Title: **The PAIN (Pelvic Area Injection for Numbness) Study**

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PAIN Research Protocol

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Project Title:
A randomized controlled trial of bupivacaine with epinephrine for local pain control following perineal laceration repair in patients with pre-existing epidural analgesia: The PAIN (Pelvic Area Injection for Numbness) Trial.

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Background:
Perineal lacerations, the disruption of the skin, mucosa and sometimes muscles that happen commonly during vaginal birth secondary to stretching of the introitus; are present in more than 75% of all vaginal deliveries. These lacerations can be classified based on the location and depth (layers injured). However, the classification of these lacerations does not correlate necessarily with postpartum pain. Severe lacerations, as those compromising the external or internal anal sphincter are less common and associated with more postpartum pain.[1]

It is common practice that only those lacerations causing bleeding, or distortion of normal pelvic anatomy are repaired. The repair of such lacerations in our institution is usually done using lidocaine for non-epiduralized patients; however, for patients with a functional epidural, no anesthetic agents are given locally to aid on long term pain control.

The prevalence of epidural analgesia use among women who underwent vaginal delivery in a cross-sectional study of over 2 million deliveries in the United States was 71.1%.[2] Once the analgesic effect of the epidural analgesia fades, the laceration may cause uncontrolled postpartum pain which can affect both the physical and mental recovery period, extend hospital stays, and increase the potential for serious adverse reactions with pain medications.[3]

Our institution, a large academic center in New York, delivered a total of 4,469 deliveries in the year of 2022. Of those deliveries, 2,832 (63.4%) were vaginal deliveries, of which 2,170 (76.6%) were epiduralized and of those epiduralized, 1,070 (49.3%) had a perineal laceration requiring repair. Most of our patients are placed on NSAIDs for postpartum pain, but some, specifically those with more severe lacerations can require opioid for pain control. Postpartum pain can interfere with patient's ability to care for themselves, and their newborn, and untreated pain is associated with risk of greater opioid use, postpartum depression, and development of persistent pain.[4]

Our research hypothesis is that adding a long acting locally injected anesthetic, which will take effect once the epidural analgesia fades away, will alleviate perineal pain and improve women's overall well-being, pain score level and satisfaction.

There have been two different studies analyzing the difference between different locally injected analgesic medication for perineal laceration/episiotomy repair. The first looked at perineal infiltration with lidocaine 1%, ropivacaine 0.75%, or placebo for episiotomy repair in parturient who received epidural labor analgesia.[5] They found that time to first oral analgesic request was shorter for ropivacaine compared to both lidocaine and saline. Visual analog pain scores were low and not different between the three groups (ropivacaine 16.8 ± 11.6, lidocaine 12.4 ± 9.7; and saline 16.2 ± 11.5, P = 0.08). The second study compared Lidocaine Versus Ropivacaine Infiltration for Postpartum Perineal Pain, and they concluded that those patients on Ropivacaine had a longer time of pain control before the need to request first analgesic (2.20 ± 0.44 h vs. 10.2 ± 1.54 P < 0.0001) and higher percentage of maternal satisfaction (44% vs. 86%).[6]

To support our hypothesis, we propose a randomized, placebo-controlled, double blinded prospective trial in which patient with a working epidural and status post a

vaginal delivery involving a second- degree or higher-level perineal laceration will be invited to participate and will be randomized into one of two medications including: bupivacaine with epinephrine or normal saline.

Women in the bupivacaine with epinephrine arm will get 10 milliliter (ml) of bupivacaine 0.50% with epinephrine 1:200,000 injected to the laceration and women in the sham arm will get an injection with 10ml of normal saline to the laceration site. The differences in perineal pain between the groups will be evaluated at time of the first analgesic (TFA) demand, maternal satisfaction at 24hours/48hours/7days, and visual analog scale (VAS) pain score. Our study will enroll 30 patients per group (total to 60 patients) to obtain at >80% power with alpha=0.05, to detect a reduction in incidence of perineal pain at day one when using Bupivacaine, compared to placebo, assuming incidence of perineal pain among patients receiving placebo is 70%, incidence of perineal pain among patients receiving Bupivacaine is 30% and using Fisher's exact test for comparing the proportions.

Study Design

This is a superiority double blinded randomized controlled trial with the objective to determine if prolonged analgesia and higher rate of maternal satisfaction are found when bupivacaine with epinephrine infiltration is used for perineal repair as compared to sham injection in patients with pre-existing effective epidural analgesia at time of perineal laceration repair.

This will be a parallel study with one treatment group (bupivacaine with epinephrine) and one placebo group (normal saline).

Sealed opaque randomization envelopes with a study-specific patient number will be supplied by a Montefiore statistician separate from research team statistician. The randomization sequence is computer-generated with randomization blocks of a variable size which is unknown to any of the research team. After the provider determines that the patient has a second-degree perineal laceration, the patient's nurse will present to the obstetrics anesthesiologist in the Weiler Labor and Delivery floor who is not otherwise involved in the research study. The anesthesiologist will take the sealed opaque numbered envelopes in order, by number, and open it. The envelope contains a piece of paper which is labeled with the same study participant specific number, plus the group assignment (placebo versus bupivacaine with epinephrine). The anesthesiologist will then prepare the 10mL of normal saline or the 10 milliliter (ml) of bupivacaine 0.50% with epinephrine 1:200,000. The anesthesiologist will then give the syringe to the patient's nurse unlabeled. The nurse will return to the patient's provider with the syringe so the provide will administer it before the perineal laceration repair. The assignments will be communicated for the purpose of data analysis in coded form. The code will only be revealed when the data analysis is complete.

Randomization will be blinded to the patient, the nurse carrying for the patient and providing the randomized, unlabeled syringe, the provider performing the perineal repair, the research team asking the maternal satisfaction questions, and researcher analyzing the data. To assure blinding, the selection of the medication given, and the preparation of such medication will be performed by the labor and delivery anesthesia team, and no one involved directly in the perineal laceration repair, or obtaining research information, nor the patient will know what was injected.

Monitored Safety outcomes:

The healthcare provider who will be injecting the study participants with either the bupivacaine with epinephrine or the placebo group, unknown to the healthcare provider which one, will monitor for local anesthetic toxicity (LAST). The most important way to prevent LAST is draw back Specifically, they will look for hypotension, arrhythmias, seizures, and cardiac arrest. There are overall extremely rare with studies reporting 0 events after over 12,000 nerve blocks to an incidence of up to 25 per 10,000 nerve blockades.[7]

Outcome measure:

Time to First analgesic (TFA), maternal satisfaction at 24h, 48h, and at 7 days (measured by participants' rating their ability to carry out their activities of daily living as poor, very poor, good, and very good), and visual analog scale (VAS) pain score.

Inclusion Criteria

18 years old or older, with a singleton pregnancy, English or Spanish speaking, with an ongoing functioning epidural throughout the laceration repair, multiparous woman, nulliparous woman, and can consent for themselves to be part of the study.

Exclusion Criteria

Women who underwent an operative vaginal delivery, who's vaginal delivery was complicated by a postpartum hemorrhage, who have multiple gestation, who are complaining of non-functioning epidural, who are allergic to bupivacaine and/or epinephrine, who has received an epidural top-off (bolus of local anesthetic injected into the epidural catheter) less than three hours from the perineal repair, and participants experiencing extreme pain at time of study consent will be excluded. Extreme pain will be determined by asking all study participants before the start of the study consent process to rate their pain scale from 0 to 10. The participant must have a pain scale less than or equal to 3 out of 10 to participate in the study.

Participant Recruitment

All pregnant patients, meeting the inclusion criteria and not meeting the exclusion criteria, with a functioning epidural in place at our Labor and Delivery unit will be invited to participate in the study by receiving a study pamphlet with 4th grade level educational information explaining the PAIN trial.

Informed Consent Process

Study staff will obtain informed consent by discussing the risks and potential benefit of medication changes and make medication decisions with patients. Patients will be consented in their delivery room in Weiler Labor and Delivery floor at any point in their labor course as long as their pain scale is less than or equal to 3 out of 10 and before giving birth.

Risk/Benefit

The risk of participating in the study include risks include allergic reaction to the medication, hematoma formation, infection at the site of injection, loss of time spent during their participation, and loss of confidentiality. The benefit to study participants are none as subjects will have no guarantee of receiving study drug.

Blinded Study

Subject treatment assignments will remain blinded until the final subject has completed follow up and all data has been recorded and validated. Urgent, immediate unblinding due to medical emergency may be authorized by the Investigator. When possible, the treatment assignment will be provided to the treating physician to maintain the blind for the Investigator and study staff.

All instances of subject unblinding will be documented in the study record.

Data Analysis

Outcome measures and statistical analysis will be conducted via SAS. Background characteristics (age, parity, race, ethnicity, income) will be summarized by treatment group. The comparison of the proportion of patients reporting perineal pain between the placebo group and the treatment group will be done using Fisher's exact test.

Data Quality Control, Database Management, and Data Safety

Protected health information used in this project will be stored in MonteBox or Montefiore Outlook application, both of which are routinely used in our institution for protected health information. Study analysis will be conducted via Montebox, Montefiore Outlook, or on computers on the Montefiore campus.

Reference

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