

Randomized Double-blinded Study Designed to Optimize the Dose of Bupivacaine in Combined Spinal Epidurals
to Reduce the Incidence of Fetal Bradycardia and Maternal Hypotension

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Randomized double-blinded study designed to Optimize the Dose of Bupivacaine in Combined Spinal Epidurals to Reduce the Incidence of Fetal Bradycardia and Maternal Hypotension

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Specific Aims:

The primary objective of this study is to identify whether a smaller dose of spinal bupivacaine combined with fentanyl reduces the incidence of maternal hypotension and fetal bradycardia in laboring parturients receiving combined spinal-epidural analgesia.

The secondary objective is to evaluate the adequacy of pain relief with the reduced dose of spinal anesthetic.

Outcomes to be measured include:

1. Maternal hypotension. Defined as 20% decrease in systolic blood pressure (when compared with baseline) or a systolic blood pressure less than 100 mm Hg.
2. Fetal bradycardia. Defined as a fall in heart rate to less than 110 bpm, or a prolonged deceleration defined as a fall in heart rate to less than 110 bpm lasting more than 2 minutes.
3. The need to administer ephedrine, phenylephrine, terbutaline, or nitroglycerin to support blood pressure and/or improve the fetal heart rate following the spinal dose
4. Adequacy and duration of pain relief following the spinal using a numeric pain rating scale from zero to ten.
5. Mode of Delivery- Normal spontaneous vaginal delivery, vacuum assisted/forceps, or caesarean section

Significance:

Combined spinal epidural anesthesia (CSE) is a safe and simple procedure which provides adequate analgesia in laboring patients. Two possible complications of this technique are maternal hypotension and fetal bradycardia, which have been demonstrated to result from both rapid pain relief and sympathetic blockade.² Untreated hypotension leads to diminished uteroplacental blood flow which could result in fetal hypoxia and acidosis.

Previous studies have determined the ED₉₅ of bupivacaine to be 1.66 mg, less than the standard 2.5 mg being routinely given in CSE for laboring patients. It has also been demonstrated that half the typical dose of bupivacaine provides adequate pain relief in the majority of parturients. Whether the complication rate with a smaller dose of local anesthetic is diminished has yet to be determined.

We postulate that by reducing the amount of bupivacaine given in a CSE, maternal hypotension and fetal bradycardia will also be reduced, while still providing adequate analgesia. Prevention of these complications will lead to fewer rescues with sympathomimetic and uterine relaxation agents, fewer invasive treatments, and an increase in patient satisfaction.

Experimental Design and Method:

The clinical trial will take place between January 1, 2014 to January 1, 2015 in the Labor and Delivery unit at the **Roosevelt site of Mount-Sinai-Roosevelt Hospital Center.**

This randomized prospective double-blinded study is designed to investigate the development of maternal hypotension and fetal bradycardia in patients receiving CSE for labor analgesia. ***The target population are laboring patient admitted to the Labor and delivery unit. Any patient requesting an epidural for labor will be a potential candidate for this study.*** Discussion regarding the patient's participation in the trial will occur when she requests labor analgesia, as this is the customary first point of contact with the anesthesiology team. After informed consent and discussion of the technique for combined spinal-epidural, patients will be blindly randomized to one of three groups. ***The randomization will be done by blindly choosing one of these papers from the envelope, which will assign you to one of the three groups.***

These groups relate to the dose of bupivacaine that will be administered intrathecally during placement of the spinal anesthetic. Syringes will be prepared in advance by pharmacy containing one of the three doses of bupivacaine being identified only by a syringe number. Twenty micrograms of fentanyl is routinely administered in combination with bupivacaine in the spinal. ***The total amount in the syringe will be the same in the group, by adding saline when needed. Pharmacy will be providing us with prepared syringes containing either one of the 3 dosages of Bupivacaine for the spinal part of the combined spinal epidural (CSE). The syringes will be labeled with a number, and only pharmacy will know what concentration of bupivacaine is in the syringe. We will be given this information of what was in the syringe once final data are collected for the patients included in the study. The syringe will be prepared with a sterile technique, and the content will be ready to use as is by the anesthesia team providing the CSE.***

Group 1: 2.5 mg plain bupivacaine + 20 mcg fentanyl

Group 2: 1.66 mg plain bupivacaine + 20 mcg fentanyl

Group 3: 1.25 mg plain bupivacaine + 20mcg fentanyl

After randomization, a baseline pain score on a scale of **0**- 10 will be obtained. The fetal heart rate tracing will be recorded for 15 minutes with an external continuous heart rate monitor prior to placing the CSE in order to obtain an adequate baseline. Patients will be seated for the placement of the CSE. A blood pressure cuff and pulse oximeter will be in place and an initial blood pressure will be taken. The time of the spinal injection will be recorded. After placement of the CSE, the patient will be placed on her side, as is customarily done. Blood pressure will be taken every 2 minutes for 20 minutes and then every 15 minutes. A continuous fetal heart rate monitor will record the readings electronically. Blood pressure readings will be

recorded again at 60 minutes. All patients will be given our standard PCEA with a continuous infusion of 12ml/hr of 0.0625% bupivacaine with 2mcg/ml fentanyl.

If hypotension and/or fetal bradycardia occur the patient will be treated with ephedrine, phenylephrine, nitroglycerin, or terbutaline as per our standard practice. The dose and timing of this will be recorded. Patients will also be asked to evaluate the effectiveness of their pain relief by asking them to rate their pain on a scale from 0-10 at 8 minutes (*time to full effect of the spinal dose*) and 60 minutes (*time when spinal dose could start wearing off*) following the spinal dose. In the event that the patient does not receive adequate pain relief, additional local anesthetic will be administered into the epidural catheter until the patient achieves comfort. The data form is attached as Appendix B.

Data collected will consist of:

- Demographics: Patient age, gestation, dilation in centimeters, gravity, parity
- Presence of labor induction/augmentation with Pitocin
- Maternal blood pressure- a baseline blood pressure and every 2 minutes for 20 minutes following the dose of spinal bupivacaine. A final blood pressure will also be recorded at 60 minutes.
- Fetal heart rate- a baseline fetal heart rate, and a continuous recording following the dose of spinal bupivacaine with an external monitor
- Cumulative ephedrine, phenylephrine, nitroglycerin, or terbutaline use and timing
- Pain scores at baseline, 8 minutes, and 60 minutes
- Delivery outcomes: normal spontaneous vaginal delivery, vacuum/forceps assisted vaginal, or caesarean section

Statistical Analysis:

Power analysis: As this is an exploratory but well controlled study, we will set the power at 0.9 and alpha at 0.05. 9 per group are required with an incidence fetal bradycardia/maternal hypotension of 7%; thus we will study 30 per group = 180 subjects. Accounting for dropouts and incomplete data, we seek to consent 200 patients. Published data estimates that the incidence of maternal hypotension after spinal bupivacaine is 10-15% at the higher 2.5 mg dose and likely reduced to 3-5% at the lower doses. The incidence of fetal bradycardia is less well studied but is estimated to occur in 3-7% of parturients after the higher 2.5mg bupivacaine dose. The occurrence of fetal bradycardia at lower doses of bupivacaine is not well studied but our prediction is that it will be reduced.

F tests- ANOVA: Repeated measures, between factors	Repetitions	=	4
Analysis: A priori: Compute required sample size	Corr among rep measures	=	0.5
Input: Effect size f	Output: Noncentrality parameter A	=	
a err prob	Critical F	=	5.143253
Power (1-err prob)			22.399999
Number of groups			3

Numerator df	=	2.000000
Denominator df	=	6.000000
Sample size	=	9
Actual power	=	0.903879
Total sample size = 180		

Human subjects:

Inclusion Criteria: ASA 1-2 parturients at term requesting labor analgesia between 37 and 42 weeks gestational age, with maternal age of 18 years or greater. Signed informed consent will be obtained from all patients prior to their enrollment in the study.

Exclusion criteria: Parturients with pre-eclampsia, or history of pregnancy induced hypertension will be excluded from the study. In addition, those patients in whom a spinal anesthetic is contraindicated (e.g. coagulopathy, local infection) or those in whom a CSE cannot be performed, will be excluded from the study. Patients who show non reassuring fetal heart rate tracings prior to placement of the CSE will also be excluded from the study.

Consent procedures

Sources of Research Material Obtained from Human Subjects:

Data will be collected from two sources: from the initial anesthesiology preoperative assessment and procedural anesthesia record (part of the medical record).

Recruitment of subjects and consent procedure: After a patient is interviewed by the anesthesia team prior to labor analgesia, and is found to fulfill the inclusion criteria, she will be asked if she wishes to participate in the study. The study and the potential risks and benefits will be explained to the patient in order to obtain written informed consent. A copy of the protocol will be available to each subject and each patient will receive a copy of the informed consent.

Potential health risks:

Combined spinal epidurals have become standard practice techniques for labor analgesia. The health risks for patients in this study will be equal to the risks associated with the routine placement of combined spinal-epidurals. These include a postdural puncture headache, bleeding and infection at the injection site, hypotension, epidural hematoma/abscess, high spinal, nerve damage, and failure of adequate pain relief. Inadequate pain relief from the lower dose of spinal anesthetic is a risk that study patients may be more likely to incur. Patients will be monitored closely for this and will be given additional boluses of local anesthetic through the epidural catheter that is already in place until relief is achieved. All research documentation that includes identifiers such as names and birthdates will be kept in a secure area in the research office.

Potential Health Benefits:

There are significant potential health benefits to patients participating in this study. It has been shown that spinal bupivacaine given at the common dose of 2.5mg can lower maternal blood pressure. Patients in the study who receive lower doses will most likely have a reduced rate of hypotension, and potentially a lower occurrence of fetal bradycardia. Lower rates of maternal hypotension and fetal bradycardia would lead to a lower incidence of nausea and vomiting, less interventions and emergency caesarian deliveries.

Potential Financial Risks:

Patients will not incur any additional financial expenses as a consequence of being enrolled in this study beyond the costs that are typically applied for regional anesthesia for labor analgesia.

Potential Financial Benefits:

Patients will not be compensated for participation in this study

Risk to Benefit Ratio:

All the potential risks of a combined spinal-epidural have been discussed. The additional risk that patients may incur if they receive a lower dose of spinal bupivacaine might be inadequate pain relief. The patient would have an epidural in place with this procedure and would receive additional local anesthetic through the epidural should this occur. The potential benefits are lower risks for maternal hypotension and fetal bradycardia. The risks are reasonable in relation to the anticipated benefits that are expected to result.

Alternative to Research Participation:

The patient's involvement in this study is completely voluntary and all subjects will be informed that they can withdraw at any time without loss of benefits to which they are otherwise entitled.

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