Title

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Journal

Journal of Trauma and Acute Care Surgery, 91(4)

ISSN

2163-0755

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Publication Date

2021-10-01

DOI

10.1097/ta.0000000000003334

Peer reviewed

HHS Public Access

Author manuscript

J Trauma Acute Care Surg. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

J Trauma Acute Care Surg. 2021 October 01; 91(4): 655–662. doi:10.1097/TA.0000000000003334.

A Pilot Study of Stored Low Titer Group O Whole Blood + Component Therapy versus Component Therapy Only for Civilian Trauma Patients

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Abstract

Background: This pilot assessed transfusion requirements during resuscitation with whole blood followed by standard component therapy versus component therapy alone, during a change in practice at a large urban level I trauma center.

Methods: This was a single-center prospective cohort pilot study. Male trauma patients received up to 4 units of cold-stored low anti-A, anti-B group O whole blood (LTOWB) as initial resuscitation followed by CT as needed (LTOWB + CT). A control group consisting of females, and males who presented when LTOWB was unavailable, received component therapy only (CT group). Exclusion criteria included antiplatelet or anticoagulant medication and death within 24 hours. The primary outcome was total transfusion volume at 24 hours. Secondary outcomes were mortality, morbidity, and ICU- and hospital-free days.

Results: Thirty-eight patients received LTOWB, with a median of 2.0 [IQR 1.0, 3.0] units of LTOWB transfused. Thirty-two patients received CT only. At 24 hours after presentation, the LTOWB +CT group had received a median of 2138 mL [IQR 1275-3325] of all blood products.

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Author Contributions: AES: Designed and coordinated study, wrote manuscript. KJB: Collected clinical data, wrote and edited manuscript. RJC: Designed study, edited manuscript. NCN, SL, JH: Clinical data collection, oversaw thromboelastography. AF, DW: Coordinated whole blood collection and distribution. NJJ, TR, JG, Designed and performed statistical analysis. AZ: Designed study, coordinated and oversaw whole blood collection, edited manuscript. HGC: Designed study, edited manuscript.

The authors declare they have no conflicts of interest.

Portions of this work have previously been presented at the 78th Annual Meeting of AAST and Clinical Congress of Acute Care Surgery (September 18, 2019 in Dallas, Texas) and at the American College of Surgeons, Southern California Chapter Resident Trauma Paper Competition (November 19, 2020, via virtual conference).

The median for the CT group was 4225 mL [IQR 1900-5425], p = 0.06 in unadjusted analysis. When adjusted for Injury Severity Score, sex, and positive Focused Assessment with Sonography for Trauma (FAST), LTOWB +CT group patients received 3307 mL of blood products and CT group patients received 3260 mL in the first 24 hours (p = 0.95). The adjusted median ratio of plasma to red cells transfused was higher in the LTOWB + CT group (0.85 vs 0.63 at 24 hours after admission, p = 0.043. Adjusted mortality was 4.4% in the LTOWB + CT group, and 11.7% in the CT group (p = 0.19), with similar complications, ICU-, and hospital-free days in both groups.

Conclusions: Beginning resuscitation with LTOWB results in equivalent outcomes compared to resuscitation with CT only.

Level of Evidence: Therapeutic, Level III (Prospective study with 1 negative criterion, limited control of confounding factors)

Keywords

Whole blood; resuscitation; coagulopathy

Background:

Hemorrhage is a leading cause of preventable death after trauma. (1, 2) Hemorrhagic shock and hypoperfusion lead to endothelial dysfunction and coagulopathy, which is worsened by hypothermia, acidosis, and dilution of platelets and clotting factors during resuscitation. (3–5) In most modern civilian trauma centers, coagulopathy in severely hemorrhaging patients is addressed by resuscitation with leukocyte-reduced red blood cells (RBC), plasma, and single donor apheresis platelets, typically in a 1:1:1 ratio. (6, 7) Balanced component therapy (CT) transfusion ratios approximate the whole blood (WB) lost by the patient, minimize dilutional coagulopathy, and improve survival compared to receiving smaller volumes of platelets and plasma.(7, 8)

Rather than transfusing CT in a ratio equivalent to WB, transfusing fresh WB may further improve outcomes. (9) Cold-stored low anti-A/anti-B titer group O WB (LTOWB) may provide the benefits of WB such as smaller transfusion volume and fewer additives, thereby facilitating resuscitation with a more physiologic product. However, unlike fresh WB, cold-stored WB can be used routinely in civilian trauma centers. (10) Multiple studies have demonstrated the safety of transfusing up to 6 units LTOWB as initial resuscitation for trauma patients (10, 11), and some studies suggest that WB may improve outcomes.(12–15)

In this prospective cohort pilot study, we assessed transfusion requirements, morbidity and mortality in patients who were initially resuscitated with LTOWB followed by CT, versus CT only for traumatic hemorrhage. We also performed an exploratory analysis of TEG coagulation measurements before, during, and after resuscitation.

Methods:

Study Design and Patient Population:

This was a prospective, observational cohort pilot study. The study took place concurrently with a change in practice approved by our institution’s transfusion committee allowing

transfusion of up to 4 units of cold-stored low anti-A, anti-B titer (< 1:100) LTOWB to replace conventional uncrossmatched RBC for resuscitation of male trauma patients. Due to concerns about transfusing Rh+ RBC to women of childbearing potential, female patients received standard CT and were eligible for enrollment in the control arm of the study. The study protocol was reviewed by the United States Food and Drug Administration (FDA) and granted exemption from Investigational New Drug Application (IND) requirements. The study was registered with the United States National Library of Medicine ClinicalTrials.gov trial registry website (Identifier NCT02926274). The UCLA Institutional Review Board (IRB) waived the need for informed consent as both LTOWB and CT were considered standard of care by our institution's division of transfusion medicine.

The primary outcome was total blood product transfusion volume received within the 24 hours after presentation. Secondary outcomes were transfusion volume within 4 hours after presentation, 30-day in-hospital mortality, morbidity which we defined as complications specified in the National Trauma Data Standard, hospital-free days, ICU-free days, and TEG measurements throughout resuscitation.

All patients presenting between November 2017 and August 2019 to our large metropolitan Level I trauma center were eligible for enrollment if they were at least 18 years of age, had massive transfusion protocol activation for pre-hospital systolic blood pressure (SBP) less than 100 mmHg, and received at least one unit of LTOWB or RBC in the first 24 hours after arrival. Exclusion criteria included age < 18 years, greater than 20% total body surface area second-or third-degree burns, and current antiplatelet/anticoagulant medication use. In order to accurately compare our primary endpoint, total transfusion volume at 24 hours, only patients who survived for 24 hours after arrival to the trauma bay were included in analysis. If medical history was unknown, patients later found to meet exclusion criteria were excluded at the time of data analysis. Trained research assistants were available to enroll patients approximately 20 hours per day.

Prior to the start of and during the study, emergency room, surgery, and anesthesiology physicians and nurses were trained regarding the protocol including transfusion of up to 4 units of LTOWB for male trauma patients only. Prior to arrival of a trauma patient, ED and trauma surgery staff are sent a text page advising of a trauma activation which specifies patient sex, so it was known prior to arrival whether the patient was eligible for LTOWB transfusion.

Supply during the pilot of a novel blood product (LTOWB) determined whether LTOWB was available at a given trauma activation. At the beginning of each shift, the blood bank stocked the trauma bay blood refrigerator with up to 4 units of LTOWB when available, as well as CT. When LTOWB had not been collected, only CT was stocked. The blood product in this refrigerator is used as initial resuscitation for hemorrhaging patients. During the pilot study there were frequently days when no LTOWB was available, or when it had previously been transfused for another patient, which allowed for a control arm. Thus, this was a quasi-experimental study in which patients meeting inclusion criteria were assigned to either LTOWB+CT or CT only based on 1) the sex of the patient and 2) if male, the availability of LTOWB.

Blood Product Preparation:

Our hospital-based donor center screened group O Rh-positive male whole blood donors for anti-A/-B antibody titer levels (<1:100). All LTOWB donations were tested for transfusion-transmitted infectious diseases, according to AABB (formerly known as the American Association of Blood Banks) and FDA regulations. Repeat anti-A/-B titer assessments were performed to confirm that these units met the titer requirements to qualify as LTOWB. LTOWB units were leukoreduced prior to storage with a platelet-sparing filter (Imuflex WB-SA, Terumo, Tokyo, Japan) and were then stored at 1-6°C for up to 10 days. CT products were collected and stored using standard methods.

Massive Transfusion Protocol:

For patients in the CT arm, coolers containing 6 group O RBC units, 6 pre-thawed group A plasma units, and 1 apheresis platelet unit were available as soon as the patient presented to the emergency department (ED). Treating physicians make every attempt to ensure a 1:1:1 transfusion ratio.

Patients who met eligibility criteria for the LTOWB + CT arm received up to 4 units of LTOWB as initial resuscitation, when LTOWB was available. If these patients had additional transfusion requirements after transfusion of available LTOWB units, the blood bank then provided 6 group O RBC units, 6 units of compatible plasma, and 1 apheresis platelet unit. Following transfusion of these products, the blood bank continued to provide type-specific RBC, compatible plasma, and apheresis platelets in a 1:1:1 ratio. Thus, patients in the LTOWB + CT arm who required large volume transfusion received as initial resuscitation 1-4 units of LTOWB (depending on LTOWB availability), followed by CT for the remainder of resuscitation.

Thromboelastography (TEG):

An exploratory analysis of TEG measurements before, during, and after resuscitation was performed. The first sample was drawn on presentation prior to any transfusion and was analyzed as the “Pre-Resuscitation” sample for all patients. During resuscitation, samples were collected serially after transfusion of each 6 units of red blood cell-containing product (whether LTOWB or RBC). If a rapid infuser system was used, samples were taken for TEG analysis every 30 minutes. This was based on typical flow rates, with approximately 6 units of red blood cell-containing product estimated to be transfused every 30 minutes during rapid infusion. To provide a meaningful analysis despite the extreme heterogeneity of transfusion requirements in the study population, the sample drawn after the first 6 units of red blood cell-containing product was analyzed as the “Initial-Resuscitation” sample. This sample best reflects any difference due to LTOWB transfusion, as a maximum of 4 units of LTOWB could be transfused as initial resuscitation, which would have been transfused by the time the “Initial Resuscitation” sample was drawn. At the end of resuscitation, an “End-Resuscitation” specimen was drawn. For patients who received ≤ 6 units of RBC-containing products, the “Initial Resuscitation” sample was also the “End-Resuscitation” sample. The final sample (“Post-Resuscitation Day 1”) was drawn the following day approximately 24 hours after presentation.

Trained research assistants performed TEG using hemostasis analyzers (TEG 5000 Thromboelastography, Haemonetics, Braintree, MA) as previously described. (16, 17) TEG R (time to first sign of clot, high values indicate coagulopathy), K (rate of clot progression, reflective of fibrinogen level, high values indicate coagulopathy), α-angle (rate of clot progression, reflective of platelet activity stimulating fibrinogen polymerization, low values indicate coagulopathy), and MA (overall clot strength, reflective of platelet aggregation, low values indicate coagulopathy), were recorded.(18) TEG measurements were used for research only and were not used to guide resuscitation, nor were TEG results known by treating clinicians.

Clinical Outcomes:

We reviewed blood bank and electronic medical record documentation to determine transfusion requirements and timing. We calculated total transfusion volume based on the following conversions: one unit of LTOWB equals 500mL, one unit of RBC equals 275ml, one unit of plasma equals 225ml, and one apheresis platelet unit equals 250mL. For comparisons of number of units of blood products transfused and ratios of platelets and plasma to RBC, one unit of LTOWB was considered equivalent to one unit of RBC, one unit of plasma, and 1/6 of an apheresis platelet unit.

We obtained patient demographics and clinical outcomes from the UCLA Trauma Registrar, which collects data according to the National Trauma Data Standard (19). We obtained pre-admission medications and clinical laboratory values by chart review by trained surgical research residents (AES and KJB).

Statistical analysis:

In our power analyses submitted to the FDA, we proposed a sample size of 31 patients in the LTOWB + CT group (study drug) and 31 in the CT group (control) (62 patients total). Using a two-sided alpha level of 0.05, we would have 80% power to minimally detect a median difference of the equivalent of 2 RBC units at 24 hours between the groups. This estimate was based on a study by Cotton et al., who reported a difference in transfusion of RBC units (median in the whole blood group 4 [IQR 2,6] vs component therapy group 6 [2,13]). (26). In addition to assessing this primary outcome, this study served as a pilot/feasibility study of TEG differences throughout resuscitation. Statistical testing of exploratory analyses in this pilot study was limited as much as possible to reduce false discovery.

Medians with interquartile range (IQR) and relative frequencies were used to describe the demographic, transfusion requirements, and clinical outcomes in the LTOWB + CT and CT groups. Bivariate between group differences were assessed using Wilcoxon Rank Sum or Fisher's exact test, as appropriate. Multivariable models for the differences between groups on transfusion requirements and clinical outcomes were conducted using quantile regression models at the 50^{th} percentile. Models for transfusion requirements adjusted for Injury Severity Score (ISS), sex, and presence of a positive Focused Assessment with Sonography for Trauma (FAST). Models for clinical outcomes adjusted for ISS, sex, age, and presence of a severe traumatic brain injury (TBI). These variables were selected based on statistically and/or clinically significant differences in bivariate analysis as well as

clinical judgment. In order to examine differences in TEG measurements, a generalized mixed effects linear regression with logarithmic linkage and patient random intercept was used to estimate differences in the LTOWB + CT and CT groups during resuscitation. The average within-subject linear association between increasing equivalent transfusion volume with TEG measurements for the LTOWB + CT and CT groups were also assessed with this model. Between group differences in these associations were examined using a group-by-volume fixed effect interaction term with a statistically significant ($p<0.05$) interaction indicating that the slopes between the groups were reliably different. Because most of the TEG measurements exhibited a positive skew, a logarithmic transformation, described above, was chosen for use in these models to minimize the impact of outliers. Because of the potential for missing data at the different time points across resuscitation, we utilized likelihood based methods (e.g. mixed effects regression) that will produce valid estimates in instances where the missing data are Missing at Random. These methods compute a separate likelihood for each of the various patterns of missing data, allowing for the produced estimates to be robust to missing data. All analyses were conducted using Stata version 16.1, Stata Corp LP (College Station, Texas).

Sensitivity Analyses

There are known sex differences in coagulation profile (20, 21), and severe traumatic brain injury (TBI) is known to contribute to a unique coagulopathy. (22, 23) We therefore repeated our analysis including only male patients without severe TBI, defined by the presence of head abbreviated injury score (AIS) of 3 or more (24, 25).

To evaluate the effect on our TEG results of the highly disparate transfusion requirements within our patient population, a second sensitivity analysis divided the study population into tertiles according to total red blood cell-containing product transfusion requirements within 24 hours of presentation (≤4 units, >4 to <10 units, and ≥10 units) and analyzed serial TEG measurements as above within each tertile. This analysis was again limited to male patients without severe TBI.

Results:

Enrollment and Baseline Data:

Ninety-one patients 18 years or older presented as trauma activations during the study period and received at least one unit of LTOWB or RBC (Figure 1). Of these, 81 (89%) presented during study hours and were evaluated for inclusion. After exclusions, 70 patients were included in this analysis; 38 received at least one unit of LTOWB, while 32 received CT only. Twenty-five male patients without TBI received LTOWB, and 15 received CT (Figure 1).

The median age of the prospective study population was 38.0 years and 37.0 years for the LTOWB + CT and CT groups, respectively (Table 1). All patients who received LTOWB were male, while n=22 (69%) were male in the CT group. Mean ISS was lower in the LTOWB + CT compared to CT group (22 vs. 28, $p = 0.035$). The proportion of patients with positive FAST trended higher in the CT group (31% vs 16%, $p = 0.16$), however the

assessment of blood consumption (ABC) scores (27), which includes the FAST exam in a calculation predicting the need for transfusion after trauma, were similar between groups. First recorded ED Glasgow Coma Scale (GCS), systolic blood pressure (SBP), heart rate (HR), international normalized ration (INR), and blood ethanol (EtOH) level were similar between groups.

Transfusion Requirements:

Within the first 24 hours of presentation to the trauma bay, LTOWB + CT group patients received a median of 2138 mL [IQR 1275-3325] of blood products, while patients in the CT group received 4225 mL [IQR 1900-5425], p = 0.06 (Table 2). Patients in the LTOWB + CT group received a median of 2.0 units of LTOWB [IQR 1.0-3.0] in the first 4 and 24 hours. Additionally, those in the LTOWB + CT group went on to receive a median of 2.0 units of RBCs compared to 8.0 in the CT group; 1.00 plasma units compared to 4.0 in the CT group; and 0.0 apheresis platelet units compared to 1.0 in the CT group. There was no significant difference in the total volume of blood product transfused in the unadjusted sensitivity analysis comparing male patients without TBI (Supplementary Table 3).

When each unit of LTOWB was calculated as equivalent to 1 unit of RBC, 1 unit of plasma, and 1/6 of an apheresis platelet unit, patients who received LTOWB had significantly more balanced transfusion ratios of plasma to RBC than those receiving CT (Table 2). At 24 hours, the median ratio of plasma to RBC transfused was 0.82 [IQR 0.67, 1.00] in the LTOWB + CT group compared to 0.61 [IQR 0.31, 0.72] in the CT group ($p<0.001$), although this was not significant at 4 hours after admission. Trends in the ratio of platelets to RBCs transfused were nonsignificant and not consistent between the 4 hour and 24 hours timepoints.

A multivariable model using quantile regression adjusted for ISS, sex, and FAST positivity. In the adjusted analysis, total volumes of blood transfused were very similar at 24 hours (LTOWB + CT group 3307 mL vs CT group 3260 mL, p = 0.95) and 4 hours after admission (LTOWB + CT group 2491 mL vs CT group 2447 mL, p = 0.93) (Table 3). The ratio of plasma to RBCs transfused remained higher in the LTOWB+CT group, and this was significant at 24 hours (0.85 vs 0.63, p = 0.043.) but not 4 hours after admission.

Secondary Clinical Outcomes:

In unadjusted analysis, mortality trended lower in the LTOWB + CT group (n=1, 2.6%) compared to the CT group (n=5, 15.6%) (Supplementary Table 1). No significant difference was seen in mortality in the sensitivity analysis limited to males without severe TBI (Supplementary Table 4). When adjusted for ISS, sex, age, and severe TBI, the 30-day in-hospital mortality was estimated to be 4.4% for the LTOWB+CT group and 11.7% for the CT group, p = 0.19. Hospital-free days, ICU-free days, and the development of any complication as specified in the National Trauma Data Standard were similar between groups (Table 4). There were no transfusion associated adverse events in either group (Supplementary Table 1).

Thromboelastography:

On presentation to the trauma bay, R was initially below normal and increased over time in both the LTOWB + CT and CT groups, normalizing at the Post-Resuscitation Day 1 time point (Figure 2, Supplementary Table 5). The other TEG measurements (K, alpha angle, and MA) were similar between groups with normal mean values in both groups throughout resuscitation.

To further evaluate coagulation in massive transfusion with LTOWB vs CT, the prospective cohort was divided into tertiles according to the amount of RBC equivalent units they received (Supplementary Figure 1). This analysis was restricted to male patients without TBI. Tertile 1 patients received ≤4 units (WB n=10, CT n = 3). Tertile 2 received >4 to <10 units (WB n=10, CT n = 7) and Tertile 3 received ≥10 units (WB n =5, CT n = 5) within 24 hours of presentation. Results in each tertile were generally similar to findings when the entire cohort was analyzed as a group, although MA was below normal at end-resuscitation in the LTOWB+CT group in the highest-volume tertile only.

Discussion:

In keeping with prior studies, (10, 11) we found that initial resuscitation with cold-stored LTOWB is overall equivalent to CT in terms of morbidity and mortality when a median of 2, and up to 4 units are transfused as initial resuscitation for traumatic hemorrhage. After adjusting for ISS, FAST positivity, and sex, transfusion requirements after initiating resuscitation with LTOWB appear similar to using CT alone. This study adds to a growing body of evidence that LTOWB is safe for trauma patients. Our exploratory TEG analysis also suggests that both resuscitation protocols result in an adequate functional coagulation profile during resuscitation.

At 24 hours after presentation, we found significantly more balanced transfusion ratios of RBC to plasma in patients who initially received LTOWB compared to CT. While every effort is made to provide RBC, platelets, and plasma in a 1:1:1 ratio, this can be challenging in the chaos of the trauma bay. (28) LTOWB offers a logistical advantage because it guarantees balanced transfusion. This may be particularly important early in resuscitation. (7) Additionally, in light of blood product shortages manifested during the COVID-19 pandemic, LTOWB transfusion offers the advantage of preserving the supply of components needed for alternative indications.

There are several limitations to this study. This was a single institutional pilot study of all patients presenting as critical trauma with massive transfusion activation. Such patients represent a wide array of physiologies, from relatively minor injuries requiring only a limited amount of blood products for resuscitation, to patients presenting with profound hemorrhagic shock. The effects of providing a more hemostatic product are expected to be most pronounced for the most critical patients requiring true massive transfusion.

We attempted to partially correct for the challenges of a small, diverse sample size by performing multiple sensitivity analyses to ensure that our results remained the same when the study population was subdivided according to total transfusion requirements, and when

sex and TBI were excluded as possible confounders. However, ISS for the LTOWB + CT group was lower than the CT group, and this difference persisted in our sensitivity analysis (Supplementary Table 2). A multivariable regression analysis was performed to account for this and other potential confounders, however with a small sample size this model risks overfitting of data. We therefore stress that while our multivariable analysis did not identify a difference in transfusion requirements after initiation of resuscitation with LTOWB, a larger study is needed to fully explore this possibility.

Importantly, our protocol allowed only up to 4 units of LTOWB to be transfused. Limited supply meant that some patients requiring massive transfusion received less than the protocol maximum of 4 units LTOWB, and in fact the median amount of LTOWB units received was 2 units. After the initial transfusion of LTOWB, the majority of transfusion for patients requiring large volume resuscitation was done with CT. This limitation results from both FDA requirements limiting the total amount of LTOWB that could be transfused based on available safety evidence, and logistical challenges affecting the supply of a nonstandard blood product. This study adds to a body of evidence that small volumes of LTOWB are safe and at least equivalent to CT, helping to lay the regulatory and logistical groundwork for blood banks to provide larger volumes of LTOWB for resuscitation of traumatic hemorrhage.

Conclusions:

Cold-stored LTOWB leukoreduced with a platelet-sparing filter and stored for up to 10 days is a safe and feasible product for resuscitation after traumatic hemorrhage, and may help facilitate balanced transfusion ratios. Providing a new blood product is logistically challenging for hospitals, and must be justified by clinical benefit. A large multicenter trial of LTOWB versus CT with larger volumes of LTOWB for massive traumatic hemorrhage, is safe and warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Support:

This work was funded by Award # NTI-NCH-1O-033 from the National Trauma Institute and sponsored by the Department of the Army, Prime award #W81XWH-11-1-084I. The U.S. Army Medical Research Acquisition Activity, 820 Chandler Street, Fort Detrick MD 21702-5014 is the awarding and administering acquisition office. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Gerald S. Levey Award: Additional funding was provided by the Gerald S. Levey Award. The Department of Surgery, David Geffen School of Medicine at UCLA, is the awarding and administering office.

CTSI grant: Statistical analysis and regulatory support for this project was provided by NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR001881.

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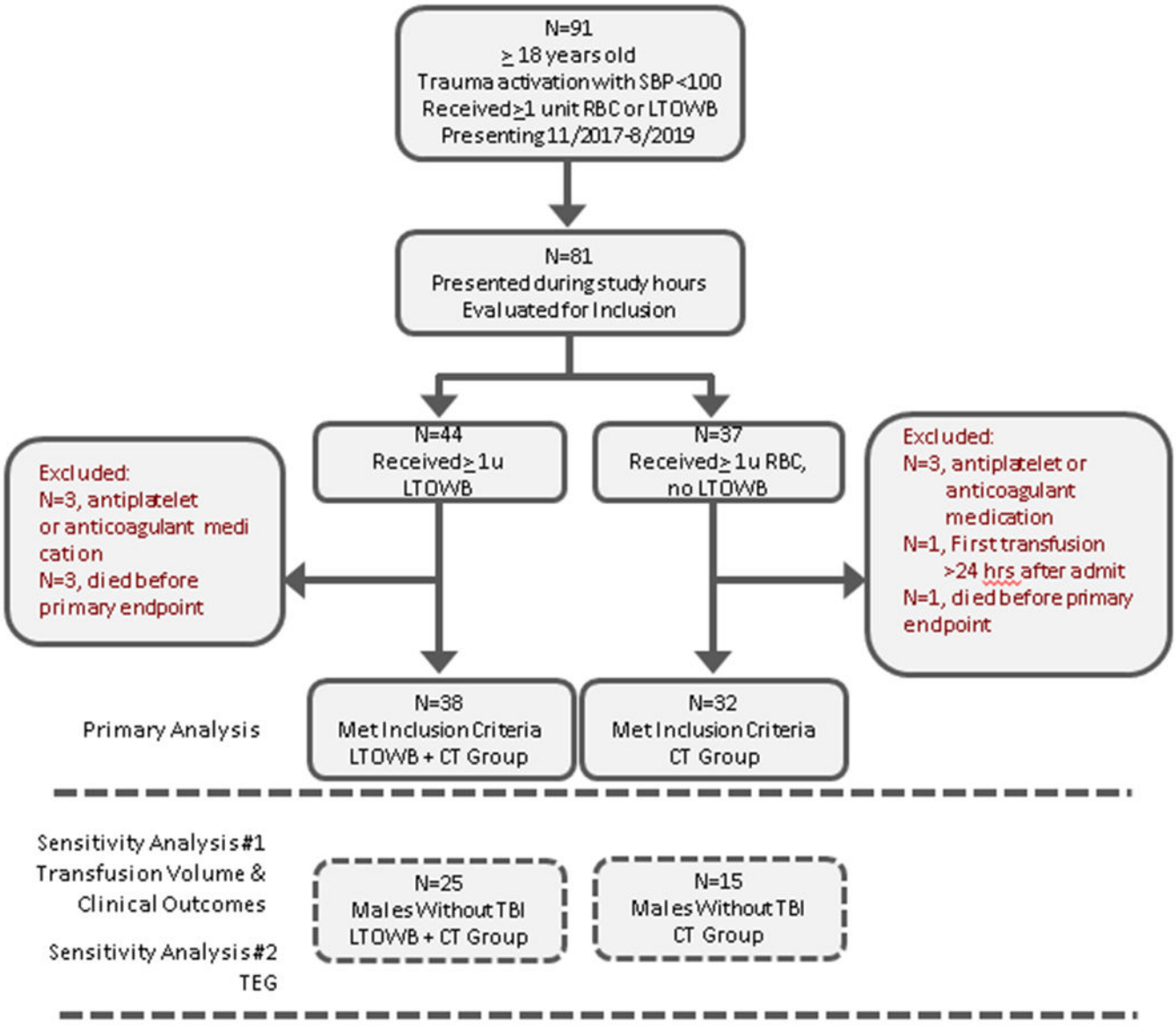

Figure 1:

Inclusion and exclusion criteria and number of patients enrolled.

Abbreviations: CT: Component therapy. LTOWB: low-titer group O whole blood. RBC: red blood cell units. TBI: traumatic brain injury, severe TBI defined as head abbreviated injury score (AIS) ≥ 3(24, 25).

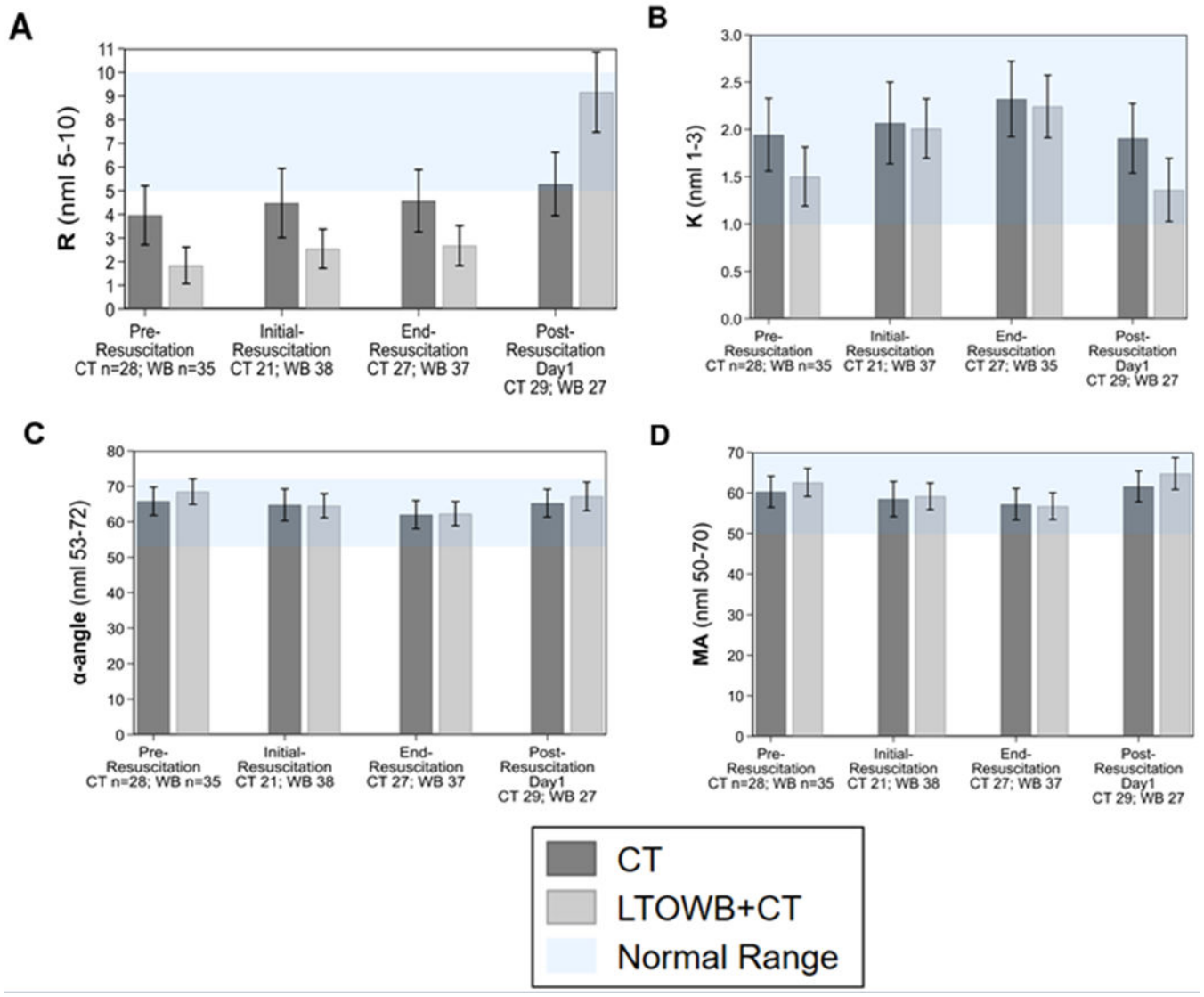

Figure 2:

Thromboelastography measurements in patients receiving LTOWB vs CT as initial resuscitation. Samples were taken upon arrival in the trauma bay, prior to any blood product transfusion (“Pre-Resuscitation”), after the first 6 units of red blood cell-containing product was transfused, regardless of how many plasma and platelet units were transfused (“Initial Resuscitation”), after transfusion of the final blood product, when patients had achieved hemostasis (“End-Resuscitation”), and approximately 24 hours after arrival in the trauma bay (“Post-Resuscitation Day 1”). For patients who had ≤6 units of red blood cell-containing product (RBC or LTOWB) transfused, the “Initial Resuscitation” sample was the same as the “End-Resuscitation” sample. Tests that produced erroneous tracings were not included in this analysis. N for each group is shown below bar graphs.

Abbreviations: CT: Component therapy. LTOWB: low-titer group O whole blood. R: time to first sign of clot, high values indicate coagulopathy, K: rate of clot progression, reflective of fibrinogen level, high values indicate coagulopathy, α-angle: rate of clot progression,

reflective of platelet activity stimulating fibrinogen polymerization, low values indicate coagulopathy, MA: overall clot strength, reflective of platelet aggregation, low values indicate coagulopathy.

Table 1:
Demographics, Injury Characteristics, and Admission Data.

The initial whole blood (LTOWB + CT) group received at least one unit of LTOWB in the first 24 hours. The component therapy (CT) group received at least one unit of RBCs in the first 24 hours, and no LTOWB.

Variable Median [IQR] or N (%)	LTOWB + CT N=38	CT N=32	p value	Δ
Age (years)	38.0 [27.0, 52.0]	37.0 [24.5, 63.0]	0.70	+1.0
Male Sex	38 (100.0%)	22 (68.8%)	<.001	+31.2%
Comorbidities			0.89	
None	26 (68.4%)	19 (59.4%)		+9.0%
One	5 (13.2%)	6 (18.8%)		−5.6%
Two	3 (7.9%)	3 (9.4%)		−1.5%
Three or more	2 (5.3%)	1 (3.1%)		+2.2%
Unable to obtain	2 (5.3%)	3 (9.4%)		−4.1%
Mechanism of Injury			0.30	
Blunt	25 (65.8%)	25 (78.1%)		−12.3%
Penetrating	13 (34.2%)	7 (21.9%)		+12.3%
Injury Severity Score	22.0 [10.0, 34.0]	28.0 [20.5, 38.0]	0.035	−5.0
Severe TBI [a]	13 (34.2%)	11 (34.4%)	0.99	−0.2%
ED GCS	15.0 [11.0, 15.0]	14.5 [10.5, 15.0]	0.96	−0.5
FAST Positive	6 (15.8%)	10 (31.3%)	0.16	−15.5%
First ED SBP mmHg	110 [96, 147]	115 [82, 140]	0.66	−5
First ED HR bpm	107 [87, 120]	109 [81, 122]	0.75	−2
ABC Score [b]			0.81	
0-1	17 (44.7%)	13 (40.6%)		+4.1%
2-4	21 (55.3%)	19 (59.4%)		−4.1%
Admission INR [c]	1.20 [1.10, 1.20]	1.20 [1.10, 1.40]	0.08	0
Admission EtOH (mg/dL) [c]	15.0 [15.0, 56.0]	15.0 [15.0, 106.0]	0.98	0

[a] Head abbreviated injury score (AIS) ≥ 3, used for sub-group sensitivity analysis.

[b] Trauma ABC Score for Massive Transfusion gives one point for each of the following: penetrating mechanism, SBP≤90 while in the ED, HR≥120 while in ED, Positive FAST. (27) Scores of 0 or 1 are not likely to require massive transfusion, while 2-4 are likely to require massive transfusion.

[c] Admission INR values were available for N=37 WB + CT group patients and N=30 CT patients. Admission EtOH values were available for N= 38 WB + CT patients and N= 31 CT patients.

Abbreviations: LTOWB (low-titer group O whole blood), CT (component therapy), GCS (Glascow coma scale), FAST (focus assessment with sonography for trauma), ED (emergency department), SBP (systolic blood pressure), HR (heart rate), INR (international normalized ratio), EtOH (ethanol)

Table 2:

Blood transfusion requirements within 4 and 24 hours of presentation, bivariate associations.

LTOWB + CT group patients received LTOWB as initial resuscitation with up to 4 units of LTOWB transfused depending on availability, and then received CT if further transfusionl was needed. CT group patients received CT only. p values were calculated for planned primary and secondary outcomes.

	4 Hours After Presentation			24 Hours After Presentation		
Variable, median [IQR]	**LTOWB + CT N=38**	**CT N=32**	**p value**	**LTOWB + CT N=38**	**CT N=32**	**p value**
Total Transfusion Volume (mL) [a]	1,750 [1,225, 2,525]	2,813 [1,275, 4,675]	0.15	2,138 [1,275, 3,325]	4,225 [1,900, 5,425]	0.06
LTOWB (units)	2.0 [1.0, 3.0]	0.0 [0.0, 0.0]		2.0 [1.0, 3.0]	0.0 [0.0, 0.0]	
Red Blood Cells (RBC) (units)	4.0 [2.0, 6.0]	7.0 [6.0, 10.0]	0.015	2.0 [0.0, 6.0]	8.0 [5.0, 11.5]	<.001
Apheresis platelets (units)	0.0 [0.0, 1.0]	1.0 [0.0, 2.0]	0.020	0.0 [0.0, 2.0]	1.0 [0.0, 3.5]	0.019
Plasma (units)	0.5 [0.0, 2.0]	3.5 [0.5, 7.0]	0.007	1.0 [0.0, 3.0]	4.0 [2.0, 8.0]	0.005
Equivalent Platelet/RBC Ratio [b]	0.67 [0.50, 1.17]	0.86 [0.60, 2.00]	0.45	1.00 [0.67, 1.17]	0.87 [0.00, 1.55]	0.38
Equivalent Plasma/RBC Ratio [b]	0.65 [0.50, 1.00]	0.58 [0.14, 0.78]	0.17	0.82 [0.67, 1.00]	0.61 [0.31, 0.72]	<.001

[a] Total transfusion volume is the combined total of transfused LTOWB, RBC, plasma, and apheresis platelets received in the first 4 or 24 hours beginning at presentation to the trauma bay.

[b] Each unit of LTOWB was considered equivalent to one unit of RBC, one unit of plasma, and 1/6 of an apheresis platelet unit

Abbreviations: LTOWB (low-titer group O whole blood), CT (component therapy), RBC (red blood cell units), mL (milliliter).

Table 3:

Blood transfusion requirements within 4 and 24 hours of presentation, multivariable analysis.

Adjusted for Injury Severity Score, sex, and presence of a positive Focused Assessment with Sonography for Trauma. Analyses conducted using quantile regression modeling for the 50th percentile. LTOWB + CT group patients received LTOWB as initial resuscitation with up to 4 units of LTOWB transfused depending on availability, and then received CT if further transfusion was needed. CT group patients received CT only. p values were calculated for planned primary and secondary outcomes.

	4 Hours After Presentation			24 Hours After Presentation		
Variable, covariate adjusted median	**LTOWB + CT N=38**	**CT N=32**	**p value**	**LTOWB + CT N=38**	**CT N=32**	**p value**
Total Transfusion Volume (mL)[a]	2,491	2,447	0.93	3,307	3,260	0.95
LTOWB (units)	2	0		2	0	
Red Blood Cells (RBC) (units)	4.75	7.18	0.47	4.28	7.46	0.052
Apheresis platelets (units)	0.23	1.23	0.016	0.85	1.14	0.68
Plasma (units)	1.99	2.64	0.60	2.19	4.33	0.30
Equivalent Platelet/RBC Ratio [b]	0.65	1.03	0.39	1.0	0.923	0.78
Equivalent Plasma/RBC Ratio [b]	0.72	0.49	0.26	0.85	0.63	0.043

[a]Total transfusion volume is the combined total of transfused LTOWB, RBC, plasma, and apheresis platelets received in the first 4 or 24 hours beginning at presentation to the trauma bay.

[b]Each unit of LTOWB was considered equivalent to one unit of RBC, one unit of plasma, and 1/6 of an apheresis platelet unit

Abbreviations: LTOWB (low-titer group O whole blood), CT (component therapy), RBC (red blood cell units), mL (milliliter).

Table 4:
Clinical Outcomes and Complications, adjusted associations.

Adjusted for Injury Severity Score, sex, age, and presence of severe traumatic brain injury. Analyses conducted using quantile regression modeling for the 50th percentile. See Supplementary Table 1 for bivariate analysis comparing specific complications between groups.

Variable, covariate adjusted median or %	LTOWB + CT N=38	CT N=32	p value
30-Day In-Hospital Mortality	4.4%	11.7%	0.19
Hospital free days	9.5	10.8	0.68
ICU free days	18.2	17.3	0.64
Any complication	37.9%	42.4%	0.73

Abbreviations: LTOWB (low-titer group O whole blood), CT (component therapy).