Study Title: Analgesics in the pre-hospital setting: Implications on hemorrhage tolerance - Morphine

Principal Investigator: Craig Crandall, Ph.D.

Sponsor/Funding Source: Department of Defense—US Army

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The University of Texas Southwestern Medical Center
Texas Health Presbyterian Hospital Dallas

CONSENT TO PARTICIPATE IN RESEARCH

Title of Research:	Analgesics in the pre-hospital setting: Implications on hemorrhage tolerance – Morphine
Funding Agency/Sponsor:	U.S. Army Medical Research and Material Command
Study Doctors:	Craig G. Crandall, Ph.D.

You may call the study doctor or research personnel during regular office hours at 214-345-4619. At other times, you may call them Dr. Crandall at 214-345-4623. You may also contact study personnel at 214-345-6502 during normal office hours.

Instructions:
Please read this consent form carefully and take your time making a decision about whether to participate. As the researchers discuss this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. The purpose of the study, risks, inconveniences, discomforts, and other important information about the study are listed below. If you decide to participate, you will be given a copy of this form to keep.

Why is this study being done?
We are examining how morphine (a commonly used pain medication) will alter responses to simulated blood loss in humans. You will be given morphine or a placebo before we simulate blood loss by applying a vacuum source (e.g., negative pressure) to your lower-body for a short period of time. This research, funded by the U.S. Army, will inform guidelines for the use of morphine in the pre-hospital (e.g., field) setting.

Why is this considered research?
This is a research study because it involves an organized, step-by-step investigation (including research development, testing and evaluation) designed to contribute information that can be used by many people. In this case, information will be collected in order to better identify the pain medication that least compromises a human's ability to tolerate a serious injury resulting in blood loss.

The following definitions may help you understand this study:

- Researchers means the study doctor and research personnel at the Institute for Exercise and Environmental Medicine (IEEM) at Texas Health Presbyterian Hospital Dallas.

Why am I being asked to take part in this research study?
You are being asked to take part in this study because you are a healthy male or female between the ages of 18 and 45.

Do I have to take part in this research study?"
No. You have the right to choose whether you want to take part in this research study. If you decide to participate and later change your mind, you are free to stop participation at any time.

If you decide not to take part in this research study it will not change your legal rights or the quality of health care that you receive at UT Southwestern Medical Center, Texas Health Presbyterian Hospital Dallas, or any of their affiliates.

How many people will take part in this study?
Approximately thirty people will take part in this study at the Institute for Exercise and Environmental Medicine.

What is involved in the study?
If you volunteer to take part in this research study, you will be asked to sign this consent form and will have the following tests and procedures. All of the tests and procedures are done solely for the purpose of the study and are not intended to diagnose or treat medical problems.

Screening Procedures
To help decide if you qualify to be in this study, the researchers will ask you questions about your health, including medications you take and any surgical procedures you have had.

You may also have to fill out certain forms or have the following exams, tests or procedures:

- Physical exam and medical history;
- Vital signs such as blood pressure and heart rhythm/rate;
- Electrocardiogram (ECG), a tracing of the electrical activity of the heart;
- Urine drug screen;
- Urine pregnancy test for female adults who are able to bear children; and
- Demographic information (age, sex, ethnic origin)

Procedures and Evaluations during the Research
This study will require 3 visits to the laboratory with a total time commitment of up to approximately 13 hours.

On the first visit, we will ask you questions about your health and obtain your vital signs (heart rate, blood pressure, etc). We will thoroughly discuss the protocol with you and will familiarize you with the procedures that will be used during later visits.

On visits 2 and 3, the procedures performed will be identical, with the exception that during one visit you will receive morphine (a commonly used pain medication) and during one visit you will receive saline (placebo) during the other visit. The order of these visits will be randomized.

You will be instrumented and rest quietly by lying down. After a period of resting measurements, we will perform two tests (pressure algometry and a cold pressor test). You will then receive morphine or placebo followed by the lower-body negative pressure (LBNP) test.

For this study, the following measures and procedures will be performed (see below for descriptions):

- Morphine infusion (via venous catheter)
- Saline infusion (via venous catheter)
- Lower body negative pressure (LBNP)
- Heart rate and rhythm
- Blood pressure (arm and finger)
- Microneurography
- Brain blood flow
- Skin blood flow
- End-tidal carbon dioxide
- Tissue oxygen saturation
- Oxygen saturation
- Intravenous (IV) catheter (and venous blood samples)
- Other test: cold pressor test and pressure algometry
- Body mass
- Urine sample

Description of Procedures

The measures and procedures in this study are designed for research, not for medical purposes. They are not useful for finding problems or diseases. However, you will be told if the researchers notice something unusual. You and your regular doctor can decide together whether to follow up with more tests or treatment. Because the measures and procedures done in this study are not for medical purposes, the research results will not be sent to you or to your regular doctor.

Morphine infusion (via intravenous (IV) catheter):

Description of Procedure: Morphine is a pain medication used to treat moderate to severe pain.

Potential Risks: Though rare, you may also experience diarrhea, constipation, dry mouth, dizziness, confusion, weakness, sweating, decreased urination, fainting, nausea, vomiting, and heavy breathing. These experiences generally go away within an hour when we stop the drug infusion. In extremely rare conditions you may have difficulty breathing. In these extremely rare conditions, you will be given a drug, Naloxone, to counteract this condition. An anesthesiologist will be present at all times to monitor and

ensure your safety. This drug exposes you to the risks of addiction, abuse, and misuse.
Duration of Procedure: For the experimental day that this drug is used, you will be given 5 mg of morphine during a 60 second administration.

Saline infusion (via venous catheter):
Description of Procedure: Saline will be infused through the venous catheter to maintain patency of the catheter. In addition, on one of the experimental days, saline will be infused as a placebo to the pain medication.
Potential Risks: There are no known risks associated with the infusion of saline. Your kidneys will eliminate this excess fluid in your system.
Duration of Procedure: This slow infusion will begin after the venous catheter is inserted with the saline infusion continuing for the duration of each experimental visit.

Lower body negative pressure:
Description of Procedure: This procedure causes fluid in your body to shift from your chest and upper body to your lower body. While lying on your back, you will be sealed in a box-like chamber from the waist down. Suction will be applied inside the box to your lower body. The level of suction will increase until the researchers determine that the test is over, or you request to stop.
Potential Risks: Dizziness, light-headedness, and nausea are common side effects. If this should happen, we will stop the procedure and you should begin to feel better almost immediately. On rare occasion, a person may faint.
Duration of Procedure: This procedure lasts up to 30 minutes (up to 60 minutes total).

Heart rate and rhythm (electrocardiogram):
Description of Procedure: Sticky patches will be applied to your skin to measure the heart's electrical signals. It is possible that a small amount of chest hair may need to be shaved to get the patches to stick.
Potential Risks: You may develop a rash or redness where the patches were attached. This mild rash often goes away without treatment.
Duration of Procedure: Heart rate and rhythm will be briefly checked during visit 1, and continuously measured during the both experimental visits (approximately 5.5 hours per visit, 11 hours total).

Arm blood pressure:
Description of Procedure: Your blood pressure will be monitored using a cuff placed on your upper arm that is inflated and deflated periodically.
Potential Risks: Other than some potential discomfort associated with cuff inflation, there is no risk to this procedure.
Duration of Procedure: The cuff will be on your upper arm briefly during visit 1 and during the entire experiment for later visits. We will take blood pressure measurements several times during visits 2 and 3. Each measurement will last ~30 seconds.

Finger blood pressure:
Description of Procedure: In order to continuously monitor your blood pressure during the experiment, a small blood pressure cuff will be placed on one of your fingers.
Potential Risks: Occasionally, some people experience some mild discomfort in the finger after a prolonged period of inflation. If this occurs, notify the researchers and the cuff will be deflated to give the finger a rest. Other than this potential discomfort, there are no known risks to this procedure.
Duration of Procedure: Finger blood pressure will be measured during the entire duration of visits 2 and 3 (approximately 5.5 hours per visit, 11 hours total).

Microneurography:
Description of Procedure: Nerve signals from the nerves in the arm [i.e. median nerve (inside portion of the middle part of your arm), radial nerve (inside portion of your forearm), or posterior cutaneous nerve (outside portion of your forearm)] will be measured. When a nerve track is located via Doppler sonography (ultrasound probe with gel on the skin), we insert a small sterile needle (an electrode about the size of an acupuncture needle) through the skin. You may feel some slight discomfort during needle insertion. The recording needle is advanced into the nerve. When the tip of the needle enters the nerve, you may notice a dull aching or tingling sensation. A second needle serves as a reference electrode and is inserted just under the skin, a few inches away from the nerve. Once the needles are in place you will not feel any discomfort. This method of recording nerve signals in human subjects has been used in over 3000 studies since 1979. We have performed over 250 recordings in our laboratory without any complications.
Potential Risks: There is a slight potential risk of a temporary pins and needles sensation or increased sensitivity to touch in the arm 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 arm muscles up to one week after the study.
Duration of Procedure: The microneurography needle will remain in position for the duration of each experimental visit and will be removed at the end of the study (approximately 5.5 hours per visit, 11 hours total).

Brain blood flow:
Description of Procedure: A gel covered probe will be placed on the side of your forehead as well as the front of your neck. Sound waves will be used to record blood flow inside your head. This procedure is similar to standard ultrasound tests done to examine the health of babies prior to birth.
Potential Risks: There is no risk associated with this procedure.
Duration of Procedure: Brain blood flow will be measured during the entire duration of the experimental days (approximately 5.5 hours per visit, 11 hours total).

Skin blood flow:
Description of Procedure: Skin blood flow will be measured using laser-Doppler devices. These devices use very low power laser light to detect the amount of blood circulating at the skin surface.

Potential Risks: There are no risks associated with using these devices to measure skin blood flow; they are painless and harmless in all respects.
Duration of Procedure: Skin blood flow will be measured during the entire duration of visits 2 and 3 (approximately 5.5 hours per visit, 11 hours total).

End tidal carbon dioxide (CO_2) (capnography):
Description of Procedure: The amount of carbon dioxide that you exhale will be monitored from a nasal cannula (a plastic tube that fits behind your ears and two small, short prongs that are placed in your nostrils).
Potential Risks: There is no known risk involved with this procedure.
Duration of Procedure: The amount of carbon dioxide you exhale will be measured during the entire duration of experimental visits (~5.5 hours per visit, 11 hours total).

Compensatory Reserve Index:
Description of Procedure: A small cuff will be placed on one of your fingers to take measurements pertaining to the blood flow in your finger.
Potential Risks: there are no known risks to this procedure.
Duration of Procedure: This procedure will be measured during the entire duration of visits 2 and 3 (approximately 5.5 hours per visit, 11 hours total).

Tissue oxygen saturation:
Description of Procedure: A small sensor will be placed on your skin in order to measure the amount of oxygen in your muscle or brain.
Potential Risks: There is no known risk involved with this procedure.
Duration of Procedure: The sensor will remain in place for the entire duration of visits 2 and 3 (approximately 5.5 hours per visit, 11 hours total).

Oxygen Saturation:
Description of Procedure: The amount of oxygen in your blood will be measured by pulse oximetry by placing a sensor on either your finger, arm, leg or earlobe.
Potential Risks: There are no known risks associated with this procedure.
Duration of Procedure: Oxygen saturation will be measured during the entire duration of visits 2 and 3 (approximately 5.5 hours per visit, 11 hours total).

Venous catheter and blood samples:
Description of Procedure: To collect blood during the experiment, a sterile IV catheter will be inserted into a superficial vein of one of your arms. This procedure allows for blood to be taken multiple times with the insertion of only one needle. Information about the blood clotting process will be examined by obtaining approximately 2 tablespoons of blood each draw from your peripheral IV catheter. The following tests will be performed:

- Plasma catecholamine and vasopressin concentrations
- Standard Complete Blood Count (CBC) and chemistry profile including platelet count
- Prothrombin Time (PT)
- Activated Partial Thromboplastin Time (aPTT)
- Thromboelastograph Hemostasis Analysis
- D-dimer
- Fibrinogen
- Tissue Plasminogen Activator (tPA)
- Antithrombin III
- Protein C
- Plasminogen activator inhibitor-1 (PAI-1)
- Von Willebrand factor (vWF) antigen
- Factors V and VIII

Potential Risks: 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. You may have discomfort, bleeding, and/or bruising and on rare occasions, you may feel dizzy or faint.
Duration of Procedure: The catheter will be inserted once at the beginning of both the experimental days and will remain in a vein for the duration of the experiment. Blood will be taken approximately 4 times during the visits 2 and 3 (8 times total). A total of approximately 80 to 100 mL of blood will be collected during your visit. The catheter will be removed at the end of the experiment days.

Cold pressor test:
Description of Procedure: For this test, you will place one hand up to the wrist in ice slurry water for a period of 2-3 min. You will report the pain that you are experiencing on a scale of 0 to 10, 0 being no pain and 10 being the worst imaginable pain.
Potential Risks: For the cold pressor test, there is a risk that the procedure may become too painful and your blood pressure may rise. If this occurs, the procedure will be terminated by removing your hand from the ice water slurry.
Duration of Procedure: The cold pressor test will be performed for a period of 2-3 min throughout visits 2 and 3 (approximately 6-9 min per visit, 12-18 min total).

Pressure algometry:
Description of Procedure: For this test, a digital algometer will be placed on your finger or thumb. Pressure to that area will increase until you first start to feel discomfort.
Potential Risks: For this test, you will begin to experience pain. As soon as you experience the pain, the procedure will be terminated by removing the tip of the device.
Duration of Procedure: This test will be performed for a period of ~2 minutes up to 3 times during visits 2 and 3 (approximately 6 min per visit, 12 min total).

Body mass:
Description of Procedure: You will be asked to stand on a scale.
Potential Risks: There are no risks associated with this procedure.
Duration of Procedure: Each mass measurement will take about 30 seconds.

Urine sample:
Description of Procedure: You will be asked to urinate into a cup from which we will assess the density of your urine, conduct a pregnancy test (if applicable), and conduct a drug screening test. Drugs that your urine will be screened for include marijuana, cocaine, opiates (such as heroin, morphine, hydrocodone, oxycodone and methadone), barbiturates, benzodiazepines, and methamphetamines. If this drug test is positive for one of these agents, you will not be permitted to participate in the study. A positive drug test will not be indicated in your records and this information will remain confidential.
Potential Risks: There is no risk associated with this procedure.
Duration of Procedure: You will be asked to urinate into a cup at the beginning of each experimental visit.

How long can I expect to be in this study?
You will be required to spend no more than 3 partial days (a total of approximately 13 hours) in the laboratory at the Institute for Exercise and Environmental Medicine at Texas Health Presbyterian Hospital Dallas.

You can choose to stop participating for any reason at any time. However, if you decide to stop participating in the study, we encourage you to tell the researchers. You may be asked if you are willing to complete some study termination tests.

What are the risks of the study?
Study Procedure/Intervention
See risks associated with each of the measures and procedures listed above. Because of your participation in this study, you are at risk for the above mentioned side effects. You should discuss these with the researchers and your regular health care provider.

Loss of Confidentiality
Any time information is collected; there is a potential risk for loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

Other Risks
There may possibly be other side effects that are unknown at this time. If you are concerned about other, unknown side effects, please discuss this with the researchers.

How will risks be minimized or prevented?
You will be closely monitored at all times during your participation in the study to determine whether there are complications that need medical care. It is your responsibility to report any unusual signs, symptoms, or pain to the research team, keep appointments, and follow the recommendations of the researchers or the research nurse. Also, report any change in your legal name, address, or telephone number.

Throughout the tests, you will be closely monitored by a highly skilled research nurse under the direction of Dr. Benjamin Levine, Professor of Medicine and Cardiology at UT

Southwestern Medical Center and founding Director of the Institute for Exercise and Environmental Medicine. Moreover, Joseph Hendrix, MD (a board certified anesthesiologist) will administer 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.

Due to the side effects from taking morphine, you are not permitted to drive home after the experimental days. You will need to have a responsible adult bring you home. The responsible adult can either drive you home or accompany you home using ground transportation (bus, train, or taxi service). It is also recommended that you have someone watch over you for the rest of the day and overnight.

What will my responsibilities be during the study?
While you are part of this study, the researchers will follow you closely to determine whether there are problems that need medical care. It is your responsibility to do the following:

- Ask questions about anything you do not understand.
- Keep your appointments.
- Follow the researchers' instructions.
- Let the researchers know if your telephone number or address changes.
- Tell the researchers before you take any new medication, even if it is prescribed by another doctor for a different medical problem or something purchased over the counter.
- Tell your regular doctor about your participation in this study.
- Report to the researchers any injury or illnesses while you are on study even if you do not think it is related.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
Yes. You will be told if any new information becomes available during the study that could cause you to change your mind about continuing to participate or that is important to your health or safety.

What should I do if I think I am having problems?
If you have unusual symptoms, pain, or any other problems while you are in the study, you should report them to the researchers right away. Telephone numbers where they can be reached are listed on the first page of this consent form.

If you have a sudden, serious problem, like difficulty breathing or severe pain, go to the nearest hospital emergency room, or call 911 (or the correct emergency telephone number in your area). Tell emergency personnel about any medications you are taking, including any medications you are taking for this study.

What are the possible benefits of this study?
If you agree to take part in this study, there will not be any direct benefit to you.

We hope the information learned from this study will benefit the U.S. military by aiding in the treatment of soldiers injured on the battlefield. Information gained from this research could lead to better treatment and management of individuals involved with traumatic injuries in the pre-hospital setting, e.g. traffic collisions.

What options are available if I decide not to take part in this research study?
This is not a treatment study. You do not have to participate.

Will I be paid if I take part in this research study?
Yes, you will be paid $35.00 per hour. You will receive a check in the mail from Texas Healthy Presbyterian Hospital Dallas approximately 6 weeks after your visit. There is no maximum amount you can be paid. You will simply be compensated for your time on an hourly basis.

There are no funds available to pay for lost time away from work and other activities, lost wages, or childcare expenses.

If required, you will be reimbursed for your transportation to and from the research center (for example cab or bus fare). In order to receive reimbursement, you will need to turn in all your receipts to the research coordinator.

Your Social Security Number (SSN) will be given to Texas Health Presbyterian Hospital Dallas in order to process your payment as required by law. This information will remain confidential unless you give your permission to share it with others, or if we are required by law to release it.

Will my insurance provider or I be charged for the costs of any part of this research study?
No. Neither you, nor your insurance provider, will be charged for anything done only for this research study (i.e., the Screening Procedures, Experimental Procedures, or Monitoring/Follow-up Procedures described above).

What will happen if I am harmed as a result of taking part in this study?
It is important that you report any illness or injury to the research team listed at the top of this form immediately.
Compensation for an injury resulting from your participation in this research is not available from the University of Texas Southwestern Medical Center at Dallas or Texas Health Presbyterian Hospital of Dallas – Institute for Exercise and Environmental Medicine.

You retain your legal rights during your participation in this research

Can I stop taking part in this research study?
Yes. If you decide to participate and later change your mind, you are free to stop taking part in the research study at any time.

If you decide to stop taking part in this research study, it will not affect your relationship with the UT Southwestern staff or Texas Health Presbyterian Hospital Dallas doctors. Whether you participate or not will have no effect on your legal rights or the quality of your health care.

If you are a medical student, fellow, faculty, or staff at the Medical Center, your status will not be affected in any way.

If I agree to take part in this research study, can I be removed from the study without my consent?
Yes. The researchers may decide to take you off this study if:

- The researchers believe that participation in the research is no longer safe for you.
- The sponsor or the FDA stops the research for the safety of the participants.
- The sponsor cancels the research.
- You are unable to keep appointments or to follow the researcher's instructions.

Will my information be kept confidential?
Information about you that is collected for this research study will remain confidential, unless you give your permission to share it with others or if we are required by law to release it. You should know that certain organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The U.S Army Medical Research and Material Command and/or the Department of Defense;
- Representatives of government agencies, like the U.S. Food and Drug Administration (FDA), involved in keeping research safe for people;
- The UT Southwestern Institutional Review Board; and
- Texas Health Resources Institutional Review Board.

In addition to this consent form, you will be asked to sign an "Authorization for Use and Disclosure of Protected Health Information". This authorization will give more details about how your information will be used for this research study, and who may see and/or get copies of your information.

Are there procedures I should follow after stopping participation in this research?
Yes. If you, the researchers, or the sponsor stops your participation in the research, you may be asked to do the following:

- Let the researchers know immediately that you wish to withdraw from the research.
- Discuss your future medical care, if any, with the researchers and/or your personal doctor.

Whom do I call if I have questions or problems?
For questions about the study, contact Craig Crandall, Ph.D. at 214-345-4623 or the research laboratory (IEEM) at 214-345-6771 during regular business hours. You may also contact Dr. Crandall at 972-522-8859 after hours and on weekends and holidays.

For questions about your rights as a research participant, contact the UT Southwestern Institutional Review Board (IRB) Office at 214-648-3060.

SIGNATURES:

YOU WILL BE GIVEN A COPY OF THIS CONSENT FORM TO KEEP.

Your signature below certifies the following:

- You have read (or been read) the information provided above.
- You have received answers to all of your questions and have been told who to call if you have any more questions.
- You have freely decided to participate in this research.
- You understand that you are not giving up any of your legal rights.

_____
Name of Participant (Printed)

_____ _____ _____ AM / PM
Signature of Participant Date Time

_____
Name of Person Obtaining Consent (Printed)

_____ _____ _____ AM / PM
Signature of Person Obtaining Consent Date Time