Research Protocol Form
Northwestern University Feinberg School of Medicine
Department of Anesthesiology Research Committee

Title: A Randomized Controlled Trial Evaluating the Effect of the Oxytocin Infusion Rate on Fetal Heart Rate Changes and Maternal Fetal Outcomes during the Initiation of Combined Spinal-Epidural Labor Analgesia

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1.0 Research Aims:

.1 Research Questions(s):

11. Is there an association between the rate of oxytocin administration and non-reassuring FHR changes after the initiation of combined spinal- epidural (CSE) analgesia?

.2 Hypotheses: Patients who receive a lower rate of oxytocin administration will have fewer non-reassuring FHR changes.

2.0 Research significance:

Background:

Combined spinal-epidural (CSE) analgesia is a well-accepted technique for labor analgesia. The incidence of fetal heart rate changes after the initiation of neuraxial analgesia has been reported between 3-23% (1,2) and it is controversial whether the risk is increased with a CSE technique compared to an epidural analgesia technique (3). This wide range in reported risk may be due to fluid and oxytocin management prior to and during the initiation of neuraxial analgesia.

There are many factors that contribute to alterations in the fetal heart rate including stage of labor, fetal head compression, cord compression, and uteroplacental insufficiency. Oxytocin is used in labor and delivery to increase the frequency of contractions and augment uterine contractile strength, thereby establishing a regular pattern of labor. However, the administration of exogenous oxytocin in the presence of an uncoordinated labor pattern confers a risk for increase in uterine contraction frequency, resulting in inadequate relaxation periods. This leads to an increase in the basal tone of the uterus, which may lead to a tetanic contraction with risk decreased uteroplacental blood flow and fetal hypoxemia (3,4). Since the introduction of oxytocin for labor induction in 1948, there have been multiple protocols for the administration of oxytocin, both for labor induction, as well as for augmentation of labor. Many institutions use an active management of labor protocol (AMOL) to facilitate labor and delivery through oxytocin management. Use of the AMOL protocol decreases the duration of labor and the Cesarean delivery rate for dystocia (5). The evidence is divided as to the effect of high- versus low-dose oxytocin administration on fetal heart rate abnormalities (6-10). Merrill et al. randomized patients to low- versus high-dose oxytocin for augmentation or induction of labor (9). Oxytocin was decreased or discontinued more commonly in the high-dose group, both for uterine hyperstimulation and FHR abnormalities. In contrast, a study comparing high-dose oxytocin management with standard care found that there were no differences in fetal outcomes or the incidence of fetal distress between groups (10). One of the limitations of the previous studies is that the labor analgesia was not standardized; and consisted of either traditional epidural (high dose) analgesia or

intravenous opioids. Labor analgesia itself has been implicated as a cause of non-reassuring fetal heart rate tracings. The combination of low-dose combined spinal epidural analgesia and the high-/low-dose oxytocin have not been evaluated.

One of the proposed mechanisms for non-reassuring fetal heart tracings after initiation of analgesia is that the pain relief from neuraxial analgesia causes a decrease in catecholamine release by the sympathetic nervous system (5). The subsequent decrease in the circulating epinephrine concentration contributes to an increase in uterine tone, as epinephrine is a potent tocolytic agent. The increased tone, in turn, leads to a decrease in placental blood flow, and eventually fetal bradycardia.

The optimal oxytocin management in the peri-analgesia initiation period in terms of effects on uterine activity, uteroplacental perfusion, and fetal oxygenation, is not known. Anecdotally, some institutions arbitrarily decrease (or do not increase) the oxytocin infusion rate during initiation of analgesia. We hypothesize that decreasing the oxytocin infusion rate immediately before the initiation of CSE analgesia will cause fewer adverse fetal heart rate changes in the first 60 minutes following initiation of labor analgesia compared with maintaining the infusion rate.

3.0 Literature:

1. Hofmeyr GJ, Cyna AM, Middleton P. Prophylactic intravenous preloading for regional analgesia in labour. The Cochrane Database of Systematic Reviews. 2007.
2. Mardirosoff C, Dumont L, Boulvain M, Tramer MR. Fetal bradycardia due to intrathecal opioids for labour analgesia: a systematic review. BJOG 2002;109: 274-281.
3. Abrão KC, Francisco RP, Miyadahira S, Cicarelli DD, Zugaib M. Elevation of uterine basal tone and fetal heart rate abnormalities after labor analgesia: a randomized controlled trial. Obstet Gynecol. 2009; 113:41-

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4. Clarke VT, Smiley RM, Finster M. Uterine hyperactivity after intrathecal injection of fentanyl for analgesia during labor: a cause of fetal bradycardia? Anesthesiology 1994; 81: 1083.
5. Lopez-Zeno JA, Peaceman AM, Adashek JA, Socol ML. A controlled trial of a program for the active management of labor. N Eng J Med 1992;326:450.
6. Lindmark G, Nilsso B. A comparative study of uterine activity in labour induced with prostaglandin F2□ or oxytocin and in spontaneous labor. Acta Obstet Gynecol Scand 1976; 55: 453-60.
7. Satin AJ, Leveno KJ, Sherman ML, Brewster DS, Cunningham FG. High versus low-dose oxytocin for labor stimulation. Obstet Gynecol 1992; 80: 111-116.
8. Hourvitz A, Alcalay M, Korach J, Lusky A, Barkai G, Seidman DS. A prospective study of high-versus low-dose oxytocin for induction of labor. Acta Obstet Gynecol Scand 1996; 75: 636-641.
9. Merrill DC., Zlatnik FJ. Randomized double masked comparison of oxytocin dosage in induction and augmentation of labor. Obstet Gynecol; 1999: 455-463.
10. Sadler LC, Davison T, McCowan LM. A randomized controlled trial and meta-analysis of active management of labour. BJOG 2000; 107: 909-15.
11. Kinsella SM, Pirlet M., Mills MS, Tuckey JP, Thomas TA. Randomized study of intravenous fluid preload before epidural analgesia during labour. Br J Anesth. 2000; 85: 311-3.

.1 Significance: Fetal heart rate patterns are an important parameter in the diagnosis of non-reassuring fetal status. Combined-spinal epidural analgesia is a method of initiating labor analgesia used by approximately 90% of the parturients at Prentice Women's Hospital. Optimizing the variables which could affect fetal heart rate patterns at the time of initiation of analgesia, such as oxytocin management, could help us provide better care for our patients and their fetuses.

4.0 Investigational Plan

.1 Study design: Double blinded randomized, controlled study.

.2 Methods:

.2.1 Size of study groups The primary endpoint is the incidence of non-reassuring fetal heart rate tracings after the placement of CSE. Group sample sizes of 162 in each of two groups 80% power to detect an effect size (W) of 0.1560 using a 1

degree of freedom Chi-Square Test with a significance level (alpha) of 0.05000. The incidence of fetal heart rate changes was estimated based on data from Kinsella, et al (11). The proportion of subjects with adverse fetal heart rate changes in the low-oxytocin and fluid bolus treatment group is estimated to be 8%, Therefore 350 patients will be enrolled to account for patient drop-out or ineligibility.

.2.2 **Subject entry, exclusion and dropout criteria:** Healthy nulliparous or multiparous women with a term (37≥ week gestation), singleton pregnancy in spontaneous labor or with spontaneous rupture of membranes, who request neuraxial analgesia, and who receive oxytocin augmentation per institutional protocols, will be eligible to participate in the study. Maternal exclusion criteria will include the presence of any systemic disease (e.g., diabetes mellitus, hypertension, preeclampsia); use of chronic analgesic medications; prior administration of systemic opioid labor analgesia; non-vertex presentation; scheduled induction of labor; or any contraindication to neuraxial analgesia.

.2.3 **Protocol specific methods:** Eligible women will be asked to participate shortly after admission to the Labor & Delivery Unit at Prentice Women's Hospital during the routine pre-anesthetic interview. Informed, written consent will be obtained. Randomization based on a computer generated random number table; group assignments will be concealed in sealed, opaque envelopes. At the time of request for labor analgesia, group assignment will be determined by opening an opaque envelope. Patients will be randomized to one of two groups:

Group Assignment		Oxytocin Regimen
A		Routine oxytocin
B		Half-dose oxytocin

Fluid Management:

For patients in Groups A or B, an intravenous bolus of 500 mL LR will be initiated when the patient is positioned for CSE placement by the L & D nurse. The bolus will be administered through a free-flowing wide open intravenous catheter until complete.

Oxytocin Management:

The Prentice Women's Hospital oxytocin augmentation protocols will be used. At the time of request for analgesia, if the patient is in group A the oxytocin management will continue as per the normal oxytocin protocol.

If the patient is randomized to groups B the dose of oxytocin currently being administered will be halved and not increased for the duration of the study period (60 minutes after the initiation of CSE). Care providers other than the Labor & Delivery nurse managing the fluid and oxytocin infusions, will be blinded to group assignment.

Analgesia Management:

All subjects will receive a maintenance infusion of 125 mL lactated Ringers (LR) solution throughout the study period as per Labor and Delivery protocol. Per institutional protocol, all patients will receive a 500 mL bolus of LR solution at the start of the neuraxial procedure ("wide-open rate") via the mainline IV. Labor analgesia will be initiated in the sitting position at the L3-4 or L2-3 interspace with a routine combined spinal-epidural (CSE) technique. The epidural space will be located with the loss of resistance technique and a 27-g x 5-in pencil point spinal needle will be passed through the epidural needle to the subarachnoid space. The intrathecal injection will consist of bupivicaine 2.5 mg and fentanyl 15 μg. A 20 gauge epidural catheter will be threaded and secured 4-5 cm in the epidural space. A test dose of 3 mL lidocaine 1.5% with epinephrine 1:200,000 will be administered through the epidural catheter. The epidural catheter will be

secured and the patient will be positioned in a lateral recumbent position. Patient-controlled epidural analgesia (PCEA) infusion of bupivicaine 0.0625% with fentanyl 1.95 μg/mL will be started at a rate of 8 mL/h with bolus dose = 8 mL, lock-out interval = 10 min and maximum volume = 32 mL/h.

Fetal heart rate monitoring:

Fetal heart rate monitoring and frequency of uterine contractions will be recorded by external tocodynamometry.

Treatment of hypotension:

Any decrease of 10% or greater from baseline in maternal systolic blood pressure after placement of the CSE will be treated by the IV administration of ephedrine or phenylephrine as guided by maternal heart rate, as per standard practice.

Treatment of non-reassuring fetal heart rate changes:

If there are prolonged fetal heart rate decelerations, recurrent late decelerations, severe variable decelerations, or tachysystole, the Prentice Women's Hospital protocol for oxytocin management and intrauterine resuscitation will be followed.

Study completion:

The study is complete after 60 min after the intrathecal injection. After this time, obstetric and anesthesia management, including fluid and oxytocin management, will not be dictated by study protocol.

Fetal heart rate tracing assessment:

Fetal heart rate tracings will be examined for 30 minutes before and 60 minutes after the initiation of analgesia by a perinatologist blinded to study group off-line after delivery. NICHD guidelines (13) will be used to assess FHR patterns. Non-reassuring FHR patterns will be defined as any one or more of the following: minimal or absent variability, late decelerations, and persistent deceleration (see

Appendix).

.2.4 Risks/Benefits: All of the techniques and medications used in this study are routinely used for CSE analgesia during labor and for management of labor. The risks of the CSE procedure itself are unchanged by participating in this study. These risks include: epidural analgesia may not be effective, the epidural procedure may need to be repeated, pruritus, nausea, vomiting, or hypotension. Less common risks include maternal postdural puncture headache. Rare complications include maternal or fetal respiratory depression, total spinal anesthesia, a toxic reaction to the anesthetic agents, and bleeding or infection in the epidural or spinal space that may lead to nerve damage. The risk of oxytocin administration includes nausea, vomiting, confusion, allergic reaction, uterine hyper stimulation, fetal bradycardia, or maternal cardiac arrhythmias. There are no direct benefits to the patient for participating in the study.

.2.4.1 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. 7 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: The following data will be collected:

Demographic data: age, race, height, weight, gravidity, parity, and gestational age, history of prior inductions.

Labor data: time of rupture of membranes, cervical examination prior to placement of CSE (dilation, effacement, and station); start and stop time of fluid bolus, time of intrathecal injection, oxytocin dose at time of placement of CSE, vasopressor use and dose, maximum oxytocin dose in 60 minutes following placement of CSE, number of times oxytocin infusion is stopped or decreased for hyperstimulation or non-reassuring fetal status, time to complete cervical dilation, time of delivery, maximal maternal body temperature in study period.
Mode of delivery: normal spontaneous vaginal, instrumental vaginal, Cesarean.

Neonatal data: 1- and 5-minute Apgar scores; fetal umbilical cord gases (if taken); birth weight; neonatal sepsis workup or ICU admission.
Fetal heart rate tracing data: see appendix

.2 Data evaluation:

The primary endpoint is the incidence of non-reassuring fetal heart rate tracings during the first 60 minutes after the placement of CSE. Cross tabulation tables will be constructed with the presence or absence of the endpoint as rows and the groups as columns. Differences in the frequency among groups will be assessed using a X^2 statistic. Exact tests will be computed using Monte-Carlo sampling of 10,000 samples with a confidence level of 99%. An interim data analysis will be conducted after completion of the first 175 evaluable participants.
Secondary outcomes and demographics: Age, height, weight, gestational age, fetal station, and frequency of contractions will be compared using ANOVA or Kruskal Wallis ANOVA with post-hoc comparisons correction for multiple comparisons. Binominal and ordinal data will be compared between groups using the X^2 statistic or the Fisher's exact test. A $P < 0.05$ will be required to reject the null hypothesis.

6.0 Interpretation of Anticipated Results:

We anticipate that the lower dose of oxytocin will cause fewer adverse fetal heart rate

changes in the first 60 minutes following initiation of labor analgesia.

7.0 Budget:

.1 Materials: No additional materials will be required as all of the materials used in the study are routinely used in the management of patients.

.2 Labor Requirements: Existing anesthesia personnel on Labor & Delivery Unit.

.3 Presentation Cost: Anticipated presentations at MARC, SOAP and ASA meetings.

8.0 Consent: see attached