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Evaluating the Efficacy and Safety of Pregabalin in Total Knee Arthroplasty Patients with Central Sensitization

NCT# 05460871

Lee Kral, PharmD
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INFORMED CONSENT DOCUMENT

Project Title: Evaluating the Efficacy and Safety of Pregabalin in Total Knee Arthroplasty Patients with Central Sensitization

Principal Investigator: Lee Kral

Research Team Contact: Lee Kral [redacted]

This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you have grade 3 to 4 osteoarthritis and you are going to undergo a total knee replacement (arthroplasty).

The purpose of this research study is to compare pain and function after surgery between patients who receive a medication (pregabalin) to reduce central sensitization and those who do not receive the medication. We would like to see if the medication can offer better pain relief and better outcomes for patients who have central sensitization. We will also evaluate whether the medication might reduce the central sensitization itself. The medication we are going to use (pregabalin) is a nerve pain medication that has been used in patients undergoing knee arthroplasty in the past and is also used commonly for chronic pain associated with central sensitization.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 400 people will be recruited for this study conducted by investigators at the University of Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, you would be involved in the study for up to 6 weeks following surgery. It will include two visits with the surgery team and study staff

for pre-surgery work-up and a 6-week post-surgery follow-up (usually about 30 minutes per visit). You will also work with a physical therapist doing standard physical therapy appointments. These visits may vary from 1-3 times/week, depending on your needs. It minimally will include a pre-surgery visit, an evaluation within about a week after surgery with a physical therapist, and a visit at 6 weeks after surgery. These are usually about 30 minutes per visit.

The study team will also visit with you on the day of surgery. As part of this research study, if you receive study medication the study team will ask how you are faring with the study medication (e.g. If you are taking the study medication and if you are comfortable proceeding in the study). This will take about 15 minutes. The study team will also call you about 1 week after surgery to check in with you and ask some questions about how you are doing with your medications (usually about 10-15 minutes).

WHAT WILL HAPPEN DURING THIS STUDY?

If you meet the criteria to participate in the study and sign the consent form, you will complete surveys about your nervous system sensitivity to pain (Central Sensitization Inventory) and your risk of suicide (Columbia Suicide Severity Rating Scale). We will collect the lab value for kidney function from your medical record. If you have not had this lab drawn in the previous 3 months, we will draw your blood and check that lab value for purposes of the study. If you are a woman capable of becoming pregnant, we will also do a pregnancy test.

- If you still meet the criteria to participate in the study, you will complete a questionnaire about general demographic information, and surveys about your knee pain (Pain, Enjoyment of Life, and General Activity scale – PEG-3) and function (Knee Injury and Osteoarthritis Outcome Score – KOOS). These will be done in person in the clinic.
- You will meet with a physical therapist to evaluate your knee function. There are at least three assessments that are done. The Timed Up and Go (TUG) measures how long it takes to stand from a seated position and walk 3 meters (about 10 feet). The Stand-Up, Sit-Down (STS) measures how long it takes for you to stand up and sit down five times. The Patient-Specific Functional Scale assessment (PSFS) asks you about activities that you are unable to perform or having difficulty with and would like to improve. You may also be completing some basic exercises and learning how to use an assistive device for support after surgery.
- You will be randomized (assigned by chance to either receive the study medication or continue without the medication (usual care). You will have a 50/50 chance of receiving the study medication.
- If you are not randomized to the study medication group, you will proceed with the stand of care for total knee arthroplasty patients.
- If you are randomized to the study medication group, you will pick up your study medication at the UIHC Discharge Pharmacy. The team and the pharmacist will provide you with information about the medication and possible side effects.

Your dosing schedule can be found in the Table below.

	Pre-Surgery		Post-Surgery	Post-Surgery
Time	**Days 1-7**		**Days 1-7**	**Days 8-14**
7:00 AM	1capsule (75 mg)		2 capsules (150 mg)	1 capsule (75 mg)
7:00 PM	1 capsule (75 mg)		2 capsules (150 mg)	1 capsule (75 mg)

- Someone from the research team will meet with you on the day of surgery in the Day of Surgery Area (DOSA). They will answer any questions about continued participation in the study. For those in the study medication group, the research team will ask if you have completed the pre-surgery medication regimen and ask you about any possible side effects that you might be having with the medication. If you did not tolerate the medication, you will be released from the study and receive usual surgical care. The study team will also ask you to answer the suicide severity rating scale. If you feel that your mood is not stable or are thinking about suicide, they will immediately take you to get help. If this does occur, you will be released from the study and the surgery team will re-evaluate your care. They will remind you of the dosing of the medication after surgery. You will take your morning dose of study medication on the day of surgery. While in the hospital, nursing staff will give you the medications. Your dosing schedule can be found in the Table below.
- You will receive a phone call from the study pharmacist about 7 days after surgery to see how you are doing and see how much pain medication you are taking. She will also answer any questions that you might have. She will also ask you to complete the suicide severity rating scale. If you feel that your mood is not stable or are thinking about suicide, she will immediately call your local emergency services to get you help. If this does occur, you will be asked to stop the medication and will be released from the study. She will ask you about any other side effects with your study medication or other pain medication. Lastly, if you will be continuing the study medication, she will remind you of your last set of study medication doses. These can be found in the Table above.
- You will meet a physical therapist within a week after surgery. At your outpatient physical therapy evaluation, you will proceed with standard of care post-operative therapy and be re-evaluated on the 3 functional assessments (TUG, STS, and PSFS). You will work with your outpatient physical therapy team per the standard of care for total knee arthroplasty over the next 10 – 12 weeks (after the end of the study) as part of standard care.
- At your 6-week post-operative follow-up visit (either in person or via telemedicine) with the surgery and research teams, you will complete the surveys (KOOS, PEG-3 and CSI) again. If your follow-up is on telemedicine, we will send you secure REDCap links to your email. If you forget or are unable to complete these, we will contact you by telephone. You will also be asked about

how much opioid medication you are taking (if any). You will report any unused study medication and dispose of any remaining medication.

- At the 6-week point of time from the date of surgery, you will complete the functional assessments again with your physical therapist.
- The information reported on the KOOS, PEG-3, and CSI surveys as well as the physical therapy assessments and the amount of pain medication you need will be taken from your medical record and analyzed in this study. We will collect any lab values (e.g. kidney function, pregnancy test) that were checked. We will also review any information that you may have shared with the study team in phone calls or concerns that you may have had with regard to side effects.
- This will complete your study participation.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study. All of the side effects, if they occur, are expected to resolve within 72 hours of stopping the medication.

The possible risks or side effects from taking the study medication (pregabalin) are as follows. Other medications that at taken at the same time as pregabalin (like opioid medications) may increase the risk of these side effects

Less Likely / Less Common (10% - 35%)

Mild (these resolve when the medication is stopped)

- Fluid retention
- Weight gain
- Dizziness
- Uncoordinated walking
- Sedation
- Erectile dysfunction (males)
- Lack of libido
- Orgasm incapacity

Rare (less than 10%)

Life Threatening (this resolves when the medication is stopped but may require medical treatment)

- Swelling of the face/throat
- Suicidal thoughts

Serious (these resolve when the medication is stopped)

- Decreased platelet production
- Increased liver enzymes
- Skin redness
- Blisters and hives/rash

- Shortness of breath
- Wheezing

Mild (These resolve when the medication is stopped)

- Increased appetite
- Constipation
- Excessive salivation (saliva production)
- Nausea and/or Vomiting
- Dry mouth
- Fatigue or lack of energy or strength
- Headache
- Difficulty with memory, possible confusion, or disturbance in thinking
- Disturbance in speech
- Insomnia
- Tremor
- Blurred/Double vision
- Euphoria (feeling extremely happy or "high")
- Upper airway congestion
- Joint pain
- Muscle spasm

If your physician prescribes you opioid medication, there may be additional side effects to those listed above. Your care team will describe the potential effects to you.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because we may know if prescribing a medication to reduce central sensitization will improve pain and function following knee replacement surgery.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. You could have the surgical procedure without using the study medication. You can choose not to participate.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You will not have any additional costs for being in this research study. If you are randomized to receive the study medication (pregabalin), you or your insurance will not be charged for it. If we have to draw blood for the lab test or perform a pregnancy test, the study will also cover those costs.

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

The University and the research team are receiving no payments from other agencies, organizations, or companies to conduct this research study.

A grant was awarded by the Anesthesia Research Institute to cover the cost of the study medication. No one on the research team will receive a direct payment or increase in salary for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.
- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a university employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

To help protect your confidentiality, we will keep the information from the study secured so only authorized people working on this study can obtain. All paper data will be kept in a locked cabinet. Electronic data has password protections and stored behind UIHC approved data security systems. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document your

participation in research occurring in a University of Iowa Health Care facility. This documentation will be in either your medical record or a database maintained on behalf of the institution reflecting that you are participating in this study. The information included will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. A copy of the informed consent document will be available on this website. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires The University of Iowa Health Care to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study. Once The University of Iowa Health Care has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research related. Your signature on this Consent Document authorizes The University of Iowa Health Care to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written [redacted] However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your

identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

Leaving the study early may cause you to experience the following harms or discomforts: you may have more pain after your knee surgery.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers might decide to end your participation in this research study earlier than planned. This might happen because in our judgement it would not be safe for you to continue, or you developed an allergy to the study medication.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact [redacted] If you experience a research-related injury, please contact: [redacted]

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

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This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed):

_____

_____ _____
(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____
(Signature of Person who Obtained Consent) (Date)