The Effect of Pudendal Nerve Block Analgesia on Postoperative Pain Control in Patients Undergoing Vaginal Surgery: A Randomized Double-blind Placebo-controlled Trial

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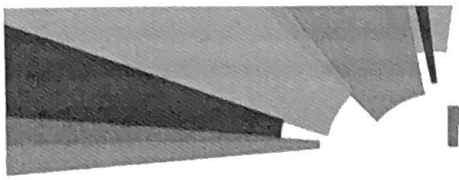



1. **Protocol Title: Pudendal nerve block analgesia at the time of vaginal surgery: a randomized, double-blinded, placebo controlled trial**

   **Short Title: PACE-72**

2. **Principal Investigator**: Jeffrey Mangel, MD
   **Research Team**:
   Sarah Sears, MD – Co-investigator and Study Coordinator
   Kasey Roberts, MD – Co-investigator
   Robert Pollard, MD – Co-investigator
   Megan Abrams, MD – Co-investigator
   Rozina Aamir – Co-investigator

3. **Hypothesis/Specific Aims**: The objective of this this randomized controlled study is to determine whether a pudendal nerve block at the time of vaginal surgery is associated with improved postoperative pain control and decrease opioid consumption compared to a sham pudendal nerve block in patients undergoing vaginal surgery.

4. **Primary, Secondary and Exploratory Endpoints**:
   **Primary Endpoints:**
   1. Compare visual analog pain scores (VAS) the morning after vaginal surgery in women who received a pudendal nerve block or placebo / sham block.
   2. Evaluate opioid analgesia given in the Post Anesthesia Care Unit (PACU) after vaginal surgery after receiving a pudendal nerve block intraoperatively.
   3. Evaluate total opioid analgesia use in the first 24 hours after vaginal surgery after receiving a pudendal nerve block intraoperatively.

   **Secondary Endpoints**:
   1. Compare patient satisfaction scores with postoperative pain control between women who received a pudendal nerve block or placebo / sham block during vaginal surgery
   2. Compare rates of postoperative urinary retention and other adverse events between women who received a pudendal nerve block or placebo / sham block during vaginal surgery.

5. **Background/Significance:**
   Female pelvic floor disorders encompass multiple disorders of the genital and lower urinary tract and pelvic floor musculature, including pelvic organ prolapse, urinary and fecal incontinence, and pelvic pain syndromes. This family of disorders is estimated to affect up to 25% of all adult women in the United States with increasing prevalence with age.[1,2] Surgical

treatment is often elected, with 1 in 5 women undergoing surgery for pelvic organ prolapse and/or incontinence by 80 years of age.[3] Furthermore, the demand for such surgical interventions is estimated to increase up to 40% in the next 30 years, as the population ages in the United States.[4,5]

6. **Premise**: Given the high prevalence of surgical management for pelvic floor disorders and the now recognized opioid crisis, it is imperative to optimize postoperative pain control in these patients. Historically, postoperative pain control has been largely focused on opioid medications, and very few studies have targeted vaginal surgery, which is central to surgical management of most pelvic floor disorders. A recent review identified only one study that evaluated postoperative pain control after vaginal reconstructive surgery, and the mainstay of therapy was opioid driven.[6,7] The problematic use of opioid analgesia is now well documented, including side effects of nausea, vomiting, constipation, urinary retention, and central nervous system alterations, as well as the widely publicized addictive nature of the medications.[6,8,9]

   In order to minimize opioid use postoperatively, it is prudent to optimize multimodal therapy with non-narcotic analgesia. Use of treatments such as ice packs, NSAIDs and acetaminophen are effective, but we may also maximize analgesia with regional nerve blocks.[10] This may be particularly helpful for patients with contraindications to non-narcotic medications.

   The objective of this this randomized controlled study is to determine whether a pudendal nerve block at the time of vaginal surgery is associated with improved postoperative pain control and decrease opioid consumption compared to a sham pudendal nerve block in patients undergoing vaginal surgery.

7. **Preliminary data**: In abdominal surgery, a transversus abdominis plane (TAP) block has been shown to improve postoperative pain control and reduce opioid consumption.[11,12] During vaginal surgery, then, regional analgesia with a pudendal nerve block would be appropriate.

   The pudendal nerve innervates much of the lower pelvis, including the pelvic floor musculature, the perineum and the urethral and anal sphincters.[13,14] Pudendal nerve blocks provide effective pain relief for patients with chronic pelvic pain and during childbirth.[15,16,17] In the acute perioperative setting, anesthesiologists have utilized preoperative pudendal blocks as an alternative to general anesthesia with improved subjective pain scores and decreased use of all postoperative pain medications.[18,19] Female pelvic surgeons demonstrated a reduction in NSAID use after sacrospinous ligament colpopexy with an intraoperative pudendal block.[20]

8. **Feasibility** (subject recruitment/anticipated problems/alternatives): We performed a power calculation and determined that we will need 30 patients in each arm in order to achieve a

90% power to detect a mean difference of ~20 mm on a 100mm VAS scale for a significance level of 0.05. We added 20% to this number to account for loss of follow up. In total, then, we will need **72 patients, 36 in each arm.**

9. **Approach / Specific Methodologies:**

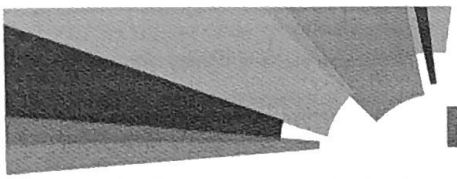
IRB approval will be obtained at MetroHealth Medical Center. This will be a randomized controlled trial that will be conducted at MetroHealth Medical Center. Preoperative written informed consents explicitly explaining the risks and benefits of the study will be obtained from the patients.

The **inclusion** criteria are the following:

1. Subject is willing to provide written informed consent
2. English speaking female ≥18 and ≤80 years of age
3. Subject is willing and able to comply with follow-up regimen
4. Subject is able to read a visual analog scale
5. Specific vaginal procedures include, but are not limited to:
   - Perineoplasty
   - Complete vaginectomy
   - Le Forte colpocleisis
   - Anterior repair, posterior repair, and/or enterocele repair
   - Transvaginal mesh use
   - Transvaginal mesh excision
   - Sacrospinous ligament fixation
   - Uterosacral ligament suspension
   - Vaginal paravaginal defect repair
   - Midurethral sling placement
   - Pelvic floor injections
   - Sphincteroplasty
   - Vaginal hysterectomy, with or without removal of tube(s) and/or ovary(s), with or without repair of enterocele

The **exclusion** criteria are the following:

1. History of chronic pelvic pain
2. Currently taking sedatives
3. Liver disease
4. Renal disease
5. Intraoperative concern for increased blood loss
6. Unable to understand visual analog scales
7. Undergoing concomitant abdominal or laparoscopic procedures
8. Allergy to bupivacaine or triamcinolone
9. Patients who are ineligible for non-narcotic pain medications, such as acetaminophen and NSAIDs
10. Women who did not consent for the study
11. Unable to speak English
12. Unable to understand visual analog scales




Demographic factors are recorded including, age, BMI, ethnicity, preoperative diagnosis, comorbid conditions, and surgery performed. Intraoperatively, duration of anesthesia, duration of surgery, estimated blood loss and intraoperative medications are recorded for each type of surgery.

Once patients are selected and informed consents are obtained, they are randomized into the active and control groups using computer generated randomization with sequentially numbered opaque sealed envelopes.

The operating room nurse will randomly pick an envelope; half of them will indicate placebo and half will indicate medication. The nurse will then obtain the medication or saline as indicated. The attending physician will create the block. The fellow will then give the block or sham block. Only the attending physician (Dr. Jeffrey Mangel or Dr. Robert Pollard) will be unblinded, and they will not do any block administration, data collection or analysis. Double blinding will be achieved by blinding of the patient and the practitioners that will administer the block, collect data, and perform data analysis. The surgical fellows, who will administer the block and perform the analysis, will be blinded to the medication. Only the attending surgeon (Dr. Mangel or Dr. Pollard) will be unblinded, and they will not do any block administration, data collection or analysis.

Depending on randomization, the patient will be given either an active or sham pudendal nerve block at the conclusion of surgery but while still under anesthesia. The ischial spine is palpated transvaginally. The medication is then injected through the vaginal tissues in the area of the ischial spine, which is where the pudendal nerve runs. Light pressure is then applied for a short period of time. This procedure is repeated on the contralateral side.

**Pudendal Nerve Block:**

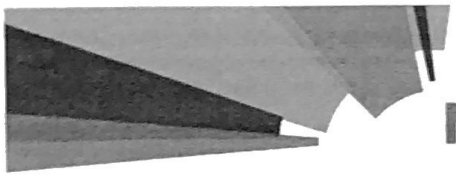
9cc of 0.25% Marcaine + 1cc of 40mg/mL triamcinolone
5cc will be injected in the area of the pudendal nerve on each side.

**Sham Block:**

10cc normal saline
5cc will be injected in the area of the pudendal nerve on each side.

Once out of PACU, all patients will be ordered the same post-operative pain regimen, unless the patient has specific contraindications. These medications will be ordered through our standard postoperative order set. The medicine will be provided by the nursing staff as per pharmacy orders:

1. Acetaminophen PO 975mg q8h
2. Ketorolac 15mg IV Q6H x24 hours
3. Ibuprofen 600mg PO Q4H PRN for mild (1-3) pain after 24 hours
4. Oxycodone 5mg PO Q4H PRN for moderate (4-6) pain
5. Oxycodone 10mg PO Q4H PRN for severe (7-10) pain
6. Hydromorphone 0.2mg IV Q3H PRN for breakthrough pain
7. Patients will be discharged home with an appropriate pain regimen for the nature of their surgery – acetaminophen and ibuprofen, with or without tramadol or oxycodone




10. **Safety Plan:** To ensure subject safety, Dr. Kavita Arora, not otherwise engaged in the study, has agreed to monitor the study from the standpoint of subject safety. Dr. Arora will review the aggregate safety data and evaluate any safety issues that may arise during the conduct of study. The DSMB will review any individual adverse events. All adverse events will be documented. All reported adverse events will be graded using the Common Grading Scale:

    *0 - No adverse event or within normal limits or not clinical significant*

    *1 - Mild AE, did not require treatment*

    *2 - Moderate AE, resolved with treatment*

    *3 - Severe AE, resulted in inability to carry on normal activities and required professional medical attention*

    *4 - Life threatening or disabling AE*

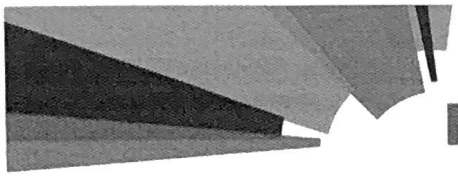
    *5 - Fatal AE*

If Dr. Arora determines there is sufficient concern for subject safety, the IRB will be notified, and appropriate actions will be taken. Adverse events will be followed until closure or documented as chronic. Safety Monitoring will also be established in the statistical analysis.

Data and safety monitoring will be performed by the study team and Dr. Arora throughout the study to ensure all policies are being followed. Study investigators will actively monitor for unanticipated problems, adverse events, or protocol deviations, with specific emphasis on any events involving risk to subject or others. The patients will be monitored closely in the hospital for any abnormalities which is standard for perioperative care. Investigators will again address any questions or concerns during the scheduled postoperative telephone follow up to discuss the questionnaire. Any unexpected or significant adverse event may prompt a preliminary statistical analysis and/or immediate halt in enrollment or cancellation of the study.

Record of any adverse events will be kept in a Safety Monitoring Log. Monitoring will take place during preoperative communication with patient, during hospital stay, at the follow-up phone call, and in the postoperative period. In addition to monitoring and record keeping, events will be reported as appropriate. Unanticipated problems and any adverse events that may change the risk/benefit ratio will be reported to the IRB within 3 days of discovery per institutional guidelines. Serious adverse events will be immediately reported to the IRB and the patient's primary provider as soon as the investigator is aware of the incident. Any adverse events that are felt to alter the risk/benefit ratio of the study may prompt a review and revision of study protocol and/or consent form.

Any internal Serious Adverse Events related to the study will be reported to the IRB within 24 hours of site awareness per IRB Reporting Guidelines.




11. **Statistical Analysis:** Data will be kept in RedCap. Statistical analysis will be performed using statistical software, GraphPad or STATA. Continuous variables will be analyzed using the t-test/Mann-Whitney test, and categorical variables will be analyzed using Chi-Square methods.

12. **Budget**: The patient's insurance will be charged for the block. We use local anesthetic routinely in pelvic surgery, with virtually every case, so these medications will be provided as part of standard perioperative care. We are not aware of cases of insurance not covering these medications or standard local anesthesia.

    Any additional necessary budget will be internal from residual funds.

13. **Study Time Lines**: We expect recruitment to take approximately one year.

14. **Appendix** (study visit grid): N/A

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***Investigator Signature*** ***Date***

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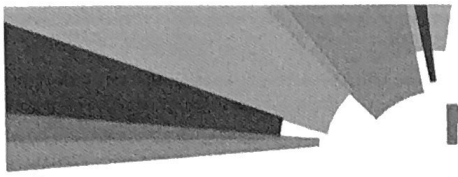
***Investigator, Print Name and Title***

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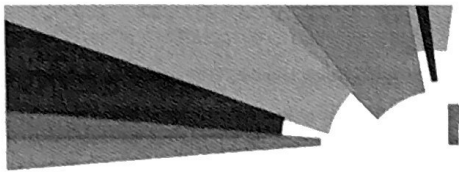

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