Comparing low-dose bupivacaine with epidural volume extension to standard bupivacaine dosing for short obstetric procedures: A prospective, randomized study

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1.0 SUMMARY OF STUDY (Abstract with a maximum of 300 words)

This study will address the efficacy of using low dose bupivacaine spinal anesthesia (SA) in combination with epidural volume extension (EVE) for pregnant patients undergoing short obstetric procedures. The use of neuraxial anesthesia – spinal, epidural, or combined spinal-epidural (CSE) – is standard of care in this patient population. However, one downfall of neuraxial anesthesia is the prolonged post-anesthesia care unit (PACU) stays patients incur while waiting for the numbness to subside after having a short procedure. The aim of this study is to determine if low doses spinal bupivacaine in conjunction with EVE can decrease the PACU recovery time for short obstetric procedures while still providing an adequate surgical block.

This study will be conducted at the UAB Women and Infants Center on the labor and delivery unit. Patients undergoing short (<1 hour) surgical procedures such as cerclage placement or dilation and curettage (D&C) for fetal demise will be recruited for this study. Inclusion criteria: patients undergoing short obstetric procedure in the operating room (OR) requiring spinal anesthesia. Exclusion criteria: BMI >35, coagulopathy, platelets <80,000, allergy to local anesthetic or fentanyl, previous spinal surgery, and spinal or intracranial mass.

Once informed consent is obtained, study participants will be randomized into two different groups: low dose spinal bupivacaine with EVE (BE), and standard-dose spinal bupivacaine (B). Spinal anesthesia will be administered via CSE in routine fashion by a qualified anesthesia provider that is independent of this study. The primary outcome will be total PACU time defined as the time from admission to PACU until the time patient meets PACU discharge criteria (Modified Bromage scale of < 2, blood pressure and heart rate within 20% of baseline, return of baseline oxygenation status as measured by pulse oximetry, alert with baseline mentation, pain well controlled) (Modified Bromage scale: 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 extremeties). Secondary outcomes will be: (1) time until sensory level of T10 achieved, (2) degree of peak motor block after spinal placement (3) time until return of motor function (Modified Bromage score < 2), (4) duration of the block (defined as time from placement until PACU discharge criteria met), (5) quality of the block (as determined by any pain reported during surgery and/or the need to supplement through the epidural) and (6) patient satisfaction (based off of a 0-10 scale). A total of 40 patients will be recruited for the study.

2. BACKGROUND & RATIONALE

In OB anesthesia, a neuraxial technique is frequently used for a variety of surgical procedures as it is associated with reduced maternal morbidity and can provide for faster maternal bonding and a more direct experience during childbirth.[1]

Multiple local anesthetics (LAs) can be used for this purpose, but each can come with undesired effects. Lidocaine was used frequently in the past for short surgical procedures due to its shorter duration of action; however, its use has declined significantly due to its high incidence of transient neurologic symptoms (TNS).[1-4] Despite the high potential of cardiotoxicity when given in large doses, bupivacaine is widely used for SA because of its fast and reliable onset to surgical block.[5,6] There have been many studies comparing the efficacy of different LAs for SA in lower extremity and abdominal surgeries with goals of T10 and T6 surgical levels respectively. [5,7,8] The results prove the utility of bupivacaine in SA, but do note the presence of prolonged motor and sensory blockade at doses necessary for adequate analgesia compared to other LAs. [8]

CSE is a popular and very common practice in anesthesia today as it offers reliable and quick anesthesia with the ability for the provider to administer subsequent medication to improve the efficacy of the block. [9,10,11,12] It was originally thought that additional boluses of LA through the epidural increased the spread of the block through epidural analgesia as well as leakage of LA through the punctured dura into the intrathecal space. However, some studies have demonstrated a rise in analgesic level after administering only saline into the epidural space after first introducing intrathecal LA and/or opioids. [11,12] One study looked at the difference of injecting equal amounts of LA or saline into the epidural space after induction of SA and found that both groups achieved similar levels, both of which were significantly higher than the group without EVE. [11] Another small study looked at myelograms before and after injecting different amounts of saline into the epidural space. They found that contrast medium spread in a cephalad direction up to 4 levels and that the subarachnoid space decreased in diameter by over 25%. [12] These studies suggest that increased volume alone in the epidural space can increase the surgical level of a SA.

Another advantage of the CSE technique is the ability to treat inadequate surgical anesthesia during surgery. If a spinal technique is performed, no additional medication can be given in the neuraxial space due to the fact it is just a one-time shot. With a CSE, an epidural catheter is placed in the epidural space after the spinal block is performed. This allows the provider to administer LA medication through the epidural catheter to maintain an adequate surgical block throughout the procedure. Therefore, if the spinal block begins to regress and the patient experiences any pain, LA can be administered through the epidural catheter to re-establish an adequate surgical block.

The ability to administer less bupivacaine will allow for a shorter duration of anesthesia and a quicker return to baseline function.[12] Although we would like to reduce PACU times, we also understand the importance of providing an adequate surgical block. There is evidence that supports adequate surgical levels with low dose bupivacaine. One study has shown that equipotent doses of 10mg of bupivacaine with high opioid administration can produce up to T2 level

analgesia when combined with EVE.[13] In this study, there was not only a significant difference in maximum block achieved, but also in time to onset of block. Yet another study demonstrated adequate analgesia for cesarean section when combining doses as low as 5mg of bupivacaine with EVE.[14] Given that only a T10 level would be required for cerclage or D&C, it is reasonable to believe that low doses of bupivacaine combined with EVE would provide an adequate surgical block while reducing the time needed to recover from the spinal block.

3. SIGNIFICANCE OF STUDY

Neuraxial anesthesia remains the standard of care for parturients or recently postpartum patients requiring anesthesia for surgical procedures. At UAB, we routinely use 10-12mg of hyperbaric bupivacaine with 12.5mcg of fentanyl in our spinal anesthetics for these procedures. This combination effectively delivers fast and reliable analgesia for our patients, but also comes with the burden of prolonged sensory/motor blockade and ultimately an extended stay in PACU(>1 hour). Many of these patients are otherwise stable but must be maintained under our care until their motor block recedes. More time spent in the PACU equates to an increase in healthcare resource and cost consumption, much of which we do not recuperate. If we are able to demonstrate satisfactory surgical anesthesia with an agent that could provide a faster recovery and shorter PACU stay, we could decrease our cost of care for these cases. Another important factor that must be considered is patient satisfaction. It is thought that patients just recently having a D&C for fetal demise suffer emotional distress as they sit in PACU and hear all of the new mothers interact with their children for the first time. Decreasing the length of time in the PACU will decrease healthcare resource and cost consumption and potentially lessen some of the emotional hardships suffered by our patients.

4.0 OBJECTIVE(S) & HYPOTHESIS

Purpose: The purpose of this study is to conduct a single site, prospective, randomized study to compare low-dose bupivacaine with fentanyl in combination with EVE to our traditional bupivacaine dose with fentanyl for short obstetric procedures.

Outline of Therapy: Patients who are undergoing either placement of cerclage or D&C will be randomized into two groups: 2 ml of preservative-free, isobaric bupivacaine 0.5% (10mg) with 12.5mcg of fentanyl (Group B), or 1 ml of preservative-free isobaric Bupivacaine 0.5% (5mg) with 12.5mcg of fentanyl (Group BE). Group B will serve as our control group. Each group will receive the spinal medications via a CSE technique. The epidural catheter will then be inserted into the epidural space in the B group, whereas a 10 mL bolus of sterile

saline will be injected through the epidural needle into the epidural space before the epidural catheter is threaded in the BE group. All CSEs will be placed by certified anesthesia providers working at UAB's WIC. Also, the epidural catheters that are placed in both groups can be used at any time throughout the procedure if the surgical anesthesia level is believed to be inadequate. Standard demographic data (age, height, and weight) will be collected in addition to data pertaining to primary and secondary endpoints.

Primary endpoints or outcomes: The primary outcome will be time until PACU discharge requirements are met (modified bromage scale of < 2, blood pressure and heart rate within 20% of baseline, return of baseline oxygenation status, alert with baseline mentation, pain well controlled).

Secondary endpoints or outcomes: Secondary outcomes will be the time elapsed to achieve T10 sensory level to pinprick, degree of peak motor blockade (recorded at the time of consecutive identical dermatomal sensory levels), time elapsed until motor block regresses to modified Bromage score < 2, duration of the block, quality of the block (as determined by any pain reported during surgery and/or the need to supplement through the epidural), and patient satisfaction.

Study Hypothesis: We hypothesize that patients in the EVE group will meet the criteria for PACU discharge significantly quicker than the traditional bupivacaine group while having adequate surgical anesthesia. We also hypothesize that patients in group BE will reach a T10 sensory level quicker, have a lesser degree of peak motor blockade, and will have a faster recovery of motor function.

5.0 INTERPRETATION OF EXPECTED RESULTS

For each CSE performed, multiple factors will be recorded: patient's age, height, weight, time to onset of T10 sensory level, peak sensory level and peak level of motor block (described by modified Bromage scale), patient pain during surgery, need to use epidural catheter, time to return of motor function, and length of PACU stay. Data will be analyzed by our statistician looking for significant differences in outcomes in the BE group compared to the B group.

6.0 ELIGIBILITY & EXCLUSION CRITERIA

Eligibility criteria:

1. Any patient 18 or older undergoing D&C or cerclage placement under neuraxial anesthesia.

Exclusion criteria:

1. BMI >35

2. Coagulopathy
3. Platelets < 80,0000
4. Prior spinal surgery
5. Intracranial or spinal mass
5. Allergy to study medications
6. History of lower extremity weakness

7.0 RANDOMIZATION/RECRUITMENT PROCEDURES

Recruitment: Eligible patients will be identified using the Horizon WIC operating schedule. Once identified, one of the study investigators will screen the patients using the inclusion and exclusion criteria. If patient has no contraindications, the study will be explained and risks and potential benefits will be discussed by one of the study investigators.

Randomization: Once the patient is enrolled into the study, they will randomly be assigned into one of the two study groups. Randomization will be performed via random drawing of sealed envelopes which indicate either B or BE. A qualified anesthesia provider independent of the study will perform the spinal procedure and administer the medication in routine fashion.

8.0 STUDY INTERVENTIONS/PROCEDURES

1. **Study design.**
   There will be two groups in this study differentiated by the dose of LA: 10 mg of preservative-free isobaric bupivacaine with 12.5mcg of fentanyl (B) and 5 mg of preservative-free isobaric bupivacaine with 12.5mcg of fentanyl (BE). Patients undergoing cerclage placement or D&C who meet the inclusion/exclusion criteria will be approached about the study. Informed consent will be obtained, and the patient will be randomized into either the B or BE group. The CSE will be performed by a certified anesthesia provider at UAB in the standard fashion. Patients in the B group will have an epidural catheter placed after the spinal. Patients in the BE group will receive a 10 mL bolus of sterile saline through the epidural needle before the epidural catheter is placed. Routine care will be provided to the patient throughout the procedure by an anesthesia provider that is independent of the study. This includes administering LA through the epidural catheter to ensure patient comfort during the surgery. Data pertinent to the study will be recorded on the IRB-approved data sheet that will be kept locked in a secure cabinet in the PI's office. Information recorded will include: time of spinal placement, presence of epidural saline bolus, drugs administered, time to achieve T10 sensory level to pinprick, peak sensory and motor block, PACU times, and patient satisfaction with her anesthetic. Information from the data sheet will be

transferred to a secured password protected database. Once a sufficient number of participants have been recruited, our data will be assessed by a statistician.

2. **Comparison groups.**
(B) Preservative-free isobaric bupivacaine10 mg with 12.5mcg of fentanyl
(BE) Preservative-free isobaric bupivacaine 5 mg with 12.5mcg of fentanyl with addition of 10 mL of sterile saline for EVE

3. **Study and timeline of interventions.**
Discussion of the study to potential participants and obtaining informed consent will take about 15 minutes. As patients will receive routine care, no added time will be needed to perform this study. Therefore, routine CSE placement will take about 15 minutes, the operative procedure about 1 hour, and PACU recovery about 1 hour. Total time for recruitment and completion of the study will take approximately 2 hours and 30 minutes per patient, with 2 hours and 15 minutes being routine care. Total recruitment will take approximately one year to complete.

4. **Measured end-points and timeline of end-point measurements.**
All endpoints will be measured prior to discharge from the WPACU
   a. Time until WPACU discharge criteria met
   b. Time elapsed until T10 sensory level achieved
   c. Time until score of <2 reached on Modified Bromage scale
   d. Duration of the spinal block
   e. Patient satisfaction of a scale of 1-10
   f. Patient pain during surgery
   g. Need to use epidural during surgery

Projected Overall Study Timeline

	Study Start-Up	Enrollment	Data Entry and Analysis	Study Write-Up
06/2016	X			
06/2016 – 07/2017		X		
07/2017 – 08/2017			X	
08/2017 – 09/2017				X

9.0 CONCOMITANT THERAPIES

None

10.0 DRUG INFORMATION

Drug Name: Preservative-free isobaric bupivacaine 0.5%
Other Names: Marcaine 0.5%
Classification: Amide Local Anesthetic
Mode of Action: Blocks sodium influx into nerve cells by binding to voltage gated sodium channels
Storage and Stability:
Metabolism: Metabolized by the liver
Preparation: Mixed with glucose in sterile fashion
Administration: Administered intrathecally
Incompatibilities:

- *Contraindications* – Allergy to amide local anesthetics
- *Precautions* – Cardiotoxicity

Side Effects:

Adverse effects indicated in *italics* are the most frequent adverse effects. Adverse events in **bold** are severe/life-threatening, otherwise they are mild to moderate in reaction.

- CNS: Tinnitus, perioral numbness, seizure, coma
- CV: Hypotension, arrhythmia, bradycardia, heart block, cardiac arrest
- EENT: N/A
- ENDO: N/A
- GI: Fecal Incontinence
- GU: Urinary incontinence
- INTEG: N/A
- MS: N/A

Nursing Implications:

- Blood pressure: Hypotension
- Pain: N/A
- Edema: N/A
- I&O (intake & output): N/A
- Allergic reaction: Rare
- Signs and symptoms:

Drug Name: Fentanyl
Other Names: Sublimaze

Classification: Opioid analgesic
Mode of Action: Mu receptor agonism
Storage and Stability: Requires storage in access controlled container. (Omni cell); No issues with stability at normal temperatures
Metabolism: Metabolized by the liver
Preparation: Prepared in sterile fashion
Administration: Administered intrathecally
Incompatibilities:

- *Contraindications* – Allergy to fentanyl
- *Precautions* – Respiratory Depression

Side Effects:

Adverse effects indicated in *italics* are the most frequent adverse effects. Adverse events in **bold** are severe/life-threatening, otherwise they are mild to moderate in reaction.

- CNS: Confusion, loss of consciousness, headache
- CV: Hypotension
- PULM: Respiratory depression, Apnea
- EENT: N/A
- ENDO: N/A
- GI: Constipation, Nausea
- GU: Urinary retention
- INTEG: N/A
- MS: N/A

Nursing Implications:

- Oxygenation: Apnea
- Blood pressure: Hypotension
- Pain: N/A
- Edema: N/A
- I&O (intake & output): N/A
- Allergic reaction: Rare
- Signs and symptoms:

Investigational New Drug (IND) Application Required?: No

Investigational Device Exemption (IDE) Required?: No

11.0 STATISTICAL CONSIDERATIONS

Demographic Variables: Age, weight, height, past medical history, procedure type.

Control Variables: Group B (10 mg of preservative-free isobaric bupivacaine and 12.5 mcg of fentanyl) vs Group BE (5 mg of preservative-free isobaric bupivacaine and12.5 mcg of fentanyl with 10 ml of sterile saline through epidural)

Study Variables: The primary endpoint is the time until PACU discharge requirements are met. The secondary endpoints are time elapsed to achieve T10 sensory level, degree of peak motor blockade, time elapsed until motor block regresses to modified Bromage score < 2, duration of the spinal block, and patient satisfaction score.

General Data Analysis: All demographic and clinical variables with continuous measures will be expressed as means and standard deviations; categorical factors will be expressed as proportions. For non-normal data, the medians and interquartile ranges will be displayed. The distribution of the continuous factors will be examined using the Kolmogorov-Smirnov test. For data that are normally distributed, One-way analysis of variance (ANOVA) will be used to compare the two types of anesthesia. For data that are not normally distributed, the Kruskal-Wallis test will be used for comparisons. Chi-square and Fisher's exact tests will be used to analyze categorical data. For all comparisons, a p-value less than 0.05 will be considered statistically significant.

Primary Outcome Analysis. The primary endpoint for this study is the length of time until PACU discharge requirements are met. One-way ANOVA (or the Kruskal-Wallis test, as appropriate) will be used to assess whether PACU length of stay is significantly associated with type of spinal anesthesia. Linear regression will also be used to evaluate the relationship between method of spinal anesthesia and PACU length of stay, while controlling for relevant clinical and demographic variables.

Secondary Outcome Analysis: One-way ANOVA will also be used to compare groups on time to achieve T10 sensory level, degree of peak motor blockade, time elapsed until motor block regresses, and patient satisfaction.

Additional Data Analysis: N/A

Statistical Power and Sample Size Estimates: Approximately 40 subjects (20 per group) are expected to be enrolled in this study. Assuming a standard deviation of 20 minutes for PACU length of stay, a study with this sample size will have approximately 80.7% power to detect a 20 minute difference and approximately 98.9% power to detect a 30 minute difference in PACU length of stay between Group B and Group BE.

Study Population Availability: Approximately 3-5 of these procedures are performed per week, which equals about 200 cases per year. About 80% of these cases will be done under spinal anesthesia for a total of 160 per year. Assuming a 50% enrollment rate, it should take 7 to 8 months to complete enrollment.

12.0 PATIENT SAFETY AND DATA SECURITY MONITORING

Assessment of Level of Risk:
Low

Oversight of this investigation will be provided by:
Oversight of this investigation will be provided by the Principal Investigator as well as the UAB department of Human Subjects Research Committee.

The mechanisms for HIPAA compliance [including a detailed electronic personal health information (PHI) data path]:
Data will be collected on the IRB-approved data sheet. These forms will be stored in a locked cabinet in the PI's locked office. Data from the forms will be transferred to our HIPPA-compliant, password-protected database.

13.0 REPORTING ADVERSE EVENTS

Adverse events will be reported to the IRB.

14.0 REFERENCES CITED (minimum of 10 citations)

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APPENDIX A (Starting as a new page) (For Internal Departmental Use **Only**)

STUDY BUDGET AND FUNDING SOURCES

Study Title:
Principal Investigator:

Itemized Budget:

Is extramural funding presently being sought for this study? Yes/No
If yes, from what source or agency?
If not now, is this planned at some point in the future? Yes/No
Please provide brief pertinent details:

Present this completed appendix to the Director of Research for the Applicable Division for review and approval (Anesthesia Services Division and Cardiovascular Anesthesiology Division: Keith Jones, M.D.; Critical Care Medicine: Sadis Matalon, Ph.D.; Pain Treatment: Timothy Ness, M.D., Ph.D.)

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Director of Research Comments:

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Signature of Director of Research: _____

Name: _____ Date: _____