Post-cesarean analgesia with epidural morphine following epidural 2-chloroprocaine

NCT04369950

Version Date: 05/04/2020

Protocol Title:	Post-cesarean analgesia with epidural morphine following epidural 2chloroprocaine
Principal Investigator:	Linden O. Lee
Co-Investigators:	Ana-Lisa Ramirez-Chapman, Maya Suresh
Study Coordinator:	N/A
Population:	80 pregnant female subjects (40 subjects in two groups), age 18-50, scheduled for cesarean delivery of live singleton birth at MHH-TMC or LBJ Hospital, with a functional labor epidural in place
Number of Sites:	MHH-TMC and LBJ Hospital
Study Duration:	March 2020-March 2021
Subject Duration:	24 hours

General Information

An investigation into whether or not 3% 2-chloroprocaine administered via epidural for cesarean delivery antagonizes epidural morphine resulting in diminished post-operative analgesia.

Background Information

Patients with labor epidurals in place who require cesarean delivery are typically dosed with either 2% lidocaine with 1:200,000 epinephrine or 3% 2-chloroprocaine to achieve surgical anesthesia. The utility of 3% 2-chloroprocaine lies in that it has a more rapid onset of action compared to 2% lidocaine with 1:200,000 epinephrine, making it a valuable medication in emergent cesarean deliveries when trying to avoid general anesthesia. However its duration of action is shorter (30-45 minutes) compared to that of epidural 2% lidocaine with 1:200,000 epinephrine (60-120 minutes). Neuraxial morphine is frequently administered during cesarean deliveries and provides post-operative analgesia for approximately 24 hours.

Studies have suggested that administration of epidural 3% 2-chloroprocaine prior to epidural morphine results in decreased effectiveness of epidural morphine.[1,2] Karambelkar et al. compared patients given epidural 3% 2-chloroprocaine to those given epidural 2% lidocaine with 1:200,000 epinephrine prior to epidural morphine. As epidural 3% 2-chloroprocaine has a duration of action of 30-45 minutes and the onset time of epidural morphine is at least 1 hour, Karambelkar et al. re-dosed those receiving epidural

[1] Karambelkar DJ, Ramanathan S. 2-Chloroprocaine antagonism of epidural morphine analgesia. Acta Anaesthesiol Scand 1997;41:774-8.

[2] Toledo P, et al. The Interaction Between Epidural 2-Chloroprocaine and Morphine: A Randomized Controlled Trial of the Effect of Drug Administration Timing on the Efficacy of Morphine Analgesia. Anesth Analg 2009;109(1):16873.

3% 2-chloroprocaine with additional doses of 3% 2-chloroprocaine when patients became uncomfortable. The results of this study were that patients who received epidural 3% 2-chloroprocaine had faster regression of their sensory block, increased IV PCA morphine use at 4 and 24 hours, and increased pain scores at 1 and 2 hours compared to those given epidural 2% lidocaine with 1:200,000 epinephrine. Toledo et al. investigated patients undergoing post-partum tubal ligations comparing those receiving epidural 3% 2-chloroprocaine to those given epidural 2% lidocaine with 1:200,000 epinephrine prior to epidural morphine. If patients became uncomfortable, no additional epidural medications were administered, with the authors opting for IV midazolam or surgical infiltration with lidocaine. The results demonstrated that patients who received epidural 3% 2-chloroprocaine had higher pain scores on admission to PACU, 33% compared to 0% in the epidural 2% lidocaine with 1:200,000 epinephrine group requested analgesia within 90 minutes of epidural morphine administration, however 48 hour opioid consumption was similar between the groups.

The belief that administration of epidural 3% 2-chloroprocaine prior to epidural morphine results in decreased effectiveness of epidural morphine is controversial and may be an effect of 3% 2-chloroprocaine wearing off prior to the peak action of epidural morphine rather than true antagonism.[3] Our hypothesis from anecdotal observation is that this phenomenon is secondary to 3% 2chloroprocaine wearing off prior to the peak action of epidural morphine rather than true antagonism. We believe that the results seen from Karambelkar and Toledo were secondary to the latency period between epidural 3% 2-chloroprocaine wearing off and the peak onset of epidural morphine. By redosing those that initially received epidural 3% 2-chloroprocaine with epidural 2% lidocaine with 1:200,000 epinephrine, the latency period could be bridged and higher pain scores immediately after cesarean delivery may be avoided. This is an important question to answer as obstetric anesthesiologists attempt to avoid general anesthesia whenever safely possible and alleviating or confirming concerns about diminished post-cesarean analgesia with 3% 2-chloroprocaine will help guide future practice.

Objectives

Primary objective is to show that the effect of 3% 2-chloroprocaine on total opioid use for 24h after epidural morphine administration will be not inferior to the effect of epidural 2% lidocaine with 1:200,000 epinephrine. Secondary objectives will be to evaluate the following endpoints between two arms: time until first opioid request, pain (11 point scale; 0-10), nausea and pruritis (3 point scale; none, mild, moderate-severe) – every 4h for the first 12h, and every 12h for 24h.

The study's purpose is to determine if the previously observed diminished analgesia with epidural chloroprocaine and epidural morphine is secondary to antagonism or a latency period. If we are able to demonstrate that epidural chloroprocaine followed by epidural lidocaine top-ups and epidural morphine provides equivalent analgesia to epidural lidocaine followed by epidural morphine, it would support our hypothesis of a latency period. These results would help guide future anesthetic practices and reduce concerns that some anesthesiologists have in using chloroprocaine for cesarean deliveries.

[3] Hess PE, et al. Chloroprocaine may not affect epidural morphine for postcesarean delivery analgesia. J Clin Anesth 2006;18(1):29-33.

Study Design

This study will be a prospective comparison between epidural 2% lidocaine with 1:200,000 epinephrine and 3% 2-chloroprocaine on the analgesic effect of epidural morphine. We intend the duration of the study to be 12 months and include a total of 80 subjects (40 subjects in each group)

Patients with labor epidurals in place scheduled for cesarean delivery due to arrest of dilation or arrest of descent will be recruited. The patients will be randomized via a computer-generated random number sequence to one of two groups (lidocaine, chloroprocaine) with 40 subjects in each group. Epidurals will be dosed with 3% 2-chloroprocaine or 2% lidocaine with 1:200,000 epinephrine to T4 level in 5ml increments, epidural morphine 3mg will be given after delivery of neonate. The patient will be blinded to which medication she receives however the physician administering the medication will not be blinded. T4 level maintained throughout cesarean delivery with additional epidural doses of 2% lidocaine with 1:200,000 epinephrine for both groups. This is the critical component to bridge the latency period between the offset of 3% 2-chloroprocaine and the peak action of epidural morphine. Post-operative orders of scheduled acetaminophen and ibuprofen, and oxycodone as needed will be written.

3% 2-chloroprocaine without epinephrine will be used which has a concentration of 30mg/ml. A maximum of 20ml (600mg) will be used, which is below the recommended maximum recommended dose of 800mg. 2% lidocaine with epinephrine will be used which has a concentration of 20mg/ml. A maximum of 20ml (400mg) will be used, which is below the recommended maximum recommended dose of 500mg.

Primary endpointswill be total opioid use for 24h after epidural morphine administration. Secondary endpoints will be time until first opioid request, pain (11 point scale; 0-10), nausea and pruritis (3 point scale; none, mild, moderate-severe), total opioids used at each timepoint – every 4h for the first 12h, and every 12h for 24h.

The patients who receive epidural 2% lidocaine with 1:200,000 epinephrine and epidural morphine are receiving routine therapy for urgent cesarean delivery in patients with labor epidurals in place. The patients who receive 3% 2-choloroprocaine and epidural morphine are receiving routine therapy for stat cesarean delivery in patients with labor epidurals in place. Both will have scheduled acetaminophen and ibuprofen, and PRN PO oxycodone available for breakthrough pain.

The adverse event rates of chloroprocaine and lidocaine are quite low; allergic reactions to local anesthetics are very rare, hypotension as a result of sympathectomy secondary to neuraxial anesthesia is an expected side effect and is regularly treated with fluids and vasopressors. Local anesthetic systemic toxicity is the most serious complication however the risk is minimized by frequent aspiration of the epidural catheter, small incremental doses of local anesthetics, and ensuring the sensory level is rising appropriately with each intervention.

There are frequent minor side effects with neuraxial morphine that include nausea, vomiting, and pruritis – which are side effects of all opioids. Respiratory depression with neuraxial morphine is described but is extremely rare.

Study Population
All patients with labor epidurals in place scheduled for cesarean delivery due to arrest of dilation or arrest of descent will be recruited. Patients may refuse to participate in this study or withdraw at any time. Inclusion criteria includes pregnant females, between age 18-50 years, with live singleton pregnancy. Exclusion criteria includes BMI >40, obstructive sleep apnea, drug abuse, chronic pain, chronic opioid use, nonfunctioning epidural.

Study Procedures
Patient will have pre-existing labor epidurals in place prior to recruitment. Following the consent and randomization process, the epidural will be dosed with either 3% 2-chloroprocaine or 2% lidocaine with 1:200,000 epinephrine in 5ml increments until a T4 sensory level to pinprick is achieved. Epidural morphine 3mg will be given after delivery of neonate and a T4 level maintained throughout cesarean delivery with additional epidural re-dosing with 2% lidocaine with 1:200,000 epinephrine in 5ml increments for both groups. The number of additional epidural lidocaine top-ups, total dose, and timing of top-ups will be documented for each patient and compared between groups. Post-operative orders of scheduled acetaminophen 650mg PO q4h and ibuprofen 600mg PO q6h, and oxycodone 5mg PO q4h PRN as needed will be written.

Patients will be followed during the duration of their hospital stay with data being collected every 4h for the first 12h, and every 12h for 24h. We will record time until first opioid request, pain (11 point scale; 0-10), nausea and pruritis (3 point scale; none, mild, moderate-severe), total opioids used at each timepoint, and total opioids used for 24h. Each patient will participate for 24h. Data will be collected and recorded, with paper records secured in a locked filing cabinet.

Study Benefit
The study's purpose is to determine if the previously observed diminished analgesia with epidural chloroprocaine and epidural morphine is secondary to antagonism or a latency period. If we are able to demonstrate that epidural chloroprocaine followed by epidural lidocaine top-ups and epidural morphine provides equivalent analgesia to epidural lidocaine followed by epidural morphine, it would support our hypothesis of a latency period. These results would help guide future anesthetic practices and reduce concerns that some anesthesiologists have in using chloroprocaine for cesarean deliveries. This could increase the usage of chloroprocaine which could reduce the number of women that require general anesthesia for emergent cesarean delivery. The possible benefit to patients is the less frequent use of general anesthesia for emergent cesarean delivery which is associated with an increased incidence of failed intubation.

Data and Safety Monitoring
The potential adverse event that could occur is that patients dosed with 3% 2-chloroprocaine may experience antagonism with epidural morphine. They may then experience increased post-operative pain and may require more supplemental pain medications. However this therapy is the standard of care for patients undergoing stat cesarean delivery with labor epidurals in place. If patients have breakthrough pain over the post-operative pain medications ordered, they will be evaluated on a caseto-case basis with the option of increasing the dose or switching to a different modality (PCA). The rest of the risks are those standard for neuraxial anesthesia and for cesarean delivery.

Local anesthetic systemic toxicity is the most serious complication however the risk is minimized by frequent aspiration of the epidural catheter, small incremental doses of local anesthetics, and ensuring the sensory level is rising appropriately with each intervention. These and other adverse events will be noted and reported in the manuscript; if these events are occurring at an increased rate than what is normally expected then the study will be halted and study design re-evaluated by the research team. The research team will review the results monthly to ensure patients are receiving safe care and will notify the Data and Safety Monitoring Board if adverse events are occurring at a higher than expected rate. The Data and Safety Monitoring Board will hold meetings twice per year.

Specific adverse drug reactions that will be measured are local anesthetic systemic toxicity (expected incidence 0.03%[4]), epidural failure requiring conversion to general anesthesia (expected incidence 0.35%[5]), intravascular injection (expected incidence 0.02%[6]), intrathecal injection (expected incidence 0.035%[6]), and high/total spinal (expected incidence 0.024%[6]). If these adverse events are occur, the research team will halt the study and evaluate these events. As all of these events occur at a rate of less than 1% (total study population is 80 subjects, if any event occurs more than twice the study will terminated.

Statistics

We plan to enroll 60 patients at MHH-TMC and 20 patients at LBJ Hospital. We intend to include all randomized subjects. Patients will be randomized at 1:1 ratio to two arms using the block randomization method with block size 4.

In a prior study of similar arms [1], mean 24-hour morphine consumptions in lidocaine and 2chloroprocaine arms were 4.07mg (SD=6.34) and 27.72mg (SD=18) respectively. We assume that our proposed 2-chloroprocaine arm will yield the same mean 24-hour opioid consumption as the lidocaine arm. We conservatively estimate the standard deviation to be 15mg. Let μ_c and μ_l denote the mean 24hour opioid consumption for the 2-chloroprocaine and lidocaine arm, respectively. We use 90% twosided t confidence interval (CI) for μ_c-μ_l to evaluate non-inferiority. The arm of 2-chloroprocaine arm will be considered as no worse than the lidocaine arm if the upper limit of CI is less than 10mg. The target enrollment of 40 per arm provides the power of 90.8% for proving non-inferiority of the 2chloroprocaine arm given the non-inferiority margin 10mg. If we permit 10% of dropout on enrolled patients, 36 eligible patients per arm provide the power of 87.4% for this non-inferiority assessment.

We will conduct Kolmogorov–Smirnov test to examine distributions of continuous variables. If normality is satisfactory, we will report mean and standard deviation of the continuous variable in two arms. Twosample t test will be used to compare means. For 24-hour opioid consumption, we will construct a 90% t CI for the difference in mean between two arms (μ_c-μ_l). The upper limit of CI will be assessed against the non-inferiority margin 10mg. If data follow skewed distribution, we will summarize data as

[4] Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med 2013; 38:289.

[5] Katircioglu K, Hasegeli L, Ibrahimhakkioglu HF, Ulusoy B, Damar H. A retrospective review of 34,109 epidural anesthetics for obstetric and gynecologic procedures at a single private hospital in Turkey. Anesth Analg 2008;107:1742–5

[6] Jenkins JG. Some immediate serious complications of obstetric epidural analgesia and anaesthesia: a prospective study of 145,550 epidurals. Int J Obstet Anesth 2005;14(1):37-42.

median and interquartile range, and use Wilcoxon rank sum test to compare medians. In case that 24-hour opioid consumption is skewedly distributed, we will construct a 90% CI based on Wilcoxon rank sum test.

For side effects, we will report number of incidences as well as incidence rates in two arms. Score test will be used to compare the incidence rates. If a side effect appears only in one arm, Fisher's exact test will be used to evaluate its association with intervention.

Ethics

We do not plan on obtaining approval from another IRB. Once it has been determined that a patient will require cesarean delivery, an investigator will obtain consent and describe the research project. If necessary, live or electronic translation services will be employed.

Data handling and record keeping

Data will be obtained from electronic medical records as well as from questioning during patient interactions. These paper records will be secured in a locked filing cabinet. These data will then be deidentified and transferred to a password protected spreadsheet document.

Quality control and assurance

The steps that will be taken to assure that the data collected are accurate, consistent, complete, and reliable will be periodic reviews of patients' electronic medical records to ensure that our data collected is consistent with what has been documented by nursing staff. We do not plan to have ongoing third party monitoring.

Publication Plan

We plan to publish our research results in an obstetric anesthesiology journal. We do not plan to return any results to the research subjects unless they specifically request them.