Determining the ED90 for Intrathecal 3% Chloroprocaine for Elective Cervical Cerclage Surgery

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addressed by adminitration of epidural top up doses. Research related risk to study participants include the potential for loss of confidentiality. Measures to protect the confidentiality of study participants will be implemented as described in the Data Handling and Recordkeeping section below.

Research Summary

State your primary study objectives

The aim of this study is to identify the dose of intrathecal (IT) chloroprocaine that provides effective anesthesia in 90% of patients undergoing elective cerclage placement (intraoperative analgesic supplementation not required).

State your secondary study objectives

The secondary outcome will be the highest level of sensory anesthesia measured at 10 minutes after spinal chloroprocaine administration. This will be measured prior to surgical incision as the highest dermatome level blocked as measured by loss of pinprick/sharp sensation using a tootpick.
Sensory testing will be performed from caudad to cephald (i.e. from blocked to unblocked dermatomes) to identify the first unblocked dermatome bilaterally.
To identify the level where the sensation of touch is first appreciated, the investigator will ask the question: "Tell me when you feel something sharp touch your skin."

Exploratory Outcome

- Maximum pain Numerical Pain Rating Scale (NPRS) during surgery (as reported by patient, scored from 0-10 in the PACU).
- Incidence of side effects intraopertively:
- Nausea (self-reported by patient, yes or no).
- Vomiting (observed yes or no).
- Itching (self-reported by patient, yes or no).
- Use and dose of vasopressor phenylephrine (and ephedrine). Indicated to be given if the BP drops greater than 15% below baseline or < 100mg Hg systolic.
- Overall patient satisfaction and maximum pain score at PACU discharge (asked and scored from 0-10).
- Motor block at end of the cerclage placement (measured in the PACU).
- Time to hospital discharge as measured as the time difference between local anesthetic injection and discharge time as recorded in the medical notes
- Time from spinal block to ambulation
- Time from spinal block to micturition
- Time to complete sensory regression
- Time to resolution of motor block (Bromage score of 0)
- Time to readiness for PACU discharge (pre-defined nursing criteria)

Please select your research summary form:

Standard Research Summary Template

This is the regular (generic) research summary template which is required for all regular applications (unless your protocol fits under the other research summary templates in this category). Use of these instructions is helpful for ensuring that the research summary contains all necessary elements.

Standard Research Summary

Purpose of the Study

- Objectives & hypotheses to be tested

We hypothesize that the ED90 for IT chloroprocaine would range between 33 – 54 mg.

The aim of this study is to identify the dose of IT chloroprocaine that provides effective anesthesia in 90% of patients undergoing elective cerclage placement (intraoperative analgesic supplementation not required).

Background & Significance

- Should support the scientific aims of the research

Cervical cerclage is a procedure performed on pregnant women with cervical incompetence to reduce the risk of second trimester spontaneous abortion and preterm labor. This outpatient procedure is performed commonly under both general and regional anesthesia. In an effort to ensure rapid discharge some institutions prefer the use of general anesthesia; however, this has the disadvantage of exposing the fetus to general anesthetic drugs, increased risk of aspiration and a higher requirement for opioid analgesia post operatively. The benefits of neuraxial anesthesia for cerclage placement includes rapid onset of a dense sensory block, reduced fetus exposure to medications, and maintenance of maternal airway reflexes. Successful analgesia for cerclage placement requires a sensory block from S4-T10 dermatomes. Inadequate sensory coverage with a spinal anesthetic typically necessitates the conversion to general anesthesia adding risk to the mother and fetus while increasing intraoperative times and resources. Currently there are no studies determining optimum dose of spinal chloroprocaine for cervical cerclage. We propose a dose determining study to determine the ED90 of intrathecal lidocaine and chloroprocaine which will help decrease incidence of inadequate anesthesia for cervical cerclage.

Design & Procedures

- Describe the study, providing detail regarding the study intervention (drug, device, physical procedures, manipulation of the subject or the subject's environment, etc.). Discuss justifications for placebo control, discontinuation or delay of standard therapies, and washout periods if applicable. Identify procedures, tests and interventions performed exclusively for research purposes or more frequently than standard of care. Include alternative therapies, concurrent therapies discontinued per protocol, risk benefit ratio, and use of tissue/specimens. Discuss monitoring during washout periods if applicable. Include brief description of follow-up, if any.

This is a multicenter, double blinded, dose ranging, biased-coin design study. Our usual practice for regional anesthesia for cerclage placement consists of a mixture of 3% chloroprocaine and fentanyl. The exact dosing of the local anesthetic mixture used is dependent on the anesthesiologist's preference. Chloroprocaine provides a rapid onset of surgical anesthesia with little need for intraoperative analgesic supplementation. If there are contraindications for spinal anesthesia or patient refusal than general anesthesia is offered as an alternative.
The aim of this study is to assess the anesthetic quality of various doses chloroprocaine and in elective cerclage placement. Chloroprocaine is licensed and commonly administered intrathecally for cerclage placement.

To mitigate against the occurrence of inadequate analgesia in this ED90 study, a combined spinal-epidural technique will be utilized in order to provide supplemental analgesia via epidural top up if needed.

We propose testing our hypothesis in patients scheduled for elective cervical cerclage placement. Participants will receive standard of care for anesthesia but in the context of a clinical trial with the addition of randomization, blinding, and more comprehensive evaluation of the trial outcomes (see outcomes objectives below).

The proposed study will be conducted over a 2 year period from September 2018 to September 2020.

Spinal Study Solutions
The solutions and their administration procedures are identical to those used outside this research and are almost exclusively used for patients requiring spinal anesthesia for cervical cerclage. The only deviation involves diluting the chloroprocaine with saline so that study solutions are of equal volume to maintain blinding.

Initial Patient (A#X)

45mg (1.5mL) of Chloroprocaine 3% (Nesacaine — Fresenius Kabi), will be drawn up into a 3 ml syringe (a 1 ml 'TB syringe' will be used to aspirate the drug in aliquots to ensure accuracy). The following additive will be added:

1. 10 mcg (0.2ml) of fentanyl (50 mcg/ml)
2. 0.3 ml of sterile 0.9% sodium chloride

Thus the total volume in the syringe will be 2 ml. Study drugs will be prepared by one anesthesiologist (un-blinded) and administered by another anesthesiologist (blinded).

Subsequent Patient (A#X+1)
The dose of Chloroprocaine 3% based on outcome from prior subject and calculations mentioned previously will be added to 10 mcg (0.2ml) of fentanyl (50 mcg/ml). Sterile 0.9% sodium chloride will be added until the total volume in the syringe is 2 ml.

Rescue
If the subject has discomfort and requests analgesia, then 5 ml of 3% chloroprocaine via the epidural route will be given, alternatively the anesthesiologist can treat the discomfort at his discretion. Other alternatives include intravenous fentanyl, ketamine, inhalational nitrous oxide and conversion to general anesthesia.

Riks/Benefit
Risks of the procedure include the following: discomfort during placement (10% or 1 in 10), drop in blood pressure (1% or 1 in 100), headache (1% or 1 in 100), allergic reactions (0.001% or 1 in 100,000), bleeding or infection (0.001% or 1 in 100,000), damage to nerves (0.001% or 1 in 100,000), failure of the anesthetic or inadequate anesthesia and need for general anesthesia (0.1% or 1 in 1,000). The benefit of participating in the study is that perceived pain may be better controlled, however this cannot be guaranteed.

This study will be conducted at two study sites, the University of Arkansas for Medical Sciences in Little Rock, Arkansas and Duke University in Durham, North Carolina.

Selection of Subjects

- List inclusion/exclusion criteria and how subjects will be identified.

Inclusion Criteria:

- ≥ 18 years of age
- Singleton pregnancy
- ASA class II or III
- Cervical cerclage 1st or 2nd trimester of pregnancy
- Simple prophylactic cervical cerclage

Exclusion Criteria:

- Patient refusal
- Abdominal and complex cervical cerclage (e.g. bulging bag)
- BMI ≥ 50 kg/m2
- ASA class IV or above
- Contraindication to neuraxial anesthesia
- Allergy to chloroprocaine

Subject Recruitment and Compensation

- Describe recruitment procedures, including who will introduce the study to potential subjects. Describe how you will ensure that subject selection is equitable and all relevant demographic groups have access to study participation (per 45 CFR 46.111(a) (3)). Include information about approximately how many DUHS subjects will be recruited. If subjects are to be compensated, provide specific prorated amounts to be provided for expenses such as travel and/or lost wages, and/or for inducement to participate.

A memeber of the clinical team will introduce the study to eligible subjects. If interested, a member of the study team will then discuss the study with the subject.

The goal enrollment for the study is 45 subjects (assuming a 10% withdrawal rate). 40 subjects will be required to participate in the study.

No compensation is offered to patients participating in the study.

Consent Process

- Complete the consent section in the iRIS Submission Form.

Subject's Capacity to Give Legally Effective Consent

- If subjects who do not have the capacity to give legally effective consent are included, describe how diminished capacity will be assessed. Will a periodic reassessment occur? If so, when? Will the subject be consented if the decisional capacity improves?

Subjects unable to give informed consent will be excluded from the study population.

Study Interventions

- If not already presented in #4 above, describe study-related treatment or use of an investigational drug or biologic (with dosages), or device, or use of another form of intervention (i.e., either physical procedures or manipulation of the subject or the subject's environment) for research purposes.

The initial dose for chloroprocaine was chosen from dosages in current use and as determined by previous research. The dose for the first subject (A#X) in will be 45mg 3% chloroprocaine. Two possible outcomes will be recorded: satisfactory or unsatisfactory analgesia which is determined by occurrence of the need for intraoperative analgesia supplementation.

The dose for the next (A#X+1) will be adjusted based on the outcome from previous subjects respectively using up-down sequential allocation method with a biased-coin design. This process will continue in similar fashion with dose adjustments for next subjects to be based on outcome from subjects immediately prior.

The possible doses for IT 3% Chloroprociane (mg) are as follows (starting dose in italics)
33 – 36 – 39 – 42 – *45* – 48 – 51 – 54

When ED_{90} is to be determined ($\tau = 0.9$), the probability (B) = $(1 - \tau)/\tau = (1 - 0.9)/0.9 = 0.1/0.9 \approx 0.11$ (as described prior research).

If analgesia was ineffective and the previous patient required supplemental analgesia, then the dose would be increased for the next patient randomized to that drug.

If satisfactory analgesia was achieved the next patient randomized to receive that drug received with probability B ≈ 0.11 the next lower dose and with probability 1 − B = 0.89, the same dose as the previous patient.

Spinal Study Solutions
The solutions and their administration procedures are identical to those used outside this research and are almost exclusively used for patients requiring spinal anesthesia for cervical cerclage. The only deviation involves diluting the chloroprocaine with saline so that study solutions are of equal volume to maintain blinding.

Initial Patient (A#X)
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Subsequent Patient (A#X+1)
The dose of Chloroprocaine 3% based on outcome from prior subject and calculations mentioned previously will be added to 10 mcg (0.2ml) of fentanyl (50 mcg/ml). Sterile 0.9% sodium chloride will be added until the total volume in the syringe is 2 ml.

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Risk/Benefit Assessment

- Include a thorough description of how risks and discomforts will be minimized (per 45 CFR 46.111(a) (1 and 2)). Consider physical, psychological, legal, economic and social risks as applicable. If vulnerable populations are to be included (such as children, pregnant women, prisoners or cognitively impaired adults), what special precautions will be used to minimize risks to these subjects? Also identify what available alternatives the person has if he/she chooses not to participate in the study. Describe the possible benefits to the subject. What is the importance of the knowledge expected to result from the research?

The benefits and risks to the study participants will be the same as all patients presenting to L&D for cervical cerclage placement. That is, whether a patient decides to participate or not in the study, the normal standard of care is neuraxial anesthesia (spinal, epidural or combined spinal-epidural) for cerclage placement as opposed to general anesthesia. Therefore, whether participating in the study or not, it is likely the same drugs would be given in the same manner, as this is our normal practice. This study is designed to assess how much of study solution works in 90% of patients.

The potential benefit to subjects is their pain may be better controlled by participating in this study, however this cannot be guaranteed.

The potential risks associated with participation in this study will be detailed in the informed consent form as well as explained to the participant during the informed consent process. The study intends to minimize all risks where possible. Potential risks related to study specific procedures include the following: discomfort during placement (10% or 1 in 10), drop in blood pressure (1% or 1 in 100), headache (1% or 1 in 100), allergic reactions (0.001% or 1 in 100,000), bleeding or infection (0.001% or 1 in 100,000), damage to nerves (0.001% or 1 in 100,000), failure of the anesthetic or inadequate anesthesia and need for general anesthesia (0.1% or 1 in 1,000).

Costs to the Subject

- Describe and justify any costs that the subject will incur as a result of participation; ordinarily, subjects should not be expected to pay for research without receiving direct benefit.

There is no financial responsibility for the patients participating in this study.

Data Analysis & Statistical Considerations

- Describe endpoints and power calculations. Provide a detailed description of how study data will be analyzed, including statistical methods used, and how ineligible subjects will be handled and which subjects will be included for analysis. Include planned sample size justification. Provide estimated time

to target accrual and accrual rate. Describe interim analysis including plans to stop accrual during monitoring. Phase I studies, include dose escalation schema and criteria for dose escalation with definition of MTD and DLT.

A sample size of 40 patients was chosen. The unknown distribution of data in an up - down study prevents the calculation of the necessary sample size. However, previous studies have demonstrated that a sample size of 20 - 40 patients provides stable estimates of the target dose. Isotonic regression using the pooled-adjacent-violators algorithm will be used to obtain point estimates for the success rates that were constrained to be monotonic increasing with dose. The modified isotonic estimator for ED90 was then obtained via linear interpolation between the highest dose with an estimated success rate < 90% and the lowest dose with an estimated success rate >90%.Isotonic regression with bias corrected 95% confidence interval (CI) derived by bootstrapping will be used to calculate the ED90. Fisher's exact test will be used for nausea or pruritus treatment.

Two-tailed test will be performed with *P* values < 0.05 considered statistically significant.

Based on prior work that 20-40 patients provides a stable estimate of target dose utilizing an up-down sequential allocation method, we chose a sample size of 40 patients.

Demographics and baseline characteristics, such as age, sex, ethnicity, weight, height and gestation will be summarized using means (± standard error) or medians (range) for continuous variables and proportions for categorical variables. All summaries will be presented by intervention group.

Data & Safety Monitoring

- Summarize safety concerns, and describe the methods to monitor research subjects and their data to ensure their safety, including who will monitor the data, and the frequency of such monitoring. If a data monitoring committee will be used, describe its operation, including stopping rules and frequency of review, and if it is independent of the sponsor (per 45 CFR 46.111(a) (6)).

Data will be monitored closely for the occurrence of AEs, and reported to the IRB as needed. If unanticipated AEs or if expected events appear to be occurring more frequently than expected, those AEs will be explored per treatment arm.

In accordance with federal regulations the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), all AE reports will be reported per the DUHS IRB policies.
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Privacy, Data Storage & Confidentiality

- Complete the Privacy and Confidentiality section of the iRIS submission form.

Describe Role of External Personnel:

The role of external personnel will be identical to those outlined above for DUHS personnel.

Study Scope

Does the subject population contain >50% malignant hematology or oncology patients, or their caregivers?

○ Yes ◉ No

Are you using a drug, biologic, food, or dietary supplement in this study?