MILITARY MEDICINE, 00, 0/0:1, 2021

The Use of Whole Blood Transfusion During Non-Traumatic Resuscitation

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ABSTRACT
Background:
Evidence from military populations showed that resuscitation using whole blood (WB), as opposed to component therapies, may provide additional survival benefits to traumatically injured patients. However, there is a paucity of data available for the use of WB in uninjured patients requiring transfusion. We sought to describe the use of WB in non-trauma patients at Brooke Army Medical Center (BAMC).

Materials and Methods:
Between January and December 2019, the BAMC ClinComp electronic medical record system was reviewed for all patients admitted to the hospital who received at least one unit of WB during this time period. Patients were sorted based on their primary admission diagnosis. Patients with a primary trauma-based admission were excluded.

Results:
One hundred patients were identified who received at least one unit of WB with a primary non-trauma admission diagnosis. Patients, on average, received 1,064 mL (750–2,458 mL) of WB but received higher volumes of component therapy. Obstetric/gynecologic (OBGYN) indications represented the largest percentage of non-trauma patients who received WB (23%), followed by hematologic/oncologic indications (16%).

Conclusion:
In this retrospective study, WB was most commonly used for OBGYN-associated bleeding. As WB becomes more widespread across the USA for use in traumatically injured patients, it is likely that WB will be more commonly used for non-trauma patients. More outcome data are required to safely expand the indications for WB use beyond trauma.

INTRODUCTION

In injured patients with hypotension or ongoing bleeding, the principle of damage control resuscitation is well described and focuses on control of hemorrhage, early blood transfusion, and mitigation of acidosis, hypothermia, and coagulopathy.[1] With challenges associated with blood supply logistics within theater, especially for platelet transfusions, the U.S. military frequently employs whole blood (WB) as mitigation. The use of fresh whole blood has improved outcomes in combat casualties when compared to a balanced 1:1 ratio of packed red blood cells (PRBCs) and fresh frozen plasma (FFP).[2] WB has an approximately 30% higher oxygen carrying capacity, has improved platelet function, requires decreased volumes of anticoagulants for storage, and reduces recipient exposure to only one donor's antigen.[3] Given the improved outcomes with WB and to address the need for platelets in far-forward areas, the Armed Services Blood Program dispersed uncrossmatched low-titer O whole blood (LTOWB) throughout the battlespace.[2,4] The wartime lessons regarding WB transfusion have been implemented in civilian trauma centers and emergency medical service agencies in the USA with positive outcomes in both adults and children.[5–11]

Although the majority of blood products are transfused in the setting of trauma, there are a number of non-trauma settings in which WB may benefit patients including obstetrics, gastroenterology, surgery, oncology, and critical care. One study reported that non-trauma patients received 37.8% of all massive transfusions and up to 25% of total blood products consumed at a trauma center.[12] However, there is a paucity

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doi:10.1093/milmed/usab128

of data available for the use of WB in non-trauma patients requiring transfusion. We are seeking to describe one institution's use of LTOWB for non-traumatic indications within the USA.

METHODS

Subjects and Setting

The U.S. Army Institute of Surgical Research regulatory office reviewed protocol H-20-016 and determined it was exempt from institutional review board oversight. We obtained only de-identified data. Our study took place at the Brooke Army Medical Center (BAMC) in San Antonio, Texas. The BAMC is a large, academic hospital and the only level 1 trauma center with the Department of Defense. It had approximately 84,000 emergency department visits during 2019. We submitted a data request to our Information Management Division for all patients within our electronic medical record (EMR) system with a primary nontraumatic admission diagnosis who received a LTOWB transfusion. All WB were stored in 450-mL volumes using the Teruflex Blood Bag System with citrate phosphate dextrose (CPD) anticoagulant (Terumo Corporation, Tokyo, Japan). Providers could order WB individually or as part of a massive transfusion protocol. Any discrepancy regarding the reason for WB transfusion was resolved by using the primary admitting diagnosis to differentiate between a traumatic or nontraumatic indication. Patients with a probable medical event, such as syncope or seizure, which led to a traumatic event requiring WB transfusion, were included in the final analysis provided their primary admitting diagnosis was nontraumatic.

ClinComp

Clinical personnel enter data into the Essentris EMR system (Health IT Outcomes, Erie, PA, USA) as part of usual care. Investigators retrieved study variables using the Clinicomp Database (CliniComp International, San Diego, CA, USA). Clinicomp provides a secondary database for reporting purposes called "GDR" (Global Data Repository). This database comprises an Oracle 11 g database, which receives transactions from the main Essentris system in a near-real-time fashion. Standard Structured Query Language client applications extract data from this database. We extracted demographic data, admission diagnosis, blood volumes by product, vital signs, concurrent medications, interventions, and outcome data (i.e., survival to hospital discharge).

Data Analysis

All statistical analysis was performed using Microsoft Excel (version 10, Redmond, Washington) and JMP Statistical Discovery from SAS (version 13, Cary, NC). Continuous variables are reported as means and 95% confidence intervals. Ordinal variables are reported as medians and interquartile ranges.

TABLE I. Demographics, Outcome, Vitals, and Laboratory Data

Demographics	Age	51 (32–66)
	Male	46% (46)
	Weight (kg)	79.6 (74.9–84.2)
Affiliation	Military beneficiary	82% (82)
	Non-beneficiary	18% (18)
Outcome data	Total LOS	6 (3–16)
	Admitted to ICU	44% (44)
	ICU LOS	6 (3–19)
	Ventilator days	10 (4–14)
Final discharge status	Alive	88%
	Died	12%
Pertinent vitals	Minimum systolic blood pressure	92.0 (88.0–96.0)
	Minimum diastolic blood pressure	48.8 (46.0–51.7)
	Minimum oxygen saturation	83.0 (77.6–88.3)
	Maximum heart rate	117.9 (113.3–122.6)
	Maximum respiratory rate	34.3 (29.9–38.8)
Pertinent laboratory values	Minimum hemoglobin	7.4 (7.1–7.8)
	Minimum platelets	178.6 (152.8–204.4)
	Minimum serum calcium	7.7 (7.5–8.0)
	Minimum ionized calcium	1.0 (0.9–1.1)
	Minimum pH	7.2 (7.2–7.3)
	Maximum prothrombin time	18.9 (17.1–20.7)
	Maximum partial thromboplastin time	49.2 (40.0–58.4)
	Maximum international normalized ratio	1.6 (1.4–1.8)
	Maximum lactate	4.7 (3.5–5.9)

Demographics, outcome data, pertinent vitals, and pertinent laboratory values from the 100 non-trauma patients that received whole blood. Vital sign and laboratory information lists the average maximum and minimum from throughout the hospital course. Abbreviations: ICU, intensive care unit; LOS, length of stay.

RESULTS

From January to December 2019, there were 100 patients that received at least one unit of WB with a primary non-trauma admission diagnosis. Patient demographic information, vital signs, and pertinent laboratory values are shown in Table I. Most patients were female, below the age of 60, and were a military beneficiary.

Whole blood (WB) was used in a wide variety of non-traumatic, medical conditions, as shown in Table II. Obstetric/gynecologic (OBGYN) patients represented the largest percentage of non-trauma patients who received WB (23%), followed by hematologic/oncologic patients (16%). The average volume of WB was 1,064 mL (95% CI, 750–2,458 mL). Patients received more total blood volume through component therapy, receiving an average volume of 2,226 mL (1241–3211) of PRBCs, 2,463 (744–4183) of FFP, and 1,341 mL

TABLE II. Clinical Indications Data

Obstetric/Gynecologic	23
Hematologic/Oncologic	16
Respiratory	14
Cardiac/Vascular	13
Gastrointestinal/Abdominal	11
Burn	7
Infection	7
Other	7
Orthopedic	2

List of the type of pathologies in each of the 100 non-trauma patients who received whole blood, broadly sorted by medical specialty. Numbers listed represent the number of patients included in each category and the percentage of the total cohort. "Other" includes conditions not easily sorted into a single specialty of medicine or rare medical pathology.

TABLE III. Concomitant Procedures and Medications

Procedures	Central line	25
	Arterial line	22
	Dialysis	17
	PICC	15
	Intubation	13
	Bronchoscopy	12
	ECMO	9
	EGD/colonoscopy	7
	Chest tube	6
Medications	Opioid analgesic	71
	Calcium	26
	Propofol	21
	Benzodiazepine	20
	Vasopressor	18
	Dexmetatomidine	6

List of the procedures and medications received by the 100 non-trauma patients who received whole blood. Numbers listed represent the number of patients included in each category and the percentage of the total cohort. Abbreviations: ECMO, extracorporeal membrane oxygenation; EGD, esophagogastroduodenoscopy; PICC, peripherally inserted central catheter.

(478–2203) of platelets in addition to the WB they received.

The non-trauma patients who received WB required a variety of surgical and nonsurgical procedures, as shown in Table III. The patients, on average, had minimum serum calcium of 7.7 mg/dL (7.5–8.0) and ionized calcium of 1.0 mmol/L (0.9–1.1). However, only 26% of patients who received WB received calcium supplementation (either calcium gluconate or calcium chloride). Of the patients who died, the most frequent primary diagnosis was burn without other traumatic injury ($n = 5$ of 12).

DISCUSSION

Given recent studies showing survival benefits in patients receiving WB following trauma,[2,10] it is likely that WB will become more widely available as trauma centers and hospitals gain experience and more data on WB's safety and efficacy becomes available. Given blood supply limitations and the importance of blood transfusion during resuscitation of hemorrhagic shock, it is essential to identify which patients may benefit from WB. In this study, we described the current use of WB in a variety of nontraumatic settings. WB was used in both hemodynamically stable and critically ill medical patients, intra- and post-operatively, and during advanced procedures such as extracorporeal membrane oxygenation.

There are previous reports of the use of WB in obstetric bleeding,[13,14] gastrointestinal bleeding,[15] malignancy-related hemorrhage,[16] and during procedures.[17,18] However, the scope and relevance of these reports vary. There is no literature available to date that discusses the safety or efficacy of the use of WB for all non-trauma patients. This is likely due to the fact that WB is typically available only as emergency release blood within large, tertiary care trauma centers or austere military treatment facilities. The BAMC, by contrast, is a unique hospital where WB was available as emergency release blood to both trauma and non-trauma patients. There were no formal policies in place that limited the use of WB for nontraumatic bleeding during this study period nor was there a clear guideline for when to transition to component therapy. As WB becomes more readily accessible across the USA for trauma patients, it is likely that an increasing number of non-trauma patients will receive WB due to trauma activation overtriage, triage misclassification, or provider preference. This study shows that providers of numerous specialties will use WB in patients who do not have traumatic injuries when WB is available.

While WB may directly mitigate acute traumatic coagulopathy, it is unclear if WB has additional benefits or risks to patients with non-trauma-related hemorrhage, given the wide variety of medical causes of hemorrhage. For example, WB may have a different role in an oncology patient with pancytopenia, an obstetrics patient with disseminated intravascular coagulation, or an anticoagulated patient with a large volume upper GI bleed. It is notable that obstetric bleeding was the most common non-trauma indication for WB in this study, as OBGYN providers were also early adopters of component therapy after its use in the trauma setting.[19,20] As transfusion practice is commonly regulated by local hospital or blood bank officials, we believe this manuscript highlights the need to identify which non-trauma patients may benefit from WB, indications for transition to component therapy, and impacts on regional blood supply.

The use of WB in non-trauma patients may also impact lower-resource medical facilities in rural areas, developing nations, and austere locations. Forward staged military surgical and special operations medical personnel currently carry WB for the treatment of personnel sustaining traumatic injury.[2] Stored WB has a shelf-life of 21 to 35 days at 1–6°C, depending on storage medium.[21] Furthermore, with appropriate prescreening of donors and communicable disease testing, transfusions of fresh WB do not necessitate the robust blood banking resources required by component therapy.[22] This provides logistical advantages of WB compared to component therapy for non-trauma patients in austere or low-resource locations.

The potential benefits of WB administration are dependent, in part, upon the processing of the product during blood banking. The Armed Services Blood Program and the Department of Defense predominantly use Terumo Blood Collection System with CPD and Optisol (AS-5) to manufacture blood components (packed red blood cells, cryoprecipitate anti-hemolytic factor, and FFP). When compared to a 1:1:1 transfusion, WB will have similar amounts of anticoagulant, but will have ~63mL less fluid required for storage.[23] This difference in crystalloid may provide an advantage to patients during massive transfusion of blood products as it prevents dilution of cellular and protein components. More research is required to determine if specific WB processing techniques provide advantages to trauma versus non-trauma patients.

Recent updates to military clinical practice guidelines stress the importance of calcium supplementation during massive transfusion of blood products.[22] This was in response to studies showing that trauma patients who received massive transfusions were at risk of hypocalcemia, which worsened mortality.[24–26] In our study, patients minimum serum and ionized calcium levels were both consistent with hypocalcemia. Although we are unable to specify the timing of the hypocalcemia relative to the administration of WB given the limitations in data extraction, only 26% of the patient's received calcium supplementation. This may indicate that while there has been significant focus on addressing hypocalcemia in trauma, this message has yet to take hold in other medical specialties and may be an area for future quality improvement.

These conclusions must be taken in the context of the limitations of this study. First, this study was a descriptive, retrospective cohort study, and patients were categorized by their primary admitting diagnosis. Effort was taken to exclude all patients with sustaining trauma as a primary reason for admission. However, patients with critical illness often have multisystem involvement or have an unknown diagnosis at the time of admission. It is possible that patients were miscategorized due to this uncertainty on admission or due to limitations using de-identified personal health information. Second, WB was transfused at provider discretion throughout the study period, as there was no established protocol for WB transfusion in non-trauma patients at BAMC during this period. This provides a convenience sample of patients; however, provider comfort may have influenced which patients or medical pathologies received WB. The patients, on average, received more component therapy than WB. This limits discussion about the relative impact, efficacy, or safety of WB compared to component therapy, or the impact on the order to blood product delivery in this patient population. Furthermore, data are not available on which patients received formal massive transfusion therapy as opposed to large, but temporally spaced transfusions. Finally, the 100 patients included in this study were transfused for a variety of pathologies, represented a wide range of ages, and were at various stages of illness. The only common trait within the cohort was the delivery of at least one unit of WB. We believe, however, that this manuscript provides a proof-of-concept that WB may have a role in the resuscitation of non-trauma patients. More research will be required to further explore the safety, efficacy, and indications for appropriate use of WB for non-trauma patients in the civilian population.

CONCLUSIONS

In this retrospective study, WB was used in a wide variety of non-trauma pathologies, with OBGYN-related bleeding being the most common. As WB becomes more widespread across the USA in the resuscitation of trauma patients, WB transfusion in non-trauma patients will likely become more common. More outcome data are required to safely expand the indications for WB beyond trauma.

ACKNOWLEDGMENTS

We would like to thank Mr. Eric Hobbs for providing us with this data.

FUNDING

None declared.

CONFLICT OF INTEREST STATEMENT

None declared.

CONTRIBUTIONS

Study concept and design (S.G.S.); acquisition of the data (S.G.S.); analysis of the data (C.D.N. and S.G.S.); drafting of the manuscript (C.D.N.); critical revision of the manuscript (A.D.F., M.A.B., K.S.M., R.L.H., and S.E.N.); and approval of the final manuscript (C.D.N., S.G.S., A.D.F., M.A.B., K.S.M., R.L.H., and S.E.N.).

ETHICS

The U.S. Army Institute of Surgical Research regulatory office reviewed protocol H-20-016 and determined it was exempt from institutional review board oversight. We obtained only de-identified data.

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