Form "EAST Multicenter Study Proposal"
Details #66 (submitted 10/01/2018)

Study Title	A Comprehensive and Collaborative Review of the Use of Whole Blood at Trauma Centers in the United States
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Are you a current member of EAST?	Yes
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My Multicenter Study proposal is...	Prospective

The foundation for blood transfusions for traumatic injuries was established by Dr. Oswald Robertson during the First World War, when blood banking during military combat became available.(1) However, civilian establishment of organized blood banking lagged by several decades, and only became readily available during the Second World War. Stored Whole blood was the mainstay of transfusion through the beginning of the Vietnam era. In 1965, during the Vietnam War, blood component therapy was introduced, and by the 1970s, whole blood resuscitation had nearly ceased.(2) Component therapy, including packed red blood cells (PRBC), fresh frozen plasma (FFP), and platelets (PLT) has been adopted as the gold standard for both military and civilian trauma resuscitation. Strategies in component resuscitation have evolved over the past several decades, with the adoption of damage control resuscitation (DCR). DCR principles include early administration of blood products in a balanced ratio, prevention and correction of coagulopathy, and minimization of crystalloid fluid resuscitation.(3) Typical initial resuscitation using a massive transfusion protocol uses component therapy from universally compatible donors prior to laboratory testing. The concept of a balanced component resuscitation that supports achieving hemostasis with transfusion of PRBC, FFP, and PLT in a 1:1:1 ratio that approximates whole blood has been largely supported by recent evidence.(4, 5)

Use this area to briefly (1-2 paragraphs only) outline the burden of the problem to be examined

While component therapy has dominated civilian resuscitation of hemorrhagic shock, fresh whole blood (stored at 22C for 24 h) has continued to be used in military trauma resuscitation in austere environments where storage of component therapy is unavailable. In fact, over 6,000 units of type-specific warm fresh whole blood were transfused during the Iraq and Afghanistan conflicts to patients with severe hemorrhage, and these patients showed increased 24-hour and 30-day survival and decreased transfusion requirements.(6, 7) However, warm fresh whole blood still only comprised 4% of transfusions during this era, reflecting the current practice of using component therapy when available.(6) Civilian interest with the use of whole blood for resuscitation of traumatic hemorrhagic shock has resurged in the past decade. Unlike in austere military environments, civilian usage of whole blood has been in the form of cold-stored whole blood. Stored whole blood has an established safety profile; over 350,000 units were transfused during the Vietnam war with low rates of hemolysis.(8) Low-titer, leukocyte-reduced, platelet-sparing Group O whole blood has been used in several small series at three Level 1 trauma centers in the United States with initial published data suggesting a trend towards decreased transfusion requirements, but studies have been small and underpowered to detect a survival benefit.(8, 9) However, these studies did establish a safety profile for the practice of transfusing Group O whole blood, with no reports of transfusion reactions or differences in serum haptoglobin as a marker of hemolysis.(8) There has been preliminary investigation by one series into markers of coagulation as assessed by thromboelastography, with improvement in markers of coagulopathy seen in groups receiving whole blood and platelet transfusion.(10) Further investigation into the role of stored whole blood and its role in resuscitation of traumatic hemorrhagic shock is clearly indicated.

Primary aim

Aim 1: To evaluate the effect of whole blood resuscitation on survival, as assessed at 4 and 24 hours post-injury.

Aim 2: To evaluate standard labs, total transfusion requirements, and need for damage control resuscitation at 4 and 24 hours, and 30 days.

Secondary aims

Aim 3: To evaluate the potential complications of whole blood transfusion, including hemolysis and thrombotic complications

Inclusion Criteria

•All patients ages 16 and older who receive whole blood or packed red blood cells during the acute resuscitation period or in the operating room from September 1, 2016 through present.

•All patients ages 15 and younger who receive whole blood or packed red blood cells during the acute resuscitation or in the operating room.

Exclusion Criteria

•All patients age 90 and over.

Retrospective subjects will be identified using the trauma registry and prospective subjects will be identified by attending trauma surgeons as well as the trauma registry and will be enrolled upon recognition of meeting institutional indications for stored whole blood (sWB) transfusion. Venipuncture and standard trauma laboratory testing will be performed in concordance with standard of care. No additional testing or procedures outside of standard of care will be performed as a part of this study. Other clinical and laboratory data that will be collected will be obtained from chart review and trauma registry information.

Therapeutic Interventions

A waiver of consent is being requested for the prospective portion of this study. Patients who are candidates for the study are in hemorrhagic shock and generally unable to provide informed consent due to altered mental status. Many of these patients may undergo emergent intubation for airway control, and thus will be unable to provide informed consent due to sedation/intubation. Obtaining consent from family members for the purposes of this study is logistically impossible, as next-of-kin may not be immediately identified at the time of injury, and the patient is typically not able to provide information regarding next-of-kin due to the degree of injury and shock, as well as significant emotional distress after sustaining a major trauma. In addition, the number of subjects anticipated to meet criteria for enrollment into this study is small. Failure to capture all eligible subjects due to need for informed consent would significantly skew results and would bias the research results deeming them inaccurate and not reflective of the general population.

Primary Outcome

Determine if there is a significant difference in mortality among sWB recipients versus component therapy recipients.

Secondary Outcomes

Determine if there is a significant difference in product usage among sWB recipients versus component therapy recipients.

List specific variables to be collected & analyzed

All of the information to be collected for these patients is as follows: Group (control (PRBC) or WB), Age, Race, Arrival Year, Arrival Time, Transfer from Outside Hospital, Method of Arrival, Approximate time from Injury to Arrival, Approximate time from first Pre-hospital Medical Contact to Hospital Arrival, Mechanism of Injury, GCS, Arrival SBP, SBP Nadir, Arrival HR, Fast Exam, Tourniquet Use, AIS, ISS (Head & Neck), ISS (Face), ISS (Chest), ISS (Abdomen), ISS (Extremity), ISS (External), ABC Score on arrival, Shock Index on arrival, WB (units transfused Initial Resuscitation), Titer Level of WB, PRBCs (units transfused Initial Resuscitation), Plasma (units transfused Initial Resuscitation), PLT (units transfused Initial Resuscitation), IVF (units transfused Initial Resuscitation), TXA, Factor 7, Kaycentra, Cryo, Fibriongen Concentrate, Initial Hemoglobin, Initial Hematocrit, Initial INR, Initial PT, Initial PTT, Initial TEG, 4 Hour Hemoglobin, 4 Hour Hematocrit, 4 Hour INR, 4 Hour PT, 4 Hour PTT, 24 Hour Hemoglobin, 24 Hour Hematocrit, 24 Hour INR, 24 Hour PT, 24 Hour PTT, Disposition from Trauma, Procedure, Total Units WB infused (over 24 hours), Titer Level of WB, Total PRBCs infused (over 24 hours), Total Plasma infused (over 24 hours), Total Platelets infused (over 24 hours), Total IVF infused (over 24 hours), Time to Hemostasis, Hemolytic Reaction, Transfusion React, VTE/PE, Survival Hospital, Survival 30 Days (If applicable), Cause of Death, If MOF (Denver Score >3 on Day 2).

This study will be collaborative in nature between Cooper University Hospital and other Trauma Centers infusing sWB as standard of care. All participating sites will send their de-identified data to Cooper University Hospital for inclusion in overall analysis. REDCap will be used for ease of data transmission.

Outline the data collection plan and statistical analysis plan succinctly

Plan for Statistical Analysis: Risk factors for complications (both procedural and outcome-related) and mortality, complications and in-hospital outcomes will be assessed using univariate and multivariate analysis. Continous variables will be compared using Student t-test and the Mann Whitney U test. The Chi-squared tests or Fisher's exact test will be used to compare categorical variables. All variables with a p value less than 0.2 on univariate analysis will be entered into a multivariable logistic regression analysis to identify independent risk factors for transfusion requirement, coagulopathy, complications, and mortality. Data will be reported as adjusted odds ratios with 95% confidence intervals. Statistical significance will be set at a p 0.05.

Outline consent procedures here, if applicable

A waiver of consent is being requested for the prospective portion of this study as there will be no research related intervention for the included patients. All treatment is standard of care and the prospective portion of this study will be observational.

Succinctly outline a risk/benefit analysis

There are no physical risks associated with this study as this is a retrospective/prospective observational study. There is a small risk of breach of confidentiality for the cases reviewed. This risk will be minimized by using a case ID key, a template of which will be supplied to participating sites. Having data on the outcomes of the use of sWB compared to the us of component therapy has the potential to change the way all civilian patients in hemorrhagic shock are treated across the United States as well as the rest of the world.

Include a brief listing of key references

1.Robertson OH. Transfusion with Preserved Red Blood Cells. British Medical Journal. 1918;1(2999):691-5.

2.Bahr MP, Yazer MH, Triulzi DJ, Collins RA. Whole blood for the acutely haemorrhaging civilian trauma patient: a novel idea or rediscovery? Transfusion medicine (Oxford, England). 2016;26(6):406-14.

3.Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. Jama. 2015;313(5):471-82.

4.Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA surgery. 2013;148(2):127-36.

5.del Junco DJ, Holcomb JB, Fox EE, Brasel KJ, Phelan HA, Bulger EM, et al. Resuscitate early with plasma and platelets or balance blood products gradually: findings from the PROMMTT study. J Trauma Acute Care Surg. 2013;75(1 Suppl 1):S24-30.

6.Spinella PC. Warm fresh whole blood transfusion for severe hemorrhage: U.S. military and potential civilian applications. Crit Care Med. 2008;36(7 Suppl):S340-5.

7.Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Holcomb JB. Warm fresh whole blood is independently associated with improved survival for patients with combat-related traumatic injuries. J Trauma. 2009;66(4 Suppl):S69-76.

8.Yazer MH, Jackson B, Sperry JL, Alarcon L, Triulzi DJ, Murdock AD. Initial safety and feasibility of cold-stored uncrossmatched whole blood transfusion in civilian trauma patients. J Trauma Acute Care Surg. 2016;81(1):21-6.

9.Cotton BA, Podbielski J, Camp E, Welch T, del Junco D, Bai Y, et al. A randomized controlled pilot trial of modified whole blood versus component therapy in severely injured patients requiring large volume transfusions. Annals of surgery. 2013;258(4):527-32; discussion 32-3.

10.Rahbar E, Cardenas JC, Matijevic N, Del Junco D, Podbielski J, Cohen MJ, et al. Trauma, Time, and Transfusions: A Longitudinal Analysis of Coagulation Markers in Severely Injured Trauma Patients Receiving Modified Whole Blood or Component Blood Products. Shock. 2015;44(5):417-25.