STUDY: Perioperative Ketamine in Opioid-Tolerant Patients Undergoing Lumbar Spine Surgery: A Randomized, Double-blind, Place-controlled Trial

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IRB: STUDY19020144

NCT: 04220489

Informed Consent Form – Approved 01/04/2022

University of Pittsburgh

Department of Anesthesiology

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Perioperative Ketamine in Opioid-Tolerant Patients Undergoing Spine Surgery: A Randomized, double-blind, placebo-controlled trial

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SOURCE OF SUPPORT: P01 Pilot Program

Why is this research being done?
Individuals with chronic, or constant reoccurring, pain tend to need large doses of opioids (strong pain medications) to get through their daily lives. Overtime, however, they can develop opioid tolerance, or immunity, which makes the opioids less effective. These individuals can have, due to their opioid use, difficultly managing their pain during surgery and throughout their recovery. Standard of care for spine surgeries requires doctors to prescribe opioids to reduce post-surgical pain. Unfortunately, these individuals suffering from chronic pain and opioid tolerance tend to need larger doses of opioids than average for their pain management. However, there is evidence to suggest that ketamine, administered during surgery and/or during recovery may be the solution to this problem. There is also evidence to suggest that ketamine used in surgery and throughout recovery may have long term effects on individual opioid use. However, nearly all of the studies up to this point have investigated the short-term effects of ketamine on post-surgical pain and opioid use. This pilot study (small-scale preliminary research) will investigate the impact of surgical and recovery use of ketamine on pain and opioid use six weeks after surgery and will support a larger National Institute of Health (NIH) funded research trial.

Who is being asked to take part in this research study?
You are being asked to participate in a research study because you are scheduled to have cervical, thoracic, or lumbar spine surgery and you receive opioid prescriptions for back pain. Approximately 20 subjects will be screened and asked to participate in this study. The length of time that you would be asked to be a part of this study is up to 6 weeks.

You will be identified as a potential participant for this study during your visit to the UPMC Neurosurgical Clinic. If you are interested in learning more about the study, you will be given this consent form and asked to review it at home. You will receive phone call from research staff in the days following your clinic visit to determine if you would like to come in to the Posner Pain Research Clinic to provide consent and be enrolled in the study. If you think would like to provide consent to participate in the study, the study investigator will ask you your opioid dose regimen to determine a good time to come to the Posner Pain Research Clinic to review and sign the informed consent with a study doctor. After you discuss the study with the study doctor and sign the informed consent, you will undergo Screening Visit procedures.

What procedures will be performed for research purposes?

Screening Visit:
The screening process will be completed by the investigators with the Anesthesia Department.

You will be asked to come to the Posner Pain Clinic in the Aiken Medical Building on a date after your clinic visit but before your day of surgery for this Screening Visit. The address for the Posner Pain Clinic is 532 South Aiken Avenue, Suite 407, Pittsburgh PA 15232. At this screening visit you will be asked to review your current pain medication use and complete seven health questionnaires.

In addition to reporting on your current pain medications and completion of the health questionnaires, additional procedures that will take place at this Screening Visit include completing McGill Pain Questionnaire-Short form after the administration of a pain threshold and tolerance test called a Cold-Pressor Pain Sensitivity Test. The total time for the visit is approximately 2.5 hours.

Health Questionnaires
At your Screening Visit, you will be asked to complete seven health questionnaires that will ask you about your pain level, pain tolerance, mental health, and social activities. These questionnaires will take approximately 20-30 minutes to complete. You will be asked to repeat these same questionnaires in recovery with your surgeon, and during your 6-Week Follow-Up visit.

Pain Scale
You will be verbally asked to rate your pain on a scale of 0 to 10, 0 being no pain, and 10 being the most severe pain imaginable. For this research, this will be done at the Screening Visit, while you are in the hospital (from the time you arrive in the PACU until 72 hours after surgical wound closure), at your Post-Operative Visit (10-14 days after your surgery) with your surgeon, and at your 6-Week Follow-up Visit.

Medical Record
We will be looking into your electronic medical record for medical history and other information including the amount of narcotics and non-narcotic analgesics that were administered to you in the operative and postoperative period. This information will be recorded from the time you are in the operative room up until 72 hours after wound closure.

Cold-Pressor Pain Sensitivity Test

Study doctors will work with you to determine your pain-medication doses, and you will be asked to come into the Aiken Medical Building thirty minutes before your pain medication dose is due. You will be asked to bring with you your upcoming dose of pain medication. Prior to taking your pain medication, you will then be administered a Cold-Pressor Pain Sensitivity test. For this test, you will place your non-dominant hand in a bowl of ice water up to the wrist. Pain threshold is measured as the time in seconds that it takes for you to first report the sensation of pain in your hand that is in the ice water. Pain tolerance is measured by as the time in seconds that it takes for you to withdraw your hand from the ice water because it has become too uncomfortable for you to keep their hand in the ice water any longer. A cut-off of four minutes will be imposed to limit the potential for any tissue damage. At this time, you will be asked to remove your hand from the ice water, even if you feel that you could keep your hand in the ice water for longer. Pain threshold, tolerance and cut-off will be recorded using a stop watch. Heart rate and blood pressure will be recorded before and after the cold-pressor test. Once the cold pressor test is completed, the McGill Pain Questionnaire-Short form will be administered. After this questionnaire is complete, you will take the dose of opioid medication you have brought from home and are scheduled to receive and will wait in the clinic for 30 minutes for the pain medication to take effect. Once the 30 minutes is complete, the cold-pressor test will be repeated, heart rate and blood pressure collected before and after, and McGill Pain Questionnaire-Short form will be administered again.

You will be compensated $50 for this Screening Visit.

Surgical Visit

On your day of surgery, you will be randomized to receive either ketamine or placebo during and after surgery for 24 hours. You cannot decide whether you will receive a ketamine or placebo for pain management. This will be randomly decided, like a lottery. There is a fifty-fifty chance of you being in either group.

If you agree to participate, you will be in one of the two groups;

Group #1 – “Ketamine” Group:
You will receive intravenous (IV) ketamine 15 minutes after induction of general anesthesia. Thereafter, a continuous IV drip of low dose ketamine will be run to conclude at 24 hours after the end of the surgery. The use of Ketamine will not change the type of anesthesia you get in the operating room. After the surgery, when you are in recovery, you will receive pain medications in

addition to the ketamine to help control your pain, and a Patient Controlled Analgesia (PCA) will be started for you, where you will be able to give yourself pain medicine as needed by the press of a button.

Group #2 – "Placebo" Group:
You will receive an intravenous infusion of normal saline (placebo) 15 minutes after induction of general anesthesia. Thereafter, a continuous IV drip of saline will be run to conclude at 24 hours after the end of the surgery. The use of this saline will not change the type of anesthesia you get in the operating room. After the surgery, when you are in recovery, you will receive pain medications in addition to the placebo to help control your pain, and a Patient Controlled Analgesia will be started for you, where you will be able to give yourself pain medicine as needed by the press of a button.

Each day, an Anesthesiologist or another member of the Acute Interventional Perioperative Pain Service (AIPPS), will visit you. They will ask you to rate your pain on a scale of 0-10. If your pain is not well-controlled, the AIPPS team are on call 24 hours a day to make adjustments to your care to ensure you are comfortable. The amount of pain medicine that you need will be part of the information collected for the research.

As is standard of care, pain will be monitored every four hours, except during the night when you are asleep. We will use a scale from 0-10, 0 being no pain, 5 being moderate pain and 10 being the worst imaginable pain. We will also ask you to score pain at its best and worst over the period since you were last asked. The amount of pain medication you use while in the hospital will also be collected.

Ketamine is FDA approved for anesthesia. Ketamine has been approved and used for surgical and post-surgical pain management by UPMC since 2009; it is, however, not FDA approved for pain management.

Post-Operative Visit

As is standard after this surgery, you will follow-up at Neurosurgery clinic at 10-14 days postoperatively. At this time you will be asked to complete the 6 health questionnaires again (Pain Medication review form, the Pain Catastrophizing Scale (PCS), the PROMIS Emotional Distress-Anxiety Short Form and PROMIS Emotional Distress-Depression Short Form, Brief Psychiatric Rating Scale and Neuro-QoL Short Form v1.1 - Satisfaction with Social Roles and Activities) and we will review your overall recovery and ask if you have had any complications since being discharged from the hospital. This visit will take approximately 1 hour. If for any reason, a visit in the clinic is not conducted during this time frame, you will be contacted by a study team member via phone to complete the above assessments.

6-Week Follow-up Visit

You will be asked to come to the Posner Pain Clinic in the Aiken Medical Building approximately 6-weeks after your surgery for a 6-Week Follow-Up Visit. The address for the Posner Pain Clinic is *532 South Aiken Avenue, Suite 407, Pittsburgh PA 15232*. The procedures that will take place at this 6-Week Follow-Up Visit include completing a pain questionnaire after the administration of a pain threshold and tolerance test called a Cold-Pressor Pain Sensitivity Test. The total time for the visit is approximately 1.5 hours.

Cold-Pressor Pain Sensitivity Test

Study doctors will work with you to determine your pain-medication dose regimen, and you will be asked to come into the Aiken Medical Building thirty minutes before your pain medication dose is due. You will be asked to bring with you your upcoming dose of pain medication. Prior to taking their pain medication, you will then be administered a cold-pressor pain sensitivity test, in a manner identical to that use during the pre-operative assessment. In addition to the McGill Pain Questionnaire-Short form, the Pain Medication review form, the Pain Catastrophizing Scale (PCS), the PROMIS Emotional Distress-Anxiety Short Form and PROMIS Emotional Distress-Depression Short Form, Brief Psychiatric Rating Scale and Neuro-QoL Short Form v1.1 - Satisfaction with Social Roles and Activities will also be completed.

You will be compensated $50 for this 6-week follow-up visit.

What are the possible risks, side effects, and discomforts of this research study?

You will be asked questions regarding your pain level, and you will also fill out health questionnaires for the study. This information will be considered protected health information and will be kept confidential per HIPAA privacy act. There is, however, a possibility of breach of confidentiality. That is, in very rare cases, people not associated with this research study may inadvertently see your identifiable research results.

We will do everything in our power to prevent this from happening by keeping all research records in locked files, and identify medical information by a research record number, rather than by your name or social security number. The codebook file containing your name and number will be kept secure by the Study Team.

There are risks and side effects of your surgery and anesthesia that your surgeon and anesthesiologist will discuss with you. These are separate from this study. You will be required to sign UPMC's surgical consent form and anesthesia consent form in order to have your spine surgery. Again, these risks, side effects, and discomforts would still be present without participation in this study.

For your information, there are risks associated with medications and tests in this study. You can speak to your anesthesiologist about these if you want more information.

Risks of Ketamine

Infrequent Risks:
- Blurred vision
- Confusion
- Drowsiness
- Increased or decreased blood pressure or heart rate
- Mental or mood changes
- Nausea and vomiting
- Dreams, hallucinations and delirium

Rare Risks:

- Liver injury
- Allergic Reaction (rare)

With respect to the risk of liver injury, there have been reports of reversible, elevated liver enzymes associated with long term, repetitive use of high dose ketamine, although there are currently no reports of liver injury associate with low dose ketamine, which is used in this study. That being said, you are instructed to notice the following signs and symptoms of liver injury, and report to physicians with the information of previous exposure of ketamine infusion:

- Discolored skin and eyes that appear yellowish
- Abdominal pain and swelling
- Itchy skin that doesn't seem to go away
- Dark urine color
- Pale stool color
- Bloody or tar-colored stool
- Chronic fatigue
- Nausea
- Loss of appetite

If you are randomized to the ketamine group, you will receive ketamine infusion at the in-patient units during your hospital stay. Should any complications associated with the medication occur, an emergency cart is readily available at the units. Acute Interventional Perioperative Pain Service (AIPPS), which is responsible for your postoperative pain management, is available 24/7 to address any associated issues.

Risks of completing questionnaires

- Boredom
- Frustration
- Embarrassment

Risks of Cold-Pressor Test

Rare Risks:

- Excessive painful sensation
- Tissue damage as a result of painful stimulation

What are possible benefits from taking part in this study?

Subjects with chronic pain and opioid dependence may experience better analgesia in the postoperative period.

What treatments or procedures are available if I decide not to take part in this research study?

Pain management plans for your surgery are available to you whether or not you participate in this study. The anesthesiologist who will have direct care in your case will discuss alternative treatments for pain control with you.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?

You will be promptly notified if, during the conduct of this research study, any new information develops which may cause you to change your mind about continuing to participate.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
You will not be billed for research procedures.

Some of the services you will receive during this study are considered to be "routine clinical services" that you would have even if you were not in the study. These services will be billed to your health insurance company or you, if you do not have health insurance. You will be responsible for paying any deductibles, co-payments or co-insurance that are a normal part of your health insurance plan.

You may want to get more detailed information about what "routine clinical services" your health insurance is likely to pay for. Talk to a member of the study staff and/or a UPMC financial counselor to get more information.

Alternative treatments
If you do not participate in this study, you will likely still receive a post-operative pain management plan that is standard of care at Presbyterian Hospital.

Will I be paid if I take part in this research study?
You will be paid $50 upon completion of the Screening Visit
You will be paid $50 upon completion of the 6-Week Follow-Up Visit

Who will pay if I am injured as a result of taking part in this study?
University of Pittsburgh researchers and their associates who provide services at UPMC (UPMC) recognize the importance of your voluntary participation in their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

Who will know about my participation in this research study?
Any information about you obtained from this research will be kept as confidential (private) as possible. All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. You will not be identified by

name in any publication of the research results. We will attempt to preserve your medical record and participation in this study as confidentially as possible, but breach of confidentiality is a risk of participation. In the future, the investigators may decide to share data with other investigators both within and outside of this institution. If that were to occur, we would de-identify all of the information prior to sharing any data in this way.

Will this research study involve the use or disclosure of my identifiable medical information?

This research study will involve the recording of past, current and/or future identifiable (pertaining to only you) medical information from your hospital and/or other health care provider (e.g. physician office) records. This information that will be recorded will be limited to diagnostic information, lab results, medications, and medical history. The information will be used to determine your eligibility for this study and to follow your care once you are enrolled in the study.

This research study will result in identifiable information that will be placed into your medical records held at UPMC facilities. The nature of the identifiable information resulting from your participation in this research study that will be recorded in your medical record includes response to study treatment including adverse events (side effects).

Who will have access to identifiable information related to my participation in this research study?

In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study:

Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

Authorized representatives of the study team, who are also part of the Department of Anesthesiology and the Acute Interventional Perioperative Pain Service, will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives of the U.S Food and Drug Administration (FDA) and other regulatory agencies may review and/or obtain your identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for an indefinite period of time. Your research information may be shared with investigators conducting other research. This information may be identifiable.

Per University of Pittsburgh policy all research records must be maintained for at least 7 years following final reporting or publication of a project.

May I have access to my medical information that results from my participation in this research study?

In accordance with the UPMC Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information resulting from your participation in this research study) contained within your medical records filed with your health care provider.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. 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.

There is no plan to share study results with participants at this time.

Is my participation in this research study voluntary?

Your participation in this research study is completely voluntary. Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your anesthesiologist is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the

conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your anesthesiologist.

May I withdraw, at a future date, my consent for participation in this research study?

You may withdraw, at any time, your consent for participation in this research study. Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

If you decide to withdraw from study participation after you have received the study drug, no study assessments will be done after your withdrawal.

Rights to revoke authorization/how to revoke

You can always withdraw your authorization to allow the research team to review your medical records by contacting the investigator listed on the first page and making the request in writing.

Implications of revocation of authorization

If you do so, you will no longer be permitted to participate in this study. Any information obtained from you up to that point will continue to be used by the research team

If I agree to take part in this research study, can I be removed from the study without my consent?

It is possible that you may be removed from the research study by the researchers if, for example, you have an unexpected change, complication in your anesthesia or surgery or serious adverse reaction. If you are withdrawn from participation in this research study, you will still be treated for your post-surgical pain. Please consult your surgeon or anesthesiologist if you have any further concerns.

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VOLUNTARY CONSENT

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by a qualified individual or by the principal investigator listed on the first page of this consent document at the telephone number given. I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator.

I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

By signing this form, I agree to participate in this research study and to authorize Dr. Chelly and the members of his research team to access my medical records and extract research data from them, as described in this document. Dr. Jacques Chelly will sign this consent and a copy of this consent form will be given to me. Also, I further certify that no research component of this protocol was begun until after the consent form was signed.

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Participant's Signature

_____ _____

Printed Name of Participant Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Printed Name of Person Obtaining Consent Role in Research Study

_____	_____
Signature of Person Obtaining Consent	Date