The University of Texas Southwestern Medical Center at Dallas
Institutional Review Board

Study Title: Analgesics in the pre-hospital setting: Implications on hemorrhage tolerance - Morphine
Principal Investigator: Craig Crandall, Ph.D.
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1. Introduction and Purpose:

The purpose of this project is to test how an analgesic dose of morphine alters 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. Background:

Hemorrhage is the leading cause of battlefield and civilian trauma deaths (1–3). During the recent Iraq and Afghanistan conflicts, 91% of potentially survivable casualties in US soldiers were hemorrhage related (4). Hypovolemic shock associated with hemorrhage occurs in concert with a reduction in circulating blood volume, culminating in low tissue perfusion pressure and accompanying insufficient organ perfusion to meet metabolic demands. In the early stages of a hemorrhagic injury, compensatory mechanisms that are vital to maintain perfusion pressure. Depending on the severity of the hemorrhagic insult, these compensatory mechanisms are sufficient to maintain perfusion to vital organs, such as the heart and brain. As hemorrhage continues, however, these physiological responses are no longer able to compensate for the loss of blood volume. The individual then transitions into a state of non-compensable hemorrhage, manifested by profound parasympathetic stimulation coupled with withdrawal of sympathetic stimulation resulting in decreases in systemic vascular resistance and cardiac output (5–8). Arterial pressure then falls to the point where it is insufficient to perfuse these vital organs, culminating in death.

Hemorrhagic injuries are always accompanied with pain, as long as the individual remains conscious. Pain management of an injured soldier is a critical component of the medical care of that casualty (9–11). Current recommendations for analgesics in the pre-hospital setting, i.e., on the battlefield, include opioids (morphine, fentanyl) and N-methyl-D-aspartate (NMDA) antagonists (ketamine) (10,11). Combat medics receive guidelines that originate from the Committee on Tactical Combat Casualty Care (CoTCCC) in choosing the ideal analgesic, based upon the type and severity of the injury (10,11). Specifically, if the causality is experiencing moderate to severe pain AND the casualty is not in circulatory shock or respiratory distress and is not expected to develop either condition, then fentanyl is recommended, with morphine as an alternative if intravenous access has been obtained (10). Conversely, if the casualty is in hemorrhagic shock or respiratory distress, or s/he is expected to develop either of these conditions, then ketamine is recommended (10). However, the scientific basis for such recommendations are primarily limited to research in fully anesthetized (i.e., unconscious) animals. For example, anesthetic doses (i.e., high doses that are unlikely to be employed in the pre-hospital setting) of drugs such as ketamine reduce or remove the otherwise beneficial sympathoexcitatory responses and corresponding peripheral vasoconstriction during a hemorrhagic insult in mammals (7,12,13). Moreover, morphine reduces hemorrhagic tolerance in fully anesthetized rats (14), greatly increasing mortality. To our knowledge, no studies have evaluated the effects of analgesic doses of medications commonly employed in the pre-hospital setting on tolerance to a simulated (or actual) hemorrhagic insult in humans. Consistent with this concern, it is particularly noteworthy that “No studies have been published from the current conflict that review outcomes in combat causalities as a function of the type and route of analgesia used in combat casualties as well as the type and severity of wounds sustained, and physiological parameter indicative of circulatory or respiratory status.” Quote from 2014 by Butler et al. (10).

We propose that if sufficient doses of commonly employed analgesics are administered to humans, otherwise appropriate cardiovascular responses to the hemorrhagic insult will be suppressed, thereby reducing the ability of the individual to tolerate that insult. That said, the effects of analgesic doses of such agents (i.e., doses that are recommended for the pre-hospital setting) on physiological responses necessary to preserve tolerance to a hemorrhagic insult in humans is entirely unknown. Moreover, the aforementioned guidelines by the CoTCCC for condition-specific analgesics are not based upon hypothesis driven scientific evidence in humans, but rather primarily from fully anesthetized animals. Thus, the applicability of that research to a soldier experiencing a hemorrhagic injury is questionable and remains a significant gap in the knowledgebase.

3. Concise Summary of Project:

Three separate protocols, one for each analgesic—fentanyl, morphine, and ketamine will be employed.

Three laboratory visits will be required for this protocol.

The first visit will begin with the consenting process. Should the interested subject qualify and agree to participate in the study, he/she will undergo two separate experimental visits (placebo and morphine) each conducted on a different day. The protocol for each experimental visit is identical. After instrumentation, subjects will rest quietly followed by baseline data collection and then assessments of pain (via algometer and the cold pressor test). Subjects will then receive the drug along with the progressive lower-body negative pressure (LBNP). This will be followed by a recording of post-drug data and re-performance of the pain assessments. For the placebo trial, saline (sodium chloride 0.9% or if unavailable, 5% dextrose in water) will be administered where “Drug Administration” is indicated above. The enrolled subject will be required to complete both placebo and morphine conditions.

4. Study Procedures:
All procedures in this protocol are experimental. Therefore, none of the procedures are "standard of care."

Experimental Protocol:
Each subject will undergo two separate experimental visits (placebo and drug), each conducted on a different day, with the order randomized. The selected dose (see below) is not expected to cause unconsciousness or significant sedation. For females, testing will be conducted during the same phase of the menstrual cycle or contraceptive use.

The protocol, and approximate times, for each experimental visit is illustrated in Figure 1.

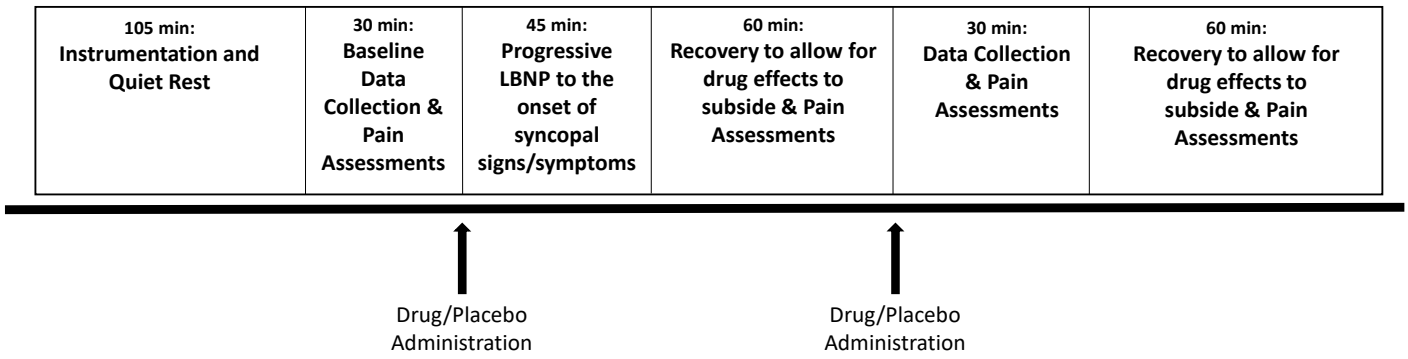

Figure 1: Timeline of each experimental day.

Following instrumentation and a quiet resting period, baseline data will be obtained. This will be followed by two validated methods of pain assessment via a digital algometer and a cold pressor test. Following the pain assessment, morphine (or placebo) will be administered, with the dose being consistent with the US Army's CoTCCC guidelines (10):
Morphine: (placebo and 5 mg intravenous)

Next, a progressive LBNP challenge will be completed until the onset of syncopal symptoms (defined as: profound bradycardia, a precipitous drop in arterial blood pressure and accompanying narrowing of pulse pressure, a sustained systolic blood pressure less than 80 mmHg, and/or subjective symptoms such as light-headedness, sweating, nausea, or dizziness). This will be followed by a re-performance of the pain assessments. Blood for the assessment of hemostatic responses will be drawn at the following time points to evaluate hemostatic function: baseline, after drug administration but before progressive LBNP, immediately after LBNP, and up to 30 minutes after LBNP.

The following data/specimens will be measured/collected and recorded.

- Heart rate and rhythm: electrocardiogram (ECG)
- Arterial blood pressure:
    - R-wave gated automated auscultation of the brachial artery (Tango+)
    - Beat-by-beat arterial blood pressure will be obtained via photoplethysmography (Finometer/Nexfin)
- Muscle sympathetic nerve activity: microneurography
- Forearm blood flow: doppler ultrasound of brachial artery
- Cerebral blood flow: transcranial Doppler and vessel diameters via Doppler ultrasound
- Skin (cutaneous) blood flow: laser Doppler flowmetry

- End tidal carbon dioxide: capnography
- Oxygen saturation: pulse oximetry
- Muscle and brain oxygen saturation: near infrared spectroscopy
- Compensatory reserve index: photoplethysmography of finger blood flow
- Body mass
- Venous catheter and blood samples: see list below
- Saline infusion (via venous catheter)
- Subjective pain reporting to pain assessments (cold pressor test)
- Threshold for pressure discomfort: digital algometer
- Urine specific gravity
- Drug screening
- Pregnancy test

The following assays may be performed for each of the blood draws on the experimental visits:

- Plasma catecholamine and vasopressin concentrations
- Standard Complete Blood Count (CBC), venous blood gas and chemistry profile including platelet count
- Prothrombin Time (PT): Evaluates the integrity of the extrinsic coagulation pathway.
- Activated Partial Thromboplastin Time (aPTT): Evaluates the integrity of the intrinsic coagulation pathway.
- Thromboelastograph Haemostasis Analyzer (TEG 5000): Provides multiple markers of clot formation and degradation from a cell-based whole-blood assay using a computer based analysis.
- D-dimer: A marker of fibrinolysis.
- Fibrinogen: Protein that thrombin coverts to fibrin during the clotting process.
- Tissue Plasminogen Activator (tPA): A protein that contributes to the breakdown of clots through catalyzing the conversion of plasminogen to plasmin.
- Antithrombin III: Inactivates enzymes facilitating coagulation (factors Xa and IIa).
- Protein C: An anticoagulant that contributes to the regulation of clotting by inactivating factors V and VIII, as well as by disinhibiting fibrinolysis through inactivation of PAI-1 (see below).
- Plasminogen activator inhibitor-1 (PAI-1): It inhibits tissue plasminogen activator (tPA, see above), thereby inhibiting fibrinolysis.
- Von Willerand factor (vWF) antigen: A measure of the quantity or mass of Von Willerand protein in plasma, which contributes to the early stages of clotting.
- Factors V and VIII: Factors essential in blood coagulation. Factor V is a critical cofactor for factor X which in turn activates factor II to IIa (Thrombin). Factor VIII is a critical cofactor for the factor IX-medicated activation of factor X.

How Data/Specimens will be Collected

- Cardiac and vascular variables: Heart rate and rhythm will be obtained from the ECG. Blood pressure will be obtained on the upper arm by automated auscultation of the brachial artery, while beat-by-beat blood pressure will be obtained from the finger via photoplethysmography. Oxygen saturation will be measured using a pulse oximeter. Cerebral perfusion will be measured by transcranial Doppler. Cerebral and forearm blood flow will be measured by Doppler ultrasound.
- Pain variables: Pain assessments will be conducted using a digital algometer to obtain the threshold for discomfort caused by pressure. Pain assessment will also be measured by the subject rating his/her pain level (range 0 to 10, with 0 being no pain and 10 being the worst pain imaginable) during hand placement into an ice water bath (cold pressor test).
- Other data/specimens: Muscle/brain oxygenation will be measured using a near infrared spectroscopy sensor that will be secured to the skin. End-tidal carbon dioxide will be measured

via capnograph. Muscle sympathetic nerve activity will be measured using microneurography. Compensatory reserve index will be estimated by recording photoplethysmography signals from the finger. Body mass will be measured using a scale. Venous blood samples will be collected from a peripheral arm vein. Urine specific gravity, drug screening and a pregnancy test will be determined from a urine sample collected at the beginning of the visit.

Volume Collected

- Urine: 1 – 2 ounces collected at the beginning of each visit
- Blood: A maximum of 100 mL of blood will be collected during visits 2 and 3.

De-identified blood samples may be sent to the U.S. Army Institute of Surgical Research (USAISR) at Ft. Sam Houston, Texas. No subject information will be sent with the blood samples and no subject information will be exchanged with USAISR.

Chronological Detail

The times listed below are approximate and listed in order, from subject arrival.

All Specific Aims – 3 visits/subject (preliminary session: ~1 hour; 2 experimental visits: up to ~5.5 hours each; total time ~12 hours):

Visit 1 (preliminary visit) (~1 h)

- 60 min: consent form, HIPAA authorization, W-9 tax form, and self-reported medical history; resting blood pressure, 12 lead ECG, pregnancy test, if applicable, procedure familiarization, and drug screen; instruction sheet for experimental visits will be provided

Visits 2 and 3 (experimental visits) – 2 visits (~5.5 hours each visit)

- 15 min: urine sample (pregnancy test, if applicable), body mass measurement, instrumentation with ECG, blood pressure cuff
- 90 min: supine position assumed, insertion of an IV catheter in a vein of the arm, and muscle sympathetic nerve activity signal obtained
- 30 min: baseline data collection followed by pain assessments (cold pressor test and pressure algometry)
- 45 min: drug administration (placebo or morphine) followed by progressive LBNP to the onset of syncopal signs/symptoms (blood pressure, cardiac output, forearm blood flow, cerebral blood flow, pulse oximeter, blood samples collected; heart rate, muscle sympathetic nerve activity measured continuously)
- Up to 60 min: recovery
- 30 min: pain assessments (cold pressor test and pressure algometry)
- Up to 60 min: recovery followed by pain assessments (cold pressor test and pressure algometry)

Primary Outcome Variables

The primary outcome variable will be the ability to tolerate the LBNP challenge prior to the onset of signs and symptoms associated with ensuing syncope.

Study Endpoints

Data collection will end when 30 subjects (15 male and 15 female) have completed the experimental protocol.

Sample Size Justification

No study has evaluated the effects of analgesics on LBNP tolerance in humans. The power and sample size estimates are based on findings from Dr. Crandall's laboratory showing reduced LBNP tolerance

in the heat-stressed individuals (15). In that study heat stressed reduced LBNP tolerance by ~70% (997 cumulative stress index units to 303 cumulative stress index units; P<0.001). Though we expect the analgesics to likewise reduce LBNP tolerance, we do not anticipate as large of a reduction as that observed with heat stress. Thus, the sample size calculation was based upon an anticipated reduction in LBNP tolerance of half that seen with heat stress, i.e., ~35% reduction in the cumulative stress index. Given this anticipate outcome, coupled with the associated variances observed in that study (15), we anticipate 15 subjects per drug trial will be sufficient to address the primary hypothesis that the administered analgesic reduces tolerance to a simulated hemorrhagic insult, with a study power=0.80 at an adjusted alpha=0.015 to account for comparisons between drugs. That value was inflated to 30 subjects in total (15 male and 15 female) to permit a comparison in the primary responses between sexes for each of the administered drugs. That said, interim power analyses will be performed, with the number of required subjects adjusted based upon the variance of the obtained data.

5. Sub-Study Procedures:
Not applicable

6. Criteria for Inclusion of Subjects:

- 18-45 years of age
- Healthy
- Body mass index less than 35 kg/m^2
- Body mass greater than or equal to 60 kg
- Speak English

7. Criteria for Exclusion of Subjects:

- Subjects who have cardiac, respiratory, neurological and/or metabolic illnesses
- Any known history of renal or hepatic insufficiency/disease
- Pregnancy or breast feeding
- Current smokers, as well as individuals who regularly smoked within the past 3 years
- Positive urine drug screen
- Currently taking pain modifying medication(s)

Although this study requires relatively uncomplicated procedures, inclusion of non-English speaking subjects would compromise subject safety. Consequently, it is imperative that the research and medical staff are able to communicate instantly and effectively with subjects, without the need of a translator. Therefore, the investigators feel that inclusion of non-English speakers would markedly and unnecessarily increase the risk to those participants.

8. Sources of Research Material:
"Research Material" (i.e., data) will be obtained from healthy human subjects. See section 4: Study Procedures for a list of data that will be obtained.

Healthy individuals: Complete datasets will be obtained from a total of 30 individuals (15 male and 15 female). Subjects will be 18-45 years old.

Due to screening failures (e.g., not determined to be healthy, use of medication, etc.), we anticipate 50 subjects will be consented to achieve the desired 30 subjects.

9. Recruitment Methods and Consenting Process:

Subjects will be recruited from the Dallas/Fort Worth area using an IRB approved existing database of over 2500 subjects held at the Institute for Exercise and Environmental Medicine, IRB# STU 122010-188. Subjects will also be recruited using approved recruitment texts and flyers informing them of the study and requesting potential subjects to contact our recruiting staff. The text will be used to recruit via ResearchMatch, CenterWatch, the Community Research Registry at UT Southwestern Medical Centre, Facebook, twitter, home owner associations, local churches, health and fitness centers/clubs, university and community alumni associations, country clubs, local university campuses, as well as e-mail notices sent within UT Southwestern Campus Updates and throughout the Texas Health Resources network. Qualified staff within the Thermal and Vascular Physiology Laboratory at the Institute for Exercise and Environmental Medicine, will assist with subject recruiting, obtaining informed consent, and scheduling logistics. Participants will have the opportunity to complete a brief REDCap survey to share their interest in being contacted for enrollment consideration.

A qualified member of the research team will typically perform an initial contact with interested individuals via the telephone. During this initial contact, the member of the research team will explain the study (purpose, procedures, risks, benefits, alternatives to participation, etc.) in lay language. Furthermore, the research team member will perform an initial screening to ensure that the inclusion criteria are met and that the subject does not meet any of the exclusion criteria to participate in the study. If all inclusion criteria are met, the individual will be familiarized with the procedures used during data collection. The interested individual will subsequently be invited to visit the laboratory, during which he/she will be provided adequate time to read the consent, ask additional questions and consider his/her options. Care will be taken that the subject is not pressured but that staff is available to address any questions. If the potential subject indicates that they would like to participate, open-ended questions will be asked to assess comprehension. If, however, the potential subject needs additional time he/she can take the consent home to consider further. Staff phone numbers will be provided for questions. For subjects that agree to participate in the study, the potential subject will be asked to sign the consent form, fill out a self-reported medical history and we will measure their resting blood pressure, perform a resting 12 lead ECG, and collect a urine specimen to complete a urine drug screen to ensure they qualify for the study.

A partial waiver of HIPAA Authorization will be sought for the purpose of recruiting. Screening information is required to determine the eligibility of potential subjects, which is necessary in order to meet the study aim. This research cannot practicably be carried out without this waiver to determine eligibility, as it will not be practical to contact/consent before determining eligibility. Excessive amounts of time and other resources could potentially be wasted inviting subjects to participate without proper preliminary screening that would help determine eligibility. With regard to information collected, all preliminary screening information will be shredded if it is determined that the individual does not qualify or if the subject is not consented. If the individual qualifies and is consented, the preliminary screening information will be included in the subject's laboratory chart.

Persons from vulnerable populations will not be invited to participate. Potential subjects will not be coerced to participate, nor will coercive language be used in any recruitment materials. When presenting the study to subjects, all risks will be outlined, and it will be explained as completely voluntary.

Subjects will be paid $35.00 per hour. If a subject stops taking part in the study or is withdrawn by the research team, they will receive payment for the hours they have competed. Subjects will receive a check in the mail from Texas Health Presbyterian Hospital Dallas approximately 6 weeks after each visit. There is no maximum amount that subjects can be paid. There will be no funds available to pay for lost time away from work and other activities, or lost wages. If needed, ground transportation to and from the research center (IEEM) will be provided or reimbursed.

10. Potential Risks:

The techniques utilized in the research project that pose potential risks are outlined below:

Peripheral intravenous (IV) catheter and saline infusion: A sterile catheter will be inserted into an arm vein for the purposes of analgesic administration (i.e. fentanyl, morphine, and ketamine) and blood collection. In order to maintain patency of the catheter, saline will be infused through the venous catheter. There is a small risk of infection and a still smaller risk of a blood clot or breakage of the catheter. The likelihood of these complications is remote (about 1 in 10,000) when the procedure is carried out by trained personnel and proper equipment is used, as during this study. There is also a small risk of the catheter perforating the vein or not being inserted into a blood vessel. The subject may have discomfort, bleeding, and/or bruising and on rare occasions, a person may feel dizzy or faint.

Analgesic (Morphine) administration:
Morphine is a naturally occurring opiate. In addition to being a mu-opioid receptor agonist, it is also an agonist at the kappa-opioid receptors and delta-opioid receptors. Morphine has a set of common side effects that occur infrequently including diarrhea, nausea, vomiting, constipation, dry mouth, somnolence, confusion, weakness, sweating, hallucinations, dyspnea, apnea, hypoventilation, and urinary retention. Morphine tends to have more sedation than other opiates. Morphine has a therapeutic index of 70. This drug exposes you to the risks of addiction, abuse, and misuse. Respiratory depression is the most serious risk when administering with morphine. Naloxone will completely reverse all opioid effects within 2 minutes IV, 5 minutes IM, and 8 minutes intranasal administrations. This provides several routes of administration as a safety backup should IV access be lost. However, at the dose and time in the study proposed, we do not expect that significant respiratory depression will occur. We will monitor the patient's vital signs continuously. We will monitor pulse oximetry and end tidal carbon dioxide continuously. These two monitors will provide sufficient accuracy and robustness to administer this medication safely. An anesthesiologist will be present at all times to observe and intervene should the patient should the slightest evidence of respiratory depression well before any patient danger should arise. All standard airway intervention equipment will be readily available at all times.

Microneurography: There is a slight risk of a temporary pins and needles sensation or increased sensitivity to touch in the leg or arm during and following the test; however this feeling goes away within 2 to 7 days. This sensation may be similar to what is felt after jogging. A few subjects have noted some tiredness, soreness, or tingling in their muscles up to one week after the study.

Cold pressor test: This widely used technique for pain assessment presents minimal risk. For this test, immersion of the hand in ice cold water will elicit painful sensations as well as an increase in blood pressure. These typical responses are immediately lessened to pretest levels with the removal of the subject's hand from the ice water. The maximum duration for this test is three minutes and the subject can voluntarily remove the hand from the ice water at any time.

Pressure algometry: This pain assessment technique is conducted by applying the rubber tip of a hand-held digital algometer on the subject's digit. Force will be gradually increased and the peak force is recorded when the subject first reports a painful sensation. Removal of the pressure from the algometer immediately relieves the painful sensation and the subject can voluntarily stop the test at any time.

Electrocardiogram: In some cases, individuals have developed a rash or redness where the patches were attached. This rash is mild and typically resolves without treatment.

Lower body negative pressure: The possible risks of this procedure are light-headedness, feeling faint, nausea and rarely a subject may faint. If this occurs, the procedure will stopped and the subject will begin to feel better almost immediately.

Loss of confidentiality: Anytime information is collected there is a potential risk for loss of confidentiality. Every effort will be made to keep information confidential, however, this cannot be guaranteed.

All other procedures (blood pressure, cardiac output, stroke volume, skin temperature, forearm blood flow, cerebral blood flow, skin blood flow, compensatory reserve index, end tidal carbon dioxide, oxygen saturation, muscle and brain oxygen saturation, body mass, urine specific gravity, drug screening, and pregnancy test) have little or no risk involved.

Overall, it is our opinion that the benefits derived from the proposed studies far outweigh the risks. The researchers are experienced with all procedures outlined in this study. A critical care trained RN will monitor the well-being of each subject and will be available as needed. Moreover, Joseph Hendrix, MD (a board certified anesthesiologist) will oversee the administration of the analgesics and will continuously monitor the subjects throughout the protocol. Dr Hendrix has specialized training in Pain Medicine, which includes the administration of the assessed drugs in his clinical practice; thus, he is well versed in the administration of these drugs and any potential adverse effects. In addition, Benjamin D. Levine, MD, Medical Director of the Institute for Exercise and Environmental Medicine, or cardiology fellows currently working at the Institute for Exercise and Environmental Medicine, will be available to assist as needed.

11. Subject Safety and Data Monitoring:

The researchers are experienced with all procedures outlined in this study. All subjects must be healthy to participate. The risks and benefits will be explained to the subjects before each signs an institutionally-approved consent form.

Craig Crandall, Ph.D will oversee subject safety and data integrity throughout the study. Dr. Crandall has conducted studies such as these for ~20 years and is qualified to perform these responsibilities. Data monitoring will include study accrual rate, participant experience, study attrition/withdrawals/dropouts, patterns of adverse and/or unanticipated events, patterns of protocol violations and/or deviations and changes in risk/benefit. The data will be reviewed at least on a quarterly basis. A progress report summarizing the data will be submitted to the IRB at the time of continuing review and more frequently as indicated.

As with all studies involving human subjects, there are risks associated with experimentation. To reduce these risks, all subjects must be healthy to enroll. Since the CoTCCC guidelines for dosing of the indicated drugs are not weight specific, each subject must have a body mass of at least 60 kg to enroll in the study to further reduce the risk to any subject. As stated above, Joseph Hendrix, MD (a board certified anesthesiologist) will oversee the administration of the analgesics and will continuously monitor the subjects throughout the protocol. Dr. Hendrix has specialized training in Pain Medicine, which includes the administration of the assessed drugs in his clinical practice; thus, he is well versed in the administration of these drugs and any potential adverse effects. The protocol dictates that subjects remain awake/conscious throughout the procedures. The absence of significant sedation or altered of mental status will be ensured by prompt reply to verbal commands given to the subject. The subjects will have their vital signs monitored continuously with standard patient monitors. Resuscitative equipment will be readily available, including but not limited to supplemental oxygen, suction capacity, cardiac arrest cart with intravenous fluid and drugs (including naloxone), airway and intubation devices. Dr. Hendrix will intervene to ensure patient safety with any or all of these resources should the subject have any derangements outside of acceptable normal parameters for their vital signs. Upon the conclusion of the protocol, subjects will not be permitted to leave the laboratory until all of the following discharge variables are met:

- The subject presents with an Aldrete score (post-anesthesia discharge scoring system) matching baseline,

- The subject demonstrates an awareness of time, person, and place and is able to answer questions appropriately
- The subject is able to stand up and walk for 5 minutes without assistance (supervised)
- The subject is able to drink water and eat crackers without reports of nausea
- The subject is able to void

To be consistent with THR/UTSW hospital guidelines—the subject will be required to have a responsible adult bring them home. The responsible adult can either drive the subject home or accompany the subject home using ground transportation (bus, train, or taxi service). The subject will also receive the recommendation to have someone observe them for the rest of the day and overnight.

The doses of the drugs are expected to cause analgesia, but with the subject remaining conscious and responsive to verbal commands. These drugs are routinely administered for pain control in the absence of significant sedation. Nevertheless, if after the first or second administration of the selected analgesic the subject is not responding appropriately to verbal commands (e.g., is excessively sleepy/sedated) or experiences any related adverse responses to the administered drug, the trial will be cancelled for that subject.

Subjects who, during the study, manifest a new onset, previously hidden or unknown cardiovascular, neurological or metabolic disease/illness will be removed from the study.

The study will be stopped immediately for safety if a serious, unexpected problem or adverse event occurs. The entire project will be terminated if this event is determined to place future participants at undue risk.

12. Procedures to Maintain Confidentiality:

1) Information will be given to the principal investigator and his staff only.
2) Information concerning subject's medical histories will be furnished by the subjects to the staff.
3) This information will be used to determine qualification for participation in the investigation.
4) Personal information will remain in the subject's study chart and will not be released in any form to others unless permitted by the subject.
5) The consenting process for each subject will be conducted in a private room.
6) No subject will be identified by name or initials outside the laboratory records. All computer records will be coded and will not include the subject's name. All coded computer records will be saved on password protected computer systems and data files are maintained on a secure server.
7) The signed consent form will be kept on file in the subject's laboratory chart. Paper records of experiments and copies of executed consent forms will be locked in cabinets located in the research nurse's office which is locked whenever the nurse is not present.
8) The urine specimens collected for the drug screening will not be labeled and will be directly handed to a member of the study team by the participant (making it anonymous). There is no processing required as the results appear on the side of the specimen collection cup.

Screening is conducted by staff via the phone or face-to-face interview in a private area. Study visits (including consenting) take place in the lab and are restricted to authorized personnel only.

As part of Texas Health Presbyterian Hospital Dallas, we utilize two identifiers (name and date of birth) to process subject samples through the IEEM biochemistry lab.

All data collected will be de-identified and only research personnel will have access. All digital recordings will be locked and password protected. Paper records will be handled as stated above. After three years, if the information is no longer needed, it will be shredded or otherwise appropriately destroyed so as to be unreadable. However, any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep information confidential; however, this cannot be guaranteed.

13. Potential Benefits:
We do not anticipate that individuals participating in the research will receive any direct benefit.

As a result of the proposed studies, upon the completion of this objective, the Department of Defense will be provided with critical information regarding improved care of the hemorrhaging victim in a pre-hospital setting. Combat injuries associated with hemorrhage are almost always accompanied with severe acute pain. This project focuses on evaluating analgesics employed by combat medics in the pre-hospital setting, with an objective of identifying the/those analgesic(s) that do not, or only minimally, impair tolerance to a simulated hemorrhagic challenge in humans. Since hemorrhage is often encountered on the battlefield, it is imperative that the administered analgesic does not impede physiological responses that protect against ensuing hypovolemic shock. That is, the optimal analgesic used for battlefield trauma should provide pain control without impeding appropriate physiological responses to hemorrhage. The proposed experiments will serve to identify the effects of three currently recommended analgesics in the pre-hospital setting (morphine, fentanyl, and ketamine) on tolerance to a simulated hemorrhage in conscious humans. The proposed work will also explore possible sex differences that may affect one's ability to compensate for a hemorrhagic challenge while receiving each of these three analgesics.

With regard to those outside the military, the experiments outlined in this application will determine the effect of currently employed pain medications on tolerance to a simulated hemorrhage in humans. These data will identify the pain medication that least compromises a human's ability to tolerate such an insult, thereby providing critical information to the pre-hospital medics on which pain medication should be employed for such an injury. Obtaining these data will be the first step in the continuum of research that will culminate in an increased understanding of the link between analgesia and hemorrhage. Moreover, the proposed work is particularly unique in that it will be the first investigation conducted in conscious humans to identify the optimal pain medication that will only minimally impair compensatory responses to a hemorrhagic injury, and thus the ability to "survive" that insult. This information will be valuable to both the military and civilian populations as it will improve pre-hospital care of the hemorrhaging victim.

14. Biostatistics:
The primary outcome variables are tolerance to the LBNP challenge with and without analgesic administration. The effects of morphine on LBNP tolerance, as well as pain assessment, will be evaluated via a paired T-test (i.e., placebo versus drug).

The effects of the administered drugs on hemodynamic and autonomic responses to each LBNP stage will be compared via two way mixed model ANOVA design, with main factors of drug and LBNP level (analyzed both by stage and by % completion of the entire LBNP protocol to pre-syncope). A significant interaction from those ANOVAs will be further explored via pairwise multiple comparison analyses.

Analysis assumptions will be carefully evaluated, data transformations considered, and Bonferroni-Hochberg will be used to adjust for multiple testing as appropriate.

15. References
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