; COMPONENT, blood component resuscitation; LTOWB low-titer group O whole blood; RR relative risk.

resuscitation are poorly characterized. The results of this prospective observational cohort study demonstrate that the LTOWB resuscitation is safe and adds important information to the growing literature on this practice. Whole blood resuscitation was not independently associated with a mortality benefit in the overall enrolled cohort or in the specific subgroup of brain-injured patients, yet a significant and robust survival advantage was afforded to patients with an elevated probability of death based on prehospital and injury characteristics. This survival advantage of LTOWB was observed for patients with a prehospital predicted mortality of 5% or greater.

The current results are similar to other recent prospective observational studies that have characterized whole

blood resuscitation by demonstrating its safety, feasibility, and survival benefits.[8,9,12] The current results differ in that survival benefit was only observed in those patients with an elevated probability of death based on prehospital characteristics. This may be due to differences in the specific inclusion and exclusion criteria used and/or the trauma centers selected for the study. Similarly, there may be injury characteristic differences of patients that are enrolled at a whole blood capable trauma center yet do not receive LTOWB resuscitation. It may be that the current cohort selected included a portion of patients where the quality or character of early resuscitation may not matter, specifically those with a low probability of death. Similar to previous studies,[8,9,12] patients who received whole blood resuscitation in the current study were more severely injured, had lower Glasgow Coma Scale scores and lower presenting systolic blood pressures and a higher rate of massive transfusion.[30] We found no major differences in coagulation parameters despite having a higher rate of massive transfusion and higher estimated total transfusion volume. We used a definition for massive transfusion that minimizes survival bias, incorporates both a rate and volume at early time points, and has been demonstrated to be associated with superior mortality prediction relative to historic definitions.[28] After appropriate and robust confounder adjustments, despite these more severe injury characteristics, unadjusted and adjusted mortality rates were similar across LTWOB and COMPONENT groups for the entire cohort.

In the subgroup of patients with an elevated risk of mortality as predicted by our regression models, it is interesting that the proportion of deaths in the COMPONENT group rise in step with increasing predicted mortality, but the LTOWB group curve plateaus and remains relatively flat, despite increasing predicted mortality. This may explain the higher incidence of multiple organ dysfunction (nonsignificant) and lower ICU and ventilator–free days in the LTOWB group because the patients who survived with high predicated mortality, who otherwise may not have, will demonstrate significant organ dysfunction and high critical care needs.[17]

It was unexpected to find a lack of outcome benefit in patients with documented TBI. Previous studies demonstrate benefit in this cohort when plasma is provided soon after injury.[13-16,18] It may be that the timing of an intervention, whether it is provided in the prehospital as compared with the in-hospital phase of care, is most relevant for the brain-injured population.[36]

The current study has limitations. First, it is an observational cohort study and patients who received LTOWB or COMPONENT early resuscitation had significant differences in injury characteristics and severity that may play a role in the results and conclusions demonstrated. The potential for unknown or unmeasured confounders exists and represents a major limitation in any observational study. The inclusion criteria did not specify the type of resuscitation (LTOWB vs COMPONENT), and during the time period of the study, whole blood resuscitation practice became increasingly common across the country. Enrolling sites had differences in resuscitation practice that may be important confounders. Multiple trauma centers used for the study who initially had only component resuscitation capabilities started whole blood programs after participation began. There may be differences in trauma centers who have recently changed their early resuscitation practice relative to those centers who have had whole blood capabilities for longer periods of time. Similarly, there may be relevant injury severity and outcome differences in a group of patients who are enrolled at a whole blood capable trauma center but do not receive LTOWB. The underlying reasons an enrolled patient at a trauma center with LTOWB capabilities did not receive LTOWB were not recorded in the dataset. The analysis focused on the specific resuscitation strategy individual patients received. There was a relatively high percentage of penetrating mechanism of injury enrolled, and, despite attempting to adjust for all important confounders, there may be differences in the response to LTOWB vs COMPONENT resuscitation based on mechanism of injury. Specific transfusion volumes of all components transfused were not able to be recorded and were estimated based on blood bank volume estimates and prior literature. Due to the observational design of the study, there was variability in resuscitation practice across LTOWB sites as in leukoreduction, titer levels, and specific indications for LTOWB transfusion (eg childbearing age status). Transfusion volumes for either group were based on patient need and site-specific transfusion practice. There was a relatively low median volume of LTOWB transfusion for the overall cohort, and attributing survival outcome differences from this strategy may be confounded. Similarly, some trauma centers had prehospital transfusion capabilities, but others did not. We controlled for this capability in our regression models but the potential for confounding remains. Importantly, ratios of blood components (red blood cell:plasma:platelet) were not protocolized for either the COMPONENT group or for the LTOWB group beyond the early resuscitation period, and this variability represents a major limitation. The laboratory measurements are associated with missingness due to the logistics of care management for severely injured patients. Although the missingness

did not differ across comparison groups, this could lead to measurement differences and represents a significant limitation.

CONCLUSIONS

In conclusion, LTOWB resuscitation was safe but not independently associated with survival benefits in the overall enrolled cohort of this observational study. When patients were selected with an elevated probability of mortality based on prehospital injury characteristics, LTOWB was independently associated with a lower risk of mortality starting at 4 hours after arrival through 28 days after injury. Further high-level, randomized clinical trials are needed to appropriately characterize the injured population that benefits most from this valuable transfusion resource.

APPENDIX

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Invited Commentary

The Use of Whole Blood in Trauma

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On my first night on call as an intern, I was told, "It's quite simple. Air goes in and out. Blood goes round and round. To keep your patient alive, just keep those 2 things happening." Well, as any intern will tell you, it is not that simple. And when it comes to the resuscitation of the injured patient in hemorrhagic shock, keeping the blood going round and round has been the focal point of much research. It seems straightforward that a patient who is losing whole blood should have whole blood put back in them. There is even historical data to support it! So, why then, are we still trying to use whole blood surrogates like component therapy, or even nonblood products like normal saline? Again, because it is not that simple.

A full history of resuscitative efforts is beyond this commentary but can be found in an excellent review by Dr McCoy and colleagues[1] that should be read in its entirety. In brief, it should be noted that whole blood has already been demonstrated to have an improved survival rate as far back as World War I, where injured soldiers who were resuscitated with blood fared better than those who were not. So why the long delay in getting back to whole blood? One unfortunate reason is Dr Carrico's publication of "Fluid resuscitation following injury: rationale for the use of balanced salt solutions"[2] which had the unintended consequence of ushering in the era of primary crystalloid resuscitation for injured patients. This was not due to a robust overall improvement of survival, but rather, a gross misinterpretation of the findings by the medical community. Indeed, their original article stated that crystalloid was to be used "while the preparation of whole blood was being completed." But the near-universal availability of crystalloid, ease of use, and an overly confident misinterpretation of the findings resulted in several decades of inappropriate resuscitation conduct.

The advancement of blood banking techniques that allowed for the separation of blood into its components also contributed to our regression from whole blood use. Using an amalgamation of these components is certainly better than saline. However, Dr Holcomb's trial showed that most patients receive transfused components in unequal distributions that do not resemble whole blood.[3]

There are also concerns regarding the storage and safety of transfusing whole blood. Despite large amounts of data suggesting it is safe, many believed there were significant risks. As a young attending, I was actively involved in the blood transfusion program for trauma patients at a center that was a component therapy site in this study. Despite the long history of trauma care at that institution, whole blood was available, just not for trauma patients. Even after the Association for the Advancement of Blood & Biotherapies stated that stored whole blood was safe, there was a significant hesitancy in its use. As I moved to a new institution with a more robust blood transfusion program that included whole blood for trauma patients, I discovered that there are still many limitations to its use.

Whole blood is a rather limited resource—part of the reason that component therapy became so popular. With so few whole blood products on hand, they can easily be depleted by a single hemorrhaging patient. As a result, many institutions limit the total volume of whole blood products that can be transfused per patient before mandating a transition to component therapy. This practice likely has a significant impact in this study.

Dr Sperry, in his continuation of large-scale clinical trials of resuscitation, has now added a prospective observational cohort study of whole blood resuscitation in injured patients.[4] However, they did not find their hypothesized survival benefit in the whole blood cohort. This is not in line with other studies suggesting improved survival with whole blood.[5,6] These findings could be disheartening to proponents of whole blood use, but on further analysis,