PROTOCOL OUTLINE AND GUIDELINES

Investigators must submit well-organized, detailed information about the study, demonstrating sound research design that minimizes risks to the subject. PI should assure that the content outlined below is addressed and may exercise some discretion as to how the information is organized. The quality and content of the protocol should demonstrate that scientific and merit review of the study has occurred at the departmental level prior to submission to the IRB.

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1. PROTOCOL INFORMATION

Title: Low-Titer Type O Positive Whole Blood Versus Component Therapy for Emergent Transfusion in Trauma Patients
Funding Source: Internal
Phase of Study: RCT (Phase IV)
Version Date of Protocol: 3/25/2021

2. PRINCIPAL INVESTIGATOR'S INFORMATION

Kaushik Mukherjee	**N/A**	**Acute Care Surgery**	**4-4286**	**kmukherjee@llu.edu**	**Faculty**

3. STUDY PERSONNEL

Anthony Michael Strada	**N/A**	**Acute Care Surgery**	**4-4286**	**astrada@llu.edu**	**Resident Physician**
Xian Luo-Owen	**N/A**	**Acute Care Surgery**	**4-4877**	**xluoowen@llu.edu**	**Faculty**
Martin Gideon Rosenthal	**N/A**	**Acute Care Surgery**	**4-4286**	**mrosenthal@llu.edu**	**Faculty**
W. Tait Stevens	**N/A**	**Pathology**	**4-3209**	**wstevens@llu.edu**	**Faculty**

4. STUDY INFORMATION

Location(s) of Research Activity: Loma Linda University Medical Center
Expected Start/Stop Dates of Research: 07/01/2021 to 06/30/2023
*Special Time Sensitivities:*N/A
Type of Research: Randomized controlled trial of two alternative standard-of-care transfusion strategies

5. INCLUSION / EXCLUSION CRITERIA

Criteria for inclusion of subjects: Adult male patients brought to the emergency department as Level A trauma activations who are receiving emergency blood transfusion
Criteria for exclusion of subjects (other than those opposite the inclusion criteria): Female patients (specifically excluded due to risk of alloimmunization of Rh-negative female patients of childbearing age against Rh-positive blood), children, prisoners, patients classified as dead on arrival who will still be randomized but who will have their data excluded to eliminate the effect of survivor bias in the remaining subjects.

6. SUBJECT RECRUITMENT & SCREENING

Based on the results from Cotton et al, median transfusion in the component therapy group was 6 PRBC in the first 24 hours and 4 PRBC equivalents in the whole blood group. The standard deviation (estimated from the interquartile range) was approximately 4. Thus with an expectation of alpha = 0.05 and expected power of 90% to detect a similar 2 unit difference in transfusion volume, a sample size of 190 should be sufficient; thus our projected sample size of 200 should be more than adequate. Age range will be 18 years and older, and only males will be included in the study. Our expected racial/ethnic distribution will be approximately 60% white, 15% black, 8% Asian, and 18% other race. No actual recruitment will be performed; rather all qualifying patients will be included. Consent waiver is being requested.

7. INFORMED CONSENT PROCESS

Consent waiver is being requested.

8. STUDY DESIGN

a. Background or rationale for this study.

Whole blood transfusion was used in World War I, World War II, Korea and Vietnam. By the end of the Vietnam conflict, whole blood had been separated into components for ease of use and more focused transfusion. As a result, transfusion practices did not catch up with the available units. More recent investigations have revealed that patients have fewer deaths from hemorrhage when the ratios of FFP:RBC units and platelet:RBC units approaches 1:1. Furthermore, the success of "walking blood banks" with fresh whole blood transfusion in the 2nd Iraq war and the war in Afghanistan have prompted new interest in the civilian use of whole blood. While civilian centers cannot use walking blood banks as we do not have a pre-screened population from which to draw, low-titer type O positive whole blood (LTOWB) can be used. One LTOWB unit is equivalent to one unit of PRBC and one unit of FFP. While LTOWB has been studied, the inclusion criteria for past studies has been less inclusive than in this trial, specifically excluding patients with severe traumatic brain injuries even if they also had exsanguinating hemorrhage. Furthermore, at Loma Linda University Medical Center we will have the opportunity to randomize patients to receive whole blood as their first transfusion, thus maximizing the potential benefits. Finally, we have the opportunity to study the coagulopathy associated with these patients by using viscoelastic testing.

b. Objectives

1. Evaluate PRBC equivalents transfused in each group in the first 24 hours (Primary outcome)
2. Evaluate total transfusion in each group in the first 24 hours (Secondary Outcome) including breakdown by FFP equivalents, platelet units, and cryoprecipitate
3. Evaluate 6 hour, 24 hour, and hospital mortality (Secondary Outcome)
4. Evaluate ICU outcomes in each group:
    1. ICU length of stay

2. Ventilator days
3. SOFA score on day of ICU discharge
4. Presence of ARDS?
5. Presence of TRALI?
6. Presence of DVT/PE?
7. Necessity for Dialysis?
8. Necessity for Tracheostomy?

5. Evaluate viscoelastic testing parameters in both groups when sent on arrival in ICU
    1. Percentage of patients with EXTEM clotting time > 80 sec
    2. Percentage of patients with EXTEM amplitude at 10 min < 40mm and FIBTEM amplitude at 10 min ≤ 10mm
    3. Percentage of patients with EXTEM amplitude at 10 min < 40mm and FIBTEM amplitude at 10 min > 10mm
    4. Percentage of patients with maximum thrombolysis > 15%
6. Interval analyses to be performed after 6 and 12 months with provision to continue the study out to 24 months.
    1. Stopping rule: A statistically significant difference in hospital mortality at 6 months or 12 months
        1. If in favor of LTOWB, consideration of trial termination and making LTOWB the primary standard of care for all trauma patients receiving emergency transfusion except for child-bearing age females (unless Rh immunoglobulin can be administered)
        2. If in favor of component therapy, consideration of trial termination and making component therapy the primary standard care for all trauma patients receiving emergency transfusion

c. Procedures involved (Research Interventions)

Chronological order of all research interventions, ***distinguishing standard of care vs. research intervention****.*

1. Level A trauma paged out with gender of patient
2. For female patients, care proceeds as normal
    1. Standard trauma cooler containing 4 units O- PRBC and 4 units FFP dispatched to trauma bay (if overall supply is short the first cooler may contain 2 units O- PRBC and 2 units FFP)
    2. Transfusion proceeds per trauma and ED team
    3. Patient data not included in the study

3. For male patients, the blood bank will randomize patients to the LTOWB group or the CT (component therapy) group based on a prespecified calendar-based randomization scheme by week:
    1. LTOWB: Cooler containing 2 or 4 units of LTOWB dispatched to trauma bay depending on supply
    2. CT: Standard trauma cooler containing 4 units O+ PRBC and 4 units FFP dispatched to trauma bay (if overall supply is short the first cooler may contain 2 units O+ PRBC and 2 units FFP)
    3. Transfusion proceeds per trauma and ED team
    4. Blood work (CBC, BMP, tox screen, ROTEM viscoelastic test, PT/INR, PTT, venous lactate) sent as per standard of care for all patients.
    5. Hemorrhage control and other diagnostic evaluations performed in all patients per standard of care.
    6. Patients arrive in ICU and have additional blood work (CBC, CMP, possibly ABG, ROTEM viscoelastic test, PT/INR, PTT, venous lactate, possibly fibrinogen) sent per standard of care by the ICU team.
    7. Clincial data on survival and transfusion monitored

d. Alternative procedures, if any, that are not included in the study but might be advantageous to the subject. N/A

e. If any deception is required for validity of this study, explain why this is necessary and how subject(s) will be debriefed. N/A

f. Concise review of literature that supports the rationale, objectives, and methodology of the proposed study.

Whole blood transfusion has been used in multiple military conflicts for more than one hundred years. (1) As mentioned above, during the 1960's and 1970's advancements in blood banking allowed for the transfusion of isolated components, although this was done without detailed investigation. The institution first of fresh whole blood, followed by cold-stored whole blood, was made necessary during the recent conflicts in Iraq and Afghanistan. Cold-stored whole blood has since been adapted for the civilian setting, with one unit considered equivalent to 1 unit of PRBC and 1 unit of FFP.

Low-titer O negative whole blood has been safely administered through a trial performed at UT Houston, with no transfusion reactions in the whole blood group. (1)The group at Barnes-Jewish Hospital in St. Louis, MO, performed a prospective observational trial over an eighteen-month comparing outcomes before and after whole blood was introduced into their system. In this study of 86 patients, there was no unadjusted difference in survival, although there was an improved odds of survival in the whole blood group after adjusting for maximum clot firmness as measured by viscoelastic testing. (2) A retrospective cohort study of 270 matched patients indicated no difference in clinical outcomes. (3)A large retrospective analysis of the data from the Trauma Quality Improvement Program indicated that 280 patients receiving whole blood had reduced 24-hour and hospital mortality, reduced rate of complications after adjustment for clinical covariates. (4) However, none of these studies are randomized, most use O-negative whole blood or a mixture of O-positive and O-negative whole blood, and there is no discussion of alloimmunization of female recipients against the Rh positive whole blood.

There is only one previously published randomized clinical trial of leukoreduced type specific whole blood for type O and type A recipients. In this trial of 107 patients, performed at the

University of Texas at Houston, patients were blood typed prior to inclusion in the study. Furthermore, all type B and AB patients were excluded, as were patients with significant traumatic brain injury or if they received more than 4 units of blood prior to randomization. Patients were also excluded if they could not, in the judgment of the attending surgeon, wait for blood typing. Thus, out of 357 patients who could have met criteria for inclusion, only 107 were actually randomized, introducing selection bias. In particular, the exclusion for the patients felt to be "too sick to wait" for blood typing may have excluded some sicker patients who would have benefited from whole blood. However, this study did demonstrate a reduction in transfusion volumes for patients after those with brain injury were excluded. (5)

As can be seen, the current field of literature leaves multiple unanswered questions that will be answered by the proposed study.

1) Does transfusion with low-titer O-positive whole blood reduce the amount of transfusion within 24 hours of arrival?
2) Does transfusion with low-titer O-positive whole blood reduce 6 hour, 24 hour, or hospital mortality?
3) What is the effect of low-titer O-positive whole blood transfusion on coagulopathy after trauma, as demonstrated by viscoelastic testing?
4) Is the potential benefit of transfusion with low-titer O-positive whole blood restricted only to patients receiving massive transfusion (6 units PRBC or more) or in all patients receiving emergency transfusion?

g. If an Investigational New Drug (IND) is involved, provide the following information: (1) name of drug, (2) source of drug, (3) dosage and schedule of administration, (4) status with Food and Drug Administration and IND#, (5) review of animal studies and previous human studies, (6) reported side effects

N/A

h. For an approved drug used in an experiment, provide similar information: (1) name, (2) source, (3) dosage, (4) how administered, (5) side effects.

N/A

i. If an Investigational Device (ID) is involved, provide the following information: (1) name of device, (2) manufacturer, (3) status with Food and Drug Administration and ID#, (4) review of animal studies and previous human studies, (5) reported adverse effects.

N/A

9. DATA COLLECTION

Data collection procedures: to include lab evals, tests, specimen amounts and schedules, clinical assessments/schedule/follow up procedures, case report forms, data collection forms (with description of subject codes), study instruments, rating scales, interview guides.

RedCap Database to be created with the following data

Age (years)
Penetrating Trauma (0=no, 1=yes)
Penetrating Mechanism (1=stab, 2=gsw, 3=impalement, 9=other)
Blunt Mechanism (1=MVC, 2=Fall, 3=MCC, 4=ped vs auto, 5=assault, 9=other)
Scene transport (0=no, 1=yes)
Injury Severity Score (1-75)
Abbreviated Injury Score-Head (0-6)
Predominant site of hemorrhage (1=upper extremity, 2=lower extremity, 3=axilla, 4=groin, 5=head/neck, 6=chest, 7=abdomen, 8=pelvis, 9=other)
Tourniquet in Place (0=no, 1=yes)

Pre-LLUMC PRBC (# units)
Pre-LLUMC FFP (# units)
Pre-LLUMC PLT (# unitss
Pre-LLUMC Cryo (# units)
Pre-LLUMC Crystalloid (# liters)
Pre-LLUMC Cardiac Arrest? (0=no, 1=yes with ROSC, 2=yes without ROSC)

Arrival SBP (0 = in arrest)
Arrival HR (0 = in arrest)
Arrival Temperature (Celsius)
Arrival O2 saturation (0 = in arrest)
Arrival GCS (3-15)
Treatment Group (0 = Component Therapy, 1 = LTO+WB)

LLUMC ED WB (# units)
LLUMC ED PRBC (# units)
LLUMC ED FFP (# units)
LLUMC ED PLT (# unitss
LLUMC ED Cryo (# units)
LLUMC ED Crystalloid (# liters)
LLUMC ED Cardiac Arrest? (0=no, 1=yes with ROSC, 2=yes without ROSC)
LLUMC ED Thoracotomy (0=no, 1=yes)
LLUMC ED Laparotomy (0=no, 1=yes)
LLUMC ED Death? (0=no, 1=yes)

LLUMC ED ABG results
pH
Hgb
Lactate

LLUMC ED Hgb from CBC
LLUMC ED PLT count from CBC
LLUMC ED INR
LLUMC ED PTT
LLUMC ED Fibrinogen

LLUMC ED ROTEM results
EXTEM CT

EXTEM A10
If EXTEM A10 < 40mm, FIBTEM A10
EXTEM ML

Hemorrhage Control Environment (HCE) (0=none, patient died in ED, 1=none, patient direct to ICU, 2=OR, 3=IR, 4=OR and IR, 5=Hybrid OR)
LLUMC HCE WB (# units)
LLUMC HCE PRBC (# units)
LLUMC HCE FFP (# units)
LLUMC HCE PLT (# unitss
LLUMC HCE Cryo (# units)
LLUMC HCE Crystalloid (# liters)
LLUMC HCE Cardiac Arrest? (0=no, 1=yes with ROSC, 2=yes without ROSC)
LLUMC HCE Thoracotomy (0=no, 1=yes)
LLUMC HCE Laparotomy (0=no, 1=yes)
LLUMC HCE Pelvic Packing (0=no, 1=yes)
LLUMC HCE Neck Exploration (0=no, 1=yes)
LLUMC HCE Exploration for Axilla/Upper Extremity (0=no, 1=yes)
LLUMC HCE Exploration for Groin/Lower Extremity (0=no, 1=yes)
LLUMC HCE Death? (0=no, 1=yes)

LLUMC HCE ABG results #1 (first in HCE)
pH
Hgb
Lactate

LLUMC HCE ABG results #2 (last in HCE)
pH
Hgb
Lactate

LLUMC HCE ROTEM results #1 (first in HCE, if sent)
EXTEM CT
EXTEM A10
If EXTEM A10 < 40mm, FIBTEM A10
EXTEM ML

LLUMC HCE ROTEM results #2 (last in HCE, if sent)
EXTEM CT
EXTEM A10
If EXTEM A10 < 40mm, FIBTEM A10
EXTEM ML

LLUMC ICU/Floor Transfusion within first 24 hours (not including blood given prior to LLUMC, in LLUMC ED, and in LLUMC HCE)
LLUMC ICU WB (# units)
LLUMC ICU PRBC (# units)
LLUMC ICU FFP (# units)
LLUMC ICU PLT (# unitss
LLUMC ICU Cryo (# units)

LLUMC ICU Crystalloid (# liters)

LLUMC ICU ABG results
pH
Hgb
Lactate

LLUMC ICU Hgb from CBC
LLUMC ICU PLT count from CBC
LLUMC ICU INR
LLUMC ICU PTT
LLUMC ICU Fibrinogen

LLUMC ICU ROTEM results
EXTEM CT
EXTEM A10
If EXTEM A10 < 40mm, FIBTEM A10
EXTEM ML

Clinical Endpoints
Patient Dead on Arrival (0=no, 1=yes)
Patient Died within 6 hours of arrival (0=no, 1=yes)
Patient Died within 24 hours of arrival (0=no, 1=yes)
Patient Died Prior to Discharge (0=no, 1=yes)
Duration of Mechanical Ventilation (Days)
Duration of ICU Stay (Days)
Duration of Hospital Stay (Days)
Presence of ARDS?
Presence of TRALI?
Presence of DVT/PE?
SOFA Score on Day of ICU Discharge
Need for Dialysis During Hospitalization (0=no, 1=yes)

10. LABELING & STORAGE OF DATA & SPECIMENS

No data to be stored in hard copy form. Data will be entered into secure REDCAP database, with a master list correlating study ID number, MRN, and treatment arm to be kept on LLUMC secure server.

11. DATA ANALYSIS

Analysis to be performed by median/IQR with nonparametric comparison of medians for central tendency. P value of 0.05 indicates statistical significance. Patients with death on arrival will be excluded from data reporting as they are a different patient population. Intentional sub-analysis will be performed on patients who received less than 6 units PRBC or equivalent in the first 4 hours or 6 units and more PRBC in the first 4 hours (massive transfusion). Also, an intentional sub-analysis will be performed on the patients who were classified as dead on arrival. Separate sub-analyses will be performed on patients with Abbreviated Injury Score (Head) of 3 or greater indicating severe traumatic brain injury.

12. RISK AND INJURY

This trial is a randomized clinical trial involving a test of two different standard-of-care transfusion strategies. As such, it has been verified by the director of the blood bank that neither of these transfusion strategies involves more than minimal risk. Female patients are excluded at this time to ensure that there is no possibility of inadvertent alloimmunization of Rh-negative childbearing women with Rh-positive blood products. As both the component therapy (O+ or O-) and the O+ whole blood that is administered at LLUMC would be uncrossmatched, there is a risk of transfusion reaction but this risk is not different between groups.

13. BENEFIT(S)

It is possible that patients transfused with LTO+WB may experience improved resolution of coagulopathy. As such it is possible that they may experience either reduced transfusion or even a survival benefit. Thus far, available literature has not demonstrated a survival benefit consistently, nor has it consistently demonstrated reduced need for transfusion. As such, it is felt by the investigators that clinical equipoise still exists between the two randomized treatment arms.

14. COMPENSATION

N/A

15. CONFIDENTIALITY

At the time of data entry into the database, MRN and date of birth will be redacted. A single master list will exist on a LLUMC secure server with the assignment list until the data collection is complete. The RedCap database is endorsed by LLUMC and felt to be secure, and in addition will not contain PHI.

16. LITERATURE REVIEW

1. Williams J, Merutka N, Meyer D, Bai Y, Prater S, Cabrera R, et al. Safety profile and impact of low-titer group O whole blood for emergency use in trauma. J Trauma Acute Care Surg. 2020 Jan;88(1):87–93.

2. Shea SM, Staudt AM, Thomas KA, Schuerer D, Mielke JE, Folkerts D, et al. The use of low-titer group O whole blood is independently associated with improved survival compared to component therapy in adults with severe traumatic hemorrhage. Transfusion. 2020 Jun;60 Suppl 3:S2–S9.

3. Seheult JN, Anto V, Alarcon LH, Sperry JL, Triulzi DJ, Yazer MH. Clinical outcomes among low-titer group O whole blood recipients compared to recipients of conventional components in civilian trauma resuscitation. Transfusion. John Wiley & Sons, Ltd; 2018 Aug;58(8):1838–45.

4. Hanna K, Bible L, Chehab M, Asmar S, Douglas M, Ditillo M, et al. Nationwide analysis of whole blood hemostatic resuscitation in civilian trauma. J Trauma Acute Care Surg. 2020 Aug;89(2):329–35.

5. 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 Aug;:1.