Comparing Bupivacaine, Lidocaine, and a Combination of Bupivacaine and Lidocaine for Labor Epidural Activation: A Prospective, Randomized, Double-Blind Study

Study Protocol & Statistical Analysis Plan

NCT03103100

DATE April 29, 2020

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Version Date: 06/12/2014
IRB Study Number: XXXXXXX

INDEX

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

The ideal local anesthetic (LA) solution for activation of a labor epidural would be one that provides rapid pain relief with minimal side effects such as hypotension and motor blockade. Commonly used LA in obstetrics includes bupivacaine and lidocaine. Due to either slow onset (bupivacaine)[1] or a higher incidence of hypotension (lidocaine)[2] neither meet the criteria for the ideal LA. This is where the thought of combining the two LA solutions arises. Maybe a 1:1 mix will produce a faster onset than bupivacaine with a lower incidence of hypotension than lidocaine.

We hypothesize that lidocaine will achieve a T_{10} level the fastest when compared to bupivacaine and bupivacaine plus lidocaine. The bupivacaine plus lidocaine onset of action will not be significantly faster when compared to bupivacaine. Given the concentration of the bupivacaine, less hypotension and motor block will be present when compared to the lidocaine and bupivacaine plus lidocaine. The bupivacaine plus lidocaine will offer no increased benefit of having a faster onset with less hypotension or motor blockade than either LA solution alone.

We will conduct a prospective, randomized, double-blind study on 45 patients receiving a lumbar epidural for labor analgesia. After a negative test dose, the anesthesia provider will administer the randomized LA via epidural catheter: 10 mL 0.125% bupivacaine, or 10 mL 1% lidocaine, or 5 mL 0.125% bupivacaine plus 5 mL 1% lidocaine. The investigator will assess the patients sensory level to pin prick and ice, degree of motor block, blood pressure, heart rate, and fetal heart rate at intervals of 0, 5, 10, 15, and 20 minutes. Primary outcome will be the time to achieve a T_{10} level. Secondary outcomes include the total spread of the block, onset and degree of motor block, incidence of hypotension and need for vasopressor therapy, and fetal well-being.

2.0 BACKGROUND & RATIONALE

The most common and effective method for controlling labor pains is a local anesthetic infusion through a lumbar epidural.[1] To achieve adequate pain control during the first stage of labor – onset of contractions to complete cervical dilation – nerve fibers up to the T_{10} dermatome must be anesthetized.[1] When a patient is in active labor and an epidural catheter is placed, the anesthesiologist must activate the epidural by administering LA through the epidural to promote spread of the LA in the epidural space to anesthetize the nerve fibers involved in the conduction of labor pains. The ideal LA to achieve this goal is one that would allow for the fastest onset to achieve quick pain relief with the fewest side effects. Common side effects of LA used in labor epidurals include maternal hypotension and motor blockade.[3]

Two commonly used LA to provide labor analgesia are bupivacaine and lidocaine. When low concentrations – 0.125% bupivacaine and 1% lidocaine – are used for labor analgesia, both of these LA can be administered safely with very little concern of major adverse effects associated with LA toxicity. However, more common side effects such as maternal hypotension requiring vasopressor therapy and motor blockade can often occur.[3]

Though both are amide LA, bupivacaine and lidocaine display different properties that give each an advantage in certain situations. Lidocaine's onset of action is faster than that of bupivacaine's (5-15 vs. 10-20 minutes for epidural injection).[1] Whereas bupivacaine has a longer duration of action (180-300 vs. 60-180 minutes).[1] Through a sympathetically mediated veno- and vaso-dilation, both LA commonly cause hypotension. Although the time to develop hypotension was not noted, several studies have noted a higher incidence of hypotension with the administration of epidural lidocaine vs. bupivacaine.[2,4]

Despite the novel idea that combining these two LA in an effort to achieve the ideal properties of each – lidocaine's faster onset and bupivacaine's tendency towards less hypotension – only a few studies have been published on this topic. Two articles assessing the onset of action of bupivacaine, lidocaine, and a combination of both for local infiltration found no difference in onset of action.[5,6] One article did note a significant decrease in time to onset of sensory and surgical block in patients receiving bupivacaine plus chloroprocaine (ultra-fast acting LA) vs. bupivacaine in patients undergoing an axillary block.[7] Two studies looking at adding lidocaine to a bupivacaine spinal in an effort to achieve the opposite effect – decreasing the duration of the spinal – had conflicting results with one showing a shortened duration while the other showing no difference. Both studies report no difference in onset of action.[8,9] In patients requiring conversion of a labor epidural to a surgical block, one study found no difference in time to achieve a T_4 surgical level in the lidocaine, bupivacaine, or combination groups.[10] In non-pregnant patients undergoing lower abdominal surgery, Seow et al. showed no difference in development of a sensory block but the onset of a complete motor block was significantly faster in the 1:1 bupivacaine:lidocaine concentration group.[11] The one study that was found assessing time of onset and extent of sensory and motor block in parturients receiving a labor epidural found no significant difference comparing bupivacaine to a bupivacaine and lidocaine combination.[3]

Given that there is limited and conflicting evidence for the usefulness of the bupivacaine and lidocaine mixture especially as it relates to labor epidural activation, we hope to readdress these questions in an effort to determine whether or not the LA combination offers any distinct advantage over the individual LA. In contrast to Sinatra et al's study, we intend to determine the time it takes to achieve an adequate level (T_{10}) for labor analgesia, the total spread of local anesthetic (both caudal and rostral), and the time it takes to develop hypotension – not just the overall incidence – as these factors will be important in determining the most optimal LA solution to activate a labor epidural. We will also reevaluate the degree of motor block, as patients in Sinatra's study received a much higher concentration of bupivacaine (0.5%) than we use for epidural activation (0.125%). With the results of our study, we hope to recommend a LA solution that will allow for the fastest pain relief in the laboring mother with the fewest side effects.

3.0 SIGNIFICANCE OF STUDY

This study will compare and determine the most ideal LA solution to activate a labor epidural: lidocaine, bupivacaine, or a combination of bupivacaine plus lidocaine. We hope to determine which solution will provide the fastest onset and best coverage with the fewest side effects such as maternal hypotension and motor blockade. This will allow anesthesiologists to select a LA

solution that will provide the best analgesic properties (quick onset and adequate spread for labor analgesia) with the fewest side effects (hypotension and motor weakness).

4.0 OBJECTIVE(S) & HYPOTHESIS

Our overall goal is to determine which commonly used LA or combination of LA demonstrates the most ideal properties in a patient receiving an epidural for labor pains. As anesthesiologists, we strive to provide a fast-acting and safe anesthetic in these patients to elicit rapid pain relief in laboring mothers.

Currently, there are several ways in which we activate a labor epidural with LA. Three of the more common LA solutions used are 1% lidocaine, 0.125% bupivacaine, or a combination of bupivacaine and lidocaine. In a prospective, randomized, double-blinded study, we plan to determine if one solution is more superior to the others.

Briefly, after consent is obtained, a standard anesthesia provider will place a labor epidural in regular fashion. After a negative test dose, the anesthesia provider will then administer the study solution the patient was randomized to receive (10 mL of 0.125% bupivacaine, 10 mL of 1% lidocaine, or 5 mL of 0.125% bupivacaine plus 5 mL of 1% lidocaine). The standard epidural infusion bag will then be started by the anesthesia provider. Both the patient and investigator will be blinded to the study. Once the study drug bolus has been given, the investigator will collect the data.

Data to be collected will be: sensory level (by pin prick and ice), degree of motor block by using a modification of Bromage's scale[3] (see section 8.0), maternal heart rate (HR) and blood pressure (BP), the need to administer a vasopressor agent (phenylephrine or ephedrine) to treat hypotension, the amount of vasopressor given, and fetal heart rate (FHR). Starting with the initial bolus (Time 0 or T_0), data will then be collected 5, 10, 15, and 20 minutes after the bolus.

The primary outcome for this study is the time it takes to achieve a T_{10} dermatome level by pinprick (which signifies an adequate epidural level for labor analgesia).

Secondary outcomes include: the total spread (both cephalad and caudal) of the LA (dermatome level to be determined by pin prick and ice), degree of motor block, incidence of maternal hypotension defined as a BP >20% decline from baseline, the need to administer a vasopressor to treat the hypotension, the amount given, and if there is any change in fetal status by monitoring FHR.

We hypothesize that lidocaine will achieve a T_{10} level the fastest when compared to bupivacaine and bupivacaine plus lidocaine. The bupivacaine plus lidocaine solution's onset of action will not be significantly faster when compared to bupivacaine. Given the concentration of the bupivacaine, less hypotension and motor block will be present when compared to the lidocaine and bupivacaine plus lidocaine. The bupivacaine plus lidocaine will offer no increased benefit of having a faster onset with less hypotension or motor blockade than either LA solution alone.

5.0 INTERPRETATION OF EXPECTED RESULTS

If we see a significant decrease in time to achieve a T_{10} dermatome level with the bupivacaine and lidocaine mixture compared to the bupivacaine only solution, then that would imply that the addition of the lidocaine did speed up the onset of action of the LA solution we used to activate the epidural. We would also need to account for each LA solution's side effect profile. By measuring the incidence of hypotension and degree of motor blockade, we will be able to determine if one solution's side effect profile is more favorable. By determining the advantages vs. disadvantages of each solution, we would be able to recommend the most ideal LA solution of those studied as the solution best suited for activation of labor epidurals.

5.0 ELIGIBILITY & EXCLUSION CRITERIA

Pregnant patients over the age of 18 who are scheduled for an induction of labor and request an epidural are eligible for the study.

Exclusion criteria are: age <18, allergy to the drug or drug class, preexisting neuropathy, history of back pain prior to pregnancy or history of back surgery, history of chronic opioid use, history of hypertension or hypertensive disorders of pregnancy, congenital or acquired cardiac disease, and contraindication to epidural placement (patient refusal, severe coagulopathy, infection at site of epidural needle insertion, severe hypovolemia)

6.0 RANDOMIZATION/RECRUITMENT PROCEDURES

Patients who are admitted to the labor and delivery (L&D) suite at the Women and Infants' Center (WIC) for induction of labor will be approached about recruitment into the study. The recruitment process will begin prior to any obstetric intervention that may induce pain or altered mental status to the patient.

As this will be a double-blinded study, the randomization process will be performed by someone other than the investigator gathering the data. Cards containing the LA to be given along with a code will be placed in a sealed envelope and numbered. There will be an equal number of patients randomized to each group. A card will be chosen by the anesthesia provider performing the procedure. The provider will administer the LA solution the patient is randomized to receive. The provider will write the code from the card on the data sheet. The code will be used to identify the LA solution given.

8.0 STUDY INTERVENTIONS/PROCEDURES

Our study will be a prospective, randomized, double-blind study comparing three commonly used methods to activate a labor epidural. These three solutions will be 10 mL of 0.125% bupivacaine (B), 10 mL of 1% lidocaine (L), and 5 mL of 0.125% bupivacaine plus 5 mL of 1% lidocaine (BL). The primary outcome of the study will be measurement of the time it takes to achieve an adequate anesthetic level (T_{10}) to control labor pains. Secondary outcomes include: the total level achieved, degree of motor blockade, incidence of maternal hypotension (>20% decline from baseline), the need for vasopressor use, the amount of vasopressor needed, and fetal

well-being (monitoring of FHR). Since LA will be required to produce our primary outcome, no group will receive a placebo. The three groups (B), (L), and (BL) will be compared to each other.

Pregnant patients who are admitted to the L&D floor at the WIC and have none of the above mentioned exclusion criteria will be approached about enrolling in the study. Informed consent will be obtained before any obstetric intervention occurs that might cause pain or altered mental status to the patient. Once the patient requests for her epidural to be placed, the investigator will be notified. Any qualified anesthesia provider will then place the labor epidural. Per our routine practice, the epidural will be placed in the L_{2-3} or L_{3-4} interspace, secured at plus 5 cm from the loss of resistance distance at the skin, and the routine test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine will be administered to rule out spinal or intravascular placement of the epidural catheter. After the epidural catheter is deemed safe to use (from a negative test dose), the anesthesia provider will administer the LA solution the patient has been randomized to receive: 10 mL (B), 10 mL (L), or 10 mL (BL), and the standard LA infusion will be connected to the epidural and started. The time that the LA bolus occurred will be marked as T_0. The patient's BP, HR, anesthetic level to pin prick and ice, degree of motor blockade, and FHR will be recorded at that time by the blinded investigator. Motor blockade will be tested by a modification of Bromage's scale where: 0 = the ability to maintain a leg lift for prolonged periods; 1 = the ability to lift legs briefly; 2 = the ability to bend knees; 3 = the ability to wiggle toes; 4 = no movement in lower extremities.[3] Then at intervals of 5, 10, 15, and 20 minutes, the investigator will document the above mentioned data with the addition of any vasopressor (phenylephrine or ephedrine) required to treat maternal hypotension and the dose.

If, on administration of the test dose, the epidural catheter is believed to be intravascular (increase in HR > 20% above baseline) or spinal (an acute anesthetic level is noted by hip flexor weakness), then the catheter will be deemed not safe to use, and the patient will be removed from the study. The epidural catheter can be replaced by the anesthesia provider; however, since the data will be flawed from the initial positive test dose, the patient will not be allowed to participate in the study at that point. Also, if the patient does not receive an anesthetic level from the initial bolus plus infusion after 20 minutes, the epidural catheter will be documented as a failed catheter, and the patient will be removed from the study. The anesthesia provider will replace the epidural catheter in standard fashion if the patient requests to have it replaced.

The endpoint for our primary outcome will be the time it takes to achieve the T_{10} level to pin prick, which should occur before 20 minutes; however, we will continue to monitor the patient throughout the 20 minute interval to determine the maximal spread of the LA (via measurement of the dermatome level by pin prick and ice), the degree of motor weakness, and if any hypotension occurs. During this time, the patient will have standard monitoring that all patients in labor receive: non-invasive BP and pulse recording and non-invasive FHR tracing. The L&D nurse, obstetricians, and anesthesiologists involved in the patient's care will deliver the same standard of care given to all patients on the L&D floor. Once the study is complete (after 20 minutes), the patient will continue to receive LA infusion through the epidural catheter throughout the remainder of labor and delivery. The anesthesia provider will continue to care for the patient throughout the patient's labor and delivery.

On average 5 to 10 patients are scheduled for induction each week. If 60% are consented for the study, then it should take approximately 3 months to enroll 45 patients.

Projected Overall Study Timeline

	Study Start-Up	Enrollment	Data Entry and Analysis	Study Write-Up
MM YYYY	08/2014			
MM YYYY		08/2014-11/2014		
MM YYYY			11/2014	12/2014

9.0 CONCOMITANT THERAPIES

Throughout the entire study, there will be no change to the standard of care for the patient. Both drugs, bupivacaine and lidocaine, and the combination of the bupivacaine and lidocaine are used on a daily basis for labor epidural administration. Once the patient receives the (B), (L), or (BL) bolus, the standard epidural infusion of bupivacaine 0.1% with 2.5 mcg/mL fentanyl will be connected to the patient and infused at 10 mL/hr, which is our standard infusion rate. The patient will have standard monitoring (BP, pulse rate, FHR) and have 1:1 monitoring with an L&D nurse who will be able to assess maternal well-being. The risk of intravascular or spinal injection of the LA would be a very rare event in patients who have a negative test dose as described above. In addition, the risk of LA toxicity from an intravascular injection would still be extremely rare as the amount of each LA given would be considerably less than the toxic dose. In the unlikely event the patient experienced cardiovascular collapse, drugs of the ACLS protocol and intralipid will be administered to the patient. A more common side effect of the LA would be maternal hypotension. Maternal hypotension is routinely treated with crystalloid fluid hydration and either phenylephrine or ephedrine boluses through the IV as both have been shown to be safe in pregnancy.

10.0 DRUG INFORMATION

Drug Name: 0.125% bupivacaine
Other Names: Marcaine
Classification: Amide local anesthetic
Administration: The medication will be injected into the epidural space via an epidural catheter.
Mode of Action: Sodium-channel blocker
Storage and Stability: The medication is stored and is stable at room temperature.
Metabolism: Liver
Preparation: The drug comes as an injectable liquid. It does not need to be reconstituted.
Contraindications: Patients with known allergy to the drug or drug class.
Side Effects: The most common side effect is hypotension due to veno- and vaso-dilation from LA-induced sympathectomy. Extremely rare events include CNS events (seizure, coma) and cardiovascular collapse from toxic levels of LA.
Nursing Implications:
Blood pressure: Potential for LA-induced sympathectomy leading to hypotension.
Pain: This medicine will relieve pain associated with labor.

Edema: No effect.
Intake and Output: No effect.
Allergic reaction: Reactions are very rare.
IND Required: No.

Drug Name: 1% lidocaine
Other Names: Xylocaine
Classification: Amide local anesthetic
Administration: The medication will be injected into the epidural space via an epidural catheter.
Mode of Action: Sodium-channel blocker
Storage and Stability: The medication is stored and is stable at room temperature.
Metabolism: Liver
Preparation: The drug comes as an injectable liquid. It does not need to be reconstituted.
Contraindications: Patients with known allergy to the drug or drug class.
Side Effects: The most common side effect is hypotension due to veno- and vaso-dilation from LA-induced sympathectomy. Extremely rare events include CNS events (seizure, coma) and cardiovascular collapse from toxic levels of LA.
Nursing Implications:
Blood pressure: Potential for LA-induced sympathectomy leading to hypotension.
Pain: This medicine will relieve pain associated with labor.
Edema: No effect.
Intake and Output: No effect.
Allergic reaction: Reactions are very rare.

DEVICE INFORMATION

N/A

IDE: Not Required

11.0 STATISTICAL CONSIDERATIONS

The outcome Y is time to T_{10} sympathectomy. An ANOVA will be used to estimate the overall difference of the mean onset times between study groups. An estimateof onset times of 5, 6 and 7 minutes and an estimated variance of 1 min is based on the existing literature.[12] Using an alpha = 0.05, 80% power and a calculated effect size of $f = 0.82$, the total sample size sample size based on an ANOVA is N=18. Accounting for some prediction inaccuracy, we propose a target sample size of N=45, n=15 per study group.

12.0 PATIENT SAFETY AND DATA SECURITY MONITORING

Assessment of level of risk: Low
Oversight of this investigation will be provided by the Principal Investigator as well as the departmental Human Subjects Research Committee. Data will be securely stored on our password-protected, HIPPA-compliant departmental research data server.

13.0 REPORTING ADVERSE EVENTS

Any major 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: _____