A Randomized Controlled Trial for Epidural Analgesia in the Morbidly Obese Parturient: Comparison of Dural Puncture Epidural with Standard Labor Epidural Techniques

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Title: A Randomized Controlled Trial for Epidural Analgesia in the Morbidly Obese Parturient: Comparison of Dural Puncture Epidural with Standard Labor Epidural Techniques

Background and significance:

The incidence of morbid obesity in the United States is increasing, and in the last 30 years, the number of the super morbidly obese [body mass index (BMI) over 50 kg/m^2] has risen 10-fold.[1] In obstetric patients, morbid obesity often complicates the placement of neuraxial labor analgesia due to difficulties in positioning patients for placement and identifying landmarks. Morbid obesity also significantly increases a woman's risk of requiring operative vaginal delivery or cesarean delivery after a trial of labor.[2] Further, there is a strong correlation with increasing BMI and risk of emergency cesarean section.[3] A study by Hood *et. al* reports that in laboring women, 48% of morbid obese women (median BMI 52 kg/m^2) require emergency cesarean while only 9% of the control group went on for emergency cesarean delivery.[4]

Neuraxial anesthesia is well-established as the preferred anesthetic technique for cesarean delivery due to the increased risks of administering general anesthesia to pregnant women. This is particularly relevant in the obese population since obesity increase the risk of difficult intubation. The Confidential Enquiry into Maternal Deaths in the United Kingdom cites obesity as a major risk factor in failed intubations, and Hawkins *et. al* report that aspiration of gastric contents during intubation is the leading cause of anesthesia-related death in the US obstetric population.[5,6] A labor epidural which can be satisfactorily extended to anesthetic conversion avoids the need for general anesthesia for cesarean section after trial of labor. Therefore, an early, established epidural (EPL) may prevent emergent administration of general anesthesia and greatly reduce the associated risks of serious complications.

Unfortunately, placement of an adequate neuraxial block can be challenging for the

anesthesiologist. Usual landmarks, such as spinal processes to indicate midline and iliac crests for vertebral level are often not visible or even palpable. Furthermore, adipose pockets in the subcutaneous layer result in false spaces with loss-of-resistance technique. One study has found a 42% EPL failure rate in the morbidly obese.[4] Therefore, it should be a priority to establish regional anesthesia early in labor.

In modern practice, combined-spinal epidurals (CSE) have been used widely for labor analgesia. Benefits of the CSE include: more rapid onset, decreased motor block, and uniform sensory blockade.[7] In practice, however, some clinicians avoid CSE technique due to concerns about associated risk factors such as fetal bradycardia. Fetal bradycardia is thought to occur from the rapid onset of spinal analgesia and reduction of beta adrenergic activity. The remaining alpha activity leads to uterine contraction and therefore decreased uteroplacental blood flow.[8,9] The CSE technique can further delay confirmation of a functional epidural catheter. This delay could result in complications if instrumented or emergent delivery is imminent.

In a novel technique described by Cappiello *et.al*, a dural puncture epidural (DPE) is performed by creating a perforation in the dura with a spinal needle through an epidural needle without drug administration into the intrathecal space.[10] The return of cerebral spinal fluid (CSF) through the spinal needle is thought to provide indirect confirmation of the correct position of the Tuohy needle.[11,12] The EPL catheter is then tested and dosed in usual fashion with more immediate assessment of a functional EPL catheter. In theory, the DPE technique provides confirmation of midline placement of epidural catheter. Additionally, the dural perforation allows for translocation of medications administered in the epidural space into the spinal cavity.[13] This has been shown to reduce time to achieve adequate pain relief from labor and reduce rates of uneven sensory block. As reported by Cappiello *et. al*, catheter replacement

decreased from 13% to 3% when introducing DPE. Their group also reports that unilateral blocks decreased from 25% to 8% and catheter adjustments from 28% to 13%.[10] The same group completed a subsequent study that has been accepted for publication, which reports that clinician-administered epidural interventions, or "top-ups" also decreased from 50% to 22.5% when introducing the DPE technique.[14]

There has been no prospective study to date to compare the standard epidural technique to the DPE technique for labor analgesia in the morbidly obese population.

Purpose of the study:

The primary purpose of this study is to determine if there are differences in block quality between the DPE and standard EPL techniques for labor analgesia in the morbidly obese patient. Establishing superiority of a technique is multifaceted and complex; therefore, the design of the study will define a set of measureable outcomes to assess these properties, which will be addressed in the subsequent sections. We hypothesize that when compared to the standard EPL, the DPE technique will significantly improve block quality in this population.

The secondary purpose of the study is to find an optimal maintenance regimen for epidural analgesia in the morbidly obese population. For the maintenance of epidural analgesia, it is common practice to use either continuous epidural infusion or a programmed intermittent bolus using a solution of ropivicaine 0.1% with fentanyl (2 mcg/mL). To date, there are no randomized prospective studies that investigate maintenance regimens in the morbidly obese parturient population. What has been shown is that super morbidly obese patients have increased intra-abdominal and intracranial pressure which increases pressure in the epidural space. Because of this elevated pressure, the epidural spread is increased, resulting in higher sensory blocks than necessary for adequate labor analgesia.[15] An important consequence is that the morbidly obese

parturient may experience additional undesirable side effects to a labor epidural: increased respiratory function, increased incidence of hypotension, and increased motor block.

Design and procedures:

We propose a prospective, double-blinded, randomized trial. According to our patient population and incidence of morbid obesity, enrollment would likely occur over a 2 to 3-year period. We have a delivery rate of 3500 per year. Previous data from our institution show that at least 11% of our patients are morbidly obese.[16] We will therefore expect 800-900 morbidly obese women to deliver at our institution per year. We anticipate to complete enrollment before the protocol's third annual renewal.

Subject identification and recruitment:

Women admitted to the Duke Birthing Center for spontaneous or induced vaginal delivery will be screened. After usual consultation with the anesthesia team is completed and consent for anesthesia services are obtained, eligible patients will be approached to by a member of the study team. As indicated below, we will plan to enroll 130 patients (65 for the DPE group and 65 for the EPL group) and consent 150 women to reach this goal.

Inclusion criteria for study eligibility include: ages 18-45, singleton, vertex fetuses at 37-41 weeks' gestation, nulliparous and multiparous women, cervical dilation of 2-7cm, BMI $\geq$ 35 kg/m^2, pain score > 4, and English-speaking ability. Women with diseases of pregnancy that increase the risk of assisted vaginal delivery or cesarean delivery (i.e. major cardiac disease, chronic pain, chronic opioid use, prior cesarean delivery, and maternal pelvic/hip disease) are will be excluded from the study. Women who cannot speak English will be excluded.

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

Costs to the subject:

There will be no additional cost to the subjects as a result of participation in this research study. There will be no compensation to patients for their participation in this study.

Epidural technique:

Once the patient requests a labor epidural, the usual standard of care for epidural placement will be initiated. The patient will have at least one 18g intravenous catheter and will receive 500-1000mL fluid administration. Vitals will be monitored by the labor nurse, including continuous pulse oximetry, non-invasive blood-pressure monitoring, and external tocodynamometry. Anesthesia time-out will be performed by the anesthesia provider with participation from the nurse and the patient.

All patients will receive a neuraxial technique in the sitting position at L3/4 or L4/5 using loss of resistance to saline. In the DPE group, a 25-g Whitacre needle will be used to puncture the dura. In both groups, the epidural catheter will be threaded 5 cm in the epidural space with an initiation dose of 15 ml of ropivacaine 0.1% with fentanyl (2 mcg/ml) over 6 minutes as per standard practice. Labor analgesia will be maintained by programmed intermittent bolus with 6 ml of the same solution every 45 minutes starting 30 minutes after the initial dose. Patients will have patient-controlled epidural analgesia (PCEA) available with an 8 ml dose per demand, every 10 minutes, for a maximum dose of 45 ml for every hour.

Assignment of Study Cohorts:

Study participants will be randomized by computer-generated sequence to EPL or DPE arms, stratified by class of obesity (BMI $\geq 35 < 40$ kg/m^2 , $\geq 40 < 50$ kg/m^2 and ≥ 50 kg/m^2) and by parity (nulliparous versus multiparous). Patients will be assigned to one of the four study arms by computer-generated, randomized sequence in order to balance baseline characteristics across the arms. This will be a double-blinded study. After the consented and enrolled participant

requests labor epidural, a study member will give the anesthesia provider a sealed envelope with study assignment for either standard EPL or DPE technique.

Protocol for Breakthrough Pain

- If the patient has uneven or unilateral level, the provider will withdrawal catheter 1cm from skin and bolus 5ml of epidural mix. As fetal heart rate allows for maternal repositioning, the patient will lay lateral position with unblocked side in the dependent position. (up to 3 catheter adjustments)
- If the patient has bilateral levels at that below T10 to ice, the patient will be administered 5 ml off epidural pump, up to 3 times in 15 minutes.
- If the patient has pain despite T10 levels, the provider will administer Fentanyl 100 mcg via epidural.
- If analgesia continues despite these interventions up to 3 times within 60 minutes, the attending anesthesiologist will determine if epidural catheter needs replacement.

Data analysis and monitoring:

The primary outcome of this study is block quality which will be defined by a composite of five components (1) asymmetric block after 30 minutes of initiation, (2) top-up interventions, (3) catheter adjustments (4) failed catheter requiring replacement, and (5) failed epidural requiring general anesthesia or replacement neuraxial anesthesia for emergency cesarean section. The composite outcome is a practical endpoint for our study because while necessary to determine block quality, incidence of failed epidural or one-sided epidurals are rare. All five components are of similar importance when assessing the quality of epidural analgesia. Therefore, this outcome definition will increase the power of the study, without sacrificing clinical relevance or feasibility.

Block level will be measured by temperature discrimination with ice, and levels that are greater than two dermatomal levels would be considered asymmetric. Lower extremity dermatomal levels will be assessed by stimulating the inguinal crease (L1), anterior thigh (L2), medial knee (L3), medial malleolus (L4), between the great and second toe (L5), the lateral heel (S1), and the medial popliteal fossa (S2). On the thoracic levels, the torso will be assessed bilaterally at the mid-clavicular line.

Secondary outcomes include time to numeric pain rating scale ≤1, maternal adverse events (hypotension, fetal bradycardia, PDPH), motor block, duration of second stage of labor, total labor epidural time, total anesthetic dose required, PCEA use, and mode of delivery.

Statistical Methods:

The primary assessment of difference in the composite outcome between the two epidural techniques will be conducted via chi-square test. Using data from a recent retrospective study on labor maintenance regimens published by our group, we expect the composite event rate to be 35% in the group receiving EPL.[17] Based on the findings by Hess *et al.* of a 62% relative reduction in breakthrough pain with a CSE technique compared to an EPL, we will define a clinically meaningful effect in our study as a similar reduction in the composite outcome to be 14% in the DPE group, which corresponds to an odds ratio of 0.30.[18] A two-sided χ^2 test for the difference in composite outcome rates between epidural techniques at alpha level 0.05 will reach 80% power to detect an odds ratio of 0.30 comparing DPE to EPL in a study of 130 patients (65 DPE and 65 EPL).

Further analysis of the difference in the composite outcome between the two epidural techniques will be conducted via multivariate logistic regression to account for potential confounders. Comparison of additional secondary outcomes between the epidural techniques of

maternal adverse events, total labor epidural time, total anesthetic dose required, mode of delivery, and degree of motor block will be compared with χ^2 tests and logistic regression. The time to numeric pain rating scale ≤1 will be compared between the two epidural techniques via Kaplan-Meier estimates and log-rank tests.

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.

Data storage and 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. Ashraf Habib's office.

Risk/benefit 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

DPE offers benefits over standard EPL for initiation and maintenance of labor analgesia in our practice. Risks of epidural analgesia are the same irrespective of participation in the study. These are 1.5% rate of unintentional dural puncture with epidural needle, <1% risk of post-dural pucture headache, inadequate analgesia, and unintentional intravascular or subarachnoid injection.[19,20]

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