THE EFFECT OF HIGH-DOSE VS. LOW-DOSE EPIDURAL FENTANYL ON GASTRIC EMPTYING IN NON-FASTED PARTURIENTS

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A Prospective Double-Blinded Randomized Controlled Trial

STUDY PROTOCOL

This single-center, prospective blinded randomized-controlled trial will be conducted over a twelve-month period after receiving IRB approval (*IRB request number 0040-19-TLV*), at the Tel Aviv Sourasky Medical Center ("Lis Maternity Hospital"). Written consent will be obtained upon arrival to the delivery room and prior to the request for epidural analgesia.

Inclusion criteria: Laboring women ≥18 years of age, ≥37 weeks gestation with a singleton pregnancy, cephalad fetus, with cervical dilatation ≤5cm and who request epidural analgesia for labor.

Exclusion criteria: Contraindications to neuraxial analgesia, chronic opioid consumption, and factors increasing risk of cesarean delivery and/or risk of aspiration. These include disorders of the upper gastrointestinal tract (severe gastro-esophageal reflux, history of bariatric surgery), neurological and endocrine disorders associated with gastroparesis (such as multiple sclerosis, diabetes with autonomic neuropathy), trial of labor after cesarean delivery (TOLAC), non-reassuring fetal heart rate (NRFHR), dysfunctional labor, estimated fetal weight >4000g, body mass index (BMI)≥40kg/m^2.

Women who received ineffective epidural analgesia, defined as verbal numerical rating scale (VNRS) >3, thirty minutes after placement will be withdrawn from the study and will not be followed up further. Their subsequent management will be according to department protocol.

1. **Epidural Analgesia Protocol**

Laboring women will be approached and requested to enroll upon arrival to the delivery room and prior to their request for epidural analgesia. Women who consent to participate will be randomized into one of two groups according to high versus low dose fentanyl administered in the labor epidural solution.

Upon request for labor epidural analgesia, the epidural will be performed by one of the anesthesiologists working in the delivery room. The epidural will be performed in the sitting or lateral decubitus position with a 18G Touhy needle (Portex Epidural Minipack), and upon identification of the epidural space using the loss of resistance technique, the epidural catheter will be inserted.

The epidural drugs will be administered according to randomization group by the anesthesiologist performing the epidural:

- **Group LF** - "Low dose fentanyl" - 10ml bolus: bupivacaine 0.1% + 25mcg fentanyl, followed by a solution of bupivacaine 0.083% + fentanyl 1mcg/ml
- **Group HF** - "High dose fentanyl" - 10ml bolus: bupivacaine 0.1% + 100mcg fentanyl, followed by a solution of bupivacaine 0.083% + fentanyl 2mcg/ml

Both groups will receive an identical patient controlled epidural analgesia (PCEA) protocol comprising a 6 ml/hour background infusion with 5ml bolus, 10min lockout time.

Breakthrough pain will be treated with physician administered "top-ups" of 10 ml bupivacaine 0.1-0.25% or 8ml lidocaine 1% to the physician's discretion. Women will be blinded to group allocation.

2. **Gastric Ultrasonography (US)**

The Gastric US will be performed using a portable device (Sonosite Edge II) with an abdominal probe by the same operator (EF) for all women. The operator will be blinded to the woman's oral intake and to her randomization group.

The Cross Sectional Area (CSA) of the antrum will be measured as described by Arzola et al[23] in the supine position with the head elevated 45 degrees. The antrum of the stomach will be identified in the sagittal plane using the left lobe of the liver, aorta and inferior vena cava as anatomical landmarks. CSA will be calculated using the formula (AP x CC x pi)/4, where AC is the anterio-posterior diameter and CC the cranio-caudal diameter. Three consecutive measurements will be performed and the average of the three will be used as the final data. The cutoff used to define a "full stomach" will be a CSA≥381 mm^2, which has been validated in previous studies on laboring women [22, 24].

Gastric US will be performed immediately after verification of effective epidural analgesia (T_0) and intrapartum, two hours after the baseline measurement (T_{2h}), corresponding to a cumulative dose of 37-97mcg fentanyl in Group LF and 124-240mcg fentanyl in Group HF.

3. **Oral Intake Protocol**

At the time of consent women will be told they may eat, in line with departmental policy, and encouraged to note oral intake (drink volume, food amount and type).

4. **Data Measurements**

Ultrasound measures: Baseline CSA at epidural placement (T_0) will be measured. The primary data measurements corresponding to the study aim will be CSA measured by US two hours (T_{2h}) after baseline measurement.

Patient characteristics: Age, parity, gestational age, BMI and smoking.

Oral intake: At the time of epidural placement (T_0) oral intake within the previous 8 hours will be recorded. At the time of the intrapartum ultrasound (T_{2h}), women will be asked about oral intake during the previous two hours.

Epidural management: Number of PCEA boluses (attempts and given) and physician administered "top-ups" between T_0 and T_{2h}, and pain scores at T_0 and T_{2h} (VNRS scale) will be recorded.

Obstetric characteristics: Cervical dilation at T_0 and T_{2h}, use of labor induction and augmentation agents.

Other measures: Occurrence of vomiting and use of anti-emetics.

STATISTICAL ANALYSIS

The primary study endpoint is the CSA at T_{2h} according to HF versus LF. Our sample size was calculated on the assumption that women who receive HF will have a significantly slower gastric emptying (and thus higher mean CSA) than women who receive LF[14,15,16]. Based on Porter et al.[14], each group requires at least 14 subjects in order to detect a significant difference with a power 80% and 0.05 two-tailed significance level. However, as opposed to Porter et al. who examined only fasted women, our subjects will have unknown fasting status. Thus the change in CSA from T_0 to T_{2h} among women randomized to HF versus LF is a relevant variable. In order to take this into consideration, we require enough women with both an empty and a full stomach at T_0 to calculate the change at T_{2h}. Previous studies on gastric US in laboring women have demonstrated that approximately 60% of laboring women have a full stomach and 40% have an empty stomach regardless of prior fasting state[22,24]. Therefore we calculated that in order to account for the expected differences in CSA at T_0, 80 women are required for the study; 48 would be expected to have a full stomach (CSA>381mm^2) and 24 would be expected to have an empty stomach (CSA<381mm^2) at T_0 (epidural insertion), as presented in Figure 1. Data will be assessed for normal distribution using the Kolmogorov-Smirnov test and Q-Q plots. Continuous data will be summarized as mean (standard deviation), and median (interquartile range) as appropriate for normal or non-normal data. Categorical variables will be tested using Chi-square and presented as counts (percentages). Data will be analyzed using Microsoft Excel Office 2013 and SPSS (IBM) 25.0 (SPSS Inc. Chicago, IL). P-value <0.05 will be considered significant for the primary outcome.

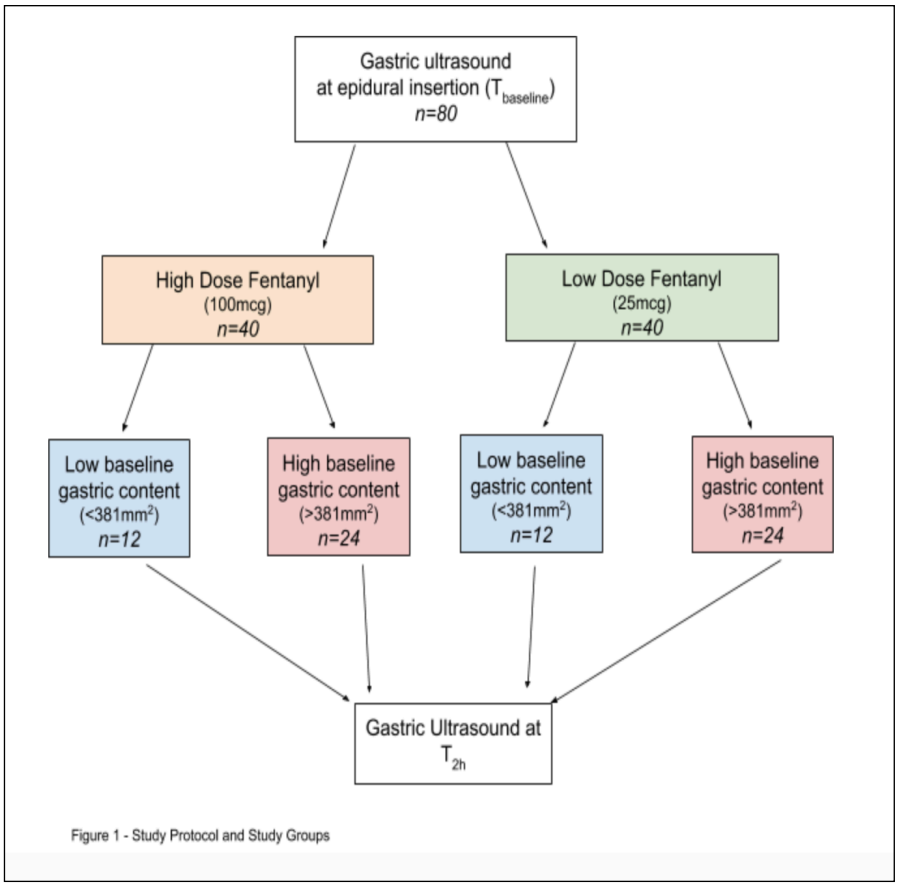

Figure 1 - Study Protocol and Study Groups