WAKE FOREST
UNIVERSITY
HEALTH SCIENCES

Department/Section of *Anesthesiology*

THE EFFECT OF INTRATHECAL KETOROLAC ON MECHANICAL HYPERSENSITIVITY FOLLOWING SURGERY

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INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any benefit from being part of the study. There may also be risks associated with being part of research studies. You are being asked to take part in this study because you have are having a hip replacement. Your participation is voluntary. Please take your time to make your decision, and ask your study doctor or the study staff to explain any words or information that you do not understand. You may also discuss the study with your friends and family.
You are being asked to be in this study to help the investigators test a medication called Ketorolac. Ketorolac is commonly given by IV (into a vein) to treat certain types of pain. We believe that spinal ketorolac (given into the back near the spine) may prove to be an excellent painkiller for pain after surgery.

WHY IS THIS STUDY BEING DONE?

You have been scheduled to have total hip replacement surgery. The most common type of anesthesia for this surgery at this hospital is a spinal anesthetic. Anesthesiologists choose local anesthetic (Novocain-like drugs) for spinal anesthesia. They also often add other medicines to the local anesthetic to give patients better pain relief after surgery. These medicines often relieve pain longer when injected with the local anesthetic into your spinal fluid than they do given by mouth or by vein (IV). The investigators want to find out how long patients stay comfortable when a small dose of ketorolac (non-narcotic, pain reliever) is given into the fluid in your back near the spine. Ketorolac is commonly given by IV (into a vein) to treat certain types of pain. Ketorolac, is currently approved by the Food and Drug Administration (FDA; the department of the U.S. government that regulates research and the development of new medications), but it is considered to be an investigational drug in this study because it will be given to you in your spinal fluid.

In this study ketorolac will be compared to placebo. A placebo is a substance that is not thought to have any effect on your disease or condition. In this study you will receive the active study medication, ketorolac, or placebo which is not active. Placebos are used in research studies to see

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if the drug being studied really does have an effect.

How Many People Will Take Part in the Study?

About 50 people at Wake Forest University Baptist Medical Center will take part in this study. There will be about 100 people included at all sites across the country included in the study. You will not be able to participate in this study if you have severe renal (kidney) or hepatic (liver) disease, allergy to ketorolac, amino amide local anesthetic, or contraindications to spinal anesthesia. You will not be able to participate in the study if you routinely take narcotic pain medications for pain other than your primary hip pain. Additionally if you are taking Lyrica (Pregablin) or Gabapentin (Neurontin) we will ask you to stop taking these medications three days prior to your surgery day. If you are taking Ultram (Tramadol) we will ask you to stop taking this drug 24 hours prior to your surgery day. If you are taking other narcotic pain medications for your primary hip pain we will evaluate the dosage you are taking to see if you are eligible to participate in the study. Women will not be able to participate in this study if they are pregnant.

What Is Involved in the Study?

After reading the consent form and having your questions answered, if you then agree to participate in the study, the following things will occur.

Screening:
You will be required to provide a medical history and have a physical examination, including measuring your blood pressure, heart rate, and temperature. These assessments will be completed in the preoperative assessment clinic or in the Regional Anesthesia Holding Area. Baseline pain levels as well as anxiety levels will be obtained using a scale of 0-10, where 0 is no pain or anxiety at all and 10 is pain as bad as you can imagine or as anxious as you can imagine. We will also ask you to complete 2 short questionnaires that will tell us how you are doing and how pain is affecting your activities of your daily living.

Day of Surgery:
As with all patients having spinal anesthesia and surgery, an intravenous catheter (IV) will be started, routine monitors (blood pressure, oxygen monitor, and EKG) will be placed, and you will receive intravenous medicine to make you drowsy and lessen the discomfort of the spinal procedure. You will breathe extra oxygen through your nose.

The spinal procedure will be done in the usual fashion by anesthesiology faculty or by anesthesiology residents under the supervision of anesthesiology faculty. After turning on your side, your back will be washed with antiseptic, local anesthetic will be injected to numb your skin, and a needle will be placed in the lower part of your back. You will be randomized (like the flip of a coin) to receive the bupivacaine (numbing medicine) with or without ketorolac added to the mixture. You will have an equal chance of being placed in either group. Neither you nor the anesthesiologist will know which mixture you receive. This is done so that a fair evaluation of results can be made. This information is available to the researchers if needed in an emergency.

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Once the spinal needle is in place and just before the spinal medication is administered, a small amount (< ½ teaspoon) of cerebrospinal fluid will be withdrawn (this is the clear fluid that fills the cavities of the brain and covers the surfaces of the brain and spinal cord). This sample will be used to test for spinal prostaglandins (naturally occurring chemicals) in the spinal fluid, and the amount we take is half as big a volume as we inject with the numbing medicine. The medication to make you numb for your surgery will then be administered. When your surgery is over and you are in the recovery room you will receive the normal pain medications to help control your pain. While you are in the recovery room we will evaluate how numb you are and also follow your blood pressure every 30 minutes.

Once you are discharged from the recovery room to the general ward you will receive a device called a Patient Controlled Analgesia (PCA). This is a device that allows you to administer pain medication as needed to control your pain. The PCA will have either morphine (narcotic pain reliever) or hydromorphone (narcotic pain reliever) that you will administer to yourself to help you control your pain after your surgery. The PCA will be discontinued the first morning after your surgery. You will then receive pain medication by mouth that is prescribed by your surgeon. This is standard care for the procedure you are having done. At 24 hours and 48 hours after your surgery the area around your surgical incision will be evaluated to determine its sensitivity to light touch using an instrument called a von Frey filament. This is similar to a paint brush bristle. It will also be evaluated using a cotton swab to determine its sensitivity to its touch.

From the time of injection, we will measure how long the spinal block keeps you comfortable by seeing when you need your first dose of extra pain medicine. After the spinal procedure, other procedures may follow that are necessary for your anesthesia and surgery but not directly related to the study. Other nerve blocks may be performed to numb other nerves to your leg with a different long-acting local anesthetic mixture. After surgery, you will have other pain medicines available if you request them to help decrease your pain. The amount of this medicine will be recorded as part of the study.

Eight weeks and 6 months after your surgery

You will be contacted 8 weeks and again 6 months after your surgery by telephone by one of the study personnel for them to evaluate your level of pain since your surgery and to see if you are experiencing any new pain. The study person contacting you will be asking you questions from 2 short questionnaires that will tell us how you are doing and how pain is affecting your activities of daily living. At the 6 month phone call if you are continuing to experience pain related to your surgery, you will be asked to return to the Geriatric General Clinical Research Center (G-GCRC) at Wake Forest University Baptist Medical Center for your pain to be evaluated by one of the study staff. A physical examination will be performed and the area of your pain will be evaluated by testing its sensitivity to touch as was done the first 2 days after your surgery.

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Do you request that we send important medical findings from your study tests/exams to your personal physician? Even if you do not wish to have any of your medical information sent to your physician, you can still participate in this research study.

[ ] Yes	[ ] No

HOW LONG WILL I BE IN THE STUDY?

You will be in the study for the 48 hours following the completion of your surgery. We will contact you by telephone 8 weeks and 6 months after your surgery. You can stop participating at any time.

WHAT ARE THE RISKS OF THE STUDY?

Risks of anesthesia and surgery

There are risks involved in having anesthesia and surgery. These will be discussed and you will be asked to give consent for the type of anesthesia you choose, before you consider participation in the study. Needles for IVs can cause bruising and infrequently result in infection. Very rarely one can experience long term numbness, tingling or weakness after a block. When local anesthetics are injected into the body, it is possible to have a serious reaction at the time of injection, or about 15-30 minutes later when your body absorbs the most drug. This reaction can result in fainting, seizure (convulsion,) and serious drop in blood pressure or heart rate, and may occur about once in 2000 cases. Preparation to treat these reactions is a routine part of the anesthetic procedure. Mild backache is not uncommon following spinal anesthesia. Nausea is common after receiving morphine for postoperative pain in your vein. You may also experience discomfort with needle and catheter insertion and a risk of post-operative spinal headache. The usual side effects and risks of spinal analgesia apply. These include itching, nausea, hypotension, unilateral (one-sided) pain relief, headache, bleeding, and infection. 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, paid for by departmental funds**.** There is always a rare chance of nerve damage following a spinal anesthetic (1 in 10,000).

If you should develop nausea or vomiting, there are medicines that can be given to help. Since spinal anesthesia is a common (not experimental) procedure, all usual monitoring, sedation, and precautions will be taken to minimize your discomfort and risk of complications. There also may be other side effects that we cannot predict. You should tell the research staff about all the medications, vitamins and supplements you take and any medical conditions you have. This may help avoid side effects, interactions and other risks. Since this study involves the use of a placebo, there is a chance that you will not get any ketorolac as part of your spinal anesthesia. However, many patients having hip replacement surgery do not receive ketorolac as part of their nerve block either, and there is no additional risk associated with this.

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Risks of study drug, Ketorolac
Ketorolac given by mouth or by shot into the arm has been shown to increase the chance of bleeding, and, even though these doses are much larger than what you will receive, there could be a risk of bleeding from this medication. The safety of spinal ketorolac has been extensively examined in animals, with no evidence of any nerve damage or other lasting effects, and the FDA has approved this investigational study for humans. The study medication ketorolac is also approved by the FDA; however the way we will administer this medication (by spinal injection) and the effects that the medication has on your response to the testing are considered by the FDA to be investigational. The chance of having any permanent nerve injury, paralysis or death is extremely rare. Animals that received large doses of spinal ketorolac did develop kidney problems and stomach ulcers, and these side effects have been observed with large doses of ketorolac given by mouth or by shot in people as well. We will monitor you for problems that could possibly occur, such as changes in your blood pressure, how fast your heart is beating, and your urge to breathe. Kidney problems and stomach ulcers are extremely rarely associated with the dose we are using.

Taking part in this research study may involve providing information that you 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 your information safe.

Reproductive risks: Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, Norplant, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your physicians if you have any questions. Pregnant women are excluded from participation in this study. Because some methods of birth control are not 100% reliable, a pregnancy test is required at least 10 days from your last normal menstrual period, if you are a sexually active woman of childbearing potential.

Two medical experts who are not part of this study will be reviewing safety and other data for this study on a regular basis.

Storage of your spinal fluid for future research: If you agree to participate in this study, we will keep your spinal fluid to use for future research. This sample will be kept and may be used in future research to learn more about other diseases. Your sample will be obtained in the Regional Anesthesia holding area at Wake Forest University Baptist Medical Center. The spinal fluid sample will be used to test for spinal prostaglandins. If there is any spinal fluid remaining after we conduct the testing for spinal prostaglandins, the sample will be stored in the Pain Mechanisms Laboratory at Wake Forest University School of Medicine and it will be given only to researchers approved by Dr. James C. Eisenach. An Institutional Review Board (IRB) must also approve any future research study using your tissue sample. We will not conduct any

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genetic testing on your spinal fluid.

Your spinal fluid sample will be stored with a unique identifier and will not include any identifiable information about you such as your name, address, telephone number, social security number, medical record number or any of the identifiers outlined in the HIPAA Privacy Rule regulations. The unique identifier will be a randomly assigned number and only the principal investigator will have access to the code that links the unique identifier to you. Your name, address, social security number, etc. will never be disclosed to future researchers and neither will the code that links your identifiers to the sample.

The research that may be done with your spinal fluid sample is not designed to help you specifically. There is no personal benefit to you from taking part in this aspect of the research study. It might help people who have diseases at some point in the future, but it is not known if this will happen. The results of the research done with your spinal fluid sample will not be given to you or your doctor. These results will not be put in your medical records. The research using your spinal fluid sample will not affect your care. Your spinal fluid sample will be used only for research and will not be sold. The findings from this research may result in the future development of products that are of commercial value. There are no plans to share any of the profits with you which may occur as a result of this research.

The choice to let your spinal fluid sample be kept for future use is up to you. No matter what you decide to do, it will not affect your care in this study. If you decide now that your spinal fluid sample can be kept for research, you can change your mind at any time. Just contact your study investigator, Dr. James C. Eisenach at (336) 716-4498 and let him know that you do not want your spinal fluid sample used and it will no longer be used for research. Otherwise, the spinal fluid sample may be kept until it is used up or it is destroyed.

Permission to store your spinal fluid sample
In the future, people who do research may need to know more about your health. While the study investigator may give reports about your health, he will NOT be given your name, address, phone number, or any other identifying information about who you are, unless you agree to being contacted in the future.

_____ Yes I do want to participate in the storage of tissue samples portion of this study.
_____ NO I do not want to participate in the storage of tissue samples portion of this study.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

There may be direct benefit if you receive the ketorolac, it may provide you with additional pain relief after your surgery. By participating in this study, you may require less narcotic pain medication after your surgery, yet experience good pain relief. You may also be more alert and have less chance of experiencing nausea due to not requiring as much narcotic. It is hoped that the knowledge gained will be of benefit to other patients in the future.

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WHAT OTHER CHOICES ARE THERE?

If you do not participate in the study, you may still decide with your anesthesiologist to have spinal anesthesia and the procedure will be as we described above. The difference is that your anesthesiologist will know whether or not you are receiving ketorolac mixed in with the local anesthetic, and measuring the time and doses of extra pain medicines will not be done as part of the study after surgery. Other standard anesthetic choices used by doctors at this hospital are available and include general anesthesia (unconscious during surgery) with no nerve block, spinal anesthesia, or epidural anesthesia.

WHAT ABOUT THE USE, DISCLOSURE AND CONFIDENTIALITY OF HEALTH INFORMATION?

By taking part in this research study, your personal health information, as well as information that directly identifies you, may be used and disclosed. Information that identifies you includes, but is not limited to, such things as your name, address, telephone number, and date of birth. Your personal health information includes all information about you which is collected or created during the study for research purposes. It also includes your personal health information that is related to this study and that is maintained in your medical records at this institution and at other places such as other hospitals and clinics where you may have received medical care. Examples of your personal health information include your health history, your family health history, how you respond to study activities or procedures, laboratory and other test results, medical images, and information from study visits, phone calls, surveys, and physical examinations.

Your personal health information and information that identifies you ("your health information") may be given to others during and after the study. This is for reasons such as to carry out the study, to determine the results of the study, to make sure the study is being done correctly, to provide required reports and to get approval for new products.

Some of the people and agencies that may receive and use your health information are the institutional review board and representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any publication or presentation that may result from this study.

Information collected or created as part of the study may be placed in your medical record and discussed with individuals caring for you who are not part of the study. This will help in providing you with appropriate medical care. In addition, all or part of your research related health information may be used or disclosed for treatment, payment, or healthcare operations purposes related to providing you with medical care.

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

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When you sign this consent and authorization form you authorize or give permission for the use of your health information as described in the consent form. This authorization does not have an expiration date. You can revoke or take away your authorization to use and disclose your health information at any time. You do this by sending a written notice to the investigator in charge of the study at the following address:

James C. Eisenach, MD
Department of Anesthesiology
Wake Forest University Baptist Medical Center
Medical Center Boulevard
Winston-Salem, NC 27157

If you withdraw your authorization you will not be able to be in this study. If you withdraw your authorization, no new health information that identifies you will be gathered after that date. Your health information that has already been gathered may still be used and disclosed to others. This would be done if it were necessary for the research to be reliable. You will not have access to your health information that is included in the research study records until the end of the study.

This authorization is valid for six years or five years after the completion of the study, whichever is longer.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All the study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

You will be paid $100 for completion of the study during your hospitalization. Should you elect to return to this facility for an examination of your residual pain after 6 months then you will be compensated further in the amount of $50.00

To receive payment, you must provide your social security number, name and address so that we can comply with IRS (Internal Revenue Service) reporting requirements. When payments are reported to the IRS we do not let them know what the payment is for, only that you have been paid. If you do not wish to provide this information you can still take part in this study but you will not be paid.

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WHO IS SPONSORING THIS STUDY?

This study is being sponsored by The National Institutes of Health. The researchers do not hold a direct financial interest in the product being studied.

WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management, at (336) 716-3467.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call James C. Eisenach, MD at (336) 716-4498 (night time - page operator).

WHAT ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time if it is felt to be in your best interest to do so. You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, James C. Eisenach, MD at (336) 716-4498 (night time - page operator).

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, you should contact the Chairman of the IRB at (336) 716-4542.

You will be given a signed copy of this consent form.

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SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

_____

Subject Name (Printed)

_____ _____

Subject Signature Date/Time

_____ _____

Person Obtaining Consent Date

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