Chloroprocaine Lavage to Improve Outcomes Related to Operative Cesarean Delivery
CLOR-PRO

Phase 1 Protocol and Statistical Analysis Plan
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INTRODUCTION

Compared to general anesthesia, neuraxial anesthesia (spinals and epidurals) is associated with a lower risk for maternal aspiration and airway compromise, exposes the baby to less anesthetic, and allows for greater maternal involvement in the birth process. For these reasons, it has become the preferred method of anesthesia for cesarean delivery.[1–3] A spinal anesthetic is a one-time injection of numbing medicine (local anesthetic) and typically opioid into the intrathecal space. Spinals have a limited duration. Spinals that are placed to facilitate cesarean delivery have a duration of one to two hours. Currently, if that duration is exceeded patients must have general endotracheal anesthesia.

Suboptimal surgical anesthesia is not uncommon with neuraxial anesthesia. In a prospective observational study of 3568 cesarean deliveries, Rukuwe et al found a 9% incidence of spinal failure.[4] The rate of required conversion from regional to general anesthesia was found to be 2% for elective cesarean sections,[5] and 5% when a labor epidural was already in place[6]. In addition, incomplete neuraxial anesthesia may raise the concern of legal liability.[7,8] Currently, patients with suboptimal neuraxial anesthesia must have general endotracheal intubation.

In 1975 Ranney et al described using intraperitoneal local anesthetic (IPLA) instillation in 218 patients that underwent cesarean section under local field block alone.[9] Patients were administered up to 100 ml of 1% procaine. Some of this was injected into the skin and fascia, and the remainder was diluted to 0.5% and "spilled" into the peritoneum.[9] Although IPLA received little attention following this publication, recent publications have surfaced showing that IPLA can treat intraoperative pain, prevent postoperative nausea, decrease early postoperative pain and opioid administration, and shorten hospital length of stay. [10–16] In this manner, IPLA may be useful as part of a multimodal approach to avoiding general endotracheal intubation when neuraxial anesthesia is failing.

We have shown in a 40-month case series that 2-chloroprocaine, a local anesthetic, may be used as an agent for IPLA to facilitate women with inadequate pain relief avoiding general anesthesia. In this case series, no patients exhibited clinical signs of systemic local anesthetic toxicity. To our knowledge, this was the first study to report the effect of IPLA instillation on intraoperative pain scores during cesarean delivery as well as the first study evaluating 2-chloroprocaine (3%) as an effective agent for IPLA administration. Chloroprocaine is advantageous due to its short plasma half-life (11 to 21 seconds) and the possibility of significant vascular uptake when poured into a surgical wound that may have open venous channels.[17]

Our long-term goal is for intraperitoneal chloroprocaine to be used as an alternative option to avoid general anesthesia during cesarean sections, to alleviate women's discomfort from surgical pain, reduce complications, and improve the birth experience. To achieve our goal, we need to accomplish the following aims: (1) Determine the amount of chloroprocaine that is absorbed into the blood after intraperitoneal administration to ensure that blood levels are low and do not raise safety concerns, (2) define a safe dose of chloroprocaine for intraperitoneal administration and (3) Demonstrate that intraperitoneal chloroprocaine decreases intraoperative pain, decreases the use of rescue sedatives and opioid class medications, and can be used as a safe alternative to help women avoid general anesthesia. Aim 3 will be pursued after the completion of Aim 1 and Aim 2. This protocol only addresses Aim 1 and Aim 2.

STUDY OBJECTIVES

Aim 1: Primary Objective (to be determined with Aim 2)

To determine the amount of chloroprocaine that is absorbed in the blood after intraperitoneal administration to ensure that blood levels are low and do not raise safety concerns. There is no generally agreed upon threshold for the upper limit of "low" chloroprocaine plasma concentrations. In mice studies the median lethal dose of chloroprocaine with intravenous administration is 97 mg/kg and the median lethal dose with subcutaneous administration is 950 mg/kg[18]. The lowest concentration of intravascular chloroprocaine that has been reported to cause symptoms of systemic toxicity in humans is 2.8 mg/kg[19]. For purposes of this study, low plasma concentration will be defined as less than 0.97 mg/kg or 1/100 of the median lethal dose in mice.

Aim 2: Primary Objective

To define a safe concentration of chloroprocaine for intraperitoneal administration using a parallel dose comparison study.

STUDY OVERVIEW

Aims 1 & 2 Study Design: Phase I Safety and Dose Finding Trial Phase

Design: Open label, uncontrolled, single center, parallel group, multiple dose escalation study

Intervention: Three level doses are planned for administration after delivery of the baby with 5 subject per dose level: (Dose level 1) 40 ml of preservative-free 1% chloroprocaine; (Dose level 2) 40 ml of preservative-free 2% chloroprocaine; and (Dose level 3) 40 ml of preservative-free 3% chloroprocaine. The planned dose escalation scheme may be altered based upon emerging pharmacokinetic and tolerability results. Enrollment of each dose cohort will not occur until data analysis is complete for the previous dose cohort.

Number of Subjects: 15 subjects will be enrolled with 5 subjects per dose level.

Research Integrity: The study will be assessed for initial approval by the Institutional Review Board (IRB) at OHSU, Portland, OR, USA, and given a unique identifier for ongoing review.

Study Location: Single center study performed at OHSU in Portland, OR, USA. Subjects will be called at home prior to the date of their scheduled surgery to assess interest. Subjects will be enrolled and consented at a preoperative visit or on the labor and delivery unit (OHSU Floor 12C) on the day of their scheduled surgery. All study interventions will occur in the preoperative area for 12C, the operating rooms on 12C, or in the Post-Anesthesia Care Unit on 12C. Data collection will occur in the operating room and in the PACU.

Timeline**:** In a review of scheduled cesarean sections from 9/1/17 to 3/31/18, a total of 99 cases were found. Assuming 25% enrollment we should be able to enroll the necessary 15 subjects in 4 months, with a projected enrollment of one subject per week.

SUBJECTS

Inclusion and Exclusion Criteria

Inclusion Criteria

- Subjects ≥ 18 to 50 years of age having scheduled cesarean sections on 12C (Labor and Delivery) within Oregon Health & Science University (OHSU).
- Only subjects having spinal anesthesia will be eligible.
- Only subjects that can have a Pfannenstiel incision will be enrolled.

Exclusion Criteria

- Subjects with chronic narcotic usage
- Subjects that are deemed to need a combined spinal epidural due to the expected duration of surgery
- Patients who are unable to successfully get a spinal block
- Subjects with known atypical cholinesterase activity
- American Society of Anesthesiologist physical status IV or higher
- Patients with contraindication to neuraxial anesthesia (coagulopathy, infection)
- Subjects with stage 4 chronic kidney disease or worse (eGFR < 30 ml/min)
- Subjects with significant hepatic dysfunction (AST or ALT > 2x the upper limit of normal)
- Subjects with allergies to drugs required for this protocol.
- Subjects with multifetal gestations
- Subjects with BMI > 40 kg/m^2

Vulnerable Populations - The following protected populations will be excluded from the study:

- Children (age < 18 years)
- Prisoners
- Decisionally impaired adults

There will be a two-step process to ensure that vulnerable populations are not approached for inclusion in the study. First, the research coordinator will review the electronic medical record to screen for vulnerable population status. Second, the research coordinator will consult with the labor and delivery nurse caring for the patient to ensure that the patient is not included in a vulnerable population.

Due to the nature of the study, pregnant subjects will have to be enrolled to obtain the medical knowledge that we seek. We have attempted to minimize risk by administering the study drug after delivery of the fetus so that the fetus is not immediately exposed to the study drug. A very small quantity of drug may possibly be transferred to the fetus through breast milk, but we believe the risk to the fetus is not greater than minimal. Chloroprocaine has a long history of safe use in pregnant women and the maternal half-life is very short (mean 11.2 seconds, SD 2.8 seconds). In this manner, the drug concentration can be considered to be negligible after 45 seconds (4 half-lives), which is long before first latch.

Recruitment Methods

Most subject recruitment is expected to occur by approved study staff as early as two months prior to a potential subject's scheduled cesarean section via a review of the OHSU Labor and Delivery surgical schedule as posted in Epic (Verona, Wisconsin). The study staff will work with obstetricians to identify and screen for potential eligible subjects. We will review all the inclusion/exclusion criteria as early as two months prior to a potential subject's scheduled surgery. If a potential subject has been identified as meeting all inclusion criteria and none of the exclusion criteria, an approved member of the study team will call the subject, using an approved phone script (included in 'Consent Form and Recruitment Materials' section of application) to introduce the study. If the subject is amenable to the study, study staff will make arrangements to meet with the subject to provide formal consent materials and signature at their pre-op visit or day of surgery. If the subject is not interested in participating in the study, the inclusion/exclusion criteria and any other information related to this subject will be destroyed.

The study will be listed on ClinicalTrials.gov to provide subjects, family members, and the public background information on the study.

Other than posting this study on OHSU Study Participation Opportunities, we do not expect to create advertisements for the study.

Subjects that complete the study protocol will be given a $100 VISA gift card.

Consent Process

The consent process will take place in a private and confidential area. All subjects that are approached for recruitment will hear a description of the study, reasons for pursuing this research study, options for opting out the research protocol or not completing data collection, and potential risks, advantages, and disadvantages from participating. We will ask subjects to reiterate their understanding of how the study will affect their care and allow time for questions before collecting a signature for consent. Subjects that agree to participate in the study will be asked to sign a written informed consent that has been approved by our Institutional Review Board. An electronic copy of the signed consent will be scanned into the subject's medical records system. A copy of the signed consent, describing the research study and providing contact information for the principal investigators will be given to subject.

Medical Monitor

Dr. Michael Aziz will serve as medical monitor and will conduct periodic reviews to ensure that proper consent devoid of coercion is being collected, steps outlined in this protocol are followed to ensure human subject protection, and data safety monitoring is conducted with integrity as the study progresses. Dr. Aziz is the Vice Chair for Clinical Anesthesia and has significant experience conducting and serving as a safety monitor for clinical trials.

Study Procedures

Aims 1 & 2 Study Design: Phase I Safety and Dose Finding Trial Phase

Maternal plasma concentrations of chloroprocaine after intraperitoneal instillation have not been previously established and a safe concentration for intraperitoneal chloroprocaine has not been defined. To accomplish aims 1 and 2, we propose a safety trial in which 15 healthy patients scheduled for elective cesarean sections under spinal anesthesia are administered intraperitoneal chloroprocaine after cesarean delivery.

Before starting the cesarean section, the following baseline demographic data will be collected:

- Maternal age
- Height
- Weight at time of cesarean delivery
- Body mass index at time of cesarean delivery
- Gestational age
- Parity
- History of previous cesarean delivery
- History of previous abdominal surgery

All subjects will receive a spinal anesthetic in the operating room with a standardized solution containing 1.6 mL of hyperbaric 0.75% bupivacaine, 15 mcg fentanyl, and 150 mcg preservative-free morphine. Subjects will receive a 1 liter co-load of crystalloid (Ringer's Lactate or Normal Saline) solution during spinal placement. The patient will then be positioned supine on the operating room table with placement of a bump under their right hip to maintain left lateral tilt position. Non-invasive blood pressures will be obtained every 2 minutes after spinal placement and a phenylephrine infusion will be started at 0.4 mcg/kg/min and titrated to maintain maternal blood pressure within 20% of baseline. In accordance with standard practice all patients will have telemetry monitoring during surgery and during PACU recovery.

After obtaining spinal anesthesia, an intravenous line will be placed into the subject's lower extremity for study purposes. The subject's lower extremity will be numb at this time, which should help to minimize discomfort. Immediately after the intravenous line is placed 2 mL of blood will be drawn to determine the subject's dibucaine number. This blood will be placed in a purple top tube and kept by the research coordinator until the subject has completed the study protocol. No special temperature control is necessary. The purple top tube will then be walked to the clinical core lab. The core lab will send the sample to the ARUP Laboratories in Salt Lake City for analysis. The official title of the Dibucaine number test is "Pseudocholinesterase, Dibucaine Inhibition," lab order LAB00576 in EPIC. The turnaround time for the lab is 2-6 business days. The dibucaine number will be used to differentiate subjects with decreased butyrylcholinesterase (plasma cholinesterase) enzyme function. Butyrylcholinesterase is the enzyme responsible for metabolizing chloroprocaine.

Dibucaine is an amide local anesthetic that inhibits normal butyrylcholinesterase. In normal individuals, dibucaine will inhibit 80% of enzyme activity, which corresponds to a dibucaine number of 80. Dibucaine numbers less than 70 are associated with atypical butyrylcholinesterase. Around 1.3% of the population is known to have atypical cholinesterase activity and pregnancy can decrease cholinesterase activity.

Prior to skin incision the study drug will be transferred to a sterile receptacle on the surgical scrub field. After Pfannenstiel incision, uterine incision and extraction of the baby, the uterus will be exteriorized and intraperitoneal chloroprocaine will be administered. Chloroprocaine will be

administered in the following manner: the uterus will be retracted in a caudal direction to expose the intraperitoneal space, chloroprocaine will be poured in, two sides of the Pfannenstiel incision will be grasped by an obstetrician and the solution will be agitated with a goal of widespread dissemination. The uterus, parietal peritoneum and fascia will be closed according to obstetrician preference.

After receiving intraperitoneal chloroprocaine a small volume of blood will be taken from the lower extremity venous line (the lower extremity will be numb from spinal anesthesia) at 1, 5, 10, 20, and 30 minutes after chloroprocaine instillation. Plasma samples will be mixed with a cholinesterase inhibitor to prevent hydrolysis after blood collection. A custom assay for measuring plasma concentrations of chloroprocaine and its major metabolite, chloroaminobenzoic acid, has been established in the Bioanalytical Shared Resource/Pharmacokinetics Core Lab showing good sensitivity and accuracy (see accompanying document "Chloroprocaine stability, sensitivity, and accuracy curves). This was accomplished by altering an existing assay for lidocaine that uses liquid chromatography tandem mass spectrometry. PK study will allow us to determine the plasma concentration-time profile after intraperitoneal chloroprocaine administration.

A research coordinator will be with the patient throughout their time in the operating room and the PACU. Active, non-standard of care, monitoring for the following signs and symptoms of local anesthetic toxicity will occur in the operating room and PACU at the following time intervals after chloroprocaine administration: 5 minutes, 10 minutes, 15 minutes, 30 minutes, 60 minutes, upon PACU arrival and upon discharge from the PACU:

- seizures
- tinnitus
- metallic taste
- anxiety
- agitation
- muscle twitching
- sedation
- respiratory depression with desaturation (sat < 88%)
- dizziness
- nausea
- vomiting
- vision changes
- paresthesias
- perioral numbness
- hypotension (drop in MAP > 20% within 5 minutes of chloroprocaine administration)
- arrhythmias

Manifestations of significant systemic local anesthetic toxicity will prompt saline lavage of the abdomen with 60 ml of 0.9% normal saline followed by immediate suctioning. For purposes of this study, significant clinical manifestations will include the following: seizures, respiratory depression with desaturation (sat < 88%), hypotension (drop in MAP > 20%), any arrhythmias associated with hypotension, and cardiac arrest.

Patients that exhibit seizures, arrhythmias, hypotension (drop in MAP >20%), or cardiac arrest will be immediately administered intralipid. Intralipid is already available on labor and delivery in the epidural cart. Intralipid would be dosed according to the American Society of Regional Anesthesia

guideline (i.e. initial bolus of 1.5 ml/kg followed by 0.25 ml/kg/minute). The intralipid infusion would be continued for 10 minutes after restoration of hemodynamic stability. All patients that require intralipid will have telemetry monitoring on the floor.

After the patient leaves the PACU, the research coordinator will review the electronic medical record to determine and record the following:

- Did the patient receive a tubal ligation at the time of their cesarean section
- Was the patient's peritoneum closed
- What was the length of the surgery (time from skin incision to surgery end as documented in EPIC)

Subjects enrolled that do not have intraperitoneal instillation of the study drug, for any reason, may be withdrawn from the study without their consent. In addition, a subject may be removed from the study if the investigator or funder stops the study, the subject's clinical status changes, or if the subject does not follow study instructions. In the event that such a situation occurs the subject would be informed at the earliest reasonable time.

The subject's status in the research project will show up clearly in their electronic medical record problem list, until the subject's participation is complete. A progress note will be placed in the subject's chart to allow other providers to easily contact study investigators.

Subjects that enroll in the study and then decide to withdraw before chloroprocaine administration will be excluded from further data collection and analysis. In the event that a subject withdrawal occurs an additional subject would be recruited.

DATA and SPECIMENS

Handling of Data and Specimens

Study subjects will be assigned a unique study number after enrollment in the study. All data points, procedure related data, and electronic files for data analysis will be linked only to this unique study number. This study number will not contain any of the 18 HIPAA identifiers such as: geographic location, dates related to the individual, medical record number, account numbers, etc. The key linking study subjects to study code will be kept in an OHSU approved cloud location with special protection for confidential and restricted health information (the OHSU Box). Only the principal investigator and other study staff will have access to this key. The key will be maintained for 3 years after publication in accordance with the US Department Office of Research Integrity guidelines for responsible data management in scientific research.

Clinical data will be entered into APOM OCEAN, a 21 CFR Part 11-compliant electronic data capture system provided by the Department of Anesthesiology and Perioperative Medicine. The EDC includes password protection. Secure data will be stored in APOM OCEAN DCS for 3 years after publication. Data in the EDC will be linked only to subject study code, not to any of the 18 HIPAA identifiers.

The following clinical data will be entered into APOM OCEAN:

- Baseline demographic and surgical parameters
    - Maternal age
    - Height

  - Weight at time of cesarean section
  - Body mass index at time of cesarean section
  - Previous cesarean section history
  - Abdominal surgery history
  - Tubal ligation history
  - Whether the peritoneum was closed during the cesarean section
  - Cesarean Section duration
- Signs and symptoms of local anesthetic toxicity 5 minutes, 10 minutes, 15 minutes, 30 minutes, 60 minutes, upon PACU arrival and upon discharge from the PACU
  - Seizures
  - Tinnitus
  - Metallic taste
  - Anxiety
  - Agitation
  - Muscle twitching
  - Sedation
  - Respiratory depression with desaturation (sat <88%)
  - Dizziness
  - Nausea
  - Vomiting
  - Vision changes
  - Paresthesias
  - Perioral numbness
  - Hypotension (drop in MAP >20% within 5 minutes of chloroprocaine administration)
  - Arrhythmias
- Data obtained from the patient's plasma
  - Dibucaine number
  - Chloroprocaine plasma concentrations 1, 5, 10, 20, and 30 minutes after chloroprocaine administration

Any data that is shared will be transmitted in an encrypted manner over a secure network. Transmitted data will be labeled only with the study code, none of the 18 HIPAA identifiers. When data is transmitted, the transmitter (research personnel with access to APOM OCEAN EDC) will be responsible for sending the data in a protected manner. Any person receiving data will then assume responsibility for patient confidentiality and data integrity.

Plasma samples will be kept on ice in the operating room until all samples for a given subject are obtained. Samples will then be prepared by centrifuge at 2000xg at 4C for 15 minutes. Samples will be stored in a freezer at -80C in the Maternal Fetal Medicine Research Refrigerator located next to the obstetric operating rooms. This is a secure locked area used for research. Samples will be stored in this room for 1 to 4 weeks. Samples will be batched and taken to the Bioanalytical Shared Resource/Pharmacokinetics Core at OHSU where they will be analyzed and discarded in accordance with blood waste guidelines in the Bioanalytical Shared Resource/Pharmacokinetics Core at OHSU. There will be no long term storing of plasma samples in the Bioanalytical Shared Resource/Pharmacokinetics Core.

Sharing of Results with Subjects
Study results will not be available to subjects at the time of participation. All subjects will be given the contact information of the principal investigator and told that they may contact him to obtain their individual data once analysis is complete. Patients will also be able to obtain a free copy of any published data should they indicate interest. Chloroprocaine plasma concentration-time profiles for study subjects will be made available by request. The Plasma concentration-time profiles will be created in the Bioanalytical Shared Resource/Pharmacokinetics Core, which is a research lab and thus not CAP/CLIA certified. Dibucaine numbers will be made available upon request. Dibucaine numbers will be run in a CAP/CLIA certified lab. This study will not generate genetic information or imaging studies.

Data and Specimen Banking
Data will not be stored in a repository for 3 years after publication. Plasma samples will not be banked.

Data Analysis - Power/Sample Size:
Aims 1 &2 Study Design: Phase I Safety and Dose Finding Trial Phase
We estimate that a sample of 5 subjects will allow us to determine if intravascular concentrations of chloroprocaine reach concerning levels after intraperitoneal instillation at each dose level.

The chloroprocaine plasma concentration-time profile for each dose level will be examined after each cohort has completed the study. Enrollment of a subsequent dose cohort will not occur until data analysis is complete for the previous dose cohort.

Adverse events will be tallied. Baseline characteristics and surgical details will be presented in summary.

The statistical software STATA (Stata Corporation, College Station, TX) will be used for all analyses.

PRIVACY, CONFIDENTIALITY AND DATA SECURITY
The results of the study as well as all other information collected on the data collection sheet will be stored in the locked office of the research coordinator. The office requires a key for entry. Only research personnel are allowed access to the office. No protected health information or other data collected during the completion of this randomized controlled trial will be taken off campus. All data gathered for this study will be coded before any analysis or publication occurs.

This study number will not contain any of the 18 HIPAA identifiers such as: geographic location, dates related to the individual, medical record number, account numbers, etc. The key linking study subjects to study code will be kept in an OHSU approved cloud location with special protection for confidential and restricted health information (the OHSU Box). Only the principal investigator and IRB approved study staff will have access to this key.

Clinical data (including adverse events (AEs) and expected adverse reactions data) and laboratory data will be entered into APOM OCEAN, a 21 CFR Part 11-compliant electronic data capture system provided by the Department of Anesthesiology and Perioperative Medicine. The EDC includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

In order to maintain patient privacy, data capture tools, study drug accountability records, study reports, and communications will identify the patient only by the assigned patient number. The investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authorities access to the patient's original medical records, including medical history, laboratory studies, and medication administrations, for verification of data gathered and to audit the data collection process. This information will be accessed for the duration of the research study, including the follow-up period, for the purpose of data reconciliation. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

DSMP submitted as a separate document.

A finding of plasma chloroprocaine concentrations > 0.97 mg/kg will halt the study and we will immediately (within two working days) report the finding to the IRB. In addition, the exposed patient will be notified and the medical team will be notified. Due to the short plasma half-life of chloroprocaine patients will have cleared the drug long before any data on plasma concentrations can be obtained.

Significant clinical manifestations of local anesthetic systemic toxicity will similarly halt the study and prompt immediate (within two working days) notification of the IRB. In addition, all medical teams involved in the patient's care will be notified and the patient will receive a detailed summary of the event upon resolution of the event. In the scenario that the patient lacks the ability to comprehend the adverse event the patient's family will be notified. For purposes of this study significant clinical manifestations will include the following:

- Seizures
- Respiratory Depression with desaturation (sat < 88%)
- Hypotension defined as a greater then 20% drop in mean arterial pressure within 5 minutes of receiving chloroprocaine
- Any arrhythmias associated with hypotension
- Cardiac Arrest

RISKS AND BENEFITS

Risks to Subjects

As with all studies, breach of confidentiality is a common risk. In addition, there is the possibility of slightly increased anxiety on the day of surgery for patients approached for inclusion in the study. There is also likely to be a loss of free time in the preoperative area as consent and study education will likely take 20 minutes to complete. As data collection will continue to occur throughout the patient's surgery and postoperative care, inconvenience is possible.

Chloroprocaine has a long history of safe use and is assumed to have a low potential for systemic toxicity because of its very short maternal (mean 11.2 seconds, SD 2.8)[20] and fetal plasma half-life (mean 15.4 seconds, SD 5.2)[20] and relatively high maximum recommended dosage (11 mg/kg without epinephrine).

The clinical presentation of local anesthetic systemic toxicity is quite variable[21]. Most case reports describe local anesthetic systemic toxicity after administration of local anesthetics with a much longer duration of action than chloroprocaine[21,22]. In general, local anesthetics first cause central nervous system excitation (e.g. anxiety, agitation, muscle twitching, seizures) followed by central nervous system depression (e.g. sedation, respiratory depression) and then cardiovascular effects (e.g. bradycardia, hypotension, arrhythmias, cardiac arrest)[21].

In a review of reported cases of local anesthetic systemic toxicity published in 2015 there were no cases of local anesthetic systemic toxicity attributed to chloroprocaine.[21] A search of PubMed and Google revealed 3 articles that describe systemic toxicity from chloroprocaine[19,23,24]. Cladis et al[24] described a 30 second self-limited wide complex bradycardia after a 30 mg/kg inadvertent vascular injection through a caudal catheter in a 2 month old infant. Hernandez et al[23] described a 40 second self-limited seizure after a 28.7 mg/kg inadvertent vascular injection through a paravertebral catheter in a 9 month old infant. Marsch et al[19] described 34 patients with non-life threatening symptoms of local anesthetic systemic toxicity after direct intravenous injection of 200 to 400 mg of chloroprocaine into patients with an average weight of 70 kg (2.8-5.7 mg/kg). Symptoms lasted 3 to 11 minutes and included the following: dizziness (34 patients), tinnitus (13 patients), metallic taste (10 patients), nausea or vomiting (4 patients), and slight bradycardia (2 patients). None of the patients described in any of the 3 articles had any long term morbidity or mortality[19,23,24].

Chloroprocaine has been touted as the preferred local anesthetic for providing epidural anesthesia to laboring women with a decompensating fetus because it does not participate in ion trapping like other local anesthetics. Local anesthetics are weak bases which become ionized when exposed to acidotic environments. Ion trapping occurs when non-ionized local anesthetics cross the placenta and become ionized by the more acidotic fetal circulation, compared to maternal blood pH. After local anesthetics become ionized they cannot cross back into maternal circulation. Accumulating local anesthetic causes the fetus to become more acidotic which results in more ion trapping. Placental transfer of chloroprocaine has not been shown to be influenced by the degree of fetal acidosis.[25]

Literature describing chloroprocaine instillation into the intraperitoneal space is sparse. Accordingly, there is a possibility of local anesthetic systemic toxicity in this study. To this extent adverse experience reporting will include monitoring for and publishing the occurrence of any of the following adverse events associated with chloroprocaine instillation:

- Seizures
- Tinnitus
- Metallic taste
- Anxiety
- Agitation
- Muscle twitching
- Sedation
- Respiratory Depression with desaturation (sat < 88%)
- Dizziness
- Nausea
- Vomiting
- vision changes
- paresthesias

- perioral numbness
- Hypotension (drop in MAP >20% within 5 minutes of chloroprocaine administration)
- Arrhythmias defined as a change in EKG rhythm
- Cardiac Arrest

Participants will not incur any additional cost for participating in this study.

Potential Benefits to Subjects

We are performing this study because the incidence of intraoperative pain during cesarean sections is high and standard practice in developed countries is to induce general endotracheal anesthesia when spinals are inadequate. General endotracheal anesthesia in the pregnant population is associated with an increased incidence of pulmonary and airway complications, compared to neuraxial anesthesia. Furthermore, general anesthesia hinders early maternal-baby bonding. Whether intraperitoneal chloroprocaine can safely and effectively treat intraoperative pain is unknown. We anticipate that patients that receive intraperitoneal chloroprocaine will have less intraoperative pain, require less systemic narcotics, and have less nausea. Intraperitoneal chloroprocaine may also decrease the need to convert to general endotracheal anesthesia during cesarean sections. While the purpose of this study is not to assess intraoperative pain, narcotic usage, and nausea, patients may still receive these benefits.

DRUGS

Chloroprocaine is an ester type local anesthetic that decreases pain by blocking sodium channels and preventing transmission of pain signals to the brain. It is available as a 1%, 2% and a 3% solution. On labor and delivery at OHSU we stock 20 ml vials of 2-chloroprocaine (3%). There are case reports of neurologic complications after chloroprocaine injection into the intrathecal space. There are now thought to be related to the preservative sodium bisulfate.[26] Consequently, the chloroprocaine stocked at OHSU is preservative free. Chloroprocaine is FDA approved as well as approved for OHSU use by the Pharmacy and Therapeutic Committee. FDA indications include infiltration, nerve block, spinal, epidural and caudal anesthesia. Chloroprocaine is not FDA approved for intraperitoneal lavage. It was introduced into anesthetic practice decades ago and has been used safely to provide rapid and reliable epidural blockade for obstetric procedures. The mean in vitro half-life of chloroprocaine in maternal and fetal plasma is 11.2 seconds (SD 2.8) and 15.4 seconds (SD 5.2), respectively.[20] Placental transfer of chloroprocaine is minimal because of the drug's high rate of metabolism.

The chloroprocaine available in the anesthesia cart will be used for intraperitoneal administration. A researcher involved in the study will dilute chloroprocaine to the desired concentration with sterile saline.

Each patient will be administered all 40 ml of study solution. There will not be residual medication after patient administration that requires disposal. Any unused study drugs at the conclusion of the study will be destroyed at OHSU in a manner consistent with ICH/GCP guidelines, city of Portland regulations, state of Oregon regulations, federal policy, and OHSU institutional policy.

BUDGET

The cost to create the collection protocol that included inhibition of chloroprocaine degradation after collection and liquid chromatography tandem mass spectrometry assay for measuring blood

concentrations of chloroprocaine and its major metabolite, chloroaminobenzoic acid, with validation was under $5000. An OHSU SOM Research Core Grant was used to fund this. We received funding for this study from The Collins Medical Trust in the amount of $30,000 (PPQ#1016328). Departmental support was obtained to fund study initiation.

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