ANESTHESIA & ANALGESIA® Infographic

Now Serving a Trauma Victim Near You: *Whole Blood for Civilian Trauma Resuscitation*

Based on clinical data from the military setting, a narrative review discusses the potential use of whole blood resuscitation in civilian trauma.[1]

Further prospective comparisons are required to substantiate the specific advantages of whole blood use during massive transfusion. Our current understanding is limited by largely retrospective data. Furthermore, implementation of whole blood use requires a strong committment to education of staff and a well-developed coordination plan with a local blood supplier.

A narrative review in this issue considers the use of whole blood resuscitation during massive hemorrhage in the civilian sector based on the interpretation of military data. Retrospective studies have illustrated the benefits of whole blood, namely, the preservation of physiological proportions and viability of platelet function and coagulation. Implementation of whole blood protocols at civilian trauma centers requires an intense education campaign spanning personnel and staff from the emergency department to the operating room and critical care unit. Additionally, it mandates a coordinated program of acquisition from the local blood supplier. Limitations of our ability to apply knowledge gained from the military studies include retrospective designs, selection and survivor bias, and comparisons to historical controls.

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The author declares no conflicts of interest.

REFERENCE

1. Pivalizza EG, Stephens CT, Sridhar S, et al. Whole blood for resuscitation in adult civilian trauma in 2017: a narrative review. *Anesth Analg*. 2018;127:157–162.

IARS International Anesthesia Research Society

CME

Whole Blood for Resuscitation in Adult Civilian Trauma in 2017: A Narrative Review

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After a hiatus of several decades, the concept of cold whole blood (WB) is being reintroduced into acute clinical trauma care in the United States. Initial implementation experience and data grew from military medical applications, followed by more recent development and data acquisition in civilian institutions. Anesthesiologists, especially those who work in acute trauma facilities, are likely to be presented with patients either receiving WB from the emergency department or may have WB as a therapeutic option in massive transfusion situations. In this focused review, we briefly discuss the historical concept of WB and describe the characteristics of WB, including storage, blood group compatibility, and theoretical hemolytic risks. We summarize relevant recent retrospective military and preliminary civilian efficacy as well as safety data related to WB transfusion, and describe our experience with the initial implementation of WB transfusion at our level 1 trauma hospital. Suggestions and collective published experience from other centers as well as ours may be useful to those investigating such a program. The role of WB as a significant therapeutic option in civilian trauma awaits further prospective validation. (Anesth Analg 2018;127:157–62)

In 2012, an expert review of fresh whole blood (WB) transfusion for hemorrhagic shock in *Anesthesia & Analgesia* discussed primary applications at that time that were in critically injured patients in the military arena and the pediatric surgical population.[1] Spinella et al[1] recommended future research on appropriate risk–benefit profiles and suggested strategies to reduce theoretical risks. In the interim period, despite limited attention in the anesthesiology literature,[2–4] there have been continued developments in WB storage and processing at the blood collection agency level. This has coincided with a steady increase in published reports of the clinical application, potential benefit or equivalency of WB used in combination with component therapy in both civilian and military populations.[5–8] Given the significant military experience of fresh WB transfusion in forward-deployed areas and initial supportive data in the civilian trauma population in the United States, our institution has recently implemented a limited WB transfusion protocol.

Herein, a multidisciplinary collection of anesthesiologists, a trauma surgeon, and pathologists with experience in WB use review WB for emergency resuscitation in civilian adult patients. This will be useful for acute care anesthesiologists who may not yet have experience with or availability of WB at their institutions. We briefly explore the concept and historical perspective of WB, the WB product itself, and potential risks and benefits; review the currently available clinical data in military and civilian cohorts; and provide advice on practical development and implementation of a local or regional WB program.

CONCEPT AND HISTORICAL PERSPECTIVE

The use of WB began with the origin of blood banking during World War I but not in earnest until World War II.[9] WB became the preferred product for the treatment of bleeding patients, and remained the primary resuscitation fluid in military settings through the start of the Vietnam War and in the civilian arena.[10] However, after dramatic advances in blood component separation, blood centers were able to supply hospitals with individual components, and WB decreased as a readily available product. While some studies suggested noninferiority in elective surgical cases, no studies of efficacy or hemostatic potential for patients in hemorrhagic shock were performed before these changes.[11] The response of the medical community was to implement resuscitation of bleeding patients with red blood cells (RBCs) and crystalloids solutions,[12] partly driven by a misinterpretation of landmark studies that noted that plasma and platelets were unnecessary in bleeding trauma patients, and that crystalloids were safe.[13,14] Carrico et al[13] noted that the use of saline for hemorrhagic shock was safe "until WB is available."

During the past 20 years, limitations of this approach were exposed, initially with laboratory and clinical military data followed by civilian trauma findings documenting the coagulopathy of trauma. The acute need for balanced resuscitation with plasma, platelets, and cryoprecipitate has been well summarized.[15,16] Current practice within US level 1 trauma centers is to aim for a 1:1:1 plasma:platelets:RBC transfusion ratio to help ameliorate this acute coagulopathy.[17]

Use of fresh WB in military conflicts resurfaced at the turn of this century in Iraq and Afghanistan, partly in response

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Accepted for publication April 3, 2018.

Funding: Departmental.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000003427

to logistic necessity, with prolonged transport for replacement of products, platelet shortages, and the challenges in maintaining refrigeration or freezing in austere environments.[18] Initial retrospective analysis of prospectively collected data from a large cohort of transfused patients at 6 forward surgical teams suggested that addition of type-specific, uncrossmatched fresh WB was independently associated with improved survival in a cohort in which platelets were unavailable.[19] With subsequent establishment of the feasibility of WB to the Department of Defense transfusion algorithm, a consensus statement from both civilian and military experts in 2007 advocated for use of WB or component therapy approaching (but not reaching WB) 1:1:1 ratios.[20] Growing retrospective evidence and expert opinion supporting use of WB in the military arena is discussed later in more detail, with acknowledgement of the limitations of the available data.

While the concept of damage control resuscitation was adopted in trauma care, the use of WB in the civilian setting was initially felt to be impractical because of the need for cold storage, unlike fresh WB in military scenarios. Purported benefits of WB included avoiding increased costs and labor associated with creation and administration of component therapy. However, accumulating evidence and experience from military medical applications that suggested that type-specific WB is a safe and feasible alternative to 1:1:1 component therapy have prompted current civilian initiatives. A recent prospective, randomized controlled trial of modified WB + platelet transfusion appeared to provide hemostatic resuscitation with less overall blood component volumes in subanalysis.[6] This concept will also be further explained later in this article.

BLOOD BANKING PERSPECTIVE: PRODUCT, AVAILABILITY, AND RISKS

During the past 3 decades, the standard approach in civilian trauma programs to use component blood therapy stems from advantages of efficient storage and maximized therapeutic effect to target specific deficiencies. As massive transfusion (MT) protocols became accepted practice in trauma care, there was concern that summation of coagulation factor and platelet function in reconstituted products was inferior to WB. This was recently confirmed in a mathematical laboratory study, with significant losses of coagulation factor (38%) and platelet (56%) function in the combined 1:1:1 product ratio.[21]

Component Therapy

RBCs contain antigens that confer blood group identity (A, B, AB, or O) with or without the D (Rhesus [Rh]) antigen, and are stored at refrigerated temperatures (1°C–6°C) for up to 42 days. Plasma is preserved frozen, either within 8 (fresh frozen plasma [FFP]) or 24 hours (PF24) and contains antibodies to ABO antigens. Similarly, liquid (never-frozen) plasma, stored up to 26 days at 1°C–6°C, has been used in MT scenarios. Rh-negative individuals do not naturally have anti-D antibody, but may make it on exposure to D-positive cells via transfusion or exposure to cells from a D-positive fetus. Red cells and plasma to be transfused have traditionally been compatible with the recipient's ABO group and D type in the civilian setting. Platelets, suspended in anticoagulated donor plasma when collected and processed, are stored at room temperature, and have a limited storage time of 5 days (occasionally 7) because of the risk of bacterial contamination.

Whole Blood

Cold WB in the civilian arena is collected in an anticoagulant solution and maintained in a refrigerated condition (1°C–6°C) without agitation. The labeled expiration date is 35 days if stored in citrate phosphate dextrose adenine-1 (CPDA-1) and up to 21 days if stored in citrate phosphate dextrose (CPD). All currently recommended infectious disease testing is performed before distribution. This is in contrast with fresh WB in the military setting, which is usually issued within hours of collection, is not refrigerated (stored for <8 hours at 22°C) and not necessarily tested with standard infectious disease tests.

As anticipated, fresh WB retains platelet and coagulation factor function.[22] Despite historical concern of decreased platelet and overall hemostatic function of cold WB compared to traditional platelet storage at room temperature, evidence suggests that hemostatic potential is preserved in laboratory, functional, and applied clinical studies for up to 14–21 days.[7,23] In an in vitro evaluation, platelet aggregometry to epinephrine and adenosine diphosphate was preserved until day 21 of storage, and thromboelastographic variables did not appear to decrease until day 14.[24] In a similar study, there were no effects of pathogen reduction techniques on hemostatic potential up to 21 days of storage, and refrigeration better preserved standard laboratory and platelet function parameters.[25] Available data and potential mechanisms have been well summarized recently by Bahr et al[26] and Spinella et al,[27] although both caution that sufficient clinical data are not yet available to confirm safety and outcome signals despite the preserved hemostatic function.

A single unit of WB (570 mL) has less total dilution from anticoagulants and added preservative solutions than a combination of 1:1:1 components (660 mL). There are thus higher platelet counts (≥200 vs 88 × 10^9/L) and coagulation factor levels (≥90% vs 65%), leading to superior in vitro and in vivo hemostatic potential in WB than combined individual components.[21,27]

Ideally, WB should match the recipient's ABO group, and D-negative individuals should receive Rh-negative WB. However, in an emergency when the blood type is unknown, group O red cells can be transfused to individuals of any blood group because these cells do not have A or B antigens. Rh-positive red cells can be transfused safely to the 85% of the population that is Rh-positive and most males who are Rh-negative. Women of childbearing age, a small proportion of trauma victims, remain a concern for receipt of Rh-positive WB. Group O WB will contain anti-A and anti-B in the plasma, and the amount of plasma in a unit of WB is equivalent to FFP and similar to an adult platelet dose. Because of the theoretical risk of hemolysis, several institutions test to ensure the absence of strong anti-A or anti-B immunoglobulin M/immunoglobulin G antibodies before transfusion.[28] A titer that might be considered safe has not been clinically established because reported titers vary from 1:50 to 1:256, complicated by variability between laboratories. In small studies to date, reassuring hemolytic safety signals have been confirmed with no clinically significant changes in laboratory markers.[29]

Most component products in the United States are currently leukoreduced, with advantages of reduced febrile transfusion reactions, transmission of cell-associated viruses such as cytomegalovirus, and reduction of human leukocyte antigen alloimmunization. Traditional white blood cell filters will remove a substantial number of platelets and are not recommended for filtration of WB. However, continued developments in filtration systems have led to the introduction of appropriate platelet-sparing filtration, either at the source of the donated unit (Imuflexs Whole Blood Filter Saving Platelets; Terumo BCT, Inc, Lakewood, CO) or by the addition of a filter at the time of WB administration.

MILITARY PERSPECTIVE: CURRENT USE

During the course of combat trauma care in recent Iraq and Afghanistan campaigns, fresh WB has become a cornerstone of resuscitation. Often borne of necessity because of logistical challenges in isolated environments,[30] evaluation of WB use has rapidly increased.[31] Similar to the experience and description of ratio-based blood component resuscitation in the military arena, initial reports with WB, although compelling, are frequently limited by their retrospective nature, potential selection bias, possible survivor bias, comparison to historical controls, and use of both WB and combination therapy in resuscitation, without discrete separation of a WB effect (Table).

Spinella retrospectively compared 2 groups who received >1 U of RBCs from 2004 to 2007, effectively comparing fresh warm WB with apheresis platelets as both groups received RBCs and FFP, at multiple locations in the military theater.[32] Groups were unequal in size (110 fresh WB, 254 component) with similar injury severity. Both 24-hour and 30-day mortality were improved in the WB group, and both use of and amount of WB were confirmed as independent associations with multivariable analysis, acknowledging the limitations alluded to.[32]

Retrospective analysis of single military center data by many of the same experts (2004–2006) in subjects undergoing MT identified groups who received either fresh WB (85) or platelets (284) during resuscitation.[31] Because there was no difference in outcome or survival in patients receiving an MT, the authors suggested feasibility of fresh WB and impetus for further study, with many of the aforementioned limitations in study design.[33]

Further evaluation confirmed the improved survival signal when fresh WB was added to RBC and FFP resuscitation, despite the WB group having a higher injury severity score.[19] In this study, an additional limitation was the logistic unavailability of platelets for transfusion, which differs from current civilian practice.

Even when not conferring survival benefit in a smaller sample, use of fresh WB reduced traumatic coagulopathy in a group with greater injury severity score and physiological compromise.[34] Limitations in this retrospective study were the small sample size and frequent unavailability of platelets. Increasing application has been reported in austere combat environments internationally.[35,36] Swedish authors reviewed risks of hemolysis due to transfusion of

Table. Summary of Relevant Military WB Studies

Author	Products Studied	Retrospective	Outcome	Limitations
Spinella et al[32]	FWB + components versus components alone	Y	Better 24-h and 30-d survival in FWB group	Risk of selection and survivor bias Unequal group size (354 of 968 database, 204 component versus 100 FWB) No discrete separation of FWB
Perkins et al[33]	FWB versus apheresis platelets during component resuscitation	Y	No survival difference between FWB and platelets, suggesting equivalent effect.	Risk of selection and survivor bias Unequal groups (85 FWB versus 284 platelets) No discrete separation of FWB
Nessen et al[19]	FWB + components versus components alone Neither received platelets due to unavailability	Y	Addition of WB improved survival but not discrete separation of effect.	Risk of selection and survivor bias Unequal groups (394 without, 94 with FWB) Platelet unavailability would be unusual in civilian population.
Keneally et al[8]	FWB + components versus components alone	Y	FWB group >physiological trespass, >total transfusion, no mortality effect	Risk of selection and survivor bias Unequal groups (9281 FWB versus 3656 component) No discrete FWB group Significant cohort with incomplete data
Auten et al[34]	FWB + components versus components alone Frequently without availability of platelets	Y	FWB group >injury severity, <coagulopathy, seems to provide benefit	Small (61) Risk selection and survivor bias Platelet unavailability would be unusual in civilian population.

Abbreviations: FWB, fresh whole blood; WB, whole blood; Y, yes.

potentially ABO-incompatible plasma, confirming minimized risks with low titers and affirming the maintained benefit.[37]

Although current military data suggest a benefit using WB as an adjunct to resuscitation along with traditional component therapy, the aforementioned limitations must be considered until more robust data are available. Despite these considerations, the Tactical Combat Casualty Care committee, under the auspices of the National Association of Emergency Medical Technicians, issues evidence-based guidelines and recommendations for trauma care on the battlefield, and currently lists WB as the priority fluid of first choice in a casualty with hemorrhagic shock.[38]

CIVILIAN PERSPECTIVE: CURRENT USE

Lifesaving reports of WB use in the military arena inevitably led to investigations, usually cold WB, in the civilian population. In a prospective, single-center, randomized trial of trauma patients predicted to require an MT, patients were randomized to either a unit of WB or component therapy (1 U of RBC + 1 U of plasma) immediately on arrival. Each group also received 1 dose of platelets (apheresis or random donor) for every 6 U of either WB or RBC + plasma.[6] Although there were no transfusion differences in the 107 subjects in the intent-to-treat analysis, when patients with severe traumatic brain injury were excluded, the WB group received significantly fewer individual and total products during 24 hours (the primary outcome of the study). Similar to other prospective trauma studies, logistics of such studies are challenging, with exception from informed consent (US Food and Drug Administration 21 code of federal regulations 50.24).

In a smaller study of 47 male trauma patients, up to 2 U of uncrossmatched group O-positive cold WB was compared to a historical control group treated with component therapy to assess feasibility. There were no adverse safety signals detected.[39] With these initial positive findings, cold WB is currently being used in several large level 1 trauma facilities across the nation,[40] often introduced in smaller volumes (2–4 U).

Earlier experience from Australia reported a linked cohort study of patients receiving an MT (353), of whom 77 received fresh, unrefrigerated WB (mean 4 U) as part of their resuscitation. Although there were small improvements in coagulation and fibrinogen profiles, overall transfusion and survival were equivalent.[41] As with military data, it is difficult to isolate a signal from a small WB volume in an MT algorithm.

DEVELOPMENT AND IMPLEMENTATION OF WB AT THE INSTITUTIONAL LEVEL

Given the supportive evidence of clinical utility, potential benefit, and safety, our institution sought implementation of cold WB at our busy level 1 trauma center. For those contemplating similar proposals, several strategies are necessary for success.

Regulatory

Substantial preparation for WB transfusion is critical, given regulatory oversight by both the US Food and Drug Administration and the American Association of Blood Banks (AABB). Planning was initiated via the committee on patient blood management of the institutions, the chief medical officer, and interested parties, with approval granted by all. AABB approval for "variance use" was obtained for an initial use of 4 U group O WB.[42] The variance is in response to AABB recommendation for ABO group–specific transfusion. Revisions to this AABB standard have been made, and use of low-titer group O WB will be permitted in the 31st edition, effective April 1, 2018. A thorough recent review of the development and implementation process at a civilian level 1 trauma center summarizes the process.[39]

Blood Supplier

Without coordinated cooperation of the local blood supplier for the institution, a WB initiative cannot succeed. Our supplier, Gulf Coast Regional Blood Center (GCRBC), which has worked closely with the institution on numerous WB and component-based protocols, committed to provide group O WB from male-only donors with a 21-day expiration, no leukoreduction and anti-A and B titers <1:200. Lower titers are not feasible given the local donor pool (S. Rossmann, Gulf Coast Regional Blood Center, personal communication, 2017). Unused blood will not be accepted back by the supplier, necessitating close stewardship of a precious resource by the local pathology and blood bank departments. Daily inventory is 20 U, with a routine supplement of 2 U/d. Initial implementation with exclusive use of O Rhesus-negative WB required reducing production of an equivalent number of O Rh-negative RBCs. Thus, as in military and early civilian experience, O Rhesus-positive WB should be the product of choice for males.

The success of WB implementation at our institution is based on a longitudinal, productive relationship with GCRBC, which has been solidified with continuous communication, blood donation collection drives at the institution, physician involvement on the board of trustees of GCRBC, and educational interactions for postgraduate trainees at the local blood collection facility led by GCRBC medical staff.

Education

Concerted multidisciplinary education was conducted within the surgical, emergency medicine, anesthesiology, and pathology departments, along with nursing, emergency medical technician, medical technologist, and administrative colleagues in locations where WB was to be used. Initial supplies are 4 U in the emergency department (ED) and 2 U on the Life Flight helicopters. WB will have a distinctive tag to differentiate from an RBC bag (Figure). Contraindications to use have been publicized, although many of these may be unknown or undetermined in an emergency encounter:

- Known non-O blood groups;
- History of clinically significant alloantibodies;
- Age <15 years and body weight <40 kg in the emergency department (if there is only WB available in the helicopter, <20 mL/kg can be given to patients ≤12 years of age); and
- Candidates for irradiated blood products (eg, lymphoma, leukemia, and bone marrow transplant).

Safety

After any WB transfusion, a hemolysis panel including haptoglobin, lactate dehydrogenase, and bilirubin is drawn

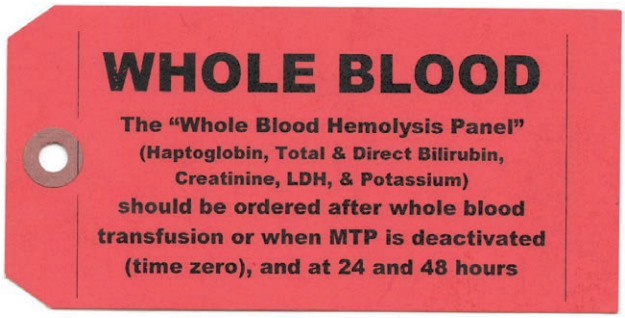

Figure. Local WB unit identifying tag. LDH indicates lactate dehydrogenase; MTP, massive transfusion protocol; WB, whole blood.

at 0, 24, and 48 hours after transfusion to prospectively evaluate for any potential hemolytic effect.

Early Process Improvement

After implementation of the WB program, there were instances of WB wastage, likely due to the shorter 21-day shelf life and unfamiliarity with availability. Posttransfusion hemolysis laboratory studies were occasionally overlooked. Additional education was conducted to capture all staff given the frequent shift changes in the ED. WB was moved to the top of the ED refrigerator, an electronic WB order set was instituted to ensure uniform capture of laboratory values, and each WB transfusion was reviewed by blood bank staff within 24 hours. At 3-month follow-up of 53 cases, wastage was 0 in the second and third months, with only 1 incomplete posttransfusion hemolysis marker in 40 cases. The majority of cases had a single WB unit transfused before switching to type-specific components, and the maximum used in a case was 3, within the initially proposed algorithm.

With the potential impact on Rh-negative WB units, Rh-positive WB is now being used preferentially except for females <50 years of age.

CONCLUSIONS

Initial enthusiasm and increasing retrospective data from the military medical community for use of WB in combination with component therapy resuscitation have led to similar efforts in civilian trauma patients. Implementation of WB transfusion strategies has begun in several level 1 trauma institutions in the United States, as suggested by experts in the field.[43] Anesthesiologists should be aware of the scientific rationale, details, and potential risks of WB and suggested avenues for local policy development. Further prospective data are necessary to examine discrete comparisons of WB without simultaneous use of components, verification of appropriate safety, and hemolysis and determination of cost–benefit analyses. We eagerly anticipate vigorous investigation of WB in the acutely injured civilian patient given the initial potential in retrospective military studies and small civilian reports. With increasing utilization and evidence, national regulatory support for such endeavors is anticipated. ■

DISCLOSURES

Name: Evan G. Pivalizza, MD.
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