The Maternal CLIMB Trial: ChLoroprocaine to Reduce the Impact of Motor Block on Patient Recovery After Short Obstetric Surgery

Principal Investigator: Brandon M. Togioka, M.D.

Co-Investigator: N David Yanez, MS, PhD
Co-Investigator: Miriam Treggiari, MD, PhD, MPH

Medical Monitor: Ryan Ivie, M.D.

Submission Date: February 21, 2019

Protocol Update: September 19, 2019

Tax ID: 931176109

Trial Registration: clinicaltrials.gov Identifier: NCT03967288

IRB#: OHSU 19846

PI Contact Information:

Address: Oregon Health & Science University School of Medicine
Department of Anesthesiology & Perioperative Medicine
Mail Code UHS-2
3181 SW Sam Jackson Park Road
Portland, OR 97239
Office Number: 503-494-4572
Mobile Number: 503-569-3064
Email Address: *togioka@ohsu.edu*

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the B. Braun Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed:  Date: 2/21/2019

Name: Brandon M. Togioka, M.D.

Title: Assistant Professor in Anesthesiology & Perioperative Medicine
Obstetric, Fertility, and Gender Identity Anesthesia Medical Director
Oregon Health & Science University

TABLE OF CONTENTS PAGE

1 LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine Transaminase
APOM	Anesthesia and Perioperative Medicine
ASA	American Society of Anesthesiologists
AST	Aspartate Transaminase
CFR	Code of Federal Regulations
CRF	Case Report Forms
CSF	Cerebrospinal Fluid
EDC	Electronic Data Capture
EKG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice Guidelines
HCAHPS	Hospital Consumer Assessment of Healthcare Providers and Systems
Hg	Mercury
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IRB	Institutional Review Board
kg	kilograms
LAST	Local Anesthetic Systemic Toxicity
m	meters
mg	milligrams
min	minutes
mL	milliliters
mm	millimeters
NIH	National Institutes of Health
OCEAN	Outcomes and Clinical Epidemiology in Anesthesia
OHSU	Oregon Health and Science University
PACU	Post-Anesthesia Care Unit
PDPH	Post-Dural Puncture Headache

PI	Principal Investigator
PTT	Partial Thromboplastin Time
SAE	Serious Adverse Events/Serious Adverse Experience
SBP	Systolic Blood Pressure
SD	Standard Deviation
SUSAR	Suspected, Unanticipated, Serious Adverse Reactions
UP	Unanticipated Problems
US	United States

2 PROTOCOL SUMMARY

Title: **Comparison of Clorotekal® and Bupivacaine for Short Obstetric Surgery**

Précis: This will be a single-blind, randomized, controlled, single center clinical trial assessing the efficacy of Clorotekal® on resolution of motor block and associated patient flow through the PACU.

Masking:

1. Subject
2. Obstetric provider
3. Investigator
4. Outcomes assessor

The anesthesia provider will be unblinded because of the large difference in volume between Clorotekal® (5 mL) and hyperbaric bupivacaine (1.4 mL). The block characteristics and safety profile of a dilution of 10.5 mg hyperbaric bupivacaine to a volume of 5 mL are unknown.

Fifty patients will be equally randomized to receive either Clorotekal® or hyperbaric bupivacaine.

Objectives: Primary Objective:

1. To compare duration of motor block, defined as the number of 5-minute intervals since completion of spinal injection to achievement of a Bromage scale score of 2 (able to flex knees), between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.

Secondary Objectives:

1. To compare duration of motor block, defined by patient report since completion of spinal injection to

achievement of a Bromage score of 2 (able to flex knees), between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.
2. To compare Phase 1 PACU length of stay between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.
3. To compare PACU time (Phase 1 + Phase 2) between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.
4. To compare time to first ambulation between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.
5. To compare incidence of bladder catheterization (Foley or straight catheter insertion) between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.

Population: Patients will be ASA category 1-3 women, 18 years old or greater, undergoing one of the following obstetric procedures: bilateral tubal ligation, external cephalic version, cerclage insertion, cerclage removal, minimally invasive fetal surgery, or evacuation of retained products of conception at Oregon Health and Science University in Portland, Oregon.

Number of Sites: Single center trial

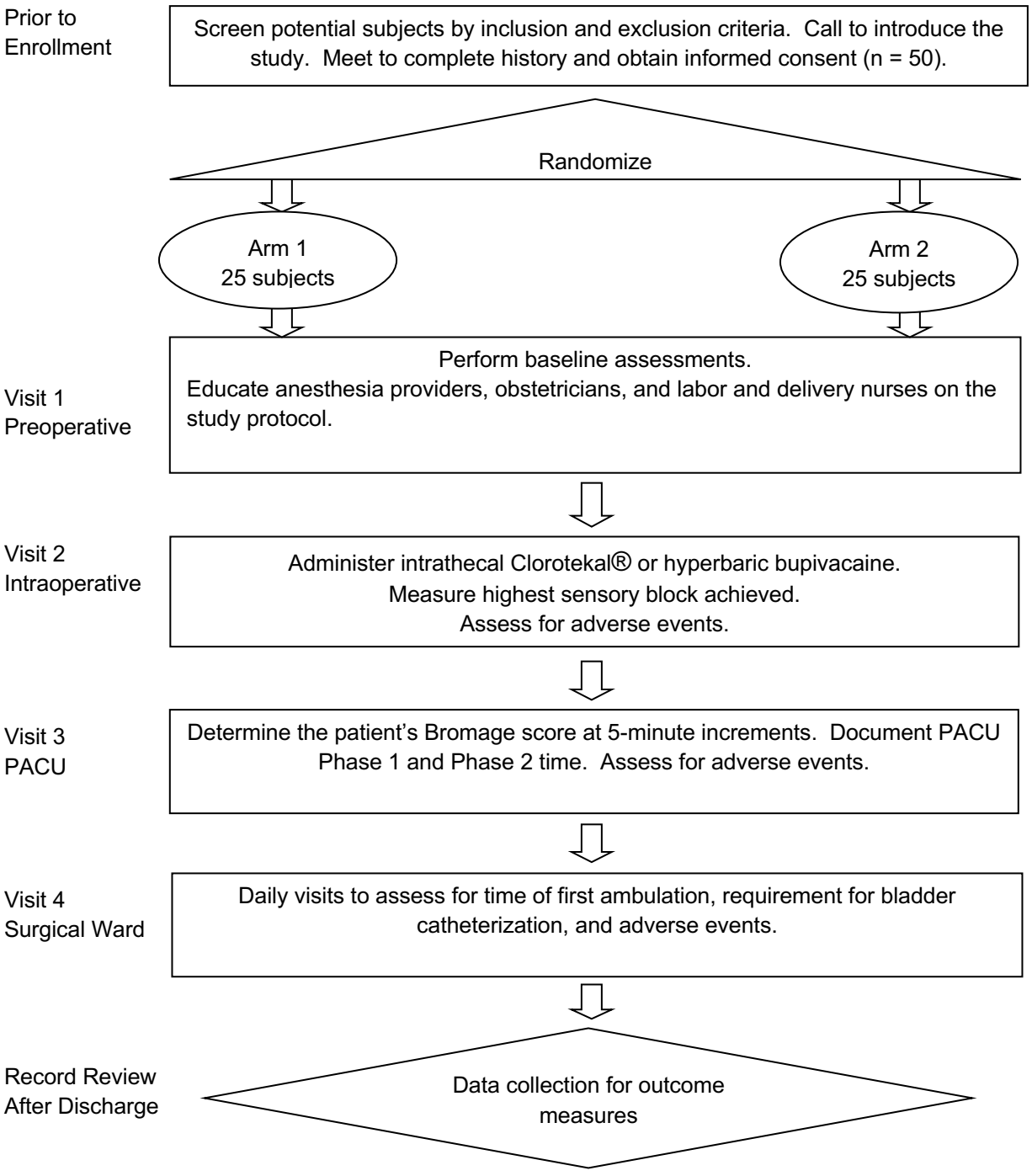
Treatment Arms: Experimental: Intrathecal injection of Clorotekal® 50 mg (5 ml of 1% chloroprocaine)

Active Comparator: Intrathecal injection of hyperbaric bupivacaine 10.5 mg (1.4 ml of 0.75% bupivacaine hydrochloride in 8.25% dextrose)

Study Duration: The study duration including initiation, enrollment, data collection, and close out is expected to be 24 months. In addition, IRB submission and obtaining IRB approval is expected to take 3 months. Data analysis, writing, editing and submission to a peer-reviewed journal is expected to take 6 months.

	In summary, the study should be completed within 3 years of obtaining approval for funding.
Subject Participation Duration:	Individual subjects will be included the study for three days or until discharge, whichever comes first.
Estimated Time to Complete Enrollment:	Estimated time from enrollment into study of the first subject to enrollment into study of the last subject is 18 months.

3 SCHEMATIC OF STUDY DESIGN:



4 KEY ROLES AND CONTACT INFORMATION

Principal Investigator:	Brandon M. Togioka, MD Obstetric, Fertility, and Gender Identity Anesthesia Medical Director in the OHSU School of Medicine Director of Clinical Research Department of Anesthesiology & Perioperative Medicine Mail Code UHS-2 3181 SW Sam Jackson Park Road Portland, OR 97239 Office Number: 503-494-4572 Mobile Number: 503-569-3064 Email Address: *togioka@ohsu.edu*
Co-Investigator:	N. David Yanez, MS, PhD Co-Director of the OHSU Biostatistics and Design Program within the Oregon Clinical and Translational Research Institute Email Address: *yanezn@ohsu.edu*
Co-Investigator:	Miriam M. Treggiari, MD, PhD, MPH Vice Chair for Clinical Research Email Address: *treggiar@ohsu.edu*
Medical Monitor:	Ryan Ivie, MD Director of Regional Anesthesia at OHSU Email Address: *ivie@ohsu.edu*
Research Coordinator:	Janna Higgins, MSW Senior Research Associate Email Address: *higginsj@ohsu.edu*
Institution:	Oregon Health and Science University Portland, OR

5 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

5.1 Background Information

The standard anesthetic for surgical procedures on labor and delivery is a spinal. Gastrointestinal and airway changes during pregnancy increase maternal risk for aspiration, difficult mask ventilation, and failed endotracheal intubation[1]. Furthermore, spinal anesthesia exposes the fetus to less anesthesia and allows for maternal involvement in labor and delivery procedures. General anesthesia is so rarely performed on labor and delivery floors that many nurses are not trained or credentialed to recovery patients after general anesthesia. This is true at Oregon Health and Science University where the policy is to relocate a main operating room nurse to the labor and delivery Post-Anesthesia Care Unit (PACU) each time a general anesthetic is performed. This can impact patient safety, hospital cost, and perioperative patient throughput.

The following obstetric procedures are commonly performed with spinal anesthesia on labor and delivery: bilateral tubal ligation[2-4], external cephalic version[5-7], cerclage insertion[8,9], cerclage removal, minimally invasive fetal surgery[10], and evacuation of retained products of conception[1]. These procedures are typically completed within 30 minutes. Patients prefer rapid PACU discharge to facilitate getting back to their families; short PACU recovery times are associated with improved mother-baby bonding[11] and less interruption with breastfeeding[11]. Not surprisingly, a short PACU stay is associated with higher Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey scores[12] and a more favorable impression of hospital staff[12],

Shorter labor and delivery PACU recovery times are also preferred by anesthesiologists and labor and delivery nurses. Labor and delivery units are typically not staffed with dedicated PACU nurses or multiple anesthesia teams. Longer PACU times increase nursing burden and can impact nursing-associated hospital costs[13]. In addition, nursing and anesthesia time spent in the PACU is time that these providers are not available for laboring patients or for responding to urgent or emergent unit needs. This staffing model has been suggested as a contributor to the high rate of unfulfilled requests for bilateral tubal ligation—half of requests for immediate postpartum bilateral tubal ligation go unfulfilled[14,15].

Patients must achieve the following in order to be discharged from the PACU: hemodynamic stability, return to baseline oxygen saturation, stable electrocardiogram rhythm that is consistent with baseline, independent maintenance of airway, respiratory rate greater than or equal to 10 breaths per minute, temperature greater than 36 degrees Celsius, return to baseline level of consciousness, surgical hemostasis, pain less than or equal to 4/10 or for chronic pain patients less than or equal to 2 points above baseline, either no nausea or mild nausea without vomiting, and either full return of sensory or motor function (discharge home) or evidence that motor block is receding (discharge to the ward)[16]. After spinal anesthesia, the rate limiting criterion for most patients is return of motor function.

Bupivacaine is currently the standard spinal medication on labor and delivery. It is favored because of its long history of safe use, its low incidence of transient neurologic symptoms (a temporary sensation of radiating pain down the buttock and thighs associated with spinal anesthesia)[17], and its ability to provide a dependable, dense block with a high degree of maternal satisfaction[1]. While bupivacaine has the aforementioned advantages, it unfortunately has a long duration of action, up to 240-380 minutes[18], which far exceeds the time necessary to complete most obstetric procedures. Low-dose bupivacaine, with a shorter duration of action, has been suggested as a potential alternative. Unfortunately, low-dose bupivacaine has been associated with inadequate anesthesia, urinary retention, and prolonged discharge times[19].

5.2 Rationale

Clorotekal®, the first FDA approved chloroprocaine solution created for spinal injection, is a potential alternative that can address bupivacaine's shortcomings. Clorotekal® carries a FDA indication for intrathecal injection to provide spinal anesthesia for adults undergoing short duration lower extremity and lower abdominal surgical procedures. A vial of Clorotekal® includes 50 mg of preservative-free 1% chloroprocaine in 5 mL (10 mg/mL). Clorotekal® has been shown to provide well tolerated, rapid onset, reliable spinal anesthesia for surgeries of short duration[20]. When compared with bupivacaine spinals, chloroprocaine spinals have been shown to facilitate clinically significant shorter times to resolution of motor and sensory block[18,21-23], first ambulation[18,22,23], micturition[22,23], and discharge readiness[18,22-24]. Importantly, the incidence of transient neurologic symptoms with chloroprocaine appears to be very low[25,26]. Therefore, chloroprocaine can have significant advantages to allow the performance of short

obstetric procedure on labor and delivery, while affording a safety profile similar to bupivacaine.

We designed a randomized, controlled, single-blind trial to test the hypothesis that administering Clorotekal® has shorter resolution time of motor block, which is typically the rate limiting step for moving patients from the PACU to the postpartum ward or to home, compared with equivalent block with hyperbaric bupivacaine[21].

5.3 Potential Risks and Benefits

5.3.1 Potential Risks

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 take 15 minutes to complete. As data collection will continue to occur throughout the patient's surgery and postoperative care, inconvenience is possible.

Spinal anesthesia is generally very safe, but all anesthetic interventions are associated with some risk. The side effects associated with spinal anesthesia with local anesthetics (chloroprocaine and bupivacaine) include[1]:

- Hypotension
- Nausea
- Vomiting
- Urinary retention
- Motor block
- Shivering

Complications associated with spinal anesthesia include[1]:

- Inadequate anesthesia
- High block which can cause anxiety, breathing problems, and cardiac arrest
- Post-dural puncture headache (PDPH)
- Bleeding
- Infection
- Nerve injury
- Fetal heart rate changes
- Local anesthetic systemic toxicity (LAST)

The following steps will be taken to mitigate the aforementioned risks:

- Hypotension: All patients will receive a co-load of 1 liter lactated Ringer's solution, vasopressors will be drawn up and ready for administration, all patients greater than 20 weeks gestational age will have left uterine displacement
- Nausea and vomiting: Hypotension will be treated if present and ondansetron will be available for administration.
- Urinary retention: Patients will be managed according to the "OB Urinary Retention Guide," which is attached as Supplement 1. The "OB Urinary Retention Guide" was recently approved by the Perinatal Best Practice Committee. The Algorithm was created to balance the avoidance of unnecessary Foley insertion because of infection risk and patient discomfort against risks associated with urinary retention.
- Motor block: Patients will be assessed by labor and delivery nurses prior to allowing ambulation.
- Shivering: Warm blankets and upper body convective warmers will be used.
- Inadequate anesthesia: Intravenous opioid administration will be used to supplement spinal anesthesia. If this is inadequate, general endotracheal anesthesia will be considered.
- High block: Strict adherence to the doses described in this protocol will be mandated.
- PDPH: Patients will be assessed for a PDPH daily and if present, treated with fluid resuscitation, acetaminophen, butalbital, and caffeine. Patients that do not respond to conservative treatment will be offered a blood patch.
- Bleeding: Only patients will platelet counts higher than 80,000, INR > 1.2, or PTT > 36 seconds will be offered spinal anesthesia.
- Infection: Strict aseptic technique will be followed with hand washing, use of sterile gloves, mask, cap, and skin preparation with chlorhexidine gluconate.
- Nerve injury: Only trained MD anesthesia personnel will be allowed to place the spinal. Patients will be assessed for nerve injury daily. Patients with nerve injuries that do not resolve on their own will be referred for neurology consult.
- Fetal heart rate changes: Hypotension will be mitigated as described above. Fetal bradycardia will be treated with discontinuation of intravenous oxytocin if applicable, changes in patient position, administration of supplemental oxygen, and for recalcitrant uterine hypertonus tocolytic medications will be administered.
- LAST: The dose of bupivacaine (10.5 mg) and chloroprocaine (50 mg) that will be administered will be far below the maximum recommended dosage for bupivacaine (3 mg/kg)[27] and chloroprocaine (11 mg/kg)[28].

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)[28]

and fetal (mean 15.4 seconds, SD 5.2)[28] plasma half-life and relatively high maximum recommended dosage (11 mg/kg without epinephrine).

The clinical presentation of local anesthetic systemic toxicity is quite variable[29]. Most case reports describe local anesthetic systemic toxicity after administration of local anesthetics with a much longer duration of action than chloroprocaine[29,30]. 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)[29].

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[29]. A search of PubMed and Google revealed 3 articles that describe systemic toxicity from chloroprocaine[31-33]. Cladis et al[33] 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[32] 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[31] 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[31-33].

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. Ionized particles cannot cross the lipid membrane of the placenta. Ion trapping occurs when non-ionized local anesthetics cross the placenta, become ionized in relatively acidotic fetal blood, compared to maternal blood, and get stuck in fetal circulation. This creates a cycle in which accumulating local anesthetic causes the fetus to become more acidotic which results in more ion trapping. Because only non-ionized local anesthetic equilibrates across the placenta and the ratio of ionized to non-ionized local anesthetic is higher in fetal blood, a sink is created driving local anesthetic into fetal circulation. Placental transfer of chloroprocaine has not been shown to be influenced by the degree of fetal acidosis.[34]

Literature describing intrathecal chloroprocaine administration in pregnant women 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 administration:

- Seizures
- Tinnitus
- Metallic taste
- Anxiety
- Agitation
- Muscle twitching
- Sedation
- Respiratory depression with desaturation (oxygen saturation < 88%)
- Dizziness
- Nausea
- Vomiting
- Vision changes
- Paresthesias
- Perioral numbness
- Hypotension (drop in systolic blood pressure >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

5.3.2 Potential Benefits

We are performing this study because the duration of anesthesia provided by hyperbaric bupivacaine exceeds the time necessary to complete short obstetric procedures. Intrathecal chloroprocaine may shorten the duration of motor block after spinal placement, compared to hyperbaric bupivacaine. Shorter motor block may translate to a shorter duration of PACU Phase 1 recovery, a shorter PACU stay, earlier ambulation, and less required bladder catheterization procedures. Patient satisfaction may improve with short PACU times, earlier ambulation, and less bladder catheterizations.

6 OBJECTIVES

6.1 Study Objectives

6.1.1 Primary Objective:

1. To compare duration of motor block, defined as the number of 5-minute intervals since completion of spinal injection to achievement of a Bromage scale score of 2 (able to flex knees), between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.

6.1.2 Secondary Objectives:

1. To compare duration of motor block, defined by patient report since completion of spinal injection to achievement of a Bromage score of 2 (able to flex knees), between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.
2. To compare Phase 1 PACU length of stay between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.
3. To compare total PACU time (Phase 1 + Phase 2) between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.
4. To compare time to first ambulation between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.
5. To compare incidence of bladder catheterization (Foley or straight catheterization) between patients randomly assigned to receive Clorotekal® or hyperbaric bupivacaine.

6.1.3 Tertiary Objectives:

1. To compare IV opioid consumption, in milligram morphine equivalents, between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.
2. To compare highest sensory block level achieved, measured by pinprick, between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.

6.1.4 Safety Objectives:

1. To compare incidence of intraoperative hypotension (systolic blood pressure <100 mm Hg or > 20% drop from baseline systolic blood pressure requiring intervention) between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.
2. To compare intraoperative vasopressor requirement between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine.
3. To evaluate the safety of Clorotekal® comparing the occurrence of adverse events including perioperative respiratory depression, new postoperative neurologic deficits, nausea or vomiting between patients randomly assigned to Clorotekal® or hyperbaric bupivacaine, and any other serious adverse events.

6.2 Study Outcome Measures

6.2.1 Primary Outcome Measure

Motor Block (interval assessment): Bromage scale score at 5 minute intervals, since spinal injection. Interval assessment motor block will be defined as the number of 5-minute intervals since completion of spinal injection to achieve a Bromage score of 2 (able to flex knees).

Definition: Bromage scale:
Bromage score 1: Free movement of legs and feet (no block)
Bromage score 2: Able to flex knees and move feet (partial block)
Bromage score 3: Unable to flex knees, but able to move feet (near complete block)
Bromage score 4: Unable to move legs or feet (complete block)

6.2.2 Secondary Outcome Measures

Motor block (patient report): The patient will be instructed to notify the outcomes assessor when they are able to flex their knees (Bromage score 2). Patient report motor block will be defined as the time interval in minutes since completion of spinal injection to achieve a Bromage score of 2 (able to flex knees).

Phase 1 PACU time: Phase 1 PACU time will be defined as the interval between "out of operating room" and "end of Phase 1" as documented by the PACU nurse. Patients must achieve the following after spinal anesthesia in order to complete Phase 1 of PACU recovery:

- Hemodynamic stability defined as a systolic blood pressure and heart rate within 20% of baseline

- Safe oxygen saturation defined by an oxygen saturation > 94% on room air or for patients with low baseline saturation an oxygen saturation within 2% of baseline
- Stable electrocardiogram rhythm that is consistent with baseline
- Independent maintenance of airway
- Respiratory rate greater than or equal to 10 breaths per minute
- Temperature greater than 36 degrees Celsius
- Return to baseline level of consciousness
- Surgical hemostasis
- Pain less than or equal to 4/10 or for chronic pain patients, less than or equal to 2 points above baseline
- Either no nausea or mild nausea without vomiting
- Bromage score of 2 or less

PACU time (Phase 1 + Phase 2): PACU time will be defined as the interval between "out of operating room" and "end of Phase 2" as documented by the labor and delivery nurse for patients discharged home and as mutually agreed upon by the outcomes assessor and nurse for patients discharged to the ward. In addition to meeting Phase 1 criteria, patients must be able to ambulate, micturate, and tolerate food intake in order to exit Phase 2 of PACU recovery. Completing Phase 2 of PACU recovery is also requires that a responsible adult can escort the patient out of the hospital and remain with the patient for the first 24 hours.

Time to ambulation: Defined as the time interval in minutes between intrathecal medication administration and time to first ambulation. Ambulation requires a Bromage score of 1 and a standard nursing assessment that is already in practice at Oregon Health and Science University (OHSU).

Bladder Catheterization: Defined as the insertion of a Foley catheter or a Straight catheterization within 24 hours of spinal insertion.

6.2.3 Tertiary Outcome Measures

Opioid consumption: Defined as the total intraoperative opioid consumption in milligram morphine equivalents.

Peak block sensory level: Defined as the most caudal dermatome with sensation to pinprick at the time of "anesthesia ready."

6.2.4 Safety Outcome Measures

Incidence of hypotension: Defined by the proportion of patients given intraoperative vasopressor (phenylephrine or ephedrine) for a systolic blood pressure drop greater than 20% below baseline or any SBP < 100 mm Hg.

Vasopressor requirement: Defined by the total intraoperative quantity of phenylephrine administered in mcg.

Respiratory depression: Defined by a respiratory rate less than 10 breaths per minute.

New neurologic deficits: Defined as a new, persistent sensory deficit, motor deficit, or dysesthesia diagnosed during the patient's hospitalization.

Nausea: Defined by a self-report of intraoperative nausea by the patient, yes or no.

Vomiting: Defined by an observed intraoperative vomiting episode by the outcomes assessor, yes or no.

7 STUDY DESIGN

Study Design:

This will be a single-blind, randomized, controlled, single center clinical trial assessing the efficacy of Clorotekal® on resolution of motor block and associated patient flow through the PACU. Fifty patients will be equally randomized to receive either Clorotekal® or hyperbaric bupivacaine.

Masking:

1. Subject
2. Obstetric provider
3. Investigator
4. Outcomes assessor

The anesthesia provider will be unblinded because of the large difference in volume between Clorotekal® (5 mL) and hyperbaric bupivacaine (1.4 mL). The block characteristics and safety profile of a dilution of 10.5 mg hyperbaric bupivacaine to a volume of 5 mL are unknown.

8 STUDY ENROLLMENT AND WITHDRAWAL

8.1 Subject Inclusion Criteria

1. Women 18 years old or greater
2. ASA category 1-3
3. Undergoing one of the following obstetric procedures: bilateral tubal ligation, external cephalic version, cerclage insertion, cerclage removal, minimally invasive fetal surgery, or evacuation of retained products of conception.

8.2 Subject Exclusion Criteria

1. Refusal of consent
2. Multiple gestations
3. History of ester local anesthetic or para-aminobenzoic acid allergy
4. Height less than 5 feet or greater than 6 feet
5. Body mass index less than 18.5 kg/m^2 or greater than 45 kg/m^2
6. Any coagulopathy defined by platelets < 80k/microliter, INR > 1.2, or PTT > 36 seconds
7. Signs of hypovolemia that is not corrected by routine management including hypotension (systolic blood pressure <90 mm Hg) at the time of evaluation
8. Liver disease including jaundice and ascites, with elevated liver function tests, AST > 2x institutional normal, ALT > 2x institutional normal
9. Renal disease including history of dialysis, with elevated renal function tests on admission labs, glomerular filtration rate <60 ml/min/1.73 m^2
10. Infection at the site of potential spinal insertion
11. Neurologic condition that contraindicates spinal anesthesia, tethered spinal cord or multiple sclerosis
12. Known atypical plasma cholinesterase activity
13. Other contraindications to receive a spinal anesthetic
14. Vulnerable populations including prisoners and decisionally impaired adults

Due to the nature of the study, pregnant subjects will have to be enrolled to obtain the medical knowledge that we seek. A very small quantity of drug may possibly be transferred to the fetus through the placenta, 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).

8.3 Strategies for Recruitment and Retention

Most subject recruitment is expected to occur by approved study staff as early as two months prior to a potential subject's scheduled operation 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 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 will not be offered remuneration as incentive for completing the study protocol.

8.4 Treatment Assignment Procedures

8.4.1 Randomization Procedures

Subjects will be randomly assigned to either the intervention (chloroprocaine) or control (hyperbaric bupivacaine) arm. Before initiation of the clinical portion of the study, 50 opaque sealed envelopes will be prepared by a researcher not involved in subject recruitment or enrollment: 25 for the intervention arm and 25 for the control arm. These envelopes will be randomized without stratification via a computer generated random allocation sequence and numbered in ascending order from 1 to 50. Subjects enrolled in the study will be assigned to the next free envelope and given the corresponding treatment contained therein. All researchers involved in patient recruitment, allocation, and assessment will be kept blind to the allocation sequence.

8.4.2 Masking Procedures

Assessment of outcomes will be conducted by a researcher blind to treatment allocation. The subject and the obstetric providers will also be blinded to treatment allocation. To blind the outcome assessor and obstetric provider they will remain outside of the operating room while the spinal is being placed. The anesthesia provider will be unblinded because of the large difference in volume between Clorotekal® (5 mL) and hyperbaric bupivacaine (1.4 mL). The block characteristics and safety profile of a dilution of 10.5 mg hyperbaric bupivacaine to a volume of 5 mL are unknown. The anesthesia provider will be strongly inculcated not to disclose the treatment allocation to the subject, outcomes assessor, or obstetric providers after spinal placement. A member of the research team not involved in patient recruitment, allocation, or assessment will feed collected data into the APOM OCEAN, a 21 CFR Part 11-compliant electronic data capture system provided by the Department of Anesthesiology and Perioperative Medicine, so that data analysis can occur without disclosing information about allocation.

The medical safety monitor will not be blinded.

8.5 Subject Withdrawal

8.5.1 Reasons for Withdrawal

Subjects enrolled that do not receive a spinal anesthetic, for any reason, may be withdrawn from the study. In addition, a subject may be removed from the study if the investigator or funder stops the study, a member of the care team feels like the study is no longer in the best interest of the subject. In the event that such a situation occurs the subject would be informed at the earliest reasonable time.

8.5.2 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

The study will follow a modified intention-to-treat approach. Subjects that enroll in the study and then decide to withdraw before spinal placement will be excluded from further data collection and analysis.

Subjects that decide they no longer want to participate in research after completion of the study protocol, data will be collected up to the time of withdrawal.

8.6 Premature Termination or Suspension of Study

There is no planned interim analysis, but the study may be suspended or prematurely terminated by the medical monitor for safety concerns after discussion with the study PI and the sponsor.

9 STUDY INTERVENTION

9.1 Study Product Description

9.1.1 Acquisition

The product for the intervention arm (Clorotekal®) has been acquired from B. Braun Medical Inc.

The active comparer (hyperbaric bupivacaine) is available in all operating rooms at OHSU.

9.1.2 Formulation, Packaging, and Labeling

Clorotekal® is a 1% formulation of chloroprocaine indicated for intrathecal injection. Each mL of Clorotekal® contains 10 mg chloroprocaine HCL, equivalent to 8.81 mg chloroprocaine base, sodium chloride 1 N, water for injection. Clorotekal® comes in single dose 5 mL glass ampules.

Hyperbaric bupivacaine is a 0.75% formulation of bupivacaine that contains 8.25% dextrose for intrathecal injection. Each mL of solution contains 7.5 mg bupivacaine. Hyperbaric bupivacaine comes in 2 mL glass ampules.

9.1.3 Product Storage and Stability

Clorotekal® is stored in cartons containing ten single-dose 5 mL glass ampules. The product will be stored at room temperature in the cartons. The product acquired has an expiration date of April 2020 when kept in unbroken vials.

Hyperbaric bupivacaine is stored in the drug trays of all labor and delivery operating room equipment carts. The product will be stored at room temperature. Due to the high quantity of hyperbaric bupivacaine used at OHSU vials with different expiration dates are available. Only unexpired hyperbaric bupivacaine will be used.

9.2 Study Procedures

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

- Age
- Height
- Weight at time of surgery
- Body mass index at time of surgery
- Gestational age
- Parity
- History of previous neuraxial anesthesia
- Type of surgery

Before study activation a sample of 50 sequentially numbered opaque envelopes will be prepared by a researcher not involved in patient recruitment, allocation, consent, or assessment: 25 for the Clorotekal® arm and 25 for the bupivacaine arm. Patient allocation will occur in the operating room when the anesthesia provider responsible for patient care opens the lowest remaining numbered free envelope. Group assignment will be determined by a computer generated random number sequence [Excel, Redmond WA]). The random number sequence will be generated by a researcher not involved in either patient enrollment or patient assignment. The medication for intrathecal injection (i.e. Clorotekal® or bupivacaine) will be defined in the opened opaque envelope. Once a study subject signs a consent form, a unique number corresponding to the opened opaque envelope will be assigned to that subject. This subject number will never be reused and will remain with the subject for the entirety of the study. No subject will ever be allowed to have more than one unique subject number. The envelope will not be opened until the anesthesia provider is ready to prepare and administer the spinal anesthetic. The envelope will not be opened in the presence of the outcomes assessor or a member of the obstetric team. The patient will have their back to the envelope when it is opened. The envelope will be disposed of prior to the outcomes assessor entering the operating room.

Subjects will receive a 1 liter co-load of crystalloid (Ringer's Lactate or Normal Saline) solution during spinal placement. All patients will have standard ASA monitors plus five lead EKG applied. Additional monitoring needs will be left up the anesthesia team directing patient care.

Subjects will be allocated to either intrathecal injection of 50 mg Clorotekal® or 10.5 mg (1.4 mL) hyperbaric bupivacaine. The intrathecal space will be accessed with a 25 gauge Whitacre needle. Upon obtaining CSF, the syringe of study solution will be attached the end of the Whitacre needle. The syringe will be pulled back to reveal aspiration of CSF. The study solution will then be administered over approximately 5 seconds. The Whitacre needle and spinal introducer needle will be removed from the patient's back. The patient will be placed supine on the operating room table. The outcomes assessor will then be allowed to enter the operating room.

Decisions on when to administer additional sedative and analgesic medications will be left to the discretion of the anesthesia team. The level of block will be initially assessed by the anesthesia team. When the block is felt to be at peak height the outcomes assessor will test with pinprick to determine the peak block height.

In accordance with standard of practice at our institution all patients will have convective warmers used during the case and patient temperature will be monitored. Non-invasive blood pressures will be obtained every 2.5 minutes after spinal placement. The frequency of blood pressure measurement will be changed to every 5 minutes, 15 minutes after spinal placement. Anesthesia providers will administer phenylephrine via intravenous bolus to maintain maternal blood pressure within 20% of baseline or for a

SBP < 100 mm Hg. Anesthesia providers will be allowed to add ephedrine or glycopyrrolate to phenylephrine for maternal hypotension with co-existent bradycardia.

A research coordinator will remain 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 spinal placement: 5 minutes, 10 minutes, 15 minutes, upon PACU arrival, upon completing Phase 1 of PACU recovery, and upon discharge from the PACU:

- Seizures
- Tinnitus
- Metallic taste
- Agitation
- Sedation
- Respiratory depression (respiratory rate < 10 breaths per minute)
- Dizziness
- Nausea
- Vomiting
- Vision changes
- Paresthesia
- Perioral numbness
- Hypotension (drop in MAP > 20% or SBP < 100 mm Hg)
- Arrhythmias

The dose of chloroprocaine and bupivacaine used in the study are very unlikely to cause symptoms of local anesthetic systemic toxicity. However, patients that exhibit seizures, arrhythmias, 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.

The research coordinator will obtain from anesthesia, upon arrival to the PACU, the total dose of intraoperative opioids administered, whether the patient had intraoperative hypotension, and the total dose of intraoperative phenylephrine administered. In the PACU, the research coordinator will determine the patient's Bromage scale score at 5-minute increments. The research coordinator will also ask the patient to notify them when they have a Bromage scale score of 2 (able to flex knees). While in the PACU, the research coordinator will also document the time of PACU arrival, the end of Phase 1 of PACU recovery, and the time that the patient leaves the PACU (end of Phase 2).

The research coordinator will meet with the patient on the evening of their surgery as

well as daily for the duration of their hospitalization to assess for time of first ambulation, whether a Foley or Straight catheter was inserted into the bladder, and for adverse events including, new postoperative neurologic deficits and any other potential adverse events.

To gather information on the incidence of new postoperative neurologic deficits all patients will be called 1 week after spinal insertion. A telephone script will be used to obtain this information.

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.

10 STUDY SCHEDULE

Study initiation including IRB submission and obtaining IRB approval is expected to take 6 months. Assuming we can enroll one patient per week, study enrollment should take approximately 50 weeks (12 months). Data collection will occur during the study enrollment period. Data analysis, writing, editing and submission to a peer-reviewed journal is expected to take 6 months.

In summary, the study should be completed within 2 years of obtaining approval for funding.

10.1 Screening

Patients will be screened weekly by the PI for the duration of the enrollment period (12 months).

10.2 Enrollment/Baseline

Subject enrollment and collection of baseline characteristics are expected to occur in the preoperative area on the morning of surgery. Patients arrive to the preoperative area 2 hours before their scheduled surgery. There is a significant amount of research that occurs on labor and delivery at OHSU. Accordingly, built into this 2 hour time period is time for patients to meet with research coordinators.

10.3 Outcome Assessor Visits

After enrolling the patient, the outcome assessor will remain outside of the operating room while the intrathecal injection is completed. This will keep the outcome assessor blinded. The outcome assessor will then enter the operating room and remain with the patient for the duration of their surgery. The outcome assessor will go with the patient to the PACU and remain with the patient until discharge to the surgical ward or home. The outcome assessor will visit the patient daily on the surgical ward until discharge.

11 ASSESSMENT OF SAFETY

11.1 Reporting Procedures

Serious adverse events will be reported to the study medical monitor within 48 hours of learning of the event and followed up until resolution. Serious, unanticipated adverse events will be reported to the sponsor and to regulatory authorities within 5 business days, in accordance with Federal Regulations. Listings of adverse events will be generated quarterly to assess for trends, and examined for possible patterns between the groups and over time. If potential trends or unexpected events are noted, a summary will be provided to the Institutional Review Board and to the sponsor for further review and evaluation.

11.2 Halting Rules

Significant clinical manifestations of local anesthetic systemic toxicity will 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 (oxygen saturation < 88%)
- Any arrhythmias associated with hypotension
- Cardiac arrest

The study will also be halted and the IRB notified if two or more patients in the Clorotekal® group are unable to complete their surgery under spinal anesthesia, requiring general endotracheal anesthesia. Only a few patients a year require general endotracheal anesthesia to complete the surgeries included in this study. In this manner, two failed spinals would constitute enough concern to halt the study and prompt investigation.

12 STUDY OVERSIGHT

In addition to the PI's responsibility for oversight, an independent Medical Monitor will be assigned to review serious adverse events (SAEs) and unanticipated problems (UPs). The PI will review a listing of serious adverse events, unanticipated problems and adverse events every 3 months. If an unexpectedly high incidence of SAEs (Suspected, Unanticipated, Serious Adverse Reactions related to the study drug - SUSARs), UPs or unusual trends in AEs is observed, the PI will discuss with the Sponsor if the trial should be terminated early, in accordance to a predefined Data Safety Monitoring Plan. If necessary, additional steps may be taken to ensure data integrity and protocol compliance.

13 CLINICAL SITE MONITORING

Clinical site monitoring is conducted to ensure that the rights of human subjects are protected, that the study is implemented in accordance with the protocol and/or other operating procedures, and that the quality and integrity of study data and data collection methods are maintained. Medical Monitoring for this study will be performed by Dr. Ryan Ivie. Dr. Ivie is the Director of Regional Anesthesia at OHSU and has significant experience and expertise providing spinal anesthesia. Dr. Ivie will evaluate the study SAEs and UPs in accordance with the International Conference on Harmonisation (ICH), E6: Good Clinical Practice guidelines (GCP), and local regulations. The Institutional Review Board will have oversight on the study conduct.

14 STATISTICAL CONSIDERATIONS

14.1 Study Hypotheses

We hypothesize that subjects administered Clorotekal® will have a shorter duration of motor block than subjects administered hyperbaric bupivacaine, defined as the number of 5-minute intervals since completion of spinal injection to achievement of a Bromage scale score of 2.

14.2 Sample Size Considerations

We plan to enroll 50 patients. A sample of 50 patients will provide at least 90% power to detect a 40-minute reduction in the duration of motor block, assuming a standard deviation of 40 minutes and a two-sided alpha level of 5%[18].

14.3 Planned Interim Analyses

14.3.1 Safety Review

For the safety endpoints, we will compare the pre-specified adverse events and any additional adverse events reported between the two groups. In addition, safety will be monitored on an ongoing basis throughout the trial by an independent Medical Monitor. The Medical Monitor will not be an investigator, but will have experience providing neuraxial anesthesia for the surgical procedures being studied. There will not be an *a priori* planned interim safety or tolerability review, however, the study can be stopped anytime for safety concerns.

14.3.2 Efficacy Review

There is no planned interim efficacy review.

14.4 Final Analysis Plan

Data analysis will be completed by N. David Yanez, co-director of the OHSU Biostatistics and Design Program within the Oregon Clinical and Translational Research Institute, upon conclusion of enrollment and follow up for patient #50.

The main analysis will use an intention-to-treat approach. Descriptive statistics will be used to describe the distribution of baseline characteristics using two-sample Student's t-test or chi-square statistic, as appropriate. The primary endpoint, number of assessments at 5-min intervals from spinal injection to Bromage score of 2, will be compared using an independent two-sample Student's t-test with assumption of unequal variances. We will also evaluate the number of minutes from spinal injection to Bromage score of 2 based on participant's report to return of knee flection. This test will also be used for other secondary endpoints with symmetric distribution. A test of homogeneity using the chi-square statistic will be performed for dichotomous or categorical variables. A two-sided level of significance of .05 will be considered for all analyses. The analyses will be performed using the statistical software STATA (Stata Corp, College Station, TX).

15 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of subjects. Study staff will permit authorized representatives of B. Braun and regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress and data validity.

16 ETHICS/PROTECTION OF HUMAN SUBJECTS

16.1 Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

16.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

16.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Consent forms will be IRB-approved, and the subject is required to read and review the document or have the document read to him or her. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

16.4 Exclusion of Women, Minorities, and Children (Special Populations)

The study will only include women because obstetric procedures are being studied. Women of all racial/ethnic groups may participate. Children will be excluded from this study as that is our institutional standard for clinical trials on labor and delivery.

16.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the sponsor and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests (not applicable to this study) in addition to any study information relating to subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

17 HANDLING OF DATA AND SPECIMENS

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation.

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.

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.

Clinical data will be entered into APOM OCEAN, a 21 CFR Part 11-compliant Electronic Data Capture (EDC) system provided by the Department of Anesthesiology and Perioperative Medicine. The EDC system includes password protection. Secure data will be stored in APOM OCEAN 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
    - Age
    - Height
    - Weight at time of surgery
    - Body mass index at time of surgery
    - Gestational age
    - Parity
    - History of previous neuraxial anesthesia
    - Type of surgery
    - Level of intrathecal injection

- Signs and symptoms of local anesthetic toxicity at the following time intervals after spinal placement: 5 minutes, 10 minutes, 15 minutes, upon PACU arrival, upon completing Phase 1 of PACU recovery, and upon discharge from the PACU:

    - Seizures
    - Tinnitus
    - Metallic taste
    - Agitation
    - Sedation
    - Respiratory depression (respiratory rate < 10 breaths per minute)
    - Dizziness
    - Nausea
    - Vomiting
    - Vision changes
    - Paresthesias
    - Perioral numbness
    - Arrhythmias

- Primary, secondary and tertiary endpoints

    - Duration of motor block, defined as the number of 5-minute intervals since completion of spinal injection to achievement of a Bromage scale score of 2
    - Duration of motor block, defined by patient report since completion of spinal injection to achievement of a Bromage scale score of 2
    - PACU Phase 1 length
    - PACU length of stay
    - Time to first ambulation
    - Bladder catheterization
    - Intraoperative opioid consumption in parenteral morphine equivalents
    - Highest sensory block achieved
    - Incidence of hypotension (drop in MAP > 20% or SBP < 100 mm Hg)
    - Intraoperative phenylephrine requirement in mcg
    - Occurrence of adverse events including perioperative respiratory depression, new postoperative neurologic deficits, or any other potential adverse events

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.

18 PUBLICATION/DATA SHARING POLICY

The current plan is to present the study results at a future American Society of Anesthesiologists annual meeting. The manuscript will be submitted to a peer-reviewed journal.

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. This study will not generate genetic information or imaging studies.

19 LITERATURE REFERENCES

1. Palmer CM, D'Angelo R, Paech MJ. *Obstetric anesthesia.* Oxford ; New York: Oxford University Press; 2011.
2. Huffnagle SL, Norris MC, Huffnagle HJ, Leighton BL, Arkoosh VA. Intrathecal hyperbaric bupivacaine dose response in postpartum tubal ligation patients. *Reg Anesth Pain Med.* 2002;27(3):284-288.
3. McKenzie C, Akdagli S, Abir G, Carvalho B. Postpartum tubal ligation: A retrospective review of anesthetic management at a single institution and a practice survey of academic institutions. *J Clin Anesth.* 2017;43:39-46.
4. Viscomi CM, Rathmell JP. Labor epidural catheter reactivation or spinal anesthesia for delayed postpartum tubal ligation: a cost comparison. *J Clin Anesth.* 1995;7(5):380-383.
5. Chalifoux LA, Bauchat JR, Higgins N, et al. Effect of Intrathecal Bupivacaine Dose on the Success of External Cephalic Version for Breech Presentation: A Prospective, Randomized, Blinded Clinical Trial. *Anesthesiology.* 2017;127(4):625-632.
6. Weiniger CF, Ginosar Y, Elchalal U, Sela HY, Weissman C, Ezra Y. Randomized controlled trial of external cephalic version in term multiparae with or without spinal analgesia. *Br J Anaesth.* 2010;104(5):613-618.
7. Weiniger CF, Sultan P, Dunn A, Carvalho B. Survey of external cephalic version for breech presentation and neuraxial blockade use. *J Clin Anesth.* 2016;34:616-622.
8. Lee GY, Kim CH, Chung RK, Han JI, Kim DY. Spread of subarachnoid sensory block with hyperbaric bupivacaine in second trimester of pregnancy. *J Clin Anesth.* 2009;21(7):482-485.
9. Lee MH, Son HJ, Lee SH, et al. Comparison of spread of subarachnoid sensory block and incidence of hypotension in early and late second trimester of pregnancy. *Korean J Anesthesiol.* 2013;65(4):322-326.
10. Van de Velde M, De Buck F. Fetal and maternal analgesia/anesthesia for fetal procedures. *Fetal Diagn Ther.* 2012;31(4):201-209.
11. Maes S, Laubach M, Poelaert J. Randomised controlled trial of spinal anaesthesia with bupivacaine or 2-chloroprocaine during caesarean section. *Acta Anaesthesiol Scand.* 2016;60(5):642-649.
12. Maher DP, Wong W, Woo P, et al. Perioperative factors associated with HCAHPS responses of 2,758 surgical patients. *Pain Med.* 2015;16(4):791-801.
13. Dexter F, Tinker JH. Analysis of strategies to decrease postanesthesia care unit costs. *Anesthesiology.* 1995;82(1):94-101.
14. Zite N, Wuellner S, Gilliam M. Failure to obtain desired postpartum sterilization: risk and predictors. *Obstet Gynecol.* 2005;105(4):794-799.
15. Committee on Health Care for Underserved W. Committee opinion no. 530: access to postpartum sterilization. *Obstet Gynecol.* 2012;120(1):212-215.
16. Marshall SI, Chung F. Discharge criteria and complications after ambulatory surgery. *Anesth Analg.* 1999;88(3):508-517.

17. Zaric D, Pace NL. Transient neurologic symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics. *Cochrane Database Syst Rev.* 2009(2):CD003006.
18. Saporito A, Ceppi M, Perren A, et al. Does spinal chloroprocaine pharmacokinetic profile actually translate into a clinical advantage in terms of clinical outcomes when compared to low-dose spinal bupivacaine? A systematic review and meta-analysis. *J Clin Anesth.* 2019;52:99-104.
19. Gupta A, Axelsson K, Thorn SE, et al. Low-dose bupivacaine plus fentanyl for spinal anesthesia during ambulatory inguinal herniorrhaphy: a comparison between 6 mg and 7. 5 mg of bupivacaine. *Acta Anaesthesiol Scand.* 2003;47(1):13-19.
20. Prescribing Information: Clorotekal. In: Inc. BBM, ed2018.
21. Camponovo C, Wulf H, Ghisi D, et al. Intrathecal 1% 2-chloroprocaine vs. 0.5% bupivacaine in ambulatory surgery: a prospective, observer-blinded, randomised, controlled trial. *Acta Anaesthesiol Scand.* 2014;58(5):560-566.
22. Lacasse MA, Roy JD, Forget J, et al. Comparison of bupivacaine and 2-chloroprocaine for spinal anesthesia for outpatient surgery: a double-blind randomized trial. *Can J Anaesth.* 2011;58(4):384-391.
23. Teunkens A, Vermeulen K, Van Gerven E, Fieuws S, Van de Velde M, Rex S. Comparison of 2-Chloroprocaine, Bupivacaine, and Lidocaine for Spinal Anesthesia in Patients Undergoing Knee Arthroscopy in an Outpatient Setting: A Double-Blind Randomized Controlled Trial. *Reg Anesth Pain Med.* 2016;41(5):576-583.
24. Yoos JR, Kopacz DJ. Spinal 2-chloroprocaine: a comparison with small-dose bupivacaine in volunteers. *Anesth Analg.* 2005;100(2):566-572.
25. Forster JG. Short-acting spinal anesthesia in the ambulatory setting. *Curr Opin Anaesthesiol.* 2014;27(6):597-604.
26. Goldblum E, Atchabahian A. The use of 2-chloroprocaine for spinal anaesthesia. *Acta Anaesthesiol Scand.* 2013;57(5):545-552.
27. Thiele R, Nemergut E. Local anesthetics: systemic toxicity. *Open Anesthesia*. Accessed Febrary 15th, 2019, 2019.
28. Kuhnert BR, Kuhnert PM, Philipson EH, Syracuse CD, Kaine CJ, Yun CH. The half-life of 2-chloroprocaine. *Anesth Analg.* 1986;65(3):273-278.
29. Vasques F, Behr AU, Weinberg G, Ori C, Di Gregorio G. A Review of Local Anesthetic Systemic Toxicity Cases Since Publication of the American Society of Regional Anesthesia Recommendations: To Whom It May Concern. *Reg Anesth Pain Med.* 2015;40(6):698-705.
30. Di Gregorio G, Neal JM, Rosenquist RW, Weinberg GL. Clinical presentation of local anesthetic systemic toxicity: a review of published cases, 1979 to 2009. *Reg Anesth Pain Med.* 2010;35(2):181-187.
31. Marsch SC, Sluga M, Studer W, Barandun J, Scharplatz D, Ummenhofer W. 0.5% versus 1.0% 2-chloroprocaine for intravenous regional anesthesia: a prospective, randomized, double-blind trial. *Anesth Analg.* 2004;98(6):1789-1793, table of contents.

32. Hernandez MA, Boretsky K. Chloroprocaine: local anesthetic systemic toxicity in a 9-month infant with paravertebral catheter. *Paediatr Anaesth.* 2016;26(6):665-666.
33. Cladis FP, Litman RS. Transient cardiovascular toxicity with unintentional intravascular injection of 3% 2-chloroprocaine in a 2-month-old infant. *Anesthesiology.* 2004;100(1):181-183.
34. Philipson EH, Kuhnert BR, Syracuse CD. Fetal acidosis, 2-chloroprocaine, and epidural anesthesia for cesarean section. *Am J Obstet Gynecol.* 1985;151(3):322-324.