Study Title: Defining Outcomes after Ultra-Massive Transfusion in the Modern Era of Balanced and Goal-Directed Resuscitation

Lead: Zachary A. Matthay, MD
PI: Lucy Z. Kornblith, MD
Co-PI: Rachael A. Callcut, MD, MSPH

Background and Significance

Blood transfusions are valuable and limited in supply, and treating medical and surgical patients in hemorrhagic shock with large volumes of blood products over short periods of time requires the mobilization of extensive resources and personnel. Massive transfusion protocols (MTP) have been developed to better serve these patients, and their use has been associated with improved survival (1-4). There is vast variability in the amount of blood products used in the setting of massive transfusion, although on average medical and surgical patients who received MTP are transfused a median of 12 units of packed red blood cells (pRBCs) over 24 hours (5). However, up to 20% of patients requiring activation of these protocols receive 'ultra-massive transfusion' (UMT), defined in the literature as greater than 20-30 units of pRBCs over 24 to 48 hours (5-9). These patients present both clinical and ethical dilemmas given the challenging nature of their underlying disease processes, their high mortality rates (ranging from 29-70%) (6-9), and their profound use of limited resources.

Changes in resuscitation protocols for hemorrhagic shock to limit crystalloid and transfuse in balanced ratios of pRBCs: plasma: platelets have led to significant improvements in outcomes for massive hemorrhage in injured patients (10-13). These strategies have been adopted across specialties, particularly following the publication of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) randomized controlled trial in 2015, demonstrating a reduction in death due to exsanguination in injured patients transfused with a 1:1:1 ratio of pRBC: plasma: platelets (12, 14-16). However, the impact of these practice changes in the setting of UMT has not been examined. Given this, and that UMT continues to pose significant clinical, ethical, and resource-specific challenges, it is critical that the drivers of outcomes after surgical and medical UMT in a modern era of balanced and goal-directed resuscitation be evaluated.

Prior research studying UMT has sought to develop criteria predictive of outcomes and attempted to establish thresholds for futility (6-9). In a single center study of injured patients undergoing an emergency operation who required UMT, the only factors associated with futility were the combination of >90minutes of hypotension, use of inotropes, and aortic cross clamping, though the study was limited by a modest sample size and missing data (6). Notably, although increasing transfusion requirements are associated with increased mortality (7, 8), no clear cutoff for futility has yet been defined. In the only study specifically evaluating UMT in medical and surgical patients, survival was associated with underlying diagnosis rather than the total number of pRBCs transfused (7). However, none of these studies have been performed in the modern era of balanced and goal-directed resuscitation.

In this study, we aim to determine what clinical, physiologic, and transfusion parameters are predictive of outcomes in surgical and medical patients receiving UMT in a modern time period, and compared to historic time periods. Given UMT is a relatively rare occurrence, we

propose a multi-center, retrospective cohort design in order to recruit a sufficiently large sample size. We hypothesize that balanced transfusion ratios in UMT will be associated with improved mortality and secondary outcomes. Additionally, we hypothesize that we will identify differences in mortality and secondary outcomes following UMT between our proposed historic and modern study periods (2005-2009, 2010-2014, & 2015-2019).

Specific Aims

Primary

In this study we aim to determine what clinical, physiologic, and transfusion parameters are predictive of outcomes in surgical and medical patients receiving UMT (defined as ≥20 units of pRBCs transfused in any 24 hours period) in a modern time-period (2015-2019).

Secondary

We additionally aim to compare what clinical, physiologic, and transfusion parameters are predictive of outcomes in surgical and medical patients receiving UMT between our proposed historic and modern study periods (2005-2009, 2010-2014, & 2015-2019).

Experimental Design/Methods

Multicenter, retrospective, cohort study

Inclusion

1) Adult trauma patients aged 18 years and older
2) Massive transfusion protocol activations with ≥20 units pRBCs in any 24hour period
3) 2005-2019 (15 year period)

Exclusion

1) Pediatric patients (<18 years of age)

Therapeutic interventions: none as this is a retrospective cohort study

Outcome measures

Primary:

-Mortality (6 hours, 24 hours, 30 days, in-hospital)

Secondary:

-Venous thromboembolism (VTE)
-Acute respiratory distress syndrome (ARDS)
-Multiple organ failure (MOF)

Variables to be collected and analyzed:

Demographic: Age, sex, race, Body mass index (BMI)

Comorbidities: Diabetes, cirrhosis, liver failure, chronic kidney disease (CKD), dialysis, cancer, immunocompromised, Acquired Immunodeficiency Syndrome (AIDS), stroke, myocardial infarction (MI), congestive heart failure (CHF), substance use, smoking

Anticoagulant Medications: Aspirin, Plavix, coumadin, rivaroxaban, apixaban, other anticoagulant

Physiologic/clinical:
All patients:
-Denver multiple organ failure score (17)
-Apache III score (18)

Trauma Patients:
-Injury Severity Score (ISS) and abbreviated injury scale (AIS)
-Mechanism of injury
-Glasgow Coma Scale (GCS)
-ED vitals

Obstetrics and gynecology patients:
-Placental abnormalities
-Gravida/Para status
-Pre-eclampsia
-HELLP syndrome

Surgical subspecialty and medical patients:
-Admission diagnosis
-Bleeding diagnosis

Transfusion and Resuscitation related
-Total number transfused of pRBCs, platelets, plasma, and cryoprecipitate (at 6h, 12h, 18h, and 24h after MTP activation).
-Volume of crystalloid administered, volume of colloid administered (at 6h, 12h, 18h, and 24h after MTP activation).
-Prehospital blood product administration
-Prehospital crystalloid administration

Use of hemostatic adjuncts/reversal agents: Tranexamic acid (TXA), prothrombin complex concentrate (PCC), fibrinogen concentrate, Factor VII, other reversal agents

Clinical and Physiologic Variables During Massive Transfusion Protocol Activation
To be measured at time of activation and at 6h, 12h, 18h and 24h:
-Vital signs
-pH, base excess, bicarbonate, lactate, calcium
-Hemoglobin, platelet count

-International normalized ratio (INR), partial thromboplastin time (PTT)
-Creatinine, sodium, potassium
-Intubated
-Use of vasopressors
-ROTEM/TEG values (if test performed)

Diagnoses and Procedures: ICD 9 or 10 codes, procedure cpt codes, use of resuscitative endovascular balloon occlusion of the aorta (REBOA), resuscitative thoracotomy, and aortic cross clamping

Outcomes and complications: Mortality at 6 hours, 24 hours, 30 days and in hospital mortality, VTE, ARDS, MOF, stroke, sepsis, acute renal failure (ARF), MI, length of stay (LOS), ICU LOS, ventilator days, discharge location

Site information: Level of Trauma Center (if applicable)

Data Collections and Statistics

Data collection:

Standardized data will be collected on patients retrospectively at all participating institutions. Each center will review their respective blood bank's records to identify MTP activations between 2005-2019 and identify all adult patients who received 20 or more pRBCs in any 24 hour period. These patients will be included in the study and their data will be securely entered into RedCap using the attached data collection tool. Data analysis will be performed using Stata. Descriptive statistics will be calculated for all categorical and continuous variables. Student's t-test will be used to compare characteristics for continuous variables (or ANOVA for comparisons of 3 or more groups) and chi square tests for categorical variables. Multivariable logistic regression will be performed to analyze the association between transfusion predictors with the primary and secondary outcomes. Data will be reported as adjusted odds ratios with 95% confidence intervals. Statistical significance will be set at $p<0.05$.

Consent

This is a minimal risk study since it is retrospective cohort study, and all information will be de-identified prior to upload into the database. No intervention or treatment will be administered and the variables collected are those generated during treatment. We therefore will be seeking a waiver of consent.

Risk/Benefit

This is a retrospective study that will analyze data obtained from medical records, and therefore presents minimal risk to participants. The small risk of violating confidentiality during will be minimized by limiting access to medical records to study personnel and by deidentifying data as soon as possible during the data collection process. There will be no direct benefits to the participants, however, the results of this study may benefit future patients by providing physicians with tools and knowledge to guide clinical management during UMT.

References

1. Dente CJ, Shaz BH, Nicholas JM, Harris RS, Wyrzykowski AD, Patel S, Shah A, Vercruysse GA, Feliciano DV, Rozycki GS, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma. 2009;66(6):1616-24.
2. Callcut RA, Johannigman JA, Kadon KS, Hanseman DJ, Robinson BR. All massive transfusion criteria are not created equal: defining the predictive value of individual transfusion triggers to better determine who benefits from blood. J Trauma. 2011;70(4):794-801.
3. Callcut RA, Cotton BA, Muskat P, Fox EE, Wade CE, Holcomb JB, Schreiber MA, Rahbar MH, Cohen MJ, Knudson MM, et al. Defining when to initiate massive transfusion: a validation study of individual massive transfusion triggers in PROMMTT patients. J Trauma Acute Care Surg. 2013;74(1):59-65, 7-8; discussion 6-7.
4. Bawazeer M, Ahmed N, Izadi H, McFarlan A, Nathens A, Pavenski K. Compliance with a massive transfusion protocol (MTP) impacts patient outcome. Injury. 2015;46(1):21-8.
5. Callcut RA, Cripps MW, Nelson MF, Conroy AS, Robinson BB, Cohen MJ. The Massive Transfusion Score as a decision aid for resuscitation: Learning when to turn the massive transfusion protocol on and off. J Trauma Acute Care Surg. 2016;80(3):450-6.
6. Velmahos GC, Chan L, Chan M, Tatevossian R, Cornwell EE, 3rd, Asensio JA, Berne TV, Demetriades D. Is there a limit to massive blood transfusion after severe trauma? Arch Surg. 1998;133(9):947-52.
7. Dzik WS, Ziman A, Cohn C, Pai M, Lozano M, Kaufman RM, Delaney M, Selleng K, Murphy MF, Hervig T, et al. Survival after ultramassive transfusion: a review of 1360 cases. Transfusion. 2016;56(3):558-63.
8. Yu AJ, Inaba K, Biswas S, de Leon LA, Wong M, Benjamin E, Lam L, Demetriades D. Supermassive Transfusion: A 15-Year Single Center Experience and Outcomes. Am Surg. 2018;84(10):1617-21.
9. Allen CJ, Shariatmadar S, Meizoso JP, Hanna MM, Mora JL, Ray JJ, Namias N, Dudaryk R, Proctor KG. Liquid plasma use during "super" massive transfusion protocol. J Surg Res. 2015;199(2):622-8.
10. Holcomb JB, Wade CE, Michalek JE, Chisholm GB, Zarzabal LA, Schreiber MA, Gonzalez EA, Pomper GJ, Perkins JG, Spinella PC, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg. 2008;248(3):447-58.
11. Holcomb JB, del Junco DJ, Fox EE, Wade CE, Cohen MJ, Schreiber MA, Alarcon LH, Bai Y, Brasel KJ, Bulger EM, et al. The prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. JAMA Surg. 2013;148(2):127-36.
12. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, del Junco DJ, Brasel KJ, Bulger EM, Callcut RA, 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.

13. Holcomb JB, Zarzabal LA, Michalek JE, Kozar RA, Spinella PC, Perkins JG, Matijevic N, Dong JF, Pati S, Wade CE, et al. Increased platelet:RBC ratios are associated with improved survival after massive transfusion. J Trauma. 2011;71(2 Suppl 3):S318-28.
14. Tanaka H, Matsunaga S, Yamashita T, Okutomi T, Sakurai A, Sekizawa A, Hasegawa J, Terui K, Miyake Y, Murotsuki J, et al. A systematic review of massive transfusion protocol in obstetrics. Taiwan J Obstet Gynecol. 2017;56(6):715-8.
15. Mesar T, Larentzakis A, Dzik W, Chang Y, Velmahos G, Yeh DD. Association Between Ratio of Fresh Frozen Plasma to Red Blood Cells During Massive Transfusion and Survival Among Patients Without Traumatic Injury. JAMA Surg. 2017;152(6):574-80.
16. Delaney M, Stark PC, Suh M, Triulzi DJ, Hess JR, Steiner ME, Stowell CP, Sloan SR. Massive Transfusion in Cardiac Surgery: The Impact of Blood Component Ratios on Clinical Outcomes and Survival. Anesth Analg. 2017;124(6):1777-82.
17. Sauaia A, Moore EE, Johnson JL, Ciesla DJ, Biffl WL, Banerjee A. Validation of postinjury multiple organ failure scores. Shock. 2009;31(5):438-47.
18. Knaus WA, Wagner DP, Draper EA, Zimmerman JE, Bergner M, Bastos PG, Sirio CA, Murphy DJ, Lotring T, Damiano A, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. Chest. 1991;100(6):1619-36.