The Journal of Emergency Medicine, Vol. 56, No. 5, pp. 491–498, 2019
Published by Elsevier Inc.
0736-4679/$ - see front matter

https://doi.org/10.1016/j.jemermed.2019.01.024

Clinical Reviews in Emergency Medicine

WHOLE BLOOD IN TRAUMA: A REVIEW FOR EMERGENCY CLINICIANS

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☐ **Abstract—Background: Blood products are a cornerstone of trauma resuscitation. From the historically distant battlefields of World War II through present-day conflict around the globe, whole blood (WB) has been a potent tool in the treatment of massive hemorrhagic shock. Component therapy with a targeted ratio of packed red blood cells, platelets, and plasma has previously been utilized. Objectives: This narrative review describes modern-day WB transfusion, its benefits, potential drawbacks, and implementation. Discussion: The current form of stored low-titer O WB seems to be the safest and most effective solution. There are many advantages to WB, including the maintenance of coagulation factors, the lack of subsequent thrombocytopenia, and the reduction of infused anticoagulant. Several studies suggest its utility in trauma. Most of the disadvantages of WB stem from a lack of prospective data on the topic, which are likely forthcoming. Logistical issues likely present the greatest barrier to this therapy, but an advanced prehospital protocol developed in San Antonio, Texas, has successfully overcome several of these challenges. Conclusions: Although stored WB holds promise, it is not without its distinct challenges, including logistical issues, which this article addresses. There are programs underway currently that demonstrate its feasibility in metropolitan areas. As demonstrated in military settings, WB is likely the ideal resuscitation fluid for civilian trauma in the prehospital and emergency department settings. Published by Elsevier Inc.**

☐ **Keywords—whole blood; transfusion; protocol; blood products**

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INTRODUCTION

In the setting of trauma, massive hemorrhage is the most common cause of death within the first hour of arrival to a trauma center (1). The mortality of trauma patients requiring massive transfusion exceeds 50%, and it has been shown that at least 10% of these deaths are potentially survivable (2). Much of what is known about the treatment of trauma and the tenets of resuscitation come from modern combat history. From the 1940s to the 1960s, whole blood (WB) was the mainstay of the military blood program. This reached its peak during the Vietnam War, where the military transfused more than 1 million units of cold-stored WB (3). However, in an effort to conserve blood as a resource and target specific component deficiencies, WB was subsequently relegated to highly specific uses.

Received: 12 November 2018; Final submission received: 9 January 2019;
Accepted: 21 January 2019

The introduction and growth of component therapy in the 1970s and early 1980s fostered a more tailored approach to resuscitation, along with increased storage times and decreased risk for infection. By 1990, trauma resuscitation was utilizing component blood almost exclusively. Hoping to correct trauma's lethal triad of hypothermia, acidosis, and coagulopathy, management focused on rewarming the patient, correcting acidosis early, and aggressively resuscitating with intravenous fluid. Largely owing to advances in military medicine, this strategy delivered significant mortality advantages, especially with the replacement of crystalloid infusion with blood products (4).

During the mid-2000s there were several efforts to re-examine fluid resuscitation, beginning with Brohi et al., who described the concept of an Acute Coagulopathy of Trauma-Shock, which seemed to be an independent marker of morbidity and mortality (5). Building on that work, a large retrospective cohort study of casualties during recent Middle East conflicts suggested there was a significant survival benefit when red blood cells (RBCs), fresh frozen plasma, and platelets were transfused at a 1:1:1 ratio, as opposed to the large volumes of packed RBCs being administered previously (6).

As conflict is the great motivator for medical innovation, or in this case, re-invention, the capabilities of the U.S. military have been stretched with the transition from large-scale urban battles to austere forward operating bases. Given the far-forward nature of conflict and the necessity to maintain a supply of blood for readily available transfusion, recent deployments have witnessed the resurgence of fresh whole blood (FWB) in areas where component therapy is difficult (7). Pioneered by the Norwegian and Swedish military programs, the 75th Ranger Regiment developed and implemented a Tactical Damage Control Resuscitation protocol, which has since become the standard for FWB collection and transfusion throughout the U.S. military (8). As with many medical advances, this strategy has begun to make its way to the civilian sector, with building evidence that at least the partial use of WB may confer a survival advantage (9). This has led some to advocate that WB may be the optimal resuscitation fluid for massive hemorrhage (10).

METHODS

The authors searched PubMed and Google Scholar for articles using a combination of the keywords and Medical Subject Headings "whole blood" OR "transfusion" AND "trauma" up to October 31, 2018, for production of this narrative review, including case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, and other narrative reviews. The literature search was restricted to studies published in English; the search revealed 432 articles. Authors decided which studies to include for the review by consensus, with focus on WB. A total of 56 resources were selected for inclusion in this review. As this is a narrative review, authors did not pool individual study data.

DISCUSSION

Definition of Whole Blood

WB is collected in several anticoagulants and is currently Food and Drug Administration (FDA) approved for administration when collected, stored, and tested appropriately for transfusion-associated diseases (11). A distinction should be made between two types of WB: FWB and stored whole blood (SWB). FWB, commonly known as the "walking blood bank," is viable at room temperature for up to 24 h of collection, or can be refrigerated within 8 h of collection, after which point it becomes SWB (12). FWB is not approvable by the FDA in the civilian setting, given it does not undergo disease screening prior to transfusion. It has been shown that, at least in the short term, SWB provides the same hemostatic effect as FWB (13). Therefore, for current practice, SWB is the only solution that should be utilized in the civilian setting. SWB can be stored for up to 21 days at 1–6°C in the anticoagulants citrate phosphate dextrose, or for 35 days at 1–6°C in citrate phosphate dextrose adenine (14,15).

Advantages of Whole Blood

One of the main disadvantages of component therapy, even in a 1:1:1 ratio, is that it yields a dilute blood mixture. The hematocrit is estimated to be 29%, a platelet count of approximately 90,000/μL, and diluted coagulation factors to approximately 62% of WB concentrations, largely attributed to necessary addition of anticoagulants and additive solution. Current transfusion of component therapy is typically accompanied by thrombocytopenia, whereas studies performed using WB during the Vietnam War found that platelet counts did not fall below normal limits even after transfusion of 6 liters (16). WB also contains platelets, which are difficult to store due to their short shelf life and storage issues. One study reported that one unit of stored FWB had the equivalent hemostatic effect of 8–10 platelet units (17). To this end, WB addresses concerns about higher volumes of infused anticoagulant during resuscitation and provides the ultimate physiological replacement (18,19).

DISADVANTAGES OF WHOLE BLOOD

Overall, both SWB and FWB offer at least comparable performance and safety compared with components, although they differ in some of their disadvantages (20). FWB may

incur increased risk of transfusion-transmitted disease (e.g., human immunodeficiency virus, hepatitis B/C, syphilis), and increased risk of clerical errors leading to major mismatch when ABO-identical WB is provided, specifically due to its immediate collection and storage time frame (19,21). As discussed, SWB may be the optimal resuscitation product. SWB collected in licensed blood centers offers the same level of transfusion-transmitted disease safety as component therapy, as it undergoes the same level of testing. The primary disadvantage of SWB is that it may increase the risk of plasma-associated transfusion reactions such as transfusion-related acute lung injury, which is related to the presence of antibodies to human leukocyte antigen or leukocytes in the donor's plasma (22). One possible risk-mitigation strategy is the use of recently approved leukoreduction filters, which can be used for warm fresh blood. The other important disadvantage of using SWB is that conclusive evidence from randomized controlled trials is still lacking, although studies are underway (23).

Administration/Practical Solutions

Prior to the implementation of WB in the civilian sector, some of the concerns concerning WB must be addressed:

1. Platelet (PLT) efficacy after cold storage
2. Risk of hemolytic transfusion reactions
3. Logistical issues in providing WB

Current practice under American Association of Blood Banks (AABB) standards is to store PLTs between 22° and 24°C, considered to be room temperature (RT). Given the storage temperature, there exists an inherent safety concern due to the increased risk of bacterial contamination. Also, the efficacy of RT PLTs decreases over time in a process known as the "platelet storage lesion." For these reasons the FDA allows PLTs to be stored for no more than 5 days, and PLTs must also undergo bacterial testing (24,25). However, more recent evidence demonstrates that PLTs maintain hemostatic function for at least 21 days during cold storage and that these PLTs are superior to RT-stored PLTs in the setting of acute hemostasis (26–29). It is therefore reasonable to suggest that SWB may present a simpler alternative to current PLT transfusion practice, although it has not been demonstrated to be comparable in human trials to date (30).

One of the primary concerns about SWB is the risk of hemolytic transfusion reactions if group O WB is used in non-group O recipients, as a result of preformed immunoglobulin M (IgM) type anti-A and anti-B. Each unit can contain up to 300 mL of plasma, which can cause clinically relevant direct intravascular hemolysis of the transfused RBCs, depending on the levels of antibodies present. To address this, the donor can be tested for low IgM anti-A and anti-B titers (<128), as was done in the predeployment setting by the Ranger O Low Titer program (31). These donors are then designated as 'universal donors' and are then available for local blood collection and 'buddy transfusions' during treatment of a traumatic patient in hemorrhagic shock (8). Current opinion supports titers of anti-A and anti-B of < 100 for IgM and 400 for IgG as minimal risk of ABO-incompatible hemolysis (32,33). Using the civilian guidelines set by the program of the University of Pittsburgh Medical Center, Pittsburgh, donors must be O positive, male, and low titer of anti-A and anti-B, < 50 using an immediate spin saline tube method (34). Recently, the AABB approved the use of prescreened, low-titer group O whole blood (LTOWB) based on the recommendation of a joint Trauma Hemostasis and Oxygen Research (THOR)-AABB working group (35,36). The 31st edition of the standards goes on to indicate that the definition of "low titer" shall be made locally by each transfusion service, and that the transfusion service must have a policy specifying which patients are eligible to receive WB, the maximum quantity of WB per patient, and how to monitor for potential adverse events post transfusion (15). It would follow that the previous AABB mandate, which required issued WB to be ABO-identical to the recipient, required adaptation to accommodate issuing group O WB to recipients during trauma resuscitation, which typically does not allow time for the traditional type and cross match (37). One alternative solution is that WB units be considered equivalent to RBC units, thereby facilitating the release of group O WB for patients without a valid ABO group at the time of their trauma resuscitation.

Prescreened, low-titer group O WB is a safe and effective solution for emergency transfusion (Figure 1). Civilian risk of hemolytic transfusion reactions due to plasma-incompatible transfusions, using titered donors, is approximately 1:120,000, and therefore, early resuscitation with LTOWB could be performed safely with fewer donor exposures than currently occur with 1:1:1 massive transfusion protocols (31). In terms of isoimmunization and Rh type, the primary concern is hemolytic disease of the fetus and newborn in women of childbearing age (38). This concern is mitigated by the immunosuppression of trauma patients, which has been well described, and by the administration of anti-D immune globulin (i.e., RhIg) (39). Therefore, women of childbearing age, who receive Rh + pRBCs or LTOWB should be evaluated for RhIg administration candidacy and obstetric and pathology consultation within 24 h (40).

Challenges

There exist major logistical issues in developing a WB program in the civilian sector. Hospitals must develop a collection program and set a standard operating procedure for performing titer testing. The introduction of any

Figure 1. Whole blood use in San Antonio, Texas.

new therapy is likely to be met with unforeseen obstacles. For example, a pilot study at Memorial Hermann in Texas faced an additional delay for WB randomization with the unintended consequence of trauma faculty often excluding the sickest patients from the study, including those who may have benefited most (41). To address this, in a recent letter to the editor, Navarrete et al. advocated for the initial transfusion of plasma to prevent the complications of supplying emergency centers with WB (41,42). However, if the logistical issues can be overcome, WB remains the most promising point of trauma resuscitation re-modernization given that plasma has not shown significant benefit (43).

Although currently the benefits of WB over component therapy have demonstrated statistically significant benefits only in austere environments and prehospital practice, this may be due to a lack of trials involving WB in the civilian world (9,44–46). Currently, the only randomized controlled trial on the use of WB in the civilian population is a 2013 single-center randomized study (41). However, this should only prompt the continued research into LTOWB practices, especially in the prehospital environment, especially given its recent use within advanced emergency medical services (EMS).

Emergency Services District 48 and Cypress Creek in Texas were first to begin carrying WB and have now administered 100-plus units of WB through their protocol (47). Serving a population of > 1.5 million in the greater San Antonio metro area, the South Texas Blood and Tissue Center (STBTC), University of Texas (UT) Health Office of the Medical Director San Antonio, San Antonio Military Medical Center, U.S. Army Institute for Surgical Research, and Southwest Texas Regional Advisory Council for Trauma collaborated to incorporate LTOWB into all phases of their trauma system (40). As part of this performance improvement initiative, the San Antonio Fire Department EMS began carrying LTOWB in 2018.

The current guidelines developed by the aforementioned programs are geared toward critical illness transfusion triggers (Figure 2). They include blood pressure, heart rate, and end-tidal carbon dioxide parameters. These are based on previous trials showing that the initial prehospital shock index values of 1.0 and 1.2 were associated with the need for massive transfusion (48,49). Studies also show that low end-tidal carbon dioxide has a strong association with standard indicators for shock and is predictive of patients requiring operative intervention (50,51). The use of blood products in cardiac arrest remains controversial, and although there is some literature describing potential benefit in achieving return of spontaneous circulation, further study is required in this area (52,53).

One component of the logistical challenge is the scalability of WB transfusion in the prehospital setting, especially given WB's limited shelf life. To address this issue, the San Antonio EMS system has developed a close relationship with the STBTC, which also performs all infectious screening. SWB is collected at STBTC, placed in a precooled patented temperature-controlled container, and then placed in the appropriate transport vehicle. The cooled SWB is then cycled through the helicopter EMS for 14 days, where it is stored in a refrigerator; ground EMS for 14 days stored at 1–9°C, and returned to a hospital for 7 days. This process ensures the viability of WB, as well as its availability when necessary. Although this protocol streamlines WB use in high-population areas, the short shelf life may prove cost prohibitive for small hospitals that do not regularly see trauma, and in these locations, it may increase blood waste. Future efforts include the possibility of delivering WB to mass casualty incidents, where it is arguably most needed. This involves delivering WB to either the scene via EMS command vehicles, helicopter, or to local hospitals directly.

In civilian medicine, the use of WB as a therapeutic blood component in trauma patients has generally been avoided in favor of component therapy. However, conflict continues to be a potent stimulus to innovation, and it is these authors' opinion that revisiting LTOWB is the new frontier in civilian trauma resuscitation (54).

Pediatric Considerations

Literature regarding pediatric massive transfusion, and particularly WB transfusion, is scarce. Transfusion guidelines in pediatric patients are mainly based on expert

SAFD COG Version 1.1 January 1, 2019

Low Titer O+ Whole Blood – Trauma

History
- What was the mechanism of injury – blunt (MVC, fall, blow to body) vs. penetrating (stabbing, GSW, foreign body)?
- Did a medical condition contribute to the mechanism of injury? Other medical conditions?
- Medications – Coumadin? Plavix? Aspirin? Pradaxa? Xarelto? Eliquis? (any blood thinners or anticoagulants)
- Beta Blockers and Calcium Channel Blockers may not allow HR to increase appropriately

Key Concepts
- Low Titer O + Whole Blood is now being used to treat severely injured trauma patients who have or are at risk for severe hemorrhage

MARCHES Protocol
- **M**assive bleeding control
- **A**irway – NPA/OPA/ Crich
- **R**espiratory – decompress chest if tension pneumothorax, occlusive dressing for open pneumothoraces
- **C**irculation- IV/IO Tqx, pelvic binder, wound packing
- **H**ypothermia care
- **E**ye injuries – cover with rigid shield and no pressure on the eye
- **S**pinal motion restriction if indicated

Criteria
HEMORRHAGIC SHOCK in medical or trauma Adult and Pediatric (≥ 6 yo) patients

Relative Contraindications
- Patient < 6 years old
  - Consult Medical Direction if patient is in hemorrhagic shock and < 6 yo
  - Medical Director may elect to give blood in patients < 6 yo

Contraindications
- Religious objection to receiving whole blood—consult On Call Medical Director

EMT
- Follow Trauma General Patient Care Guideline
- Follow appropriate Trauma Guideline

Paramedic

For Patients in HEMORRHAGIC SHOCK:
Administer Whole Blood with signs of acute hemorrhagic shock as evidenced by:

- Systolic Blood Pressure < 70 mmHg **OR**
- Systolic Blood Pressure < 90 mmHg with Heart Rate ≥ 110 beats per min **OR**
- ETCO2 < 25 **OR**
- Witnessed traumatic arrest < 5 min prior to provider arrival and continuous CPR throughout downtime **OR**
- Age ≥ 65 yo and SBP ≤ 100 **AND** HR ≥ 100 beats per minute

In general only 500mL (1 unit) of Low Titer O+ Whole Blood (LTO+WB) will be available per patient. If more than 500 mL of Whole Blood is available on scene the following general guidelines apply:

- 6-10 yo are eligible for 500 mL of Whole Blood
  - Consult Medical Direction for further orders, if needed
- 11-13 yo are eligible for 1000 mL of Whole Blood
  - Consult Medical Direction for further orders, if needed
- ≥13 yo are eligible for >1000 mL of Whole Blood
  - Consult Medical Direction for further orders, if needed

Of Note: At this time the LTO+WB does not have volume markings on the bag.

Figure 2. Low-titer group O whole blood (LTOWB) prehospital treatment parameters in San Antonio, Texas. MVC = motor vehicle collision; GSW = gun shot wound; NPA = nasopharyngeal airway; OPA = oropharyngeal airway; crich = cricothyrotomy; IV = intravenous; IO = intraosseous; Tqx = tourniquet; yo = year old; ETCO2 = end tidal carbon dioxide; CPR = cardiopulmonary resuscitation; SBP = systolic blood pressure; HR = heart rate.

opinion or studies performed in adults (49). The type of injury further complicates the matter, as pediatric trauma is more likely to be blunt as opposed to penetrating (55). It does make logical sense that a ratio of 1:1:1 would be most appropriate in this population, but component therapy is complicated by the increased risk of over-

resuscitation, given dosages must be weight based. WB may be the answer, given it contains all components in one container, which can be given as a single weight-based dose or titrated depending on ongoing blood loss.

Future Directions

The current literature suffers from lack of prospective patient outcome data concerning WB transfusion, though studies based on retrospective data have suggested improved 30-day survival with WB (8). Further randomized controlled data are needed evaluating patient outcomes such as mortality and complications, as well as viscoelastic hemostatic assay testing evaluating WB. Cost-analysis studies are also needed.

CONCLUSIONS

The efficacy and safety of WB have been well demonstrated in the military setting. Although more study is needed to compare WB with component therapy, emerging research suggests at least substantial theoretical advantage with the use of WB. SWB, which will, in practice, be LTOWB, is likely the preferred product for prehospital and emergency department trauma resuscitation, as it simplifies transfusion and provides the ideal resuscitation solution. Although there are logistical issues in the ideal storage time and its use in prehospital transport, several systems have already integrated WB into the emergency medical system with success using a predefined prehospital algorithm.

Acknowledgments—The authors would like to acknowledge the following for their contributions to this article as well as the emerging field at large: Dr. Julian Mapp, Dr. David Wampler and Dr. David Miramontes, of University of Texas Health San Antonio Department of Emergency Health Sciences, Office of the Medical Director, San Antonio, Texas; and Chief Michael Stringfellow of San Antonio Fire Department, Texas.

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ARTICLE SUMMARY

1. Why is this topic important?

Whole blood is a recent advancement in the resuscitation of severely injured trauma patients and is at the forefront of both military and civilian applications to mitigate morbidity and mortality.

2. What does this review attempt to show?

This review of the literature describes what modern day whole blood transfusion entails, its benefits, potential drawbacks, and implementation.

3. What are the key findings?

Although stored whole blood for use in trauma holds promise, it is not without distinct challenges including storage, cycling, and defining use parameters.

4. How is patient care impacted?

This article reviews the use of whole blood in trauma. Whole blood demonstrates promise as an optimal prehospital and in-hospital resuscitation solution administered to severely injured trauma patients.