Programmed Intermittent Epidural Bolus (PIEB) Compared to Continuous Epidural Infusion (CEI) Relative Efficacy and Mechanism of Efficacy For Labor Anlagesia: A Minimal Local Analgesic Concentration (MLAC) Study

Study Protocol and Statistical Analysis Plan

NCT02573597

November 11, 2015

Title
PIEB Compared to CEI Relative Efficacy and Mechanism of Efficacy: A Minimum Local Analgesic Concentration (MLAC) Study

PI and other key investigators
Dr. Carvalho is an anesthesiologist, with an emphasis in obstetrical anesthesia and research. Dr. Riley is an anesthesiologist, with an emphasis in obstetrical anesthesia and research. [redacted] is an experienced clinical research coordinator. Dr. Malachy Columb at University Hospital of South Manchester.

Funding
None. Anesthesia Department

Seeking funding
No

Specific aims and basic hypothesis
There is limited data on the mechanism of action for short acting opioids in the presence of local anesthetic in the epidural space. The recent popularization of administering epidural local anesthetic with opioid by programmed intermittent boluses (PIEB) for labor analgesia may be preferential to the traditional continuous epidural (CEI) infusion of solution for maintenance analgesia.
The aims of the study are to first determine the relative potency of PIEB compared to CEI and secondly to determine the mechanism to explain the potential PIEB efficacy advantage. The study aims will be accomplished by utilizing a validated minimal local analgesic concentration (MLAC) study design.

General background
Ginosar, et al. performed a minimal local anesthetic (MLAC) study comparing intravenous fentanyl with epidural fentanyl (continuous infusion) in the setting of a continuous epidural infusion of bupivacaine for labor analgesia. These findings were suggestive of a predominately spinal mechanism of action of epidural opioids.
A recent meta-analysis by George, et al. found a local anesthetic sparing effect and improved maternal satisfaction in the setting of labor epidural analgesia with programmed intermittent boluses (PIEB) of local anesthetic and short acting opioids compared with continuous epidural infusions (CEI). This finding in favor of automated intermittent boluses of solution for the maintenance of labor analgesia has popularized the technique. It remains unclear if the advantageous effects of PIEB are from the potentially greater spread of solution associated with the bolus or the bolus administration of opioids into the epidural space enhancing a potential concentration effect across with the intrathecal space. Given that the mechanism of action of epidural opioids remains poorly characterized, the effect of bolusing epidural opioids may alter the pharmacodynamic profile.

Preliminary unpublished data
None. We are relying on previously published work on labor analgesia using PIEB, CEI and patient-controlled epidural analgesia (PCEA).

Experimental design
Pregnant women who present to Labor and Delivery for an anticipated vaginal delivery will be identified as potential participants based on inclusion/exclusion criteria and their desire for labor epidural analgesia. Once identified, interested candidates will be fully informed of the study procedures, have all

questions answered, and informed consent obtained. Pregnant participants will receive a labor epidural upon the patient's request and the epidural catheter will be initiated with 15 ml 0.125% bupivacaine with 10 mcg of sufentanil (our current standard of care loading dose).
Patients will be randomized into 1 of 4 group. Either group I or II in Study Part A and group III or IV in Study Part B in a double-blinded design. Each study part will run in parallel and independently. We have separated the study into 2 parts to clarify the methodology and aims for purposes of IRB and study design protocols.

Study Part A:
Group 1 Starting Concentration CEI: Bupivacaine 0.06% at 10 ml/hour + Sufentanil 5 mcg (2 ml) /hour (start at 0 mins)
Group 2 Starting Concentration PIEB: Bupivacaine 0.06% 10 ml q 60 + Sufentanil 5 mcg (2 ml) q60 (start at 30 mins)
Top-Up: 5-15ml 0.25% bupivacaine for all instances of request of additional analgesia (a current standard of care treatment option for breakthrough pain)
Bupivacaine 0.06% mg/ml in 250 ml NS bag and sufentanil 2.5 mcg/ml in 100 ml NS bag.
*Top-up is an additional dose provided upon patient request in the setting of inadequate analgesia during labor. Bupivacaine concentration to increase or decrease by 0.01% in subsequent patient depending on success or failure of previous patient

Study Part B:
Group 3: CEI Bupivacaine 0.06% 10 ml/hour + PIEB Sufentanil 5 mcg (2 ml) bolus q60 mins
Group 4: PIEB: Bupivacaine 0.06% 10 ml q 60 mins + CEI Sufentanil 5 mcg (2 ml)/hr continuous infusion 0.5 mcg/ml
PIEB start at 30 mins and CEI start at 0 mins.
Top-Up: 5-15ml 0.25% bupivacaine for all instances of request of additional analgesia (a current standard of care treatment option for breakthrough pain)
Bupivacaine 0.06% mg/ml in NS; 250 ml bag.
Sufentanil bag 2.5 mcg/ml in NS; 100 ml bag.
Bupivacaine concentration to increase or decrease by 0.01% in subsequent patient depending on success of failure of previous patient. Protocol success/failure/reject in each group (which will affect the subsequent patient's dose in the randomized group) will be determined by the following criteria:
Success - No supplemental analgesia request until vaginal exam c/w 8 cm dilation or more -> 0.01% w/v reduction in subsequent participant's local anesthetic.
Failure - Supplemental analgesia request c vaginal exam c/w less than 8 cm dilatation ->0.01% w/v increase in subsequent LA infusion.

Reject (NC in subsequent LA epidural infusion)
1. Pain >2 at 30 mins s/p initial LA load of 15 ml 0.125% bupivacaine with 10 mcg of sufentanil, without a bilateral T10 sensory level
2. Top-up (5-15ml 0.25% bupivacaine epidurally for all instances of request of additional analgesia) c/out pain >1 c/in 30 mins (i.e. catheter malfunction)
3. Progression to cervical dilatation >8 cm c/or delivers in 2 hrs from epidural placement (i.e. precipitous labor)
4. Progression to CS before 8 cm cervical dilatation
5. Patient request
6. Managing clinician's request
7. Changes to the maintenance regimen

8. Other

*No study number assigned to patients who meet protocol 'reject' criteria. Upon reject, catheter management at discretion of anesthesia care provider. No collection of subsequent data (secondary outcome measures).

In addition to demographic and obstetric data, data collection as described below.

Data Points:

i. Times

1. Initial Epidural Bolus (Labor Epidural Initiation)
2. Time of each anesthesia intervention request
3. Pain scores
4. Delivery

Ii. Cervical Exam (Dilatation (cm); performed by RN or Obstetrician)

1. Epidural Placement (if known; c/in 2 hrs before/after)
2. At time of request for additional analgesia (if known)

iii. Verbal Pain Scores (0-10; average pain at peak of contractions; obtained by investigator):

1. Initial epidural request
2. 30 mins s/p epidural initial dosing (average peak of last contraction)
3. q 1 hour (average pain at peak of contractions)
4. At request for addl analgesia
    a. 30 mins s/p top-up
5. At time of exam that establishes complete cervical dilatation (if known)
6. Average peak pain score during pushing (obtained c/in 1 hour post-partum)

iv. Additional Data Points

1. Overall Satisfaction c Labor Analgesia (0-100%; measured c/in 1 hr of delivery)
2. Labor Outcome: Spontaneous/Instrumented/Cesarean and total number of hours of oxytocin infusion prior to delivery
3. Neonatal Apgars (1 and 5 mins; assigned by pediatrician)
4. Pruritus q2 hrs (Y/N)
    a. Requiring treatment
5. Nausea (0-10) Vomiting q2 hrs Y/N
    a. Requiring treatment
6. Hypotension Requiring Treatment (Y/N)
7. Motor Weakness c Labor Analgesia (q2 hours; Straight leg raise Y/N)
8. Sensory level q2hrs
9. Duration of first and second stage of labor
10. Rupture of membranes (spontaneous or artifical) prior to epidural

Inclusion criteria: ASA I & II, Nulliparous and Multiparous, Spontaneous/Induced/Augmented Labor, Early active labor (cervix <5 cm (if known)), Pain (VPS) > 3, 18-45 years of age.

Exclusion criteria: <37 weeks gestation, H/o Cesarean Section, Multiple Gestation, Pre-eclampsia, Narcotics within 3 hours prior to labor epidural placement, Chronic Pain (as defined by chronic opiate consumption), Women who are participating in another study that will impact protocol

Our primary outcome or determinant of different treatments for labor pain is the minimal local anesthetic concentration of the final participants in each respective group upon study completion. Interim analysis will be performed at 20 patients (10 in each group) in study part A and B, respectively. If

no important differences are detected, the study will end with the recruitment of 160 patients (80 for each study group) per our sample size calculation, based off an MLAC study by Ginosar, et al. Demographic, obstetric and clinical outcome measures data will be analyzed using unpaired Student's, Mann-Whitney U-test, and Chi-Squared or Fisher's exact test as appropriate.
MLAC analysis: The median effective concentrations will be estimated from the up-down sequences using the method of Dixon and Massey (Dixon WJ, Massey FJ. Introduction to statistical analysis. 4th ed. New York: McGraw-Hill, 1983) that will enable MLAC with 95% confidence interval (CI) to be derived. The sequences will also be subjected to Wilcoxon and Litchfield probit regression analyses using ln(1+x) transform as back-up or sensitivity tests.

DATA SAFETY MONITORING PLAN will follow standard of clinical care. Any adverse events will be reported to the PI and necessary adjustments to the protocol will be immediately instituted.

Significance
These findings will facilitate a better understanding of the mechanism of action of short acting opioids in the presence of local anesthetic in the epidural space, which have the potential of optimizing strategies to provide maintenance of labor analgesia. Part 1 of our study will determine relative potency of PIEB compared for labor analgesia to CEI using MLAC to better facilitate appropriate initial epidural pump settings and maternal dosing. Part 2 of our study will determine mechanism to explain the PIEB efficacy advantage, so that the epidural technique can be optimize.

Key references
George et al. "Intermittent epidural bolus compared with continuous epidural infusions for labor analgesia: a systematic review and meta-analysis." Anesth & Analg 2013; 133-144.
Ginosar et al. "The Site of Action of Epidural Fentanyl Infusions in the Presence of Local Anesthetics: A Minimum Local Analgesic Concentration Infusion Study in Nulliparous Labor." Anesth & Analg 2003; 1439-1445.
Polley et al. "Effect of sufentanil on minimum local analgesic concentrations of epidural bupivacaine, ropivacaine and levobupivacaine in nullipara in early labour." Anesthesiology 2000; 122-128.
Ginosar et al. "The Site of Action of Epidural Fentanyl in Humans: The Difference between Infusion and Bolus Administration." Anesth & Analg 2003; 1428-1438.