The use of low-titer group O whole blood is independently associated with improved survival compared to component therapy in adults with severe traumatic hemorrhage

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BACKGROUND: There is a resurgence in the use of low-titer group O whole blood (LTOWB) for hemorrhagic shock. We hypothesized the use of LTOWB compared to component therapy (CT) would be independently associated with improved 24-hour mortality.

STUDY DESIGN AND METHODS: In this prospective observational study, trauma patients 18 years of age or older with massive transfusion protocol activations were included from August 17, 2018, to May 14, 2019. The primary outcome was 24-hour mortality. Secondary outcomes included 72-hour blood product totals, multiple organ dysfunction scores (MODS), and 28-day mortality. Multivariable logistic regression (MVLR) and Cox regression were performed to determine independent associations.

RESULTS: There were no clinically meaningful differences in measures of injury severity between study groups (CT, n = 42; LTOWB, n = 44). There was no difference in MODS between study groups. The unadjusted mortality was not statistically different between the study groups (9/42 [21%] for CT vs. 7/44 [16%] for LTOWB; p = 0.518). In the MVLR model, LTOWB increased the odds of 24-hour survival by 23% (odds ratio 0.81, 95% confidence interval 0.69-0.96; p = 0.017). Adjusted survival curve analysis indicated improved survival at both 24 hours and 28 days for LTOWB patients (p < 0.001). Further stratification showed an association between LTOWB use and survival when maximum clot firmness (MCF) was 60 mm or less (p = 0.009).

CONCLUSIONS: The use of LTOWB is independently associated with improved 24-hour and 28-day survival, and does not increase organ dysfunction at 72 hours. Use of LTOWB most impacted survival of patients with reduced clot firmness (MCF ≤60 mm). Collectively, these data support the clinical use and continued study of LTOWB for hemostatic resuscitation.

Trauma is a leading cause of death worldwide, with as many as 40% of trauma-associated mortalities resulting from hemorrhage.[1] In the United States, approximately 30,000 annual traumatic hemorrhagic shock deaths are estimated to be preventable after injury due to untimely or inadequate care.[2] To address the high rate of death from hemorrhage, there has been a resurgence in the use of low-titer group O whole blood (LTOWB) for hemostatic resuscitation due to its increased potency, safety, and logistical benefits compared to component therapy (CT).[3,4] The AABB added LTOWB as a standard product in 2018, and since then, its implementation at trauma centers has rapidly increased in the United States, Norway, and Israel.[4] There are currently approximately 70 centers in the United States using LTOWB, with at least six of these centers

ABBREVIATIONS: BJH = Barnes Jewish Hospital; CPD = citrate-phosphate-dextrose; CT = component therapy; GCS = Glasgow Coma Scale; INR = international normalized ratio; ISS = injury severity score; LTOWB = low-titer group O whole blood; MCF = maximum clot firmness; MODS = multiple organ dysfunction scores; MTP = massive transfusion protocol; MVLR = multivariable logistic regression; REDCap = Research Electronic Data Capture; ROTEM = rotational thromboelastometry.

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LTOWB provides a more concentrated product than CT due to the reduced volume of anticoagulants and additive solutions compared to the amount in each constituent product of an equivalent CT transfusion.[5] LTOWB has increased oxygen-carrying capacity (higher hemoglobin concentration), is more hemostatic (higher coagulation factor and platelet concentration), and is less acidotic relative to 1 unit each of red blood cells (RBCs), plasma, whole blood–derived platelets with CT.[6,7] In addition, LTOWB contains platelets that have been stored cold (4°C). Cold-stored platelets are more hemostatically active compared to room temperature–stored platelets, which are currently used in CT.[8,9] Bacterial contamination risk is therefore mitigated with the use of LTOWB, and donor exposure is also reduced.[10] In addition, the use of only one bag of LTOWB over the multiple bags and vascular access points needed with CT simplifies the logistics of transfusion, resulting in more rapid administration of therapy in the field and at the bedside, potentially improving outcomes in a situation where every minute counts.[10,11] This logistic benefit of LTOWB is pronounced in the prehospital phase of resuscitation, where deaths from hemorrhage are most common.[2]

We hypothesized that the use of LTOWB is independently associated with improved 24-hour mortality and 28-day mortality, reduces the total amount of blood products transfused in the first 72 hours after injury, and does not increase 72-hour multiple organ dysfunction scores (MODS) compared to the exclusive use of CT in adult patients with traumatic injury requiring massive transfusion protocol (MTP) activation.

MATERIALS AND METHODS

Study design

In this prospective observational study, patients were included in the analysis if they were at least 18 years of age, had traumatic injury, and had an MTP activation at Barnes Jewish Hospital (BJH). A waiver of informed consent was obtained for this study (IRB 201909200). The methods for data collection and analysis were designed in July 2018. On December 12, 2018, LTOWB was included in the MTP at BJH. Data for the control group were collected on patients exclusively transfused with CT from August 17, 2018, to December 5, 2018. Data for patients in the LTOWB group were collected between December 12, 2018, and May 14, 2019. During this period, the trauma program policy was to limit the use of LTOWB to 8 units (2 units available in the emergency department and another 6 units delivered from the blood bank when needed) during initial resuscitation. Therefore, patients who were still bleeding and needed additional transfusions in the LTOWB group could have received CT after 8 units of LTOWB were transfused. Patients were required to receive LTOWB during MTP activation for trauma to be included in the LTOWB cohort. The LTOWB was supplied by the American Red Cross, and was leukoreduced with a platelet-sparing filter (IMUFLEX, TerumoBCT). The anti-A and -B titer for all LTOWB units was less than 200. The maximum storage duration at BJH for LTOWB is 21 days. Blood components were provided by the American Red Cross: RBCs were all leukoreduced before storage, platelets were collected by apheresis, and the plasma was all frozen prior to thawing (no never-frozen liquid plasma was used). There were 6 units of both type O RBCs and thawed type A plasma available in the emergency room during the study.

The primary outcome was selected as 24-hour mortality. Secondary outcomes included 28-day mortality, 72-hour total blood products transfused, and 72-hour MODS.

Data collection

Data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Washington University in St. Louis School of Medicine. REDCap is a secure, web-based software platform designed to support data capture for research studies.[12,13] Data collected include all blood product information (LTOWB, RBCs, platelets, plasma, cryoprecipitate) up to 72 hours after admission, injuries sustained, transfusion reactions, and laboratory results upon admission. In addition, the minimum or maximum (whichever represented a greater degree of severity) laboratory results were recorded every 24 hours of hospital admission for up to 72 hours. To examine organ injury, laboratory measures recorded included renal (e.g., blood urea nitrogen and creatinine), hepatic (e.g., alanine aminotransferase, aspartate aminotransferase), hemostatic (e.g., prothrombin time [PT], and rotational elastometry [ROTEM, EXTEM reagent only]) measurements. Samples for baseline laboratory result generation were drawn within 30 minutes of admission. Laboratory values were captured only if they were performed clinically (i.e., no additional tests were ordered solely for the purpose of this study). Blood product data for the first 72 hours after admission were extracted from the BJH blood management system database. The secondary outcome of 72-hour blood product administration is reported as a weight-adjusted volume (mL/kg) to account for both a wide variation in weight in the patient population and variation in volume of blood products units. Fluids (crystalloids and colloids) administered were also normalized by weight and reported in mL/kg.

To calculate the amount of blood and additive solutions administered to both study groups, the following assumptions based on data were made: a single unit of RBCs contains approximately 259 mL of RBCs and plasma, and approximately 118 mL of citrate-phosphate-dextrose (CPD) and additional preservative solution; a single unit of apheresis platelets contains approximately 270 mL of platelets and plasma and approximately 70 mL of CPD; a unit of plasma contains approximately 186 mL of plasma and

48 mL of CPD; finally, a unit of LTOWB contains approximately 500 mL of blood, and 70 mL of CPD.[14] It was also assumed that the entire unit was transfused.

Organ dysfunction was compared at 24 hours, 48 hours, and 72 hours with MODS both by category and in sum. MODS were calculated according to Marshall et al.[15] In brief, each category (respiratory, renal, hepatic, cardiac, hematology, and neurology) is assigned a score (0-5), with a higher score indicating more severe injury. If a value is missing, it is treated as a 0 value (minimum) under the assumption that if the test was not performed, it was due to clinician discretion and not medically necessary. Maximum scores for the 72-hour period were also compared.

Statistical analysis and model selection

Statistical analyses were done with computer software (R 3.6.1, 2019-07-05, with use of additional packages: "coxphf," "readxl," "pROC," "ROCR," and "survival"[16–21]; and Prism version 8.3.0, GraphPad Software, LLC). Epidemiology

TABLE 1. Baseline patient characteristics

Parameter		CT Cohort		LTOWB Cohort	
Patient Descriptors		*n (%) OR median (IQR)*		*n (%) OR median (IQR)*	*p*
Sex					0.708
Male		31/42 (74%)		35/44 (80%)	
Female		11/42 (26%)		9/44 (20%)	
Injury					0.197
Penetrating only		24/42 (57%)		32/44 (74%)	
Blunt only		18/42 (43%)		12/44 (26%)	
Race					0.221
Black or African American		29/42 (74%)		34/44 (77%)	
White or Caucasian		13/42 (26%)		7/44 (16%)	
Other or Unknown		0/42 (0%)		3/44 (7%))	
ISS		22 (17-33)		18 (10-29)	0.162
AIS					
Head		0 (0-3)		0 (0-0)	***0.013***
Face		0 (0-1)		0 (0-0)	***0.010***
Neck		0 (0-0)		0 (0-0)	0.702
Thorax		3 (0-3)		2 (0-3)	0.790
Abdomen		2 (0-3)		1 (0-4)	0.392
Spine		0 (0-2)		0 (0-0)	0.150
Upper Extremities		0 (0-2)		0 (0-2)	0.578
Lower Extremities		1 (0-3)		0 (0-1)	***0.009***
External		0 (0-0)		0 (0-1)	0.071
Other Trauma		0 (0-0)		0 (0-0)	NA*
Admission Variables	*n*	*median (IQR)*	*n*	*median (IQR)*	*p*
Age, y	42	28 (22-38)	41	32 (28-32)	0.158
Weight, kg	41	80.0 (72.6-100.0)	41	80.0 (68.7-90.5)	0.174
BMI	39	27.0 (24.3-33.3)	39	25.6 (22.7-28.4)	0.087
Baseline Labs	*n*	*median (IQR)*	*n*	*median (IQR)*	*p*
GCS	40	12 (3-15)	40	11 (3-15)	0.796
Creatinine, mg/dL	24	1.29 (1.11-1.43)	33	1.26 (1.02-1.44)	0.977
PTT, sec	33	26.1 (23.0-37.6)	30	25.3 (22.4-25.9)	0.032
PT, sec	33	12.6 (11.7-14.2)	29	12.2 (11.8-13.3)	0.533
INR	33	1.2 (1.1-1.3)	29	1.1 (1.1-1.2)	0.944
Hb, g/dL	34	11.8 (10.4-13.7)	29	11.9 (10.6-13.1)	0.995
Platelet count, $X10^3$ cells/μL	34	231.0 (159.5-303.5)	29	238.0 (194.0-275.0)	0.847
Base excess, mEq/L	31	−7 (−13.0-−3.5)	27	−6.0 (−10.0-−4.0)	0.725
Lactate, mmol/L	27	5.40 (4.00-8.05)	23	4.80 (3.10-7.35)	0.430
ROTEM CT, sec	33	72 (66-88)	28	70 (67-80)	0.389
ROTEM MCF, mm	33	59 (51-64)	27	60 (83-63)	0.982
ROTEM α, °	33	69 (62-72)	27	71 (67-73)	0.479
ROTEM LI30	33	100 (100-100)	27	100 (100-100)	0.434
BUN, mg/dL	23	13.0 (10.5-17.0)	32	11.5 (8.8-14.0)	0.095

Any p value that reached significance is bolded.

Patient parameters of interest at baseline split by CT and LTOWB cohorts. Baseline labs were taken within 30 minutes of hospital admission. Parameters are reported either as number of patients/total cohort patients (%) or as median (IQR) where appropriate. Not all patients had a given test result generated within this time period, therefore the n patients of the cohort who did have a result are reported in addition to median (IQR).

* Note that all patients had a 0 score for the AIS–Other Trauma category.

AIS = Abbreviated Injury Scale; BMI = body mass index; BUN = blood urea nitrogen; CT = component therapy; GCS = Glasgow Coma Score; Hb = hemoglobin; INR = international normalized ratio; IQR = interquartile range; ISS = injury severity score; LI30 = lysis index at 30 minutes; LTWOB = low-titer group O whole blood; MCF = maximum clot formation; NA = not applicable; PT = prothrombin time; PTT = partial thromboplastin time; ROTEM = rotational thromboelastometry.

TABLE 2. Blood products and other treatments

Parameter	CT Cohort	LTOWB Cohort	
Blood Product Volumes, weight-adjusted	*median (IQR)*	*median (IQR)*	*p*
RBCs, mL/kg	43.3 (25.0-70.0)	12.3 (0-29.9)	***<0.001***
Platelets, mL/kg	2.8 (1.7-5.5)	0 (0-6.0)	0.100
Plasma, mL/kg	25.7 (12.7-38.1)	7.6 (0-18.6)	***<0.001***
Cryoprecipitate, mL/kg	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.526
Other Treatments	*n (%) OR median (IQR)*	*n (%) OR median (IQR)*	*p*
Normal Saline, n received	36/42 (86%)	36/44 (82%)	
Volume, mL	2316 (820-4230)	2077 (183-2885)	0.326
Weight-adjusted volume, mL/kg	27.6 (9.5-59.7)	23.3 (12.3-51.6)	0.626
Lactated Ringer's, n received	33/42 (79%)	33/44 (75%)	
Volume, mL	2438 (548-5301)	1697 (75-4031)	0.389
Weight-adjusted volume, mL/kg	20.03 (3.1-55.1)	26.0 (5.3-59.8)	0.838
Total Crystalloid Fluids, n received	37/42 (88%)	38/44 (86%)	
Volume, mL	6964 (3971-9630)	4464 (2191-8975)	0.498
Weight-adjusted volume, mL/kg	74.4 (48.3-110.4)	62 (34-100)	0.458
Albumin, n received	18/42 (43%)	18/44 (41%)	
Volume, mL	0 (0-500)	0 (0-563)	0.931
Weight-adjusted volume, mL/kg	0.0 (0.0-6.6)	0 .0 (0.0-9.7	0.700
TXA, n received	21/42 (50%)	15/44 (34%)	0.139
TXA bolus dose, g	1 (1-1)	1 (1-2)	0.066
TXA infusion use, n	8/21 (38%)	0/15 (0%)	
TXA infusion dose, g	1 (1-1)		
Calcium, n received	39/42 (93%)	34/44 (77%)	
Total, g	2.0 (1.0-3.8)	2.0 (1.0-4.1)	0.356
Weight-adjusted 72-hour total dose, mg/kg	25 (10-43)	31 (13-55)	0.603

Any p value that reached significance is bolded.
Crystalloids, colloids, tranexamic acid (TXA), and calcium received for both CT and LTOWB cohorts. Results are reported as n patients/total cohort patients (%) or median (IQR) as appropriate. Crystalloids, colloids, TXA, and calcium are reported as n patients/total cohort, then in median (IQR) volume or dose.
CT = component therapy; IQR = interquartile range; LTOWB = low-titer group O whole blood; TXA = tranexamic acid.

and treatment data are displayed using medians and interquartile ranges or counts and proportions, and compared with use of the Wilcoxon rank-sum test or the chi-square test. P-values less than 0.05 were considered significant. Univariate logistic regression and multivariable logistic regression (MVLR) analyses were performed, with 24-hour and 28-day mortality as outcomes. Area under the curve (AUC) was used to assess the strength of the MVLR models.

To select the final MVLR and survival models, covariates with p-values less than 0.1 for 24-hour mortality were selected from the univariate analysis to adjust the association of the exposure variable in the MVLR model in addition to LTOWB use. Injury severity score (ISS) was forced into the model due to clinical relevance. The correlation coefficients were used to eliminate variables that were highly collinear ($R^2 > 0.6$), and collinear variables with higher clinical

TABLE 3. Primary and secondary clinical outcomes

Parameter	CT Cohort	LTOWB Cohort	
	n (%) OR median (IQR)	*n (%) OR median (IQR)*	*p*
24-hour mortality	9/42 (21%)	7/44 (16%)	0.518
28-day mortality	14/42 (33%)	14/44 (32%)	0.886
LTOWB, mL/kg		23.6 (11.9-45.2)	
Total blood products, mL/kg	74.9 (40.2-116.1)	44.1 (25.8-107.0)	0.093
MODS			
Respiratory	0 (0-0)	0 (0-0)	0.386
Renal	1 (0-1)	0 (0-1)	0.461
Hepatic	0 (0-0)	0 (0-0)	0.838
Cardiologic	0 (0-0)	0 (0-0)	NA*
Hematologic	1 (0-2)	0 (0-2)	0.182
Neurologic	2 (0-3)	3 (0-4)	0.427
Total Score	4 (2-7)	4 (0-7)	0.913

Any p value that reached significance is bolded.
Mortality and weight-adjusted blood product volumes for both CT and LTOWB cohorts. Weight-adjusted blood product volumes (mL/kg) are reported as median (IQR). MODSs reported are the maximum value per category and sum scores over the period of 24 and 72 hours post-admission.
* Note that no patients had a central venous pressure recorded and thus all scores in the cardiologic category were 0.
CT = component therapy; IQR = interquartile range; LTOWB = low-titer group O whole blood; MODS = multiple organ dysfunction scores; NA = not applicable.

relevance and patient representation were kept. The resulting covariates were LTOWB use, Glasgow Coma Scale (GCS) score, ISS, PT, and maximum clot firmness (MCF). Backwards stepwise selection for covariates was then employed to arrive at a fitted model. Variables were eliminated from the model one at a time to determine the covariates with the greatest impact on the model. The resulting model, with LTWOB as the exposure of interest, has only one covariate: MCF. The same covariates were then used to adjust the survival curves with Cox regression, as detailed below.

Survival analyses were performed with use of Cox regression, with follow-up starting at time of admission. The outcome variable was mortality at either 24 hours or 28 days. The study groups were LTWOB versus CT, and survival was adjusted for the previously specified covariate (MCF). Adjusted survival curves were created with use of a marginal estimation model with inverse probability weighting.[22] The proportional hazards assumption was checked using Schoenfeld's residuals, and this assumption was met.

The median MCF value of all patients was 60 mm. Histogram analysis revealed equal distribution of patients about the median (data not shown). Therefore, MCF = 60 mm was selected to divide both LTOWB and CT patients into two new cohorts, "MCF-high" with an MCF greater than 60 mm, and "MCF-low" with an MCF of 60 mm or less. Stratified Kaplan–Meier survival curves were generated to compare the effect of LTOWB versus CT use in the MCF-high and MCF-low cohorts.

TABLE 4. Use of LTOWB improves survival in an adjusted MVLR model

Univariate Regression		24-hour mortality			28-day mortality	
Covariate	*OR*	*95% CI*	*p*	*OR*	*95% CI*	*p*
ISS	0.95	(0.90-1.00)	0.064	1.01	(0.98-1.05)	0.459
AIS - Head	1.00	(0.96-1.38)	0.980	1.61	(1.20-2.25)	***0.003***
AIS - Face	1.04	(0.12-1.91)	0.910	1.11	(0.63-1.90)	0.707
AIS - Neck	0.00	(NA-124.55)	0.991	0.71	(0.24-1.47)	0.428
AIS - Thorax	0.70	(0.47-0.99)	0.053	1.02	(0.77-1.34)	0.889
AIS - Abdomen	0.90	(0.65-1.22)	0.514	0.88	(0.67-1.13)	0.311
AIS - Spine	0.79	(0.39-1.32)	0.435	1.04	(0.68-1.56)	0.834
AIS - Upper Extremities	0.46	(0.19-0.91)	***0.049***	0.75	(0.45-1.20)	0.251
AIS - Lower Extremities	0.76	(0.48-1.11)	0.193	1.05	(0.78-1.39)	0.766
AIS - External	0.80	(0.19-1.81)	0.674	1.67	(0.82-4.33)	0.212
AIS - Other Trauma	NA	NA	NA	NA	NA	NA
BMI	0.98	(0.86-1.09)	0.769	1.01	(0.92-1.09)	0.865
Weight	0.98	(0.95-1.02)	0.390	1.00	(0.98-1.03)	0.861
TXA	1.10	(0.36-3.29)	0.865	0.85	(0.33-2.13)	0.737
LTOWB	0.69	(0.22-2.07)	0.512	0.93	(0.38-2.31)	0.881
Age	0.99	(0.95-1.02)	0.500	1.03	(1.00-1.06)	***0.043***
Creatinine	0.85	(0.23-1.75)	0.724	1.23	(0.63-2.38)	0.507
GCS score	0.87	(0.77-0.97)	***0.020***	0.75	(0.65-0.84)	***<0.001***
PTT	1.03	(1.00-1.09)	0.111	1.04	(1.00-1.10)	0.105
PT	1.66	(1.17-2.62)	***0.015***	2.12	(1.42-3.46)	***<0.001***
INR	534.32	(8.14-1.15E5)	***0.011***	1.9E5	(148.86-8.5E6)	***<0.001***
Hb	0.85	(0.62-1.16)	0.310	1.05	(0.81-1.37)	0.706
Platelet Count	0.98	(0.97-0.99)	***0.002***	0.98	(0.97-0.99)	***<0.001***
Base Excess	0.80	(0.70-0.90)	***0.001***	0.86	(0.77-0.94)	***0.002***
BUN	0.99	(0.92-1.04)	0.793	1.02	(0.98-1.07)	0.299
Lactate	1.24	(1.03-1.52)	***0.024***	1.17	(1.00-1.39)	0.056
ROTEM Clotting Time	1.03	(1.08-1.06)	0.073	1.04	(1.01-1.08)	***0.013***
ROTEM MCF	0.88	(0.80-0.95)	***0.003***	0.93	(0.87-0.99)	***0.022***
ROTEM α	0.90	(0.82-0.96)	***0.009***	0.93	(0.87-0.99)	***0.041***
Multivariable Logistic Regression		**24-hour mortality**			**28-day mortality**	
Mortality Predictor	*OR*	*95% CI*	*p*	*OR*	*95% CI*	*p*
LTOWB	0.81	(0.69-0.96)	***0.017***	0.81	(0.65-1.02)	0.059
Baseline MCF	0.98	(0.97-0.99)	***<0.001***	0.99	(0.98-1.00)	***0.009***
AUC	*0.94*	*(0.87-1.00)*		*0.73*	*(0.58-0.90)*	
Cox Regression		**24-hour adjusted mortality**			**28-day adjusted mortality**	
Survival Predictor	*HR*	*95% CI*	*p*	*HR*	*95% CI*	*p*
LTOWB	0.15	(0.05-0.49)	***0.001***	0.30	(0.14-0.65)	***0.002***
MCF	0.90	(0.87-0.93)	***<0.001***	0.93	(0.90-0.96)	***<0.001***

Any p value that reached significance is bolded. AUC and 95% CI is also reported for MVLR models.
ORs and HRs, 95% CIs, and p values for univariate logistic regression, MVLR, and Cox regression for both 24-hour and 28-day mortality. An increase in OR or HR represents increased likelihood of mortality. Values are group by analysis.
AIS = abbreviated injury scale; AUC = area under the curve; BMI = body mass index; BUN = blood urea nitrogen; CI = confidence interval; GCS = Glasgow Coma Scale; Hb = hemoglobin; INR = international normalized ratio; ISS = injury severity score; LTOWB = low-titer group O whole blood; MCF = maximum clot formation; MVLR = multivariate logistic regression; OR = odds ratio; PT = prothrombin time; PTT = partial thromboplastin time; ROTEM = rotational thromboelastometry; TXA = tranexamic acid.

RESULTS

There were 42 patients analyzed in the group that received CT exclusively, and 44 patients analyzed in the group that received LTOWB. Demographic, injury characteristic, and admission lab data are presented in Table 1. Penetrating injury occurred in 24 of 42 (74%) patients in the CT cohort and 32 of 44 (74%) patients in the LTOWB cohort (p = 0.197). Males constituted 31 of 42 (74%) patients in the CT cohort and 35 of 44 (80%) in the LTOWB cohort (p = 0.708). The median age of the CT cohort was 28 years (interquartile range, 22-32), and the median age of the LTOWB cohort was 32 years (28-42) (p = 0.158). The median ISS was 22 (17-33) in the CT cohort and 18 (10-29) in the LTOWB cohort (p = 0.162). Three Abbreviated Injury Scale (AIS) score categories (head, face, and lower extremities) were statistically different between the cohorts, although the differences do not appear to be clinically meaningful. Admission GCS score was not statistically different between the study groups. In addition, all epidemiological parameters, including laboratory results (hemoglobin, base deficit, platelet count, PT, ROTEM MCF), were not significantly different between the study groups.

Treatments are reported in Table 2. The study groups did not receive different amounts of crystalloids and colloids or calcium. Tranexamic acid (TXA) was administered to 21 of 42 (50%) CT patients and 15 of 44 (34%) LTOWB patients (p = 0.139), with the same median bolus of 1 g in both groups.

Primary and secondary outcomes are reported in Table 3. The unadjusted 24-hour mortality was not statistically different between the study groups: 9 of 42 (21%) for CT and 7 of 44 (16%) for LTOWB (p = 0.518). The unadjusted 28-day mortality was also not statistically different: 14 of 42 (33%) for CT versus 14/44 (32%) for WB (p = 0.86), respectively. Regression results are detailed in Table 4. Univariate regression for the primary outcome of 24-hour mortality was significant for AIS-upper extremities, GCS score, PT, international normalized ratio (INR), platelet count, base excess, lactate, and ROTEM MCF and α angle. INR was collinear with PT, and PT was selected arbitrarily over INR to be included in the MVLR. ROTEM α, platelet count, lactate, and base excess were all collinear with ROTEM MCF. The selection of ROTEM MCF over base excess and lactate allowed inclusion of more patients in the analysis due to missingness in the latter variables. ROTEM MCF was chosen to be included in the MVLR over platelet count since it is a functional measure, and it was chosen over ROTEM α based on clinical relevance. Backwards stepwise regression was implemented, starting with a model including LTOWB, ISS, GCS score, PT, and MCF (Table S1, available as supporting information in the online version of this paper), and arrived at the fitted model with covariates LTOWB and MCF shown in Table 4. In the fitted model, use of LTOWB over CT increased the odds of 24-hour survival by 23% (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.69-0.96; p = 0.017) when adjusted for

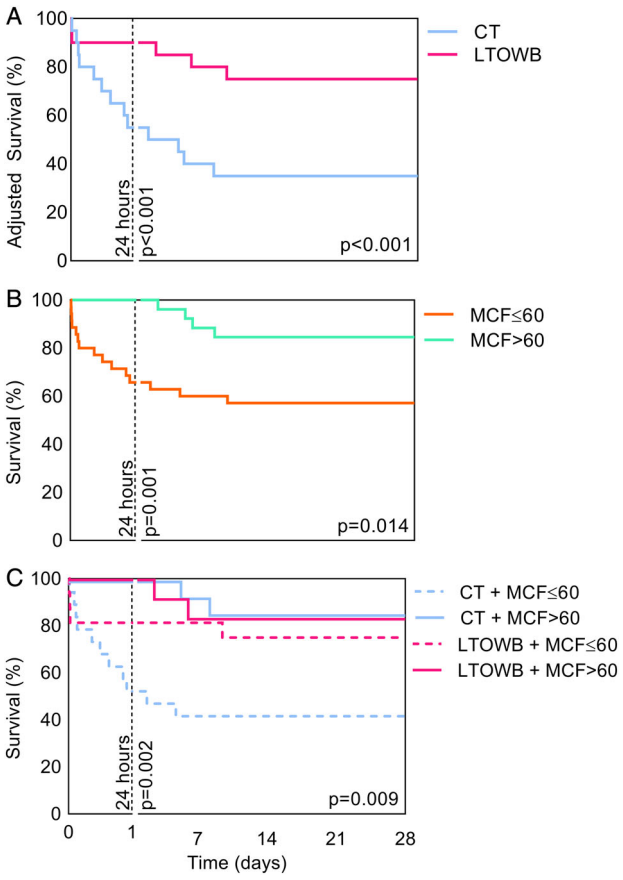

Fig. 1. Use of LTOWB over CT improves survival, especially in coagulopathic patients. Survival curves for three different patient groupings. X-axis labels at bottom. Dashed line denotes 24 hours. (A) Adjusted survival for the LTOWB and CT cohorts. Improved survival with use of LTOWB is significant both for 24-hour (p < 0.001) and 28-day (p < 0.001) mortality. There were 33 CT patients and 28 LTOWB patients with an MCF that served as a basis for the analysis. (B) Survival by the ROTEM MCF parameter. Patients were split into MCF-high and MCF-low cohorts by MCF >60 mm and MCF ≤60 mm, respectively. MCF-high patients have 100% survival versus approximately 60% survival for MCF-low at 24 hours (p = 0.001). MCF-high patients also have improved 28-day survival versus MCF-low patients (p = 0.014). Note: 24-hour survival is at 100% in this subfigure versus subfigure A as not all patients had a ROTEM result. There were 35 patients with an MCF >60 mm and 26 patients with an MCF ≤60 mm. (C) Survival further stratified by LTOWB or CT and MCF category. The improvement in survival imparted by LTOWB is magnified in coagulopathic (MCF ≤60 mm) patients. LTOWB use improved 24 hour survival for both MCF-high and MCF-low patients over CT (p = 0.004), and improved 28-day mortality as well (p = 0.012). There were 19 patients with an MCF <60 mm and 14 patients with an MCF >60 mm who received CT, and 16 patients with an MCF <60 mm and 12 patients with an MCF >60 mm who received WB.

MCF, and 28-day mortality between the groups was unchanged and approached significance (OR, 0.81; 95% CI, 0.65-1.02; p = 0.059). Cox regression is also shown in Table 4 for both 24-hour and 28-day mortality. In the adjusted analyses, LTOWB over CT use was associated 24-hour survival (hazard ratio [HR], 0.15; 95% CI, 0.03-0.49; p = 0.001) compared to CT, as well as 28-day survival (HR, 0.30; 95% CI, 0.14-0.65; p = 0.002). The adjusted survival curve for LTOWB versus CT is shown in Fig. 1A. In these adjusted survival analyses, LTOWB use was independently associated with both increased 24-hour and 28-day adjusted survival (p < 0.001).

The strength of the impact of the ROTEM MCF parameter on survival warranted further exploration. The 24-hour and 28-day unadjusted survival for patients with MCF of 60 mm or less (n = 26) versus greater than 60 mm (n = 35) at baseline is significantly different (24-hour, p = 0.001; 28-day, p = 0.014) and is shown in Fig. 1B. Further stratification of survival of the MCF cohorts into CT or LTOWB recipients is shown in Fig. 1C. LTOWB has the largest association with survival for patients with MCF of 60 mm or less, both for 24-hour (p = 0.002) and 28-day (p = 0.009) time periods.

There was a significant difference between study groups for the amounts of each individual blood product transfused (Table 2). A difference in medians of 1.4 L more of blood products were transfused per patient to the CT group compared to the LTOWB group in the first 72 hours after admission (p = 0.039). When the volume of each product transfused was normalized to patient weight, the reduction in 72-hour total blood product use in the LTOWB group, 44.1 mL/kg (25.8-107), compared to the CT group 74.9 (40.2-116.1) approached significance (p = 0.093). The total units of products transfused, and therefore donor exposures, was increased in the CT compared to the LTOWB group (Table S2, available as supporting information in the online version of this paper). The CT cohort received a median of 7 RBC units, 1 platelet unit, and seven plasma units, which is 3385 mL of actual blood and 1232 mL of additional additive solutions (anticoagulants and preservatives) combined. Comparatively, the LTOWB cohort received a median of 3 RBC units (p < 0.001), 0 platelet units (p = 0.032), 2 plasma units (p < 0.001), and 4 units of LTOWB, which is about 3149 mL of actual blood and 730 mL of additional additive solutions. The LTOWB cohort thus received about 90% of actual blood but only about 60% of the additive solutions that the CT cohort received.

There were no differences in maximum 72-hour MODS for each category, nor for the total score. The median 72-hour maximum MODS for the CT cohort was 4 (2-7) and for the LTOWB cohort was 4 (0-7) (p = 0.913).

DISCUSSION

The results of our study are unique. In this prospective study, we report that the use of LTOWB is independently associated with improved survival at both 24 hours and 28 days without increased 72-hour multiple organ dysfunction. As the LTOWB group was transfused fewer actual blood products (subtracting the volume of additive solutions) and had improved outcomes, it appears that LTOWB is a more potent and perhaps efficacious product.

Our findings are consistent with other reports of cold-stored LTOWB in the literature. In a propensity-matched study of 135 patients where the maximum amount of LTWOB was 4 units, Seheult et al.[14] reported a significant time to normalization of lactate concentrations with LTOWB use compared to CT patients. In our study, the LTOWB cohort was able to get up to 8 units (one patient received 10 units, in violation of hospital policy). In another single-center, prospective, observational study of 198 patients where with either prehospital or in-hospital transfusions, LTOWB over CT use was associated with a 53% reduction in post–emergency department blood product transfusion (OR, 0.47; 95% CI, 0.23-0.94; p = 0.033) and a two-fold increase in likelihood of 30-day survival (OR, 2.19; 95% CI, 1.01-4.76; p = 0.047).[23]

In addition to LTOWB use, an MCF of 60 mm upon admission was a striking predictor of mortality (Fig. 1B). Interestingly, LTOWB also had the greatest impact on survival in the subset of patients with an MCF of 60 mm or less (Fig. 1C). MCF reflects clot strength, and a low MCF can be indicative of a number of pathologies, including a reduced platelet count, reduced platelet function, reduced fibrinogen levels, fibrinogen disorders, or low factor XIII activity. MCF has been shown previously to be a predictor for massive transfusion and mortality.[24,25] Further exploration of MCF indications for transfusion and impactful use of LTOWB in the hemorrhaging patient may provide insight into the use of targeted LTOWB therapy.

It is important to note that LTOWB is a different product than warm fresh whole blood (WFWB). These differences have been recently reviewed.[4] Data in retrospective studies of WFWB have also indicated improved survival when transfused.[5,25]

Our study has its limitations. As it was a single center study of 86 patients, the small sample size limits the generalizability of the results. Another limitation is the lack of data available regarding time of injury and prehospital treatments, though in the area of service of our trauma center, blood products are not given before hospital admission and the use of tranexamic acid before hospital admission is very limited. Admission labs were collected within a half-hour time period from admission and, as a result, may be influenced by the initial course of care. Missing data for laboratory values is another limitation at all time points, as this may have introduced bias in our analysis of organ injury for the 72 hours after hospital admission.

CONCLUSIONS

The use of LTOWB use is independently associated with improved 24-hour and 28-day survival without increased 72-hour organ dysfunction score. Use of LTOWB most

impacted survival of patients with reduced clot firmness (MCF ≤60 mm). Collectively, these data and analyses support the use of LTOWB for hemostatic resuscitation in the hemorrhaging trauma patient and the potential for the development of goal-directed indications for LTOWB transfusion. Large multicenter clinical trials are needed for definitive evidence regarding the efficacy and safety of LTOWB compared to CT in severely bleeding patients.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplemental Table S1. Backwards Stepwise Regression for 24-Hour Mortality Multivariate logistic regression (MVLR) model progression for elimination of covariates. Initial covariates: use of low-titer group O whole blood (LTOWB), injury severity score (ISS), Glasgow Coma Score (GCS), prothrombin time (PT), and rotational thromboelastometry (ROTEM) maximum clot firmness (MCF). Selection was narrowed down to MCF and LTOWB use for the fitted MVLR model.

Supplemental Table S2. Units and Volumes of Blood Products Received Blood products received for both component therapy (CT) and low-titer O whole blood (LTOWB) cohorts. Results are reported as n patients/total cohort patients (%) or median (IQR) as appropriate. Blood products are first reported as n patients/total cohort patients that received the product and the median (IQR) units received for all cohort patients, then in median (IQR) volume. Significant differences ($p < 0.05$) are bolded.