Proposed Research Protocol Form
Northwestern University Feinberg School of Medicine

Title: Association between bolus rate and the adequacy of labor analgesia using timed-intermittent boluses for maintenance of labor analgesia

Principal Investigator: Elizabeth Lange, M.D.

Co-investigator (s): Paloma Toledo, MD, MPH,

Affiliation: Department of Anesthesiology, Northwestern University Feinberg School of Medicine

1.0 Research Aims:

Aim 1: To evaluate the association between bolus rate and duration of adequate labor analgesia.

Hypothesis: Patients whose labor analgesia is maintained using timed intermittent boluses with a high-rate bolus (300 mL/h) will have a longer duration of adequate analgesia (time to first manual redose request) than patients whose timed bolus is delivered with a lower-rate bolus (100 mL/h).

2.0 Research significance:

Background:

Neuraxial labor analgesia is usually maintained by the intermittent or continuous injection of local anesthetic combined with opioid through a catheter sited in the lumbar epidural space. Pain from 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 vaginal 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.

Administration of anesthetic solution into the epidural space is usually accomplished by a combination of continuous infusion, provider-administered boluses and patient-administered boluses (patient controlled epidural analgesia [PCEA]). The optimal method for maintaining labor analgesia is unknown. Several studies have demonstrated that timed-intermittent boluses, in combination with patient-controlled epidural analgesia (PCEA), provide superior

maintenance of labor analgesia (less need and longer latency for provider intervention, lower local anesthetic consumption, less motor block) 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 subsequent 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 timed boluses of local anesthetic with PCEA recently became commercially available. Several infusion rates are available for delivering the timed bolus, and the optimal bolus rate is unknown. We hypothesize that patients whose labor analgesia is maintained using timed intermittent boluses with a high-rate bolus (300 mL/h) will have a longer duration of adequate analgesia (time to first manual redose request) than patients whose timed bolus is delivered with a lower-rate bolus (100 mL/h).

.1 **<u>Significance:</u>** The findings from this study will help us better understand whether there is an association between bolus rate and adequacy of labor analgesia. This is important for guiding future clinical practice.

3.0 Investigational Plan

.1 <u>Study design:</u>

Randomized controlled double-blinded study

.2 <u>Methods:</u>

<u>Size of study groups(s):</u>

The primary outcome is the proportion of subjects in each group that have breakthrough pain requiring a manual bolus (redose) by the anesthesiologist. In previous studies that have used timed-intermittent boluses for maintenance of

labor analgesia, the percentage of patients that have required supplemental manual boluses of local anesthetic has ranged between 30-50%. We hypothesize that patients randomized to the rate of 300 mL/h will be less likely to require a supplemental manual bolus than those in the 100 mL/h group.[1,7] Assuming that 50% of the patients in the 100 mL/h group will require supplemental manual boluses and 30% of patients in the 300 mL/hr group will required supplemental manual boluses, using a power of 0.8, and an alpha of 0.05Due to the dynamic nature of the labor and delivery floor in patients' clinical course and resultant decisions regarding their choices on pain control during labor there is a greater degree of unpredictability of enrolled patients being excluded from this study for both clinical and personal reasons. As a result 300 patients meeting inclusion criteria will be recruited to account for dropout and still maintain the ability to recruit the estimated 106 patients per study group.
Secondary outcomes are the total number of requested and delivered PCEA boluses, and bupivacaine consumption per hour of labor analgesia.

.2.1 Participant entry, exclusion and dropout criteria:

Inclusion criteria:
Nulliparous parturients who presents to the labor and delivery unit for an induction of labor or who are in spontaneous labor, and request neuraxial labor analgesia at < or = to 5cm 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, who experience failed CSE analgesia, need to have the epidural catheter replaced during labor, or who deliver within 90 minutes of initiation of labor analgesia will be excluded from the study.

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

Cervical dilation will be confirmed by a member of the obstetric team prior to epidural catheter placement as is routinely done at our institution. 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 as routine (1.5% lidocaine with epinephrine 1:200, 3 mL).

Labor analgesia will be maintained using timed-intermittent boluses of local anesthetic with PCEA using the CADD-Solis pump (Smiths Medical). An unblinded anesthesia research nurse will program the epidural pump and initiate the maintenance of labor analgesia.

The maintenance epidural solution for both groups will be bupivacaine 0.625 mg/mL with fentanyl 1.95 mcg/mL. The intermittent bolus volume will be 10 mL administered every 60 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 rate will be 300 mL/h (2 minute 10 ml bolus infusion) in the high-rate bolus group, and 100 mL/h (6 minute 10 ml bolus infusion). In addition to the programmed boluses patients will be able to administer patient-controlled epidural analgesia (PCEA) boluses of 5 mL every 10 minutes to a maximum of 15 mL (three PCEA boluses in a one hour period).
The patient, anesthesiologist, and research nurse recording clinical data will be blinded to group assignment.

Fifteen minutes following the intrathecal dose, a VAS score and a sensory level of analgesia will be obtained. The following information will be obtained hourly 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).

The time to the first request for supplemental analgesia will be recorded on the study data sheet. The time, type and volume of local anesthetic used, and VAS scores before and 15 minutes after the redose 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 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.

4.0 Risks/Benefits:

Risks:

There is no risk of physical harm in this study. The study will not result in any change in management of the patient's pain other than the infusion rate of the timed-bolus epidural bolus, nor in any delay in diagnosis and treatment of pain.

Participants are at risk for loss of confidentiality. Strict measures will be in place to ensure that no loss of confidentiality occurs. All participants will be assigned a participant study number that will be used to identify them. One document will link the participant name to their participant number, and this will be kept in a password-protected computer in a locked office in the Prentice Women's Hospital. Only study investigators will have access to the study data.

Benefits:

Participants will derive no specific benefit from participation in this study; however, participation in this study will help us better understand the optimal rate for delivery of bolus doses of local anesthetic during maintenance of labor analgesia using timed-boluses.

Confidentiality:

The subjects' identity will be guarded by assigning a numerical code which is only known by the principal investigator. Data is 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 the data both electronic and paper will be destroyed using the current departmental standards.

5.0 Data Analysis:

.1 **Data collection form:** Data collection forms will include all of the information outlined above in study methods.

.2 Data evaluation: The primary outcome will be the proportion of patients requiring supplemental manual boluses of local anesthetic. Secondary outcomes are the total number of requested and delivered PCEA boluses, and bupivacaine consumption per hour of labor analgesia. In addition, time to first PCEA request, time to first supplemental manual bolus, and motor block at 10 cm cervical dilation will be evaluated. Categorical data between groups will be compared using a chi-squared 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 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.

1.0 Labor Requirements: All labor will be performed by study investigators and the anesthesiology research nurses.

2.0 Consent: Please see attached consent form for this study.

.1 Additional information for preparation of an IRB Submission: N/A

References:

1. Wong CA, Ratliff JT, Sullivan JT, Scavone BM, Toledo P, McCarthy RJ. A randomized comparison of programmed intermittent epidural bolus with continuous epidural infusion for labor analgesia. Anesth Analg 2006;102:904-9
2. Lim Y, Sia AT, Ocampo C. Automated regular boluses for epidural analgesia: a comparison with continuous infusion. Int J Obstet Anesth 2005;14:305-9
3. Chua SM, Sia AT. Automated intermittent epidural boluses improve analgesia induced by intrathecal fentanyl during labour. Can J Anaesth 2004;51:581-5
4. Capogna G, Camorcia M, Stirparo S, Farcomeni A. Programmed Intermittent Epidural Bolus Versus Continuous Epidural Infusion for Labor Analgesia: The Effects on Maternal Motor Function and Labor Outcome. A Randomized Double-Blind Study in Nulliparous Women. Anesth Analg 2011
5. Kaynar AM, Shankar KB. Epidural infusion: continuous or bolus? Anesth Analg 1999;89:534
6. Hogan Q. Distribution of solution in the epidural space: examination by cryomicrotome section. Reg Anesth Pain Med 2002;27:150-6
7. Wong CA, McCarthy RJ, Hewlett B. The effect of manipulation of the programmed intermittent bolus time interval and injection volume on total drug use for labor epidural analgesia: a randomized controlled trial. Anesth Analg 2011;112:904-11