Study Title: Pain and function after orthopedic surgery

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Background, Rationale and Context

Chronic Pain After Surgery

Primary indications for major joint surgery include limited joint function and pain. Although joint replacement or repair surgery is usually remarkably effective, in some cases pain and function are worse or not improved after surgery. Chronic pain after some surgical procedures, e.g., phantom limb pain after extremity amputation, has been long recognized, but more recent investigations suggest that chronic pain after physical injury including that of major surgery is not uncommon. The purpose of this study is to provide preliminary data for a Program Project Grant to the National Institutes of Health to examine specific hypotheses regarding identifying patients at risk for chronic pain after surgery and probing mechanisms which may be manipulated to decrease this risk.

Chronic pain after surgery is typically defined as pain outlasting the normal healing process from uncomplicated surgery. Although there is some disagreement regarding the time normal healing is required, most investigators consider pain beyond 2 months, and certainly beyond 6 months after surgery as abnormal. As such, patients with chest wall pain 2 months after augmentation mammoplasty have a nearly 18-fold relative risk of having chest wall pain 4 years later compared with those without pain at 2 months (1).

The incidence of chronic pain after surgery ranges from 10-50% (2). After breast surgery for cancer, nearly half of those with chronic chest wall pain after surgery rate it as moderate to severe and seek treatment for it (3). Given that there are nearly 250 million major surgical procedures performed annually on a global basis, the problem of chronic pain after surgery is thus a major public health problem.

The etiology of chronic pain after surgery is unknown. Since most patients with chronic pain after surgery exhibit symptoms consistent with neuropathic pain, it is assumed that peripheral nerve injury, either to small nerve branches or larger, peripheral nerves, may be an important cause. Alternatively, primary afferent nerve traffic after surgery to the spinal cord may elicit plastic changes in pain transmission and procession in the spinal cord and supraspinally which underlie chronic neuropathic pain. In animal models of chronic pain after surgery, many such plastic changes can be demonstrated.

Descending modulation

The central hypothesis for the Program Project Grant application for which this is a preliminary study is that descending modulation of pain processing to the spinal cord plays an essential role in determining whether pain after surgery resolves or continues to become chronic. This follows from several observations and builds on the concept that the perception of pain after a peripheral noxious stimulus is not constant, but can be powerfully decreased or increased by sub-cortical neurons in the brainstem which project to the spinal cord and alter pain neurotransmission. Powerful pain inhibition has long been recognized in the early period after major trauma in military or civilian life, with temporary absence of pain despite major injury that can last from minutes to hours. Similarly, experimental pain can be amplified acutely by enforcing anticipation of pain, and several changes in the spinal cord which amplify pain after peripheral trauma are depending on descending facilitation pathways.

We have spent 25 years examining the role and mechanisms of one of the major descending pain inhibitory pathways, comprised of cells in the pontine locus coeruleus and adjacent nuclei which project to and release norepinephrine in the spinal cord. This pathway is activated by traditional analgesics such as morphine as well as those used primarily in chronic pain settings such as gabapentin, or can be amplified by other drugs used to treat chronic pain, such as monoamine reuptake inhibitors. More recently, we have shown in animals that selective destruction of this descending noradrenergic system prior to surgery results in greatly prolonged or absent recovery in pain behaviors after surgery, suggesting that this system is essential for normal recovery and prevention of chronic pain after injury. As part of the Program Project Grant application we will explore in detail the mechanisms by which this pathway is regulated and by which it protects the individual from chronic pain after injury.

Descending inhibition of pain can be temporarily engaged in normal humans by applying a noxious stimulus. This concept of 'pain inhibiting pain' is most easily demonstrated by placing a foot in a mildly noxious cold water bath and testing for pain perception on another extremity (4). The noxious stimulus applied to the foot results in reduction in pain perceived by an experimental hot stimulus to the arm. In humans this effect is blocked by naloxone, indicating a role for endogenous opioids (5). In animals, this effect is blocked by naloxone administered to several brainstem sites and by spinal injection of a noradrenergic receptor antagonist, indicating engagement of descending noradrenergic inhibition.

There is wide inter-individual variability in the degree to which pain inhibits pain using this experimental method. Since we believe that activating descending inhibition is essential to normal recovery of pain after surgery, it is not surprising that the degree to which this system can be demonstrated experimentally using this pain-inhibits-pain test correlates strongly with the risk of chronic pain after surgery (6).

Stress and reward

In addition to surgical factors (specific procedure and likelihood of nerve injury) and biologic factors (including ability to engage descending modulation), several psychosocial factors are associated with an increased risk of chronic pain after surgery. Especially prominent and consistent factors associated with increased risk are pre-existing depression, anxiety, fear of pain, and catastrophizing. Our central hypothesis is that these cognitive aspects reflect brain connectivity and patterns of activity which gate pain perception. Several lines of converging evidence indicate important roles for medial prefrontal cortex, amygdala and basal ganglia in processing noxious stimuli within the overall context of the internal and external environment.

This subconscious processing can significantly alter pain processing and the normal resolution of pain after injury. For example, we recently observed a remarkably low incidence of chronic pain after childbirth, including cesarean delivery. Similarly, in animals we showed that the immediate post-delivery period is associated with protection from chronic pain from peripheral nerve injury and that this protection was lost when oxytocin receptors in the spinal cord were blocked pharmacologically. Centrally released oxytocin has long been known to enhance social interactions, bonding, and trust, while reducing fear and anxiety. In addition, we propose that individuals or populations, such as new mothers, with increased oxytocin signaling are protected from chronic pain after physical injury. Initial studies in our laboratory indicate that oxytocin does this by increasing descending noradrenergic inhibition and by decreasing descending facilitation.

In contrast to reduced pain responses and positive psycho-social engagement encouraged by oxytocin, high levels of psycho-social stress produce nearly opposite effects. As such, a model of high stress in rodents induced by repeated social defeat results in anxiety behavior, exaggerated responses to noxious stimuli, and evidence of plasticity associated with chronic pain (7). Within the laboratory studies of our Program Project Grant application will be manipulation of environmental and neurohormonal factors to understand the link between higher

ordering cognitive function and chronic pain after injury. The presumed link includes engagement of descending noradrenergic pathways. We will propose parallel clinical trials to examine the role of psychosocial factors on resolution of pain after surgery.

Context of this IRB application

As noted above, chronic pain after surgery is a major health problem and we have minimal understanding of whether cognitive and provocative pain testing factors associated with increased risk of this problem are mere associations or causations. We propose to test, within the context of a multi-investigator NIH application, whether chronic pain after surgery is caused by an inadequate response from descending inhibition and whether cognitive and psychosocial factors determine whether pain after surgery resolves or becomes chronic by controlling descending inhibitory tone.

We will submit a Program Project Grant application for the October, 2011 deadline and the purpose of this IRB application is to acquire preliminary data to demonstrate feasibility and allow an accurate power analysis for the size of the proposed study within that grant application.

Objectives

The objectives of this pilot effort are:

1) To demonstrate the feasibility of conducting this protocol in this clinical population. The execution of this study will allow us to identify expected enrollment rates, patient drop-out rates, and other threats to the accurate assessment of the course of pain after major joint surgery.

2) To estimate the individual variability in pain trajectories over time and to obtain effect size estimates for factors that predict pain trajectory.

3) To demonstrate feasibility of providing a pre-surgical teaching intervention in this clinical population.

Methods and Measures

Design

The proposed study is a prospective longitudinal observational study. Patients who are undergoing elective orthopedic surgery: unicompartmental knee replacement, a total knee replacement or total hip replacement will be approached and asked to provide consent to participate in 6 months of observation after their surgery. During this time, participants will not alter their usual treatment in any way (i.e., no treatment algorithms will be altered for this study), but will complete diaries and survey instruments at numerous intervals.

Setting

The study will be conducted on patients scheduled for major joint orthopedic surgery at Wake Forest University Health Sciences WFUHS. Informed consent and pre-surgical surveys and CBT Intervention will be performed during the preoperative visit in the Joint Replacement Education Conference Room, Preoperative Assessment Clinic or in the Orthopedic Clinic. Perioperative care will be provided at the surgical and post-surgical areas of WFUHS.

Subjects selection criteria

- **Inclusion Criteria**

Adult patients scheduled for elective unicompartmental, total knee replacement, or total hip replacement surgery, will be included. Patients will be American Society of Anesthesiologists physical status 1, 2, or 3.

- **Exclusion Criteria**
  We will exclude patients who do not understand English (subjects must be able to read English to answer the questionnaires. The questionnaires are not available in multiple languages), those who are pregnant or within 1 year of childbirth, those with Raynaud's phenomena of the foot, and those with neuropathy of the lower extremities with loss of temperature sensation.

- **Sample Size**
  The proposed pilot study aims at identifying effect size estimates and indicators of feasibility. As such, the proposed sample size is not intended to provide definitive estimates of the hypotheses underlying the research. Instead, we propose to enroll N = 75 participants to obtain estimates of drop-out rates (this sample size will allow 95% confidence interval precision of +- 8.2% assuming a 25% drop-out rate) as well as initial estimates of effect sizes for the predictors in the study.

Interventions and Interactions

All patients will complete written informed consent. In addition to review of medical history, indication for major joint surgery and current joint function will be recorded.

The following questionnaires will be completed:

Daily Stress Inventory (DSI, Brantley et al., 1987; 58 items)

Catastrophizing Scale of the Coping Strategies Questionnaire (CATS, 7 items)

McGill Pain Questionnaire-SF (MPQ-SF)

Pre-surgical Intervention:

After completion of baseline questionnaires (MPQ-SF, DSI, CATS) the Brief CBT Intervention will be viewed by the subject. Upon completion of the presentation, the CATS questionnaire will be administered again. The subject will receive a packet containing "The Power of the Mind," they will be asked to read this information and complete the exercise at the end of the packet. The study staff will call the subject one week after the initial meeting and ask if they have read the packet and will also have the subject to complete the CATS questionnaire again. A postage paid, addressed envelope will be provided for the subject to return the questionnaires to the study team. The questionnaires will be de-identified and only contain subject initials and study identification number.

At Home Diary Assessments

The subject will be given a notebook with paper questionnaires and instructions on how to complete the questionnaires per the schedule below. All participants will complete the assessments in a sequence using one of several methods:

A. Inpatient evaluation (surgery to discharge): Nursing staff will inquire about the patients pain levels using standard of care methods and assessment tools (e.g., numerical rating scale 0 – 10).

B. Ecological Momentary assessment (discharge to day 14): The subject will complete the questionnaires in the morning and in the evening.

C. Once daily (day 15 to day 28): The patient is instructed to complete a diary entry at the end of their day, just prior to going to sleep.

D. Once weekly (day 29 to day 85): The patient will be called at their home and participate in a brief interview.

E. Once monthly (day 86 to day 168): The patient will be called at their home and participate in a brief interview once each month.

Each of the assessments will only require about 5 to 10 minutes to complete. At each of the at home assessments the McGill Pain Questionnaire-SF will be administered.

In addition, information from the postoperative care from the orthopedic surgery division will be recorded, including range of joint motion and functional limitations, if any, at the times of routine postoperative clinic visits.

Table 1. A summary of the data collection procedures for the observational study

Assessment Type	Time (Days)	Questionnaires	Joint Sensory Testing	Thermal Pain Testing	DNIC Protocol	Diary type
Visit 1	-14 to 0	X	X	X	X	NA
Post-op	0 to 3					NA
Home	4 to 14					Ecological Momentary Assessment
Home	15 to 28					Once-daily
Home	29 to 85					Weekly
Home	86 to 168					Monthly

Outcome Measure(s)

The primary outcome measure for this study is self-reported pain intensity. To obtain estimates of pain intensity, we will use the McGill Pain Questionnaire - Short Form (MPQ). This instrument has been extensively used to assess pain in a wide variety of settings, and is uniquely suited to our present study in that the items can be completed while in a post-operative setting as well as a daily diary setting.

Analytical Plan

The proposed pilot study aims at identifying effect size estimates and indicators of feasibility. As such, the analytical plan is primarily descriptive in nature. Careful attention will be given to missing data due to any reason, participant withdrawal, and evidence of corrupted or invalid assessments. These threats to data collection will be itemized and descriptive statistics will be used to summarize the rates and expected proportions (with 95% confidence intervals) of measurements that may be lost due to any reason.

To estimate individual variability in the trajectory of pain over time (i.e., healing and diminishing pain reports), and predictors of that trajectory, hierarchical linear modeling (Raudenbush & Bryk, 2002) will be used. The application of HLM in individual change data is well suited for the examination of post surgery pain. Briefly, change trajectories are created for each participant. Because of the nature of the expected change, the trajectories will be modeled using an intercept, slope, and quadratic term. The intercept is coded to represent the baseline level of the pain score (day of surgery). The slope estimates the linear change over time and represents the increase or decrease in the variable. Finally, the quadratic term estimates the acceleration or deceleration over time and reflects changes in the rate of change in pain reporting.

To assess our specific hypotheses, we will first evaluate the appropriateness of a model that consisted of only intercept (starting value), time, and time-squared as first-level predictors. This first level model describes individual trajectories (change) across time. This model will be evaluated for fit, redundancy, and variability in the parameters and will be reduced to a linear change model if conditions indicate. When a suitable first-level model is developed, and if there is significant variation across participants in either the intercept or change parameters, a second level model will be specified. The second level model will examine the impact of the questionnaires and baseline sensory testing on the trajectories (i.e., linear and quadratic components of the first level model). In all cases, the model coefficients and their standard errors will be of primary interest to inform out later, definitive study.

Risks

Taking part in this research study may involve subject's providing information that they consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep research related information safe.

Human Subjects Protection

Subject Recruitment Methods

Patients scheduled for unicompartmental knee, total knee replacement, or total hip replacement surgery at WFUHS will be contacted by telephone by our research nurse at least 2 days before surgery. All adult patients scheduled for surgery within the inclusion criteria discussed above will be considered as eligible, regardless of sex, race, or ethnicity. Privacy will be protected by safekeeping and then destruction of surgical posting lists obtained from the Division of Orthopedic Surgery and by the maintenance of all records on password protected computers.

Patient name, age, telephone number, surgical indication, date and procedure scheduled for major joint surgery will be collected to identify and contact potential participants.

This information will be kept on print out in a locked location or on a WFUHS password protected computer. Print out will be shredded and file containing the name will be deleted within 24 hr of declining to participate.

Informed Consent

Signed informed consent will be obtained from each subject. Subjects will be recruited from the Orthopaedic Clinic. The staff in the Orthopaedic Clinic may call the study coordinator to see patients in the clinic for discussion of the research study and patients may also be contacted by telephone and the study discussed with them. However, the study coordinator will obtain the informed consent from the subject in the Orthopedic Clinic, Preoperative Assessment Clinic or in the Joint Replacement Education session.

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 three years after closure of the study 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. Because this is an observational study, with minimal risk, no data and safety monitoring board will be convened. However, threats to participants' confidentiality will be minimized using the following methods. First, the collected data will be stored on University networked, password protected computers. The databases will be created such that only a patient ID number identifies participant records, and that ID will be linked to actual patients in a separate file that itself is password protected on the PIs computer. The diary information, recorded at the participant's home will not contain any protected health information, and will only be linked to the participant through internal database keys.

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

1. Kaasa T, Romundstad L, Roald H, et al. Hyperesthesia one year after breast augmentation surgery increases the odds for persistent pain at four years. A prospective four-year follow-up study. Scandinavian Journal of Pain 2010;1:75-81.

2. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618-25.

3. Gartner R, Jensen MB, Nielsen J, et al. Prevalence of and factors associated with persistent pain following breast cancer surgery. JAMA 2009;302:1985-92.

4. Talbot JD, Duncan GH, Bushnell MC, Boyer M. Diffuse noxious inhibitory controls (DNICs): psychophysical evidence in man for intersegmental suppression of noxious heat perception by cold pressor pain. Pain 1987;30:221-32.

5. Willer JC, Le Bars D, De Broucker T. Diffuse noxious inhibitory controls in man: Involvement of an opioidergic link. Eur J Pharmacol 1990;182:347-55.

6. Yarnitsky D, Crispel Y, Eisenberg E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain 2008;138:22-8.

7. Wohleb ES, Hanke M.L., Corona AW, et al. β-Adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. J Neurosci 2011;31:6277-88.

8. Ursini G, Bollati V, Fazio L, et al. Stress-Related Methylation of the Catechol-O-Methyltransferase Val158 Allele Predicts Human Prefrontal Cognition and Activity. J Neurosci 2011;31:6692-8.

9. Rodrigues SM, Saslow LR, Garcia N, et al. Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. Proc Natl Acad Sci U S A 2009;106:21437-41.

10. Shafer SL, Eisenach JC, Hood DD, Tong CY. Cerebrospinal fluid pharmacokinetics and pharmacodynamics of intrathecal neostigmine methylsulfate in humans. Anesthesiology 1998;89:1074-88.

11. Rosier EM, Iadarola MJ, Coghill RC. Reproducibility of pain measurement and pain perception. Pain 2002;98:205-16.

12. Coghill RC, McHaffie JG, Yen Y-F. Neural correlates of inter-individual differences in the subjective experience of pain. Proc Natl Acad Sci USA 2003;100:8538-42.

13. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56:217-26.