Effect of intrathecal ketorolac on mechanical hypersensitivity following surgery

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Introduction

This is a revision of a protocol previously approved by the Forsyth Hospital IRB and, by cooperative agreement, by the WFUSM IRB. It is funded by NIH grant GM48085. The purpose of the protocol is to test whether intrathecal ketorolac, by selectively and effectively blocking cyclooxygenase in the spinal cord, will reduce hypersensitivity surrounding the surgical wound in patients with high risk for developing chronic pain after surgery.

The original study population was women at cesarean section who, according to preoperative screening, were at high risk to experience severe postoperative pain and were also at high risk to experience chronic pain after cesarean section. Since the time that the grant and the protocol were approved, however, we have completed a large study showing that the incidence of chronic pain after cesarean section is remarkably low (< 0.5%). This rendered the original study design incapable of testing the hypothesis because, even with screening and examining high risk subjects, the likelihood of chronic pain was very small.

For this reason, we have decided to submit a new application to perform this study in a population at higher risk for chronic pain after surgery, patients undergoing hip replacement surgery. The primary outcome measure, area of hypersensitivity to mechanical stimuli surrounding the wound 48 hr after surgery, remains the same and is only a surrogate measure for developing chronic pain. This proposed study, like the previously funded and IRB protocol, is powered to examine effects of intrathecal ketorolac on this surrogate measure, and is inadequately powered to examine ketorolac's effect on the incidence of chronic pain. Moving to this population at higher risk for chronic pain, however, will allow us to expand on the results of the proposed study, if positive, to subsequently design a study to test the effect of intrathecal ketorolac on chronic pain after hip replacement surgery. This would likely require additional funding from the NIH in the form of a competitive renewal of the existing grant.

A secondary purpose of this study is to determine the predictive value of 3 simple preoperative tests for severity of acute pain following surgery. These tests were defined in the cesarean section patient population, and we wish to determine their generalizability to other patient populations.

Background

Surgery results in hypersensitivity to mechanical stimuli surrounding the wound and, in a subset of patients, also results in chronic pain. An emerging literature suggests that these two are related. In a series of studies aimed at identifying measures to prevent chronic pain after abdominal surgery (1-3), there is a remarkable correlation between activity of treatments to reduce the area of hypersensitivity in the acute postoperative period and the incidence of chronic pain (Figure 1). Interestingly, there is a weaker relationship between acute analgesic activity and reduction in hypersensitivity and the incidence of chronic pain.

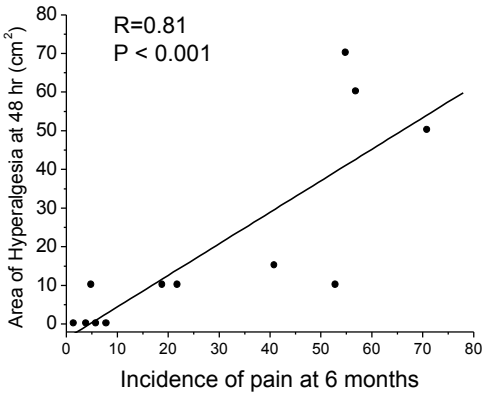

Figure 1: Relationship between area of hyperalgesia 48 hr after surgery and pain 6 months later.

Surgery activates spinal cyclooxgenase (COX), as evidenced by increases in CSF prostaglandins in postoperative patients. Ketorolac, nonselective, and selective COX-2 inhibitors

reduce these increased prostaglandin concentrations in CSF (4-6)(Figure 2), and such reductions correlate with reduced pain and opioid consumption. Interpretation of these studies is limited, since COX inhibitors were administered systemically, and it is uncertain whether they penetrated the CNS and directly reduced spinal COX activity, or rather reduced peripheral inflammation and thereby reduced afferent signals to the cord which activate COX. Clearly, systemically administered nonselective and COX-2 selective inhibitors produce postoperative analgesia and reduce opioid consumption (7), most likely by actions at multiple peripheral and central sites. We focus in this proposal, however, on the role of spinal COX, using ketorolac as a probe in animals and humans to test COX isoenzymes and mechanisms involved in its postoperative analgesia. We do so in part because transient blockade of spinal COX activity at the time of surgery prevents development of hypersensitivity in a surgical model of chronic neuropathic pain (8).

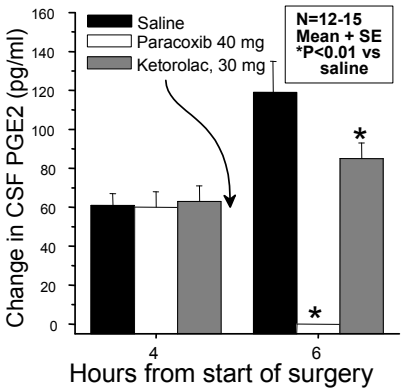

Figure 2: Effect of IV COX inhibitors on CSF PGE2 after surgery.

We recently showed that intrathecal ketorolac, 2 mg, produces analgesia following vaginal hysterectomy in humans, consistent with a direct role for spinal COX in postoperative pain. In that study 30 evaluable patients were randomized to receive either ketorolac or saline with bupivacaine for spinal anesthesia, with primary outcome measure duration of analgesia. Ketorolac significantly increased duration of complete analgesia in PACU (median 160 with ketorolac vs 120 min with saline) without a difference in resolution of sensory blockade, reduced 24 hr PCA morphine use by a 30% (1.8 ± 0.3 mg/hr with ketorolac vs 2.6 ± 0.4 mg/hr with saline), and reduced the need for supplemental analgesics to PCA morphine (20% with ketorolac vs 75% with saline). The adverse event profile for the 15 subjects receiving IT ketorolac in this study was no different that the AE profile for the 15 control subjects. This study suggests that a dose of spinal ketorolac which is <10% of the minimally effective dose when administered systemically, produces analgesia after surgery. We also conducted other 2 mg, IT ketorolac studies that involved a total of 103 healthy volunteers or chronic pain subjects. 64 of the 103 healthy volunteers or chronic pain subjects received 2 mg of intrathecal ketorolac. We conducted two dose escalation studies: (1) 20 healthy volunteers and (2) 14 chronic pain patients

prior to initiating the four Phase II b studies that have been completed. We have seen no adverse events directly related to the administration of intrathecal ketorolac.

The current proposal will expand these observations be examining the role of spinal prostaglandins in postoperative hypersensitivity and chronic pain. The role of intrathecal ketorolac in preventing chronic pain is especially promising, since brief inhibition of spinal COX-1 totally prevents development of chronic pain after nerve injury surgery in animals (8).

Chronic pain in patients following total hip arthroplasty (THA) seems to be a significant problem. In a study reviewing responses to a questionnaire given 12 – 18 months after THA, the number of patients reporting chronic ipsilateral hip pain was 28.1%, with pain limiting daily activities to a moderate, severe, or very severe degree in 12.1%. This study showed that the chronic pain state was related to the recalled intensity of early postoperative pain [95% confidence interval (CI), 20-4-33.4%] (9). This study supports the hypothesis that more effective pain management in the early postoperative period may decrease the incidence of the development of chronic pain states.

Pain and analgesic drug use after surgery exhibits wide inter-individual variability, some of which can be predicted by genetic, psychologic, and individual pain response characteristics (10). We recently performed an exploratory study of > 20 variables obtained in preoperative interviews and testing in order to develop a combination of simple tests to predict severity of acute postoperative pain after cesarean section (11). A secondary purpose of the current study is to test whether these 2 simple preoperative tests have sensitivity and specificity to predict severity of acute postoperative pain in another surgical population. This will be a multi-site study.

Hypothesis: Intrathecal ketorolac will reduce area of mechanical hypersensitivity following surgery.

Study population

Inclusion criteria: ASA physical status 1, 2, or 3 patients, aged 18 years or above, who are scheduled for primary unilateral total hip arthroplasty or Birmingham Hip Replacement under spinal anesthesia.

Exclusion criteria: Known allergy to study medications. Weight > 300 lb. Presence of obstructive sleep apnea. Patients with severe renal (kidney) or hepatic (liver) disease, allergy to ketorolac, amino amide local anesthetic, or contraindications to spinal anesthesia will be excluded. Patients will be excluded if on dialysis for kidney failure or if they are jaundice or have a diagnosis of liver failure. Patients routinely taking narcotic pain medications for pain other than their primary hip pain will be excluded. Patients taking Lyrica (Pregablin) or Gabapentin (Neurontin) for hip pain will be asked to stop taking these medications three days prior to their surgery day. Patients taking Ultram (Tramadol) will be asked to stop taking this drug 24 hours prior to their surgery day. Subjects who are taking opioids for their primary hip pain will be excluded if they are taking a dosage that exceeds an equivalent of Oxycodone 20 mg per day. If patients are taking opioid analgesics for hip pain before surgery, they will be stratified to a secondary randomization group. These patients will likely require additional postoperative opioids to include their preoperative dose requirement in addition to the opioid analgesic requirement for postoperative pain control. Pregnant women will not be able to participate (this will be determined by urine pregnancy test if needed). We will exclude patients that are taking Lyrica (Pregablin) or Gabapentin (Neurontin) for the treatment of seizures.

Informed consent: Patients scheduled for surgery will be seen during their preoperative assessment visit to North Carolina Baptist Hospital. During the patient's routine preoperative visit for their anesthesiology evaluation or preoperative education/orientation visit to the Sticht Center, one of the research nurses will talk with the patient about the study. If the patient desires to participate in the study, informed consent will be obtained during this visit. Additionally the study physicians and research nurse will talk with appropriate patients not seen during their preoperative visit, on the day of surgery in the Regional Anesthesia Holding Area and offer them the opportunity to participate in the study. All elements of informed consent will be met and all necessary data will be obtained and recorded prior to any medication administration. Written informed consent will be documented on the patient's medical record. A copy of the signed informed consent will be placed in the patient's medical record.

Study Procedures

Preoperative procedures: One hundred patients scheduled for unilateral primary total hip arthroplasty or Birmingham Hip Replacement under spinal anesthesia will be included. The study will be explained, all questions answered, and written informed consent obtained. Preoperative screening will include 2 experimental measures, based on our previous study of predictive factors for severity of postoperative pain (10). These are level of anxiety and expected severity of postoperative pain (patient verbal report on 0-10 scale for each).

Randomization and Study Drug Treatment: Patients will be randomized to receive 13.5mg hyperbaric bupivacaine spinally plus 0.4ml saline or preservative free ketorolac (5mg/ml=2.0mg). Drugs will be mixed and injected by an individual not involved in subsequent data collection or clinical care. For spinal injections, a #25 Whitacre spinal needle will be inserted in a mid to lower lumbar interspace and one milliliter of cerebrospinal fluid (CSF) will be sampled for subsequent PGE2 analysis. We will ship de-identified CSF samples to Professor Torsten Gordh, Jr., at the University of Uppsala, Sweden for analysis of PGE2 and of lipid mediators.

The study medication will then be injected per the randomization (above). All patients will receive 1000 mg of acetaminophen PO prior to surgery.

Intraoperative Care: Anesthesia will be routine, with recording of duration of surgery, sensory level to pinprick 10 minutes after spinal injection and at the start and end of surgery, and all intraoperative drugs and dosages, including vasopressors for hypotension, morphine or fentanyl for pain in 2 milligram or 50 microgram increments, respectively, and midazolam, 2 milligram increments for anxiolysis. Patients may also be maintained on a continuous IV infusion of propofol for sedation during the surgical procedure. Ondansetron may be given in 2mg increments for the treatment of nausea. Sensory level assessments and VAS pain assessment will be performed every 30 minutes while in the PACU and intravenous morphine or hydromorphone will be administered for pain management. Ondansetron may be given in 2mg increments for the treatment of nausea.

Postoperative Care: Analgesia in the first 24 postoperative hours will be provided by intravenous (IV) Patient Controlled Analgesia (PCA) with morphine 1mg/ml or hydromorphone 0.2mg/ml (1.5 ml dose, 10 minute lockout interval, 6 ml hourly limit, no basal infusion). Morphine or Hydromorphone doses will be increased in 0.5ml dose increments if the patient is not achieving adequate analgesia. Upon discontinuation of IV PCA, oral Oxycodone 5 – 15 mg

PO q3h as needed will be given. Oxymorphone 5-7.5 mg PO q 4-6h as needed will be administered for patients with a known sensitivity to Oxycodone. Acetaminophen 1000 mg PO will be given every 6 hours for the duration of the patients hospital stay. Ondansetron may be given in 2mg increments for the treatment of nausea. Analgesic medication total and area of hyperalgesia with a 225mN von Frey filament testing surrounding the wound will be obtained at 24 and 48 hours postoperatively.

Patients will be contacted by telephone at 8 weeks and 6 months after surgery and queried regarding presence of new pain since surgery and its interference with activities of daily living. In addition to current, worst, and average pain, the short McGill pain inventory and a validated neuropathic pain inventory (12) will be used.

Patients with ipsilateral hip pain at 6 months after surgery will come to the Geriatric General Clinical Research Center for physical examination, including mapping of location of pain as well as areas of hyperalgesia to von Frey filament testing and allodynia to brush with a cotton swab.

Safety Measures: Standard monitoring will be applied in the operating room, PACU, and hospital wards. We will record blood pressure every 5 min for 60 min, then every 30 min for 3 more hours, as well as the timing and dose of vasopressor administered to treat hypotension associated with spinal anesthesia.

Power Analysis:

Bases on preliminary data indicating an area of hyperalgesia at 48 hours of 66 ± 28 cm^2 (mean $\pm$ SD) in this surgical population, study of 50 subjects per group will allow us to detect a reduction in this area by as little as 18 cm^2. Additionally, based on estimates of residual pain at 6 months of 20% in this pre-screened population, study of 80 subjects will allow us to detect a reduction incidence to 4% or less.

The desirable power of the study is to be able to observe a difference in area of hypersensitivity surrounding the wound of 30% or greater. This is based on the correlation between area of hypersensitivity and likelihood of developing chronic pain. The study is powered at 80% to observe a difference in area of hypersensitivity of 18 cm2, which represents a 30% reduction from an average area of 60 cm2 observed in preliminary observations.

The statistical analysis plan is as follows. The primary outcome measure is area of hypersensitivity, and the two groups will be compared for this measure, which is obtained only once at 48 hr after surgery, by Student's t-test. Groups will be compared for all other measures by either Student's t-test or Mann Whitney U test according to normality of data. Analysis will be performed using SigmaStat, version 3.1.

Anticipated outcomes and Rationale:

We anticipate, based on our previous hysterectomy study, that area of hyperalgesia will be reduced in patients who receive intrathecal ketorolac and that ketorolac will also prolong the period of complete analgesia, reduce analgesic drug use after surgery, and numerically reduce the incidence of residual pain. This study will include two key outcome measures, postoperative hypersensitivity and residual pain, not included on our previous hysterectomy study.

This study is powered to examine a large reduction in the incidence of chronic pain, but primarily is powered to examine a much smaller reduction in the surrogate measure of area of hyperalgesia surrounding the wound. We chose hyperalgesia as the primary outcome measure since mechanical hypersensitivity is the measure used in the parallel animal studies, and since there is a close relationship between this measure and the incidence of chronic pain after surgery.

Risks and Benefits

Risks to be discussed include discomfort with needle and catheter insertion, risk of postdural puncture headache and spinal needle insertion, and potential period of pain if the study drugs are ineffective. The usual side effects and risks of spinal analgesia apply. These include itching, nausea, hypotension, unilateral pain relief, headache, bleeding, and infection. Risks associated with the use of ketorolac are: Bleeding when given orally or intravenously; in animals, spinal ketorolac caused no side effects except stomach ulcers when very large doses were given. This is a known side effect from large doses of ketorolac, much larger than those used in this study.

We will discuss options for headache treatment including oral caffeine and epidural blood patch at the time of original consent and again should a headache occur. These will be provided at no charge to the subject, paid for by departmental funds. All data acquired will remain confidential.

Volunteer Payment

Subjects will be paid $100 for completion of the study during their hospitalization. Should they elect to return to this facility for an examination of any residual pain after 6 months they will be compensated further in the amount of $50.

Data Safety Monitoring Plan

This study will be performed in the North Carolina Baptist Hospital, which includes monitoring and resuscitation equipment and trained nursing support staff. 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 with no reference to individuals in publications.

These are Phase II efficacy trials, and monitoring will be performed with a data safety monitoring board consisting of 2 physicians who are not involved in the study. Data and adverse events will be reported to these individuals, and reviewed on a regular basis. Unexpected or serious adverse events will also be reported to the WFUSM IRB and the FDA (since trials are being conducted under an IND). Serious adverse events will be reported to all of these groups and the data safety monitoring individuals within 24 hr and the trials halted until feedback is obtained from each. All additional sites will be responsible for reporting any adverse/serious adverse events to the WFUSM Data Safety Monitoring Committee. These events will be monitored and submitted to the FDA as required during annual reports.

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