Official Title: Generate a pharmacodynamic model of oxytocin for peripheral analgesic effects
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Background, Rationale and Context

Oxytocin itself is the only tool we have to translate preclinical findings to the clinic, yet we know very little about its pharmacology in humans outside of obstetrics. Most experimental studies utilize the intranasal route of administration resulting in minimal serum concentrations and uncertain brain penetration. Until 3 years ago, oxytocin was measured by ELISA and RIA and those values are now considered suspect. Rigor of previous pharmacokinetic (PK) modeling is poor, there are no pharmacokinetic/pharmacodynamic (PK/PD) models for oxytocin by any route of administration for peripheral or central effects and, aside from contracting the pregnant uterus, there are no PD outcome measures appropriate to generate PK/PD models.

This series of studies, submitted to the NIH for funding in Jan, 2020, translates work in animals to define peripheral and central PK/PD relationships of oxytocin action in normal volunteers, those with advanced knee arthritis, and those recovering from total knee arthroplasty (TKA). We leverage novel hypotheses that light-touch sensitive, low threshold mechanoreceptors (LTMRs) are desensitized and nociceptive, A-conducting high threshold mechanoreceptors (A-HTMRs) are sensitized in the pathology of pain. We test these novel ideas with multiple complex or novel pharmacokinetic/pharmacodynamic (PK/PD) models. Together these 8 studies in 226 normal volunteers and patients over 5 years will address critical gaps in our understanding of the pharmacology of oxytocin as it relates to sensory processing and pain.

Define oxytocin PK/PD relationships at peripheral sites of somatosensation

Systemic oxytocin reduces pain from a 5 min, 45°C heat stimulus on the skin and studies suggest this effect occurs primarily in the periphery. We propose a series of studies, each in both healthy volunteers and those with painful knee arthritis, using this outcome measure to create and validate a PK/PD model for oxytocin action in the periphery.

GOAL OF THIS STUDY

We aim to create pharmacokinetic/pharmacodynamic (PK/PD) models for oxytocin action at peripheral sites and at central sites as they relate to sensory transmission and pain. This is the second of 4 studies to accomplish generation and validation of a PK/PD model for oxytocin in the periphery. Its goal is to generate a PK/PD model by obtaining pharmacodynamic measures (reduction in pain report to sustained heat) at frequent intervals during and after a fixed rate intravenous infusion of oxytocin. Serum concentrations will be changing throughout the study as will the degree of pharmacodynamic effect. It is the time relationship between the serum concentration simultaneous to the effect which allows the model to be constructed. The study design assumes that Study 3 will find the 90% maximum serum oxytocin concentration to produce analgesia to a sustained heat stimulus is 90 pg/ml and that distribution of oxytocin from serum to its site of action in the periphery is rapid (< 5 min), based on our completed preliminary pharmacokinetic study.

GENERAL STUDY DESIGN

We aim to create pharmacokinetic/pharmacodynamic (PK/PD) models for oxytocin action at peripheral sites and at central sites as they relate to sensory transmission and pain. This is the second of 4 studies to accomplish generation and validation of a PK/PD model for oxytocin in the periphery. Its goal

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GENERAL STUDY DESIGN

This is a single site study at Wake Forest School of Medicine. Thirty two subjects in total (16 volunteers, 16 subjects with painful knee arthritis), will receive a constant iv infusion of oxytocin for 30 minutes with a total dose of 14 µg (micrograms), and verbal pain on a 0-10 scale to a 5 minute heating of the lateral calf to 45°C - 47 °C will be recorded. We will enroll up to 38 subjects if needed to obtain complete data sets for 32 subjects. We will provide this stimulus using an FDA-approved, commercially available device (Medoc TSA II). This short period of infusion will not result in steady state, but will produce slowly changing effects needed to create the pharmacokinetic / pharmacodynamic (PK/PD) model. The temperature to be delivered during the 5 minute heating will be determined during the screening visit. The primary outcome measure (pain at the end of 5-min heating) will be obtained before infusion and then at 4 times at 15 min intervals during and after the 30 min infusion. Subjects will be randomized to begin the first 5-min outcome measure test 3 min before infusion, at the time the infusion is started, or 2 or 5 min after it has begun (n=8 per cohort, n=32 in total). This staggered time of testing will allow the measurement at 5 min to be obtained frequently during increasing and decreasing serum concentrations (Figure 1). A PK/PD model will be calculated based on targeted OXT concentrations.

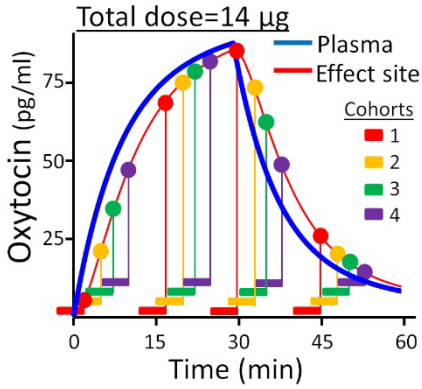


Fig. 1. Part 1 study design. Duration of testing (bars) and time of measurement (vertical line) is shown for each cohort of 8 subjects. Simulated plasma and effect site OXT levels assume an equilibration of 5 min and an EC90 of 90 pg/ml.

RATIONALE FOR USE OF PAIN REPORT TO SUSTAINED HEAT

Aside from contracting the pregnant or early postpartum uterus, there is no validated measure of OXT action in the periphery. Four lines of evidence suggest that pain intensity report from sustained noxious heat is such a stimulus. *First,* OXT binds to the same site in the TRPV1 extracellular domain as the tarantula double knot toxin (DkTx) and, like DkTx, mildly gaits, then dramatically desensitizes this channel, leading to insensitivity to capsaicin injection in rodents [3]. That OXT has a similar effect in humans is suggested by our recent study in which pain from a 30 min topical application of capsaicin in breast feeding women two weeks after delivery was reduced compared to age-matched controls [4]. This effect is likely peripheral, since hypersensitivity after capsaicin, thought to reflect central sensitization, was no different in the postpartum period. *Second,* pain rating of a 5 min, 45°C stimulus was reduced following iv OXT, 17 µg, in our PK study (Fig. 2-left panel). *Third*, intrathecal OXT, 15 µg, also reduces pain to this sustained heat stimulus (Fig. 2-middle panel), which is consistent with actions on afferent neurons in the DRG or their central terminals, although we cannot exclude an action on inhibitory

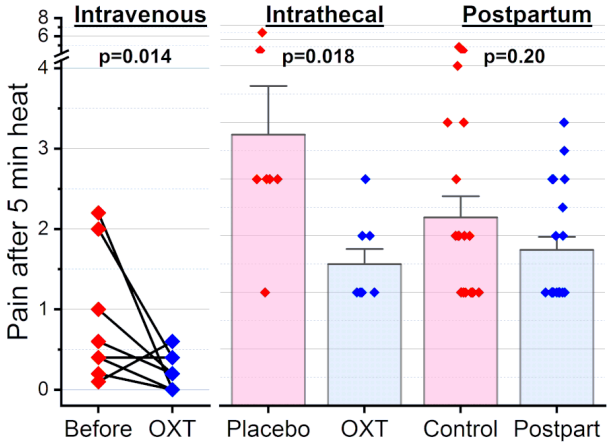


Fig. 2. Left) Verbal pain score after 5-min, 45°C heating before and 40 min after a 17 µg IV OXT infusion (n=10). **Middle)** Verbal pain score after 5-min, 45°C heating 40 min after i.t. placebo or OXT, 15 µg (n=7-8). **Right)** Verbal pain score after 5-min 45°C heating in postpartum (Postpart) women vs age-matched controls (n=20/group).

dorsal horn neurons [5]. *Fourth,* pain from this sustained heat stimulus is numerically (although not statistically) reduced in lactating, early postpartum women (with estimated serum OXT concentration of 120 pg/ml at the time of study [6]) compared to controls [4] (Fig. 2-right panel).

WHY THIS STUDY IS NEEDED

A single study of 10 young women used the LC/MS assay for oxytocin to define its pharmacokinetics after intramuscular injection [1]. Our long term goal is to examine efficacy of oxytocin in outpatient clinic settings (where intravenous infusion is not practical) in older men and women after major orthopedic surgery. The dose and timing of intramuscular oxytocin injection in that setting will depend on pharmacodynamic studies in this series, but also on knowing the pharmacokinetics in this population.

Objective

Main objective

Determine the effect of oxytocin during and after a fixed rate intravenous infusion on reduction in pain to a sustained heat stimulus in order to generate a PK/PD model for peripheral analgesia.

Methods and Measures

METHODS:

Equal numbers of adult men and women will be recruited from 2 populations. Sixteen patients with advanced knee arthritis being seen in the Orthopedic Clinic in consultation for potential total knee arthroplasty will be recruited after their doctor visit if the decision is made not to perform surgery at this time. Sixteen healthy volunteers without pain or taking pain medication will also be studied. At least 1 day prior to study subjects will be trained to rate pain in response to heat applied to the lateral calf using a Peltier controlled thermode.

Subjects will return for study visit two in which an intravenous catheter will be inserted, in the forearm for drug infusion. Oxytocin (Pitocin®) will be administered through a constant iv infusion for 30 minutes with a total dose of 14 micrograms (mcg) and verbal pain on a 0-10 scale to a 5 minute heating of the lateral calf to 45°C- 47 °C will be recorded. We will provide this stimulus using an FDA-approved, commercially available device (Medoc TSA II). This short period of infusion will not result in steady state serum levels, but will produce changing levels and effects needed to create the pharmacokinetic / pharmacodynamic (PK/PD) model. The primary outcome measure (pain at the end of 5-min heating) will be obtained before infusion and then at 4 times at 15 min intervals during and after the 30 min infusion. Subjects will be randomized to begin the first 5-min outcome measure test 3 min before infusion, at the time the infusion is started, or 2 or 5 min after it has begun (n=8 per cohort, n=32 in total). We will abandon an individual participant's study and schedule another participant should we be unable to successfully place the intravenous catheter.

STUDY DESIGN

This is an unblinded PK/PD study in which oxytocin is infused constantly and the PD effect of pain relief from each level of oxytocin determined. Participants will not be blinded to the experimental plan, although they will not be informed when oxytocin levels are changing.

In this study healthy people or those with knee arthritis so severe that they may need joint replacement are recruited for two study visits. They will come to the Clinical Research Unit for the first study visit; during this visit informed consent will be obtained, a detailed medical history will be recorded and vital signs will be taken. Urine pregnancy testing will be performed for appropriate female subjects. We will also do a pain test for training purposes. We will perform thermal heat training by applying thermal temperatures that range from 100°F to 122 °F with a 5 second presentation of varying temperatures to the forearm and then we will place a probe on the skin and heat it to 113 degrees for 5

minutes. Subjects will score any pain they feel on a 0 to 10 scale, and most people find that pain rises during the 5 minutes, but remains mild, usually around only 1 or 2 on the 0 to 10 scale. However some subjects will score the thermal pain less than 1 or zero during the heating of 113 degrees. If this occurs, we will move the probe and repeat the 5 minute heating with a 115 degree heating for 5 minutes. If the subjects scores this heating less than 1 or zero, we will move the probe again and increase the temperature to 117 degrees for 5 minutes. If the subject scores this heating 1 or less they will be excluded from the study. Subjects will come to the Clinical Research Unit for study visit two and one IV inserted in the forearm for oxytocin infusion. Oxytocin will be administered IV by constant rate infusion for 30 min, with a total dose of 14 μg. This de-identified data will be analyzed by a pharmacokineticist at Stanford University to calculate how quickly oxytocin moves from the blood to where it reduces pain.

We will repeat the thermal testing; 113°F- 117°F temperature for 5 minutes on the lateral calf 5 additional times at different time points. This temperature will be determined from the training session on study visit 1.

The research participants will not benefit from this study, but the knowledge we get will be important to adjust oxytocin dose to individuals. The sample size we chose is based on getting a good estimate for the size of the effect on sensations with each level of oxytocin in blood. This is an unblinded study and all subjects will get the same doses of oxytocin.

Phase II trials

The experimental drug or treatment is given to a larger group of people (fewer than 100) to see if it is effective and to further evaluate its safety.

Setting

Study visits will occur on the main campus at Wake Forest Baptist Medical Center in the Clinical Research Unit.

Subjects selection criteria

The study will enroll healthy subjects and subjects with advanced knee arthritis.

Inclusion Criteria:

1. Male or female > 18 and < 75 years of age, Body Mass Index (BMI) <40.
2. Generally in good health as determined by the Principal Investigator based on prior medical history, American Society of Anesthesiologists physical status 1, 2, or 3.
3. For healthy volunteers, normal blood pressure (systolic 90-140 mmHg; diastolic 50-90 mmHg) resting heart rate 45-100 beats per minute) without medication. For knee arthritis subjects, normal blood pressure or, for those with hypertension, pressure controlled with anti-hypertensives and with a resting heart rate 45-100 beats per minute.
4. Female subjects of child-bearing potential and those < 1 year post-menopausal, must be practicing highly effective methods of birth control such as hormonal methods (e.g., combined oral, implantable, injectable, or transdermal contraceptives), double barrier methods (e.g., condoms, sponge, diaphragm, or vaginal ring plus spermicidal jellies or cream), or total abstinence from heterosexual intercourse for a minimum of 1 full cycle before study drug administration.

Exclusion Criteria:

1. Hypersensitivity, allergy, or significant reaction to any ingredient of Pitocin®
2. Any disease, diagnosis, or condition (medical or surgical) that, in the opinion of the Principal Investigator, would place the subject at increased risk (active gynecologic disease in which increased tone would be detrimental e.g., uterine fibroids with ongoing bleeding), compromise the subject's compliance with study procedures, or compromise the quality of the data

3. Women who are pregnant (positive result for urine pregnancy test at screening visit), women who are currently nursing or lactating, women that have been pregnant within 2 years

4. Subjects with neuropathy, chronic pain (located in any extremity other than the knee(s) or any other body location that is being treated), diabetes mellitus, or taking benzodiazepines or pain medications on a daily basis.

5. Subjects with current or history of ventricular tachycardia, atrial fibrillation or prolonged QT interval.

6. Subjects with past or current history of hyponatremia or at risk for hyponatremia; anyone taking thiazide diuretics, loop diuretics, combination diuretics, lithium, carbamazepine, enalapril, Ramipril, celecoxib, temazepam, gliclazide, glimepiride, glibenclamide, glipizide, omeprazole, pantoprazole, desmopressin, SSRI's, MAOI, or the recreational drug ecstasy.

7. Subjects with a known latex allergy.

8. Subjects with a pain score rating of 1 or less during the initial training session to a 5 minute heating of 45°C- 47 °C to the lower calf.

Sample Size

We request permission to study up to 20 subjects with knee arthritis and 18 healthy volunteers so that we will have 32 evaluable subjects, respectively, with complete data at all time periods.

Interventions and Interactions

Study Visit 1: The participant will report to the Pain Research Unit at Piedmont Plaza II or the Clinical Research Unit (CRU) of the Wake Forest CTSI at least 1 day prior to study visit 2. The participant will review and sign the Informed Consent, if not already obtained. After informed consent is adequately obtained, a detailed medical history will be obtained from the participant, female participants will provide a urine sample to determine pregnancy status. Vital signs to include blood pressure (BP), heart rate (HR), respiratory rate Resp) and peripheral oxygen saturation (POX) will be measured and recorded along with height and weight. The research nurse will train the participants to estimate pain quantitatively using a 2 cm^2 Peltier controlled thermode (TSA®) applied to a forearm with 5 sec presentation of stimuli at 39, 41, 43, 45, 47, 49, and 50°C, using a 11 point numerical verbal scale (NRS) anchored at 0 for no pain and 10 for the worst pain imaginable. Typically, the participant is exposed to temperatures between 38^0 and 51^0 C using a random staircase method. After this training, we will ask them to report pain intensity on the 0-10 NRS scale every minute for 5 minutes upon exposure to a 4 cm^2 Peltier controlled thermode at 45°C. If the subject scores the thermal pain less than 1 or zero during the heating of 113 degrees, we will move the thermal probe and repeat the 5 minute heating with a 115 degree heating for 5 minutes. If the subjects scores this heating less than 1 or zero, we will move the probe to a different location and one more increase will be made to a 117 degree heating for 5 minutes. If the subject scores this heating 1 or less they will be excluded from the study and we will replace them with another subject.

We have found this training session significantly reduces anxiety and variability in pain and hypersensitivity ratings on subsequent study days. The duration of this visit will be approximately 2 hours.

Study Visit 2

On the second visit, the participant will report to the CRU, in the morning after having had nothing to eat or drink since midnight. Baseline vital signs (BP, HR, Resp, POX) will be obtained for a baseline measurement and then at 15, 30, and 60 minutes after the infusion. One intravenous catheter will be inserted in the arm for the infusion. Then oxytocin (Pitocin®), obtained from the research pharmacy will be administered through a pump to for 30 minutes. Pain report at the end of a 5-min heating of the skin of the lateral calf to 45°C - 47 °C (temperature determined during Study Visit 1) using an FDA approved, commercially available device (Medoc, TSA II) will be performed at baseline and then the participant will be randomized to have the thermal testing repeated at one of the following time points: 3 minutes prior to the infusion, when the infusion begins, 2 minutes after the start of the infusion or 5 minutes after

the start of the infusion. After all data collection the intravenous catheters will be removed and the subject discharged from the CRU. The duration for study visit 2 will be approximately 3 hours.

Safety and Monitoring:

Assessment of Side Effects*:* Significant side effects are defined as changes > 30% from baseline in the mean arterial pressure, HR, or oxyhemoglobin pulse oximetry < 90. Any unexpected or serious side effects will be reported to the IRB within 24 hrs. Peripheral oxyhemoglobin saturation, BP and HR will be measured non-invasively before and 15, 30, and 60 minutes after intravenous oxytocin injection. If either BP or HR change by > 30%, or oxyhemoglobin saturation decreases to less than 90, and require treatment, these vital signs will be repeated at 5-minute intervals until vital signs are stabilized. Prior to discharge from the study visit blood pressure and heart rate will need to be within 10% of the baseline measurement and the subject will not have any side effects that are worrisome to the study investigators such as; nausea, dizziness, lightheadedness, or palpitations.

Treatment of Side Effects: Mean blood pressure elevations greater than 30% of baseline will be treated with labetalol 5-15 mg IV incrementally until BP elevation is less than 30% elevated. Reductions in mean BP > 30% of baseline will be treated with incremental ephedrine 5-20 mg, IV. Heart rate (HR) reductions or elevations > 30% of baseline will be treated with incremental glycopyrolate 0.2 mg IV or propranolol 0.2 mg IV, respectively. Peripheral oxyhemoglobin desaturation (< 90) will be treated with supplemental oxygen, nasal cannula, face mask, or non-rebreathing mask depending upon the degree desaturation and the response to therapy.

RISKS

Risks include privacy of data from their medical history and the result of the pregnancy test. Risks of the intravenous catheter include pain on and after insertion and local bruising. Risks of oxytocin in the nonpregnant individual are allergic responses and, during rapid infusion, transient (<15 min) headache and facial flushing. Additionally the following events have been reported as associated with the administration of oxytocin in the laboring female population:

- Anaphylactic reaction
- Postpartum hemorrhage
- Cardiac arrhythmia
- Fatal afibrinogenemia
- Nausea
- Vomiting
- Premature ventricular contractions
- Pelvic hematoma
- Water intoxication
- Subarachnoid hemorrhage
- Hypertensive episode
- Uterine rupture

Additional precautions are used in the presence of specific anesthetic medications; we are not administering any of these medications during this research study.
Risks from the heat testing are temporary pain during testing and a superficial burn should the device malfunction. Please note that these devices are used in many pain clinics routinely and have multiple fail-safe designs to avoid thermal burn. The subject can ask for testing to be stopped at any time and withdraw from the study if they are uncomfortable with the thermal heating.

Outcome Measure(s)

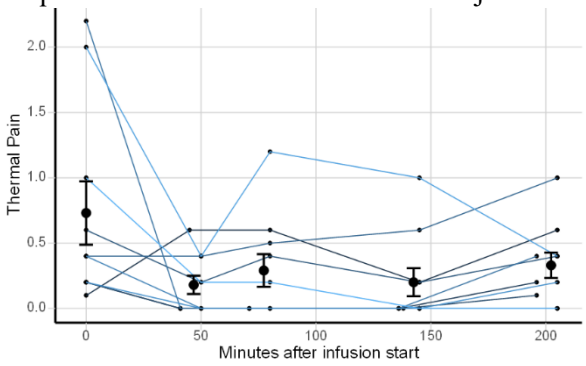
Primary Outcome Measure

Name: Pharmacodynamics of heat pain after oxytocin
Type: Primary
Time Frame: Before and during infusions of oxytocin lasting 30-105 min
Description: Pain at the end of 5 minutes of heating the skin to 45 – 47 degrees C will be determined before, during and after infusions in order to create a PD model and validate the PK/PD model.

Analytical Plan

This is an unblinded study with primary measure of drug effect to reduce heat pain in order to generate and then validate a PK/PD model. In the first study, 4 cohorts will be studied. The use of 4 cohorts is dictated by the desire to obtain 4 samples in the first 10 minutes after the beginning and end of infusion using a measurement that requires approximately 5 minutes to obtain and cannot be repeated more often than every 5 minutes. Staggering the measurements in each cohort provides adequate resolution of the time course of drug effect despite the inability to obtain frequent measurements in individual subjects.

The figure to the right shows the pain scores in the pilot study. The average CV at each time point for the pain measurements in the pilot study is 1.26. Our desired precision is to reduce the CV to 0.5, which requires a study size of 24.1 subjects (1.96 * 1.253 / 0.5)^2. Six subjects per cohort does not quite reach an adequate number (24), and 7 subjects per cohort cannot be equally divided between men and women, so we propose 8 subjects per cohort (N= 32, 4 cohorts @ 8 subjects / cohort).



The second study will attempt to determine the accuracy of the PK/PD model developed in Experiment 2.A and the first part of experiment 2.B. The N is taken from experiment 2.A.

Human Subjects Protection

All studies in volunteers will be performed in the CRU or in the Pain research Unit, which includes monitoring and resuscitation equipment and trained nursing support staff, or in in-patient settings of the Wake Forest Baptist Medical Center. All studies will be approved by the IRB and written informed consent obtained. The Project Investigators have all performed similar studies in volunteers and patients. The purpose of the study and all risks will be discussed with each volunteer, and all questions will be answered prior to obtaining written informed consent. Risks to be discussed include discomfort with needle and catheter insertion. All data acquired will remain confidential with no reference to individuals in publications.

Subject Recruitment Methods

Healthy subjects will be recruited from our current database of volunteers BG05-468, word of mouth and Be Involved website; the advanced knee arthritis population will be recruited from the Orthopedic Clinic at the Davie Medial Center Campus.
The research nurses; Regina Curry, RN and Vonda McGee, LPN will conduct the recruitment of study subjects.

Potential subject from the database will be contacted via phone or email, per their request. Potential subjects from the Be Involved website will be contacted according to the information they provide. Potential subjects from the Orthopedic Clinic will be identified through a medical record survey of patients schedule for appointments in the Orthopedic Clinic (through a request for a limited waiver of HIPAA authorization). Information collected would include, age, medical history, medications and reason for visit. This information will be maintained on a secure server and will be destroyed once it has been determined a potential subject does not meet inclusion criteria or declines. We will not collect contact information; potential subjects will be interviewed in a private room during their scheduled clinic visit.

Informed Consent

Signed informed consent will be obtained from each subject. Regina Curry, RN or Vonda McGee, LPN will obtain consent. Potential subjects will be consented in the Orthopedic Clinic or in the CRU. A private room will be utilized during the consent process and all study visits.

Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed 3 years after closure of the study, in confidential shredding disposal bins consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

Data and Safety Monitoring Plan

Security of data and safety for anticipated and unanticipated adverse events will be monitored. Vital signs will be recorded during and after oxytocin infusion and adverse events recorded. An ongoing analysis of more than mild anticipated adverse events will be made after completion of each subject. Should there be more than 30% more than mild anticipated adverse events in the first 7 subjects, the remainder will receive a reduced or no highest planned oxytocin infusion step. Serious adverse events (SAEs) will be managed initially with stabilization within the CTSI and then with hospital admission and treatment. The study investigators are anesthesiologists well experienced in acute resuscitation and

emergency resuscitation resources are readily available within the CRU of the CTSI. SAEs will be reported within 24 hr to the IRB and the study stopped until a full report and outcome are determined.

We have obtained a waiver for Investigative New Drug (IND) approval for this study from the FDA, but will report SAEs to the FDA within 7 days.

An outside expert in oxytocin pharmacology and acute drug effects, Laura Dean, MD, Director, Obstetric Anesthesia Service, Wake Forest School of Medicine, will insure that the trial is conducted according to the approved protocol and will carry out the DSMP.

Volunteer Payment

Participants will be paid a total of $300 according to the following payment schedule which we have used throughout the last 2 cycles of this grant's protocols. We believe that this payment schedule is fair and appropriate, paying for each procedure attempted and an additional payment for completion of the entire study.

Completion of study 1: $25

Placement of IV: $25

Completion of entire study: $250

Volunteer must complete all of the above phases to receive this payment.

If the subject is excluded from the study during study visit 1 due to the lack of pain felt during the thermal testing they will be compensated $25 for this visit.

Long-term Follow-up

Volunteers will be contacted daily within the following week and questioned about adverse events from the study.

Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

Data Share Plan Stanford Pilot Data

Scope of Work: Dr. Steven Shafer at Stanford University will establish and direct a pharmacokinetic/dynamic (PK/PD) modeling to facilitate future modeling in a NIH grant to be funded late 2021/early 2022. The PK/PD modeling will generate a mathematical model of oxytocin uptake, distribution, and elimination following intravenous delivery in humans. The PK/PD Core will use these mathematical models to describe the relationship between concentration at the site of effect and therapeutic response. The models will facilitate dosing regimens for future studies. The dose effect of intramuscular oxytocin will be modeled by the relationship noted on pupil diameter and heart rate variability and pupillary hippus measurements.

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Appendix

1. Table of study related events
2. Data collection form
3. CRF Face Page
4. Consent form