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Brief Title: IV Acetaminophen for Postoperative Pain After Pelvic Organ Prolapse Repair

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BACKGROUND

POP is common with approximately 200,000 inpatient surgical procedures performed each year to treat this condition.[1] Older women tend to seek care more often than their younger counterparts, and it is estimated that women 70-79 generate 10 times more consults per 1000 woman years compared to younger women. [2] This is particularly relevant since the world population is rapidly aging, with 27% of the population estimated to be >60 years of age, with women representing 55% of the population by the year 2050.[3] With such a significant number of elderly women projected to undergo surgical repair of POP, it is of particular importance to safely and effectively treat postoperative pain.

Preemptive analgesia involves introduction of pain medication regimens prior to a noxious stimulus, such as a surgical incision, in order to prevent amplification of pain by the nervous system.[4] Although NSAIDs would be ideal for this indication due to their reduction in pain and inflammation, they are not routinely used preoperatively in elderly patients because of interference with platelet and kidney function.[5] Opioids are the standard of care for *postoperative* pain management in most practices; however, these narcotics pose a risk of constipation, nausea, urinary retention, sedation and mild cognitive impairment that can be especially problematic in an elderly population.[6] Additionally, these side effects may lead to longer hospital stays and reduced patient satisfaction. There is no current standard of care for *preemptive* analgesia in POP surgery.

IV acetaminophen, approved for use in the United States in 2010,[7] has demonstrated safe and effective *postoperative* analgesia across a wide variety of surgical procedures including gynecology, general surgery, orthopedics and ophthalmology.[8,9] However, it has not been well studied as *preemptive* analgesia and has demonstrated conflicting results about its efficacy for this indication. In two double-blind randomized placebo controlled studies of women undergoing abdominal hysterectomy, one study demonstrated significantly lower postoperative pain with preemptive IV acetaminophen compared to placebo,[10] while the other study demonstrated similar pain scores.[11] Interestingly, both of these studies reported significantly lower postoperative opioid narcotic consumption in the IV acetaminophen group compared to placebo.[10,11] Ultimately, the efficacy of *preemptive* IV acetaminophen has yet to be established, especially in an elderly population of women who may benefit immensely from a reduction in postoperative narcotics. Therefore, the overall goal of this study is to quantify the change in postoperative pain scores and narcotic requirements in women receiving preemptive analgesia with IV acetaminophen prior to POP repair. The central hypothesis is that women receiving preemptive IV acetaminophen prior to surgical correction of POP will have improved postoperative pain scores and reduced narcotic requirements. To test this hypothesis, we propose a double-blind randomized controlled trial of IV acetaminophen compared to placebo with the following aims:

Aim 1: Quantify the impact of IV acetaminophen on 1a) postoperative pain scores and 1b) analgesic requirements. 1a) To achieve this aim, we will measure the degree of postoperative pain using visual analog scales (VAS) at specified time points throughout the postoperative period, and compare results between IV acetaminophen and placebo groups. **1b)** We will use equianalgesic dosage tables to convert intra- and postoperative narcotics into morphine equivalents to compare narcotic requirements for the first week after surgery. We hypothesize that those patients receiving preemptive IV acetaminophen will have lower postoperative VAS scores and reduced narcotic requirements compared to placebo.

Aim 2: Determine the effect of IV acetaminophen on patient satisfaction, mood, and interference with activities. To determine the impact of pain control on patient centered outcomes such as satisfaction, mood, and mobility, subjects will be asked to complete the American Pain Society Patient Outcome Questionnaire (APS-POQ-R) on postoperative day (POD) #1. Interference of pain with physical, mental and social activities will be measured by the Patient Reported Outcomes Measures Information Systems-Pain Interference–Short Form 8a (PROMIS PI-SF-8a) completed on POD#7. We hypothesize that women receiving preemptive IV acetaminophen will have improved patient satisfaction, mood, and quicker return to activities as evidenced by lower APS-POQ-R and PROMIS PI-SF-8a scores compared to placebo.

Aim 3: Compare side effects of IV acetaminophen and placebo. We will assess postoperative nausea, pruritus, dizziness and drowsiness using the APS-POQ-R questionnaire. We will assess constipation and time to first bowel movement with postoperative bowel diaries. We hypothesize that all of these side effects will be reduced or eliminated in those patients receiving preemptive IV acetaminophen compared to placebo due to a reduction in opiate requirements.

RESEARCH STRATEGY

Significance

This research is significant since preemptive IV acetaminophen may demonstrate improved postoperative pain and quality of life (QOL) in patients undergoing POP surgery compared placebo. If efficacy is demonstrated in women undergoing repair of POP, this will lead to improved implementation of IV acetaminophen as preemptive analgesia in this population of elderly women who are particularly susceptible to the side effects of narcotic pain medications. Additionally, if preemptive analgesia with IV acetaminophen is effective in reducing postoperative narcotic use, this may lead to a reduction in side effects commonly seen with narcotics including nausea, pruritus, cognitive impairment, and constipation. Reducing these side effects may lead to increased patient satisfaction, faster postoperative recovery and expedited hospital discharge.

Innovation

Although IV acetaminophen has shown efficacy as postoperative analgesia, studies on its use as preemptive analgesia are lacking. Previous studies of preemptive analgesia with IV acetaminophen in Turkish and South Korean women undergoing total abdominal hysterectomy have been of low methodological quality and have shown conflicting results in reduction of postoperative VAS pain scores.[10-11] Furthermore, this study aims to include patient centered outcomes such as patient satisfaction, mood and interference with activities, which have been lacking in prior studies of preemptive IV acetaminophen. If found to be effective in reducing postoperative pain and improving patients satisfaction, preemptive IV acetaminophen may become part of routine preoperative care for patients undergoing POP surgery.

APPROACH

Overview: This randomized double-blind placebo controlled multi-center trial will determine the efficacy of preemptive IV acetaminophen in reducing postoperative pain scores and narcotic requirements in women undergoing surgical repair of POP.

Setting: This study will be conducted at Magee Womens Hospital (MWH) of the University of Pittsburgh Medical Center (UPMC), UPMC Passavant, Hamot Hospital of UPMC, West Penn Hospital of the Allegheny Health Network (AHN), and Jefferson Hospital of the AHN. Subjects will be recruited from multiple clinic sites throughout the UPMC and AHN networks. These are high-volume referral center where women with POP are treated with surgical and non-surgical options..

Recruitment: Women will be recruited from the hospital based clinics and satellite sites of UPMC Magee, UPMC Hamot, UPMC Passavant, Jefferson Hospital and West Penn Hospital. All potential participants for this study will be identified through standard clinical visits (either at initial consultation, follow-up, or preoperative appointment). As is our current standard of care, all new patients undergo a comprehensive history and physical exam. If a woman has prolapse and is considering surgical repair, she may be eligible for the study. The study will be introduced by the patient's physician. If the patient would like to discuss the study further, she will be approached by a member of the study team to be screened. If she meets inclusion/exclusion criteria, she will be offered participation and informed consent will be obtained.

Study eligibility

Inclusion Criteria: Women ≥ 18 years of age scheduled to undergo surgery for POP via a vaginal or minimally invasive (laparoscopic/robotic) route and anticipated to have a hospital stay ≥24 hours will be eligible. Subjects must be able to speak and read English.

Exclusion Criteria: Women with (1) an allergy/intolerance to acetaminophen, (2) hepatic dysfunction, or (3) significant alcohol use – defined as patient reported consumption of more than 7 standard drinks per week and/or 3 drinks per day, will be excluded.

Data collection

Baseline assessment: (Table 1).The baseline visit will occur on the same day of enrollment. If the patient meets inclusion/exclusion criteria and consents to enrollment, baseline information will be obtained including age, race/ethnicity, general medical history, parity, tobacco use, prior hormone replacement therapy use, and baseline VAS pain score. Objective measurements including height, weight, BMI, and prolapse stage will be collected from the electronic medical record (EMR). Intraoperative data from the EMR will include surgical route (vaginal vs laparoscopic/robotic), concomitant procedures, estimated blood loss, and operative time.

Table 1. Timeline of data collection

Data	Time of Data Collection/Evaluations									
	Baseline	Intervention	Surgery	Postoperative assessment						7-day follow-up
				4h	8h	12h	16h	20h	24h	
VAS pain score	x			x	x	x	x	x	x	
Narcotic requirements	x		x	x	x	x	x	x	x	x
Patient satisfaction and mood (APS-POQ-R)									x	
Interference with activities (PROMIS PI-SF-8a)										x
Demographic factors	x									
Intraoperative factors			x							
Side effects (APS-POQ-R)									x	
Bowel movements										x
Adverse events		x	x						x	x

Intervention: Study drug and placebo will be prepared by the operating room pharmacist and placed in identical appearing 250cc glass bottles. Each bottle will contain either acetaminophen 100 mL or sodium chloride 0.9% 100 mL. Preoperative nurses will administer the study medication (either 100 cc of acetaminophen (1000mg/100mL) or 100 cc of normal saline) intravenously 10-30 minutes prior to anesthesia induction in the preoperative area on the day of surgery. The administered medication will be recorded in the EMR as "investigational drug" so that blinding will be maintained. Participants will be randomly allocated in a 1:1 ratio using computer-generated fixed blocks of four, stratified by surgical route (vaginal vs laparoscopic/robotic). Allocation concealment will be maintained by the operating room pharmacist who will be in charge of preparing the study drug/placebo. The investigators, surgical team, anesthesia team, and nursing staff will be blinded to the randomization sequence. Patients will be randomized in the preoperative area on the day of surgery to prevent randomization of patients who may go on to cancel or postpone surgery. The UPMC Magee Investigational Drug service will maintain the randomization sequence. Pharmacists at Passavant, Hamot, West Penn and Jefferson will contact the Magee Pharmacy on the day of surgery to obtain the treatment assignment.

Follow-up: Subjects will be followed for a total of 7 days (Table 1). Postoperatively, subjects will be asked to mark their pain on a VAS scale administered every 4 hours for a total of 24 hours. This will be performed by nurses at the time of routine vital sign assessment every 4 hours. Twenty-four hours after surgery, patients will be asked to complete the APS-POQ-R questionnaire. Doses of narcotic and nonnarcotic pain medications will be abstracted from the EMR. After discharge, subjects will be given a 7-day diary on which they will record the time and dosage of all pain medications used (narcotic and non-narcotic) and time and date of all bowel movements. They will be asked to mail this questionnaire back to the office in a self-addressed stamped envelope. Participants will also be asked to complete the PROMIS PI-SF 8a questionnaire on POD#7. Based on participant preference, paper or electronic copies of this questionnaire will be provided. Paper copies will be mailed back with self-addressed stamped envelopes. Electronic access will be granted through the NIH PROMIS Assessment Center via a secure link emailed to participants interested in electronic completion. All patients will be called and reminded to fill out this survey 1 week following surgery. Surgical and post-operative complications will be extracted from the EMR for a period of 7 days post-operatively by research staff. Specifically, readmissions or telephone calls to the office for poor pain control or constipation will be extracted. Of note, the study coordinators at AHN and UPMC will ensure proper data collection and will be in charge of data extraction at their respective sites.

Variables and measures

Postoperative pain

Visual Analog Scale (VAS) pain: The primary outcome for this study is pain at 24 hours postoperatively. Pain will be measured every four hours following surgery (4, 8, 12, 16, 20, and 24 hours) by VAS pain scales. VAS pain scales are unidimensional measures of pain intensity that are easily completed and scored.[12] Subjects place an "X" on a 10 centimeter (cm) VAS line at the point that represents their pain intensity. The score is calculated by measuring the distance in millimeters (mm) along the 10 cm line where 0 represents "no pain"

and 10 represents “worst pain.” Scores range from 0-100mm. They have been widely used in diverse populations to assess pain, and specifically have been used to measure postoperative pain in many prior studies of IV acetaminophen.[8] VAS pain scores will be used as the primary outcome measure in this study because they are easy to complete, which is essential in a predominantly elderly population, and because they are easily compared to prior studies of preemptive IV acetaminophen.

Narcotic requirements
Morphine equivalents: Doses of narcotic pain medications administered to subjects during the intra- and postoperative period will be abstracted from the EMR. Narcotics will be converted to morphine equivalents, in grams, using an equianalgesic dosage table.[13] Narcotic use following hospital discharge will be measured by a 7-day diary, which will also be converted to morphine equivalents. Morphine equivalents have been widely used in the study of postoperative pain and specifically those investigating the efficacy of preemptive and postoperative IV acetaminophen.[8,10,11]

Patient satisfaction and mood
APS-POQ-R: The APS-POQ-R is a validated questionnaire used to assess QOL and satisfaction with pain control over the 24 hours following an operation. It is preferred over more global measures of QOL since it is validated for acute pain in the setting of recent surgery. This questionnaire was designed to assess satisfaction with pain control and impact of pain on mood and emotional well-being. It contains twelve items across six subscales: pain severity and relief, impact of pain on mood/emotions, adverse effects, satisfaction, participation in decision making, and non-pharmacological methods of pain management.[14] We are specifically interested in the impact of pain on satisfaction (item 9), mood/emotions (item 5 a-d) and adverse effects (item 6 a-d, see below). These subscales use a 0-10 rating scale. This measure has good internal consistency (alpha=0.85) and validity.

Pain interference
PROMIS PI-SF-8a: This questionnaire is a short form of the PROMIS PI item bank, designed to assess the interference of pain on an individual’s physical, mental and social activities. It is a patient reported outcomes measure and is validated for both computer and paper administration by the NIH. Specifically, it queries the interference of pain over the last week across 8 items. It has shown excellent reliability (alpha=0.90-0.95) and validity.[15] Based on participant preference, paper or electronic copies of this questionnaire will be provided. Electronic access will be granted through the NIH PROMIS Assessment Center, with questionnaires emailed to participants via a secure link.

Side effects
APS-POQ-R: The APS-POQ-R questionnaire contains four items on the side effects of pain medication including nausea, drowsiness, itchiness and dizziness (Items 6a-d). Respondents use a rating scale 0-10 to indicate the severity of each side effect. Psychometric properties of this questionnaire are discussed above.

Bowel diaries: Because the APS-POQ-R questionnaire does not query constipation, patients will be asked to provide the date/time of all bowel movements during the first postoperative week. Validated measures of constipation are complicated by the fact that most are validated for chronic constipation.[16] Therefore, we chose to survey constipation through the use of a self-reported bowel diary through POD#7.

Data management plan
After informed consent is signed, de-identified demographic and objective data from the baseline visit will be abstracted from the EMR into an excel file which will transferred into a SPSS (Armonk, NY) document for analysis. Data exchange between AHN and UPMC will be done through secure password protected servers. No protected health information will be exchanged between the two sites. The APS-POQ-R questionnaire will be administered on paper. Based on participant preference, paper or electronic copies of the PROMIS PI-SF-8a questionnaire will be provided. Paper copies will be abstracted by members of the study team and electronic copies will be automatically downloaded. All files will be stored on a password protected network drive within the health system firewalls. Security will be maintained by limiting login access to members of the study team. Data security will be monitored at weekly research meetings.

Data analysis

Aim 1: Quantify the impact of IV acetaminophen on 1a) postoperative pain scores and 1b) analgesic requirements. The primary outcome is VAS pain score at 24 hours. VAS scores will be measured on a scale of 0-100mm with higher scores indicating worse pain. Linear mixed models will be used to compare pain scores at baseline, 4, 8, 12, 16, 20 and 24 hours postoperatively between IV acetaminophen and placebo groups. Patient effects will be treated as random with fixed effects for group, time and group*time. Narcotic requirements measured in morphine equivalent grams will be compared by T-tests (and Wilcoxon rank-sum tests if non-parametric). Since route of surgery likely contributes to the amount of postoperative pain, we plan to stratify our analysis by vaginal and laparoscopic/robotic surgery. Both VAS pain scores and narcotic requirements will be compared in an intention to treat analysis. Heterogeneity of treatment effects will be analyzed by racial subgroups and menopausal status. Multivariable logistic regression analysis will be used to identify independent risk factors that predict pain at 24 hours postoperatively. We plan to adjust for operating time, estimated blood loss, and concomitant procedures, as all of these may predict worse postoperative pain. Anything found to be different at baseline will also be included as covariates. Age may affect postoperative pain through alteration of the pain response or differences in pain medication metabolism. For this reason, we plan to explore whether age moderates postoperative VAS scores.

Aim 2: Determine the effect of IV acetaminophen on patient satisfaction, mood, and interference with activities. T-tests (and Wilcoxon rank-sum tests if non-parametric) will be used to analyze results of APS-POQ-R rating scales and PROMIS PI-SF-8a scores. Individual analysis of APS-POQ-R questionnaire items 5 and 9 is planned to determine the impact of IV acetaminophen on mood and satisfaction respectively.

Aim 3: Compare side effects of IV acetaminophen and placebo. The severity of individual side effects (nausea, drowsiness, itchiness, and dizziness), as measured by the APS-POQ-R adverse effects subscale (items 6a-d), will be compared between IV acetaminophen and placebo groups using T-tests (and Wilcoxon rank-sum tests if non-parametric). Linear regression analysis is planned to quantify the effect of narcotics (measured in morphine equivalent grams) on side effect severity. Constipation, measured in time (hours) since surgery to first bowel movement, will be compared between the groups and will be included in the multivariable regression model to determine the effect of narcotics on constipation.

Sample size and power analyses

There is a paucity of information on mean VAS scores on POD#1 following gynecologic surgery. Mean ± standard deviation 24 hour VAS scores following robotic sacral colpopexy have been published (44.0 ± 20.8mm).[18] VAS pain scores at 24 hours following vaginal prolapse repair are also available (19.3±14.8mm).[19] Previous studies of adult emergency department patients demonstrate a minimally clinically significant difference (MCSD) in VAS pain scores of 9mm, 12mm, and 18 mm.[20-22] Unfortunately, MCSD have not been calculated in a gynecologic or urogynecologic surgical population. For this sample size analysis, we have chosen a MCSD in VAS pain score of 12 mm, as this is the median value of previously published values. Since we desired to power this study to detect a difference in VAS pain scores in women undergoing both vaginal and laparoscopic/robotic surgery, we performed separate sample size analyses using the larger of the two standard deviations (20.8mm) from previously published studies of robotic and vaginal surgery.[18,19] Assuming a two-sided alpha of 0.05, 96 women in each group would provide 80% power to detect a clinically significant difference in VAS scores after surgery in those receiving IV acetaminophen compared to placebo. After adjusting for a 5% loss to follow-up rate, we would need to randomize 102 women undergoing laparoscopic/robotic surgery and 102 undergoing vaginal surgery for a total of 204 subjects.

Potential issues and solutions

Patients that do not undergo surgery after enrollment: To prevent non-adherence to the study intervention, we will not randomize subjects until the day of surgery in the preoperative area. Once randomized, all participants will be followed and analyzed in an intention to treat analysis. Subjects who are lost prior to randomization, for example those that cancel surgery or are not medically cleared will be excluded from analysis.

Competing events: We plan to exclude those women with severe dementia that will be unable to accurately complete study questionnaires/VAS pain scores. Because patients with terminal diseases or those expected to have poor follow-up do not usually receive elective POP surgery, these events should not occur in a high percentage of subjects, if at all.

Missing data: Subjects with missing VAS pain scores or those that do not complete/return questionnaires and diaries will still be included in the final analysis. To reduce the chance of missing data, members of the study team will call subjects or personally visit them in their hospital room to provide reminders for completion of VAS pain scales and APS-POQ-R questionnaires. Study nurses will call the patient at 1 week to remind them to complete and return their PROMIS PI-SF 8a questionnaire, pain diary and bowel diary. We will also emphasize the importance of the data and need for completeness with subjects at the time of enrollment. We will account for missing data at the onset of the study by increasing the sample size by 5%. By keeping data collection short (limited short forms with study participation ending on POD#7), we will not overburden the subjects.

Adverse events: We will proactively monitor for allergic reaction to IV acetaminophen and hepatotoxicity throughout the first 24 hours following surgery. Hospital readmission will be proactively monitored through POD#7. Because postoperative pain medications containing acetaminophen are routinely given following surgery, we will audit the EMR on POD#1 to ensure that the maximum dose of acetaminophen (4000 mg) has not been exceeded in the 24 hour period following surgery. Because the standard dose of IV acetaminophen is 1000 mg, acetaminophen containing medications will not be given to any participant (regardless of intervention group) within the first 6 hours of surgery. This will appear as an alert in the patient chart to ensure that the pharmacy does not dose acetaminophen containing medications during this window.

Alternative strategies

We initially considered comparing preemptive IV acetaminophen to 'usual care' rather than placebo. However, IV acetaminophen is occasionally administered intraoperatively by the anesthesiology team, and due to concerns for acetaminophen overdose, this medication would have to be prohibited. We also considered an unblinded study without a placebo-controlled group in order to avoid the investigational drug costs associated with assembly of the identical appearing intervention/placebo bottles. However, lack of blinding may bias patient reported pain scores and/or physician prescribing of narcotics.

Benchmarks for success

Project benchmarks of success will include: (1) achievement of overall subject accrual goals; (2) attainment of primary outcome for all subjects (VAS pain scores and narcotic requirements); (3) high-profile presentations and papers; (4) achievement of short-term career objectives; (5) implementation of clinical intervention as standard of care (if found to be effective).

Feasibility data

The Magee Womens Center for Bladder and Pelvic Health is a large referral center with five urogynecologists and two urologists specializing in female pelvic medicine. The Allegheny Health Network is a large referral center with three urogynecologists. Therefore, attaining a sample size of 204 in the span of one year is certainly feasible. We have formally presented the study protocol to members of our division at monthly research meetings and have built consensus amongst the five urogynecologists in our division. All have pledged their support for recruitment and believe our sample size is attainable. Additionally, we have not made our inclusion/exclusion criteria overly-strict to enhance our ability to recruit subjects.

Time table and plan for completing project in established timeframe

This study is anticipated to be concluded by the end of the one-year award period (Table 2). After a short period of research staff training, we anticipate that recruitment of the 204 participants will be concluded by the end of the 3rd quarter of year one. The 4th quarter of year one will be reserved for data analysis and manuscript drafting. We aim to submit the manuscript for presentation at the 2017 American Urogynecologic Society (AUGS) meeting.

Table 2. Timeline

	Year 1				Year 2			
	Q 1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Train research staff								
Baseline data collection								
Follow-up data collection								
Analysis								
Write manuscript								

Disseminate findings								

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