Title of Study: A Comprehensive Review of the Use of Whole Blood at Level 1 Trauma Centers
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1) **Protocol Title:** A Comprehensive Review of the Use of Whole Blood at Level 1 Trauma Centers

2) **Hypothesis:** We hypothesize that survival may be improved by the use of whole blood in the setting of massive exsanguination during damage control resuscitation.

3) **Objectives:** This study aims to describe the effects of resuscitation of hemorrhagic shock from acute traumatic injury with WB during the resuscitation. In particular, effects on coagulopathy, total transfusion requirement, need for damage control resuscitation, and survival will be elicited.

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

4) **Background:** 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)

   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 whole blood and its role in resuscitation of traumatic hemorrhagic shock is clearly indicated.

5) Inclusion and Exclusion Criteria:

Inclusion Criteria:

- All patients meeting inclusion/exclusion who receive whole blood during the resuscitation period

Exclusion Criteria:

- All patients age 90 and over

6) **Number of Subjects:** This is a combined retrospective/prospective review of all patients that received whole blood transfusions during a trauma resuscitation meeting the inclusion/exclusion criteria outlined. There will be a total of 4000 patients included in this study.

7) **Study Timelines:** Reviews of patient charts will commence upon IRB approval and will remain ongoing until all records to be included in this study have been reviewed, data have been analyzed and a paper has been submitted and accepted for publication.

8) **Procedures Involved:** 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 indications for WB transfusion. Venipuncture and standard trauma laboratory testing will be performed by the nursing staff in the trauma receiving area 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.

We are requesting a waiver of informed consent for the prospective portion of this study. Patients who are candidates for the study are in hemorrhagic shock and generally are not able 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 enroll in 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.

All of the information to be collected for these patients is as follows: Age, Race, Arrival Year, Arrival Time, Transfer from Outside Hospital, Method of Arrival, Approximate time from Injury to Arrival, Pre-Arrival Blood Products, Pre-Arrival TXA, Pre-Arrival Crystalloid Volume , Mechanism of Injury, GCS, Arrival SBP, SBP Nadir, Arrival HR, Fast Exam, TRISS, AIS, ISS (Head & Neck), ISS (Face), ISS (Chest), ISS

(Abdomen), ISS (Extremity), ISS (External), ABC Score on arrival, Shock Index on arrival, WB Type (cold stored WB or warm fresh WB), WB (units transfused at 4 hours and 24 hours), Titer Level of WB, PRBCs (units transfused at 4 hours and 24 hours), Plasma (units transfused at 4 hours and 24 hours), PLT (units transfused at 4 hours and 24 hours), MTP (yes/no), IVF (units transfused at 4 hours and 24 hours), Cryo (units transfused at 4 hours and 24 hours)TXA, Factor 7, Kaycentra, Fibriongen Concentrate, PCC, Initial Hemoglobin, Initial Hematocrit, Initial INR, Initial PT, Initial PTT, Initial Platelet, Initial TEG, 4 Hour Hemoglobin, 4 Hour Hematocrit, 4 Hour INR, 4 Hour PT, 4 Hour PTT, 4 Hour Platelet, 24 Hour Hemoglobin, 24 Hour Hematocrit, 24 Hour INR, 24 Hour PT, 24 Hour PTT, 24 Hour Platelet, Disposition from Trauma, Time to Hemostasis, Hemolytic Reaction, Pulmonary Complications, Transfusion React, VTE/PE, Survival Hospital (within 4 hours, 24 hours 72 hours), Survival 30 Days (If applicable), Cause of Death, If MOF (Denver Score >3 on Day 2).

9) **Statistical Design:** Continuous variables will be presented as medians and interquartile range and compared using the Wilcoxon two-sample test. Categorical variables will be presented as percentages and analyzed with the Fisher's exact test. Statistical significance will be defined as p value ≤ 0.05. To study the predictive ability of the model, we will use the concordance index (c-index), which is equivalent to the area under the receiver operating characteristic curve (AUROC). A c-index of 0.5 indicates no predictive ability, while a value of 1.0 indicates a perfect predictive ability.

10) **Data Management:** All paper research files will be stored at Cooper University Hospital, 1 Cooper Plaza, Kelemen - Suite 203, Camden, NJ 08103 in a double locked cabinet. All electronic files will be stored on a password-protected computer at the same address. Identifiable information will be listed on a "key" that will correspond with assigned Case ID#s. This will serve to decrease the chance of privacy/confidentiality breach. Whenever possible data will be de-identified. De-identified data will be entered into spreadsheets that will be housed on password protected computers. All personnel approved for participation in the study will have access to these data sheets.

    This study will be collaborative in nature between Cooper University Hospital and Penn Presbyterian Hospital. Penn Presbyterian Hospital will send their de-identified data to Cooper University Hospital for inclusion in overall analysis. Cooper University Hospital will not send out data to Penn Presbyterian Hospital.

11) **Provisions to Monitor the Data:** All data will be monitored closely by the Principal Investigator, Sub-Investigators and the study team to ensure compliance with IRB SOPs as well as GCP.

12) **Potential Benefits to Society:** While this study does not change the way patients are treated, thus, there is no direct benefit associated with study participation for the individual. However, it is highly likely that future trauma patients will benefit from the data gathered in this study.

13) **Resources Available:** All study team members are knowledgeable about clinical research and have completed Good Clinical Practice certification prior to participation in this project.

14) **Confidentiality:** Every effort will be made to protect the confidentiality of data for the cases used in this study. All data will be de-identified and the case assigned ID# will be used to track trauma surgeon predictions.

15) 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.

EAST MULTICENTER STUDY
DATA DICTIONARY

Comprehensive Review of the Use of Whole Blood at Level 1 Trauma Centers – Data Dictionary

Data Entry Points and appropriate definitions / clarifications:

Entry space	Definition / Instructions
Patient Information	*(Use unknown if not recorded)*
Age	Age of patient enrolled
Sex	Sex of the patient enrolled (male or female)
Race	Race of the patient enrolled (White, Black, American Indian/Alaskan Native, Other – specify)
Arrival Date	Arrival date of the patient enrolled
Arrival Time	Arrival time of the patient enrolled (24 hour clock)
Transfer from Outside Hospital	Was the patient transferred from an outside hospital (Y/N)
Method of arrival	State the enrolled patient's method of arrival (Advanced Life Support, Basic Life Support, Police, Private vehicle, Walk-in, Helicopter, Other – specify)
Mechanism of Injury	Primary mechanism of the patient's injury. Select the choice that best applies (gun-shot wound, stab wound, assault, motor-vehicle crash, motorcycle crash, pedestrian versus motor-vehicle, fall, other – specify)
Approximate Time from Injury to Arrival	If known, the approximate time (in minutes) from when the injury occurred to when the patient arrived at receiving facility
Pre-Arrival Blood Products	Did the patient receive blood products prior to arrival at receiving trauma center (Y/N)

Pre-Arrival TXA	Did the patient receive tranexamic acid (TXA) prior to arrival at receiving trauma center (Y/N)
Pre-Arrival Crystalloid Volume	Amount in liters of crystalloid received prior to arrival at receiving trauma center
Vitals	(*Leave blank if not recorded)*
GCS	Total Glasgow Coma Scale value on arrival to receiving facility (numerical value)
SBP	Systolic blood pressure on arrival to receiving facility (numerical value)
Nadir SBP (4 hrs)	Lowest systolic blood pressure recorded within four hours of arrival to receiving facility (numerical value)
HR	Heart rate on arrival to receiving facility (numerical value)
FAST Exam	If completed, result of focused assessment with sonography for trauma examination on arrival to receiving facility (positive, negative, or none)
TRISS	Calculated trauma injury severity score (numerical value)
ISS	Calculated injury severity score (numerical value)
AIS Head/Neck	Abbreviated injury score body region = head/neck (numerical value)
AIS Face	Abbreviated injury score body region = face (numerical value)
AIS Chest	Abbreviated injury score body region = chest (numerical value)
AIS Abdomen	Abbreviated injury score body region = abdomen (numerical value)
AIS Extremity	Abbreviated injury score body region = extremities (numerical value)
AIS External	Abbreviated injury score body region = external (numerical value)

ABC score	Total ABC score (0-4) for massive transfusion (penetrating injury (Y/N) + positive FAST exam (Y/N) + arrival SBP of 90 or less (Y/N) + arrival HR of 120 or greater (Y/N))
Shock Index	Shock index score (HR on arrival divided by SBP on arrival to receiving facility) (numerical value)

Initial Resuscitation

Whole blood units) at 4 hours and 24 hours.	Units of WB transfused during initial resuscitation (in
Whole blood type	cold-stored whole or blood or warm-fresh whole blood
Titer level	Titer level of whole blood transfused during initial resuscitation
PRBCs	Volume of packed red blood cells transfused during initial resuscitation (in units) at 4 hours and 24 hours.
FFP	Volume of fresh frozen plasma transfused during initial resuscitation (in units) at 4 hours and 24 hours.
PLT	Volume of platelets transfused during initial resuscitation (in units) at 4 hours and 24 hours.
MTP	Massive Transfusion ProtocolGreater than or equal to 10 units of packed cells or WB in 24 hours / greater than or equal to 4 units of packed cells or WB in 1 hour.
IVF	Volume of intravenous fluids received during initial resuscitation (in liters) at 4 hours and 24 hours
Cryo	Cryo use during initial resuscitation (in units) at 4 hours and 24 hours.
TXA	Tranexamic acid use during initial resuscitation (Y/N)
Factor 7	Factor 7 use during initial resuscitation (Y/N)
Kcentra	Kcentra use during initial resuscitation (Y/N)
Fibrinogen Concentrate	Fibrinogen concentrate use during initial resuscitation (Y/N)

PCC	Prothrombin complex concentrate use during initial resuscitation (Y/N)
Laboratory Values	*(record initial, at 4 hours (+/- 2 hrs), and 24 hours (+/- 2 Hrs) for each value EXCEPT TEG – initial only)*
Hemoglobin	Initial (value recorded closest to arrival time), 4 hr, and 24 hr values (g/dL)
Hematocrit	Initial (value recorded closest to arrival time), 4 hr, and 24 hr values (%)4
Lactate	Initial (value recorded closest to arrival time), 4 hr, and 24 hr values (g/dL)
INR	Initial (value recorded closest to arrival time), 4 hr, and 24 hr values (ratio)
PT	Initial (value recorded closest to arrival time), 4 hr, and 24 hr values (seconds)
PTT	Initial (value recorded closest to arrival time), 4 hr, and 24 hr values (seconds)
TEG	*If available* - Initial (value recorded closest to arrival time)
ROTEM	*If available* - Initial (value recorded closest to arrival time)
Platelets	Initial (value recorded closest to arrival time), 4 hr, and 24 hr values.
Resuscitation Outcomes	
Disposition from Trauma	Disposition of enrolled patient upon leaving trauma admitting (operating room, floor, intensive care unit, IR, morgue, other – specify)
Time to Hemostasis	Amount of time (in minutes) until hemostasis was achieved
Hemolytic reaction	Fever, hypotension, hematuria (Y/N)
Pulmonary complications	Presence of pulmonary complications: acute respiratory distress syndrome (ARDS), transfusion related acute lung injury (TRALI), transfusion associated circulatory overload (TACO)

VTE/PE	Venous thromboembolism or pulmonary embolism (Y/N)
Mortality	Patient deceased (Y/N) *(If yes, proceed to next data point)*
Timing of Mortality	Within 4 hours, within 24 hours, if within 72 hours record the number of hours of survival
Within 30 days	Mortality within 30 days of arrival date (Y/N)
Cause of death	Primary cause of death (hemorrhage, multi-system organ failure, traumatic brain injury, other – specify) *(If MOF, proceed to next data point)*
Denver score	Denver score > 3 on day 2 of admission (Y/N)

EAST MULTICENTER STUDY
DATA COLLECTION TOOL

Multicenter Study: Comprehensive Review of the Use of Whole Blood at Level 1 Trauma Centers

Enrolling Center Number: _____
Subject Number: _____

Patient Information

Age: _____ years Sex (M/F): _____

Race (circle one): White Black Asian Other (specify) _____ Hispanic: (Y/N) _____

Arrival Date: _____ Arrival Time: _____ Transfer from Outside Hospital (Y/N)

Method of Arrival: _____ (ALS, BLS, Police, Private vehicle, Helicopter)

Mechanism of Injury: _____ (Blunt/Penetrating)

Approximate Time from Injury to Arrival (mins): _____

Pre-Arrival Blood Products: (Y/N) _____

Pre-Arrival TXA: (Y/N) _____

Pre-Arrival Crystalloid Volume (liters): _____

Vitals on Arrival

GCS: _____ SBP: _____ Nadir SBP (4 hrs): _____ HR: _____

Fast Exam (positive/negative/not done): _____

Trauma Injury Severity Score (TRISS): _____

Injury Severity Score (ISS): _____
AIS (Head/Neck): _____
AIS (Face): _____

AIS (Chest): _____
AIS (Abdomen): _____
AIS (Extremity): _____
AIS (External): _____

ABC score (0-4): _____ Shock Index: _____

Initial Resuscitation

Whole blood type _____ cold-stored _____ warm-fresh

Titer Level: _____

WB (units) at 4 hrs: _____ 24 hrs: _____
PRBCs (units) at 4 hrs: _____ 24 hrs: _____
FFP (units) at 4 hrs: _____ 24 hrs: _____
PLT (units) at 4 hrs: _____ 24 hrs: _____

Massive Transfusion Protocol (yes/no): _____

IVF (liters) at 4 hrs: _____ 24 hrs: _____
Cryo (units) at 4 hrs: _____ 24 hrs: _____

TXA (yes/no): _____
Factor 7 (yes/no): _____
Kcentra (yes/no): _____
Fibrinogen Concentrate (yes/no): _____
PCC (yes/no): _____

Laboratory Values

Hemoglobin: *initial* _____ *4-hour* _____ *24-hour* _____
Hematocrit: *initial* _____ *4-hour* _____ *24-hour* _____
Lactate: *initial* _____ *4-hour* _____ *24-hour* _____
INR: *initial* _____ *4-hour* _____ *24-hour* _____
PT: *initial* _____ *4-hour* _____ *24-hour* _____
PTT: *initial* _____ *4-hour* _____ *24-hour* _____
Platelets: *initial* _____ *4-hour* _____ *24-hour* _____
TEG: *initial* _____
ROTEM: *initial* _____

Resuscitation Outcomes

Disposition from Trauma: _____ (OR, Floor, ICU, IR, Morgue)

Time to Hemostasis (mins): _____

Hemolytic Reaction (yes/no): _____

Pulmonary complications: _____ (None, ARDS, TRALI, TACO)

VTE/PE (yes/no): _____

Mortality (yes/no): _____

If yes, Within 4 hours (yes/no): _____

Within 24 hours (yes/no): _____

If within 72 hours, number of hours survived*:* _____

Within 30 days (yes/no): _____

Cause of Death: _____ (Hemorrhage, MOF, TBI, Other)

If MOF, Denver Score > 3 on day 2 (yes/no): _____