AD_____

Award Number: W81XWH-18-2-0012

TITLE: "Analgesics in the Pre-Hospital Setting: Implications on Hemorrhage Tolerance"

PRINCIPAL INVESTIGATOR: Craig G. Crandall, Ph.D.

CONTRACTING ORGANIZATION: University of Texas Southwestern Medical Center
Dallas, TX 75390-7208

REPORT DATE: June 2019

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: (Check one)

- ✓ Approved for public release; distribution unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*	**2. REPORT TYPE**	**3. DATES COVERED** *(From - To)*
June 2019	Annual	01 June 2018-31 May 2019

4. TITLE AND SUBTITLE

"Analgesics in the Pre-Hospital Setting: Implications on Hemorrhage Tolerance"

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-18-2-0012

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Craig G. Crandall, Ph.D.

Email: CraigCrandall@TexasHealth.org

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

University of Texas Southwestern
Medical Center
5323 Harry Hines Blvd.
Dallas, TX 75390-7208

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
The U.S. Army Medical Research and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

To date our findings demonstrate mean tolerance to a simulated hemorrhagic challenge is not different between when subjects received ketamine and placebo. However, variability in the responses were high in the male subjects, with some subjects showing rather profound reductions in tolerance with ketamine while others showed improvements in tolerance with ketamine. In contrast, responses in females were more homogeneous between ketamine and placebo trials. Future work is warranted to identify sex-related differences in the obtained findings.

15. SUBJECT TERMS
Tactical Combat Casualty Care; analgesia; combat; military; pain; prehospital; hemorrhagic insult; fentanyl; morphine; ketamine

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified		**19b. TELEPHONE NUMBER** *(include area code)*

Table of Contents

Page

1. INTRODUCTION

The purpose of this project is to test how the three recommended analgesics currently employed in the pre-hospital setting by the US Army—fentanyl, morphine, and ketamine—alter the capacity to tolerate a hemorrhagic insult in humans.

Pain management on the battlefield is critical for the wellbeing of the soldier. Given that a hemorrhagic injury on the battlefield is virtually always associated with pain, it is paramount that the selected pain medication does not disrupt appropriate physiological mechanisms that are beneficial towards the maintenance of blood pressure and vital organ blood flow during that hemorrhagic insult. Current guidelines for the selection of pain medications of a hemorrhaging soldier are based upon limited scientific evidence, with the vast majority of supporting studies being conducted on anesthetized animals. Thus, the interaction between hemorrhagic shock and pain medications commonly employed on the battlefield is yet to be determined in the conscious humans.

With this background, we will address the following **Specific Aims:**

- **Specific Aim 1:** To test the hypothesis that each of the three analgesics currently employed in the pre-hospital setting by the US Army—fentanyl, morphine, and ketamine—will impair the capacity for a conscious human to tolerate a hemorrhagic insult.
- **Specific Aim 2**: To test the hypothesis that ketamine will be the least detrimental in compromising tolerance to a simulated hemorrhagic insult.

The data obtained from addressing these specific aims will provide the necessary scientific evidence in humans to support the Committee on Tactical Combat Casualty Care (CoTCCC) guidelines on the analgesic of choice for moderate to severe injuries where the casualty is in hemorrhagic shock. Notably, such data will identify the analgesic that least compromises a human's ability to tolerate a hemorrhagic insult, ultimately providing critical information to the combat medic on which analgesic should be employed for such an injury.

2. KEYWORDS

Tactical Combat Casualty Care; analgesia; combat; military; pain; prehospital; hemorrhagic insult; fentanyl; morphine; ketamine.

3. ACCOMPLISHMENTS

What were the major goals of the project:

The following are the listed milestones for the project to date:

By the 4th month of funding, we will have obtained IRB approvals from the University of Texas Southwestern Medicine and Texas Health Presbyterian Hospital Dallas, as well as HRPO approval from the US Army.

By the 14th month of funding we will have complete the LBNP trials for ketamine. Specifically, we will perform pre-syncopal limited LBNP trials, with each of the 30 subjects (15 males and 15 females) receiving placebo and the CoTCCC recommended dose of ketamine prior to each trial. This will require 60 subject visits (30 subjects x 2 visits). Data for these trials will also be analyzed during this period.

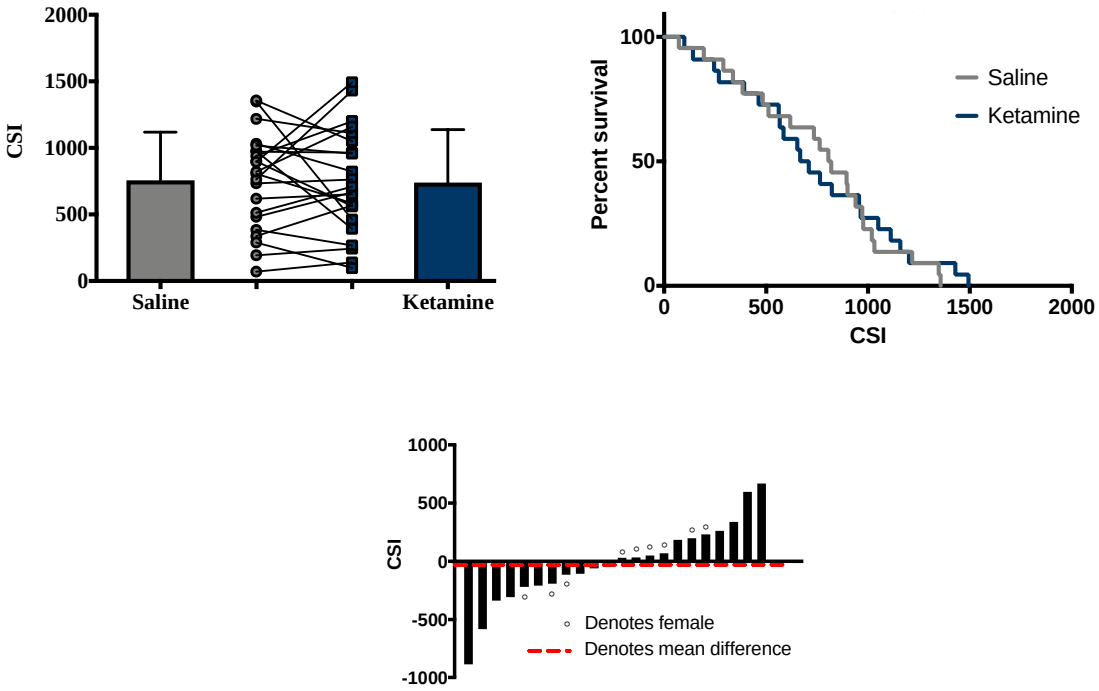
What was accomplished under these goals?:
We obtained IRB approvals to study all three drugs (ketamine, fentanyl, and morphine) from the University of Texas Southwestern Medical Center and Texas Health Presbyterian Hospital Dallas, as well as HRPO approval from the US Army.

We are pleased in that we have nearly completed the Ketamine trials of this project. We are in the midst of collecting data on the final subjects, so we anticipate that data collection for the Ketamine trials will be complete in the next quarter.

Preliminary data from the Ketamine trials were presented at the annual Experimental Biology meeting. Below is the accepted abstract of that work as well as the primary findings. These data demonstrate mean tolerance to the simulated hemorrhagic challenge was not different between the ketamine and placebo trials. However, variability in the responses were high in the male subjects, with some subjects showing rather profound reductions in tolerance with ketamine while others showed improvements in tolerance with ketamine. In contrast, responses in females were more homogeneous between ketamine and placebo trials.

ABSTRACT TITLE: **Analgesics in the Pre-Hospital Setting: Simulated Hemorrhagic Tolerance in Humans is not Impaired by Ketamine Administration**
Hemorrhage is the leading cause of battlefield and civilian trauma deaths. Given that a hemorrhagic injury on the battlefield is usually associated with pain, it is paramount that the administered analgesic does not disrupt the physiological mechanisms that are beneficial towards the maintenance of blood pressure and vital organ blood perfusion during that hemorrhagic insult. Current guidelines from the US Army's Committee on Tactical Combat Casualty Care (CoTCCC) for the selection of pain medications administered to a hemorrhaging soldier are based upon limited scientific evidence, with the clear majority of supporting studies being conducted on anesthetized animals. Specifically, the influence of ketamine, one of three analgesics employed in the pre-hospital setting by the US Army, on hemorrhagic tolerance in humans is entirely unknown. The purpose of this study is to test the hypothesis that ketamine impairs the capacity for a conscious human to tolerate a simulated hemorrhagic insult. Twenty-two subjects (9 females, 29±6 years old, 179±6 cm, 82±10 kg) participated in this double-blinded, randomized, placebo-controlled crossover investigation. Tolerance to a simulated hemorrhage was performed using a progressive lower-body negative pressure (LBNP) protocol to pre-syncope following intravenous administration of ketamine (20 mg—consistent with the US Army's CoTCCC guidelines) or placebo (saline). Tolerance was quantified as a cumulative stress index (CSI), which is the sum of products of the LBNP stage and the duration at that stage [e.g., (40 mmHg x 3 min) + (50 mmHg x 3 min) ….] until the onset of pre-syncopal symptoms and the associated cessation of the simulated hemorrhage challenge. Mean tolerance to the simulated hemorrhagic challenge was not different between the ketamine and placebo trials (CSI: 741±397 mmHg•min and 758±359 mmHg•min respectively, P=0.83). However, variability in the responses were high in the male subjects, with some subjects showing rather profound reductions in tolerance with ketamine while others showed improvements in tolerance with ketamine. In contrast, responses in females were more homogeneous between ketamine and placebo trials. These data, the first to be

obtained in conscious humans, demonstrate that administration of the US Army's CoTCCC recommended dose of ketamine does not compromise mean tolerance to a simulated hemorrhagic insult, though further work is necessary to identify sources of variability in males. Nevertheless, these findings may be insightful in choosing the most suitable analgesic medication in the pre-hospital setting during a hemorrhagic insult.



<u>What opportunities for training and professional development has the project provided?:</u>
Though the project was not intended to provide training or professional development opportunities, training has nonetheless taken place as a result of the performed work. Specifically, Mu Huang, Ph.D., Matthew Cramer, Ph.D., and Gilbert Moralez, Ph.D.,are postdoctoral fellows working on this project. As a result of this project, all three received training in the following areas: IRB approvals, subject recruitment, data collection and management, data analysis and reporting, and presentation of the data. Regarding the last point, data from these studies have been presented by trainees at weekly "Works in Progress" meetings and at Experimental Biology (2019).

<u>How were the results disseminated to communities of interest?:</u>
The obtained data have been presented at the following local, national, and international meetings in verbal or poster formats: internal "Works in Progress" meetings, Experimental Biology, and the Military Health System Research Symposium (Aug 2019). Our goal is to publish the findings of the Ketamine limb within year 2 of funding.

<u>What do you plan to do during the next reporting period to accomplish the goals?</u>:

Over the next 12 months, we will complete data collection on the last few ketamine trials. We have already started data collection on the fentanyl trials with a goal of completing that data collection by June 2020.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the project?
These data, the first to be obtained in conscious humans, demonstrate that administration of the US Army's CoTCCC recommended dose of ketamine does not compromise mean tolerance to a simulated hemorrhagic insult, though further work is necessary to identify sources of variability in males. Nevertheless, these findings may be insightful in choosing the most suitable analgesic medication in the pre-hospital setting during a hemorrhagic insult.

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

Changes in approach and reasons for change:
None

Actual or anticipated problems or delays and actions or plans to resolve them:
None

Changes that had a significant impact on expenditures:
None

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents:
None

Significant changes in use or care of human subjects
None

Significant changes in use or care of vertebrate animals:
None

Significant changes in use of biohazards and/or select agents:
None

6. PRODUCTS

Publications, conference papers, and presentations:

Journal publications**:**

1. Huang M, Moralez G, Cramer MN, Hendrix JM, Hinojosa-Laborde C, Ryan KL, Crandall CG. Analgesics in the Pre-Hospital Setting: Simulated Hemorrhagic Tolerance in Humans is not Impaired by Ketamine Adminstration. FASEB J 33 (Meeting Abstract Supplement): 01 Apr 2019. Conference abstract; published. Federal support acknowledged.

Books or other non-periodical, one-time publications: Oral and poster presentations from this project were given at the following meetings during the prior 12 months:

Experimental Biology
Military System Health Research Symposium

Other publications, conference papers, and presentations: Data from these projects were presented (in either oral or poster formats) at the meetings indicated above. Moreover, Mu Huang, Ph.D. has presented data originating from this work internally at our "works in progress."

Website(s) or other Internet site(s):
None

Technologies or techniques:
None

Inventions, patent applications, and/or licenses:
None

Other Products:
None

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name: Dr. Craig Crandall
Project Role: PI
Researcher Identifier:
Nearest person month worked: 2
Contribution to Project: Dr. Crandall has worked extensively with the lab team while planning and implementing data collection and analysis.
Funding Support: Dr. Crandall receives extramural funding from the Department of Defense and the NIH

Name: Mu Huang, Ph.D., D.P.T.
Project Role: Postdoctoral fellow
Researcher Identifier:
Nearest person month worked: 9
Contribution to Project: Dr. Huang assists with all aspects of the study, from recruitment through data analysis. This contribution has been quite extensive as each subject requires multiple visits to the laboratory to accomplish the stated aims.
Funding Support: Dr. Huang receives salary support from the School of Health Professions at the University of Texas Southwestern Medical Center.

Name:Gilbert Moralez, Ph.D.
Project Role: Postdoctoral fellow
Researcher Identifier:
Nearest person month worked: 1
Contribution to Project: Dr. Moralez assists with data collection.
Funding Support: Dr. Moralez receives extramural funding support from grants to Dr. Crandall from the NIH.

Name: Matthew Cramer, Ph.D.
Project Role: Postdoctoral fellow
Researcher Identifier:
Nearest person month worked: 1
Contribution to Project: Dr. Cramer assists with data collection.
Funding Support: Dr. Cramer receives extramural funding support from grants to Dr. Crandall from the NIH and the Department of Defense. He also receives salary support through the Natural Sciences and Engineering Research Council of Canada.

Name:Naomi Kennedy RN, BSN
Project Role: Research Nurse
Researcher Identifier:
Nearest person month worked: 4
Contribution to Project: Naomi has assisted with subject screening and consenting, data collection, and subject safety.
Funding Support: Ms. Kennedy receives extramural funding support from grants to Dr. Crandall from the NIH and the Department of Defense.

Name:Joseph Hendrix, MD
Project Role: Anesthesiologist
Researcher Identifier:
Nearest person month worked: 2
Contribution to Project: Dr. Hendrix oversees the administration of the analgesics and monitors participant safety.
Funding Support: Dr. Hendrix receives extramural funding support from grants to Dr. Crandall from the Department of Defense.

Name: Qi Fu, MD, PhD
Project Role: Associate Professor
Researcher Identifier:
Nearest person month worked: 1
Contribution to Project: Dr. Fu assisted with setting up the experimental protocol and data collection.
Funding Support: Dr. Fu receives extramural funding support from the NIH for projects unrelated to the present project.

Name:Manall Jaffrey, M.S.
Project Role: Research Associate
Researcher Identifier:
Nearest person month worked: 3
Contribution to Project: Ms. Jaffrey assists with subject recruitment, scheduling, and assisted with data collection and reduction.
Funding Support: Ms. Jaffrey receives extramural funding support from grants to Dr. Crandall from the NIH and the Department of Defense

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Yes. Dr. Crandall is a collaborator (3% effort) on an NIH R01 grant titled "Chronic Lower Leg Heating for the Treatment of Hypertension in Older Women." There is no overlap with that project and the present DOD funded project.

What other organizations were involved as partners?:
Nothing to report

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS**:**
Not applicable

QUAD CHART:
Not applicable

9. APPENDICES

Not applicable