Study Protocol

Official Title: Preoperative Levator Ani Muscle Injection and Pudendal Nerve Block With Bupivacaine and Dexamethasone for Improved Pain Control After Vaginal Reconstructive Surgery: A Three-Arm Randomized Controlled Trial

ClinicalTrials.gov ID (NCT number): NCT03040011

Protocol Date: 10/24/2019

Scientific Background

Many major gynecologic surgeries are increasingly becoming outpatient procedures (1-3). One criterion for same-day discharge is adequate pain control. Despite this, many women report suboptimal pain control after discharge following vaginal surgery (4). Furthermore, at 6 weeks postoperatively, only 50% of patients felt that they had fully recovered from surgery (4). Thus, even though a minimally invasive approach, there are areas for improvement in postoperative recovery after vaginal surgery.

Various local anesthetic techniques, including pudendal nerve blocks, have been studied as forms of preemptive analgesia to improve pain associated with vaginal surgery. While the methodologies vary making direct comparison difficult, the studies assessing preemptive analgesia at the time of vaginal surgery have yielded mixed results, particularly for apical support procedures (5-9) and an effective and generalizable way to reduce postoperative pain in a population of Female Pelvic Medicine and Reconstructive Surgery patients undergoing vaginal reconstructive surgery with apical suspension procedures has not been defined.

We utilize a novel injection technique in which we inject the study medication via a transobturator approach into the levator ani muscles directly. We utilized this approach in addition to the pudendal nerve blockade to deliver study medication to the levator ani muscles themselves and any distal nerve branches of the levator ani nerve, with the idea that this would decrease pain and edema at the operative site and improve postoperative pain control. We add dexamethasone to bupivacaine for the intervention group because of its known anti-inflammatory qualities (10). These anti-inflammatory properties have been translated to the surgical realm and the addition of perioperative dexamethasone has been demonstrated to be a safe and effective way to improve perioperative recovery in multiple disciplines, including gynecology (11-15).

Study Objectives

Our primary aim is to determine if bilateral transobturator levator ani muscle injections and transvaginal pudendal nerve blocks with bupivacaine and dexamethasone improve postoperative pain measured by the numerical rating scale (NRS) on postoperative day 1 after vaginal reconstructive apical support procedures.

Our secondary aims include postoperative nausea and vomiting (measured by the postoperative nausea and vomiting score), analgesic consumption (measured in morphine equivalents), same-day discharge, postoperative pain at 6 hours, 48 hours, 72 hours and 1 week (measured by the NRS), need for either self-catheterization or indwelling catheter, safety and adverse events, and time to resume normal activity (measured by the activities assessment scale at 1,2,6 and 12 weeks postoperatively).

Study Design & Methods

We performed a 3-arm, double-blind, randomized, placebo-controlled trial of bilateral transobturator levator ani muscle injections and transvaginal pudendal nerve blocks

prior to native tissue vaginal apical support procedures for pelvic organ prolapse. Women were randomized to one of three study medication groups distributed over 4 injection sites: 22mL of 0.9% saline (placebo group), 22 mL of 0.25% bupivacaine (bupivacaine group), or 20 mL of 0.25% bupivacaine with 4mg (2mL) of dexamethasone (combined group).

Recruitment occurred and written informed consent was obtained during regularly scheduled preoperative office visits. If no preoperative visit was scheduled, informed consent was performed by telephone and the consent form was either mailed to the patient or signed on the morning of surgery. Block randomization occurred 1-2 days prior to scheduled surgery in a 1:1:1 ratio by a research coordinator not involved in study intervention or outcome assessment. The randomization scheme was stored in a password protected, secure location and only accessed by this research coordinator. We also took additional steps to ensure a double-blinded design. After randomization but before the start of the prolapse procedure, pharmacy personnel delivered the study medication to the operating room in a single, clear syringe labeled “Study Medication” and the corresponding study identification number. All syringes were identical. Additionally, normal saline, bupivacaine and dexamethasone are all clear solutions, which allowed us to blind physicians to the study medication being administered. Patients were also blinded to the study intervention until 12 weeks of follow-up.

All 3 study groups received transobturator levator ani muscle injections and pudendal nerve blocks with either saline, bupivacaine alone or bupivacaine and dexamethasone according to randomization. The study intervention was performed after the induction of general anesthesia and prior to the start of the prolapse repair. After the patient was placed in dorsal lithotomy position, sterile preparation occurred, and a urethral catheter was inserted. The bilateral transobturator levator muscle injections were performed first. The superior medial aspect of the obturator foramen was identified by palpation approximately 2-3 cm lateral and 2-3 cm inferior to the clitoris. With the thumb palpating the superior medial aspect of the obturator foramen, the index and middle finger were inserted into the vagina to confirm identification of the obturator foramen. A spinal needle was then inserted through the superior medial aspect of the obturator foramen through the obturator internus muscle. The trajectory of the needle at this point was angled slightly posteriorly towards the ischial spine, traveling parallel to the arcus tendineus levator ani and arcus tendineus fascia pelvis. The spinal needle was advanced to the level of the ischial spine, maintaining the same trajectory and with the vaginal hand ensuring that the spinal needle did not perforate the vaginal wall. Once the tip of the needle was at a depth where it had reached the ischial spine, aspiration was performed to ensure no intravascular needle placement and the study medication was injected. Bilateral pudendal nerve blocks were performed transvaginally after the transobturator injections. The pudendal nerve blocks were performed according to previously described technique (21,22). Five milliliters of study medication were injected at each of the four injection sites for a total of 20 mL of study medication. The intervention was performed by one of five attending surgeons or one of four urogynecology fellows. After the interventions, the vaginal reconstructive procedures were performed as usual by the attending surgeon and surgical team. Both fellows and

residents participated in these vaginal reconstructive surgeries, however for study purposes, resident physicians were not permitted to administer either the study injections.

To standardize care, all study participants received the same institutional induction and intraoperative enhanced recovery after surgery general anesthesia protocol, full details of which have been previously published (23). In summary, patients received intravenous propofol, ketamine, lidocaine, muscle relaxant and dexamethasone for induction and intravenous ketamine and lidocaine for maintenance (23). The intravenous dexamethasone given upon induction is part of the protocol to prevent postoperative nausea and vomiting. To standardize intraoperative local anesthetic, the amount of additional local infiltration was limited to 50ml of 0.5% lidocaine with epinephrine. According to our ERAS protocol, all surgeries were planned to be same-day surgeries. Any deviations from protocol were documented.

Our primary outcome was a numeric rating scale (NRS) pain score on postoperative day (POD) one. The NRS is an eleven-point scale ranging from 0 to 10 presented visually on a horizontal line. Higher scores represent more postoperative pain.

Secondary outcomes included pain scores at additional timepoints (6 hours after surgery, POD 2, POD 3 and 1 week after surgery), same day discharge rates, voiding status at time of discharge, postoperative narcotic consumption measured in oral morphine equivalents, postoperative ibuprofen consumption, postoperative nausea and vomiting (PONV), postoperative activities assessment, and adverse events. PONV was assessed using the PONV Intensity scale, a four-question assessment to measure clinically significant nausea and vomiting with higher scores signifying more clinically significant PONV (26). Time to resume normal activities was measured by the activities assessment scale (AAS), a 13-point scale on which patients rate their difficulty performing a range of activities from “No difficulty” to “Not able to do it.” A final score ranging from 0-100 is transformed, with higher numbers reflecting less difficulty with activities (27). Assessments were completed by the patient at home and mailed to research staff upon completion. Women were followed for 12 weeks postoperatively and no additional office visits were required as part of the research protocol.

Eligibility Criteria

Women were eligible for inclusion if they were ≥18 years old and scheduled for a vaginal native tissue repair with apical support procedure (uterosacral ligament suspension, sacrospinous ligament fixation, levator myorrhaphy or colpocleisis) and able to undergo general anesthesia. Concomitant procedures including hysterectomy, anterior and posterior colporrhaphies, perineorrhaphies and midurethral sling placements were permitted. All patients needed to be available for at least 12 weeks of follow-up. Women were excluded for any of the following reasons: planned mesh-augmented apical support procedure or mesh excision, laparoscopic, robotic or abdominal surgery, known adverse reaction or allergy to intervention medication, evidence of fistula or infection, chronic pelvic pain as an active issue, daily opiate

consumption, history of pelvic radiation, daily steroid use, diabetes mellitus, immunosuppression, planned surgery under regional anesthesia, non-English speaking or inability to complete questionnaires, bleeding diatheses, or weight less than 50kg. We incorporated a weight less than 50kg as an exclusion criterion to ensure that the bupivacaine dosage was below the weight-based maximum dose, as recommended by our anesthesia colleagues (16).

Statistical Analysis Plan

All results will be analyzed by intention-to-treat based upon the study group to which subjects were randomized. One-way ANOVA, Kruskal Wallis, Chi-square, and Fisher's Exact will be used to compare continuous and categorical variables, respectively. Based upon prior studies demonstrating that pain after vaginal surgery ranges from a 2 to 5 on numeric scales (range 0-10) and literature suggesting that a 33% decrease in pain is clinically significant, we elected to assess a 2-point change in NRS scores between treatment groups (5,7,9,28). Based upon an ANOVA evaluated at the 2-sided 0.05 significance level and a standard deviation of 17.5, a sample size of 21 patients per arm provided 90% power to detect a 2-point change in NRS scores. To account for 20% attrition, we increased to 25 patients per arm for a total of 75 women.

We hypothesized that concurrent bilateral transobturator levator ani muscle injections and transvaginal pudendal nerve blocks with bupivacaine and dexamethasone performed prior to vaginal native tissue apical prolapse repair would result in statistically significant improved pain scores on postoperative day one.

References

1. Alton K, Sullivan S, Udaltsova N, Yamamoto M, Zaritsky E. Same-Day Discharge After Minimally Invasive Myomectomy. *Obstet Gynecol.* 2016;127(3):539-544.
2. Perron-Burdick M, Yamamoto M, Zaritsky E. Same-day discharge after laparoscopic hysterectomy. *Obstet Gynecol.* 2011;117(5):1136-1141.
3. Zakaria MA, Levy BS. Outpatient vaginal hysterectomy: optimizing perioperative management for same-day discharge. *Obstet Gynecol.* 2012;120(6):1355-1361.
4. Evenson M, Payne D, Nygaard I. Recovery at home after major gynecologic surgery: how do our patients fare? *Obstet Gynecol.* 2012;119(4):780-784.
5. Abramov Y, Sand PK, Gandhi S, et al. The effect of preemptive pudendal nerve blockade on pain after transvaginal pelvic reconstructive surgery. *Obstet Gynecol.* 2005;106(4):782-788.
6. Imbelloni LE, Vieira EM, Gouveia MA, Netinho JG, Spirandelli LD, Cordeiro JA. Pudendal block with bupivacaine for postoperative pain relief. *Dis Colon Rectum.* 2007;50(10):1656-1661.
7. Ismail MT, Elshmaa NS. Pre-emptive analgesia by nerve stimulator guided pudendal nerve block for posterior colpoperineorrhaphy. *Eur J Obstet Gynecol Reprod Biol.* 2012;163(2):200-203.
8. Rouholamin S, Jabalameli M, Mostafa A. The effect of preemptive pudendal nerve block on pain after anterior and posterior vaginal repair. *Adv Biomed Res.* 2015;4:153.

9. Unger C, Walters MD. A Randomized Double-Blind Placebo-Controlled Trial on the Effect of Local Analgesia on Postoperative Gluteal Pain in Patients Undergoing Sacrospinous Ligament Colpopexy. *Female Pelvic Med Reconstr Surg.* 2016;22(5, Supplement 1):S2.
10. Barnes PJ. Anti-inflammatory actions of glucocorticoids: molecular mechanisms. *Clin Sci (Lond).* 1998;94(6):557-572.
11. Albrecht E, Kern C, Kirkham KR. A systematic review and meta-analysis of perineural dexamethasone for peripheral nerve blocks. *Anaesthesia.* 2015;70(1):71-83.
12. Antunes AA, Avelar RL, Martins Neto EC, Frota R, Dias E. Effect of two routes of administration of dexamethasone on pain, edema, and trismus in impacted lower third molar surgery. *Oral Maxillofac Surg.* 2011;15(4):217-223.
13. Gao W, Zhang QR, Jiang L, Geng JY. Comparison of local and intravenous dexamethasone for postoperative pain and recovery after tonsillectomy. *Otolaryngol Head Neck Surg.* 2015;152(3):530-535.
14. Huynh TM, Marret E, Bonnet F. Combination of dexamethasone and local anaesthetic solution in peripheral nerve blocks: A meta-analysis of randomised controlled trials. *Eur J Anaesthesiol.* 2015;32(11):751-758.
15. Pauls RN, Crisp CC, Oakley SH, et al. Effects of dexamethasone on quality of recovery following vaginal surgery: a randomized trial. *Am J Obstet Gynecol.* 2015;213(5):718 e711-717.
16. Dexamethasone (systemic): Drug information. UpToDate; 2016. Accessed November 9, 2016.
21. Cunningham FG. *Williams obstetrics.* 24th edition. ed. New York: McGraw-Hill Medical; 2014.
22. Vidaeff A. Pudendal and paracervical block. In: Ramin S, Eckler K, eds. *UpToDate.* Waltham, MA: UpToDate; 2016. Accessed November 8, 2016.
23. Carter-Brooks CM, Du AL, Ruppert KM, Romanova AL, Zyczynski HM. Implementation of a urogynecology-specific enhanced recovery after surgery (ERAS) pathway. *Am J Obstet Gynecol.* 2018;219(5):495 e491-495 e410.
26. Allen ML, Leslie K, Jansen N. Validation of the postoperative nausea and vomiting intensity score in gynaecological patients. *Anaesth Intensive Care.* 2011;39(1):73-78.
27. Barber MD, Kenton K, Janz NK, et al. Validation of the activities assessment scale in women undergoing pelvic reconstructive surgery. *Female Pelvic Med Reconstr Surg.* 2012;18(4):205-210.
28. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. *J Pain.* 2003;4(7):407-414.