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Cold Whole Blood Transfusion in Civilian Trauma Patients Requiring Emergent Resuscitation: A Retrospective Cohort Study

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Abstract

Background: The use of cold Whole Blood (WB) is rapidly resurging as one of the treatment modalities of choice for the initial resuscitation of civilian trauma patients across the United States. The purpose of our study was to evaluate the effectiveness and safety of cold Whole Blood (WB) as compared to Blood Component Therapy (BCT) in resuscitation of civilian trauma patients.

Methods: This was a retrospective cohort study of trauma patients who received at least one unit of WB transfusion during emergent resuscitation between November 2015 and October 2019 at a level I trauma center. Primary outcome was mortality up to 30 days after trauma. Secondary outcomes included overall blood product utilization and incidence of transfusion reactions. Outcomes were compared between patients who received WB and a cohort receiving BCT who did not receive WB matched for age, sex, mechanism of injury, heart rate, systolic blood pressure, Glasgow Coma Scale, injury severity score, and FAST results.

Results: We included 78 patients who received WB transfusion and 78 matched controls. Within 30 days of injury, there were 19 deaths (24.4%) in the WB cohort and 28 (35.9%) deaths in controls (hazard ratio 0.62, 95% CI 0.33 to 1.15, p=0.086). Patients in the WB cohort received as many units of blood products as controls (median number of units was 10 (IQR 6, 20) vs. 12 (IQR 6, 23), p=0.43). The incidence of any transfusion reactions was similar between groups (7.7% in WB vs. 9.0% in controls, p=0.78). Life- threatening reactions did not occur in any of the groups.

Conclusion: There was no mortality difference between patients receiving cold WB and BCT. Cold WB was safe in this cohort with no life-threatening transfusion reactions.

Keywords: Trauma; Cold whole blood; Transfusion; Emergency; Resuscitation

Abbreviations: IRB: Institutional Review Board; WB: Whole Blood; BCT: Blood Component Therapy; RBC: Red Blood Cells; PLT: Platelets; ED: Emergency Department; SBP: Systolic Blood Pressure; HR: Heart Rate; FAST: Focused Assessment with Sonography in Trauma; INR: Prothrombin Time Test; GCS: Glasgow Coma Scale; ISS: Injury Severity Score; FFP: Fresh Frozen Plasma; CRYO: Cryoprecipitate; HER: Electronic Health Records; LOS: Length of Stay; ICU: Intensive Care Unit; TACO: Transfusion-Associated Circulatory Overload; TRALI: Transfusion-Related Acute Lung Injury; FNHR: Febrile Non-Hemolytic Reaction; DSTR: Delayed Serologic Transfusion Reaction; IQR: Interquartile Range; GEE: Generalized Estimating Equation

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Introduction

Hemorrhagic shock is responsible for a sizeable proportion of trauma deaths, especially within the first hours after injury [1,2]. Exsanguination and coagulopathy are among the main factors associated with mortality early after trauma [3]. For this reason, wide availability of blood for early transfusion is paramount to resuscitate trauma patients with severe hemorrhage. Back in history, cold Whole Blood (WB) used to be the only product available for resuscitation during the management of massive hemorrhagic events [4]. Whole blood provides a balanced amount of Red Blood Cells (RBCs), plasma, and Platelets (PLT) [4]. In the 1960s, blood component therapy (i.e., therapeutic use of specific portions of blood) became the predominant strategy for emergent resuscitation because storage and utilization of these products were optimized. In 1994, the American College of Surgeons considered the use of component therapy as an acceptable standard of care. However, no robust clinical evidence existed to justify the transition from WB to component therapy. This led to a generation of clinicians losing experience in transfusing WB for trauma patients [4]. Most recently, fresh WB transfusion resurged during the wars in Iraq and Afghanistan [5-7] followed by adoption in civilian medical centers across the United States [8]. Despite the resurgence of WB mostly in the military setting, safety concerns exist including a potential increased risk of ABO incompatibility during emergent resuscitation, transfusion-associated hemolysis, and the risk of Rh all immunization, especially in women of childbearing age [9-12]. Most recent studies comparing WB transfusion to blood component therapy suggest similar effectiveness and safety for emergent resuscitation of trauma patients [13]. In this observational study at a level I trauma center, we hypothesized that transfusing cold WB to severely ill trauma patients in the civilian setting would have similar effects to transfusing blood component therapy on the outcomes of mortality and clinically relevant transfusion reactions.

Materials and Methods

This manuscript adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting observational studies [14]. The protocol of this study was submitted and approved by the Mayo Clinic Institutional Review Board (IRB). All patients included in the analysis provided Minnesota research authorization for medical records review.

Study design and setting

We performed a retrospective cohort study of adult patients (age ≥ 18 years) who presented to the Emergency Department (ED) with severe trauma requiring emergent resuscitation with blood transfusion between November 1, 2015, and October 31, 2019. Our ED is part of a level I trauma center in the United States (Mayo Clinic Hospital, Saint Marys Campus-Rochester, MN) and it has a volume of approximately 1,800 adult trauma patients per year. We compared outcomes of interest between a cohort of patients who received WB and matched controls who received blood component therapy.

Selection of cohorts

All trauma patients who received at least one unit of cold WB during emergent resuscitation (started either by prehospital or in-hospital personnel) were included in the WB cohort. Exclusion criteria included patients who received WB due to reasons other than trauma, pediatric patients (age<18), prisoners, pregnant women, and those who denied authorization to use their medical records for research. During the study period, our institutional protocol suggested WB transfusion in patients for which the massive transfusion protocol has been activated. Pre-hospital and in-hospital specific institutional protocols for the administration of WB are available in supplementary figure. The massive transfusion protocol activation was meant for situations when the need of ≥ 10 units of packed RBC was anticipated within a 24-hour period. Objective criteria for such activation included ≥ 2 of the following signs of hemorrhage: Systolic Blood Pressure (SBP) ≤ 90 mm Hg, Heart Rate (HR)>120, penetrating mechanism of injury, positive Focused Assessment with Sonography in Trauma (FAST) exam, lactate>5.0 mg/dL, prothrombin time test (INR)>1.5, and known or presumed warfarin use. Despite such protocols, the decision of giving or not WB was ultimately left at the discretion of clinicians providing care to patients.

To create the control (comparison) cohort of component therapy, we first sampled patients from our trauma registry for whom the massive blood transfusion protocol was activated and for whom only blood component therapy was given. Our registry keeps track of all trauma activations in our ED. We then matched control patients who received component therapy with WB patients in a 1:1 fashion (pair-wise matching) for the following characteristics: age, sex, mechanism of injury, ED triage HR, ED triage SBP, ED triage Glasgow Coma Scale (GCS), Injury Severity Score (ISS), and FAST exam positivity. A 'greedy' matching algorithm was used [15]. These variables were chosen as being the most clinically relevant characteristics to be balanced between the WB and component therapy cohorts. Matching during the study design phase was performed as an attempt to mitigate confounders prior to estimating the effects of WB (as compared to component therapy) on the outcomes of interest.

Cold whole blood details

The cold WB resuscitation protocol implementation at our institution has been previously described [8]. Cold whole blood, non-leukocyte-reduced, is a resuscitation fluid not processed into individual components, remaining the same as when it was donated except for the addition of storage solution. The units were collected following US blood donation standards and regulations. A total number of four units of WB (two O positive and two O negative) each week were stored and maintained at 1°C to 6°C for up to 14 days. Units that were not used by day 14 were discarded. Two units of type O whole blood were available for transfusion to any patient and two additional units could have been transfused if the patient had confirmed blood type O and was deemed eligible for such units. All WB units were titrated for

anti-A and anti-B (immediate spin titer<200). Group O positive WB was transfused to adult men (age ≥ 18 years) and females older than potential child-bearing age (age ≥ 56 years). Women of potential childbearing age (age ≤ 55 years) were transfused with Group O negative units, and if subsequently confirmed to be O negative, they were deemed not eligible to receive additional O positive WB units. Whole blood was given until hemorrhage was controlled or two units were transfused (four units if the patient was blood type O and eligible for such additional units). If further blood product resuscitation was required, units of component therapy (Red Blood Cells (RBC), Platelets (PLT), Fresh Frozen Plasma (FFP) or Cryoprecipitate (CRYO)) were administered as necessary. We abstracted data from the Electronic Health Records (EHR) through individual chart review of eligible patients. The following variables were extracted using a standardized data collection form by a trained research fellow: age, sex, race, mechanism of injury (blunt or penetrating), ISS, triage GCS, triage HR, triage SBP, FAST exam results (positive or negative as documented in the EHR), laboratory results (hemoglobin, hematocrit, and platelet counts) at arrival, 6 and 24 hours after arrival, ED, Length of Stay (LOS), hospital LOS, days on ventilator (if intubated), Intensive Care Unit (ICU) LOS (if applicable), and mortality up to 30 days after injury. The ABO and Rh blood type were obtained as were all information regarding units of WB and/or component therapy that were given within 24 hours after injury. For patients who had missing FAST exam results (not documented or not performed), we imputed such results using the method described by Call cut and colleagues [16]. Documented transfusion reactions were also collected including acute and delayed reactions (definition below in Outcomes)

Outcomes

The primary outcome was mortality (measured at three different times: ED mortality, 24-hour mortality, and 30-day mortality). Secondary outcomes included incidence of transfusion reactions, need for invasive interventions (emergency surgery or interventional radiology after injury), hospital LOS, days on ventilator, ICU LOS, blood product utilization, and blood compatibility. For transfusion reactions, we classified them as being either acute or delayed. Acute transfusion reactions included documented anaphylaxis, acute hemolysis, Transfusion-Associated Circulatory Overload (TACO), Transfusion-Related Acute Lung Injury (TRALI), Febrile Non-Hemolytic Reaction (FNHR), and urticarial. Delayed transfusion reactions included documented Delayed Serologic Transfusion Reaction (DSTR). DSTR was defined by an anamnestic antibody response without clinical or laboratory evidence of hemolysis, which is often diagnosed as a result of repeated antibody screening performed by the blood bank [17]. For blood product utilization, we measured the total number of units given for each cohort including WB, RBC, PLT, FFP, and CRYO within 24 hours of injury. For blood compatibility, we measured both ABO and Rh compatibility. Compatibility in the WB cohort was defined as those receiving WB units with identical ABO and Rh blood types.

Data analysis

Continuous variables were summarized as median and Interquartile Range (IQR), while categorical variables are summarized as frequency counts and percentages. A univariate analysis was initially performed using paired Wilcoxon rank sum test and McNemar's or Bowker's symmetry tests, depending on the type and distribution of the data. Generalized Estimating Equation (GEE) models were used to evaluate the short-term survival rates (ED, 24-hour and 30-day) and also hospital LOS, ICU LOS, and total blood transfused during hospitalization. ED survival, 24-hour survival and 30-day survival were assessed with GEE using a binary distribution and logit link. To avoid immortal time bias, we assessed 30-day mortality using only those patients who survived the first 24 hours. When assessing the hospital LOS, ICU LOS, ventilator duration and total blood usage, GEE models using a gamma distribution with a log link were used because these variables are highly skewed. Because of the large number of variables assessed, p-values were adjusted for false discovery rate using the methods of Benjamini and Hochberg. Finally, for all survival outcomes, we performed a Kaplan-Meier survival analysis for 30-day survival, along with similar Cox proportional hazard models stratified by case/control pairing. Significance was defined as p-values < 0.05. All analyses were performed in SAS 9.4.

Results

During the study period, our institution had 2,869 trauma activations of whom 567 required any type of blood transfusion. Of those, 187 activated the WB transfusion protocol and/or the massive transfusion protocol. After excluding patients not meeting the eligibility criteria, we included for analysis a cohort of 78 patients who received WB and 78 patients as matched controls in **Figure 1** details the flowchart of patient selection. Baseline characteristics were similar between cohorts including age, sex, and mechanism of injury, trauma severity, ED laboratory parameters, and hospital laboratory parameters (**Table 1**).

Mortality

Among the cohort of patients who received WB, 19 out of 78 (24.4%) died within 30 days as compared to 28 out of 78 (35.9%) in the cohort of component therapy. Head injury was the most common cause of death in both groups (31.6% in WB and 42.9% in controls). Emergency department, 24-hour, and 30-day mortality were numerically lower in the WB cohort than the matched cohort of patients receiving blood component therapy, but differences were not statistically significant. **Table 2** and **Figure 2** illustrate the Kaplan Meier curve, stratified by case/control pair. The hazard ratio for the use of WB (as compared to component therapy) on the outcome of 30-day mortality was 0.62 (95% CI 0.33 to 1.15, p=0.086). Given concerns for immortal time bias, an effect estimate was also calculated after excluding patients who died within the first 24 hours after injury, yielding similar results (hazard ratio 0.60, 95% CI 0.22 to 1.65, p=0.32) (**Figure 3**).

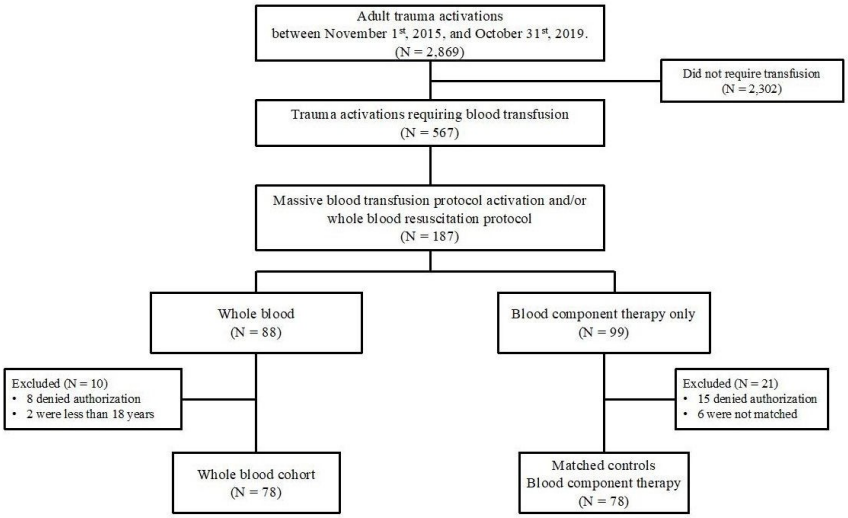

Figure 1 Flowchart of patient selection for study cohorts.

Table 1: Baseline characteristics of WB cohort and its matched controls.

Count(%) or Median (IQR)			
	Whole Blood (N=78)	Matched Controls (N=78)	P Value
Demographics			
Age (years)	50 (28, 67)	48 (33, 64)	0.89[1]
Male	51 (65.4%)	52 (66.7%)	0.32[2]
Mechanism and severity of trauma			
Blunt	64 (82.1%)	65 (83.3%)	0.32[2]
Penetrating	14 (17.9%)	13 (16.7%)	
ISS	25.5 (17, 36)	29 (18, 42)	0.29[1]
ISS ≥ 16	65 (83.3%)	65 (83.3%)	1.00[2]
ED parameters			
GCS score 3-8	40 (51.3%)	46 (59.0%)	0.33[2]
GCS score 9-12	5 (6.4%)	2 (2.6%)	
GCS score 13-15	33 (42.3%)	30 (38.5%)	
HR (bpm)	93 (72, 113)	94 (71, 117)	0.35[1]
SBP (mmHg)	103 (82, 118)	98 (79, 115)	0.20[1]
Positive FAST	19 (24.4%)	27 (34.6%)	0.17[2]
Hemoglobin (g/dL)	11.8 (10.4, 13)	11.7 (10.1, 13.5)	0.96[1]
Hematocrit (%)	34.6 (31.1, 38.5)	34.8 (30.0, 39.6)	0.80[1]
Platelets (10^9/L)	192 (153, 249)	195 (137, 242)	0.42[1]
ED LOS (minutes)	63 (32, 95)	71 (29, 99)	0.94[1]
In-hospital parameters			
24-hour HR (bpm)	89 (74, 101)	88 (73, 98)	0.66[1]
24-hour SBP (mmHg)	115 (105, 133)	116 (103, 135)	0.90[1]
6-hour Hemoglobin (g/dL)	10.8 (9.5, 12.1)	11 (10, 12.7)	0.72[1]
24-hour Hemoglobin (g/dL)	9.9 (8.8, 11.7)	10.4 (9.6, 11.6)	0.65[1]
24-hour Hematocrit (%)	29 (26.1, 34.1)	30 (27.9, 34.1)	0.69[1]
24-hour Platelets (10^9/L)	121 (97, 160)	114 (92, 170)	0.78[1]

Note: Emergency Department (ED); Focused Assessment Sonography in Trauma (FAST); Glasgow Coma Scale (GCS); Heart Rate (HR); Injury Severity Score (ISS); Systolic Blood Pressure (SBP).
[1]Wilcoxon Paired Rank Sum Test
[2]McNemar's or Bowker's Symmetry Test

Table 2: Comparison of primary outcome (mortality) between WB cohort and matched controls.

	Count (%)			
	Whole Blood (N=78)	Matched Controls (N=78)	P Value	Adjusted P value
ED mortality	4 (5.1%)	9 (11.5%)	0.118[1]	0.22
24-hour mortality	10 (12.8%)	16 (20.5%)	0.166[1]	0.22
30-day mortality	19 (24.4%)	28 (35.9%)	0.100[1]	0.22
30-day mortality in those who survived more than 24 hours (n=56 pairs)	7(12.5%)	10 (17.9%)	0.44[1]	0.44

Note: [1]Conditional logistic regression, stratified by pair.

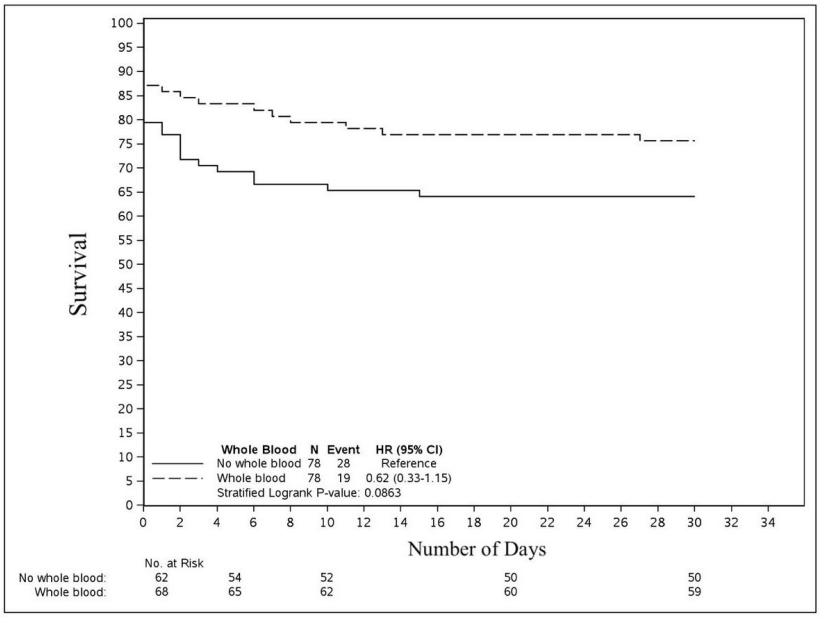

Figure 2 Kaplan Meier survival curves up to 30 days including all patients. **Note:** (——) No whole blood; (– – –) Whole blood.

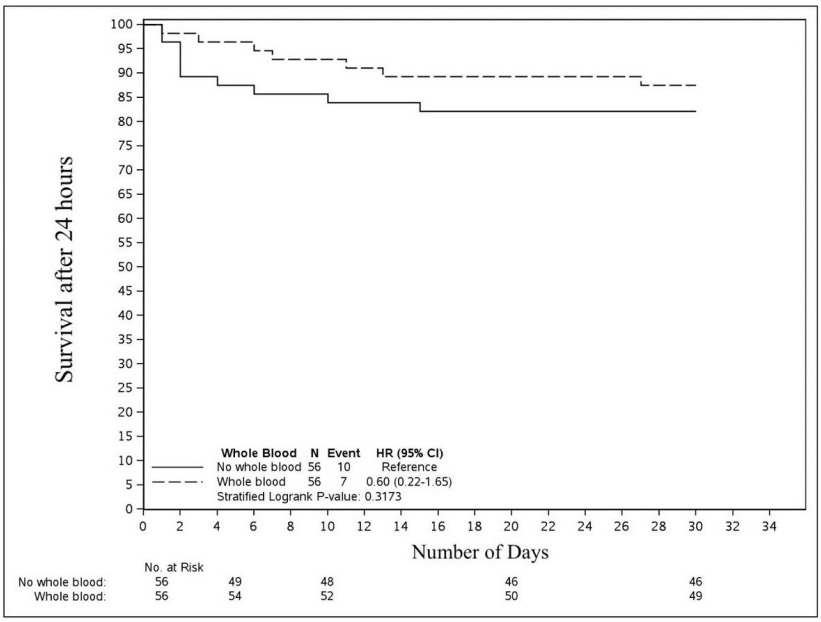

Figure 3 Kaplan Meier survival curves up to 30 days excluding patients who died within 24 hours of injury and its pairs. **Note:** (——) No whole blood; (– – –) Whole blood.

Transfusion reactions

The incidence of any transfusion reactions was similar between the WB cohort (6/78, 7.7%) and matched controls (7/78, 9.0%) (p=0.78). **Table 3** Potentially life-threatening reactions such as anaphylaxis, acute hemolysis, and TACO did not occur in neither cohort. Transfusion-Related Acute Lung Injury (TRALI) was suspected in 3 patients in the WB cohort (3.8%) and in 5 patients in controls (6.4%). These cases were documented as "possible TRALI" because there were other potential explanations that could not be excluded [18]. There was 1 case of FNHR in a patient receiving WB. It was unclear if such reaction was due to WB itself because it occurred after the patient received a unit of RBC 4 days after injury. Two cases of urticarial reactions were confirmed among controls (1 patient with diffuse erythematous rash during transfusion, and 1 patient with periorbital swelling and redness 1 hour after transfusion without other signs or symptoms). There were no cases of documented urticarial in patients receiving WB. Two patients in the WB cohort developed DSTR.

Need for invasive interventions

After ED evaluation, 52 patients (66.7%) needed emergency surgery in the WB cohort as compared to 41 (52.6%) among controls (p=0.082). Interventional radiology was required for 4 (5.1%) patients in the WB cohort as compared to 7 (9.0%) in controls (p=0.37) (**Table 3**).

Hospitalization

The number of patients admitted to the ICU was similar between groups, including 72 (92.3%) patients in the WB cohort and 66 (84.6%) among controls (p=0.121). However, patients in the WB cohort had slightly longer hospital and ICU LOS (**Table 3**).

Blood product utilization

Patients in the WB cohort received as many units of blood products as those receiving initial component therapy (median number of units was 10 (IQR 6, 20) in WB vs. 12 (IQR 6, 23) in controls, p=0.43). Total volume of blood products received throughout pre-hospital and in-hospital care was also similar between groups (median 3310 ml (IQR 2120 ml, 6465 ml) in WB vs. 3610 ml (IQR 2020 ml, 7450 ml) in controls, p=0.87) (**Table 4**).

Table 3: Comparison of secondary outcomes between WB cohort and matched controls.

Count (%) or Median (IQR)				
	Whole Blood (N=78)	Matched Controls (N=78)	P Value	Adjusted P Value
Any transfusion reactions				
Yes	6 (7.7%)	7 (9.0%)	0.78[2]	0.85
No	72 (92.3 %)	71 (91.0 %)	-	-
Acute transfusion reactions				
Anaphylaxis	0 (0.0%)	0 (0.0%)	-	-
Acute hemolysis	0 (0.0%)	0 (0.0%)	-	-
TACO	0 (0.0%)	0 (0.0%)	-	-
Possible TRALI*	3 (3.8%)	5 (6.4%)	0.48[2]	0.6
FNHR	1 (1.3%)	0 (0.0%)	1.00[2]	1
Urticaria	0 (0.0%)	2 (2.6%)	0.50[2]	0.6
Delayed transfusion reactions				
DSTR	2 (2.6%)	0 (0.0%)	0.50[2]	0.6
Need for invasive interventions				
Any	56 (71.8%)	48 (61.5%)	0.194[2]	0.39
Emergency Surgery	52 (66.7%)	41 (52.6%)	0.082[3]	0.25
Interventional Radiology	4 (5.1%)	7 (9.0%)	0.37[3]	0.6
Hospitalization				
ICU admission	72 (92.3%)	66 (84.6%)	0.121[2]	0.29
ICU LOS (days)	5 (2, 10)	3 (1, 6)	0.014[1]	0.122
Days on ventilator	3 (1, 7)	2 (1, 4)	0.031[1]	0.122
Hospital LOS (days)	13 (4, 21)	7 (1, 14)	0.021[1]	0.122

Note: Delayed Serologic Transfusion Reaction (DSTR); Emergency Department (ED); Febrile Non-Hemolytic Reaction (FNHR); Intensive Care Unit (ICU); Length Of Stay (LOS); Transfusion-Associated Circulatory Overload (TACO); Transfusion-Related Acute Lung Injury (TRALI).
[1]Wilcoxon Paired Rank Sum Test
[2]McNemar's or Bowker's Symmetry Test
[3]Logistic regression, stratified by pair, comparing this group with the 'No Intervention' group.
*TRALI was suspected but not confirmed in these cases.

Table 4: Comparison of blood product utilization between WB cohort and matched controls.

Count (%) or Median (IQR)				
	Whole Blood (N=78)	Matched Controls (N=78)	P Value	Adjusted P Value
Pre-hospital transfusions				
Any blood product*	46 (59.0%)	33 (42.3%)		0.25
Any blood product* (units)	1 (0, 2)	0 (0, 3)	0.99[1]	1
WB	21 (26.9%)	0 (0%)	-	-
WB (units)	0 (0, 1)	0 (0, 0)	-	-
RBC	31 (39.7%)	33 (42.3%)	0.75[2]	0.95
RBC (units)	0 (0, 1)	0 (0, 2)	0.165[1]	0.46
FFP	26 (33.3%)	22 (28.2%)	0.49[2]	0.92
FFP (units)	0 (0, 1)	0 (0, 1)	0.95[1]	1
Platelets	7 (9.0%)	0 (0.0%)		0.152
Platelets (units)	0 (0, 0)	0 (0, 0)		0.152
In-Hospital transfusions in first 6hours				
Any blood product*	74 (94.9%)	78 (100.0%)	0.125[3]	0.41
Any blood product* (units)	5 (3, 12)	7 (4, 13)	0.088[1]	0.35
WB	64 (82.1%)	0 (0.0%)	-	-
WB (units)	1 (1, 2)	0	-	-
RBC	59 (75.6%)	77 (98.7%)		0.08
RBC (units)	1 (1, 5)	4 (2, 7)		
FFP	58 (74.4%)	68 (87.2%)		0.26
FFP (units)	2 (0, 5)	3 (2, 5)	0.052[1]	0.26
Platelets	47 (60.3%)	39 (50.0%)	0.24[2]	0.58
Platelets (units)	1 (0, 1)	0.5 (0, 2)	0.71[1]	0.95
CRYO	14 (17.9%)	16 (20.5%)	0.67[2]	0.95
CRYO (units)	0 (0, 0)	0 (0, 0)	0.88[1]	0.98
In-Hospital transfusions between 6 and 24 hours				
Any blood product*	29 (37.2%)	32 (41.0%)	0.62[2]	0.94
Any blood product* (units)	0 (0, 2)	0 (0, 3)	0.87[1]	0.98
WB	0 (0%)	0 (0%)		
WB (units)	0 (0, 0)	0 (0, 0)	-	-
RBC	26 (33.3%)	24 (30.8%)	0.75[2]	0.95
RBC (units)	0 (0, 2)	0 (0, 1)	0.59[1]	0.94
FFP	15 (19.2%)	18 (23.1%)	0.55[2]	0.94
FFP (units)	0 (0, 0)	0 (0, 0)	0.178[1]	0.46
Platelets	10 (12.8%)	19 (24.4%)	0.09[2]	0.35

Platelets (units)	0 (0, 0)	0 (0, 0)	0.27[1]	0.62
CRYO	8 (10.3%)	8 (10.3%)	1.00[2]	1
CRYO (units)	0 (0, 0)	0 (0, 0)	0.71[1]	0.95
Total transfusions				
Any blood product*	78 (100%)	78 (100%)	1.00[2]	1
Any blood product* (units)	10 (6, 20)	12 (6, 23)	0.43[1]	0.89
Volume of blood products (ml)	3310 (2120; 6465)	3610 (2020; 7450)	0.87[1]	0.98
WB	78 (100%)	0 (0%)	-	-
WB (units)	1 (1, 2)	0 (0, 0)	-	-
RBC	74 (94.9%)	78 (100%)	0.125[2]	0.41
RBC (units)	5 (2, 10)	6 (4, 11)	0.177[1]	0.46
FFP	69 (88.5%)	73 (93.6%)	0.28[2]	0.63
FFP (units)	2.5 (1, 6)	4 (2, 8)	0.040[1]	0.26
Platelets	51 (65.4%)	50 (64.1%)	0.87[2]	0.98
Platelets (units)	1 (0, 2)	1 (0, 2)	0.62[1]	0.94
CRYO	19 (24.4%)	22 (28.2%)	0.56[2]	0.94
CRYO (units)	0 (0, 0)	0 (0, 1)	0.46[1]	0.9

Note: Red Blood Cells (RBC); Fresh Frozen Plasma (FFP)
*Patients who received WB were counted as receiving 1 unit of blood product.
[1]Wilcoxon Paired Rank Sum Test
[2]McNemar's or Bowker's Symmetry Test

Blood compatibility within WB cohort

From the 78 patients receiving WB, only 3 patients had missing compatibility data because these patients died in the ED before compatibility testing was performed. Among the remaining 75 patients, 41 received blood with compatible ABO while 34 received at least one WB unit with incompatible ABO. When comparing these 2 subsets of patients, 30-day mortality and incidence of any transfusion reaction was numerically higher among those with incompatible ABO, but differences were not statistically significant. A total of 7 out of 41 (17.1%) died within 30 days among those receiving WB with compatible ABO as compared to 9 out of 39 (26.5%) among those receiving WB without compatible ABO (p=0.32). The incidence of any transfusion reactions was 2 out of 41 (4.9%) in those receiving WB with compatible ABO as compared to 4 out of 34 (11.8%) in those receiving WB without compatible ABO (p=0.29). As for Rh compatibility, 35 patients were considered compatible (same Rh), 36 patients were Rh-positive and received at least one unit of Rh-negative WB and 4 patients were Rh-negative and received at least one unit of Rh-positive WB. 30-day mortality was very similar between patients with compatible Rh and those Rh-positive who received Rh-negative WB units (8/35 (22.9%) vs. 8/36 (22.2%)), and none (0%) of the 4 Rh-negative patients who received Rh-positive WB died within 30 days of injury (p=0.74 for the comparison across the 3 groups). Of the 6 episodes of transfusion reactions that occurred, 2 (5.7%) were among patients who received compatible Rh WB, 3 (8.3%) among Rh-positive patients receiving Rh- negative WB, and 1 (25%) among Rh-negative patients receiving Rh-positive WB (p=0.19 for the comparison across the 3 groups).

Discussion

In this retrospective cohort study of trauma patients requiring emergent resuscitation, mortality and transfusion reactions were not statistically different between patients receiving cold WB and those receiving conventional blood component therapy. Other outcomes such as need for invasive interventions and blood product utilization were also similar between the two cohorts. These data suggest that initial resuscitation with cold WB in civilian critically ill trauma patients is at least as safe and as effective as conventional component therapy. When following appropriate procedures for its administration, cold WB appears to be safe in a civilian population and no patients in our cohort had a life-threatening transfusion reaction. The limited sample size of our study precludes definitive conclusions but a sizeable portion of the 95% confidence interval for the effect estimate of WB (as compared to component therapy) on mortality lies within a potential superiority of WB that needs to be evaluated in a future well-designed randomized clinical trial.

Our results are consistent with previous studies that have shown the safety of cold WB transfusions for traumatically injured patients in the civilian setting [19-21]. In regards to transfusion

reactions, which is one of the biggest concerns for WB administration, we did not find significant differences between groups. In fact, the incidence of any transfusion reactions was numerically higher among those receiving component therapy. Despite a significant proportion of patients receiving WB with incompatible ABO or Rh, there was no acute hemolysis or other life-threatening reactions among patients receiving WB. Williams and colleagues have specifically evaluated hemolysis panels between patients receiving cold WB and those receiving component therapy [19]. They did not find any evidence of increased hemolysis or increased transfusion reaction rates in those receiving WB [19]. Also, Yazer and colleagues evaluated the incidence of adverse reactions in 47 patients who received WB, and no reactions temporally associated with the WB transfusions were reported [22]. As for blood product utilization, our study found that patients receiving WB received as many units of transfusion as those receiving component therapy. The total volume of transfusion was equivalent between groups. Similarly, in the randomized pilot trial by Cotton and colleagues, 24-hour transfusion volume was similar between patients receiving WB and those receiving initial component therapy for trauma resuscitation [23]. While there was no statistically significant difference in mortality between patients receiving WB and those receiving blood component therapy, it is clear that a definitive randomized clinical trial is needed to elucidate if a true difference exists. Our study was underpowered to detect smaller differences and there is significant uncertainty about the effect of WB when compared to component therapy. Nevertheless, a sizeable portion of the 95% confidence interval includes a potential benefit of using WB. Studies in the military setting have shown a survival benefit when WB is used for trauma patients [5-7], but data mostly come from observational studies. Most recently, Crowe and colleagues have summarized the existing evidence for published studies that compared WB to component therapy in critically ill trauma patients [13]. When meta-analysing data from 12 studies (military and civilian settings), the effect estimate was consistent with a potential benefit of WB, but the confidence interval was wide, leaving significant uncertainty (pooled odds ratio of 0.79, 95% CI 0.48 to 1.31, for the outcome of in-hospital and/or 30-day mortality) [13]. In aggregate, our study and existing evidence from prior data suggest that emergency resuscitation with WB could lead to improved survival when compared to conventional blood component therapy, but a large definitive randomized trial is needed to clarify this question.

As previously shown in the military setting, we believe that WB is likely the ideal resuscitation fluid for severely injured trauma patients [5-7]. It is more physiological, it facilitates logistics (hanging up one unit of WB is easier than hanging up one unit of each component), it exposes the recipient to only one donor (instead of three for reconstituted units in a ratio 1:1:1) and it contains a lower volume of anticoagulant/preservative solution when compared to equivalent (i.e., 1:1:1) component transfusions. More importantly, WB appears to have similar safety when compared to component therapy, and it may lead to improved survival although this is yet to be proved by a future large randomized trial.

Conclusion

Emergent resuscitation with cold WB in civilian trauma patients appears to be at least as safe and as effective as conventional blood component therapy. When following appropriate procedures for its administration, cold WB was safe in this cohort of civilians and no patients had a life-threatening transfusion reaction. Future randomized controlled trials are urgently needed to evaluate whether WB is the preferable alternative for the resuscitation of trauma patients.

Limitations

This study has several limitations. First, this was an observational, retrospective, cohort study at a single level I trauma center, and its results may not be generalizable for other populations. Second, despite matching for the most important variables at the design phase, we cannot exclude the possibility of residual confounding due to the retrospective nature of the study. Third, the choice to use WB for resuscitation was based on clinician discretion, which could inevitably lead to selection and indication bias. Third, the restriction of a maximum number of WB units per patient (up to 4 in those with blood type O) is not ideal and a significant proportion of patients in the WB cohort have also received component therapy during resuscitation. This precluded us from evaluating the effects of the exclusive use of WB. Lastly, we used documented data from the EHR to evaluate transfusion reactions and incidence of reactions might have been underestimated. Nevertheless, it is unlikely that life-threatening reactions were not captured.

Declarations

Author's contributions

Significant contributions were made by all listed authors. MMF participated in the literature search, data collection, and article writing. SCB contributed with data analysis, and critical revision. MDZ and JRS were the primary investigators and participated in literature search, study design, writing, and critical revision.

Ethics approval and consent to participate

This study was approved by the Mayo Clinic Institutional Review Board, who approved a waiver of the requirement to obtain informed consent due to the retrospective nature of the study, in accordance with 45 CFR 46.116. Any patients who declined Minnesota Research Authorization for medical records review were removed from the study cohort and none of their data were analyzed. All methods were performed in accordance with the relevant guidelines and regulations.

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Availability of data and material

All data generated or analysed during this study are included in this published article.

Consent for publication

Not applicable.

Competing interests

The authors do not have conflicts of interest to disclose

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