Title: Comparison of fentanyl- bupivacaine and clonidine- bupivacaine for breakthrough pain in advanced labor in patients with continuous epidural analgesia

Columbia University Medical Center
Attached to Protocol: IRB-AAAL4101
Principal Investigator: Allison Lee, MD
Participation Duration: 1 day
Anticipated Number of Subjects: 250

PROTOCOL

Study Purpose and Rationale:
Epidural analgesia is a popular choice among patients for relief of severe pain associated with labor and delivery. Currently, at our institution we use a continuous infusion of low dose local anesthetic and narcotic (12 ml/hr of 0.0625% bupivacaine with 2 micrograms/ml fentanyl) after the initial spinal or epidural dose to maintain patient comfort until delivery. This dose of the infusion is chosen because it often provides adequate comfort without interfering with the mobility of the patient and her ability to effectively push during delivery. However, this low-dose epidural infusion strategy often results in recurrence of pain after an initial pain-free period. This recurring pain is known as breakthrough pain and is alleviated by administering small boluses of analgesics via the epidural catheter.

The pain occurring in labor is initially of visceral origin and is mediated by pain fibers originating from the low thoracic and upper lumbar segments of the spinal cord. As labor progresses to the late first phase (also known as transitional stage), pain sensations originating from the distension of the pelvic floor, vagina and perineum adds a somatic component to labor pain. This type of breakthrough pain, mediated by nerve fibers originating from the sacral nerves at dermatomes S2-S4, is often difficult to treat. Patients may experience inadequate analgesia even after boluses of analgesics are administered. Inadequate analgesia is deleterious due to subjective discomfort with its associated neurohumoral and physiological changes, and can be an initiator of the urge to bear down (push). Pushing before complete dilation of the cervix may lead to swelling, cervical injury and premature exhaustion of the mother. Adequate pain control will allow the cervix to fully dilate and motivate the mother to push effectively at the appropriate time. Although requests from patients to alleviate late stage breakthrough pain are common, there are no established data in the literature regarding the most effective strategy for pain management in this stage of labor.

This study is designed to compare the efficacy of two treatments for controlling late first stage breakthrough pain during labor: clonidine-bupivacaine versus fentanyl-bupivacaine. Both strategies are used at Columbia University Medical Center (CUMC) in this clinical situation, and there is no clear evidence whether one is superior.

Study Design and Procedures:
After obtaining consent, the patients will be randomized into two groups using a random allocation table. At the onset of late stage breakthrough pain with a Visual Analogue Scale (VAS) greater than or equal to 5/10, subjects will randomly receive either a mixture of 100 mcg

of clonidine and 12.5 mg of bupivacaine for a total volume of 10 ml ("CLON" group) and the other group will receive 100 mcg of fentanyl and 12.5 mg of bupivacaine for a total volume of 10 ml ("FENT" group). Group assignment will be performed by opening a previously prepared numbered opaque envelope containing the assignment "CLO" or "FENT".

The patient will be evaluated every 5 minutes for 15 minutes. If the patient reports a decrease in the VAS pain score by 4 points or more, the treatment will be declared a success. If the patient does not report a decrease in VAS score by 4 or more, the treatment will be declared a failure. If the treatment fails within 25 minutes from the end of injection of the initial study drug, the patient will receive the alternative of the initial treatment, which is 100 mcg of fentanyl or 100 mcg of clonidine (i.e., whichever drug was NOT given in the study mixture) with bupivacaine 12.5mg, diluted to a total of 10ml with sterile saline, via the epidural catheter (the observer will remain blinded to the identity of the medication). If this intervention fails to alleviate the pain, the caretakers will administer 5ml of 2% lidocaine via the epidural catheter. If the pain score still has not fallen by 4 or more points from baseline, 15 min after the dose of lidocaine the epidural catheter will be considered to be non-functioning.

All drug handling/distribution/administration will be conducted in accordance with the policies of the Research Pharmacy and Columbia University Medical Center.

Demographic and labor data (patient age, height, and weight, parity, hours in labor, cervical dilation and fetal station), details of labor analgesia preceding administration of the study drug (duration, type and amount of epidural or spinal analgesics, or other forms of analgesia), maternal and fetal heart rate and maternal blood pressure prior to and following administration of the study drug will be collected along with other clinical variables.

The study terminates upon delivery of the baby. Maternal and fetal hemodynamic data (maternal BP and pulse, fetal heart rate) and other clinical data will be obtained for 2 hours after the study dose, or until delivery, whichever is earlier. Neonatal Apgar scores as well as the mode of delivery will be collected.

Patients will be recruited by a study investigator after the establishment of labor epidural analgesia. The participants will be patients of the study team physicians. Informed consent with written documentation will be obtained from the research participant.

STATISITCAL PROCEDURES

The primary outcome is "success" or "failure" of the treatment as defined above. A clinically significant difference between the two treatments would be a 0.3 (30%) difference in probabilities for adequate analgesia. Assuming that the inferior treatment is successful in half of all patients, we aim to determine if the superior treatment is successful in 80%. For a power of 80% and an alpha of 0.05, this requires 45 subjects per group, so we plan on studying 100 overall.

To obtain 100 subjects who require a dose for breakthrough pain in the late first stage or second stage of labor, we may need to recruit and consent more than 250 subjects, since women will be

recruited after they are comfortable with their epidural analgesia, and it will not be known if they will eventually need a supplemental dose. Continuous data (VAS, total use of analgesics, maternal and fetal heart rate, maternal blood pressure) will be analyzed using ANOVA (with repeated measurements as appropriate) and categorical data (use of ephedrine, supplemental oxygen, fluid boluses and positional changes associated with administration of analgesics, instrumental delivery, cesarean section) will be analyzed using Chi-Squared analysis with Yates' continuity correction or Fisher's exact test as appropriate.