

AWARD NUMBER: W81XWH-20-2-0045

TITLE: The Deployed Hemostatic Emergency Resuscitation of Traumatic Exsanguinating Shock (Deployed HEROES) Study

PRINCIPAL INVESTIGATOR: Colonel Jennifer Gurney, MD

CONTRACTING ORGANIZATION: The Geneva Foundation, Tacoma, WA

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14. ABSTRACT An estimated 90% of potentially survivable combat deaths are due to hemorrhage. A significant aspect of hemorrhage control is resuscitation. When appropriate, resuscitation facilitates optimal hemostasis, yet when inappropriate, it can cause coagulopathy and exacerbate hemorrhage; therefore, hemorrhage control includes blood transfusion. Our research team has demonstrated the importance of "when to transfuse," and now our team aims to determine the importance of "what to transfuse." Strategies for transfusion of blood products may have significance in hemorrhage control. To support "what to transfuse" in the fielding of blood products, explicit guidelines are needed for in-theater blood use and the comparative efficacy of a walking blood bank versus shipped and stored low titer O whole blood (LTOWB). By providing evidence supporting the best resuscitation guidance, the goal of this study is to reduce the number deaths from hemorrhage on the battlefield. We will perform a full-spectrum evaluation of transfusion strategies that have been employed in the combat environment over the last 18 years to assess clinical outcomes in traumatically injured casualties requiring transfusion. This retrospective cohort study will be conducted using approx. 14,000 patient records, including 3,492 patients who received whole blood, from the Department of Defense Trauma Registry, Theater Medical Data Store, and Armed Services Blood Program database. We will include patients injured from 2001-2019 in the U.S. Central Command operational environment, including both military and non-military patients, who received a blood product. Patients with >20% total body surface burn and inhalation injury will be excluded.					
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1. INTRODUCTION:

An estimated 90% of potentially survivable combat deaths are due to hemorrhage. A significant aspect of hemorrhage control is resuscitation. When appropriate, resuscitation facilitates optimal hemostasis, yet when inappropriate, it can cause coagulopathy and exacerbate hemorrhage; therefore, hemorrhage control includes blood transfusion. Our research team has demonstrated the importance of “when to transfuse,” and now our team aims to determine the importance of “what to transfuse.” Strategies for transfusion of blood products may have significance in hemorrhage control. To support “what to transfuse” in the fielding of blood products, explicit guidelines are needed for in-theater blood use and the comparative efficacy of a walking blood bank versus shipped and stored low titer O whole blood (LTOWB). By providing evidence supporting the best resuscitation guidance, the goal of this study is to reduce the number deaths from hemorrhage on the battlefield.

We will perform a full-spectrum evaluation of transfusion strategies that have been employed in the combat environment over the last 18 years to assess the clinical outcomes in traumatically injured casualties requiring transfusion. This retrospective cohort study will be conducted using approximately 14,000 patient records, including 3,492 patients who received whole blood, from the Department of Defense Trauma Registry, Theater Medical Data Store, and Armed Services Blood Program database. We will include patients injured from 2001-2019 in the U.S. Central Command operational environment, including both military and non-military patients, who received a blood product.

2. KEYWORDS:

Armed Forces Medical Examiner System - AFMES

Armed Services Blood Program - ASBP

Department of Defense Trauma Registry - DoDTR

Fresh Whole Blood - FWB

Hemostatic Emergency Resuscitation Of Traumatic Exsanguinating Shock - Deployed HEROES

Joint Trauma System - JTS

Low Titer Type-O Whole Blood - LTOWB

Red Blood Cell - RBC

Theater Medical Data Store - TMDS

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Aim 1. To determine the association of survival at 6 hours, 24 hours, and 30 days in combat casualties who received either fresh whole blood (FWB), LTOWB, or only component therapy. Milestones: These analyses will provide evidence to support fielding of blood products by informing which transfusion strategy is best. Working hypotheses: 1) Patients who receive FWB or LTOWB will have greater effect estimates of survival compared to patients who receive only component therapy (red blood cells, plasma, platelets, or cryoprecipitate).

Aim 2. To determine if the dose of crystalloid modifies the effect of transfusion on survival at 6 hours, 24 hours, and 30 days in combat casualties. Milestones: These analyses will determine

the effect of crystalloid resuscitation on patient outcomes in the deployed environment. Working hypothesis: The effect estimates for survival between whole blood and dose of crystalloid transfusion will interact greater than multiplicatively.

Aim 3. To determine if the amount of incompatible plasma in LTOWB is associated with survival at 6 hours, 24 hours, and 30 days in combat casualties. Milestones: These analyses will determine the association of incompatible plasma with survival. Working hypothesis: The amount of incompatible plasma is not associated with reduction in survival. Frequency matching will be used to evenly balance the study groups by covariates. Aim 1 and 2 will use the delayed-entry approach to Cox proportional hazards modeling with whole blood as a time-dependent variable, while Aim 3 will use multilevel mixed-effects logistic regression. For each Specific Aim, pre-specified secondary analyses will include 1) stratification by traumatic brain injury to ensure it neither confounds nor modifies the effect of the exposure and 2) comparison of exposure groups by complications using Chi-square testing.

What was accomplished under these goals?

1) Major activities:

The approved SOW was broken down by specific aims and includes several subtasks for each aim. During the previous reporting year, we achieved Specific Aim 1, Major Task 1, Subtasks 1-3, and the following milestones:

Subtask 1: Hire research staff and abstractors. Prepare cooperative research and development agreements (CRADAs). Prepare research protocol and regulatory documents.

Subtask 2: Prepare Defense Health Agency (DHA) Data Sharing Agreement Application (DSAA) including attachments.

Subtask 3: Request identifiable data [Department of Defense Trauma Registry (DoDTR), Theater Medical Data Store (TMDS), and Armed Services Blood Program (ASBP)].

Milestone Achieved: Research staff and abstractors were hired and trained. CRADA, US Army Medical Research and Materiel Command Institutional Review Board protocol, and Human Research Protections Office second level review and approval were completed.

Milestone Achieved: DHA DSAA approval was obtained.

Milestone Achieved: Access to identifiable data and databases for data abstraction was obtained for DoDTR, TMDS, and ASBP. TMDS will continue to be ongoing.

During this reporting year, Specific Aim 1, Major Task 4 and the following milestones were accomplished. Specific Aim 1, Major Task 5 was initiated, but data abstraction is ongoing.

Subtask 4: Create Health Insurance Portability and Accountability Act (HIPAA) compliant database.

Subtask 5: Obtain DoDTR dataset with identifiers for patients meeting inclusion criteria. Abstract missing data elements from TMDS in whole blood recipients. Merge DoDTR and TMDS datasets using patient identifiers to create the interim study dataset. Phase I, n=2,983 (completed n=757 records)

Milestone: Present preliminary findings. The preliminary findings were presented at The Association of Military Surgeons of the United States - AMSUS 2022 and Military Health System Research Symposium - MHSRS 2022. Manuscripts are ongoing.

Milestone: Interim study dataset will be created in HIPAA compliant database for Specific Aims 1 and 2. The interim study dataset was created and uploaded into REDCap.

2) **Specific objectives:** Accomplished Specific Aim 1, Major Task 1, Subtask 1-4 and initiated Major Task 5 (data abstraction is ongoing).

3) **Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative):**

- Determined n=20,360 patients were eligible for abstractions in this study
- Designed, finalized and launched web-based online database in REDCap
- Finalized abstraction guide and trained abstractors
- Initiated abstraction efforts June 1, 2022; Phase I n=2,983 (14.7%) patients.
 - Of those, n=757 were abstracted
 - 100% QC completed for out of range variables using programming software
 - 10% QA completed by trained abstractors
- Presented at AMSUS Hybrid Annual Conference February 2022
 - The Deployed Hemostatic Emergency Resuscitation Of Traumatic Exsanguinating Shock (Deployed HEROES) Study
- Presented at MHSRS September 2022
 - MHSRS-22-07309 Low Titer Group O Whole Blood Data Sources among Combat Casualties
 - MHSRS-22-07323 Deployed Hemostatic Emergency Resuscitation of Traumatic Exsanguinating Shock (HEROES) Data Abstraction Tool Development paper.
- Received approved renewal of DSA #20-2434B (expire on 09/30/2023).

What opportunities for training and professional development has the project provided?

The research team/data abstractors meet over MS Teams weekly for training, to discuss abstraction efforts, troubleshoot, brainstorm, review/edit abstraction guide, and review/cross-check each other's records. The purpose of these meeting are to keep the workflow process as efficient as possible and to ensure training is ongoing/consistent.

The PI presented at, and the research team/data abstractors attended the T6 Joint Trauma System meeting to learn more about the data and data capture issues and also see a BATDOK/T6 demonstration.

Other training/professional development opportunities included ongoing collaborations with subject matter experts in the area of blood transfusion, SAS programming, and database management.

How were the results disseminated to communities of interest?

During this reporting period, preliminary results and the ongoing research efforts were presented at AMSUS February 2022 and MHSRS September 2022.

The research team developed a Deployed HEROES brochure and handed out over 100 copies at MHSRS to bring awareness to the projects research efforts, The Deployed HEROES Integrated Database, and collaborative opportunities.

What do you plan to do during the next reporting period to accomplish the goals?

During the next quarter/reporting period, the research team plans to work towards accomplishing the following SOW tasks and milestones:

Specific Aim 1, Major Task 1, Subtask 5: Obtain DoDTR dataset with identifiers for patients meeting inclusion criteria. Abstract missing data elements from TMDS in whole blood recipients. Merge DoDTR and TMDS datasets using patient identifiers to create the interim study dataset. Complete phase I (completed n=757 records)

Milestone: Present preliminary findings. Manuscripts in progress:

1. Usage of walking blood banks during the Global War on Terror
2. Low Titer Group O Whole Blood Data Sources among Combat Casualties
3. Deployed Hemostatic Emergency Resuscitation of Traumatic Exsanguinating Shock (HEROES) Data Abstraction Tool Development paper

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS: Nothing to Report.

Changes in approach and reasons for change

Nothing to Report.

Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to Report.

Changes that had a significant impact on expenditures Nothing to Report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents NA

Significant changes in use or care of human subjects NA

Significant changes in use or care of vertebrate animals NA

Significant changes in use of biohazards and/or select agents NA

6. PRODUCTS:

Publications, conference papers, and presentations

- AMSUS 2022 “The Deployed Hemostatic Emergency Resuscitation Of Traumatic Exsanguinating Shock (Deployed HEROES) Study”, oral presentation
- MHSRS-22-07323: Deployed Hemostatic Emergency Resuscitation of Traumatic Exsanguinating Shock (HEROES) Data Abstraction Tool Development, poster presentation
- MHSRS-22-07309: Low Titer Group O Whole Blood Data Sources among Combat Casualties, oral presentation
- Call for abstract submission to Western Trauma Association (WTA) 2023 “Mortality by Unit of Blood” was submitted for oral presentation

Journal publications.

Gurney, Jennifer M. MD; Staudt, Amanda M. PhD; del Junco, Deborah J. PhD; Holcomb, John MD, FACS; Martin, Matthew MD, FACS, FASMBS; Spinella, Phil MD; Trevino, Jennifer D. MBA; Corley, Jason B. MD; Taylor, Audra L. MD; Rohrer, Andrew MD; Schreiber, Martin MD; Cap, Andrew MD. Determining resuscitation outcomes in combat casualties: Design of the Deployed Hemostatic Emergency Resuscitation of Traumatic Exsanguinating Shock (Deployed HEROES) study. Journal of Trauma and Acute Care Surgery: August 2022 - Volume 93 - Issue 2S - p S22-S29

<https://doi: 10.1097/TA.0000000000003681>

Del Junco, Deborah J., Amanda M. Staudt, Andrew P. Cap, Stacy A. Shackelford, and Jennifer M. Gurney. "Prehospital blood transfusion for haemorrhagic shock." *The Lancet Haematology* 9, no. 6 (2022): e395-e396. [https://doi.org/10.1016/S2352-3026\(22\)00111-9](https://doi.org/10.1016/S2352-3026(22)00111-9)

Books or other non-periodical, one-time publications. Nothing to Report.

Other publications, conference papers and presentations. Nothing to Report.

Website(s) or other Internet site(s). The Geneva Foundation highlighted the Deployed HEROES grant and PI (Dr. Jennifer Gurney) as a "Researcher to Watch": <https://genevusa.org/news/story/the-deployed-hemostatic-emergency-resuscitation-of-traumatic-exsanguinating-shock-deployed-heroes-study/> (ongoing)

Technologies or techniques. Nothing to Report.

Inventions, patent applications, and/or licenses. Nothing to Report.

Other Products

Deployed HEROES Integrated Database is going to be the largest transfusion registry of its kind. This database is linking patients across various databases (DoDTR, ASBP, AFMES, TMDS).

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	COL Jennifer M. Gurney, MD
Project Role:	USAISR Principal Investigator/Surgeon
Researcher Identifier:	NA
Nearest person month worked:	12
Contribution to Project:	COL Gurney has performed work in the area of protocol development and data analysis.
Name:	Amanda Staudt, PhD, MPH
Project Role:	USAISR/Geneva Foundation Associate Investigator (AI)/Epidemiologist
Researcher Identifier:	NA
Nearest person month worked:	12
Contribution to Project:	Dr. Staudt has performed work in the area of protocol development and data analysis.
Name:	Jennifer Trevino, MBA
Project Role:	USAISR/Geneva Foundation Program Manager/AI/Data analyst
Researcher Identifier:	NA
Nearest person month worked:	12
Contribution to Project:	Ms. Trevino has performed work in the area of protocol development, regulatory submissions, program management, and data analysis.
Name:	COL Andrew Cap, MD
Project Role:	USAISR Associate Investigators
Researcher Identifier:	NA

Nearest person month worked: 4
 Contribution to Project: COL Cap has performed work in the area of protocol development and SME support.

Name: Deborah J. del Junco, PhD
 Project Role: Geneva Foundation Associate Investigators
 Researcher Identifier: NA
 Nearest person month worked: 4
 Contribution to Project: Dr. del Junco has performed work in the area of protocol development and SME support.

Name: Matthew Martin, MD
 Project Role: Geneva Foundation Associate Investigators
 Researcher Identifier: NA
 Nearest person month worked: 4
 Contribution to Project: Dr. Martin has performed work in the area of protocol development and SME support.

Name: John Holcomb, MD
 Project Role: Geneva Foundation Associate Investigators
 Researcher Identifier: NA
 Nearest person month worked: 4
 Contribution to Project: Dr. Holcomb has performed work in the area of protocol development and SME support.

Name: Phil Spinella, MD
 Project Role: Geneva Foundation Associate Investigators
 Researcher Identifier: NA
 Nearest person month worked: 4
 Contribution to Project: Dr. Spinella has performed work in the area of protocol development and SME support.

Name: COL Jason B. Corley, MD
 Project Role: ASBP Associate Investigators
 Researcher Identifier: NA
 Nearest person month worked: 4
 Contribution to Project: COL Corley has performed work in the area of protocol development and SME support.

Name: Lt. Col. Andrew Rohrer
 Project Role: AFMES Associate Investigators
 Researcher Identifier: NA
 Nearest person month worked: 4
 Contribution to Project: Lt. Col. Andrew Rohrer has performed work in the area of SME support.

Name: Martin Schreiber, MD
 Project Role: Associate Investigators
 Researcher Identifier: NA
 Nearest person month worked: 4
 Contribution to Project: Dr. Schreiber has performed work in the area of SME support.

Name: Beatrice Stephens
 Project Role: Nurse Abstractor
 Researcher Identifier: NA
 Nearest person month worked: 12
 Contribution to Project: Ms. Stephens has performed work in the area of data abstraction support.

Name: Julie Cutright
Project Role: Nurse Abstractor
Researcher Identifier: NA
Nearest person month worked: 12
Contribution to Project: Ms. Cutright has performed work in the area of data abstraction support.

Name: April A. Chase, MSN, RN, FNP-BC
Project Role: Nurse Abstractor
Researcher Identifier: NA
Nearest person month worked: 4
Contribution to Project: Ms. Chase has performed work in the area of data abstraction support.

Name: Susan West, BSN, RN
Project Role: Nurse Abstractor
Researcher Identifier: NA
Nearest person month worked: 2
Contribution to Project: Ms. West has performed work in the area of data abstraction support.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report.

What other organizations were involved as partners?

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: Nothing to report

QUAD CHARTS: Attached

9. APPENDICES:

1. Amendment
 - a. Determination memo and email
 - b. Protocol
2. DHA DSA renewal
3. MHSRS
 - a. LTOWB presentation
 - b. Abstraction Tool poster
4. Deployed HEROES Brochure
5. Abstraction Guide v1
6. Publications
 - a. Determining resuscitation outcomes in combat
 - b. Prehospital blood transfusion for haemorrhagic shock