Fresh Whole Blood Transfusions: Efficacy, Limitations, and the Future

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Background

Loss of blood from traumas suffered on the battlefield is the most common cause of death among potentially treatable injuries in frontline military operations (Keenan and Riesberg 2017). Cessation of blood loss and fluid repletion have been major driving factors that can reduce battlefield casualties. Once the hemorrhage has been stopped, the next step is to replace lost volume to decrease cardiac failure or shock (Eastridge et al. 2012; Butler 2017). Uncontrolled hemorrhage can lead to the "trauma triad of death", which consists of hypothermia, acidosis, and impaired coagulation (Howard et al. 2017). Hemostatic resuscitation involves the blood components resembling whole blood. The goals are to avoid metabolic acidosis, hypothermia, treating coagulopathy and stabilizing the patient as soon as possible (Nickson n.d.). The resuscitation fluids of choice for casualties in hemorrhagic shock, listed from most to least preferred are: whole blood; plasma, RBCs and platelets in 1:1:1 ratio; plasma and RBCs in 1:1 ratio; plasma or RBCs alone, and crystalloid fluids (Nickson n.d.).

Between October 2001 and June 2011, 4,596 battlefield fatalities were analyzed. Non-compressible hemorrhage is the cause of over 2/3 of battlefield deaths, which makes hemorrhages the leading cause of potentially survivable deaths in combat (Keenan and Riesberg 2017). The major body region bleeding focus accounting for mortality were torso 48%, extremities 31%, and neck/groin/ axilla region 21% (Eastridge et al. 2012). Casualties with severe hemorrhagic injury, the odds of KIA mortality were 83% lower for casualties who needed and received pre-hospital blood transfusion (Shackelford et al. 2017). Evaluating the influences on mortality is helpful for planning efforts that optimize placement, proximity, and provision of timely and effective transport and treatment capabilities to minimize casualty risk (Malsby et al.

2013). Combat wounded on today's battlefield experience the highest survival rate in history. Advances in battlefield medicine during the conflicts in Iraq and Afghanistan have included the effective use of tourniquets, damage control resuscitation, trauma system development, en route care, use of tranexamic acid, and advanced topical hemostatic dressings (Malsby et al. 2013). In 2008, there was a mandate that all the injured personnel evacuation to surgeon must occur in less than 60 minutes, "The Golden Hour", that contributed to the lowest mortality rate of any conflict in history (Keenan and Riesberg 2017).

Component therapy remains the mainstay in trauma resuscitation. In prolonged field care, access to packed red blood cells, platelets, and fresh frozen plasma is often limited (Keenan and Riesberg 2017). Transfusion of fresh whole blood has been used when access to CT in these settings are limited or have been fully utilized . The process of separating and reconstituting blood can lessen its effectiveness. Current Prolonged Field Care standards identified that the best practice for transfusions would be to maintain a stock of pRBC and FFP and have type-specific donors identified for immediate FWB draw (Keenan and Riesberg 2017).

PICOT Question: What are the limitations of Fresh Whole Blood transfusions or administration of blood products in prolonged point of injury care on the battlefield?

<u>Crystalloid Fluids</u>

Isotonic IV fluids became popular in the Vietnam War due to reduced cost and prolonged shelf life because access to supplies was very limited during the campaign. Isotonic fluids also require less equipment and less training for the provider as well. The storage life of 0.9% Normal Saline which is 15 months to 3 years depending on the volume of the bag (Beckett et al. 2015).

There is no evidence that supports isotonic fluid being a life-saving measure to traumatic injuries (Beckett et al. 2015) (Beckett et al. 2015). In fact, it leads to following complications: (1) exacerbation of bleeding due to possible clot disruption, (2) exacerbation of anemia, (3) thrombocytopenia, and (4) coagulopathy due to hemodilution (Nickson n.d.). Ley et al. found that receiving intravenous crystalloid >1.5 liters in the emergency department (ED) is an independent risk factor for mortality.

Other Adjunct Methods

Many other methods have been utilized in conjunction with blood transfusions in remote environments to decrease mortality such as utilizing Factor VII and TXA (tranexamic acid) (Anon n.d.). These are used for short term resuscitation and can "buy time". TXA is an FDA approved anti-fibrinolytic that prevents clot breakdown but can lead to thromboembolic events such as deep venous thrombosis or pulmonary embolism (Anon n.d.). Factor VII is a crucial initial component of the coagulation cascade. A double-blind randomized control trial conducted by Anantharaju et al. demonstrated a statistically significant reduction in blood transfusion requirements in patients with blunt, but not penetrating, trauma.Tourniquets are user-friendly, cheap, and transportable and their role is to stop the hemorrhage. The physiological effect of an appropriately placed tourniquet will stop arterial flow to the extremity, but at a lower pressure, it will stop the venous flow to the extremity and trap the blood in the extremity. As a result, clotting occurs, and the blood lactate concentration will rise in the retained blood and will be released into the systemic circulation when the tourniquet is released (Tang et al. 2013). This can lead to hypercoagulability and lactate acidosis. The tourniquet has a role when it comes to stopping the hemorrhage and is best used in conjunction with FWB. Autotransfusion tourniquets are being utilized in the civilian setting as well. Dr. Noam Gavriely, a professor of medicine and formerly an emergency physician and member of the Israeli Defense Force, invented the FDA approved device which is currently used in the Operating Room setting (Tang et al. 2013). The device could be used on a hemorrhaging extremity or even on an open fracture if it can be rolled over the injury. The removal of the device had to be done gradually after correction of bleeding, and restoration of the blood volume (Tang et al. 2013). If it was removed too rapidly, would be the same as the immediate loss of one liter of whole blood. Another advantage over the traditional tourniquet is the shorter time it takes to apply the device. A pre-hospital study application in a California Emergency Medical System is in the process of a randomized prospective study (Tang et al. 2013).

Component Therapy

Component therapy (CT) is part of the current standard of care as well. Component therapy does convey benefits in financial, logistical and inventory management in controlled environments (Ramakrishnan and Cattamanchi 2014). CT needs to be thawed and warmed before use to avoid causing hypothermia. Blood products that have been used longer than 24 hours result in increased mortality. FWB has more clotting factors and none of the storage problems that CT has (Ramakrishnan and Cattamanchi 2014). When compared with fresh whole blood cells, the transfusion of large amounts of pRBC contributes to a dilutional coagulopathy which is primarily the result of thrombocytopenia and poor platelet function. Stored platelets demonstrate decreased thrombotic function. This is primarily because of a decrease in expression of high-affinity thrombin receptors during platelet storage (Kauvar et al. 2006). Clinically, FWB has demonstrated to reverse dilutional coagulopathy, with evidence that a single unit of FWB has a hemostatic effect similar to ten units of platelets (Kauvar et al. 2006). A 1:1:1 ratio of plasma, PRBCs and platelets component therapy does not contain equivalent amounts of clotting factors, platelets or fibrinogen as WFWB (Ramakrishnan and Cattamanchi 2014). Necessity is the mother of invention in extending time to a patient's definitive care.

Fresh Whole Blood

Battlefield blood transfusions have been used since WWII. There is data that supports the use of FWB in hypovolemic shock (Spinella 2008). It contains red blood cells that carry O2 to the tissues; platelets that promote clotting; and other proteins, such as albumin, that maintain blood pressure. Criteria indicating need for blood transfusion was defined based on the following criteria: (1) systolic blood pressure (SBP) ≤ 90, (2) heart rate (HR) ≥ 120, or (3) multiple traumatic amputations at or above the knee or elbow (Spinella 2008). FWB resuscitation can reduce the 23% mortality among hypotensive trauma patients (Smith et al. 2016). Whole blood has a 24hr lifespan and needs to be destroyed after this time has passed. They should not be left out of controlled temperature storage for more than thirty minutes and transfusion should be complete within four hours from controlled temperature storage (Mclennan et al. 2017).

Transfusion Reactions

Transfusion reactions can happen between the donor and potential patient. Compatibility is based on antigens A and B found in the red blood cells. A person can have A, B, AB, or O (none of the antigens). A person's blood will make antibodies for the other blood types. For example, type B will have anti-A in their plasma (Spinella et al. 2009). If an incompatible transfusion occurs such as an acute hemolytic transfusion reaction (Spinella et al. 2009). If this happens, the host bodies have antibodies IgG and IgM that would attach and destroy the donor's red blood cells. A systemic immune reaction would occur and the complement system would be activated. The "enemy" cells would be lysed and macrophages would clean up the mess by phagocytosis and by releasing cytokines and interleukins. The cytokines trigger the release of tissue factor which would activate the intrinsic and extrinsic coagulation pathways (Mitra et al. 2012). Previous research and publications demonstrate that whole blood with low anti-A and anti-B IgM titers present a low/negligible risk of a catastrophic acute hemolytic transfusion reaction when given to individuals that are not of the same blood group (Bassett et al. 2016).

Limitations

During combat situations blood bank capacity of forward surgical units and combat field hospitals is frequently overwhelmed. The 75th Ranger Regiment's' Ranger O Low Titer (ROLO) Whole Blood Program was the winner of the annual Army's Greatest Innovation Award at the Association of the United States Army Global Warfare Symposium. The program identified all blood group O members of the unit and then tests them to determine possible donors to be used at the point of injury. After laboratory confirmation of blood type, the team medic will maintain a roster of blood types for each Type O individual on his team. The blood products have a 35-day shelf life when stored at 1 to 6 degrees Celsius. Typically, 2-4 units are collected 24hrs prior to a mission.

Collection of the blood products are conducted by Blood Support Detachment located in overseas military theaters when the Soldier first arrives. The donors for this blood have completed the unit’s preparation, screening and vaccination program and have been included in an established “walking blood bank” (Bassett et al. 2016). The walking blood banks identify specific blood types of all the Soldiers prior to military operations, so they will their specific blood type transfused if needed (Bassett et al. 2016). Blood type for every Soldier is usually displayed on a velcro patch. Early activation of the walking blood bank based on prehospital mechanism of injury reduce the time to FWB transfusion (Bassett et al. 2016). The preferred method used when performing a transfusion is to give the exact type between donor and recipient, but in times when the environment is not controlled, type O may be used as the universal donor (Ho and Leonard 2011).

SOF medics prevent transfusion reactions with the use of blood cards that consistently provide blood type in less than 10 minutes with the FDA approved the ABORhcard (Bowling and Pennardt 2010). Viral infections such as hepatitis B and C can be screened with rapid immunoassays, but these tests are not FDA approved for donor settings (Bowling and Pennardt 2010). A challenge with blood transfusions is equipping designated personnel with the proper equipment and training, but SOF personnel utilized their training learned at the Special Operations Combat Medic Skills Sustainment Course (Bowling and Pennardt 2010).

The operational situation is changing. With the reduction of troops and decrease in true combat missions, the SOF are being relied on more now than ever before. The areas are more remote and austere than ever before (Keenan and Riesberg 2017). They do not enjoy the support of a large medical infrastructure that regular army units have. Medical evacuation to definitive care is measured in days, not hours. There aren't enough surgical and critical care resources. CASEVAC’s are constrained by landing strips, weather, and unreliable political permissions (Keenan and Riesberg 2017). With the past robust medical support available during the war, the

Special Operations Medics had a de-emphasis on their prolonged field care for the sake of point of injury trauma care. With the, limitations in equipment and transportation, Operational context was defined by "Ruck, Truck, House, Plane" (Keenan and Riesberg 2017). Medical support plans would be developed based on this aspect. Prolonged Field care includes surgical skills, fresh whole blood transfusions, ventilator management, advanced pain management, and anesthesia skills. Teleconsultation and real time Ultrasound are being considered (Keenan and Riesberg 2017).

New Technology

A study was conducted by Boscarino et al measured the biochemical and biomechanical markers affected by changes such as heat, agitation, and pressure changes on pRBC. Even though FWB was not used in this study, the same changes would happen to the RBC within the FWB (Boscarino et al. 2014). He measured physical and chemical changes during a simulated HALO (High Altitude Low Opening) airborne operation followed by a 12-hour foot patrol (Boscarino et al. 2014). HALO airborne operations are conducted by Special Operation Forces (SOF) who jump from the aircraft, free-fall for a period of time at terminal velocity, and open their parachute at a low altitude. This helps defeat identification via radar and reduces the amount of time a parachute might be visible to ground observers, enabling a stealthy insertion.

The blood samples were stored in the Series 4-EMT Golden Hour cooling containers for the duration of the experiment. The containers remained between 2.3-3.8 degrees Celsius which is in accordance with the American Association Blood Bank standards for transport (Boscarino et al. 2014). During the HALO drop, the pH did not significantly change. Lactate and Potassium levels remained the same. There was no observable evidence of rupture of the RBC's due to rapid pressure changes (Boscarino et al. 2014). The interaction between time and temperature had no significant effect on pH and lactate. Potassium levels were found to be statistically significantly different as the time progressed, but there was no clinically significant difference. Forces of agitation had no effect on pH, lactate, potassium. Temperature and duration are the limiting steps with the delivery of blood products (Boscarino et al. 2014). The acidosis changes the shape of the RBC, but the hyperkalemia is associated with cardiac manifestations. Due to the study only being conducted with pRBC, measured effects on platelets, fibrinogen, albumin, and other components could not be evaluated (Boscarino et al. 2014).

Another concept is autotransfusion, an alternative to conventional blood transfusion techniques for battlefield environments, potentially providing blood to the casualty at the point of injury . Autotransfusion technology was tested in 1982 with a study that tested a prototype device that would conserve blood and reduce replacement needs in combat (Schneiderman n.d.). With the test protocol used, the damage to the red blood cells was minimal, the recovery of blood components in the recovered blood was good, and the small changes in measured hemostatic parameters were not very different from those observed with the control group (Schneiderman n.d.). During that time, the limitations were the same as the ones we are faced with today; how to get the quantity of blood needed, how to store it, and how to get to where it needs to be.

Development of a portable blood salvage and autotransfusion device has recently been studied by Gourlay et al.. The process essentially recycles spilled blood at the point of injury, concentrating the residual blood and returning all cell species including platelets and red blood cells back to the patient (Gourlay et al. 2017). The device can be manually powered and is capable of handling up to 3 L/min of blood, returning it directly back to casualty (Gourlay et al. 2017). The new technology reduces the normal autotransfusion performed at a military treatment facility by two steps. It eliminates the HemoSep cell saver processing and the transfusion bag. Additional blood isolation technologies are required to enhance the effectiveness of the autotransfusion device (Gourlay et al. 2017). Further testing and development are needed in austere combat environments, but it is clear that this technology can reduce the donor transfusion needs of injured personnel.

Methods

I searched PubMed, Google Scholar, Cochran Database of Systematic Reviews, CINAHL Plus with Full Text, Clinical Key, Access Medicine. I limited the search to evidence-based outcomes and randomized control trials.

Keywords searched: Blood, transfusion, battlefield, military, fresh frozen plasma, survival rates, improving casualty care, traumatic injuries, Special Operations, hypovolemic shock, remote damage control resuscitation, war, surgery, training

Terms from PubMed: blood transfusion OR IV Fluids military AND mortality and Survival, Whole Blood AND battlefield, Blood transfusion OR fresh frozen plasma AND survival AND military, Special operations and Whole blood or IV Fluids, remote damage control AND whole blood AND war

MeSh Terms: Military personnel, Survival, Shock

Observational studies and retrospective / historical studies were analyzed. Observational studies could be biased in many ways; be it selection bias including survivor bias, information bias including from use of missing data or inappropriate categories, confounding bias, not to mention new sources or errors and bias upon analyses such as those due to over-adjustment, inappropriate modeling, and assumption-violations (Kovesdy and Kalantar-Zadeh 2012). Due to the constant suspicion that the results of observational studies are affected by inadequate control of some or all of these biases preference is given to RCTs in order to have an unbiased assessment of causality (Kovesdy and Kalantar-Zadeh 2012). While a randomized prospective clinical trial in US combat casualties would be ideal, this is not permitted under DoD restrictions. TCCC guidelines have always been dependent on the preponderance of evidence from animal studies, civilian and military trauma experience and expert opinion from military medical personnel (Butler 2017).

Results

Table 1. Observational studies of blood products and trauma-related outcomes

Study Author	# of observations	what was compared?	intervention	Results	Source of Trauma
Weaver et al.	50	impact on blood transfusions for injured patients	2.8u pRBC's	55% mortality among recipients	trauma unknown
Kim et al.	50	prehospital plasma improvement of coagulopathy	1u pRBC'S		measured penetrating
Bodnar et al.	71	interventions and outcomes of PHBP recipients	1.8u pRBC	10% mortality	measured blunt and penetrating

Barkana et al.	40	effects of PHBP on morbidity & mortality	1u pRBC	33% mortality	measured blast, penetrating, and blunt
Badjie et al.	79	mortality of patients who receive a 1:1 FFP:pRBC	2u FFP 2u pRBC	not annotated	trauma unknown
Brown et al.	1365	pre trauma RBC associated with reduced mortality	not annotated	25% mortality	trauma unknown

Table 1 summarizes several studies and population characteristics from a systematic review conducted by Smith et al. They researched prehospital blood product resuscitation for trauma. No blinded or randomized studies were identified and all were retrospective observational studies. Risk of bias assessments was made using the Newcastle-Ottawa Scale for comparative studies (Smith et al. 2016). Two-thirds of eligible patients were excluded due to nonavailability of pre / post transfusion vital signs. This indicates a selection bias if vital signs were non-recordable or interventions prioritized in the sickest patients (Smith et al. 2016).

Due to the different nature of populations, interventions, and outcomes, only limited meta-analysis was possible (Smith et al. 2016). In meta-analysis of both unmatched and matched studies, heterogeneity was present and significant, demonstrating the degree of uncertainty that exists about a measurable benefit of resuscitation (Smith et al. 2016). A narrative synthesis of the available evidence was constructed. The validity of the studies from predominantly younger, massively traumatized males to the civilian population was questionable (Smith et al. 2016). Pooled estimates of mortality were calculated using inverse weighting and mixed models to reflect heterogeneity between studies (Smith et al. 2016). The most significant weakness of the study is the low quality of evidence on which the review could draw (Smith et al. 2016).

Discussion

A majority of the literature regarding blood transfusions on the battlefield are retrospective or historical, thus making the evidence weak. As a result, there is an increased risk of selection bias and potentially the inability to measure and adjust for all potential confounding factors (Eastridge et al. 2012). There is limited evidence to support, in a field environment, that a whole blood based resuscitation strategy is superior to a crystalloid/colloid approach even when augmented by a limited number of RBC and plasma units (Theusinger et al. 2012).

Within the systematic reviews, many studies were observational and retrospective, providing poor quality evidence. The comparative studies contained too many confounders to adjust for, such as differences in the patients and treatment pathways (Smith et al. 2016). Many combat support hospitals, were not able to collect data that would allow researchers to precisely determine the mechanisms by which whole blood might improve survival (Mclennan et al. 2017). No definitive conclusions can be made based on the studies due to many confounding variables affecting the studies, but a generalization can be made. FWB is superior to treating with crystalloid solutions or component therapy.

The key to trauma care is based on many factors and depends on decreasing the time it takes for a patient to receive pre-hospital care (Howard et al. 2017). Fresh whole blood may be lifesaving for the unstable bleeding Soldier when other methods are not available due to prolonged field care (Howard et al. 2017). The limitation of FWB transfusions is transportation, availability of product, equipment, shelf life. These limitations are exacerbated to a depleted status as time to extraction increases. But these limitations are quickly becoming a thing of the past due to the advances in the storage capacity equipment such as the Series 4-EMT Golden Hour cooling containers.

Researchers are also looking beyond just the transportation aspect. Autotransfusion has been shown to work, but the study was performed in a lab only setting and limitations were contamination from the environment and its effectiveness in a situation mimicking a major battlefield hemorrhage. (Gourlay et al. 2017). Military units are participating in "walking blood banks" to meet the demand for whole blood products.

Next for the O-low titer blood use is the medevac Vampire system. Vampire is the code name used to identify Medevac missions where blood products were administered to patients (Malsby et al. 2013). Recently, the medevac Vampire system guidelines have been updated to include the use of whole blood. We are also seeing increased use and demand by surgical teams (Malsby et al. 2013). As more medical providers switch over to whole blood, the availability will increase while waste decreases. Advances in adjunct therapy such as the autotranfusion tourniquet are making it possible to delay bleeding time. Unfortunately, this technology is mainly being utilized in Orthopedic Surgery field (Tang et al. 2013).

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