Optimizing Anesthesia for Postpartum Tubal Ligations

Study Protocol & Statistical Analysis Plan

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BACKGROUND

Although a short surgical procedure, postpartum bilateral tubal ligation (PPBTL) can pose a significant challenge to the anesthesiologist. Due to concerns with the obstetric airway, neuraxial anesthesia remains the preferred method of anesthesia.[1] However, providing neuraxial anesthesia for these cases can be difficult. Labor epidural reactivation for PPTL has been examined; however, this technique has an unacceptably high failure rate.[2] Spinal lidocaine, a short-acting local anesthetic, has fallen out of favor due to the increased risk of transient neurologic symptoms (TNS).[3] The most common local anesthetic used for spinal anesthesia, bupivacaine, provides appropriate coverage, but has a very long duration of action and will significantly outlast the PPBTL. This prolonged duration leads to a prolonged post-anesthesia care unit (PACU) length of stay.[4]

We recently demonstrated a significant reduction in recovery time for patients undergoing short obstetric procedures using low-dose bupivacaine with epidural volume extension (EVE) when compared to our traditional bupivacaine dose.[5] At the time of our study, there was no FDA-approved short-acting local anesthetic for us to use as a comparison. Peer reviewers at the time noted the need to compare our technique to a short-acting local anesthetic in the future. In 2017, that the FDA approved chloroprocaine 1% (short-acting local anesthetic) for spinal anesthesia for short surgical procedures. The package insert reports reliable coverage for lower abdominal procedures at the T10 level. PPBTL, due to sympathetic innervation of the fallopian tubes and uterus, routinely requires a T6 level for an adequate surgical block.[6]

The EVE technique can increase the spread of local anesthetic to higher dermatome levels. The leading hypothesis, supported by radiographic evidence, is thecal sac compression from epidural injection (typically normal saline), which effectively reduces spinal CSF and thus drives local anesthetic to higher dermatomal levels in an active fashion rather than allowing for passive flow.[7] We have shown similar dermatome coverage using half the dose of bupivacaine when the EVE technique is employed.[5] With the understanding of how the EVE technique works, we believe that EVE will be able to adequately increase the surgical block of the 1% chloroprocaine from the T10 to the T6 dermatome that is required for PPBTL.

Now that there is an FDA-approved local anesthetic for short obstetric procedures, and the fact that this drug can reliably anesthetize fibers up to the T10 dermatome, we wanted to revisit our EVE study and compare our low-dose isobaric bupivacaine to 1% spinal chloroprocaine utilizing the EVE technique in an effort to determine if either medication provides an advantage for patients undergoing PPBTL.

STUDY OBJECTIVES AND HYPOTHESIS

The purpose of this study was to determine if spinal 1% chloroprocaine with EVE or low dose spinal 0.5% isobaric bupivacaine with EVE confer a significant clinical advantage over the other. We hypothesized that there will be no difference in the block height at 10 minutes after spinal injection (T_{10}), comparing 0.5% isobaric bupivacaine to spinal 1% chloroprocaine. If confirmed, our results suggest that spinal 1% chloroprocaine is a suitable alternative to 0.5% isobaric intrathecal bupivacaine.

STUDY DESIGN

Design: Randomized, Controlled Trial

Comparison groups:

1. 1 ml 0.5% isobaric bupivacaine + 15 mcg fentanyl intrathecal plus EVE
2. 5 ml 1% spinal chloroprocaine intrathecal plus EVE
    - EVE = 10 ml sterile normal saline injected into epidural space after intrathecal injection of study medication

Primary Outcomes:

1. Number of patients who achieve a T6 dermatome level or greater within 10 minutes of spinal injection.
2. Dermatome level achieved.

Secondary Outcomes:

1. Number of patients who required epidural activation during the surgery.
2. Number of patients who required intravenous (IV) sedation or general anesthesia during surgery.
3. Motor blockade as defined by the modified Bromage score at 10 minutes after spinal injection.
4. Motor blockade as defined by the modified Bromage score at 60 minutes after spinal injection.
5. Time required to meet post-anesthesia care unit (PACU) discharge criteria.

SUBJECT SELECTION AND WITHDRAWAL

Inclusion criteria:

1. Any patient scheduled for PPBTL at our Women and Infants Center (WIC) age 18 and above.

Exclusion criteria:

1. Patients less than 18 years of age.
2. Documented allergy to either local anesthetic class (ester or amide).
3. Any documented contraindication to neuraxial block.

Recruitment and Screening:

Any patient scheduled for PPBTL at the WIC will be screened for eligibility. The inclusion/exclusion criteria described above will be used to screen each patient. Because PPBTL occur within 24 hours of delivery, all patients will be screened and enrolled on the day of surgery. If a patient is eligible for the study, a member of the study team will approach the patient and discuss the study including all risks and benefits. If the patient agrees to participate in the study, informed written consent will be obtained. Patients do not receive any compensation for this study.

Because there is no long-term follow up to this study, participant withdrawal should be minimal. If withdrawal does occur, the patient will continue to receive standard of care treatment for the PPBTL.

The patient will still be included in the overall number of patients enrolled; however, the data will not be included in the analysis.

STUDY DRUGS

Drug Name: **Chloroprocaine**

Other Names: Clorotekal; Nesacaine; Nesacaine-MPF

Classification: Local Anesthetic, ester-type

Mode of Action: Prevents both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

Storage and Stability: Store at 20°C to 25°C (68°F to 77°F) in original container; protect from freezing. Protect from light. Discard Clorotekal and Nesacaine-MPF following single use. Solution in vials may become discolored with prolonged exposure to light; do not administer discolored solutions. Crystals of chloroprocaine may develop when exposed to low temperatures; when the vial is returned to room temperature, the crystals will redissolve with shaking; do not use solutions that contain undissolved matter. Do not heat before use; do not autoclave. Use immediately after initial puncture of vial or after ampule opening

Metabolism: Rapidly hydrolyzed by plasma enzymes to 2-chloro-4-aminobenzoic acid and beta-diethylaminoethanol (80% conjugated before elimination)

Preparation: Solution, Intrathecal, as hydrochloride [preservative free]: Clorotekal: 1% (5 mL)

Administration: Subarachnoid block: Do not use solutions containing preservatives. Use a filter needle to draw up solution from ampule when using Clorotekal. Do not puncture areas of the skin with signs of infection/inflammation. Intravascular injections should be avoided; aspiration should be performed prior to administration; the needle must be repositioned until no return of blood can be elicited by aspiration; however, absence of blood in the syringe does not guarantee that intravascular injection has been avoided. Clorotekal is intended for intrathecal administration only; the manufacturer recommends against using for epidural administration. Use of Clorotekal via continuous spinal catheters is not recommended (safety has not been established).

Drug Name: **Bupivacaine**

Other Names: Bupivacaine Spinal; Marcaine; Marcaine Preservative Free; Marcaine Spinal; P-Care M; Sensorcaine; Sensorcaine-MPF

Classification: Local anesthetic, amide-type

Mode of Action: Prevents both the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction

Storage and Stability: Store at 20° to 25°C (68° to 77°F). Discard unused portions of single-dose ampuls and vials. Solutions containing epinephrine should be protected from light

Metabolism: Hepatic; forms metabolite (pipecoloxylidine [PPX])

Preparation: Solution, Injection, as hydrochloride [preservative free]: Generic: 0.5% (30 mL)

Administration: Spinal: free flow of cerebrospinal fluid during the performance of spinal anesthesia is indicative of entry into the subarachnoid space. Do not inject during uterine contractions because spinal fluid current may carry the drug further cephalad than desired.

STUDY PROCEDURES

Computer-generated randomized cards were created, placed in envelopes, and sealed prior to the start of the study. Once a patient is enrolled, the next card in the sealed envelope is selected for the randomization process. As this is a double-blinded study, the researcher will hand the card to the qualified anesthesia provider performing the combined spinal epidural (CSE) procedure. Once the patient is ready for surgery, she will be moved to the operating room (OR). Standard care will be provided to the patient in the OR – basic monitors, routine nursing care, etc. The anesthesia provider caring for the patient will then open the envelope and see what group the patient is randomized to – either 1% chloroprocaine group (C) or low-dose bupivacaine group (B). [The two study drug groups are discussed in detail at the bottom of this section.] The anesthesia provider will then provide standard of care and perform a CSE technique. The provider will administer the study drug via the spinal, place 10 ml of sterile saline in the epidural space for the EVE, then thread the epidural catheter. This will be marked as time 0 (T0). The investigator will then be called into the room to begin data collection. The investigator will assess an anesthetic level by taking a blunt-tip needle and lightly scratching the skin until the patient feels a sharp sensation. The investigator will also have the patient lift her legs to determine the degree of motor blockade. Motor blockade is determined by the modified Bromage score where: 0 = ability to maintain leg lift for prolonged period; 1 = ability to lift legs briefly; 2 = ability to bend knees; 3 = ability to wiggle toes; 4 = no movement of lower extremities. The first data point will occur 10 minutes after the block was placed. Once an adequate surgical level is obtained – T6 bilaterally – the surgery will begin. Standard of care will occur throughout the surgery. If the spinal level is not adequate, the patient will receive standard medications through the epidural catheter in order to provide adequate anesthesia. If this additional medication is required, it will be documented by the investigator. At the end of the procedure, another sensory level to pinprick and motor level (having the patient lift her legs) will occur. The patient will then be taken to the recovery room where standard care will be provided. The time the patient enters the recovery room until the time they are ready for discharge will be documented. Once the patient is discharged from the recovery room, the study will be complete.

The two study groups are: 1) (C) 5 ml of 1% spinal chloroprocaine (50mg) plus the 10 ml of sterile saline for the EVE; 2) (B) 1 ml of 0.5% isobaric bupivacaine (5mg) plus 15 mcg spinal fentanyl plus the 10 ml of sterile saline for the EVE. It is important to note that we are only placing the fentanyl in the bupivacaine spinal for these reasons: 1) fentanyl is a common additive to bupivacaine spinals to help with the quality of the block; 2) fentanyl will not be added to the chloroprocaine spinal because the chloroprocaine is a newly-approved FDA drug, and currently, the FDA recommends against placing any additive into the solution. We understand that routinely we should try to make the groups have similar

additives; however, given the fact that it is standard clinical practice to add fentanyl to bupivacaine and currently the FDA doesn't allow drugs added to chloroprocaine, we felt this was an appropriate clinical design to the study.

STATISTICAL PLAN

General Data Analysis Plan: The study design is a prospective randomized parallel arm design. The primary outcome variable is block height 10 minutes, T_{10} after spinal injection.

Statistical Power and Sample Size Estimates: Using an independent group t-test assuming unequal variances, a clinically meaningful mean difference of ΔT_{10} = 2.5 dermatomes to detect, a standard deviation of the mean block height at 10 min, $\sigma_{T_{10}}$ = 2.46, we calculate that we require 22 subject per group to achieve 90% power at an type I error rate of 0.05. We propose a total sample size of N = 50 subjects to account for some inaccuracy of our assumptions.

SAFETY AND ADVERSE EVENTS

Adverse events are similar to the risks involved with placement of CSE and administration of local anesthetic. These are standard practice. For the study, breach of confidentiality is a rare but potential adverse event. Any adverse event will be documented and immediately reported to the departmental human studies research committee and institutional review board.

DATA HANDLING AND RECORD KEEPING

All data collected is stored electronically in the HIPAA-compliant, password-protected REDCap system. Only study personnel on the stud protocol have access to the data stored in this system.

STUDY MONITORING, AUDITING, AND INSPECTING

The PI of the study is responsible for oversight of the study and all co-investigators. The research division within the department tracks and ensures all investigators of the study maintain appropriate credentialing to participate in research. The research division within the department also reviews and approves all protocols. For this study, a yearly progress report is submitted to the IRB that includes all patients screened and enrolled, study update, and any adverse events. The study is also subject to audit by the IRB at any point during the time it is open.

STUDY FINANCES

No external funding was received for this study. All resources for this study were provided by the department.

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