Wake Forest University School of Medicine

Effect of epidural saline on duration and spread of subsequent spinal analgesia/anesthesia using a CSE technique

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Background:

Combined spinal epidural labor analgesia (CSE) is a common technique to provide rapid relief of labor pain. In parturients requesting labor analgesia who are appropriate for a combined spinal epidural technique (CSE), the spinal drugs are typically 1.75 to 3.0 mg of bupivacaine and 10-20 micrograms of fentanyl administered intrathecally. Combining bupivacaine and fentanyl provides synergistic effect leading to longer duration of analgesic effect. However, the pruritus that frequently occurs after the administration of intrathecal fentanyl can be particularly bothersome to some patients. We are interested in minimizing the bothersome side effects of intrathecal narcotics as well as potentially increasing the level of sensory block and the analgesia duration of the spinal block by injecting a predetermined amount of normal saline into the epidural space via the epidural needle prior to performance of the spinal block without narcotic while using a CSE labor analgesic technique. Injecting normal saline into the epidural space after but not before an intrathecal injection has been termed epidural volume extension (EVE) and has been shown to increase the cephalad spread of the block. The mechanism of extension of spinal anesthesia was suggested to be mainly the result of a volume effect in which the dural sac is compressed by the injectate which results in a cephalad shift of CSF containing local anesthetic.[1,2] The effect of epidural injectate volume on an existing spinal block has been studied but with inconsistent clinical findings in which the studies were limited by either a small sample size, a small volume of epidural injectate or variable time interval from spinal block administered and being already "fixed". However, none of the studies have evaluated the clinical effect of a pre-existing epidural volume injection on a subsequently performed spinal block as we propose to study. The study results will be clinically relevant not only for combined spinal epidural labor analgesia but also for those patients requiring an alternative neuraxial block after a failed epidural block with a large volume of epidural drugs administered. Higuchi estimated a 2.0 +/- 1.0 ml to

7.2 +/-ml reduction in mean lumbosacral CSF volume lasting for 30+ minutes and alterations in CSF velocity waveform, both associated with a 5 to 15 ml epidural volume injection with an intact dura.[3] Our study is designed to better understand the clinical effects and mechanism of pre-existing epidural injectate volume effect on subsequently performed spinal block.

Objective:

To compare in a controlled, randomized prospective fashion the clinical effect and mechanism of pre-existing epidural saline volume effect on subsequently performed spinal block. Our hypothesis is that 15 ml of a pre-existing epidural injectate volume will significantly increase the level of sensory block and increase the analgesic duration of action in a subsequently performed spinal block.

Methods and Measures

Design and Outcome Measures: This study is a prospective randomized double-blind study whereby the patients will be randomized to one of two groups with either 0 ml or 15 ml of epidural saline injections followed by injection of 3 mg of isobaric bupivacaine intrathecally. Primary outcome measures are highest sensory blockade level to pinprick and to cold. We divided anesthesia dermatome levels to a total of 20 levels from sacral (1 level) then L5 to T1 (as 17 levels) and then C7 (1 level) and C6 or higher as another level. Modified Bromage Motor Scale will be used to assess the amount of motor blockade in the lower extremities.

Secondary outcome measures are the following:

1.) Time to Onset of analgesia (VAS <=3)
2.) Duration of analgesia (time to request additional analgesia)
3.) Time to highest sensory blockade level
4.) Time for 2 dermatome level regression of sensory block
5.) Time for regression of motor blockade
6.) Occurrence of common spinal/epidural side effects: hypotension, fetal bradycardia, vasopressor use (ephedrine), excessively high blocks (higher than T4) and postdural puncture headache

Setting: The study will take place on the labor and delivery suite at Forsyth Medical Center.

Protocol and Procedures:

A. 90 healthy women with uncomplicated pregnancies in early labor (>=2cm but =<6cm cervical dilation) requesting neuraxial analgesia will be consented to participate to obtain 60 evaluable subjects enrolled in this randomized controlled trial. Patients will be greater than 12 years of age, have an assigned ASA physical status 1 or 2 with a singleton pregnancy. Patients with contraindications to neuraxial anesthesia, inappropriate for study, or with allergies to drugs used in the study will be excluded. Patients inappropriate for study would include those with an assigned ASA status 3 or 4, advanced labor (> 6cm cervical dilation) or less than 12 years of age. Patients with the potential for distorted epidural anatomy, such as Harrington rods or prior back surgery, will also be excluded.

B. Patients will be randomized into 1 of 2 groups:

Group 1. 45 subjects Epidural space will be identified with loss of resistance to minimal air or saline (<0.2-0.3 ml) with a 17 gauge epidural needle. Then, after 20-30 seconds, the spinal needle will be inserted via the epidural needle in the usual manner and 3 mg isobaric bupivacaine (1.2 ml of 0.25% isobaric bupivacaine) will be given intrathecally.

Group 2. 45 subjects Epidural space will be identified with loss of resistance to minimal air or saline (<0.2-0.3 ml) with a 17 gauge epidural needle. Normal saline 15 ml will then be administered through the epidural needle over approximately 20 seconds and held for another 10 seconds. The spinal needle will then be inserted via the epidural needle in the usual manner and 3 mg isobaric bupivacaine (1.2 ml of 0.25% isobaric bupivacaine) will be given intrathecally.

In both groups after administration of intrathecal study drug, the spinal needle will be removed followed by insertion of the epidural catheter as in the usual manner. After placement of the epidural catheter, patients will be returned to the supine position with slight left tilt. Patients will be placed with their head up at an angle of approximately fifteen degrees after the spinal injection. The epidural catheter will not be tested or dosed until the patient requests further analgesia. When additional analgesia is requested, the epidural catheter will be tested and dosed in the customary fashion. The catheter will then be connected to a patient controlled epidural analgesic pump with the settings as per our normal standard of care.

C. All patients will be required to sign an informed consent document prior to participating in the study. We anticipate that it will take 24 months to enroll and study 60 evaluable patients. The specifics of the research will be explained to patients and any questions will be answered. Patient confidentiality will be maintained.

D. All patients will have a functioning intravenous catheter and receive appropriate intravenous fluid of balanced salt solution prior to insertion of their epidural catheter. The epidural space will be located by the usual technique with the patient in the sitting position using a 17G epidural Tuohy sited at L_{3-4} +/- 1 intervertebral space. All patients will then have an 18G epidural catheter inserted the customary length (5 cm) into the epidural space. The epidural needle will be removed and the catheter secured.

E. Background information on age, height, weight, gestation age, gravid status, cervical dilation, pitocin usage, and stadol usage will be obtained from patient report or the medical record. Study participants will indicate their level of discomfort at peak contraction on a standard 0-10 verbal analog scale (VAS). We will monitor and record the dermatome, pain score, vital signs, ephedrine usage, maternal vital signs, and fetal heart rate every 5 minutes for 20 minutes after initial spinal drug administration or every 5 minutes for 15 minutes after each subsequent physician epidural drug administration. Patient will also be assessed every 15 minutes until the patient requests additional analgesia. Changes in sensory levels to temperature and pin prick perception will also be assessed using alcohol pads and dull pins, respectively, at these same time intervals. Patients will be monitored in the usual clinical manner. Side effects such as hypotension, fetal bradycardia and post dural puncture headache will be recorded and treated as in our usual clinical practice. Participants will have their need for additional medication be evaluated in the routine fashion, and the amount and type of drug administered will be recorded.

Statistical and Analytical Plan:

SigmaStat for Windows by SPSS Inc is being used for statistical analysis. Based on previous observations and our obstetric anesthesia unit quality assurance data, we estimated one standard deviation of our primary outcome measure (highest sensory dermatome level of block) to be 3 dermatome levels. We considered a clinically significant difference in highest sensory block dermatome level between groups to be 3 dermatome levels. With these assumptions and to detect at least a 3 dermatome level difference in highest sensory block between groups with a power of 0.8 to 0.9 and an alpha of 0.05, the minimum sample size

needed is 30 patients per group. For the secondary outcome measure (analgesic duration of action), we consider a difference of 15 minutes between groups to be clinically significant with an estimated 60 minutes for mean duration of action and a standard deviation of 15 minutes. Similarly, the minimal sample size required to detect a difference of 15 minutes or more in analgesic duration between groups is 23 per group with a power of 0.8 to 0.9 and alpha of 0.05. Furthermore, based on our clinical quality assurance report, labor CSE and epidural analgesia may have up to 30% needing additional supplemental dosing and/or technical technique adjustments to achieve complete labor analgesia. Therefore, we will plan to enroll 45 patients per group to obtain at least 30 evaluable patients per group. The primary outcome in dermatome level difference will be analyzed by ANOVA on ranks using Kruskel Wallis test followed by posthoc Tukey test as appropriate.

Risks:

All the usual risks of epidural catheter placement exist including dural puncture by the epidural needle, threading the epidural catheter into a blood vessel (7-16% risk) or spinal space, the epidural not functioning properly (20-32%), as well as other very rare risks of nerve injury, hematoma, infection and seizures. More common usual risks of headache (approximately 1%) are not increased by the study procedure over the usual combined spinal epidural or epidural technique. Patients will be questioned the day following delivery for the presence of headache as per usual routine postoperative follow up visit. Diagnosis and treatment of a spinal headache will be managed as per our standard of practice. This management includes conservative therapy of pain medication, hydration and caffeine, followed by an epidural blood patch if necessary. A literature search yielded no significant reports of serious adverse events associated with epidural injection of saline. Patients may occasionally experience a sensation of pressure during the saline injection that may be perceived as uncomfortable transiently. Performance of a spinal block after administration of a large amount of epidural injectate can clinically translate to a higher sensory and motor level of spinal block and increase in duration of action, both of which are what this study aims to demonstrate. Researchers have hypothesized that compression of the dural sac by residual anesthetic in the epidural space may result in rostral displacement of the CSF, and with it, the injected spinal drug.[1,4] Others have estimated that the incidence of high spinal anesthesia when performed after epidural anesthesia is as high as 11% with a mean bupivacaine dose of 12 mg[5]. In this study clinically significant high spinal

blockade is considered to be unlikely and no more than usual epidural or combined spinal epidural analgesia, as we will be using very small doses of bupivacaine and the epidural predistension will be performed using normal saline rather than local anesthetic. A higher number of blocked dermatomes may potentially lead to a greater drop in mean arterial blood pressure compared to the usual epidural. However, this decrease is unlikely to be clinically significant based on a prior study showing only a 6 mmHg difference between 2 mL and 10 mL groups.[6] Blood pressures will be monitored every minute for 15 minutes after epidural placement and treated as appropriate with intravenous medications and fluid.

Benefits:

A 15 ml pre-existing volume injectate may significantly increase the level of sensory block and increase the analgesic duration of action of a subsequently performed spinal block. Spinal bupivacaine alone for combined spinal epidural analgesia with prior epidural volume injection may also provide the following advantages over traditional CSE with bupivacaine and fentanyl:

Less pruritus or most likely no pruritis (without spinal narcotic)

Potentially provides a form a spinal analgesia with longer duration of action without the need of higher dose of drugs.

Minimizes the time of retrieving and record keeping of narcotic use

Potentially better overall patient satisfaction (with less irritating side effects)

Human Subjects Protection

Informed Consent:

Written informed consent will be obtained from each subject. Study team members or the research nurse will obtain informed consent after patient is admitted for labor and is determined to meet the eligibility criteria for participation. The study and informed consent will be reviewed with the patients, and if applicable their legally authorized representative, in their labor and delivery room. Once signed, a copy of the informed consent form will be placed in the patient's medical record and a copy will be given to the patient for their records.

Confidentiality and Privacy:

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. The master study enrollment log containing the names, group allocation, and date of study will be kept secure in the department of OB Anesthesia, with access limited to designated study personnel. Following data collection subject identifying information will be destroyed at the earliest opportunity, consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

Data and Safety Monitoring:

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff. A data safety monitoring committee made up of 1 obstetrician and 1 obstetric anesthesiologist will be utilized and unblinded to group allocation. They will review the interim results bi-annually, including review of fetal heart rate and uterine contractions, vital signs, analgesic effects and the occurrence of any adverse events/side effects.

Reporting of Unanticipated Problems, Adverse Events or Deviations:

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the Institute Review Board (IRB).

References:

1 Blumgart CH, Ryall D, Dennison B, Thompson-Hill LM. Mechanism of extension of spinal anesthesia by extradural injection of local anesthetic. *Br J Anaesth* 1992; 69: 457-490

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3 Higuchi Hirata J, Adachi Y, Kazama T. Effects of epidural saline injection on cerebrospinal fluid volume and velocity waveform. A magnetic resonance imaging study. *Anesthesiology* 2002: 102: 285-92.

4 Beck GN, Griffiths AG: Failed extradural anaesthesia for caesarean section. Complications of subsequent spinal block. *Anaesthesia* 1992; 47:690-2.

5 Furst SR, Reisner LS. Risk of High Spinal Anesthesia Following Failed Epidural Block for Cesarean Section. *Journal of Clinical Anesthesia* 1995: 7-71-74.

6 Iwama H. Injection volume of saline with loss of resistance method may affect the spread of epidural anesthesia. Anesthesiology 1997; 86(2): 507-8.