

Randomized controlled trial of gabapentin vs placebo for postoperative pain after sacrospinous ligament fixation for pelvic organ prolapse

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BACKGROUND / RATIONALE

Pelvic organ prolapse (POP), the herniation of the bladder, uterus, or rectum, into and often beyond, the vaginal opening, affects 40% of postmenopausal women, and significantly impairs quality of life.(1) POP is often managed surgically, and currently, one in every eight women will undergo POP surgery during her lifetime.(2)

A commonly performed procedure for POP is a sacrospinous ligament fixation (SSLF), which is a vaginal surgery that involves suspending the vaginal apex to the sacrospinous ligament suspension with sutures. Beyond routine postoperative pain, a SSLF may result in significant gluteal pain as a result of the vaginal sutures affecting/impinging on the sacral nerve roots.(3) Unfortunately, postoperative gluteal pain is not uncommon with 12% of patients reporting significant gluteal pain and 4% having persistent pain 6 weeks after surgery.(4)

In this study, we aim to compare the impact of gabapentin versus placebo on postoperative pain after SSLF. Our rationale is that studies have shown that preoperative gabapentin, a non-opioid analgesic, resulted in a lower narcotic use postoperatively.(5) Decreasing use of standard of care postoperative narcotic pain medications would also decrease adverse events due to narcotics such as nausea, vomiting and constipation, and potentially decrease the long-term risk of opioid dependence. (6, 7) As an additional benefit, a careful assessment of actual opioid will help to inform best practices for prescribing, as it is possible that we are overprescribing narcotic medications for this type of surgery.(6, 8, 9) We propose to evaluate a longer two-week course of gabapentin because we currently use gabapentin to treat neuropathic pain after SSLF; thus, gabapentin may help to address overall pain as well as neuropathic gluteal pain that can occur after SSLF. Furthermore, gabapentin is a relatively safe medication with the primary adverse events being dizziness and sedation.

Given the risk of overall postoperative pain and neuropathic gluteal pain after a SSLF for POP and the evidence that perioperative gabapentin may decrease acute pain and neuropathic pain, we propose a novel randomized trial to compare perioperative gabapentin versus placebo on postoperative pain after a vaginal SSLF surgery.

STUDY AIMS

Primary aim: To assess the impact of gabapentin versus placebo on postoperative pain on postoperative day (POD) #7 after a vaginal sacrospinous ligament suspension for apical pelvic organ prolapse.

We hypothesize that a one week course of post-operative gabapentin will decrease overall post-operative pain on POD #7 as compared to placebo.

Secondary aims:

- To assess the impact of gabapentin versus placebo on gluteal postoperative pain on POD#7.
We hypothesize that a one-week course of gabapentin will decrease overall gluteal pain as compared to placebo on POD#7.
- To compare narcotic use during the first two weeks between the gabapentin and the placebo group.
We hypothesize that there will be lower narcotic use in the gabapentin compared to placebo group

STUDY DESIGN & METHODS

This study is a double-blinded randomized controlled trial comparing the impact of 2 weeks of gabapentin vs placebo on post-operative pain.

Study Population

Inclusion criteria:

- Women age 18+
- English-speaking
- Planning to undergo a vaginal SSLF

Exclusion criteria:

- Pregnant or planning to become pregnant during study participation
- Prior or concurrent vaginal mesh surgery for POP (midurethral sling is not an exclusion)
- Planning a concurrent TVH, colpocleisis (total vaginectomy or LeFort colpocleisis), mesh excision, anal sphincteroplasty, fistula repair, or urethral diverticulectomy
- Cognitive impairment (indicated by a score of 0-2 on Mini-Cog)
- Currently taking gabapentin or pregabalin (Lyrica) or previous intolerance to gabapentin or pregabalin
- Daily use of narcotics for \geq 2 months
- Acute or chronic renal failure based on past medical history (PMH) or glomerular filtration rate (GFR) < 30ml/min (see meds info below)
- Severe uncontrolled depression or bipolar disease based on PMH
- Fall risk if history of fall in last year or current use of cane/walker
- Joint procedure with other service (ie colorectal surgery/gyn onc)

Intervention

Participants undergoing SSLF will be randomized to receive either 2 weeks of post-op gabapentin or placebo, starting with 300mg qhs for the first 3 days post-op, then on day 4 patients will dose escalate to 300mg bid for 11 additional days for a total of 2 weeks.

- UNC IDS will provide active and placebo capsules (300mg dose), 1 x 3d postop (subtotal 3), 2 x 11d postop (subtotal 22) = 25 total
- We will use NIH Common Terminology of Criteria for Adverse Events version 4.0 (CTCAE) criteria (15)
- Specific AEs to assess:
 - Dizziness ~ 15%
 - Sedation/somnolence ~ 15%
 - Nystagmus ~ 8% (involuntary movements of the eyeballs)
 - Ataxia ~ 3% (lack of coordination of muscle movements)

Patient incentives

- 6 wk visit - \$50

Data and Safety Management

Study data will be entered into and stored in a secure REDCap database hosted by UNC-CH.

Adverse events will be monitored and assessed using the NIH Common Terminology of Criteria for Adverse Events version 4.0 (CTCAE) criteria, which grades each adverse events from Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), Grade 5 (death related to AE). (15)

- The PI will be responsible for assessing each AE in terms of whether the AE is expected and/or attributable to the study drug along with the severity of the AE using the CTCAE ratings

- Serious AEs will be reported to the IRB per IRB UPIRSO guidelines
- Specific AEs to assess:
 - Dizziness ~ 15%
 - Sedation/somnolence ~ 15%
 - Nystagmus ~ 8% (involuntary movements of the eyeballs)
 - Ataxia ~ 3% (lack of coordination of muscle movements)

For example, dizziness is rated/described below in the NCI CTCAE(10) Table.

| Nervous system disorders | | | | | |
|--|--|---|--|---|---|
| Adverse Event | Grade | | | | |
| | 1 | 2 | 3 | 4 | 5 |
| Dizziness | Mild unsteadiness or sensation of movement | Moderate unsteadiness or sensation of movement; limiting instrumental ADL | Severe unsteadiness or sensation of movement; limiting self care ADL | - | - |
| Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking. | | | | | |

Schedule of Assessments (see Table 1.)

Baseline visit:

Interested patients will be consented and if eligible, baselined at their surgical consult visit or before their pre-op appointment. Participants who have absolute or relative contraindications to gabapentin will be excluded from participation in the study through inclusion/exclusion criteria. This visit may occur up to 3 months before their surgery. Participants will be screened for cognitive impairment by the Mini-Cognitive Assessment, and those who score 2 or less will be considered screen failures. Participants will also complete a standardized and validated symptom bother (PFIQ-sf7) and QoL questionnaires (PFDI-sf20), as well as the standardized and validated PROMIS pain interference, pain intensity, and global mental and physical health questionnaires.

Source data collected as part of routine clinical care may be used to complete CRFs as long as the window between prior data collection and the baseline visit does not exceed 18 months. This includes previously performed POP-Q exams as well as previously collected questionnaires.

- Informed consent
- Inclusion/Exclusion Form
- Baseline form (Demographics, Medical & Surgical History, pain/analgesic med use, POP-Q exam record)
- Mini-Cognitive Assessment
- PFIQ-sf7, PFDI-sf20, PROMIS questionnaires

Randomization:

The randomization table will be given to IDS who will implement randomization for the study and provide the study drug that will be given to patients before their surgery. Randomization will be done by site – Hillsborough and Rex, in a 1:1 ratio and in blocks of 4.

Surgery:

Surgical data will be collected on a Surgical Procedures Form and include items listed below.

- American Society of Anesthesiologists (ASA) grade
- Concomitant procedures performed
- Estimated blood loss (EBL)
- Intraoperative complications
- Voiding trial results

Follow-Up Procedures:

- Daily for 2 weeks after discharge: Patients will complete a Study Drug-Pain Med Count Form and Surgical Pain Scale ratings every day for the first 2 weeks after discharge.
- 2-3 days after discharge: We will call patients 2-3 days after discharge to assess for any AEs and remind pts to dose escalate. We will use the NIH Common Terminology of Criteria for Adverse Events version 4.0 (CTCAE) to determine AE severity/grade.
- Week 1 and Week 2 calls: At Week 1 and Week 2 we will call patients to administer the PROMIS questionnaires. We will also remind patients to complete the Study Drug-Pain Med Count Form and Surgical Pain Scale, and will review any potential AEs.
- Week 3, 4, 5: Patients will complete the PROMIS questionnaires, as well as a Pain Med Count Form and Surgical Pain Scale at the end of week 3, 4, and 5 post-operatively.

Week 6 Visit:

Patients will return to clinic for a postoperative visit around week 6, in which all of the assessments listed in the table below will be performed. Patients will again complete the symptom bother (PFIQ-sf7) and QoL questionnaires (PFDI-sf20), as well as the PROMIS pain interference, pain intensity, and global mental and physical health questionnaires. In addition, we will assess for any AEs or post-operative complications that may have occurred since discharge, as well as current pain/analgesic med use.

- Week 6 form (pain/analgesic med use, post-op complications)
- PFIQ-SF7, PFDI-SF20, PROMIS questionnaires
- Surgical Pain Scale

Table 1. Schedule of Assessments

| Schedule of Assessments | # ?s | Baseline | 2-3 day post-op call | Daily for 2 wks post-op (completed at home) | Wk 1 call | Wk 2 call | Every wk Wk 3-5 (completed at home) | 6 Wk visit |
|--|------|----------|----------------------|---|-----------|-----------|-------------------------------------|------------|
| PFDI-20 | 20 | X | | | | | | X |
| PFIQ-7 | 7 | X | | | | | | X |
| PROMIS pain interference/intensity | 7 | X | | | X | X | X | X |
| PROMIS depression/anxiety short forms | 8 | X | | | | | | X |
| PROMIS global mental/physical health | 4 | X | | | X | X | X | X |
| Medical/Surgical history | | X | | | | | | |
| Pain medications assessment | | X | | | | | X | X |
| Study Drug-Pain Med Count Form | | | | X | X | X | | |
| Surgical pain scale (SPS) + gluteal pain | 6 | | | X | X | X | X | X |
| Adverse events assessment | | | X | | X | X | | X |
| Total # of questions at each visit | | 46 | | 6 | 18 | 18 | 18 | 52 |

Outcome measures

Primary Outcome

Overall post-operative pain will be measured by item 2 of the surgical pain scale (SPS) on post-op day 7. This item measures the average pain felt during normal activity in the last 24 hours on a scale of 1-10.

(SPS validated by OPTIMAL study and in older women; OPTIMAL was a multicenter NIH sponsored Pelvic Floor Disorders Network study comparing SSLF to uterosacral ligament suspension surgery for POP).(11, 12)

Secondary outcomes:

1. Gluteal pain on post-op day 7 will be measured by a numeric rating scale like that used in the SPS (0-10)
2. Other pain scale items such as SPS pain at rest, pain w/normal activity (primary outcome), unpleasantness of worst pain sensation, gluteal pain at rest and gluteal pain w/normal activity on POD#7
3. Daily Narcotic pain medication use for 2 weeks post-op and then through week 6 post-op

DATA ANALYSIS

Sample size

OPTIMAL study found that SPS score for pain with normal activity

- Wk 2 = mean 2.9 (2.6 SD) median 2 (1-4 IQR) range: 0-10
- Pain is likely to be higher at Wk 1
- 17 per group to detect 2.5 difference in SPS, SD 2.6 with alpha 5%, power 80%
- **If 20% drop out, need 19 per group so 38 total at min**

Statistical Analysis Plan

- Bivariate analyses to compare our two cohorts: Student's t-test, chi-square/Fisher's exact and Mann-Whitney U for continuous variables, categorical variables and ordinal/skewed data respectively.

Primary outcome

- We will compare pain with normal activity scores on POD#7 using Student's t-test or Mann-Whitney U as appropriate

Secondary outcomes

- We will use Student's t-test or Mann-Whitney U as appropriate to compare gluteal pain scores on POD#7
- We will compare total narcotic use in average morphine milliequivalents per day during the first two weeks using Student's t-test or Mann-Whitney U as appropriate
 - Convert different narcotics into morphine equivalents and add up total narcotic use as needed
 - Compare with t-test if parametric vs Mann-Whitney U if nonparametric
 - Perform a linear regression analysis and adjust for baseline pain medication usage in order to account for the fact that baseline pain medication usage may impact postoperative narcotic use. We can also adjust for postoperative non-narcotic pain medication.

References

1. Hendrix SL, Clark A, Nygaard I, Aragaki A, Barnabei V, McTiernan A. Pelvic organ prolapse in the Women's Health Initiative: gravity and gravidity. *Am J Obstet Gynecol*. 2002;186(6):1160-6.
2. Wu JM, Matthews CA, Conover MM, Pate V, Jonsson Funk M. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. *Obstet Gynecol*. 2014;123(6):1201-6.
3. Florian-Rodriguez ME, Hare A, Chin K, Phelan JN, Ripperda CM, Corton MM. Inferior gluteal and other nerves associated with sacrospinous ligament: a cadaver study. *Am J Obstet Gynecol*. 2016;215(5):646 e1- e6.
4. Barber MD, Kenton K, Janz NK, Hsu Y, Dyer KY, Greer WJ, et al. Validation of the activities assessment scale in women undergoing pelvic reconstructive surgery. *Female Pelvic Med Reconstr Surg*. 2012;18(4):205-10.
5. Tiippuna EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. *Anesth Analg*. 2007;104(6):1545-56, table of contents.
6. Bates C, Laciak R, Southwick A, Bishoff J. Overprescription of postoperative narcotics: a look at postoperative pain medication delivery, consumption and disposal in urological practice. *J Urol*. 2011;185(2):551-5.
7. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. *BMJ*. 2014;348:g1251.
8. Kharasch ED, Brunt LM. Perioperative Opioids and Public Health. *Anesthesiology*. 2016;124(4):960-5.
9. Waljee JF, Li L, Brummett CM, Englesbe MJ. Iatrogenic Opioid Dependence in the United States: Are Surgeons the Gatekeepers? *Ann Surg*. 2016.
10. NIH. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.
11. Barber MD, Brubaker L, Burgio KL, Richter HE, Nygaard I, Weidner AC, et al. Comparison of 2 transvaginal surgical approaches and perioperative behavioral therapy for apical vaginal prolapse: the OPTIMAL randomized trial. *JAMA*. 2014;311(10):1023-34.
12. Barber MD, Janz N, Kenton K, Hsu Y, Greer WJ, Dyer K, et al. Validation of the surgical pain scales in women undergoing pelvic reconstructive surgery. *Female Pelvic Med Reconstr Surg*. 2012;18(4):198-204.