Postoperative Tizanidine Use in Pelvic Reconstructive Surgery

Background/Literature Review

An estimated 200,000 surgeries addressing pelvic organ prolapse are performed annually.[1] Understanding and improving the patient experience as it pertains to the postoperative period allows clinicians and hospitals to reduce re-admission, improve patient satisfaction, and optimize patient care. An Enhanced Recovery After Surgery Program (ERAS) pathway has been implemented in gynecologic surgeries and has been shown to decrease length of hospital stays, postoperative pain, need for analgesia, complications, re-admissions, and time to bowel function.[2] Concomitantly, ERAS has been associated with an increase in patient satisfaction.[2] There are variations in ERAS protocols that have been described and include pre-, intra-, and post-surgical pain management, with an emphasis on multimodal regimens and a goal to minimize opioid administration.[2] Opioids can aid in acute pain control postoperatively but have disadvantages in long-term recovery due to their gastrointestinal, sedative, and dependence side effects. The older population that makes up the majority of Urogynecology patients may be more susceptible to these side effects due to co-morbidities, age, and metabolism. Gabapentin is often prescribed pre- and postoperatively to mitigate pain; however, many elderly patients cannot tolerate gabapentin due its effect on the central nervous system and significantly increasing the risk of falls.

Postoperative pain after Urogynecologic surgery is multifactorial. Due to the variety of surgical modalities -- abdominal/open, laparoscopic, and vaginal -- pain can be attributed to the incisions, viscera, and pelvic floor muscles. Additionally, postoperative constipation and urinary retention requiring a Foley catheter can contribute to the postsurgical pain, that may not be mitigated by standard non-opioid or opioid analgesics. Pelvic reconstructive surgery is trauma to the pelvic floor musculature, and some of the pain is thought to be attributed to the pelvic floor spasm or dysfunction post-surgery. Pelvic floor muscle spasm can lead to dysfunctional voiding, which can manifest as urinary retention, incomplete emptying, or urinary urgency. In addition, constipation also often results when pelvic floor muscles are unable to adequately relax. To ameliorate the pain and associated voiding and bowel dysfunction, surgeons often prescribe skeletal muscle relaxants; however, these medications are not routinely included in the ERAS protocol.

Tizanidine is a skeletal muscle relaxant that acts centrally as an alpha-2 adrenergic agonist. The United States Food and Drug Administration (FDA) has approved tizanidine as an anti-spastic agent; however, off-label use includes musculoskeletal and neuropathic analgesia, enhancement of analgesia and anti-inflammatory NSAID properties, and improved gastric tolerability of NSAIDs.[3-5] As a smooth muscle relaxant, tizanidine has the unique ability to address pelvic floor muscle spasm and its contribution to postoperative pain. Compared to other skeletal muscle relaxants, tizanidine has fewer adverse events in older patients such as delirium, falls, and opioid overdose, and lower risk for dependence.[4]

One randomized control trial found favorable results of tizanidine’s effect on postoperative pain scores, analgesic consumption, return to daily activity, and quality of life for inguinal hernia repair patients. General surgery literature often is adapted for gynecology and this prior study sets a precedent for tizanidine use.[6] Despite the promising rationale for tizanidine as an adjunct, no previous studies have examined its role in postoperative recovery and pain control for gynecologic patients. This gap in literature makes adoption of tizanidine into postoperative pain regimens difficult, as no guidelines yet define its efficacy, safety, and dosing in the elderly gynecologic population.

Patient satisfaction outcomes are highly emphasized in modern healthcare in terms of clinical success, healthcare economics, and quality of care metrics. Pain is often a cornerstone of postoperative recovery and thus satisfaction. Satisfaction inherently has subjectivity as patients have varying expectations, non-clinical factors including psychosocial influences, and has the potential for recall bias. Thus, healthcare utilization allows for a more objective measure of pain, satisfaction, and morbidity. The number of interactions between a patient and the healthcare system can capture clinical and system-level sequelae. Patient experience and post-op recovery can always be improved; therefore, evaluating the

effectiveness of postoperative tizanidine as an adjunct to existing post-op pain regimens may have clinical significance and practice changing.

Study Design

The study will be conducted as a prospective, longitudinal, non-blinded, two-arm randomized controlled trial in which the postoperative experience and pain control of patients utilizing tizanidine will be compared to those who are not taking tizanidine.

Hypotheses

H_O: There is no significant difference in patient reported outcome (PRO) assessed at 4-6 weeks post-operatively between patients receiving tizanidine as part of their postoperative outpatient pain regimen compared to control.

H_A: There is a significant difference in patient reported outcome (PRO) assessed at 4-6 weeks post-operatively between patients receiving tizanidine as part of their postoperative outpatient pain regimen compared to control. Specifically, we anticipate the treatment group will have better outcomes.

Human Subjects

Inclusion criteria

- female
- age ≥18 and ≤89 years old
- any race/ethnicity
- English and/or Spanish fluency
- undergoing apical suspension:
  - sacrocolpopexy (laparoscopic or robotic)
  - uterosacral ligament suspension (vaginal, laparoscopic, or robotic)
  - sacrospinous ligament fixation
  - iliococcygeus suspension
- surgery being performed at Hartford Hospital

Exclusion criteria

- male
- age <18 or ≥90 years old
- pregnant
- breastfeeding
- documented diagnosis of hypotension in EMR problem list, BP in office or at pre-op PAC (confirmed on repeat) to be systolic <100 mm Hg and/or diastolic <70 mm Hg
- known intolerance or sensitivity to tizanidine
- current use of:
  - CYP1A2 inhibitor:
    - Allopurinol
    - Amiodarone
    - Cimetidine
    - Ciprofloxacin
    - Duloxetine
    - Erythromycin
    - Fluoroquinolones
    - Ketoconazole
    - Verapamil
    - Oral contraceptive pill (inhibitors can increase tizanidine plasma concentration and lead to more pronounced side effects due to tizanidine being a CYP1A2 metabolizer)

  - clonidine (alpha-2 agonist) antihypertensive
  - opioid
  - muscle relaxant
- pre-existing
  - hepatic impairment as defined as transaminitis with ALT or AST >2x upper limit of normal
  - diagnoses of cirrhosis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD)
  - renal impairment as defined by creatinine clearance <25 mL/min
- obstructive sleep apnea
- non-English or non-Spanish speaking
- past opioid dependence
- concurrent diagnosis of malignancy
- concurrent surgery apart from pelvic reconstructive surgery with another specialty
- unable/unwilling to consent to participate

Post-enrollment exclusion criteria

- experiences any of these adverse events after initiating tizanidine and does not improve when Dose Adjustment and Management Algorithm (see below) is followed:
  - bradycardia
  - orthostatic hypotension
  - dizziness
  - intolerable vivid dreams
  - intolerable dry mouth
  - syncope
- any other adverse event or illness that in the view of the PI would compromise patient health
- requires indwelling ureteral stent and/or beyond the short term catheterization following of the failure of the initial voiding trial or planned catheterization

Procedures

Recruitment/consenting

Potential participants will be approached after being established in the Hartford Healthcare Urogynecology clinic, diagnosed with pelvic organ prolapse and/or incontinence, decided to proceed with surgical management and met inclusion criteria.

Interest in participating in the study will be assessed during a pre-operative visit when surgical consent is signed. If a patient consents to participate, research personnel will further discuss the study, answer questions, and review and obtain informed consent and a quick survey detailing some demographic information.. If unable to consent in person, this consent process will occur over the phone and the patient will sign an electronic consent in REDCap. If a patient desires to think about it, she will be given the opportunity and the authorized research personnel will contact her later to answer any questions and complete the consent in REDCap.

Randomization

A randomization scheme will be created in Excel and provided to authorized research personnel who will be participating in the consent process. A computer-generated simple randomization scheme in a 1:1 ratio will be used (included with study application).

Study Arms

Control/standard-of-care arm

Participants will follow standard-of-care -- the current standard ERAS protocol including preoperative medication management with Tylenol and Celebrex (unless contraindicated) and postoperative outpatient pain regimen of scheduled Tylenol, Motrin, and as-needed standard amounts of opioid medication (*e.g.*, oxycodone). A placebo will not be used in this study.

Intervention/treatment arm

Participants will follow standard-of-care -- the current standard ERAS protocol above -- and will be given tizanidine 4 mg scheduled three times a day (12 mg/day) for two weeks postoperatively. The cost of the tizanidine will be paid by departmental funds.

The week prior to scheduled surgery, participants randomized to the intervention arm will be compiled in to a list and securely given to the research assistant who will be present on day of surgery. The research pharmacy will also be notified of participants in the intervention arm’s intended surgery date so that tizanidine will be ready morning of. The day of surgery, a research assistant will go to HH research pharmacy to procure tizanidine for patients randomized to intervention arm. Tizanidine will be given to patient prior to discharge, ideally in pre-op so that it will be safe with their belongings. After patient is discharged, they are to pick up the remainder of their medications sent to their preferred pharmacy that are part of standard of care.

Data Collection

According to the following timeline, demographic, medical, and surgical information will be collected at baseline. Surveys (defined in *Data Collection, Use*) will be administered electronically at four time points:

Pre-operative

- BPI-SF (establish pain baseline)
- demographic and medical/surgical information collected from Epic
- constipation scoring system (CSS)

Post-operative day (POD) #1-2

- BPI-SF (acute pain assessment)

2 weeks post-operative

- BPI-SF
- AAS (functional recovery assessment)
- CSS
- PRO
- remaining opioid pill count

4-6 weeks post-operative

- AAS
- GSR
- PRO
- healthcare utilization information collected via EMR

The physician prescribing the post-op pain medications, including tizanidine if the participant is randomized to that group, will be notified of the participant’s enrollment to allow for correct medication prescription on day of surgery. If surveys are not completed, authorized research personnel will reach out to participants to remind them to complete surveys, up to three times. If participants are unable to complete the survey electronically, a research staff member -- not involved in data entry or analysis and blinded to study arm -- will administer survey questions via telephone.

Participants will be reminded up to three times to complete surveys. For those who drop out or are withdrawn due to non-compliance with surveys or adverse events, the reason for why the participant did not complete the study will be noted.

Participant remuneration

The maximum remuneration is $40 per participant. Each participant will receive a $20 gift card after completing the first survey at POD#1-2 and a second gift card of equal value at 4-6 weeks postoperatively.

Data Collection, Use

Data will be collected from Epic and prospectively from surveys. All data will be entered into an HH-based REDCap database.

- Demographic information
  - age at time of surgery
  - BMI
  - race/ethnicity
  - parity
  - marital status
  - education level
  - employment
  - preferred language
  - mailing address for gift cards
  - phone number
  - email
- Medical history
  - medical comorbidities
  - smoking – present/past
  - cardiovascular disease
  - chronic obstructive pulmonary disease/lung disease
  - diabetes mellitus
  - hypertension
  - menopausal status
  - history of opioid abuse (as confirmation of exclusion)
  - present opioid use by prescription or recreation (as confirmation of exclusion)
  - present skeletal muscle relaxant use
  - American Society of Anesthesiologists (ASA) Physical Status Classification
  - allergies to skeletal muscle relaxants, alpha-2 agonists, NSAIDs, acetaminophen, oxycodone
- Surgical information
  - date of surgery
  - surgery performed
  - length of procedure (incision time to closing time)
  - estimated blood loss (EBL)
  - intraoperative complications
  - postoperative void trial passed/failed
  - type of anesthesia
  - day of discharge
- Healthcare utilization
  - pain

  - constipation
  - nausea/vomiting
  - UTI symptoms
  - medication questions
  - bleeding
  - readmission
  - ED visits
  - telephone encounters
  - patient portal messages
  - clinic visits
  - additional pain meds prescribed (including refills)
- Information collected from surveys
  - Brief Pain Inventory-Short Form (BPI-SF)[7]: The BPI-SF is a validated questionnaire with nine questions that evaluate pain severity as well as interference in one’s life.
  - Constipation Scoring System (CSS)[8]: The CSS is a validated questionnaire with eight questions to evaluate severity of constipation.
  - Activity Assessment Scale (AAS)[9]: The AAS is a validated questionnaire in urogynecology literature with thirteen questions that is a functional activity assessment.
  - Global Surgical Recovery (GSR)[10]: The GSR is a validated single question index that identifies a patient’s overall perception of recovery.
  - Patient Reported Outcome (PRO)[11,12]: The PRO is a single question survey "To what extent do you feel physically recovered after surgery" that identifies a patient’s perceived post-operative recovery with recent publication of content validity in urogynecology research.

Research-related Risks to/Benefits for Participants

Potential risks and mitigation strategy/ies

Tizanidine is often prescribed post-operatively to patients within our practice based on clinician judgment. The potential non-medication-related risks of this study are time and inconvenience needed to complete surveys and breach of confidentiality (inherent with all research studies). A thorough consent process that outlines the time commitment to patients will be used to mitigate this risk.

Medication-related risks, which are potential research-related risks but exist for anyone who is initiated on tizanidine post-operatively, are:

<u>Common (>10%)</u>
drowsiness/somnolence
dry mouth
dizziness
fatigue
hypotension

<u>Uncommon (1-10%)</u>
increased muscle spasm or tone
bradycardia
syncope

<u>Rare (≤1%)</u>
liver damage
hallucinations
severe allergic reactions

Potential benefits

There may be no direct benefit for participants. However, potential benefits are improvement in pain and recovery postoperatively (for those randomized to the treatment arm) as well as the altruistic

benefit of contributing to scientific/medical research. For future patients, this study allows for investigation of post-operative pain regimen that may be implemented if efficacious. If the study is successful, findings also may help to decrease opioid use for participants and future patients and mitigate the multitude of risks involved with opioids such as dependence, constipation, and sedation.

Safety

Safety Monitoring Plan

To avoid or decrease the chance of medication side effects, multiple check points will be made during each survey. Additionally, phone calls will be made by a registered nurse (RN) soon after initiation of medication, as described below, to monitor side effects and help determine if medication should, or must, be discontinued.

Adverse events/side effects

Adverse events (AE) will be actively monitored using a structured and scheduled approach:

- Initial RN check-in: An RN will contact participants within 24–72 hours after initiation of tizanidine to assess for early side effects and tolerability. A RN will also call participants in control group to assess symptoms so that these symptoms can be compared to intervention group as baseline early post-operative state.
- Survey-Based Monitoring: Participants will be systematically queried about medication-related side effects at predefined study timepoints:
  - Post-operative day 1–2
  - Post-operative day 14 (2 weeks)
- Ongoing Monitoring: Participants also will have the opportunity to report symptoms during any clinical interactions (*e.g.*, phone calls, patient portal messages, or clinic visits).

All AEs will be documented and reviewed by the study team. Appropriate reporting to the Hartford HealthCare Institutional Review Board (IRB) will occur in accordance with institutional policies.

Dose Adjustment and Management Algorithm

Given the concurrent use of opioids and the potential for overlapping side effects (*e.g.*, dizziness, sedation), a stepwise management strategy will be used:

1. Initial symptom: opioid (oxycodone) dose will be reduced or discontinued as clinically appropriate.
2. Persistent symptoms after opioid adjustment: Tizanidine dose will be reduced from three times daily to twice daily.
3. Persistent symptoms after dose reduction:
   - Participants will be evaluated in clinic for vital signs and clinical assessment.
   - Tizanidine will be further reduced to once daily dosing.
4. Ongoing or intolerable symptoms:
   - Tizanidine will be discontinued.

Participants experiencing concerning adverse effects (*e.g.*, syncope, significant hypotension, bradycardia) will be instructed to seek immediate medical evaluation and the study team will be notified promptly.

Interim Safety Review

All reported adverse events will be evaluated at each of the three post-operative time points, to assess frequency, severity, and relatedness to the study intervention. An interim safety analysis will be conducted after approximately 50% of participants have been enrolled. The study team will determine whether it remains safe to continue the protocol as designed or if modifications are required.

Data Storage/Security

All HHC data will be stored in a secure password protected HH-based REDCap file and downloaded to an SPSS data file for statistical analysis. That file will be maintained in a secure HHC OneDrive folder. Only investigators named on the study application will have access to the data. Results will be disseminated in aggregate to avoid potential disclosure of protected health information (PHI). Data will be maintained as described above for six years.

Power Analysis/Sample Size Estimate

The study plans to enroll for as long as 20 months. With a current patient census of 9-10/month, an anticipated participation rate of 60%, and an attrition rate of 10% (distributed evenly between groups), we will recruit 112 patients to achieve 100 participants who complete the study with 50 per group.

The study will be powered to compare the difference between groups in the percentage who reported at least 20% recovery (*i.e.*, an improvement of at least one quintile on the PRO). Hypothesizing that the control group will have 40% who report at least 20% improvement, the study would have 80% power to detect a 28 percentage-point difference (increase) in the percentage of the experimental/ treatment group (68%, or $^{5}/_{8}$ of the sample) who experience a similar improvement using an alpha level of 0.05.

Data/Statistical Analyses

Outcomes

Primary:

Patient-reported outcome (PRO) assessed at 4-6 weeks post-operatively

Secondary:

- composite outcome assessed at 4-6 weeks post-operatively and includes pain and recovery according to objective and subjective criteria:
  - objective criteria -- MME used
  - subjective criteria -- validated surveys (AAS, GSR, PRO, BPI-SF)
- measures of healthcare utilization (within 6 weeks postoperatively)
  - readmission
  - ED visits
  - telephone visits
  - patient portal messages
  - additional pain meds prescribed (including refills) within 6 weeks postoperatively
- constipation (measured with CSS)

Statistics

Descriptive statistics will be presented for each group to summarize participants' demographic and clinical characteristics. Continuous variables will be evaluated for normality of distribution. Normally distributed variables (*e.g.*, age, BMI) will be presented as a mean ± standard deviation; non-normally distributed variables (*e.g.*, length of procedure, EBL) will be presented as a median with interquartile range (IQR). Categorical variables will be reported as frequencies using percentages.

Inferential statistics will be used to compare outcomes and baseline characteristics for each group. Intent-to-treat (ITT), per protocol (PP) and safety analyses will be conducted. An interim safety analysis will occur when half the intended participants have been enrolled, but no adjustment(s) for multiplicity will be made because the same participants may experience multiple AEs that vary over time.

Univariate statistics will be used to evaluate group differences, if any, at baseline, and at any additional time points in which an initial/index assessment is conducted. Continuous variables will be compared using a Student's t test for normally distributed data or a Mann-Whitney U test for non-normally distributed data. Categorical variables will be compared using a Pearson chi-square test; complications will be categorized into minor, moderate, and severe.

Longitudinal evaluations will be conducted with either a repeated-measures analysis of variance (rmANOVA), an analysis of covariance (ANCOVA), a generalized linear model (GLM), or a linear mixed-effects model (LME), depending on distribution and completeness of data/variables. Differences between groups will be reported with p values, tabular statistics [*e.g.*, F or eta squared (η^2)], and 95% confidence intervals.

All analyses will be conducted with SPSS v. 29 (IBM; Armonk, NY 2022), using an *a priori* alpha level of 0.05 such that all results of $p<0.05$ will be deemed statistically significant.

Benefit/Significance for HHC and Its Patients

This study will provide valuable insights into the postoperative implication of tizanidine for pelvic reconstructive surgery. Outcome measures will have implications clinically as well as for healthcare economics. There currently exists no published research addressing tizanidine use postoperatively in gynecologic surgery. This study has the potential to create interventions that can be used within our own hospital and nationally.

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