Comparison of Programmed Intermittent Epidural Boluses with Continuous Epidural Infusion for Maintenance of Labor Analgesia

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Background:

Labor pain during childbirth is regarded as one of the most painful experiences in a woman's life with the potential to cause lasting emotional and psychological effects. Childbirth has also been associated with the development of chronic pain with the prevalence of between 4-10% after cesarean section and 6-18% after vaginal delivery (1). Hence, effective management of labor pain is instrumental in preventing the development of life altering chronic pain in women of childbearing age. Maintaining epidural analgesia with combined local anesthetic and an opioid is considered extremely safe and leads to superior neonatal and maternal short and long-term outcomes (2). Historically, maintenance of epidural analgesia involved intermittent provider-administered bolus injections, patient controlled epidural analgesia (PCEA) and continuous epidural infusions (CEI) with or without PCEA for breakthrough pain or discomfort (3). CEI has been shown to provide consistent analgesia in addition to improved patient satisfaction and reduced workload for the anesthesia providers. However, CEI is associated with greater local anesthetic consumption and increased maternal motor blockade (3). Increased motor block is associated with reduced mobility, decreased pelvic muscle tone and impaired ability for the parturient to adequately Valsalva during the second stage of labor (4). Motor blockade is also associated with increased incidence of shoulder dystocia and instrumental deliveries, which precipitate birth trauma to the fetus and the mother. Achieving adequate analgesia during labor, without compromising motor function is critical for optimizing both short-term and long-term outcomes for the mother and the neonate.

A more novel approach to labor analgesia involves the administration of small, programmed intermittent epidural boluses (PIEB) with PCEA dosing for breakthrough pain. Preliminary studies have indicated that PIEB could be a superior method of labor analgesia compared to current standard of care, CEI. A randomized double-blind study by Wong et al. compared CEI and PIEB incorporating the use of PCEA for breakthrough pain in healthy parturients with singleton pregnancies. Results suggested that the cohort receiving PIEB required less local anesthetic use, had similar analgesia and improved patient satisfaction when compared with CEI (3). Additionally, a subsequent study by Wong et al found that in healthy, term, nulliparous women in spontaneous labor, extending the PIEB interval and increasing volume decreased local anesthetic consumption, PCEA requests or rescue analgesia requirements without increasing patient discomfort or compromising satisfaction (5). Two subsequent studies allocating women to receive either PIEB or CEI in nulliparous parturients and women terminating pregnancy suggested PIEB recipients experienced less motor blockade when compared to those receiving CEI (6,7).

Our group has recently performed a systematic review and meta-analysis of studies comparing the effects of labor analgesia with either PIEB or CEI with or without PCEA in laboring women. The meta-analysis included 9 studies and evaluated various primary outcomes including: patient satisfaction, required manual anesthesia interventions, labor progression and mode of delivery (vaginal, instrumental or cesarean delivery). Secondary outcomes included: degree of motor blockade, degree of sensory blockade, time to first anesthetic intervention, local anesthetic dose delivered per hour, pruritus, shivering, maternal fever, nausea and vomiting, neonatal Apgar scores at 1 minute and 5 minutes, and umbilical artery and vein pH (8). PIEB dosing of local anesthetic was associated with reduced local anesthetic consumption, decreased required anesthetic interventions, and an improvement in maternal satisfaction in comparison to laboring women receiving CEI. Pooled results indicated that PIEB and CEI were comparable with regard to the duration of first stage labor, but there was a statistically significant 22 min reduction in the length of stage two of labor with PIEB. Similarly, this review did not suggest statistically significant differences in cesarean delivery rate or required anesthetic intervention between CEI and PIEB (8). There were several limitations to these preliminarily studies. While, each of the 9 studies reported at least one primary outcome listed in the systematic review, none of the studies included all primary outcomes. Additionally, most studies only involved nulliparous women, which may limit the ability to apply results to multiparous women. Furthermore, many of these studies involved the use of two pumps, one to deliver CEI or PEIB and another to deliver PCEA in a research setting, or involved the use of non-commercially available research pumps (3).

Currently the CADD solis v 3.0 pump system has been upgraded to allow the co-administration of epidural anesthesia with PIEB or CEI and PCEA. This new technology has been available on the labor and delivery unit of Duke University Medical Center as the standard of care since March 2015 (9). This new pump differs from those used in the preliminary studies, which utilized a two-pump approach to administer PIEB or CEI and PCEA for labor pain relief. Preliminary studies have not identified optimal PIEB settings, bolus volumes, lock out intervals, or drug concentrations, which represents a gap in literature at the present time. Our group performed a retrospective study to explore whether PIEB was associated with reduced LA use, PCEA use and rescue analgesia in comparison to CEI in laboring women. Our group also assessed whether PIEB decreased the number of instrumental deliveries and reduced motor blockade, which serves as an impediment to the progression of labor (9). The study divided patients into three groups. The first received CEI 5mL/hour, the second received PIEB 5mL every 60 min, the third used PIEB of 3mL every 30 min. Each group had access to PCEA set to 5 mL boluses with an 8-minute lockout period and maximum of 35mL per hour (9). The results of the study did not suggest what we expected as the study revealed no statistically significant difference between the LA consumption, amount of motor blockade or mode of delivery for patients receiving CEI or PEIB when using the single pump system instead of two-pump system employed by prior studies. However, this study did suggest patients who received PIEB regimen of 3mL every 30 minutes used a lower PCEA volume than patients receiving CEI. Patients

receiving PEIB regimens had more attempts/PCEA given than the CEI patients and the PIEB 3ml/30 minute group had more unsuccessful PCEA attempts/hour than CEI recipients.

Our study, unlike prior studies comparing PIEB vs. CEI with PCEA, used more concentrated solutions consisting of double the concentration and half the volume of bupivacaine. One of our speculations is that larger boluses of a more dilute LA may have improved dissemination in the epidural space and thus improved analgesia (9). Our study interpreted PCEA attempts/given and the number of unsuccessful PCEA attempts/hour as reflections of patient pain or discomfort, as an attempt is interpreted as an effort to achieve better pain relief (9). Another way to interpret the aforementioned PCEA attempts is as representation of the amount of time a patient "locked out" or prevented from receiving additional boluses of PCEA. Hence, a limitation of this study is the fact that patient satisfaction scores were not collected as they could help distinguish whether attempts reflect the lockout period or inadequate analgesia (9). Other limitations of our retrospective study include the fact that explicit instructions about how to properly use the PCEA was not standardized, and the fact that patient satisfaction or pain scores were not garnered due to the study's retrospective nature (9). Probably one of the most significant limitations of our study was the fact that patients were not randomized to treatment groups. Hence, the providers chose the analgesia received (9). On the other hand, another retrospective study utilizing a more dilute concentration of local anesthetic reported reduced need for physician interventions with PIEB compared to CEI. We have recently switched the local anesthetic in our practice from bupivacaine 0.125 % to a more dilute concentration of ropivacaine 0.1% mixed with fentanyl 2 mcg/ml (10). We therefore aim to prospectively study if the use of PIEB with the new epidural solution would be associated with improved analgesia compared to a regimen using CEI.

Purpose of the study:
The aim of this study is to compare two modes of epidural analgesia delivery, PIEB versus CEI with PCEA dosing, in the treatment of labor pain. Our primary outcome will be the volume of local anesthetic received through PCEA per hour. Secondary outcomes will measure the total required local anesthetic required per hour, time to first PCEA bolus, labor pain scores, degree of motor blockade, mode of delivery, PCEA attempts and ratio of successful to unsuccessful attempts, frequency of hypotension, duration of first and second stages of labor and level of patient satisfaction.

Study design and recruitment:
The study will be a blinded randomized, controlled trial comparing the two regimens for labor analgesia that are currently used as standard of care at our institution: a patient will be assigned to receive either delivery of epidural medication ropivacaine 0.1% with fentanyl 2mcg/mL with PIEB + PCEA dosing method or CEI + PCEA dosing method. Potential participants will be recruited from the Duke University Birthing Center as they are admitted for labor with intention for vaginal delivery.

Inclusion criteria:

American Society of Anesthesiology (ASA) class 2 and 3 women
Nulliparous and Multiparous
Age > 18 yrs
gestational age > 36 weeks
singleton pregnancies
vertex pregnancies
In labor
cervical dilatation 2-7 cm at time of epidural placement
Pain score > 5

Exclusion criteria:

BMI > 50 kg/m^2
history of past or current intravenous drug or chronic opioid abuse
chronic analgesic use
allergy or contraindication to any study medications
any maternal or fetal condition requiring planned assisted stage 2 delivery

Study Method:

After obtaining Duke University Institutional Review Board approval and informed consent, nulliparous or multiparous women in labor and cervical dilation between 2-7 cm desiring epidural for labor analgesia will be eligible to participate in this study. Subjects will be allocated to a study arm (CEI or PIEB) by computer-generated, random assignment placed in sealed opaque envelopes.

Epidural catheters will be placed at the L3/4 or L4/5 interspace with 4 cm of catheter being left in the epidural space. If the subject experiences an inadvertent dural puncture during epidural placement, she will be removed from the study. Epidural analgesia will be initiated and maintained with a solution of ropivacaine 0.1% with fentanyl 2 mcg/ml. After the initial epidural loading dose of 20 mL is administered in incremental fashion, patients will receive either 6 mL every 45 minutes in the PIEB arm (first bolus 30 minutes after epidural initiation) or 8mL/hr of continuous infusion beginning immediately after the loading dose for the maintenance of analgesia in the CEI arm, both of which are standard of care at our institution. All study participants will be provided with PCEA set to 8mL boluses with a10-minute lockout period. The maximum amount of PCEA analgesia will be set to a 1-hour maximum of 45mL. A script will be provided to anesthesia providers so that the same explanation about the use of the PCEA is provided to all subjects. Monitoring of patients will be with blood pressure measurements every 2 minutes for 15 minutes and then every 15 minutes afterwards, and with continuous heart rate and pulse oximetry as per standard of care. If the parturient does not achieve adequate

analgesia with a pain score ≤ 2 at 30 minutes, the catheter will be considered unsatisfactory, and the subject will be withdrawn from the study. Pain scores and Bromage scores will be collected at 30 minutes after epidural initiation and then every 2 hours until delivery. If the patient has inadequate analgesia, despite activating the PCEA twice in the last 20 minutes, physician boluses will be administered using 5 ml of ropivacaine 0. 2 % every 10 minutes. If the patient does not have adequate analgesia after 10 ml ropivacaine 0.2%, the catheter will be considered unsatisfactory if there is no bilateral sensory level at this stage and the patient will be removed from the study. If there is bilateral sensory level to at least T10 after the ropivacaine boluses, and the patient complains of pressure, fentanyl 100 mcg will be given epidurally. If the patient does not achieve a pain score ≤ 2 after fentanyl, the patient will be removed from the study. The study will begin with epidural insertion and terminate with delivery. Per standard of care, each participant will be evaluated 24-hours post-partum to assess for any adverse effects.

The primary endpoint will be the total volume of local anesthetic received through PCEA per hour. Secondary outcomes will include need for physician interventions per hour, volume of clinician boluses required per hour, PCEA attempts per hour, PCEA boluses given per hour, unsuccessful PCEA attempts per hour, ratio of attempts/giver per hour and motor blockade measured by the lowest recorded modified Bromage scale, frequency of hypotensive events, mode of delivery, labor pain scores and patient satisfaction.

Statistical Analysis:
Data from a pilot study suggested that the mean (SD) PCEA volume used per hour was 6 (3) ml with CEI and 4 (3) ml with PIEB. A sample size of 44 patients per group will have an 80 % power at alpha=0.05 to identify this difference. To account for drop-outs and catheter failures, we will aim to enroll 200 subjects to have 60 completed patients per group. Randomization will be stratified according to parity (nullipara or multipara). Continuous data will be analyzed using kruskal wallis test or t test as appropriate. Categorical data will be analyzed using Chi-square test or Fisher's exact test as appropriate.

Subject identification, recruitment and compensation:
Patients presenting for spontaneous or induced delivery will be screened. Those eligible will be approached to participate in the study. A member of the healthcare team known to the subject will introduce the study. There will be no compensation to the subjects as a result of participation in this study.

Subject competency:
Only competent subjects will be approached to participate in this study.

Costs to Subject:
There will be no additional cost to the subjects as a result of participation in this research study.

Data Storage & Confidentiality:
Study records will remain confidential as required by law. Federal Privacy regulations ensure privacy, security and authorized access. Patient identifiers including but not limited to name, social security number, address, and telephone number will not be disclosed outside of the Duke University Health System (DUHS). For records shared with parties outside of DUHS, patients will receive a unique code number. The key to the code will be kept in a locked file in Dr. Habib's office.

Data Integrity:
The data will be housed on the Department of Anesthesia's Parnassus server and the PI, and study team members will have access to the study data.

Data monitoring:
Data will be monitored closely for the occurrence of adverse events (AE) and reported to the IRB as needed. If unanticipated AEs or if expected events appear to be occurring more frequently than expected, those AEs will be explored per treatment arm.

In accordance with federal regulations, the PI will monitor for, review, and promptly report to the IRB, appropriate institutional officials, sponsor, coordinating center and the appropriate regulatory agency head all unanticipated problems involving risks to subjects or others that occur in the course of a subject's participation in a research study (45 CFR 46.103(b)(5)(i) and 21 CFR 56.108(b)(1)), all AE reports will be reported per the DUHS IRB policies.

Benefit / Harm Assessment:

The will be no benefit to subjects from participating in the study, since standard of care regimens will be used in this study. The information gained from the study will help elucidate if PIEB offers benefits over CEI for maintenance of labor analgesia in our practice. Risks of epidural analgesia are the same irrespective of participation in the study. Preliminary studies to date have not shown any difference in risks with PIEB compared to CEI.

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