Unique Protocol ID: IRB00036246
Title: Efficacy of Intrathecal Oxytocin to Speed Recovery After Hip Surgery
NCT03011307
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BACKGROUND

There is a strong experimental basis to support the study of oxytocin by the spinal route for analgesia and to speed recovery from pain after injury in humans. Oxytocin containing cells in the dorsal parvocellular division of the paraventricular nucleus (PVN) project to the spinal cord (1). Noxious stimulation activates these cells via the A1 noradrenergic relay in the pons (2) and produces analgesia by spinal release of oxytocin, since intrathecal injection of an oxytocin receptor antagonist worsens pain behaviors from peripheral inflammation (3). Direct electrical stimulation of the PVN reduces dorsal horn neuronal responses to noxious stimulation, and this is blocked by administration of sequestering antibody for oxytocin (4). Similarly, direct electrical stimulation of the PVN reduces behavioral sensitivity in a model of chronic neuropathic pain, and this effect is blocked by an oxytocin receptor antagonist (5). Intrathecal injection of oxytocin in normal rats reduces dorsal horn neuronal responses to noxious stimuli (6) as well as behavioral responses to noxious thermal (3), mechanical (3), and chemical (7) stimuli. Finally, intrathecal injection of oxytocin in rat models of chronic pain also reduces dorsal horn neuronal responses to sensory stimulation (6) as well as behavioral responses to thermal (5) and mechanical (7) stimuli.

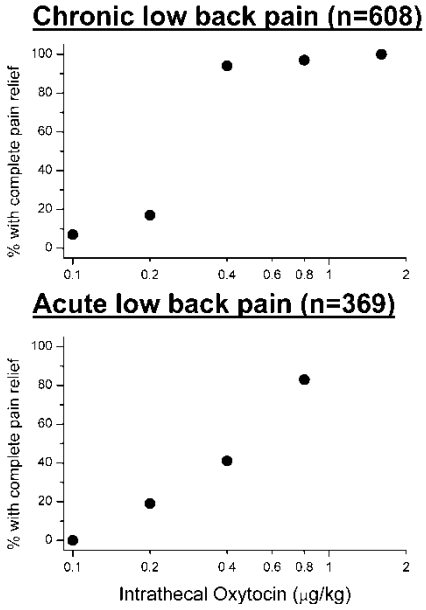

Figure 1. Percentage of patients with complete pain relief from intrathecal injection of oxytocin.

Many compounds and manipulations produce evidence of analgesia in rodents, but most studies, including the ones cited for oxytocin above, rely on reflex withdrawal responses to simulation or electrophysiologic responses in individual cells. As such, the relevance of these observations to spontaneous pain in humans is far from certain. Two observations, however, strongly suggest that intrathecal oxytocin would be analgesic in humans and would speed recovery from pain after surgery.

The first, most direct evidence, is a report from China of 608 patients with chronic low back pain and 369 patients with acute low back pain who received single intrathecal injections of oxytocin (8). Intrathecal oxytocin produced acute analgesia in both settings, with nearly

universal complete pain relief reported at doses of approximately 30 μg per injection for chronic low back pain and 60 μg per injection for acute low back pain (Figure 1). Duration of analgesia was dose dependent, with < 1 hr analgesia from approximately 7 μg per injection and > 5 hr analgesia from approximately 60 μg per injection.

The second line of evidence comes from our clinical observations in obstetric patients. Physical injury, whether from trauma or surgery, is recognized as an important cause of chronic pain, and the incidence of chronic pain after surgery ranges from 10 to 40%, depending on the procedure (9). We recently completed a clinical trial of over 1200 women examining the incidence of chronic pain after vaginal and cesarean delivery. Although approximately 10% of women had pain 2 months after delivery (10), the incidence of pain one year after delivery was remarkably low (95% confidence limit for pain at one year of 0.7%). This is at least an order of magnitude lower than that reported from any other abdominal surgery, including superficial surgery like inguinal herniorrhaphy (9). We hypothesized, based on these studies, that a factor which is present during pregnancy may be protective of chronic pain. We therefore examined hypersensitivity in rats following a surgery (spinal nerve ligation) which is commonly used as a model of neuropathic pain. To our surprise, this surgery produced similar degrees of hypersensitivity when performed during pregnancy than in nonpregnant animals (Figure 2). In contrast to this lack of effect of pregnancy, the degree of hypersensitivity significantly diminished for several weeks after delivery, abruptly returning when the pups were weaned from

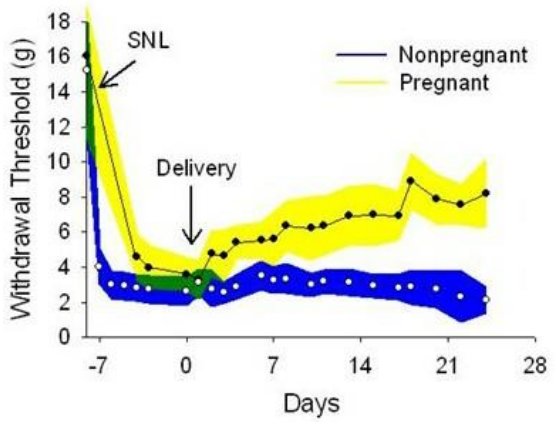

Figure 2. Withdrawal threshold drops similarly after spinal nerve ligation (SNL, a model of neuropathic pain) in pregnant and nonpregnant animals, but this hypersensitivity is alleviated after delivery. Colored areas are 95% CIs.

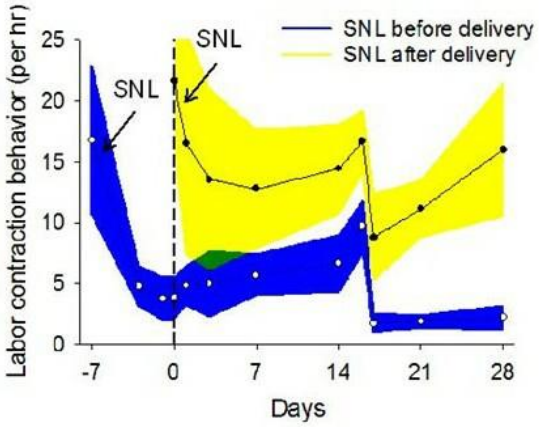

Figure 3. In animals with SNL performed during pregnancy, withdrawal threshold drops abruptly when pups are weaned at 17 days, but when SNL is done on the day of delivery, withdrawal threshold never changes from control.

the dams (Figure 3). When nerve injury surgery was performed on the same day as delivery, hypersensitivity never developed, mimicking the clinical trial results of a lack of chronic pain from surgical or vaginal delivery (Figure 3).

We subsequently performed several studies which suggest that spinal release of oxytocin represents the protective factor against chronic pain after childbirth. Intrathecal injection of the specific oxytocin receptor antagonist, atosiban, temporarily reverses the blockade of nerve injury induced hypersensitivity in the postpartum period in rats. Similarly, intracerebroventricular administration of the α-adrenoceptor antagonist, phentolamine, which is known to block the effects of lactation on activation of oxytocin-containing neurons in the paraventricular nucleus (PVN) of the hypothalamus, also temporarily reverses the blockade of nerve injury induced hypersensitivity in the postpartum period in rats. Finally, protection against hypersensitivity from nerve injury is abruptly reversed when pups are separated from dams for 24 hr, and this is accompanied by a large decrease in oxytocin concentration in cerebrospinal fluid. Although we are currently performing more laboratory studies to further define this mechanism, these data suggest that spinal oxytocin receptor stimulation in the period immediately following delivery speeds recovery from injury-induced hypersensitivity and subsequent chronic pain.

We recently completed a Phase 1 safety study of intrathecal oxytocin and observed no serious adverse events over the dose range studied (5-150 μg). One subject at the 150 μg dose had transient subjective numbness in sacral dermatomes, but this was preceded by a vasovagal episode beginning just prior to spinal injection, and this did not occur in other subjects at this dose. There were no objective signs of motor or sensory dysfunction in any volunteer, and blood pressure, heart rate, sensorium, corrected QT interval and serum sodium were unaffected.

In addition, we are progressing on two other Phase 2 studies, one in healthy volunteers and another in patients with chronic neuropathic pain, and have observed no serious adverse events in these subjects.

We anticipate that intrathecal oxytocin will speed recovery from pain after major surgery (hip arthroplasty). For these future studies, we will use a randomized, controlled and blinded study of intrathecal oxytocin in patients scheduled for hip arthroplasty, with primary outcome being the slope of change in pain over the first 60 days following surgery, using growth curve modeling and a ln(time) function.

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Protocol

Efficacy of Intrathecal Oxytocin to Speed Recovery after Hip Surgery

GOAL: Determine the effect of intrathecal oxytocin on speed of reduction in pain for the first 60 days after hip surgery.

METHODS:

Primary analysis: Slope of modeled change in daily worst pain intensity scores from the first 60 days after surgery.

Setting:

Subjects recruited at Wake Forest Baptist Medical Center will be identified by research personnel in the departments of Anesthesiology and Orthopaedics. Research personnel will approach the subjects while they are in a private exam room, the study will be explained to the subject and the subject will be given a copy of the study consent form to read. Informed consent be obtained at this time or the subject may choose to take the informed consent home and call the study personnel to schedule an appointment to come to the Headache and Pain Research Unit at Piedmont Plaza 2 (HPRU) for consent and their initial study visit. Subjects will be seen in the HPRU twice; within 2 weeks prior to surgery, and approximately 2 months after surgery.

Subjects selection criteria: We will recruit patients having primary, unilateral hip arthroplasty (HA).

Inclusion criteria: Adult, non-pregnant adults scheduled for elective HA, American Society of Anesthesiologists physical status 1-3, able and willing to perform the study procedures. Individuals must be able to read and write English and have a stable residence.

Exclusion criteria: (1) inability to complete questionnaires; (2) pregnancy; (3) litigation or workers compensation related to their joint surgery; (4) taking > 100 mg morphine equivalents/day; (5) suffering from a psychotic disorder or a recent psychiatric hospitalization.

Sample size: Single-center interventional study of 120 evaluable patients having primary HA.

Interventions and interactions:

Preoperative procedures. Eligible subjects will be identified at least 2 weeks prior to surgery, informed consent obtained, and a ~ 1.5-hr preoperative assessment will be performed, consisting of 3 parts. First, we will record demographic and history information, including pre-existing pain elsewhere. Second, we will administer the 9CH iPad game. Third, we will administer questionnaire-based measures of psychological state, physical function, and pain (Table 1). Questionnaire responses will be entered via a custom designed redcap data entry form and checked for completeness by research personnel. From these questionnaires, we will place each participant, as on another protocol approved by this IRB, on a continuum that describes their general cognitive style. We will use multidimensional scaling (MDS) to force catastrophizing and optimism as 2 ends of this continuum (Figure 4). These two constructs describe cognitive styles that are strongly inversely associated with each other; MDS will provide the optimal weights to best order individuals on this latent scale. Studies have examined the interplay of these constructs with other psychological concepts such as acceptance, pain-related disability and psychosocial adjustment and have found that both are reliably associated with the positive and negative aspects of the adjustment to pain.

Table 1. Preoperative Questionnaire
Stanford Expectations of Therapy Scale
WOMAC- Osteoarthritis Index
Life Orientation Test-Revised (LOT-R)
PROMIS- Depression
PROMIS- Anxiety
Pain Medication Attitudes Questionnaire (PMAQ)
Pain Locus of Control Scale (PLOC)
Pain Self-Efficacy Scale (PSE)
Barratt Impulsivity Test
Fear of Pain Questionnaire
Pain Catastrophizing Scale (PCS)
Tampa Scale of Kinesiophobia (TSK)
WHO Disability Assessment (WHODAS 2.0)

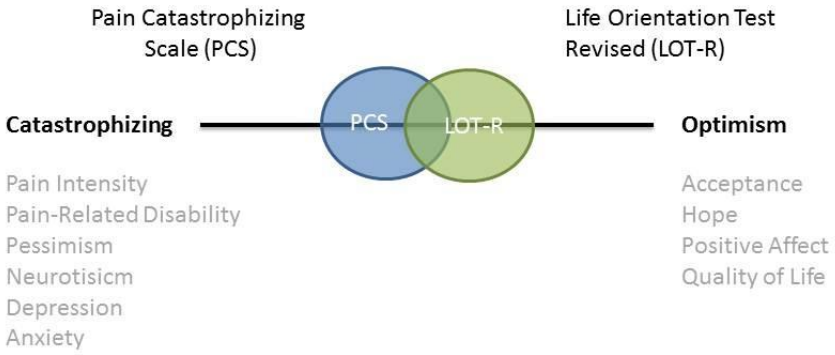

Figure 4: The dimensional structure of the continuum of cognitive style to be used, including psychosocial constructs associated with each end.

Subjects will be trained and provided with a tablet device for daily diary entries and the accelerometer. The accelerometer has wireless connectivity such that daily diary and activity will be time stamped and can be easily uploaded by the patient to the data coordinating center on a regular basis. We will utilize a password protected web based database tool for near real-time access to facilitate adherence (e.g., phone calls or emails when participants fail to wear the device during regularly scheduled time points).

We will have subjects begin using the tablet and wearing the accelerometer approximately 2 weeks prior to surgery so that they will become familiar with the devices to increase compliance and adherence to the protocol after surgery.

We will access PEBL software for cognitive assessment. This open-source software employs several cognitive tasks that look and feel like challenging games that allow the assessment of different areas of cognitive function. The specific tasks will be the Iowa gambling task to assess impulsivity, Wisconsin card sorting task to assess executive function, and the TSK to assess kinesiophobia. Participants will complete these tasks at baseline and again when returning to the HPRU 2 months after surgery, when they will return the electronic tablet and the accelerometer.

Drug treatment. Patients will be randomized to equal numbers in one of two groups to receive either **1)** intrathecal oxytocin, 100 μg or **2)** intrathecal saline. Once the spinal needle is inserted, 2 ml of cerebrospinal fluid will be withdrawn for subsequent measurement of neurotransmitters and other non-genomic modulators of pain responses, then the study solution in a 2 ml volume will be administered, followed by injection of local anesthetic with adjuvants as chosen by the anesthesiologist. Intrathecal study drug solutions will be provided by the research pharmacy and the investigators and patients will be blinded to treatment group.

Intraoperative and in-hospital care. We will not limit intraoperative surgical management or in-hospital analgesic management. Subjects will receive anesthesia and postoperative analgesia per the standard of care that is utilized by the Regional Anesthesia and Pain Management (RAAPM) team. A study team member will record a verbal pain score 24 hours after the administration of the peripheral nerve blocks, potential confounds including surgical complications, in-hospital

physical therapy, intraoperative and postoperative opioid, gabapentin, ketamine, and regional anesthesia administration, and days from surgery to discharge. Subjects will also play the 9CH iPad game that they were introduced to in the preoperative visit 24 hours after surgery.

Post-hospital discharge measures. Patients will begin daily evening electronic diary entries on the day of hospital discharge for 60 days. These assessments will typically take less than 2 minutes and assess IMMPACT recommended domains (Turk, 2006): pain intensity, physical functioning, emotional functioning, and participant ratings of global improvement and associated symptoms. Electronic diary entries are captured wirelessly using the participant's home wireless connection via a customized, secure database. Several tablets equipped with pre-paid 4G wireless access will be available to ensure that participants without home internet connections can participate. The diaries will be monitored and maintained by research personnel in real-time; if a participant misses a diary entry, they will be emailed or called (their preference) to ensure maximal adherence to the protocol. Using these procedures we have been able to obtain > 95% adherence in our previous diary studies. Participants will also wear the accelerometer for the first 60 days after discharge. Participants will also complete the cognitive tasks (Iowa gambling task, Wisconsin card sort, TSK) that they were introduced to at the baseline session at 2 months after hospital discharge. These tasks will again be administered via the PEBL software. Questionnaires done at pre-randomization will be repeated at 2 months after surgery. We will also record objective assessments of joint function at the times when the subjects return to clinic for their postoperative visits. Finally, we will contact each participant by telephone monthly until 6 months after surgery and at one year after surgery with a brief (<10 min) series of questions regarding their pain, physical function, and disability (12 item WHODAS 2.0) following surgery.

Subject payment: Subjects will be paid $700 with pro-rated payment steps (listed below) to study completion. The tablet devices will be returned to each study center for re-use.
Pro-rated payment will be made as follows:

- $100 for completion of the first HPRU study visit
- $100 for completion of the second HPRU study visit
- $100 for return of study supplies (electronic tablet, accelerometer and chargers)

- $200 for completing at least 90% of the daily diary entries on the electronic tablet and wearing the accelerometer through 8 weeks after surgery at least 90% of required time
- $200 for completion of all the scheduled study visits and telephone questionnaires

If a subject withdraws for any reason from the study before completion they will be paid according to the schedule of payment above. The accelerometer and the tablet must be returned if a subject withdraws from the study prior to completion.

Analytical plan:

Data analysis. We will examine the daily frequently obtained pain scores and the total daily (i.e., non-sleep) movement score. One growth curve model will be created for each outcome (pain, movement). Additionally, one model that combines both outcomes will examine for lagged and synchronous relationships between the two outcomes (i.e., do changes in one outcome predate changes in the other?). Multidimensional scaling (MDS) will be used to create a single dimensional scale from the catastrophizing and optimism scores (i.e., responses from these two questionnaires will be weighted and scaled to create a single-dimensional construct) as an additional, novel predictor.

Growth curve modeling, sometimes referred to as mixed-effects modeling, or hierarchical linear modeling, will allow us to specify a change trajectory (i.e., healing) that is unique to each individual/animal. The nature of the common form of changes in pain/behavior will be modeled using curvilinear forms (e.g., polynomial regression). Through the use of fixed and random effects, we will then be able to examine the influences on the changes in pain and activity measurements. In this way, we can examine the predictors immediately after surgery, the factors that predict delayed/absent recovery, patterns in these changes across individuals, examine the relationships between initial measurements and expected change, and test efficacy of the test intervention, intrathecal oxytocin.

To examine how the subjects in these studies recover over the repeated measurement occasions, we will employ hierarchical linear modeling (HLM: Raudenbush & Bryk, 2002). The application of HLM to individual change data is well suited for the expected changes that occur after surgical injury. HLM is a polynomial regression with random effects where interaction terms are used to examine impacts on the change parameters. Because of the nature of the

expected change, the trajectories will be modeled using parameters consisting of an intercept and some form of change parameter(s). Where appropriate, the slope and quadratic parameter will be estimated using the natural log of time (change in recovery). The intercept is coded to represent the initial level (first day after hospital discharge) of the outcome variable. The slope estimates the linear change over time (or ln of time) and represents the increase or decrease in the variable. Measurements taken before discharge (i.e., pain reporting immediately after surgery, analgesic use), demographic predictors (e.g., age, sex, previous history of chronic pain), and operative characteristics (e.g., surgery type, anesthesia regimen) will be used as predictors in a basic trajectory model. Variability between surgeons will be modeled using random effects by surgeon (with individual patients viewed as nested within surgeon). We will add additional predictors that measure baseline levels of affective distress, fear of pain, etc. We will utilize model fit indices (e.g., Bayesian Information Criterion (BIC)) to best characterize the change process using the most parsimonious model. Separate models will be conducted for pain reporting and physical activity.

Based on analysis of over three dozen subjects after total hip or knee arthroplasty and over 500 subjects after cesarean delivery using the methods in the current protocol, we anticipate that the ln (time) model will best fit the population and will be used as the primary outcome measure for the primary and secondary analyses involving recovery from pain and inactivity.

All analyses will be conducted with the most recent versions of SAS (SAS, Inc., Cary, NC), The R Project for Statistical Computing (R Foundation for Statistical Computing, Vienna, Austria) or SPSS (IBM Corp., Chicago, IL). Where appropriate, all analyses will be two-tailed with statistical significance interpreted at $p < 0.05$.

Statistical Power Considerations. Enrolling N = 120 participants (n = 60 per study arm) provides sufficient power to examine the study's primary hypothesis. Assuming that each individual contributes ~ 60 daily measurements, with alpha = 0.05, power = .80, a modest level of within-subject correlation, and adequate model fits (SD of the residuals < 2.0), we will be able to detect difference in slopes of d = 0.09 units. Thus, if the saline group exhibited a mean pain score of 8.0 VAS units after surgery and decreased on average 0.38 points each day (i.e., expected full recovery at 21 days), sufficient power exists to detect an enhanced slope of 0.47 in

the oxytocin group (i.e., expected full recovery in ~17 days). This difference is a clinically meaningful effect size that could substantially improve the life of patients.

Outcome measures.

Primary outcome measure: Modeled trajectory of recovery from pain (worst daily pain intensity) using a log of time form.

Several secondary analyses are planned, including slope of modeled change in other pain intensity measures (daily average pain and pain right now), activity and cognitive function tests. Interaction between preoperative cognitive style and slope of modeled change in these measures. that examine changes in cognition (e.g., impulsivity, attention) as well as kinesiophobia. The cognition measures (Iowa gambling task, Wisconsin card sort, TSK) collected at baseline and 2 months after discharge will be examined using generalized linear model with time as a fixed factor.

Human subjects protection.

Subject recruitment methods. Appropriate subjects will be identified and approached in the Department of Orthopedics during their regular scheduled appointment, by research personnel. Research personnel will utilize a private exam room to talk with subjects. Subjects will be given the study details and the opportunity to read the informed consent. The subject may take the informed consent home and make their decision regarding study participation. Contact information for the research staff will be provided to the subject so that they may call for questions or to participate. Study personnel will make every effort to approach any subject that will be scheduled for primary HA.

Informed consent. Signed informed consent will be obtained from each subject. Research personnel will obtain informed consent, the subject may sign the informed consent during their appointment time in the orthopedic clinic or the informed consent may be reviewed and signed during their first scheduled visit to the HPRU. If the subject has signed the informed consent prior to their first visit, consent will be confirmed and all questions answered prior to any study

procedures. No study information or procedures will be performed prior to the subject signing the informed consent. All subjects will be given a copy of the signed, informed consent.

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. 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.

Risks. One patient receiving intrathecal oxytocin in previous and ongoing studies at this institution exhibited hypotension and bradycardia. Although these symptoms were consistent with previous vaso-vagal episodes that the volunteer subsequently described with procedures, it is conceivable that this could be a drug effect. Blood pressure is monitored at frequent intervals (every 1-2 min) during the first 10 min after spinal injection for spinal anesthesia for HA, then every 2-5 min thereafter, and hypotension treated with intravenous fluid administration or vasopressors.

Other risks of intrathecal oxytocin uterine contractions during the 3rd trimester of pregnancy, and unforeseen adverse events. Animal studies have shown no histologic, behavioral, or neurochemical evidence of neurotoxicity with doses and concentrations several fold greater than those proposed in this study.

In a previous application, the IRB noted that questionnaires of psychologic well being, including depression and catastrophizing cognition, could produce emotional distress in participants, and we included disclosure of this risk in the informed consent document and additional resources for counseling or treatment should this occur. We will use the same approach in this protocol.

Protections against risk.

- Electronic data will be maintained in a password protected database, on password protected servers, to which only the study team has access. Daily hand-held data is de-identified, and is transferred to lab computers via a secure connection. RedCap is a HIPAA compliant, secure database system. Data validity will be maintained by validity criterion in the database, and error checking procedures. Study staff will complete training in HIPAA regulations, and will be clearly instructed not to divulge confidential information regarding subjects. The system will also be developed in accordance with FDA part 11 [21cfr11] guidelines. Participant records are kept confidential, with paper records in a secure location and computer records password protected, available only to study staff.
- Cerebrospinal fluid will be obtained by a board certified anesthesiologist during the course of routine care in providing spinal anesthesia.
- Symptoms of depression, anxiety, and other forms of psychological distress symptoms are to be measured upon enrollment. Because many patients will endorse some level of distress, and it is impossible to know for each individual when they require or are even open to mental health assistance. Therefore, and because our questions may focus patients' attention on these sources of significant distress, we will offer a referral to a mental health professional to all patients. To be specific, we will provide all patients with telephone numbers and addresses of at least three local mental health resources. We will not explicitly seek suicidal ideation. Patients spontaneously endorsing thoughts of harming themselves or others will have their treating physician informed for an assessment if they need to be guided to the emergency room, or other care pathway.

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.

The DSMP outlined below will provide appropriate oversight and monitoring to ensure the safety of participants, the validity of the data, and make intermittent recommendations whether to continue, modify or stop the study. The DSMP will utilize an independent DSMB to ensure the effective institution of the DSMP.

This DSMB will have discretion to unblind any results, or conduct any inquiry needed to ensure the safety and efficacy of the trial at the request of the DSMB chair. The committee will maintain a written record of its meetings.

Scope of data monitoring

The primary source of the data will be the entered questionnaire data and adverse event reporting.

Study admission data

Monitoring of admission data will include the number of subjects requesting participation in the study, number of subjects screened and number of subjects admitted to the study. The dsmb may request a report of the reason why subjects were disqualified from participating in the study. For subjects admitted to the study, the DSMB will review eligibility criteria for admitted subject, any protocol deviations and/or violations, and the demographic distribution of the subjects by group.

Protocol compliance

The DSMB will monitor the data to assess compliance with the protocol including the adherence to the randomization schedule. The DSMB will also monitor the quality and completeness of the data being collected, including the frequency of missing or erroneous data, and presence and frequency of outliers.

Safety data

Monitoring of safety data will include review of adverse events (AEs) and serious adverse events (SAEs), trial retention, and reason for drop out. Safety information will be reported to the DSMB in an unblinded manner. Formal statistical analyses of the safety data may be requested by the DSMB. For SAEs, data will include all the adverse event data meeting the FDA definition of

serious adverse events. In the assessment of SAEs, the DSMB will review each individual case including treatment group assignment. After each meeting of the DSMB, the secretary will forward a summary report of all serious and unexpected adverse experiences to the principal investigator to summarize the DSMB's review of the serious and unexpected adverse events reported. Furthermore, the DSMB will make a recommendation to continue, modify or halt the study protocol. This report will be transmitted to the Wake Forest University IRB, FDA, and NIH. Safety data will be prepared for review following the enrollment of each 40 subjects.

Establishing a DSMB board membership

The DSMB will be appointed by Dr. Eisenach and Dr. Houle with the purpose of reviewing, approval, and monitoring the implementation of the DSMP. The DSMB will have two members encompassing multidisciplinary expertise who are not involved in the study protocol including an anesthesiologist and clinical researcher. Thus the DSMB will encompass expertise in clinical research design and methodology. Board members will have no financial and/or scientific ties to the outcome of the clinical trial to avoid any real or perceived conflict of interest. The chairperson of the DSMB, will have previous experience in monitoring clinical trials with administrative experience.

The DSMB will also include a non-voting member as a secretary. DSMB members will disclose in writing to the irb conflict of interest representative any potential conflicts of interest, actual or implied by appearance. At the start of each new member's term, the individual will sign a confidentiality statement promising not to disclose any proprietary and nonproprietary data. The data safety monitoring board physicians will be Dr. Francis Walker, Professor, Department of Neurology and Dr. Laura Dean, Associate Professor, Department of Anesthesiology at Wake Forest Baptist Medical Center. Drs. Walker and Dean currently serve as DSMB for 2 existing spinal oxytocin studies.

Board meeting schedule

The board will have scheduled meetings twice a year and expedited meetings to review unexpected SAEs or other urgent issues that may arise during the trial. Unscheduled meetings

may be initiated by the DSMB chair, Dr. Eisenach, or Dr. Houle. The data to be reviewed by the DSMB will be available to the board members.

Conduct of the meetings

DSMB meetings will be divided into three sessions: open, closed and executive. Drs. Eisenach and/or Houle will attend the open session and present relevant information to the dsmb about the trial. The open session will focus on the status of the study, problems with accrual and follow-up, baseline demographic data, compliance issues, frequency of adverse events, data quality issues, flow of forms, and data based protocol modification issues. Following the open session, a closed session will be held. During the closed session, the dsmb chair will conduct the review of all issues and put each issue to a vote. Following the closed session, an executive meeting may be held to discuss any unmasked analysis of the trial and any sensitive issues surrounding the trial.

DSMB recommendations:

DSMB recommendations will be made in writing by the DSMB chair to Dr. Eisenach. The secretary will prepare meeting minutes for inclusion in the DSMB report. The report will outline and summarize all discussions during the open and closed sessions of the meeting. The draft report will be reviewed by all board members prior to issuance of the final report. DSMB recommendations will then be forwarded to the NIGMS program officer and Wake Forest University IRB.

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.

References

Raudenbush, S. W. and A. S. Bryk (2002). Hierarchical Linear Models: Applications and Data Analysis Methods. Thousand Oaks, CA, Sage Publications.

Turk, D. C., et al. (2006). "Developing patient-reported outcome measures for pain clinical trials: IMMPACT recommendations." Pain 125(3): 208-215.

Appendix

1. Copies of each questionnaires or surveys that will be used
2. Consent form