ED90 for Hyperbaric Bupivacaine in Spinal Anesthesia for Cesarean Delivery in Super Obese Parturients

NCT03781388

Study Protocol

Inclusion criteria:

American Society of Anesthesiology (ASA) class 2 and 3

English speaking

Gestational age > 36 weeks

Non-emergent cesarean delivery under combined spinal epidural anesthesia

18 years or older

BMI =/> 50 kg/m^2

Exclusion Criteria:

History of past or current intravenous drug or chronic opioid abuse

Allergy or contraindication to any study medications

Intrapartum cesarean delivery under epidural anesthesia

Cesarean delivery under general anesthesia

Interventions:

After obtaining Duke University Institutional Review Board approval and informed consent, women scheduled to undergo a cesarean delivery under combined spinal epidural anesthesia will be approached to participate in the study. A peripheral IV will be placed and baseline maternal vitals will be collected (BP, HR, SPO_2) and fetal heart tones will be assessed as per standard practice.

A combined spinal epidural (CSE) anesthetic technique will be performed by a member of the anesthesia team using a 17-g Tuohy needle and 27g pencil-tip spinal needle in a needle through needle technique into the L2-3 or L3-4 interspace in the sitting position. The spinal anesthesia administered to the patients will be a standardized dose of intrathecal fentanyl (15 mcg), preservative-free morphine (150 mcg) and a pre-determined dose of hyperbaric bupivacaine. Our standard intrathecal dose of hyperbaric bupivacaine in non-super morbidly obese parturients is 12mg, and we assume an ED90 of 10.5mg in the super obese parturient, which is usually effective in those patients in our practice. We will therefore consider a range of 7.5mg-12mg in this study. The starting dose of hyperbaric bupivacaine for the first patient in this study will be 9.75mg; the dose for the subsequent subject will be based on the response of the preceding subject as per the Narayana Rule, a modification of the biased-coin design (BCD) up-down sequential method (UDM).

If the patient did not respond adequately to the current dose ($failure_{operation}$ or $failure_{induction}$), the dose will be considered to have failed. If the current patient responds successfully to the current dose ($success_{induction}$ and $success_{operation}$), this will be considered a success. Determination of the dose will rely on the outcomes of the preceding 7 patients receiving the same dose, as the number of previous patients to consider is a function of the target dose. Among all patients who received a certain dose, a proportion of successful outcomes will be determined (P(d)); if P(d) <0.90, and at least one of the previous 7 patients who received the same dose had an unsatisfactory outcome, the next patient will receive a pre-determined increment of 0.75 mg of bupivacaine. Alternatively, if P(d) 0.90 and the previous 7 patients who received the same dose had successful outcomes, the next patient will receive a pre-determined decrement of 0.75mg of bupivacaine. Otherwise, the dose will remain the same. In this study, dose of hyperbaric bupivacaine is adjusted in 0.75mg increments, with a presumed ED90 of 10.5mg and ED50 of 7.5mg, and a ceiling of 12 mg. Blinded study drugs will be prepared by an anesthesia provider not involved in the study.

The anesthesia provider providing care to the patient will be blinded to the dosage of the hyperbaric bupivacaine. In order to preserve the blinding of the provider, the total volume of study drug will be maintained at a constant of 2mL. The difference in total volume based on the variation of hyperbaric bupivacaine dosing will be replaced with preservative free normal saline.

The data collection will be performed by the anesthesia provider or research assistant, who will also be blinded to the dosage of the study drug. Block assessment will be determined by sensory dermatome evaluation with pinprick at 2, 4, 6, 8, and 10 minutes after drug administration. Successful blocks for induction ($success_{induction}$) will be defined as bilateral T6 sensory level to pinprick by 10 minutes after intrathecal drug administration. A failed block for induction ($failure_{induction}$) will be defined as a T6 sensory level not obtained within 10 minutes of study drug administration. If a failure of induction is recorded, an epidural supplementation of 2% lidocaine in epinephrine 1:200.000 and sodium bicarbonate will be administered until the appropriate level is reached. A successful block for operation ($success_{operation}$) will be defined as a successful initial sensory level without requiring additional epidural anesthetic during surgery up to 90 minutes after intrathecal injection.

Intervention for inadequate block/intraoperative pain will include dosing via the epidural catheter as described above. A failure of the block in operation ($failure_{operation}$) will be defined as an initial T6 sensory level that required supplemental epidural analgesia (earlier than 90 minutes after intrathecal injection) to complete the operation, based on patient need for additional analgesia. Intraoperative and postoperative management of blood pressure, nausea, vomiting and pruritus will be according to our standard practice.

Statistical Analysis:

Power analysis was conducted by simulation, assuming an ED90 for hyperbaric bupivacaine of 10.5mg and an ED50 of 7.5mg. The simulation assumed assignment of patients to doses according to the Narayana Rule for up-down sequential allocation. A sample size of 40 patients showed good precision, with 80% of simulated samples finding a calculated ED90 within approximately 1mg of the true value and 90% having a calculated ED90 within approximately 1.5mg of the true value.

Baseline characteristics of study patients will be examined and reported as mean and standard deviation or median and interquartile range, as appropriate. ED90 will be estimated through logistic regression by using the maximum likelihood estimates (MLE) of intercept and slope from the logistic model. The logistic regression model is given by: $\log(p/1-p) = a + B * dose$, where p is the probability of successful block. The estimated ED90 is given by: $ED90 = (\log 9-á/b)$ where á and b are the MLEs of a and B , respectively.

All statistical analysis will be carried out using R (version 3.5.0; http://www.R-project.org/) or SAS (version 9.4; SAS Institute, Cary, NC).