Effect of Perioperative Gabapentin on Postoperative Opioid Requirements

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Support Provided by:
N/A

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Abbreviations

ERAS	Enhanced Recovery After Surgery
ACOG	American College of Obstetricians and Gynecologists
FDA	Food and Drug Administration
AAGL	American Association of Gynecologic Laparoscopists
ASA	American Society of Anesthesiologists
CMP	Comprehensive metabolic profile
PACU	Post-anesthesia care unit
PO	By mouth

1.0 Background & Rationale

A multimodal analgesic approach is the mainstay of controlling postoperative pain and reducing opioid consumption in Enhanced Recovery After Surgery (ERAS) protocols [ACOG 2018]. This includes scheduled acetaminophen and non-steroidal anti-inflammatory drugs, in addition to neuromodulators such as gabapentin. Perioperative gabapentin has been proven to reduce inpatient opioid use after hysterectomy. This is desirable given the ongoing opioid epidemic and risks associated with opioid use, including opioid tolerance, dependence, constipation, and dizziness. However, the ideal dose and timing of administration of gabapentin has not been defined. This is reflected by differing recommendations regarding gabapentin use in ERAS protocols from the American College of Obstetrics and Gynecology, ERAS Society guidelines for gynecologic/oncology, and the Association of Gynecologic Laparoscopists (AAGL).

The ACOG practice bulletin on ERAS protocols recommends consideration of gabapentin 600 mg preoperatively and scheduled gabapentin postoperatively [ACOG 2018]. ERAS Society guidelines for perioperative care in gynecologic/oncology surgery recommend but do not specify the dose or timing of routine preoperative administration of gabapentin in addition to consideration for postoperative use [Nelson 2019]. In contrast, AAGL released a task force in August 2020 recommending against the use of gabapentin in ERAS protocols, citing the FDA safety concerns [Stone 2021]. The FDA safety communication published December 2019 warned that serious breathing difficulties may occur in patients using gabapentin concurrently with opioid pain medications [FDA 2019].

However, as stated above, use of perioperative gabapentin decreases inpatient opioid use following gynecologic procedures. While efforts to reduce use of opioids should be maximized, judicious use of gabapentin is warranted given changes in its safety profile. Determining if preoperative gabapentin use alone is noninferior to preoperative and postoperative gabapentin in reducing opioid use furthers this goal.

The purpose of this study is to determine if preoperative gabapentin is noninferior to preoperative and postoperative gabapentin for pain control in patients undergoing surgery for pelvic organ prolapse.

2.0 Objective(s)

2.1 Primary Objective

The primary objective is to determine if preoperative gabapentin alone is noninferior to preoperative and postoperative gabapentin with respect to percentage of patients requiring opioid prescription at discharge.

2.2 Secondary Objective

The secondary objectives are to compare the frequency of opioid refill requests, pain scores in the hospital, total morphine milligram equivalents used in the hospital, length of hospital stay, and side effect rates of nausea and sedation associated with gabapentin usage.

3.0 Outcome Measures/Endpoints

3.1 Primary Outcome Measures

The primary outcome that will be measured is the **percentage of patients requiring opioid prescription at discharge** in each group based on an established algorithm for opioid discharge dosing from the medical literature [Margolis 2020]. If patient received less than 5 doses of an opioid during hospital stay, they will not receive a prescription for opioids on discharge. If patient received 5 or more doses, they will receive a prescription for opioids on discharge.

3.2 Secondary Outcome Measures

Frequency of opioid refill requests will be measured by counting how many patients in each group call the office to request a new opioid prescription (if they were discharged without a prescription) or to request an opioid prescription refill (if they were discharged with a prescription) within the 6-week postoperative time period.

Pain scores in the hospital will be measured on a numeric rating scale (0-10) with 0 being no pain and 10 being worst pain. Pain score collected will be pain recorded at 12 hours after arrival to the floor and highest score during hospital stay. This scale was chosen because this is already the standard of nursing care for assessing patient pain. Nursing staff assesses pain via numeric rating scale every 4 hours on arrival to the floor.

Total morphine milligram equivalents used will be calculated by converting total PO and IV opioids used postoperatively until hospital discharge to morphine milligram equivalents using the opioid equianalgesic chart.

Length of stay will be measured in hours by time of registration for surgery to time of discharge from hospital.

Nausea will be measured by the number of "as needed" antiemetics the patient received postoperatively.

Sedation will be measured by the Stanford Sleepiness Scale. This is a self-administered scale that the patient will complete at 10AM on postoperative day 1.

3.3 Tertiary/Exploratory/Correlative Outcome Measures

The following demographic data will be extracted from the initial history and physical note, as these are standardly collected: age (year), race (White, Black, Hispanic, Asian, Other), BMI, tobacco use (current, former, never), menopause status (premenopausal, postmenopausal), Charlson Comorbidity Index (a calculation using patient's comorbidities to predict estimated 10-year survival), number of prior abdominal/pelvic surgeries, and stage of prolapse.

The following intraoperative data will be collected from the immediate postoperative note written by the surgeon: estimated blood loss and type of surgery (native tissue laparoscopic, native tissue vaginal, mesh-augmented laparoscopic, obliterative).

Duration of surgery (from skin incision to closure) and ASA physical status class will be collected from the IntraOp nursing record.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

- Women $\geq$ 18 years old
- English-speaking
- Stage $\geq$ 2 pelvic organ prolapse
- Undergoing pelvic organ prolapse procedure (including native tissue vaginal procedure, native tissue laparoscopic procedure, mesh-augmented laparoscopic procedure, obliterative procedure)
- Planning overnight stay

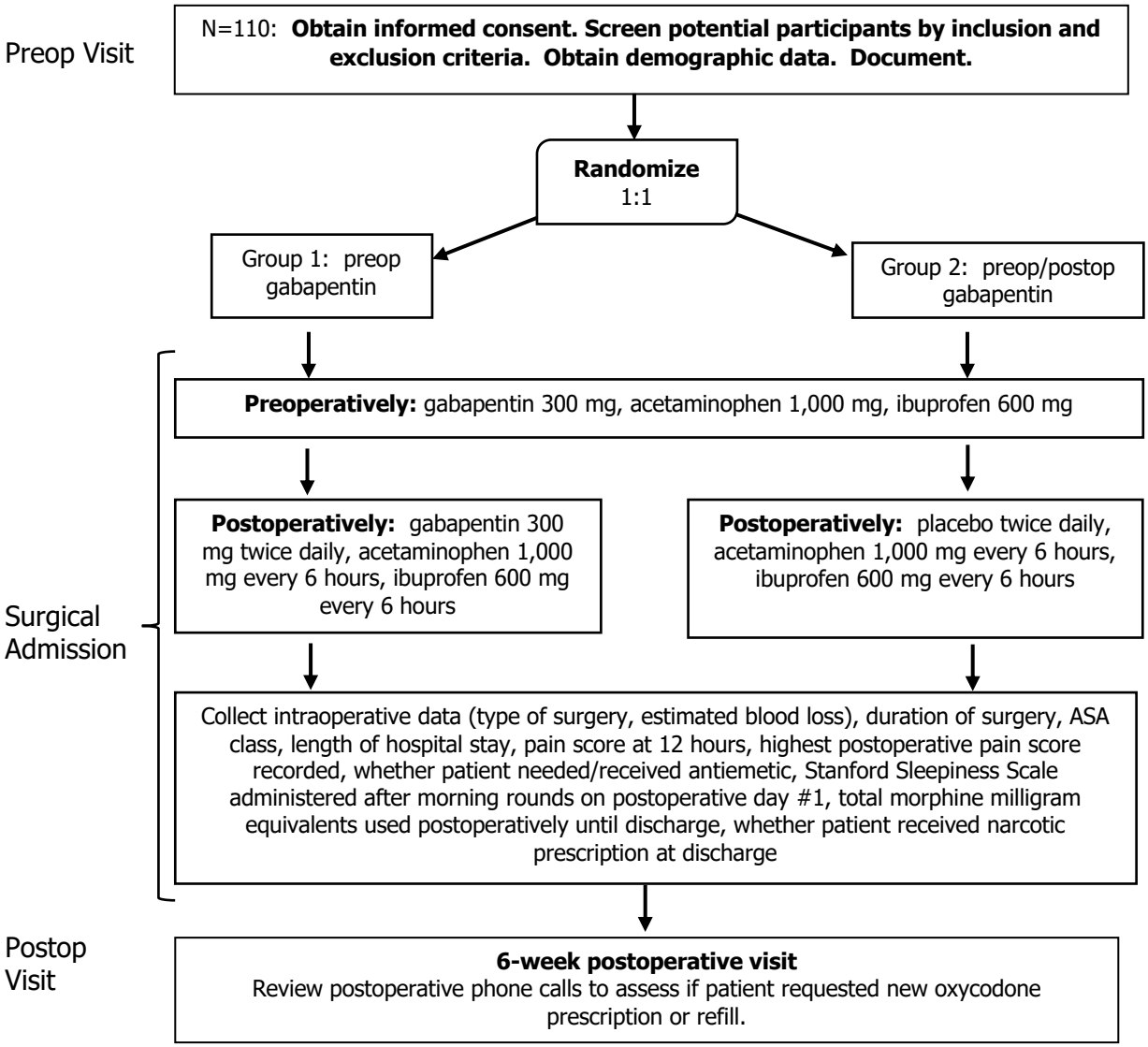
4.2 Exclusion Criteria

- Renal dysfunction (creatinine clearance <60 mL/min)
- Allergy to acetaminophen and ibuprofen
- Allergy to gabapentin
- Patients on a Controlled Substance Agreement or Opioid Contract from another provider. This information is available in the IU Health electronic medical record, Cerner.

5.0 Study Design

This will be a 2-arm single-center double-blinded randomized controlled noninferiority trial of women undergoing prolapse repair with planned overnight hospitalization. Patients will be screened for eligibility at their preoperative consultation visit and consented at that time. Patients will be randomized to receive gabapentin 300 mg preoperatively and placebo twice daily postoperatively or gabapentin 300 mg preoperatively and 300 mg twice daily postoperatively. All patients will also receive acetaminophen 1,000 mg and ibuprofen 600 mg preoperatively and scheduled acetaminophen 1,000 mg every 6 hours and ibuprofen 600 mg every 6 hours postoperatively. They will have oxycodone 5 mg every 6 hours as needed for pain and ondansetron 4 mg as needed for nausea or vomiting. During morning rounds on postoperative day 1, patients will be given the Stanford Sleepiness Scale to complete before 10AM. All patients will be discharged with acetaminophen 1,000 mg every 6 hours and ibuprofen 600 mg every 6 hours as needed for pain. Patients who received <5 doses of as-

needed oxycodone during hospital stay will not receive a prescription for oxycodone. Patients who received 5 or more doses will receive a prescription for oxycodone. The medical record will be queried at 6 weeks postoperatively to complete case report forms and obtain demographic data in addition to outcome measures.



6.0 Enrollment/Randomization

Patients will be identified for possible enrollment at their preoperative consultation. During this visit, surgical plan for management of pelvic organ prolapse is finalized. English-speaking women $\geq$ 18 years old with Stage $\geq$ 2 pelvic organ prolapse planning laparoscopic sacrocolpopexy, laparoscopic uterosacral ligament suspension, vaginal native tissue repair (intra- or extraperitoneal colpopexy or obliterative surgery) with or without concomitant hysterectomy requiring overnight hospital stay will be eligible. Patients will have Pre-Anesthesia Testing for assessment of renal function (creatinine clearance) on the same day as the

preoperative visit. Patients will be approached by research personnel (principal investigator or sub-investigators) to participate in the study. If they are not excluded from study participation, they will be counseled on potential risks, benefits, and alternatives to study participation. Any questions potential subjects have regarding the study will be answered in a language understandable to them at the conclusion of the visit. Study personnel will counsel potential subjects that they will be randomized to receive either the current standard of postoperative care (scheduled acetaminophen every 6 hours, scheduled ibuprofen every 6 hours, and scheduled gabapentin twice daily with oxycodone "PRN" or "as needed") or the current standard of care without gabapentin. Patients who are willing to participate in the study will be asked to sign informed consent/HIPAA Authorization form establishing the privacy and confidentiality standards for the study. Study subjects will receive copies of both signed forms.

An online random number generator (www.randomizer.org) will be used to create the random number set. This set will be used by the inpatient pharmacy to assign patients to one of two treatment groups upon their arrival for surgery: the preoperative gabapentin/postoperative placebo (which will receive gabapentin preoperatively and placebo postoperatively) or the preoperative/postoperative gabapentin group (which will receive gabapentin preoperatively and postoperatively). The patient and the surgical team will be blinded to group randomization.

Case report forms will be used to collect demographic data and outcome measures at the 6-week postoperative visit. Data from case report forms will be entered into a secure and private REDCap database. Pharmacy will be contacted to reveal study group assignments for data analyses after enrollment is completed.

7.0 Study Procedures

All patients will arrive at the preoperative unit of the hospital prior to surgery. They will receive the current standard of care for preoperative medications: acetaminophen 1,000 mg, ibuprofen 600 mg, and gabapentin 300 mg. They will then be induced with general anesthesia per the Anesthesiologists preference and undergo surgical prolapse repair. After surgery, they will be moved to the post-anesthesia care unit for close postoperative monitoring and initiation of postoperative pain regimens. After confirming stabilization in the PACU (usually 1-2 hours), patients will be moved to the medical floor for standard postoperative care. Patients in the preoperative/postoperative gabapentin group will receive the standard postoperative pain regimen: acetaminophen 1,000 mg every 6 hours, ibuprofen 600 mg every 6 hours, and gabapentin 300 mg every 12 hours. Patients in the preoperative gabapentin/postoperative placebo group will receive acetaminophen 1,000 mg PO every 6 hours, ibuprofen 600 mg PO every 6 hours, and placebo every 12 hours. Both groups will have oxycodone 5 mg PO every 4 hours available for "PRN" or "as needed" for pain control. Both groups will also have ondansetron available as needed for nausea. Pain is assessed by nursing staff every 4 hours based on established hospital-based protocols. Pain is assessed by asking the patient to rate their pain on a numeric rating scale from 0-10 with 0 being no pain and 10 being worst pain imaginable. On postoperative day 1, patients will be rounded on by a member of the study personnel. They will be provided the Stanford Sleepiness Scale and asked to complete this prior to 10AM.

Remaining data (demographics, surgical variables, length of stay, whether patient required opioid prescription at discharge, whether patient called within 6 weeks to request opioid prescription or refill) will be collected from chart review.

8.0 Study Calendar

	Preop Visit	Surgical Admission	6-week Postop Visit
Demographics	x		
Intraoperative data		x	
Duration of surgery		x	
Length of stay		x	
Pain at 12 hours		x	
Pain, highest during hospital admission		x	
Nausea (whether patient received antiemetics or not)		x	
Morphine milligram equivalents used postoperatively		x	
Stanford Sleepiness Scale		x	
Opioid prescription at discharge		x	
Opioid refill/new prescription request			x

9.0 Reportable Events

The current standard of postoperative care involves scheduled acetaminophen, ibuprofen, and gabapentin in addition to "as needed" oxycodone. The preoperative gabapentin/postoperative placebo group will receive placebo rather than gabapentin postoperatively. As such, anticipated risks of study participation include risk of inadequate postoperative pain control, though this is unlikely as patients will also have access to oxycodone on an as-needed basis. As such, a foreseeable risk to the study will be risk of receiving more "as needed" oxycodone to achieve pain control for patients in this group. Oxycodone 5 mg will be available every 6 hours as needed. This is the lowest initial dosage and frequency of administration recommended for oxycodone [FDA oxycodone]. This dosage and frequency is already part of standard of care for our postoperative patients. This essentially negates the risk of respiratory depression from excessive opioid use.

Should an unexpected adverse event, protocol deviation, or consent violation occur, this will be reported to the IRB within 5 business days of the study personnel becoming aware, as per the IU HRPP Reportable Events section 2.1. Collection of adverse events will begin at time of consent at the preoperative consultation visit.

10.0 Data Safety Monitoring

Our current standard of care is to administer gabapentin both preoperatively and postoperatively. The intervention in this study is to only administer gabapentin preoperatively to determine if this approach is noninferior to preoperative and postoperative gabapentin with respect to postoperative pain control. The potential benefits of only administering gabapentin preoperatively is the reduction of side effect risk rates associated with elimination of postoperative dosing. As we will be administering less medication, this is only a slightly greater than minimal risk study.

The study team, including the principal investigator and co-investigators, will be responsible for the Data Safety Monitoring Plan as this is a minimal risk study at a single site with a small number of subjects. The study team will be responsible for ensuring data quality, subject recruitment, subject accrual, and subject retention through continuous, close monitoring. Privacy will be protected by keeping patient consent forms, all case report forms, and Stanford Sleepiness Scales in a locked filing cabinet to which only the principal investigator has a key. Patient demographics, surgical details, and postoperative course are already kept private and confidential via storage in the electronic medical record which is password protected at sign on to the computer operating system. Data from case report forms entered into a REDCap database will be kept private and confidential via storage on computer files that are password protected at multiple levels: 1) sign on to the computer, 2) sign on to REDCap via Duo two-factor authentication.

The only anticipated risk or adverse event is inadequate postoperative pain control, which is unlikely as patients in both groups will have access to oxycodone as-needed. Differential opioid pain medication requests between the two groups will be monitored closely by hospital nursing staff. A physician is reachable at any time via DiagNotes, a real-time messaging system, should any concerns arise. Unexpected adverse events will be reported to the IRB within 5 business days by the principal investigator.

11.0 Study Withdrawal/Discontinuation

Study participants have the right to withdraw from this study at any time and for any reason, or no reason at all. There are no legal requirements for study participants to communicate their withdrawal in writing. In fact, they have the right to just stop coming to visits allowing the principal investigator to deduce that they have withdrawn. Withdrawal from study participation will not affect their postoperative care.

12.0 Statistical Considerations

Assuming a 15% or less dropout rate, 130 patients will need to be recruited to reach a sample size of 110 patients. Sample size was calculated for a noninferiority trial. Assuming 23.1% of patients who receive preoperative and postoperative gabapentin in addition to scheduled acetaminophen and ibuprofen require an opioid prescription at discharge and a 20% non-inferiority margin, 55 patients per arm are required to achieve a power of 80% with a significance level of 0.05 [Margolis 2020].

Two group comparisons of normally distributed study variables will be compared using the Student's T-test. Two group comparisons of nonnormally distributed study variables will be

compared using the Mann-Whitney U Test. K group categorical variables will be compared across our two treatment groups using the chi-square test for association.

Our primary outcome of interest is the percentage of study subjects receiving an opioid prescription at discharge. Given the noninferiority study design, the null hypothesis is that the difference in the percentage of subjects who receive an opioid prescription in the preoperative gabapentin/postoperative placebo group will exceed 20% compared to the preoperative/postoperative gabapentin group. The alternative hypothesis is that the difference in the percentage of subjects who receive an opioid prescription in the preoperative gabapentin/postoperative placebo group will be less than 20% compared to the preoperative/postoperative gabapentin group.

Chi-square test for association with relative risk estimates will be calculated to compare the percentage of study subjects receiving opioid prescriptions at discharge between our two treatment groups. We will accept our preoperative gabapentin/postoperative placebo group as noninferior to our preoperative/postoperative gabapentin group if the difference in percentage of subjects receiving opioid prescription at discharge is less than 20% between the two groups (alternative hypothesis).

13.0 Statistical Data Management

Data will be collected via paper case report forms which will be stored in a locked filing cabinet accessible only to the primary investigatory. Data will then be entered into REDCap and stored electronically prior to export into SPSS for data analysis.

14.0 Privacy/Confidentiality Issues

With exception of the Stanford Sleepiness Scale, data is stored in the electronic medical record as part of standard clinical care. Study personnel are also the patients' surgeons, and as such have legitimate justification to having access to the study participants' protected health information (PHI). All PHI collected will be de-identified using the Safe Harbor Method outlined in the IU HRPP Policy Statement for Use of Protected Health Information section 2.3. Study participants will be assigned a study number at enrollment. The study log will be secured in a locked filing cabinet to which only the principal investigator has a key. The de-identified database created from case report forms will also be stored in the locked filing cabinet. Only the pharmacy will have knowledge of group randomization. Group randomization assignments will not be accessed until all case report forms have been filled out, at which point each subject will be linked to their group and data will be analyzed. None of the personal health information, case report forms, or Stanford Sleepiness Scales will be made available for disclosure beyond the scope of this study.

15.0 Follow-up and Record Retention

It will require approximately 18 months to enroll 130 study participants for this study protocol, so we expect to be completed by September 30, 2022. All records produced or collected in connection with our research project, shall be retained for a period of three years from the date

of study closure with the IRB, consistent with Indiana University Human Research Protection Program section – Research Data Management section 2.2.

16.0 References

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17.0 Appendix

A – Case Report Form
B – Stanford Sleepiness Scale

Appendix A

Perioperative Gabapentin Study – Case Report Form

Subject # _____

Age: _____

Race (circle one): White Black Hispanic Asian Other

BMI: _____

Tobacco use (circle one): Current Former Never

Menopause status (circle one): Premenopausal Postmenopausal

Number of prior abdominal/pelvic surgeries: _____

Stage of prolapse (circle one): I II III IV

Charlson Comorbidity Index: _____

Type of surgery (circle one): Obliterative Native-tissue vaginal Native-tissue laparoscopic Mesh-augmented laparoscopic

Estimated blood loss (mL): _____

ASA class: _____

Duration of surgery (hours): _____

Pain at 12 hours after arrival to floor: _____

Pain, highest recorded: _____

Antiemetics (number used): _____

Stanford Sleepiness Scale: _____

Length of hospital stay (hours): _____

Total morphine milligram equivalents used after arrival to floor (mg): _____

Opioid prescription at discharge (circle one): Yes No

Opioid prescription refill/new prescription requested within 6 weeks (circle one): Yes No

Appendix B

The Stanford Sleepiness Scale (SSS)

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7
Asleep	X