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**Title of Proposal:** The Impact of Pre-Hospital Whole Blood on Mortality in Severely Injured Trauma Patients

**Hypothesis:** The administration of any volume of whole blood in trauma patients before arrival to the hospital will reduce in-hospital mortality.

**Type of Study:** Prospective, Observational

**Background:**

Hemorrhage is a major source of morbidity and mortality for trauma patients. Nearly 30% of pre-hospital trauma deaths and over 20% of in-hospital trauma deaths are due to hemorrhagic shock (1). Blood product transfusion until hemorrhage control is achieved has been shown to improve mortality (2-4). Trauma resuscitation in hemorrhagic shock has progressed from use of crystalloid fluids (CF), to balanced component transfusion therapy (BCT), and most recently toward the administration of whole blood (WB) (6-8). Transfusion of WB or BCT restores the oxygen-carrying capacity of the circulating volume by maintaining oncotic pressure and hemoglobin concentrations, while decreasing the risk of trauma induced coagulopathy. WB was the mainstay of resuscitation in the military setting until the 1970’s, at which point blood component storage and crystalloids evolved as an inexpensive alternative to increase circulating volume. However, lessons learned in the military setting have fueled, in part, the resurgence of WB use in civilian trauma (11, 12). Tantamount to *what* product is administered, however, is *when* the product is administered. Optimizing both the product offered as well as the timing of administration could dramatically reduce mortality and the associated morbidity of trauma patients, diminishing a key preventable cause of death.

Several recent studies have evaluated the viability of different resuscitative products and their relative timing of administration. The PAMPer trial sought to demonstrate the relatively deleterious effects of large volume CF versus plasma alone versus plasma and pRBC’s (5). Results demonstrated the largest effect for plasma plus pRBC’s, with a hazard ratio of 0.38, versus 0.57 for plasma alone. the PAMPer trial also demonstrated a lower per-unit mortality associated with pRBC’s, while increasing crystalloid administration demonstrated increased mortality (HR 1.65). Ultimately, the PAMPer trial demonstrated compelling evidence for superiority of BCT over crystalloids (5). However, it did not address whole blood nor did it compare outcomes of these therapies based of timing of administration.

A systematic review performed by Malkin *et al* did not demonstrate a survival benefit or reduced transfusion volumes utilizing WB, however concluded that there may be a logistic benefit (13) . In a 2022 retrospective review of the American College of Surgeons Trauma Quality Improvement Program (ACS TQIP) data base, Andrade *et al* evaluated 37,384 patients with at least moderate severity of injury. The authors demonstrated no difference in 4 or 24 hour transfusion of packed red blood cell volumes, ICU length of stay, or complication rates in patients who received WB and BCT (9). Overall, this study demonstrated that a combined administration of BCT and WB is a viable alternative to BCT alone. However, Torres *et al* demonstrated in their review of ACS TQIP data bank that WB transfusion associated with massive transfusion protocol (MTP) vs MTP alone had a survival benefit (14).

The clinical preference for BCT is being evaluated against the benefit of WB by the SWiFT trial. Currently underway, the SWiFT trial is a randomized clinical trial placing trauma patients into two study arms: pre-hospital leukocyte depleted whole blood transfusion versus component therapy and the relative impact on all-cause mortality or requirement of MTP within 24 hours of admission for trauma. While asking an important question, the SWiFT trial will not be able to address whether or not pre-hospital WB, as an adjunct to WB administration during initial trauma activation, will bear a positive impact (7).

While the use of WB has been more prevalent in civilian trauma centers, the lack of strong evidence to demonstrate a mortality benefit is striking. Further, there has been a gap in knowledge whether the use of WB transfusion in the pre-hospital setting in patients with hemorrhagic shock has demonstrated a survival benefit, compared to simply starting whole blood transfusion upon arrival to a receiving trauma center.

**Background - Define the Knowledge Gap that Study Addresses:**

The aim of this study is to investigate use of pre hospital WB + ED WB combined with component transfusions versus in-hospital WB combined with component transfusions alone, with specific attention to intensive care unit (ICU) length of stay (LOS), 4-hour and 24-hour packed red blood cells (pRBCs) transfusion volumes, and in-hospital mortality in adult civilian trauma patients sustaining injuries severe enough to merit administration of an MTP within the first 4 hours of arrival to the hospital. To our knowledge, there are presently no studies addressing this specific question.

**Objectives**

**Study Aim(s)- Primary Aim:** To evaluate use of pre-hospital administration of WB and in-ED WB transfusion in combination with BCT, versus patients who only received ED WB in combination with BCT, and associated outcomes on in-hospital mortality in significantly injured trauma patients who require MTP within the first 4 hours of arrival to the hospital.

**Study Aim(s)-Secondary Aim:** To evaluate the use of pre-hospital administration of WB and in-ED WB transfusion in combination with BCT, versus patients who only received pre-hospital crystalloid resuscitation or BCT and in-hospital WB transfusion in combination with BCT, and its associated outcomes on in-hospital mortality on significantly injured trauma patients who require MTP within the first 4 hours of arrival to the hospital.

**Proposed Study Population-Inclusion Criteria:**

Trauma patients age greater than 16 years, who arrive in hemorrhagic shock warranting pre-hospital WB, crystalloids or BCT transfusion and activation of MTP within the first 4 hours of arrival to the hospital. Any patient who requires pre-hospital or in-hospital WB and doesn’t require MTP activation will also be studied.

**Proposed Study Population-Exclusion Criteria:**

Patients who were transferred in or out of the receiving facility.

Non trauma patients in hemorrhagic shock

**Outcome Measures**

**Primary Outcome:** Mortality (ED mortality, 24 hour mortality and in-hospital mortality)

**Secondary Outcome(s):** ICU LOS; time to hemorrhage control, pRBC and other components (FFP, platelets and Cryoprecipitate), transfusion volumes at 4, 12, 24 hours from admission with records of both order time and administration time, and ventilator days.

**Data Collection Variables:**

**Pre hospital variables:** systolic blood pressure **(**SBP), heart rate (HR), Glasgow Coma Scale (GCS), units of whole blood transfused, shock index, number of crystalloids in liters, shock index, intubation, emergent procedure (i.e., decompression of chest, intubation, tourniquet placement)

**ED variables:** HR, SBP, DBP, GCS, units of whole blood and component transfusions, number of crystalloids in liters, time to transfusion, type of IV/IO access

**Demographics** : Race, age, sex, mechanism of injury, EMS transport mode, scene time, transport time, trauma center level, injury severity score (ISS), injury characteristics, Abbreviated injury severity scores (AIS) by body region.

**In-hospital variables:** 4 hour transfusions, 12 hour transfusions, 24 hour transfusions, admission Hgb, INR, platelet count, TEG values, pH, Lactate, Base deficit. pre-hospital and in-hospital TXA administration.

**Complications:** ventilator associated pneumonia (VAP), Acute respiratory distress syndrome (ARDS), Transfusion associated cardiopulmonary overload (TACO), venous thromboembolism (VTE), Acute kidney injury (AKI), Transfusion associated lung injury (TRALI)

**Definitions**

-TRALI: transfusion-associated effect occurring during or soon after allogeneic blood transfusion, manifested typically by shortness of breath, fever, and hypotension. (16)

-TACO: pulmonary edema primarily related to circulatory overload, including 3 or more of the following within 6 hours of transfusion: acute respiratory distress, radiographic pulmonary edema, elevated central venous pressure, evidence of left heart failure, elevated B-type natriuretic peptide (BNP), and a positive fluid balance. (17)

-VAP: Development of acute lung infection acquired in a health care setting developing at least after 48 consecutive hours of intubation (18)

-VTE: Aberrant thrombus formation of either a provoked or unprovoked nature in the peripheral venous circulation with or without embolization to distal capillary beds, most often in the lungs and presenting as a pulmonary embolism (19)

-AKI: This study will use the KDIGO definitions of AKI (20)

1. Increase in serum creatinine by 0.3 mg/dL or more (26.5 μmol/L or more) within 48 hours
2. Increase in serum creatinine to 1.5 times or more than the baseline of the prior 7 days
3. Urine volume less than 0.5 mL/kg/h for at least 6 hours

-ARDS: This study will use the Berlin definition for ARDS:

1. Acute onset, bilateral lung infiltrates on chest radiography or CT scan (who are of non-cardiac origin)
2. PaO2/FiO2 ratio of less than 300 mm Hg.

**Planned Duration of Study:** 2 years

**Center Participation Goal:** 15 Centers

**Patient Recruitment Goal:** 2900

**Power Analysis Performed:** Yes

**Plan for Statistical Analysis:** : Descriptive statistics (frequency, mean) will be performed to determine the study population demographics (i.e., sex, age, race/ethnicity), type of injury (penetrating versus blunt), mean injury severity score (ISS), and initial ED SBP and HR. Independent t tests will be performed to determine differences in in-hospital mortality, ICU-LOS, and complication rates among patients transfused pre hospital WB+ in-hospital WB versus no prehospital WB+ in-hospital WB. Logistic regression analyses will be used to determine associations between transfusion group and in-hospital mortality and complication rates, controlling for age, sex, race, ethnicity, initial vital signs, transport time, insurance status, type of injury, ISS, and trauma center level. Institutional Review Board approval will be sought from each institution and the primary institution. Data Use Agreements will be secured from each institution.

**Define How Findings from this Multi-Center Study Will Serve as the Foundation for Future Studies or Future Funded Research:** This study may serve as bases for a randomized control trials if pre-hospital whole blood demonstrates significant reduction in mortality and the other secondary outcomes.

**Does Study Require Informed Consent, Describe Rationale:** No. Strictly drawing on patient data; no variable imposed.

**Database Development- Do you have independent funding?** No

**Database Development-Does your study require upload of imaging studies?** No

**Database Development-If the cost of development of your database exceeds the allotted financial support from AAST, are you able/willing to fund the difference?** Yes

**Key References:**

1) Cannon JW: Hemorrhagic shock. N Engl J Med 2018; 378:370–379

2) Holcomb JB, Tilley BC, Baraniuk S, 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):471–482. doi:10.1001/jama.2015.12

3) Holcomb JB, del Junco DJ, Fox EE, et al.; PROMMTT Study Group: The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: Comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg 2013; 148:127–136

4) Holcomb JB, Tilley BC, Baraniuk S, et al.; PROPPR Study Group: 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; 313:471–482

5) Guyette FX, Zenati M, Triulzi DJ, Yazer MH, Skroczky H, Early BJ, Adams PW, Brown JB, Alarcon L, Neal MD, Forsythe RM, Zuckerbraun BS, Peitzman AB, Billiar TR, Sperry JL. Prehospital low titer group O whole blood is feasible and safe: Results of a prospective randomized pilot trial. J Trauma Acute Care Surg. 2022 May 1;92(5):839-847. doi: 10.1097/TA.0000000000003551. Epub 2022 Jan 25. PMID: 35081595; PMCID: PMC9038638.

6) Braverman MA, Smith A, Pokorny D, et al. Prehospital whole blood reduces early mortality in patients with hemorrhagic shock. Transfusion. 2021;61:S15–S21.

7) Smith, J.E., Barnard, E.B, Brown-O’Sullivan et al., “The SWiFT trial (Study of Whole Blood in Frontline Trauma) – the clinical and cost effectiveness of pre-hospital whole blood versus standard care in patients with life-threatening traumatic hemorrhage: a study protocol for a multi-center randomised trial” BMC, 2023, 24:725

8) Williams, Merutka, Meyer et al., “Safety Profile and impact of low-titer group O whole blood for emergency use in trauma”. Journal of Trauma and Acute Care Surgery, Vol 88, 2018.

9) Andrade R, Yeager M, Concepcion J, Spardy J, Ang D, Kornblith L, Elkbuli A. A National analysis of whole blood and component versus component transfusions in civilian trauma patients who underwent a thoracotomy or laparotomy: Toward improving patient outcomes and quality of care. Surgery. 2022 Dec, 172 (6): 1827-1843

10) Ngatuvai M, Zagales I, Suder et al., “Outcomes of Transfusion with Whole Blood, Component Therapy, or Both in Adult Civilian Trauma Patients: A Systematic Review and Meta-Analysis. J Surgical Red. 2023 Jul, 287:193-201.

 11) Seheult JN, Anto V, Alarcon LH, et al. Clinical outcomes among low-titer group O whole blood recipients compared to recipients of conventional components in civilian trauma resuscitation. Transfusion 2018.

12) Yazer MH, Jackson B, Sperry JL, et al. Initial safety and feasibility of cold-stored uncross matched whole blood transfusion in civilian trauma patients. J Trauma Acute Care Surg 2016; 81: 21-6.

13) Malkin M, Nevo A, Brundage SI, Schreiber M. Effectiveness and safety of whole blood compared to balanced blood components in resuscitation of hemorrhaging trauma patients - A systematic review. Injury. 2021 Feb;52(2):182-188. doi: 10.1016/j.injury.2020.10.095. Epub 2020 Oct 31. PMID: 33160609. 14) Torres CM, Kent A, Scantling D, Joseph B, Haut ER, Sakran JV. Association of Whole Blood with Survival Among Patients Presenting with Severe Hemorrhage in US and Canadian Adult Civilian Trauma Centers. JAMA Surg. 2023 May 1;158(5):532-540. doi: 10.1001/jamasurg.2022.6978. Erratum in: JAMA Surg. 2023 Apr 5; PMID: 36652255; PMCID: PMC9857728.

15) Hashmi ZG, Chehab M, Nathens AB, Joseph B, Bank EA, Jansen JO, Holcomb JB. Whole truths but half the blood: Addressing the gap between the evidence and practice of pre-hospital and in-hospital blood product use for trauma resuscitation. Transfusion. 2021 Jul;61 Suppl 1:S348-S353. doi: 10.1111/trf.16515. Epub 2021 Jun 4. PMID: 34086349.

16. Goldman M, Webert KE, Arnold DM, Freedman J, Hannon J, Blajchman MA; TRALI Consensus Panel. Proceedings of a consensus conference: towards an understanding of TRALI. *Transfus Med Rev*. 2005;19(1):2-31.

17. Roubinian N. TACO and TRALI: biology, risk factors, and prevention strategies. Hematology Am Soc Hematol Educ Program. 2018 Nov 30;2018(1):585-594. doi: 10.1182/asheducation-2018.1.585. Epub 2018 Dec 14. PMID: 30570487; PMCID: PMC6324877.

18. Leonard KL, Borst GM, Davies SW, Coogan M, Waibel BH, Poulin NR, Bard MR, Goettler CE, Rinehart SM, Toschlog EA. Ventilator-Associated Pneumonia in Trauma Patients: Different Criteria, Different Rates. Surg Infect (Larchmt). 2016 Jun;17(3):363-8. doi: 10.1089/sur.2014.076. Epub 2016 Mar 3. PMID: 26938612.

19. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. Ann Surg. 2004 Sep;240(3):490-6; discussion 496-8. doi: 10.1097/01.sla.0000137138.40116.6c. PMID: 15319720; PMCID: PMC1356439.

20. Goyal A, Daneshpajouhnejad P, Hashmi MF, et al. Acute Kidney Injury. [Updated 2023 Nov 25]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan

21. Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included? Lancet Respir Med. 2021 Aug;9(8):933-936. doi: 10.1016/S2213-2600(21)00105-3. Epub 2021 Apr 27. PMID: 33915103; PMCID: PMC8075801.