STUDY TITLE:

A Randomized Controlled Trial of Intrathecal Chloroprocaine vs. Bupivacaine for Cervical Cerclage

STUDY SPONSOR:

Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center

PRINCIPAL INVESTIGATOR

Dan Drzymalski, MD
Assistant Professor
Tufts University School of Medicine
Department of Anesthesiology and Perioperative Medicine
Tufts Medical Center
Phone: 617-913-8168
Email: ddrzymalski@tuftsmedicalcenter.org

CO-INVESTIGATOR

Alaa Basura, MD
Post Doctoral Research Fellow
Tufts University School of Medicine
Department of Anesthesiology and Perioperative Medicine
Tufts Medical Center
Phone: 202-299-4888
Email: abasura@tuftsmedicalcenter.org

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1. Study Schema

Enrollment	Randomization	Arm 1	8 patients	Bupivacaine
		Arm 2	8 patients	Chloroprocaine

2. Introduction

2.1 Background and Rationale

Cervical cerclage is an ambulatory surgical procedure of short duration commonly performed under neuraxial anesthesia. While bupivacaine is widely used for spinal anesthesia in cesarean delivery, its duration of action is significantly longer than that of the typical cerclage placement. (1) Chloroprocaine is another local anesthetic of shorter duration that has been used for neuraxial anesthesia in a variety of outpatient procedures, including procedures on the perineum. One of the major advantages of chloroprocaine is faster block resolution and earlier hospital discharge compared with spinal bupivacaine. (2,3) Chloroprocaine is also considered safer that other local anesthetics because the risk of transient neurologic symptoms is exceedingly low. (4) Bupivacaine may be specifically chosen in cases where the procedure is expected to take longer than usual (e.g. bulging bag), but oftentimes the choice between chloroprocaine and bupivacaine is completely arbitrary; good scientific practice would mean that we better understand the differences, and use the medications when clinically indicated.

Both local anesthetics are currently used at Tufts Medical Center for spinal anesthesia during cervical cerclage placement, but how their use impacts clinical care, in particular patient flow, is not well understood. A similar randomized controlled trial at Columbia University is currently comparing bupivacaine to chloroprocaine for cervical cerclage procedures, but differs from our study in several important ways. (5) First, we are not using fentanyl in our study because its use results in side effects, most significantly pruritus. Second, although the dose of chloroprocaine and bupivacaine is lower in our study compared to that at Columbia, the doses are adequate for the duration of procedure as performed at Tufts Medical Center and within the standard of care at Tufts Medical Center. Finally, while Columbia is enrolling 50 patients, we cannot enroll as many patients because our volume is significantly smaller. We perform an average of 3 cerclage procedures each month, or 36 a year. Furthermore, given our power calculation, we do not required as many patients as are being enrolled at Columbia.

Our goal is to perform a randomized controlled trial of chlororpocaine vs. bupivaciane for cervical cerclage. We hope to compare the effect of these two drugs on duration of motor block and duration until meeting discharge criteria. Our hypothesis is that chloroprocaine will result in faster resolution of motor block and meeting dischrage criteria earlier.

- Is there an active control group?

  ☐ **Yes** ☑ **No**

2.2 Risks to Subjects`

The risks of spinal anesthesia include nausea, vomiting, hypotension, pruritis, and postdural puncture headache. Given that these side effects are expected and commonly occur with spinal anesthesia regardless of drug administered, they will be managed according to our standard practices, including giving the patient antiemetics and pressers.

The risks of patient randomized to bupivacaine include dizziness, nervousness, agitation, drowsiness, apprehension, euphoria, blurred/double vision, slurred speech, tremors, convulsions, and seizure. Respiratory depression and arrest may follow. Other, more serious effects seen with IV use of this drug, particularly when it is administered rapidly, are cardiovascular collapse, central nervous system depression, and/or hypotension. We do not intend on using this medication IV.

The risks of patient randomized to chloroprocaine are generally dose related and may result from rapid absorption from the injection site, diminished tolerance, or from unintentional intravascular injection of the local anesthetic solution. In addition to systemic dose-related toxicity, factors influencing plasma protein binding, such as acidosis, systemic diseases that alter protein production, or competition of other drugs for protein binding sites, may diminish individual tolerance. Plasma cholinesterase deficiency may also account for diminished tolerance to ester-type local anesthetics.

The risk to the fetus for bupivacaine and chloroprocaine are both low. Santos 1999 described a study where the mother received bupivacaine and found no adverse effects in the fetus. Philipson 1987 also found that when the mother got chloroprocaine, the fetus had no adverse effects and there were no umbilical levels of chloroprocaine, suggesting the chloroprocaine never even reached the fetus. Maes 2006 also studied 60 women getting either chloroprocaine and bupivacaine and observed no adverse neonatal effects, including normal Apgar scores.

Another risk of participating in the study is loss of confidentiality. In order to minimize that risk, all paperwork will be stored in a secure location. Furthermore, all electronic data will be held in a Tufts Medical Center provided, password protected, encrypted, Box storage account, which is compliant with institutional policies regarding HIPAA and the IT department.

2.3 Potential Benefits to Subjects

Potential benefits to subjects include faster recovery from anesthesia and quicker discharge to home in those who are randomized to chloroprocaine. The benefits of subjects randomized to bupivacaine are none. Benefits also include improving our scientific understanding of local anesthetics and an overall improvement to our society.

2.4 Alternatives

The alternative is not participating in the study.

3 Objectives

This objective of this study is to compare the effects of chloroprocaine vs. bupivacaine on duration of motor block and duration until meeting PACU discharge criteria.

- Primary Outcome:
  - Duration of motor block [Time Frame: 6 hours]
    - The start time is defined as the moment the intrathecal local anesthetic is injected, while the end time is defined as the moment when the subject has no motor block (as measured on the Bromage scale). We will then subtract the two times to get the duration of motor block.

- Secondary Outcomes:
  - Time to resolution of sensory block [Time Frame: 6 hours]
    - The start time is defined as the moment the intrathecal local anesthetic is injected, while the end time is defined as the moment when the subject has no more sensory block as tested conventionally. We will then subtract the two times to get the duration of sensory block.
  - Time to ambulation [Time Frame: 6 hours]
    - The start time is defined as the moment the intrathecal local anesthetic is injected, while the end time is defined as the moment when the subject walks for the first time postoperatively. We will then subtract the two times to get the time to ambulation.
  - Time to micturation [Time Frame: 6 hours]

- The start time is defined as the moment the intrathecal local anesthetic is injected, while the end time is defined as the moment when the subject voids for the first time postoperatively. We will then subtract the two times to get the time to micturation.

4 Enrollment and Withdrawal

4.1 Inclusion Criteria

- Female
- Age: 18-45 years old
- BMI $\leq$ 50 kg/m^2
- Singleton pregnancy
- ASA classification II or III
- Simple prophylactic cervical cerclage
- Planning neuraxial anesthesia

4.2 Exclusion Criteria

- Abdominal cerclage
- Complex cervical cerclage (e.g. bulging bag)
- Contraindication to neuraxial anesthesia
- Known hypersensitivity to chloroprocaine (a.k.a. Ester allergy)
- Known hypersensitivity to paraaminobenzoic acid (PABA)
- Known hypersensitivity to bupivacaine (a.k.a. Amide allergy)
- Pseudocholinesterase deficiency
- Concomitant use with ergot-type oxytocic drugs

4.3 Withdrawal of Subjects

All subjects will be included in the primary analysis as dictated by the theory of intention to treat analysis. As a sensitivity analysis, subjects developing complications, as adjudicated by the surgeon, will be excluded in the secondary analysis. Patients who decide to withdraw prematurely will be withdrawn and provided the standard of care at Tufts Medical Center.

4.4 Recruitment and Retention

4.4.1 Local Recruitment Methods

All faculty in the Obstetrics and Gynecology Department at Tufts Medical Center will be informed about the study at one of the departmental meetings. They will be asked to inform their patients about this study in their clinic visits. Once the patients arrive to the pre-operative area, the co-investigator, Dr. Basura, will meet with the patients and discuss the study with them further. If they agree to participate, informed consent will be obtained.

4.4.2 Study-Wide Recruitment Methods

Is this a multicenter study where subjects will be recruited by methods not under the control of the local Tufts site (e.g., call centers, national advertisements)?

☐ **Yes** ☑ **No**

4.4.3 Payment

Will subjects receive money, gifts, or any other incentive for participating in this study?

☐ **Yes** ☑ **No**

4.4.4 Reimbursement

Will subjects be reimbursed for their expenses, such as travel, parking, meals, or any other study related costs?

☐ **Yes** ☑ **No**

5 Study Design

5.1 Study Timelines

- Individuals will participate for the duration of the anesthetic (typically within 2 hours of injection of local anesthetic, although may last up to 6 hours in rare cases).
- We expect recruitment to take approximately one year.
- The estimated date for primary analyses will be October 2018
- For each individual there will only be one study visit lasting no more than 6 hours. It will include acquiring the patient consent, administering the spinal anesthetic, and following up until the time of discharge to home
-

5.2 Procedures

- Is there a placebo control arm?

☐ **Yes** ☑ **No**

We will perform a prospective, randomized, double blinded clinical trial.

Participants meeting inclusion criteria will be approached by the co-investigator, Dr. Basura, on the day of surgery. The research study will be explained and they will be given an informed consent form to read. After the participant has had adequate time to read through the informed consent form, think about the risks and benefits, and ask questions, she will be asked to sign the form if she wishes to participate in the study. The informed consent form will then be stored in the principal investigator's locked office.

Once a study subject is enrolled, the co-investigator, Dr. Basura, will give an opaque envelope to the study subject's assigned anesthesia provider, who will be asked to open the envelope in a separate room and prepare the medication, either chloroprocaine PF 40 mg (pure Nesacaine MPF 2% in a total volume of 2ml), or bupivacaine 7.5 mg (pure Sesnorcaine 0.75% diluted with normal saline to a total volume of 2ml). The medication will be prepared according to standard preparation of intrathecal drug, including wiping the vial stopper with an alcohol wipe to reduce the risk of infectious complications. The anesthesia provider will be told that this is a blinded study and asked not to reveal the randomization group to the patient or any research personnel. Both drugs have the same volume and color further ensuring blindness.

Upon entry into the operating room, the study subject will undergo the spinal procedure and injection of the allocated local anesthetic by the anesthesia provider. No additional medications affecting motor block will be given, which is part of the standard of care at Tufts Medical Center. Furthermore, the local anesthetic will be administered as a single dose and never repeated.

Neonates will be monitored for safety by performing fetal heart rate monitoring per the standard of obstetric care.

Immediately afterwards, the co-investigator, Dr. Basura, will begin to evaluate the patient's motor and sensory block in 5 minute intervals for the first hour, and 10 minutes intervals afterwards until resolution of the motor and sensory block. Evaluation of motor and sensory block will be done in such a way as not to interfere with the

surgery, and if for any reason at any time interval it is not possible to evaluate, the reason will be noted. The motor block will be evaluated according to the Bromage scale, where:

I = free movement of feet, legs and hip = No block
II = able to flex knees, with free movement of feet = Mild block
III = unable to flex knees, but with free movement of feet = Moderate block
IV = unable to move legs or feet = Complete block

Upon resolution of motor block, the co-investigator, Dr. Basura, will ask the participant if she can walk. Any ambulation will be done with a nurse to ensure the participant does not fall and hurt herself. The participant will also be asked to urinate, and the time she urinates will be recorded. Once the participant has resolution of motor and sensory block, can ambulate, and can micturate, the study will cease and the co-investigator, Dr. Basura, will thank the participant for her participation in the study. All data will be recorded on the data collection form (see attached form).

5.3 Evaluations

Will you perform any laboratory tests for this study?

☐ **Yes** ☑ **No**

5.4 Collection and Storage of Human Biological Specimens (Tissue Banking)

Will biological specimens be stored for **future, unspecified**, research?

☐ **Yes** ☑ **No**

6 Ethics and Protection of Human Subjects

6.1 Informed Consent Process

Will subjects be required to provide informed consent?

☑ **Yes** ☐ **No**

- The informed consent will take place in the pre-operative patient area.
- The patient will have one hour before the start of the procedure to make a decision regarding enrollment.
- The consent will be obtained in person and documented in writing according to SOP: Informed Consent Process for Research (HRP-090)
- Non-English speakers will be enrolled using interpreters and IRB approved Short Forms per the IRB's Short Form policy

6.2 Waiver or Alteration of Consent Process

- Is a waiver or alteration of the consent process being requested for this study?
  ☐ **Yes** ☑ **No**
- Is a waiver of the consent process being requested for parents for research involving children?
  ☐ **Yes** ☑ **No**
- Is a waiver of the consent process for planned emergency research being requested?
  ☐ **Yes** ☑ **No**

6.3 Confidentiality

In order to maintain confidentiality, the following measures will be taken:

- All study related materials, including consent forms and data collection forms, will be stored in the principal investigator's locked office
- The principal investigator and co-investigators will have exclusive access to the forms
- Digital data will be stored in a hospital provided, password protected, Box account
- Records will be stored for 7 years after the study is closed with the IRB, as per IRB policy.

A certificate of confidentiality will not be obtained

6.4 Provisions to Protect the Privacy Interests of Subjects

Subjects will be assured that their contact with any member of the research team is optional, and that the information they share will be strictly confidential.

6.5 Provisions to Monitor the Study to Ensure the Safety of Subjects

- The standard of care at Tufts Medical Center is to collect safety information on all patients undergoing surgery through an established computerized system called Anesthesia Touch. Safety information and adverse events that will be collected includes failure of spinal anesthesia and hypotension. For the purposes of this study, the principal investigator will periodically (every 6 months) evaluate the safety data and assess the risks and benefits to assess subject safety. The statistical tests that will be performed on the safety data to determine whether harm is occurring will include a chi-squared test, to compare proportions between groups.
- Stopping rule: should we observe 2 adverse events, 1 serious adverse event, or 1 unanticipated problem, the study will be stopped and we will investigate the nature of the event. .However, we do not anticipate this to be the case, because we use both of these drugs on a daily basis on obstetric anesthesia and we have not experienced any problems.
- No Data and Safety Monitoring Board will be used in this study.

6.6 Compensation for Research-Related Injury

Does the research involve greater than minimal risk to subjects?

☐ **Yes** ☑ **No**

6.7 Economic Burden to Subjects

Does the research involve any costs to subjects?

☐ **Yes** ☑ **No**

6.10 Vulnerable Populations

Will pregnant women be enrolled?

☑ **Yes** ☐ **No**

The study will be performed exclusively on pregnant women. Although the Food and Drug Administration has labeled one of the drugs in this study, chloroprocaine, as Category C risk in pregnancy, the risk to the fetus is likely very low. Chloroprocaine is metabolized very quickly by plasma cholinesterases, such that crossing the placenta and transmission to the fetus is exceedingly unlikely. This was demonstrated by Philipson 1987 in a study where after injection of chloroprocaine, the local anesthetic was nondetectable in umblical cord veins and neonatal plasma. (7) Similarly, in a comparison of bupivacaine and chloroprocaine, Maes 2006 found no differences in neonatal outcome as measured by Apgar scores and umbilical cord gases, suggesting no harm to the fetus from chloroprocaine. (8)

Given the amount of evidence suggesting no negative effects of chloroprocaine on the fetus, the local anesthetic is commonly used in pregnancy and is part of the standard of care for cervical cerclage at Tufts

Medical Center. This is further supported by the fact that another institution, Columbia University, is currently using chloroprocaine as part of a similar IRB-approved research study. Therefore, we believe this study's risk to the fetus is not greater than minimal risk. Given that the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, performance of this research is necessary.

Furthermore, the benefits of chloroprocaine warrant the use of this local anesthetic in pregnant women. The shorter the duration of motor block with chloroprocaine decreases the duration of immobility, thereby decreasing the risk for development of deep venous thrombosis (DVT). Participants are at particularly high risk for developing DVT, and there is countless evidence that suggests pregnant women should ambulate as much as possible.

Regarding bupivacaine, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses (Maes 2006). The benefit to the fetus is survival during the pregnancy; without the procedure, the mother will not be able to carry the fetus to term and the fetus will deliver pre-term and die. The risk to the fetus is NOT greater than Minimal Risk, and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means. Any risk is the least possible for achieving the objectives of the research.

Given that termination of pregnancy is irrelevant to this study, no inducements, monetary or otherwise, will be offered to terminate a pregnancy. In the case of a fetus, the fetus is not the subject of a planned abortion. Furthermore, the research team will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy or in determining the viability of a neonate.

Will the research involve neonates of uncertain viability or non-viable neonates?

☐ **Yes** ☑ **No**

Will subjects who are not yet adults (neonates, children, teenagers) be enrolled?

☐ **Yes** ☑ **No**

Will minors who are:

i) married, widowed, divorced; or
ii) the parent of a child; or
iii) a member of any of the armed forces; or
iv) pregnant or believes herself to be pregnant; or
v) living separate and apart from his/her parent or legal guardian, and is managing his/her own financial affairs

be approached for study participation for either themselves or their child?

☐ **Yes** ☑ **No**

Will wards of the state and/or children at risk of becoming wards of the state be enrolled (this includes foster children or any child that is in state custody)?

☐ **Yes** ☑ **No**

Will cognitively impaired adults (adults with impaired-decision making capacity) or adults who may lose the capacity to consent be enrolled?

☐ **Yes** ☑ **No**

Will prisoners be enrolled?

☐ **Yes** ☑ **No**

Will students and/or employees be enrolled in this research?

☐ **Yes** ☑ **No**

7 Adverse Event Monitoring

7.1 Definitions

The study does not carry a higher risk of adverse events than typically expected. Adverse events may include side effects from spinal anesthesia including nausea, vomiting, high spinal, allergic reactions, and systemic toxicity in the event of unintended intravascular injection. Effects on the fetus are directly related to the effects on the mother.

Adverse event: An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal physical exam or laboratory finding, symptom, or disease, temporally associated with a subject's participation in the research.

Serious adverse reaction: a serious medical occurrence associated with the use of a bupivacaine or chloroprocaine, such as death.

Unanticipated problems: any incident, experience, or outcome that meets **all** of the following criteria: unexpected; related or possibly related to participation in the research; and suggests that the research places subjects at a greater risk of harm than was previously known or recognized.

7.2 Reporting Procedures

Patients are routinely monitored for development of adverse events (such as asystole, severe hypotension (MAP<30), and apnea) as part of their anesthetic care. This occurs on a continuous basis from the moment the anesthetic is administered until the moment the patient is discharged home. A computerized system exists which alerts clinicians to the development of some adverse effects, and is recorded in the medical record. The co-investigator, Dr. Basura, will be alerted in these situations and all adverse events will be forwarded to the principal investigator. Clinicians are alerted to events immediately as they occur. Clinical staff are trained to deal with such events. The co-investigator, Dr. Basura, will be responsible for contacting the principal investigator to report the occurrence of adverse events. The principal investigator will then complete any necessary safety forms, include the Anesthesia Department's Quality Assurance form. The events will be reported within 24 hours to the QI director and the Chairman of the department, and to the IRB within 5 days.

7.3 Reportable New Information

Reportable new information will be reported to the IRB per the Tufts Health Sciences IRB's "Reportable New Information policy". The PI will submit any updated information that may affect the conduct of this study or subject safety, rights, welfare or willingness to take part in the research.

8 Statistical Considerations

8.1 Study Endpoints

Primary endpoint: complete resolution of motor block
Secondary endpoint: resolution of sensory block, ambulation, and micturation

8.2 Statistical Analysis

Given that our primary outcome is duration of motor block, we will compare the difference between two independent mean times using Student's *t*-test. Given that our secondary outcomes are also duration, we will also use Student's *t*-test to compare means between the two independent variables. If any subjects withdraw from the trial prior to discharge, we will use the Kaplan-Meier method as a secondary analysis. However, we will primarily use Student's *t*-test in the analysis.

8.3 Number of Subjects

Yoos 2005 found that after the administration of 40mg chloroprocaine, the motor block resolves in 69 ± 16 minutes. (3) Kiran 2002 found that after the administration of 7.5mg bupivacaine, the motor block resolves in 100 ± 15 minutes. (9) We are designing this study to observe a 30 minute time difference. Measuring in 10

minute increments will be sufficient to find this difference. To estimate the number of subjects needed for this study, the software G*Power 3.1 was used to perform a power analysis with 80% power and alpha level of 0.05 using the results from Yoos and Kiran. The power analysis revealed that a total of 8 study subjects will be needed. In order to account for 20% attrition rate, the total number of study subjects needed is 10.

8.4 Data Management

The data to be collected will be divided into four general groups: (1) demographic data (e.g. age, height, etc.); (2) Time of local anesthetic injection; (3) time of resolution of motor block, sensory block, ambulation, and micturation. Data collection forms and an excel spreadsheet with be used to organize the data and all of the analyzed data will be stored during the study period in the principle investigator's locked office and hospital provided, password protected, Box account, where access is exclusive to the research team.

8.5 Randomization

Will subjects be randomized?

☑ **Yes** ☐ **No**

In order to randomly allocate study subjects to one of two treatment arms entirely by chance, we will use the on-line randomization tool "Research Randomizer Version 4.0, www.randomizer.org," which has been studied and validated as an adequate randomization tool, to generate a randomization list. (7) Allocation concealment will be maintained by preparing sequentially numbered, sealed, opaque envelopes, which will contain the randomization assignment consistent with the generated randomization list.

The following strategies will be implemented in order to ensure blinding:

(a) When a subject enrolls in the study, the anesthesia provider responsible for the clinical care of the patient will be given an envelope prepared during randomization. The anesthesia provider will be instructed to open the envelope and prepare the medication in a separate room, such that the investigator and patient cannot see which vial is being used to prepare the medication. The anesthesia provider will also be instructed not to reveal the allocation group to the investigator or the patient.

(b) Upon return to the operating room, the spinal medication will be injected by the anesthesia provider and the surgery will commence. Investigators will be unable to distinguish which medication is being administered just by looking at the syringe because both bupivacaine and chloroprocaine are clear liquids, and because the intended doses of both medications are the same volume.

(c) The co-investigator making clinical outcome assessments, Dr. Basura, has only research privileges but no clinical privileges. As a result, she will be unable to administer any medication. This will be one more way to ensure blinding as she will not have any influence or knowledge of the spinal medication being administered

(d) Study subjects will not be informed of which medication is administered.

9 Drugs or Devices

Will the research involve drugs?

☑ **Yes** ☐ **No**

Will the research involve devices?

☐ **Yes** ☑ **No**

The anesthesia provider taking care of the patient clinically will prepare and administer the indicated medication, either chloroprocaine 40mg or bupivacaine 7.5 mg. These drugs will be obtained from the clinical supply, which is part of the standard of care. Preparing, drawing up, and administering chloroprocaine and bupivacaine are all part of an anesthesiologist's expected clinical duties and are part of the standard of care. Although not every

parturient is part of a research study, one could argue that receiving a "random" assignment is in fact part of the standard of care. It would not be unusual for our anesthesia residents to ask the attending anesthesiologist to teach him or her how to use one or the other medication. If a resident often uses bupivacaine, he or she may want to learn and test out how to dose and use chloroprocaine. At that point, the attending would be having to use a medication other than the one he or she may have originally intended. Both are acceptable choices for this procedure. Therefore, these providers should not be considered part of the research team. Both local anesthetics will be available to subjects after completion of the study, although we do not anticipate that they would need any more local anesthetic after the procedure.

According to the FDA, when the principal intent of the investigational use of an approved, marketed drug (such as chloroprocaine) is to develop information about the product's safety or efficacy, submission of an IND may be required. Please see the FDA website: https://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm However, according to 21 CFR 312.2(b)(1), the clinical investigation of a marketed drug or biologic does **not** require submission of an IND if all six of the following conditions are met:

1) it is not intended to be reported to FDA in support of a new indication for use or to support any other significant change in the labeling for the drug;
2) it is not intended to support a significant change in the advertising for the product;
3) it does not involve a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
4) it is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively];
5) it is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7]; and
6) it does not intend to invoke 21 CFR 50.24.

In our study, all six conditions are met, therefore not requiring submission of an IND. The six conditions are met as follows: (1) we do not intend to report to the FDA in support of a new indication for use or to support any other significant change in the labeling for chloroprocaine; (2) we do not intend to support a significant change in the advertising for the product; (3) we are not using this drug in a route of administration or dosage level, use in a subject population, or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of chloroprocaine*; (4) the study will be conducted in compliance with the requirements for IRB review and informed consent; (5) the study will be conducted in compliance with the requirements concerning the promotion and sale of drugs; and, (6) the study does not intend to invoke 21 CFR 50.24.

*One concern that may arise when reading the chloroprocaine label is that it states, "not to be used for subarachnoid administration." However, chloroprocaine is very often used in the subarachnoid space "off-label," and the restriction is a bit misleading. Below is an explanation of why the use of chloroprocaine is safe, despite this label.

Regarding route of administration:

Although the FDA writes that, "Nesacaine and Nesacaine-MPF Injections are not to be used for subarachnoid administration," further reading of the labeling reveals the true intention of this statement. Throughout the package insert there are multiple references to signs and symptoms consistent with Total Spinal when chloroprocaine is administered into the subarachnoid space. For example, "Unintentional subarachnoid injection of drug during the intended performance of caudal or lumbar epidural block or nerve blocks near the vertebral column (especially in the head and neck region) may result in underventilation or apnea ("Total Spinal")." The reason that the FDA writes that chloroprocaine is not intended for subarachnoid injection is because *large doses (300-600mg) of chloroprocaine* can result in apnea and cardiovascular collapse. Small doses (30-60mg) are safe, do not result in total spinal, and are frequently *the intended site* of injection for various surgical procedures.

Multiple previous publications (Davis 2005, Gonter 2005, Warren 2004, Vath 2004, Yoos 2005, Lacasse 2011, Smith 2004) have studied chloroprocaine as administered in the subarachnoid space. The authors did not

observe any adverse effects with the use of subarachnoid chloroprocaine in the doses 10-60mg. Furthermore, Hejtmanek 2011 reports that chloroprocaine, "is widely used at Virginia Mason Medical Center, where we have performed over 4000 spinal anesthetics." These authors again observed no adverse events from the use of chloroprocaine in the subarachnoid space in over 4,000 patients. *All of these different articles demonstrate that the subarachnoid route of administration does **not** significantly increase the risks (or decrease the acceptability of the risks) associated with the use of chloroprocaine.*

Given the safety profile of chloroprocaine in the subarachnoid space, clinicians throughout the United States use it on a regular basis for spinal anesthesia. However, some may still be concerned about the label. Therefore, in order to fully inform patients about the FDA warning, we will include in the informed consent that the chloroprocaine manufacturing label specifically states, "not for spinal anesthesia." We will further inform patients that the use is considered "off-label," but has been used successfully in thousands of anesthetics.

Regarding dosage level:

Multiple previous publications (Davis 2005, Gonter 2005, Warren 2004, Vath 2004, Yoos 2005, Lacasse 2011, Smith 2004) have studied chloroprocaine in varying doses from 10-60mg. All of them found no adverse events. *These articles demonstrate that the use of 10-60mg does **not** significantly increase the risks (or decrease the acceptability of the risks) associated with the use of chloroprocaine.*

Regarding use in a pregnant population:

Although chloroprocaine is considered pregnancy category C, chloroprocaine is used regularly in clinical practice for cerclage as well as many other procedures in pregnancy. The risk of chloroprocaine crossing the placenta and reaching the fetus are exceedingly low. Chloroprocaine is metabolized rapidly by plasma cholinesterases in the maternal blood, which makes transmission to the fetus unlikely. This has been demonstrated in a study comparing varying doses of chloroprocaine, in which Philipson 1987 observed that chloroprocaine was non-detectable in both maternal and umbilical cord veins, and in neonatal plasma. Similarly, in a comparison of bupivacaine and chloroprocaine, Maes 2006 found no differences in neonatal outcome as measured by Apgar scores and umbilical cord gases, suggesting no harm to the fetus from chloroprocaine.

Chloroprocaine is being used in a similar study at Columbia University, thus making it reasonable to use the same medication that was approved by the IRB at Columbia. Chloroprocaine is also currently used at Tufts Medical Center for spinal anesthesia as part of the standard anesthesia care in cerclage. Furthermore, the manufacturing label states that, despite being considered Category C, "this does not preclude the use of chloroprocaine at term for the production of obstetrical anesthesia."

*Given all of the above mentioned evidence, the use of chloroprocaine in pregnancy does **not** significantly increase the risks (or decrease the acceptability of the risks) associated with the use of chloroprocaine.*

Given that all 6 conditions of the FDA are met, our investigation does not require submission of an IND exemption.

10 Study Administration

10.1 Setting

Tufts Medical Center will be the sole research site. Spinal anesthesia will be administered in the operating room per routine clinical care. Patients will then be followed in the recovery room until the time of discharge.

10.2 Registration

The co-investigator, Dr. Basura, will ensure the eligibility of subjects and obtain their informed consent before implementing any study related interventions.

10.3 Resources Available

The research team is composed of the following members:

- Principle investigator: Dan Drzymalski, MD, Assistant Professor of Anesthesiology
  - Dr. Drzymalski is responsible for the preparation, design, conduct, and administration of the study.
- Co-investigator: Alaa Basura, MD, Postdoctoral research fellow
  - Responsible for writing the study's protocol under the principle investigator's guidance, obtaining the informed consent, managing data collection and data analysis.
- Co-investigator: Michael House, MD, Associate Professor of Obstetric and Gynecology
  - Dr. is responsible for revising the study protocol, recruiting patients, and performing the study.

Tufts Medical Center facilities provide medical resources that might be needed by study subjects. The average number of cervical cerclage procedures performed at Tufts Medical Center is 3 per month, which makes it possible to enroll the total number of study subjects within a one year period.

10.4 IRB Review

An appropriate IRB registered with the OHRP, will review and approve this study. Any amendments to the protocol or informed consent documents will be reviewed and approved by the IRB prior to use, unless required to eliminate an apparent immediate hazard to subjects.

10.5 Multi-Site Research

Is this a multi-site study where Tufts is the sponsor, primary grant recipient, or coordinating site?:

☐ **Yes** ☑ **No**

10.6 Community-Based Participatory Research

Will this study involve community-based participatory research?

☐ **Yes** ☑ **No**

10.7 Sharing Results with Subjects

Will results (overall study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) be shared with subjects or others (e.g., the subject's primary care physician or the subject's treating physician)?

☐ **Yes** ☑ **No**

11 References

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