PROTOCOL TITLE: The Relationship between Local Anesthetic Concentration and Volume on Adequate Labor Analgesia with Programmed Intermittent Epidural Bolus

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ERSION NUMBER: 2.0

VERSION DATE: 12.14.2022

OBJECTIVES:

Aim: To evaluate the association between bolus volume and concentration of local anesthetic during maintenance of labor analgesia with programmed intermittent epidural bolus (PIEB) analgesia.

Hypothesis: Patients whose labor analgesia is maintained using PIEB with low-volume bolus (6.25 mL) of higher local anesthetic concentration solution (0.1% bupivacaine with fentanyl 2.0 mcg/mL) will have a longer duration of adequate analgesia (time to first manual re-dose request) than patients whose PIEB is delivered with a high-volume bolus (10 mL) of lower concentration local anesthetic solution (0.0625% bupivacaine with fentanyl 2.0 mcg/mL).

BACKGROUND:

Neuraxial labor analgesia is performed by the administration of a local anesthetic/opioid mixture in the epidural space. The delivery method is a combination of continuous infusion, provider-administered boluses and patient-administered boluses (patient controlled epidural analgesia [PCEA]) via epidural catheter. Pain during the first stage of labor is primarily due to lower uterine segment and cervical stretching. The pain signals enter the spinal cord through sensory nerves at the T10 through L1 dermatomes. Pain signals from the late first state and second stage of labor also arise from the vagina and perineum. These signals travel with the pudendal nerve and enter the spinal cord at S2-S4. Thus, the anesthetic solution administered through the lumbar epidural catheter must spread cephalad in the epidural space to reach the T10 nerve roots and spinal cord, and must spread caudad to reach the caudal nerve roots in the epidural space.

The optimal method for maintaining labor analgesia is unknown. Several studies have demonstrated that PIEB, in combination with PCEA, provide superior maintenance of labor analgesia (less need and longer time to provider intervention, lower local anesthetic consumption, less motor block, and improved patient satisfaction scores) than maintenance with a continuous infusion with PCEA.(1-4) The mechanism for this difference is not known; however, one suggested mechanism is improved spread of the local anesthetic within the epidural space. Kaynar *et al. injected* methylene blue dye through a multi-orifice catheter using either a continuous infusion or intermittent bolus and the area of diffusion was measured on a piece of paper.(5) The authors found that intermittent boluses were associated with a greater surface area of diffusion than continuous infusion. In a cadaver study, dye was injected into the lumbar epidural space, and cryomicrotome sections were taken.(6) Dye flowed in rivulets through small channels in the epidural space, as opposed to moving as a unified front. The authors found dye injected at high pressures had more uniform spread through the epidural space, supporting the concept of intermittent epidural injection providing superior analgesia.

Epidural infusion pumps capable of delivering PIEB of local anesthetic with PCEA have become commercially available and many studies have attempted to assess the optimal parameter settings (including volume of programmed bolus, bolus interval, rate of bolus administration) to provide superior labor analgesia. Recently we completed a double-blinded randomized control trial evaluating two bolus delivery rates, hypothesizing that those patients randomized to receive higher bolus delivery rates would have improved labor analgesia. However, no difference was found between groups.(7) What is more, both groups had a mean cephalad sensory level to cold of T6. This sensory level is higher than the traditional goal of T10 (upper dermatome level of uterine innervation), but despite the adequate sensory level, a large number of patients required

supplemental physician-delivered boluses of local anesthetic during labor. Forty percent of the women in the high-rate group and 36% of the low-rate group required a manual re-dose during labor.(7) This suggests that either a higher volume, or higher concentration of local anesthetic (i.e., higher dose) is needed to maintain adequate labor analgesia.

Traditionally higher concentration local anesthetic solutions have been associated with increased motor blockade leading to a higher incidence of instrumental vaginal delivery.(8) Several local anesthetic solutions with varying drug concentrations are available for labor analgesia and are used clinically in the United States. We plan to perform a randomized, controlled, double-blind study to test the hypothesis that patients whose labor analgesia is maintained using PIEB with low-volume bolus (6.25 mL) of a higher local anesthetic concentration solution (0.1% bupivacaine with fentanyl 2.0 mcg/mL) will require less supplemental analgesia (manual provider re-doses) than patients whose PIEB is delivered with a high-volume bolus (10 mL) of lower density local anesthetic solution (0.0625% bupivacaine with fentanyl 2.0 mcg/mL).

INCLUSION AND EXCLUSION CRITERIA:

Inclusion criteria:

Age: 18 years and above, nulliparous parturients who present to the labor and delivery unit for an induction of labor or who are in spontaneous labor, and request neuraxial labor analgesia at ≤5 cm cervical dilation are eligible to participate.

Exclusion criteria:

Patients who are not eligible to receive a combined spinal epidural (CSE) technique with 25 mcg of intrathecal fentanyl, non-English speaking, failed initiation of CSE analgesia (VAS pain score >10 15 minutes after intrathecal dose), need to have the epidural catheter replaced during labor, who deliver within 90 minutes of initiation of labor analgesia, or who require re-dose within 90 minutes of initiation of labor analgesia will be excluded from the study.

Study Drop Out:
Subjects will be removed from the study if the Ob/Anesthesiologist determines there is a need to increase the concentration and volume of the local anesthetic solution.

STUDY-WIDE NUMBER OF PARTICIPANTS:

In a previous study in which 10 mL of a bupivacaine/fentanyl mixture was injected at 300 mL/h and 100 mL/hr, the duration to the first request for supplemental analgesia (manual bolus) was 356 minutes and 301 minutes with a 36% and 40% re-dose rate respectively.(7) We hypothesize that the group with low-volume bolus (6.25 mL) of greater density solution (0.1% bupivacaine with fentanyl 2.0 mcg/mL) will have fewer patients requiring supplemental analgesia than patients whose PIEB is delivered with a high-volume bolus (10 mL) of lower density local anesthetic (0.0625% bupivacaine with fentanyl 2.0 mcg/mL).
Assuming a 20% reduction in re-dose from 40% to 20%, a power of 0.8, and an alpha of 0.05, we estimate that we will need 91 patients per group. In order to account for drop-outs, we will recruit 110 patients per group.

STUDY-WIDE RECRUITMENT METHODS:

Parturients who meet the inclusion criteria will be approached by one of the investigators, or one of the anesthesiology research nurses, for study participation on their arrival to the labor and

delivery unit. Parturients who are willing to participate in the study will provide written consent. Patient demographics will be collected at study enrollment.

MULTI-SITE RESEARCH: NA

STUDY TIMELINES:
The participants will be enrolled in the study at arrival, prior to request for labor analgesia. At the request for labor analgesia a vaginal exam will be performed by the obstetric or nursing team to ensure the patient still meets inclusion criterion. The patient will participate in the study from the time of initiation of combined-spinal epidural analgesia until the epidural catheter is discontinued after delivery. We estimate that it will take approximately 18 months to enroll 220 patients and perform data analysis.

STUDY ENDPOINTS:
Primary outcome: Need for supplemental physician-delivered bolus of local anesthetic.

Secondary outcomes: Time to first request for supplemental analgesia, total hourly bupivacaine consumption, mode of delivery, and motor block throughout labor and at 10 cm cervical dilation, sensory level throughout labor and at 10 cm cervical dilation, pain burden as defined as area under the pain-time curve, patient satisfaction.

PROCEDURES INVOLVED:
Parturients who meet the inclusion criteria will be approached by one of the investigators for study participation. Parturients who are willing to participate in the study will provide written consent. Patient demographics will be collected at study enrollment.

The research study team will determine group allocation by randomization via opaque sealed envelope. Participants will be randomized to one of two treatment groups based on a random computer-generated schedule (https://www.randomizer.org) and they will be blinded to the group to which they are assigned. The research study team will be blinded because the group will not be known other than group 1 or group 2 on the randomization card and on the pump. The CADD pump does not display the rate or the dose only group 1 or group 2.

Cervical dilation will be confirmed by a member of the obstetric team prior to initiation of CSE analgesia per routine practice. A baseline pain visual analog scale (VAS) score will be obtained using a 100-mm unmarked line with the end points labeled “no pain” and “worst pain imaginable.”

Labor analgesia will be initiated using CSE analgesia with 25 mcg of intrathecal fentanyl. An epidural test dose will be performed per routine (1.5% lidocaine with epinephrine 1:200, 3 mL).

Labor analgesia will be maintained using PIEB of local anesthetic with PCEA using the CADD-Solis pump (Smiths Medical). An unblinded anesthesia nurse will program the epidural pump and initiate the maintenance epidural infusion. The maintenance epidural solution for the high-

volume, low-concentration group will be bupivacaine 0.625 mg/mL with fentanyl 2.0 mcg/mL with a PIEB volume of 10 mL and patient-controlled epidural analgesia (PCEA) volume of 8 mL. The maintenance epidural solution for the low-volume, high-concentration group will be bupivacaine 1 mg/mL with fentanyl 2.0 mcg/mL with a PIEB volume of 6.25 mL and PCEA volume of 5 mL. The PIEB volume will be administered every 45 minutes. The first bolus will be given 30 minutes after intrathecal injection, as has been done in previous studies at our institution.(7) The bolus delivery speed will be 250 mL/h in both groups, which is our current practice. In addition to the programmed boluses patients will be able to administer PCEA boluses can be delivered every 10 minutes with a maximum of three PCEA boluses in a one-hour period. Fifteen minutes following the intrathecal dose, a VAS score and a sensory level of analgesia will be obtained. The following information will be obtained every two hours until complete cervical dilation (10 cm): VAS pain score, sensory level, a modified Bromage score (0 - no motor paralysis; 1 - inability to raise extended leg, but able to move knee and foot; 2 - inability to raise extended leg and to move knee, but able to move foot; 3 - inability to raise extended leg or to move knee and foot).

Redoses:
Up to three redoses of Bupivicaine .125% (10-15 mL) will be administered for inadequate pain control. The time to the first request for supplemental analgesia will be recorded on the study data sheet. The time, type and volume of bupivacaine used, and VAS scores before and 15 minutes after the re-doses will be recorded.

All other clinical management will be as per routine, and study participation will not interfere with anesthetic or obstetric care. Anesthesiologists will manage breakthrough pain in the usual manner (assessment of stage of labor and extend/density of neuraxial blockade, followed by the appropriate maneuver to reestablish adequate analgesia).

Following delivery, the patient will be asked to give one final VAS score and her overall satisfaction with labor using a 100 mm unmarked line (the left end labeled “not satisfied at all” and the right end labeled “extremely satisfied”). Mode of delivery, as well as the duration of the 1st and 2nd stage of labor, maximum oxytocin dose, maximum temperature recorded during labor, and any complaints for intrascapular pain will be recorded by study personnel.

Patient-Controlled Epidural Analgesia (PCEA) pump utilization data will be downloaded from epidural pumps after delivery. This will include the time to first PCEA request, the number of PCEA demands, the number of times that PCEA boluses were delivered, the total amount of local anesthetic consumed.

DATA AND SPECIMEN BANKING: NA

DATA AND SPECIMEN MANAGEMENT:
Group sample sizes of 91 in group 1 and 91 in group 2 achieve 80.276% power to detect a difference between the group proportions of 0.1250. The proportion in group 1 (the treatment group) is assumed to be 0.1250 under the null hypothesis and 0.2500 under the alternative hypothesis. The proportion in group 2 (the control group) is 0.1250. The test statistic used is

the two-sided Fisher's Exact Test. The significance level of the test is targeted at 0.0500.In order to account for drop-outs, we will recruit 110 patients per group.

Categorical data between groups will be compared using a chi-square or Fisher's exact test, and continuous data will be compared using a two-tailed t-test or Mann Whitney U test as appropriate. Time outcomes will be compared between groups using a Kaplan–Meier survival analysis technique with log rank test. Patients undergo a cesarean delivery or who do not request supplemental analgesia will be censored at the time of delivery. Labor pain will be calculated using the area under the VAS-time curve using the trapezium rule.

The subjects' identity will be guarded by assigning a numerical code, which is only known by the principal investigator. Data are stored in a department computer which is password protected. Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database. Subject data will be stored on secured computers at Northwestern University. Data access will be password-protected and only available to study investigators. The data forms will be de-identified after the chart review prior to analysis. 5 years after manuscript publication, both electronic and paper data will be destroyed using the current departmental standards.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:

A data monitoring committee consisting of the Department of Anesthesiology Director of Research, a statistician and a faculty member from the obstetrics department along with the study research personnel will periodically evaluate the data collected to determine whether participants remain safe. Safety data and adverse event data will be reviewed using the medical record and data collection form. It will be reviewed every 110 subjects or if one of the study subject experiences a rapid response team intervention and review. Data will be compared between groups using the chi2 statistic or the Fisher's exact test. A $P < 0.05$ will be required to reject the null hypothesis.

WITHDRAWAL OF PARTICIPANTS:

If the subject wishes to withdraw from the study during the hospitalization she will need to contact a study team member who will then contact the PI by secured-email to inform her about the event that led to early study termination.

RISKS TO PARTICIPANTS:

Participants are at risk for loss of confidentiality. There is also a possibility that there may be a difference between pain relief between the groups (the subject can self-administer by pressing the pump device or ask for supplemental analgesia). Subject may also be emotionally or physically uncomfortable completing the 2 hour assessments.

POTENTIAL BENEFITS TO PARTICIPANTS:

Participants will derive no specific benefit from participation in this study; however, participation in this study will help us better understand the optimal combination of local anesthetic volume/concentration for programmed intermittent bolus administration of maintenance of labor analgesia.

VULNERABLE POPULATIONS:
Checklist Pregnant Women HRP 412 has been reviewed.

COMMUNITY-BASED PARTICIPATORY RESEARCH: N/A

SHARING OF RESULTS WITH PARTICIPANTS:
Results of the study will not be shared with participants.

SETTING:
This study will be conducted on the Labor and Delivery suite on the 8th and 9th floor of Prentice Women's Hospital. Data analysis will occur on the NMH campus in the Department of Anesthesiology 9th floor office or on the 10th floor Arkes Pavilion in the Department of Anesthesiology administrative offices.

RESOURCES AVAILABLE:
The Section of Obstetrical Anesthesiology actively provides 24-hour care to 90% of 12,000 obstetric patients admitted to the Labor and Delivery Unit at Prentice Women's Hospital. As an Obstetrical Anesthesiologist and member of the Anesthesiology Service, I regularly supervise and provide care to patients in this unit. We have a dedicated group of clinical research nurses that assist with daily recruitment and follow-up of patients in clinical anesthesiology trials. Study team members all have CITI training.

PRIOR APPROVALS:
Department of Anesthesiology Research Committee

RECRUITMENT METHODS:
Subjects will be approached and recruited by a member of the anesthesia research team after admission to the 8th floor Labor and Delivery Unit at Prentice Women's Hospital. Patients who are being admitted the Labor and Delivery Unit at Prentice Women's Hospital who are nulliparous with singleton pregnancies and have a cervical dilation $\leq$ 5cm will be approached on admission to Labor and Delivery after their preanesthesia interview. The study team members will use Dashboard from the Labor and Delivery Unit at Prentice Women's Hospital and obstetric medical histories to identify potential participants. Subjects who are willing to participate in the study will provide written consent. There will be no materials used to recruit the patient. There will be no payment made to participants.

NUMBER OF LOCAL PARTICIPANTS:
A total of 91 patients will be needed in each group and to account for dropouts from the study a total of 110 patients in each group will be recruited (220 total recruited).

CONFIDENTIALITY:
Data will be stored in a department computer and departmental server which are both password protected. Each study subject will be assigned a study code number. The code will be used to link study data to patient identification (name) in a separate database. Subject data will be stored

on secured password-protected computers at Northwestern University and Department of Anesthesiology servers. Paper data will be completed by research study team members and will be entered into REDCap. The paper folders will be stored in Arkes Pavilion 10th floor Department of Anesthesiology administrative office via key card controlled front door and key controlled closet. Data access will be password protected and only available to study investigators via REDCap. REDCap access will be controlled by the Principal Investigator. Data both electronic and paper will be destroyed 5 years after manuscript preparation using current department protocol and current vendor.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
The subject will have multiple interactions with the study team members. The first interaction will be to discuss and obtain written informed consent; then multiple times over the next 24 hours for brief periods (less than 5 minutes). These brief interactions limit the amount of intrusion into the subject's labor process. These interactions will be timed with the postpartum nursing staff routine vital signs check to minimize intrusion.

The research study team is only to be allowed to view the data sheets, REDCap and Powerchart for selected data within the parameters of the study.

COMPENSATION FOR RESEARCH-RELATED INJURY: N/A

ECONOMIC BURDEN TO PARTICIPANTS:
Subjects will not be paid or charged extra for the care they receive as part of this study. All subjects will be charged for standard care they receive including the cost of the epidural labor analgesia that they would receive if they had not participated in this study. This cost will be billed to their insurance providers.

CONSENT PROCESS:
The consent process will take place in the Labor and Delivery Unit, 8th Floor, at Prentice Women's Hospital. This will be performed by a member of the research study team. There is no waiting period since subjects are in the hospital for delivery of their baby. SOP HRP 090 will be followed. The research study team will spend greater than 10 minutes discussing the study. Ample time will be allowed for patient to answer questions regarding the study and the consent document. The subject will also be informed that there is no conflict of interest between the PI and the protocol. The PI will not receive financial remuneration nor will the study participation affect the subject's financial charges for their care.

Waiver or Alteration of Consent Process: N/A

Participants who are not yet adults (infants, children, teenagers): N/A

Cognitively Impaired Adults: N/A

Adults Unable to Consent: N/A

PROCESS TO DOCUMENT CONSENT IN WRITING:

Informed consent will be documented in writing.

DRUGS OR DEVICES:

The study device is FDA approved. The PI will have the randomization table. Sealed opaque randomization envelopes hold the randomization cards which identify which program to select for the pump. The 10th floor pharmacy in Prentice Women's Hospital will dispense the medications. The anesthesiologist, nurses and study research personnel will be blinded to the study group. The Anesthesia research study team will set up the infusion pump and teach the subject how to use the pump to administer the study drug when desired. The FDA approved CADD infusion pumps will be stored on the labor and delivery unit located on the 8th floor Prentice Women's Hospital behind the key controlled anesthesiology work room.

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7. Lange EM**.** Association between bolus rate and duration of adequate labor analgesia. Abstract presented at the 2017 SOAP annual meeting, Bellevue, Washington.
8. Comparative Obstetric Mobile Epidural Trial Study Group UK**.** Effect of low-dose mobile versus traditional epidural techniques on mode of delivery: a randomised controlled trial. Lancet. 2001;358(9275):19-23.