Manual of Procedures/Protocol

Title: A Double-Blind Randomized Placebo-Controlled Clinical Trial of Preoperative Gabapentin Prior to Vaginal Apical Suspension Prolapse Procedures

Fellow: Colin Johnson, MD PGY5
Research Mentor: Joseph Kowalski, MD

University of Iowa Hospitals and Clinics
Department of Female Pelvic Medicine and Reconstructive Surgery
Iowa City, IA
July 2022

NCT 05658887

Specific Aims and Hypothesis

Primary Aim: To compare the impact of preoperative gabapentin versus placebo on post-operative opioid use.

Hypothesis: Preoperative gabapentin is associated with reduced post-operative opioid use compared to placebo for patients undergoing vaginal apical support procedures for pelvic organ prolapse.

Null Hypothesis: Preoperative gabapentin is not associated with reduced post-operative opioid use compared to placebo for patients undergoing vaginal apical support procedures for pelvic organ prolapse.

Secondary Aims:
1. To compare adverse events between groups.
2. To compare subjective pain scores and anti-emetic use between groups.
3. To compare time to discharge between groups.

Introduction, Background, and Significance

Enhanced Recovery after Surgery (ERAS) is an approach to perioperative care that focuses on evidence-based care protocols that emphasize minimizing stress as well as improving the body's response to stress.[1] Common elements to ERAS protocols include a multidisciplinary approach, preoperative optimization, emphasizing minimally invasive techniques, maintaining euvolemia, early mobilization, early postoperative oral intake, and multi-modal opioid-sparing pain control.[1,2] ERAS protocols have resulted in a significant decrease in length of stay, complications, and cost in many different surgical specialties.[1,2] The Enhanced Recovery After Surgery Society was founded in 2010 and publishes and updates evidence-based perioperative guidelines for many different surgical specialties and subspecialties.[1] In gynecology, the ERAS Society has published ERAS guidelines for gynecologic oncology (updated in 2019)[3] and for vaginal surgery (published 2020).[4] There have been many other gynecology ERAS programs/guidelines published,[5] and in 2019, Scheib et al. published a review of 50 gynecology ERAS programs.[5] Our institution implemented a gynecologic ERAS protocol in 2020, and after the protocol was introduced, patients undergoing pelvic organ prolapse surgery received significantly fewer opioids.[6]

Gabapentinoids (gabapentin and pregabalin) are anticonvulsant medications that are commonly used for chronic neuropathic pain and other chronic pain disorders but also have an anxiolytic effect.[7] Several ERAS protocols use a preoperative or perioperative gabapentinoid [2,3,5,6] as part of a multi-modal pain control approach in order to improve postoperative pain control and limit opioid use,[3] including the ERAS protocol that we currently use at our institution.[3,6]

The data regarding perioperative use of gabapentin is mixed. In 2015, Doleman et al. published a systematic review and meta-analysis of 133 randomized controlled trials (RCTs) of peri-operative gabapentin (ranging from 300 mg to 1200 mg) versus placebo and found that gabapentin was associated with reduced opioid consumption and pain scores during the first 24 hours after surgery.[8] They also found that it was associated with decreased preoperative anxiety,

decreased postoperative nausea and vomiting (PONV), and increased sedation.[8] Notably most of the trials were in non-gynecologic surgery[8] with only one of the trials looking at gabapentin in vaginal surgery[9] and none of the trials looking specifically at urogynecologic surgery.[8] In 2017, Hah et al. published a study showing that perioperative administration of gabapentin had no effect on postoperative pain resolution but it did have an effect of promoting opioid cessation after surgery.[10] In 2020, Verret et al. published a meta-analysis of 281 randomized controlled trials studying the use of perioperative gabapentinoids in adult patients and they found no clinically significant analgesic effect for the perioperative use of gabapentinoids and a greater risk of the adverse events of dizziness and visual disturbance.[11] In the minimally invasive gynecologic literature, the results of peri-operative gabapentin are also mixed: one randomized controlled trial (75 patients) found that preoperative gabapentin reduced postoperative pain and PONV in patients undergoing vaginal hysterectomy,[9] while another randomized controlled trial (129 patients) found that preoperative gabapentin does not reduce total opioid use 24 hours after surgery in patients undergoing minimally invasive hysterectomy.[12]

Adverse events are common in patients taking gabapentinoids for chronic pain.[7] Dizziness, somnolence, and gait disturbance are the most common side effects.[7] When used perioperatively it has been shown to be associated with sedation,[8] respiratory depression,[13] dizziness,[11] and visual disturbance[11]. Elderly patients may be more susceptible to these gabapentin-related adverse effects.[10] Notably, in December of 2019, the U.S. Food and Drug Administration issued a warning that serious breathing difficulties may occur in patients using gabapentin or pregabalin in patients with respiratory risk factors and is now requiring that warnings about the risk of respiratory depression be added to the prescribing information of gabapentinoids.[14]

Pelvic organ prolapse (POP) is a common benign condition with peak incidence of symptomatic prolapse occurring in women in their 70s.[15] In the United States, surgery for pelvic organ prolapse is very common,[15] with vaginal apical suspension being one of the most common surgeries for pelvic organ prolapse.[16] The data regarding perioperative gabapentin in surgery for pelvic organ prolapse is very limited. In 2018, Li et al. published a small RCT (47 patients total) comparing preoperative gabapentin to placebo in patients undergoing vaginal hysterectomy with concomitant pelvic reconstruction; they did not find a significant difference in opioid requirements in the first 24 hours after surgery between the two groups.[17] Other than this small study, to the best of our knowledge, the effects of perioperative gabapentin in patients undergoing vaginal apical suspension for pelvic organ prolapse are not well established. Due to the unclear benefits in this surgical population and the potential adverse effects of gabapentin,[7,8,11,13] especially considering that many of the patients receiving surgery for POP are elderly,[15] we think it is important to compare preoperative gabapentin to placebo for patients undergoing vaginal apical suspension for pelvic organ prolapse.

Research Methods

Study Design: Double-blind randomized placebo-controlled clinical trial

Setting: University of Iowa Hospitals and Clinics in Iowa City, IA, USA

Study Subjects:

Inclusion Criteria: All patients scheduled for a vaginal apical support procedure (sacrospinous ligament fixation or vaginal uterosacral ligament suspension), female, age 18 or higher

Exclusion criteria: (1) non-English speaking, (2) incarcerated, (3) cognitive impairment precluding informed consent, (3) chronic opioid users, (4) chronic gabapentinoid users, (5) subjects with contraindications to acetaminophen (allergy, severe liver disease), celecoxib (allergy, glomerular filtration rate<50, history of cardiovascular disease or coronary artery disease, history of peptic ulcer disease/GI bleeding), or gabapentinoids (allergy, glomerular filtration rate<50), (6) concurrent laparoscopic or abdominal surgery, (7) males

Detailed Procedure

Recruitment: Potential subjects will be recruited from all University of Iowa urogynecology clinics. All patients scheduled for a vaginal apical support procedure will be assessed for eligibility. Those that meet inclusion criteria and no exclusion criteria will be approached about study recruitment at least 7 days before their surgery either at the time of their original surgical consultation visit or preoperative clinic appointment. A study team member will discuss the study with the potential subject and review and sign informed consent. The subject will be considered enrolled at that time. Note that we will assess renal function (via a creatinine lab draw) as part of routine pre-operative evaluation in patients with risk factors for kidney disease (diabetes mellitus, heart disease, history of kidney disease, age>65 years old) in patients who have not had a creatinine drawn in the year preceding surgery. We will exclude patients from the study who have GFR <50.

A paper screening log will be maintained by the primary investigator that will include date of screening, name, medical record number, screening result (i.e. enrolled, not eligible, declined, not asked), and reason for ineligibility. This paper log will be kept in a locked file cabinet in the locked office of the primary investigator. Identifying information will be removed from the screening log at the close of patient enrollment.

Randomization, blinding, placebo compounding, and dispensing: NuCara Pharmacy will be providing the randomization (including allocation sequence), blinding, compounding, and dispensing services. Seven to fourteen days prior to an enrolled subject's planned procedure, a prescription for the capsule will be written to the compounding pharmacy. The patient will be considered enrolled and randomized at this point. The pharmacy will randomize the subject to the intervention group (active gabapentin 300 mg, preoperative celecoxib 400 mg, and preoperative acetaminophen 975 mg) or the control group (identical appearing gabapentin placebo, preoperative celecoxib 400 mg, and preoperative acetaminophen 975 mg) in a 1:1 ratio with blocks of 6 and stratified by surgery type (SSLF or ULS) and surgeon. A commercially available 300 mg gabapentin capsule will be over-encapsulated in an opaque capsule to provide blinding. The placebo capsule will contain microcrystalline cellulose and be placed in a matching opaque capsule. The medication will be mailed to the University of Iowa Investigational Pharmacy with the patient's identifying information and labeled as "active vs placebo." Therefore subjects, investigators, statisticians, and all other clinical staff (nurses,

anesthesiology team, etc.) will be blinded to placebo vs active medication. The University of Iowa investigational pharmacy will build the order for the research compound into the electronic medical record. Prior to the procedure, the compound will be brought from the investigational pharmacy to the preoperative area and dispensed to the patient within 2 hours prior to surgery along with preoperative acetaminophen 975 mg PO and preoperative celecoxib 400 mg PO. Notably, we considered gabapentin 600 mg as recommended by ACOG,[18] but we were concerned about it potentially causing a decrease in same day discharges, especially since many of our patients are elderly.

Intervention: After receiving the preoperative acetaminophen, celecoxib, and study drug (placebo or gabapentin corresponding to which study arm the patient is in), the patient will undergo the planned vaginal apical support procedure. All procedures will be performed by one of three fellowship-trained Female Pelvic Medicine and Reconstructive surgeons. Surgical management and intraoperative pain control will be at the discretion of the surgical and anesthesia teams. Postoperative pain control will be scheduled acetaminophen and scheduled NSAIDs (either ibuprofen or ketorolac) with breakthrough opioids as needed.

Data Collection: Baseline patient characteristics, demographics, and relevant histories will be obtained through the electronic medical record and stored in a secure database. Pain scores will be collected in the PACU and second stage recovery area by nurses per standard protocol. Opioid use while in the hospital will be recorded. Amounts of opioids used will be converted to morphine milligram equivalents (MME) using the CMS conversion chart.[19]

At 24 hours after surgery (starting when the patient leaves the operating room), the subject will be asked whether they experienced any dizziness, sedation, visual changes, nausea, or vomiting within the first 24 hours after surgery. They will also be asked if their pain control in the first 24 hours was adequate or inadequate. If the subject has already been discharged from the hospital, they will be called sometime between 24 and 36 hours postoperatively and asked the above questions as well as the amount of opiates they took between leaving the hospital and 24 hours after surgery ended. This list of questions and a table that allows them to keep track of opiates taken will be given to them when they are consented for the study.

Subjects will only be informed of their assigned group upon request following completion of the entire study.

Outcomes

Primary Outcome: Total postoperative opioid use in the first 24 hours postop measured in MME (starting when the patient leaves the operating room).

Secondary Outcomes: Mean postoperative pain score while admitted using the validated numerical rating scale[20] (0-10), postoperative opioid use while admitted (max of 24 hours) measured in morphine milliequivalents per hour (MMEs/hr), time to discharge, anti-emetic use, adverse events, patient reported adverse events of dizziness, sedation, visual changes, nausea, and vomiting in the first 24 hours after surgery, patient reported adequacy of pain control in the first 24 hours.

Other Covariates: Relevant medical and surgical histories (including history of pelvic radiation, inflammatory bowel disease, diabetes mellitus, history of chronic pain, prior hysterectomy, prior POP surgery, current smoking status, recent HbA1c), relevant medications (including insulin, immunosuppression, vaginal estrogen, OAB medications/treatment, and alpha blockers), and baseline patient characteristics and demographics including age, race, parity, BMI, and current exam (including POP-Q, cough stress test, pelvic muscle exam, PVR, and the presence or absence of vaginal atrophy). We will also record the surgical details including the type of surgery, suture used, number of suspension sutures, laterality, other concomitant procedures done (including hysterectomy and other prolapse or incontinence procedures).

Design, Sample Size, Analyses:

Trial Design: The trial will be designed as a superiority trial.[21] The hypothesis is that the treatment arm will be statistically significantly more effective at reducing postoperative opioid use than the control arm and the null hypothesis is that the treatment arm will not be statistically significantly more efficacious than the control arm.

The study done my Mehr et al.,[6] which was done at our institution showed that in the pre-ERAS group the total postoperative opioid use was an average of 31.6 MME with a standard deviation of 28.3. The average admission time was 27 hours which means average postoperative time is about 20 hours.[6] Extrapolating from this the average MME use would be roughly 50 MME in 24 hours with a standard deviation of roughly 30. We believe that a clinically relevant reduction in MME use would be 30% which would be 35 MME in 24 hours. Standard deviation for the post ERAS group was 13 but accounting for the decreased time in the hospital standard deviation would be closer to 20. Using these numbers (mean MME of 50 with a reduction to 35 and standard deviations of 30 and 20), and an alpha of 0.05 and a beta of 0.2 (power 80%), sample size is 46 per group which is a total of 92 subjects. Adding 20% for loss to follow up (cannot contact them 24 hours after) and cancellations after randomization is 110.

Analyses: Baseline patient characteristics and relevant histories will be analyzed and compared between the control and treatment groups. Study results will be analyzed with appropriate statistical tests of student's t-test for continuous variables and χ^2 or Fischer's exact tests for categorical variables. A stratified analysis or linear regression will be completed in order to control for key variables such as concurrent hysterectomy if these variables are unequal following randomization. The study will be registered with clinicaltrials.gov and results will be reported in accordance with the CONSORT guidelines.

Volume: We anticipate a volume of approximately 100 vaginal apical support procedures yearly. Based on enrollment rates in other ongoing studies at our institution

(roughly 75%), this volume should allow us to meet our recruitment goal of 110 subjects within a 1.5 year period.

Adverse Events and Data Safety Monitoring

Adverse events are unwanted medical occurrences associated with the use of drugs in humans, whether or not they are considered related to the drug.[22] The Clavien-Dindo classification of surgical complications is a standardized tool used to assess postoperative complications.[23] Adverse events of Clavien-Dindo grade II or higher (see below) that occur during the study period will be recorded and reported.

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
Grade V	Death of a patient

According to the FDA, an adverse event or suspected adverse reaction is considered "serious" if in the view of the investigator it results in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.[22] Notably a suspected adverse reaction is any adverse event for which there is reasonable possibility that the drug caused the adverse event.[22]

Members of the study team including PI and co-investigators will meet monthly to review data security, protocol deviations, recruitment, and adverse events. Any adverse event that is serious or unexpected (as defined by the FDA Code of Federal Regulations[22]) and possibly related to the administration of gabapentin will be reported to the IRB within 24 hours of learning of the event. Data security breaches, protocol deviations, adverse event data, and subject recruitment data will also be reported to the IRB as required.

Ethics and Patient Consent

This study will be approved by the University of Iowa Institutional Review Board (IRB). The study will be discussed in detail and informed consent reviewed with potential subjects prior to enrollment.

Risks of this study include loss of confidentiality of protected health information (PHI). We will maintain records on a secure password protected local server (REDCAP) in-order-to minimize this risk. In addition, data forms will not contain any patient names or other personal

information. Each form will contain only a unique subject identifier. Any paper data (deidentified) will be kept in a locked file cabinet in a locked office.

Other risks of this study include the risks of taking a one-time dose of 300 mg gabapentin. Notably in 2019, the U.S. Food and Drug Administration issued a warning that serious breathing difficulties may occur in patients using gabapentin or pregabalin in patients with respiratory risk factors and is now requiring that warnings about the risk of respiratory depression be added to the prescribing information of gabapentinoids. Respiratory depression has not been reported with a one-time low dose (300 mg) of gabapentin. Other rare risks include gait disturbance, somnolence, dizziness, and sedation.

As described above, there is conflicting data regarding the use of preoperative gabapentin, and therefore randomization to either the control arm or the treatment arm is currently within standard of care. Patients randomized to the gabapentin group potentially stand to benefit from better postoperative pain control and less postoperative opioid use. Patients randomized to the placebo group may potentially benefit from fewer medication side effects.

Project Timeline/Schedule

October 2022: IRB Submission
December 2022: Begin enrollment
July 2024: End enrollment
December 2024: Data analysis and manuscript preparation

References

1. Ljungqvist O, Scott M, Fearon KC. Enhanced Recovery After Surgery: A Review. *JAMA Surg.* 2017;152(3):292-298.
2. Smith TW, Jr., Wang X, Singer MA, Godellas CV, Vaince FT. Enhanced recovery after surgery: A clinical review of implementation across multiple surgical subspecialties. *Am J Surg.* 2020;219(3):530-534.
3. Nelson G, Bakkum-Gamez J, Kalogera E, et al. Guidelines for perioperative care in gynecologic/oncology: Enhanced Recovery After Surgery (ERAS) Society recommendations-2019 update. *Int J Gynecol Cancer.* 2019;29(4):651-668.
4. Altman AD, Robert M, Armbrust R, et al. Guidelines for vulvar and vaginal surgery: Enhanced Recovery After Surgery Society recommendations. *Am J Obstet Gynecol.* 2020;223(4):475-485.
5. Scheib SA, Thomassee M, Kenner JL. Enhanced Recovery after Surgery in Gynecology: A Review of the Literature. *J Minim Invasive Gynecol.* 2019;26(2):327-343.
6. Mehr AA, Elmer-Lyon C, Maetzold E, Bradley CS, Kowalski JT. Effect of Enhanced Recovery Protocol on Opioid Use in Pelvic Organ Prolapse Surgery. *Female Pelvic Med Reconstr Surg.* 2021;27(12):e705-e709.
7. Mathieson S, Lin CC, Underwood M, Eldabe S. Pregabalin and gabapentin for pain. *Bmj.* 2020;369:m1315.
8. Doleman B, Heinink TP, Read DJ, Faleiro RJ, Lund JN, Williams JP. A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain. *Anaesthesia.* 2015;70(10):1186-1204.
9. Rorarius MG, Mennander S, Suominen P, et al. Gabapentin for the prevention of postoperative pain after vaginal hysterectomy. *Pain.* 2004;110(1-2):175-181.

10. Hah J, Mackey SC, Schmidt P, et al. Effect of Perioperative Gabapentin on Postoperative Pain Resolution and Opioid Cessation in a Mixed Surgical Cohort: A Randomized Clinical Trial. *JAMA Surg.* 2018;153(4):303-311.
11. Verret M, Lauzier F, Zarychanski R, et al. Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain: A Systematic Review and Meta-analysis. *Anesthesiology.* 2020;133(2):265-279.
12. Huynh TQ, Patel NR, Goldstein ND, Makai GE. Preoperative Gabapentin for Minimally Invasive Hysterectomy: A Randomized Controlled Trial. *J Minim Invasive Gynecol.* 2021;28(2):237-244.e232.
13. Weingarten TN, Jacob AK, Njathi CW, Wilson GA, Sprung J. Multimodal Analgesic Protocol and Postanesthesia Respiratory Depression During Phase I Recovery After Total Joint Arthroplasty. *Reg Anesth Pain Med.* 2015;40(4):330-336.
14. FDA warns about serious breathing problems with seizure and nerve pain medicines gabapentin (Neurontin, Gralise, Horizant) and pregabalin (Lyrica, Lyrica CR) When used with CNS depressants or in patients with lung problems [press release]. FDA.gov: U.S. Food and Drug Administration, 12-19-2019 2019.
15. Pelvic Organ Prolapse: ACOG Practice Bulletin, Number 214. *Obstet Gynecol.* 2019;134(5):e126-e142.
16. Sammarco AG, Swenson CW, Kamdar NS, et al. Rate of Pelvic Organ Prolapse Surgery Among Privately Insured Women in the United States, 2010-2013. *Obstet Gynecol.* 2018;131(3):484-492.
17. Li ALK, Wadsworth K, Siddiqui NT, et al. Does low-dose gapapentin reduce opioid use postoperatively?: A randomized controlled trial in women undergoing reconstructive pelvic surgery. *Int Urogynecol J.* 2019;30(2):211-217.
18. Committee Opinion No. 750: Perioperative Pathways: Enhanced Recovery After Surgery: Correction. *Obstet Gynecol.* 2019;134(5):1121.
19. Services CfMM. Opioid Oral Morphine Milligram Equivalent (MME) Conversion Factors table for prescription drug coverage. https://medicaid.utah.gov/Documents/files/Opioid-Morphine-EQ-Conversion-Factors.pdf. Published 2020. Accessed July 14, 2022.
20. Karcioglu O, Topacoglu H, Dikme O, Dikme O. A systematic review of the pain scales in adults: Which to use? *Am J Emerg Med.* 2018;36(4):707-714.
21. Zhong B. How to calculate sample size in randomized controlled trial? *J Thorac Dis.* 2009;1(1):51-54.
22. Code of Federal Regulations. In: Administration FaD, ed. *21CFR312.32*.
23. Bolliger M, Kroehnert JA, Molineus F, Kandioler D, Schindl M, Riss P. Experiences with the standardized classification of surgical complications (Clavien-Dindo) in general surgery patients. *Eur Surg.* 2018;50(6):256-261.