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SUPPLEMENT ARTICLE

TRANSFUSION

Prehospital whole blood reduces early mortality in patients with hemorrhagic shock

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Abstract

Background: Low titer O+ whole blood (LTOWB) is being increasingly used for resuscitation of hemorrhagic shock in military and civilian settings. The objective of this study was to identify the impact of prehospital LTOWB on survival for patients in shock receiving prehospital LTOWB transfusion.

Study design and methods: A single institutional trauma registry was queried for patients undergoing prehospital transfusion between 2015 and 2019. Patients were stratified based on prehospital LTOWB transfusion (PHT) or no prehospital transfusion (NT). Outcomes measured included emergency department (ED), 6-h and hospital mortality, change in shock index (SI), and incidence of massive transfusion. Statistical analyses were performed.

Results: A total of 538 patients met inclusion criteria. Patients undergoing PHT had worse shock physiology (median SI 1.25 vs. 0.95, $p < .001$) with greater reversal of shock upon arrival (−0.28 vs. −0.002, $p < .001$). In a propensity-matched group of 214 patients with prehospital shock, 58 patients underwent PHT and 156 did not. Demographics were similar between the groups. Mean improvement in SI between scene and ED was greatest for patients in the PHT group with a lower trauma bay mortality (0% vs. 7%, $p = .04$). No survival benefit for patients in prehospital cardiac arrest receiving LTOWB was found ($p > .05$).

Discussion: This study demonstrated that trauma patients who received prehospital LTOWB transfusion had a greater improvement in SI and a reduction in early mortality. Patient with prehospital cardiac arrest did not have an improvement in survival. These findings support LTOWB use in the prehospital setting. Further multi-institutional prospective studies are needed.

KEYWORDS

mortality, pre-hospital transfusion, propensity match, whole blood

1 | INTRODUCTION

Hemorrhage remains the leading cause of preventable death for trauma patients.[1] Although bleeding control is paramount to improving survival,[2] the treatment of hemorrhagic shock through resuscitative efforts remains a mainstay of care until definitive management is obtained. In the case of severely injured patients with significant shock burden, prolonged hospital transport times decrease patient survival. In an attempt to improve outcomes from hemorrhage, global trauma systems focus on the importance of prehospital bleeding control and transfusion[3–6] by air or ground units. Whole blood is experiencing a resurgence of interest with the proposed advantages of lower transfusion volume, ease of administration compared to component therapy (defined as a 1:1:1 ratio of packed red blood cells, fresh frozen plasma, and platelets), and exposure to multiple donors. Reintroduced during the military conflicts in Iraq and Afghanistan, resuscitation with whole blood is practiced in all phases of care for the injured warfighter and has been incorporated into the Tactical Combat Casualty Care guidelines as a first-line agent in hemorrhagic shock resuscitation.[7] Utilizing warm fresh whole blood transfusion, the 75th Ranger Regiment's Ranger O Low Titer (ROLO) program is a walking blood bank allowing for whole blood transfusion on the battlefield.[8] Beyond the US Military, whole blood use has become a multinational practice with wartime collaboration and development of civilian whole programs around the world.[9] In civilian prehospital resuscitation, previous studies focused on the impact of prehospital plasma on patients in hemorrhagic shock secondary to trauma.[10] Few studies have specifically addressed the use of whole blood in the civilian prehospital setting.

Since January 2018, whole blood has been available in the prehospital realm for the Southwest Texas Regional Advisory Council (STRAC) Trauma Service Area—P (TSA-P), which encompasses 28,000 square miles.[11] Originally providing low titer (<1:256 anti-A, anti-B) type O, Rh+ whole blood (LTOWB) by air, LTOWB is now available across the region in both urban and rural environments by ground and air. Using predetermined transfusion criteria, prehospital providers are able to initiate emergency release transfusion of LTOWB to patients in hemorrhagic shock. When patients arrive at the Level I trauma center, resuscitation with LTOWB continues until definitive management of hemorrhage is obtained. Based on these early promising experiences, the objective of this study was to determine if prehospital LTOWB transfusion compared to no prehospital LTOWB transfusion improves survival in three distinct groups of trauma patients: in-hospital transfusion only, prehospital cardiac arrest, or patients with development of shock physiology in the field.

2 | METHODS

The institutional trauma registry at an academic Level I trauma center was queried from 2015 to 2019 for consecutive adult patients who underwent transfusion after arrival to the emergency department (ED). Institutional review board approval was obtained and a waiver of informed consent was granted due to the retrospective nature of the study. Patients were then stratified based on receiving prehospital LTOWB (PHT) or no prehospital LTOWB transfusion (NT). Patients in the NT group either received crystalloid infusion or no infusion en route to the trauma center. Patients with incomplete or missing prehospital records were excluded. Incomplete records were those that had no documented prehospital vital signs or incomplete prehospital vital signs required for comparative analysis, or those for whom a prehospital paper record was not available rendering assessment of nadir systolic blood pressure (SBP) impossible. Patient demographics, injury characteristics, prehospital vital signs, and arrival vital signs were compared. ED, 6-h and 12-h mortality, and length-of-stay (LOS) mortality, as well as incidence of either massive transfusion (defined as >10 U of product transfused in 24 h) or incidence of transfusion of >3 U of product in 1 h (CAT3+[12]) were compared between the PHT and NT groups. Transfusion volumes in the ED as well as over the LOS were also compared. Prehospital vital signs were defined by the nadir heart rate (HR) and SBP throughout transport and the corresponding shock index (SI). Shock was defined as SBP ≤ 90 mmHg. The initiation of prehospital LTOWB transfusion was based on specific previously published criteria.[11]

In a sub-group analysis, all patients who sustained prehospital cardiac arrest were identified. Prehospital arrest patients were then divided into groups based on PHT or NT. These groups were compared for demographics, injury characteristics, prehospital vital signs, and arrival vital signs as well as ED and LOS mortality.

Finally, a propensity-matched analysis comparing PHT and NT was performed for patients who presented in shock. A 2:1 propensity-matched group based on injury severity score (ISS), age, male gender, and penetrating mechanism was generated. Patient demographics, injury characteristics, and prehospital and arrival vital signs were compared. ED, 6-h and 12-h mortality, LOS mortality, incidence of MT and CAT3+, arrival transfusion volumes in the ED, and transfusion volumes over the LOS were also compared between PHT and NT groups.

Categorical variables were compared using chi-squared test. Non-normally distributed continuous variables were compared using the Mann–Whitney *U* test. A *p*-value of ≤.05 was considered significant. Statistical analysis was performed using IBM SPSS for Windows (Version 22.0. IBM Corp., Armonk, NY).

3 | RESULTS

3.1 | Study cohort

During the study period, a total of 803 patients who underwent transfusion after hospital arrival were identified with 538 patients remaining for analysis after exclusions. Of the 538 patients undergoing transfusion upon arrival, 107 patients (19.8%) received PHT with 431 patients in the NT group (Figure 1). Of the 265 excluded patients, 255 had missing prehospital run sheets precluding assessment of nadir SBP and 10 had incomplete records precluding complete analysis. These 265 excluded patients had similar injury severity and arrival vital signs compared to included patients with regard to median ISS (19 IQR 10–29 vs. 22 IQR 10–30, $p = .08$), median arrival SBP (99 mmHg IQR 76–122 vs. 95 mmHg IQR 78–120, $p = .64$), median arrival Glasgow Coma Scale score (GCS) (8 IQR 3–15 vs 11 IQR 3–15, $p = .17$), and median TRISS score (0.89 IQR 0.21–0.97 vs. 0.80 IQR 0.16–0.97, $p = .17$), respectively.

The PHT group had a higher incidence of male patients (84.1% vs. 69.4%, $p = .002$), more penetrating trauma (63.6% vs. 27.6%, $p < .001$), and lower median ISS (17 vs. 22, $p = .004$) (Table 1). PHT patients had a lower prehospital nadir SBP (81 vs. 92 mmHg, $p < .001$), higher median HR (107 vs. 94 bpm, $p = .02$), and a higher nadir SI compared to NT patients (1.25 vs. 0.95, $p < .001$) (Table 2). Change in SI (delta SI) from nadir to arrival was reduced more significantly in the PHT group compared to the NT group (−0.28 vs. -0.002, $p < .001$). Mortality between the two groups at all time points was not statistically different ($p > .05$). Although the number of patients in the PHT and NT groups were similar with regard to incidence of massive transfusion, the PHT group had fewer patients undergoing massive transfusion (defined as >10 U in 24 h) compared to the NT group (30.8% vs. 42.2%, $p = .03$). PHT patients required less blood product volume in the ED (1000 ml, IQR 0–2000 vs. 1400 ml, IQR 700–2700, $p < .03$) but ultimately received the same total volume of transfusion over the course of their hospital stay (2000 ml, IQR 1000–5000 vs. 1900 ml, IQR 700–3300, $p = .13$) compared to NT patients. The PHT group received significantly less prehospital crystalloid (median 400 ml IQR 10–510 vs. 500 ml IQR 300–1000, $p < .01$) compared to the NT group.

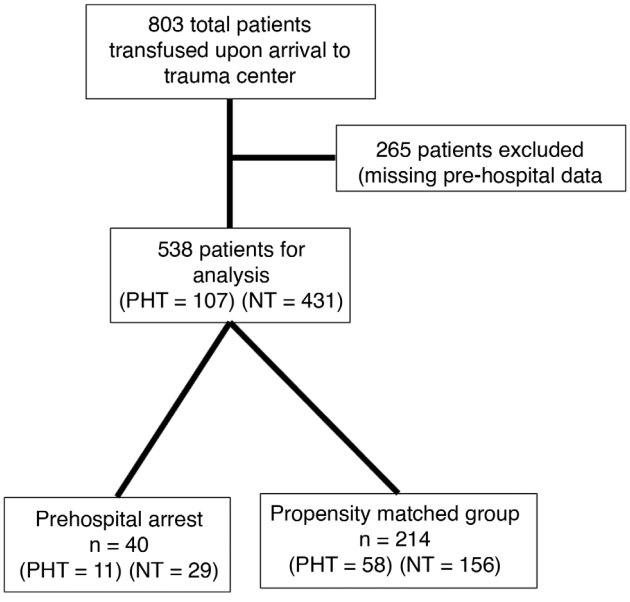

FIGURE 1 Consort diagram. NT, no prehospital LTOWB transfusion; PHT, prehospital LTOWB transfusion

3.2 | Prehospital cardiac arrest

A subanalysis was performed on patients who sustained prehospital cardiac arrest yielding a total of 40 patients who underwent on-scene CPR. This group contained 11 PHT patients (27.5%) and 29 NT patients (72.5%). Demographics including injury characteristics were similar between groups (Table 3). ED mortality was similar between PHT (63.6%, $n = 7$) and NT groups (55.0%, $n = 22$, $p = .46$) while in hospital, LOS mortality showed a trend toward improved mortality in the PHT group versus the NT group (81.8% vs. 100%, $p = .07$).

3.3 | Propensity-matched cohort for patients with prehospital shock

A total of 214 patients were in the propensity-matched cohort with 58 patients (27%) in the PHT and 156 patients (73%) in the NT. The cohorts were similar in demographics and injury characteristics with a similar median ISS (19 vs. 22, $p = .13$), similar median age (38 vs. 39 years, $p = .19$) for PHT and NT patients, respectively. The PHT patients had a higher percentage of male gender (84.5% vs. 67.9%, $p = .02$) and a higher incidence of penetrating trauma (58.6% vs. 28.8%, $p < .01$) (Table 4). PHT and NT patients had similar median nadir SBP (75 vs.

TABLE 1 Demographics and injury characteristics for all patients undergoing transfusion upon arrival to the trauma bay

	PHT ($n = 107$)	NT ($n = 431$)	*p*-value
%Male (*n*)	84.1 (90)	69.4 (299)	*.002*
%Penetrating (*n*)	63.6 (68)	27.6 (119)	*<.001*
Median age (IQR)	32 (24–46)	40 (27–60)	*<.001*
Median ISS (IQR)	17 (9–27)	22 (11–33)	*.004*
Median AIS head (IQR)	3 (2–5)	3 (3–5)	.80
Median AIS thorax (IQR)	3 (2–4)	3 (3–4)	.44
Median AIS abdomen (IQR)	3 (2–4)	2 (2–3)	.49

Abbreviations: AIS, abbreviated injury scale; IQR, interquartile range; ISS, injury severity score; NT, no prehospital transfusion; PHT, prehospital transfusion.

TABLE 2 Prehospital, arrival vital signs, mortality, massive transfusion rates, transfusion volumes upon arrival to emergency department, and LOS transfusion volumes for all patients on arrival to the trauma bay

	PHT ($n = 107$)	NT ($n = 431$)	*p*-value
Median prehospital nadir SBP (IQR)	81 (59–94)	92 (71–117)	*<.001*
Median prehospital HR (IQR)	107 (74–124)	94 (76–114)	*.02*
Median prehospital SI (IQR)	1.25 (0.97–1.61)	0.95 (0.75–1.32)	*<.001*
Median arrival SBP, mmHg (IQR)	92 (72–115)	96 (80–121)	.19
Median arrival HR, mmHg (IQR)	105 (77–122)	100 (79–123)	.79
Median arrival SI (IQR)	1.14 (0.80–1.48)	1.01 (0.77–1.39)	.16
Median delta SI (IQR)	−0.28 (−0.56–0.16)	−0.002 (−0.21–0.18)	*<.001*
Death in ED, % (*n*)	10.3 (11)	13.2 (57)	.41
Death in 6 h, % (*n*)	16.8 (18)	19.3 (83)	.56
Death in 24 h, % (*n*)	22.4 (24)	24.9 (107)	.60
Hospital death, % (*n*)	29 (31)	34.8 (150)	.25
CAT3+ transfusion requirement, % (*n*)	51.1 (47)	57.6 (228)	.26
MT (>10 U in 24 h), % (*n*)	30.8 (33)	42.2 (182)	*.03*
Median arrival transfusion volume, ml, (IQR)	1000 (0–2000)	1400 (700–2700)	*<.01*
Median LOS transfusion volume, ml, (IQR)	2000 (1000–5000)	1900 (700–3300)	.13

Abbreviations: CAT3+, critical administration threshold of >3 U of product in 1 h; ED, emergency department; HR, heart rate; IQR, interquartile range; LOS, length of stay; MT, massive transfusion (>10 U of product in 24 h); NT, no prehospital transfusion; PHT, prehospital transfusion; SBP, systolic blood pressure, SI, shock index.

TABLE 3 Demographics, injury characteristics, and outcomes of patients sustaining prehospital cardiac arrest

	PHT ($n = 11$)	NT ($n = 29$)	*p*-value
%Male (*n*)	66.7 (6)	62 (31)	.79
%Penetrating (*n*)	44.4 (4)	30 (15)	.40
Median age (IQR)	37 (35–66)	40 (27–60)	.77
Median ISS (IQR)	22 (11–27)	24 (12–38)	.39
Median AIS head (IQR)	3 (2–4)	4 (3–5)	.10
Median AIS thorax (IQR)	3 (2–5)	3 (3–4)	.57
Median AIS abdomen (IQR)	2 (2–4)	2 (2–4)	.70
Death in ED, % (*n*)	63.6 (7)	55 (22)	.46
Hospital death, % (*n*)	81.8 (9)	100 (29)	.07

Abbreviations: AIS, abbreviated injury scale; IQR, interquartile range; ISS, injury severity score; NT, no prehospital transfusion; PHT, prehospital transfusion.

TABLE 4 Demographics and injury characteristics of propensity-matched group

	PHT ($n = 58$)	NT ($n = 156$)	p-value
%Male (n)	84.5 (49)	67.9 (106)	*.02*
%Penetrating (n)	58.6 (34)	28.8 (45)	*<.01*
Median age (IQR)	38 (25–48)	39 (26–59)	.19
Median ISS (IQR)	19 (10–29)	22 (10–32)	.13
Median AIS head (IQR)	4 (3–5)	3 (3–5)	.88
Median AIS thorax (IQR)	3 (2–4)	3 (2–4)	.78
Median AIS Abdomen (IQR)	3 (2–4)	2 (2–4)	.28

Abbreviations: AIS, abbreviated injury scale; IQR, interquartile range; ISS, injury severity score; NT, no prehospital transfusion; PHT, prehospital transfusion.

TABLE 5 Prehospital, arrival vital signs, mortality, massive transfusion rates, transfusion volumes upon arrival to emergency department, and LOS transfusion volumes for propensity-matched group

	PHT ($n = 58$)	NT ($n = 156$)	p-value
Median prehospital nadir SBP (IQR)	75 (62–83)	74 (66–82)	.91
Median prehospital HR (IQR)	113 (90–128)	93 (79–125)	*.03*
Median prehospital SI (IQR)	1.5 (1.2–2.0)	1.4 (1.1–1.8)	.051
Median arrival SBP, mmHg (IQR)	92 (81–114)	86 (77–100)	.07
Median arrival HR, mmHg (IQR)	113 (92–130)	106 (83–128)	.87
Median arrival SI (IQR)	1.2 (0.87–1.48)	1.21 (0.9–1.5)	.66
Median Delta SI (IQR)	−0.38 (−0.08 to −0.72)	−0.18 (0.02 to −0.48)	.04
Death in ED, % (n)	0.0 (0)	7.1 (11)	*.04*
Death in 6 h, % (n)	5.3 (3)	14.1 (22)	.08
Death in 24 h, % (n)	17.2 (10)	23.1 (36)	.36
Hospital death, % (n)	13.8 (8)	25 (39)	.08
CAT3+ transfusion requirement, % (n)	53.4 (31)	60.3 (94)	.37
MT (>10 U in 24 h), % (n)	61.5 (16)	48.7 (75)	.23
Median arrival transfusion volume, ml (IQR)	1300 (0–2000)	1975 (1000–3175)	*<.01*
Median LOS transfusion volume, ml, (IQR)	2825 (1550–5500)	2000 (1300–4000)	.048

Abbreviations: CAT3+, critical administration threshold of >3 U of product in 1 h; ED, emergency department; HR, heart rate; IQR, interquartile range; LOS, length of stay; MT, massive transfusion (>10 U of product in 24 h); NT, no prehospital transfusion; PHT, prehospital transfusion; SBP, systolic blood pressure; SI, shock index.

74 mmHg, $p = .91$). The PHT group had a higher median HR (113 vs. 93, $p = .03$) with a trend toward a higher median SI (1.5 vs 1.4, $p = .051$) prior to transfusion.

On arrival to the trauma bay, patients undergoing PHT had a lower median HR, a trend toward a higher median SBP and a greater improvement in median SI compared to NT patients (−0.38 vs. −0.18, $p = .004$) (Table 5). ED mortality was reduced in the PHT group (0% vs. 7%, $p = .038$) with a trend toward lower 6 h mortality (5.2% vs. 14.1%, $p = .07$). 24-h mortality (17.2% vs. 23.1%, $p > .05$) and LOS mortality (13.8% vs. 25%, $p > .05$) were similar between PHT and NT groups, respectively (Table 5). There was no difference in incidence of MT (PHT 61.5% vs. NT 41.7%, $p > .05$) or CAT3+ (PHT 53.4% vs. NT 60.3%, $p > .05$) between groups. PHT patients had a lower median volume of blood products transfused in the ED on arrival (1300 ml, IQR 0–2000 vs. 1975 ml, IQR 1000–3175, $p < .01$) but ultimately required a larger transfusion volume over their entire hospital stay (2825 ml, IQR 1550–5500 vs. 2000 ml, IQR 1300–4000, $p = .048$) compared to the NT patients. The PHT group also received a significantly lower volume of crystalloid prehospital (median 475 ml IQR 40–510 vs. 500 ml IQR 500–1000, $p < .01$) compared to the NT group.

4 | DISCUSSION

As prehospital transfusion practices continue to advance across the globe, the face of resuscitation for patients in

hemorrhagic shock also continues to evolve.[9,13] The recent addition of whole blood in trauma resuscitation algorithms has led to the potential for improved survival in civilians. For severely injured patients, earlier reversal of shock physiology has the potential benefit to improve both short- and long-term outcomes. This retrospective study illustrates the potential impact of prehospital transfusion with LTOWB in severely injured patients with hemorrhagic shock. In examining all patients transfused upon arrival, despite a higher degree of shock as defined by lower nadir SBP and higher SI, the PHT group exhibited a greater improvement in SI upon arrival with a resultant reduction in subsequent massive transfusion. In examining patients with the most severe shock physiology in the field, the PHT cohort demonstrated a reduction in trauma bay mortality and a substantial improvement in shock after LTOWB transfusion compared to NT. Although short-term mortality appears to have improved, there is no observed benefit in long-term mortality outcomes. In this group, there did not appear to be a difference in the incidence of massive transfusion based on PHT or NT status.

Use of PHT also reduced the volume of prehospital crystalloid with over 25% of patients receiving almost no crystalloid compared to at least 500 ml in the NT group. Patients who undergo prehospital resuscitation across STRAC TSA-P are cared for by an array of prehospital providers via air and ground transport. All of these providers practice hypotensive resuscitation, and crystalloid administration is only used for patients in shock who require additional volume to improve perfusion pressure. Originally believed to improve outcomes in hemorrhaging patients,[14] recent evidence has pointed toward worse outcomes for patients who receive crystalloid in addition to blood transfusion. In a recent secondary analysis of the Prehospital Air Medical Plasma Trial, crystalloid volume was associated with increased mortality in patients receiving blood transfusion.[15] Although patients in the NT group required more crystalloid and were not transfused, the significant reduction in early crystalloid volume in patients undergoing PHT further supports the use of prehospital whole blood.

For patients sustaining prehospital cardiac arrest, there appears to be no survival benefit when patients are transfused LTOWB. This observation is likely due to the array of non-survivable injuries leading to prehospital arrest. The transfusion of LTOWB, which may allow for temporary return of spontaneous circulation in the prehospital setting, does not appear to significantly impact ED or hospital survival. This population should be given specific consideration when developing prehospital transfusion criteria as to determine the appropriate allocation of limited blood resources. While examining patients undergoing LTOWB transfusion across the STRAC TSA-P, transfusion triggers are continuing to be modified through process improvement.

This study has several limitations that merit further discussion. First, the study is limited by its retrospective nature and small sample size. Analysis of the original data revealed a significant difference between injury severity in the transfused population across TSA-P. The decision to transfuse patients is often multifactorial and allows for significant provider discretion. While previously described transfusion parameters[11] do include physiologic triggers, there is allotment for clinical judgment which at times led to transfusion of severely injured patients prior to physiologic decline or clinical shock. Likewise, there was some degree of transfusion of less injured patients. These transfusion triggers were not available to prehospital providers at the start of the study period, prior to the initiation of the prehospital LTOWB program. As a result, a propensity-matched cohort was necessary to allow for appropriate comparison. This group, while reflective of severely injured patients, does not reflect the entire cohort of transfused patients who undergo PHT across TSA-P. Additionally, a large portion of the original study cohort was excluded based on missing prehospital records. Nationally, scene vital signs are defined as vital signs obtained prior to leaving the scene of injury. As would be expected, a large number of patients are initially hemodynamically normal and progress toward shock, leading to the use of nadir SBP in this study as it more closely reflects the patient's vital signs at the time of transfusion. Although this allowed for better reflection of the patient's physiologic status in the prehospital setting, these records were not universally available or in some cases were incomplete. This did not allow for accurate comparison of these groups leading to a significant number of exclusions. Finally, this study is limited by sample size, which to reach 80% power would require approximately 200 patients per group.

This study represents the largest group of patients transfused LTOWB in the prehospital setting across a trauma region with a resultant reduction in early mortality for severely injured patients with a significant shock burden. To more thoroughly study the impact of PHT on severely injured trauma patients, a prospective, multi-institutional study is needed.

CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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