STUDY TITLE: Effectiveness of Clonidine, Dexmedetomidine, and Fentanyl Adjuncts for Labor Epidural Analgesia: A randomized controlled trial (CLASSIER)

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Informed Consent Document: 28 MAR 2023

University of Pittsburgh

INFORMED CONSENT STATEMENT AND AUTHORIZATION FOR RESEARCH

Dexmedetomidine Compared to Clonidine and Fentanyl as an Adjuvant to Epidural Solution for Labor Analgesia

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ABOUT THIS RESEARCH

You are being asked to participate in a research study. Scientists do research to answer important questions which might help change or improve the way we do things in the future.
This consent and authorization form will give you information about this study to help you decide whether you want to participate. It is your choice whether or not you want to be in this research study. Please read this form, and ask any questions you have, before agreeing to be in this study.

KEY INFORMATION

Research studies include only people who choose to take part. The study team will explain the study to you and will answer any questions you might have. You should take your time to make your decision.

The purpose of this study is to compare how well medications for pain during childbirth work. In this study, one of three medications will be added to the main drug that we will use for your epidural. (An “epidural” for childbirth is when we inject pain relieving medicine in an area around your spinal cord, known as the epidural space. It helps relieve labor pain.) In the United States (US), the usual medications for epidurals are to combine one medicine, called ropivacaine, with a small dose of an opioid, called “fentanyl” which is another type of pain reliever. This solution is then injected to a space between your vertebrae of your spine (called the epidural space) via a narrow tube called a catheter. This combination usually works very well.

However, some patients might benefit from an epidural protocol without opioids. For example,

- patients who are treated with opioids for chronic pain might develop opioid tolerance (when a larger dose of medication is needed to obtain the same pain reducing effect)
- patients with a known allergy to the opioid can't use them in their epidural mixture.
- patients who *have* an opioid use disorder may also develop opioid tolerance. In these patients, using opioids for epidural pain management is not the best approach.

Our study will compare ropivacaine with one of three medications

- A group that gets ropivacaine and fentanyl – what is called "usual care"
- A group that gets ropivacaine with a drug called clonidine and
- A group that gets ropivacaine with a drug called dexmedetomidine.

The other two drugs can substitute for the fentanyl in the epidural solution and offer similar pain relief.

Risks associated with this study include:

- Risks associated with epidural labor analgesia (Fetal heart rate changes associated with rapid analgesia (10-20%))
- Risks of the study drugs may differ but include low blood pressure, high blood pressure, low heart rate, rapid heart rate, drowsiness, inability to walk until the effect of the epidural wears off
- Likely: inconvenience/discomfort associated with answering study related questions
- Less likely: potential breach of confidentiality, meaning someone could see your private information that is not authorized.

Steps have been taken to minimize these risks as much as possible.

We hope that the information obtained in this research study will help us to develop effective, safer, and tailored treatment options for women requiring epidural analgesia during labor. There will be no direct benefits to you for your participation in this study. If you decide not to participate in this research, you will receive your normal routine obstetric and pain management care. Whether you decide to participate in this research, there will be no change in the routine care for you and your baby during and after your delivery.

Please review the rest of this document for more details about this study and the things you should know before deciding whether to participate in this study.

WHO IS BEING ASKED TO PARTICIPATE?

We are asking you if you want to be in this study because you:

- Are in labor and intending to deliver vaginally
- Are planning on asking for epidural analgesia

HOW MANY PEOPLE WILL TAKE PART?
Up to 200 women and their newborn babies taking part in this study.

WHAT WILL HAPPEN DURING THE STUDY?
Upon admission to Magee, we will collect some information about your medical history. This information may be collected from you or your medical record.

The research team will explain the protocol to you during a first visit and leave you this informed consent form. You will have time to read this form and choose if you desire to participate in this study. If you decide to participate in the study, the research team will be called prior to your epidural medications being decided.

The technique for initiation of epidural analgesia is the same, whether you decide to participate in our study or not. The catheter will be installed by a qualified anesthesiologist upon your request.

Your participation involves that you get a medication added to the local anesthetic solution depending on the group to which you are assigned. The nurses and doctors will not know which group you are assigned. This information is confidential, and the medication is prepared by the pharmacy so that they cannot be identified at bedside.

Here are the three epidural solutions included in this protocol

1. Ropivacaine 0.1 % (local anesthetic) and Fentanyl (opioid) – this is usual care.
2. Ropivacaine 0.1% (local anesthetic) and Clonidine
3. Ropivacaine 0.1% (local anesthetic) and Dexmedetomidine

These medications are all approved by the US Food and Drug Administration and are being used off- label as is typical in clinical care for labor epidural analgesia.

Once the epidural catheter is installed, a large initial dose of medication will be administered through the catheter as this is the standard protocol in our institution. The medications in the bolus dose will vary depending on your group. After the bolus dose is given, an epidural pump will allow pain medication to flow through the catheter in your epidural space. This medication will be a standardized local anesthetic medication (ropivacaine with fentanyl) until the time of delivery.

REDOSE PROTOCOL :

Re-doses will be done for patients requesting them per current standard of care practice. Epidural re- doses will be protocolized through a "re-dose algorithm" to standardize breakthrough pain management.

Protocolized re-dosing is a measure that will standardize the practice amongst our team of providers. Usually, when a patient is complaining of discomfort, the clinical team will be called at bedside to perform an evaluation, including a level assessment. Following this assessment, the provider at beside will "re-dose" the epidural (inject some additional medication) so that the patient achieves a better level of comfort. Given the large number of providers on our team, there may be some variance in the management and in the doses that are administered for these epidural "re-doses". The standardization of epidural boluses during this clinical trial ensures uniform and safe practice for breakthrough pain management after epidural initiation.

A person from the research team will come and collect information from you or your medical record at the time points below. This will include:

- blood pressure
- heart rate
- Amount of oxygen in your blood
- your rating of pain on a scale of 0-10
- your rating of how sleepy you are
- capacity to move your legs

This information will be collected by the study team at 5 minutes, 10 minutes, 15 minutes, 30 minutes, 60 minutes, 90 minutes, and 120 minutes after epidural initiation and again shortly after you deliver. We will also collect information about the type of delivery, how long your labor lasts, if you need any additional medication if your heart rate slows down- this is standard of care for epidurals.

We will also collect information from the medical record about your newborn, including the APGAR scores (this involves assessing the newborn's Appearance, Pulse, Grimacing (facial expression), Activity and Respiration (breathing), their heart rate, or if there are any signs of an abnormal heart rate.

WHAT ARE THE RISKS OF TAKING PART IN THE STUDY?

The medications evaluated in this study have documented side effects. The usual monitoring used in the labor and delivery room will detect these side effects. Normally, after the epidural is started, you are monitored for low blood pressure and low heart rate. There is also fetal monitoring since epidural medication can sometime induce some changes in your baby's heart rate. The usual practice in our center is to monitor blood pressure, oxygen level in your blood and heart rate for 30 minutes after the epidural is started. Your baby's heart rate is also monitored from epidural start until delivery.

The medications that we are studying in this protocol are two alternates in comparison to the standard of care (opioid). These two medications are called Clonidine and Dexmedetomidine. Here are the documented side effects that you might experience.

Research Activity	**Clonidine epidural administration**
Common Risks	Low blood pressure Low heart rate
Infrequent Risks	Sleepiness Temporary inability to move legs
Other Risks	Low blood pressure when standing up Nausea Vomiting Mild skin itching Rash (itching) Dry mouth Mild changes in your liver function tests that are temporary

Research Activity	**Dexmedetomidine epidural administration**
Common Risks	Low blood pressure Low heart rate
Infrequent Risks	Sleepiness Temporary inability to move legs
Other Risks	Nausea Vomiting Mild skin itching Dry mouth Breathing rate slowed Constipation that may last a few hours or days

Research Activity	Fentanyl epidural administration (this is usual care)
Common Risks	Drowsiness Changes in heart rate Stomach pain Anxiety
Infrequent Risks	Sleepiness Hallucinations Agitation Muscle stiffness Loss of coordination Loss of appetite Seizures
Other Risks	Nausea Vomiting Mild skin itching Dry mouth Breathing rate slowed Constipation that may last a few hours or days

Risks of local anesthesia (lidocaine, bupivacaine, ropivacaine)
Lidocaine, Bupivacaine and Ropivacaine are three medications that are widely used as local numbing agents to control pain for placement of the epidural catheter in your back. The catheter then allows medications to be administered to the epidural space in your spine (standard of care) to control pain during childbirth.

The chance of you having a "Adverse" or negative reaction to these drugs being administered to you are very rare. If there was an overdose (too much drug ordered and/or given), or if the drug was inadvertently injected directly into a blood vessel, those results can be serious. The effects of systemic overdose and unintentional blood vessel injections would need to be distinguished from the physiological effects of the nerve block itself (for example, a decrease in blood pressure and heart rate during epidural anesthesia).

Common risks of local anesthetics administered between the vertebrae are low blood pressure and urinary retention. If local anesthesia was injected into a blood vessel, you are at risk of developing signs and symptoms of problems with your central nervous system and heart rate and rhythm (see table below).

Research Activity	**Lidocaine, Bupivacaine and Ropivacaine epidural administration (this is usual care)**
Common Risks	Low blood pressure, Urinary retention
Infrequent Risks	**Nervous system disorders :** Signs and symptoms of central nervous system toxicity (seizures, tingling sensation around the mouth, numbness of the tongue, visual disturbances, tremor, tinnitus [buzzing sound in your ears], slurred speech, loss of consciousness) **Cardiovascular manifestations** (decreased cardiac output, decreased heart rate, abnormal heart rate or rhythm)
Other Risks	**Gastrointestinal disorders :** nausea, vomiting Nervous system disorders: paresthesia (abnormal sensation of the skin [tingling, pricking, numbness]), dizziness, nerve injury Immune system : allergic reaction

A risk of answering surveys is that you may be uncomfortable while answering the questions. While completing the survey, you can skip any questions that make you uncomfortable or that you do not want to answer.

You may be withdrawn from the study without your consent if there is an accidental dural puncture during the start of your standard of care epidural or if the epidural catheter has to be replaced within 60 minutes of starting the procedure.

WHO WILL PAY FOR MY TREATMENT IF I AM INJURED?

If you believe that the research procedures have resulted in an injury to you, immediately contact the Principal Investigator who is 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. Your insurance provider may be billed for the costs of this emergency treatment, but none of those 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. At this time, there is no plan for any additional financial compensation. You do not waive any rights by signing this form.

WHAT ARE THE BENEFITS OF TAKING PART IN THE STUDY?

There is no direct personal benefit to you from taking part in this study, but we hope to learn things that will help other people in the future. There may be an advantage to one of the pain medications that we are testing that you would benefit from if assigned to that group.

WILL I BE PAID FOR PARTICIPATION?

You will be paid a total of $20 for participating in this study. You will be paid on a reloadable debit card. Your name, address, and social security number are needed to create or load the card and this information will be released to the Accounting Office. All compensation is taxable income to the participant. If you receive $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in research, but the IRS requires that 24% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 76% of the expected payment.

WILL IT COST ME ANYTHING TO PARTICIPATE?

We expect neither you, nor your insurance provider will be charged for the cost of the procedures performed only for the purposes of this research study. You and/or your insurer will be billed in the usual manner for your standard medical care.

HOW WILL MY INFORMATION AND SPECIMENS BE USED?

The study team is asking your authorization to collect information from your and your baby's medical records to do this study. This may include:

1. Collecting information to make sure you meet the criteria to be in this study, including that you do not have any serious illness,
2. Gathering information about medical history to include in the research data,
3. To inspect and/or copy your research records for quality assurance and data analysis
4. Collecting information about your epidural, your delivery and your infant that is routinely collected with an epidural

The data collection will include information about your health and your delivery. Those records may contain information such as demographic data, height, weight, and gestational age. We will also collect information on the progression of delivery, vital signs, progression of labor, pain scores and data regarding the baby's health at delivery (APGAR scores, blood pH in the cord blood). This information will be available for an indefinite period of time and your authorization does not expire. At these same time points, we will ask you what your level of pain is. We will also evaluate if you have nausea, vomiting, itching of the skin and shivering.

The following individuals and organizations may access or use your identifiable health information:

- The researchers and research staff conducting the study
- Representatives of the University of Pittsburgh Office of Research Protections for the purpose of monitoring the conduct of the research.
- Regulatory agencies as required by law.
- State or Federal agencies with research oversight responsibilities, including but not limited to:
    - Office for Human Research Protection (OHRP)
    - U.S Food and Drug Administration (FDA)

A description of this clinical trial will be available on ClinicalTrials.gov, as required by U.S. 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.

HOW WILL MY INFORMATION BE PROTECTED?

Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. No information which could identify you will be shared in publications about this study.

We will store most of your study information with your name or other things that could identify you removed. Otherwise, you will be assigned a random ID number which will only be known known to study team members. This information will be stored on departmental computers that are protected by the UPMC firewall and required passwords to access. Access will be limited to study team members only. The document that links your random ID number to your name will protected by the PI, Dr. Lim. Paper records, like your consent form, will be in a locked file in a locked office.

FUTURE DATA USE

We may share de-identified data with other researchers in the future.

WHO SHOULD I CALL WITH QUESTIONS OR PROBLEMS?

For questions about the study, please contact the primary coordinator during normal business hours, Thomas Troyan at 412-641-2179. For emergencies, the PI, be contacted at 412-641-1000 Please ask for Dr. Lim to be paged.

WHAT IF I DO NOT PARTICIPATE OR CHANGE MY MIND?

After reviewing this form and having your questions answered, you may decide to sign this form and participate in the study. Or you may choose not to participate in the study. This decision is up to you. If you choose not to participate in this study or change your mind after signing this document, it will not affect your usual medical care or treatment or relationship with UPMC or the University of Pittsburgh.

If you choose to withdraw your authorization for use and disclosure of your protected health information from your medical record, you must do so in writing by notifying Dr. Lim at:

Dr Grace Lim
Department of Anesthesiology & Perioperative Medicine 300 Halket Street Suite 3510
Pittsburgh, PA 15213

If you withdraw your authorization, you will not be able to continue in this study. However, even if you cancel this authorization, the research team, research sponsor(s), and/or the research organizations may still use information about you that was collected as part of the research project between the date you signed this document and the date you cancelled this authorization. This is to protect the quality of the research results. Otherwise, this authorization remains valid until the research ends and required monitoring of the study has been completed.

Per University of Pittsburgh policy, all research records must be maintained for at least 7 years following final reporting or publication of a project and for children until they reach age of 25.

The researchers may stop your participation in the study even if you do not want to stop if the study doctor determines that it is in your interest. You will be told about new information that may affect your health, welfare, or willingness to stay in the study.

PARTICIPANT'S CONSENT AND AUTHORIZATION

The above information has been explained to me and all my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any part of this research study during this study. Any future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) 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 Human Research Protection office, University of Pittsburgh (1-866-212- 2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations that occurred during my participation. By signing this form, I consent to participate in this research study and provide authorization to use and share my and my child's medical records. A copy of this consent form will be given to me.

Printed Name of Infant Date / Time

Signature of Parent

Participant's Printed Name Date / Time

Participant's Signature

Printed Name of Person Obtaining Consent
Date / Time

Signature of Person Obtaining Consent