A PILOT RANDOMIZED TRIAL OF OPIODS VERSUS NONOPIOIDS FOR PAIN CONTROL AFTER OSMOTIC DILATOR PLACEMENT FOR ABORTION CARE

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Study Summary

Title	A Pilot Randomized Trial of Opioids versus Nonopioids for Pain Control After Osmotic Dilator Placement in Abortion Care
Short Title	*OPTION: Overnight Pain Treatment: Investigation Opioids vs. Nonopioids*
IRB Number	829723
Methodology	Randomized Controlled Trial; Pilot
Study Duration	May 2018- March 2019
Study Center(s)	PEACE Center (Hospital of the University of Pennsylvania) 3400 Spruce Street, 1000 Courtyard Philadelphia, PA 19104 PEACE Center (Penn Medicine Washington Square / Pennsylvania Hospital) 800 Walnut Street Philadelphia, PA 19107
Objectives	Primary: To compare maximum pain scores between patients seeking induced abortion and requiring cervical preparation with osmotic dilators, randomized to receive prescription for ibuprofen alone and those randomized to receive prescription for ibuprofen + oxycodone for overnight pain management after cervical preparation with osmotic dilators
Number of Subjects	70
Main Inclusion and Exclusion Criteria	Inclusion: English-speaking women, 18 years or older, access to cell phone with text-messaging capability, receiving cervical preparation for induced abortion, and able to complete baseline survey on smartphone/tablet at screening visit. Exclusion: History of opioid or alcohol abuse, contraindications or allergy to ibuprofen, contraindications or allergy to opioid medications, seeking uterine evacuation for premature preterm rupture of membranes or advanced cervical dilation or intrauterine fetal demise.
Intervention	Comparison of prescription of 4 tablets of 600 mg ibuprofen, one tablet every 6 hours as needed for pain to the above ibuprofen + Oxycodone (8 tablets of 5mg) one tablet every 6 hours as needed for pain, for pain control following osmotic dilators placement.

Statistical Methodology	Demographic and perioperative characteristics between groups will be compared using a Chi-square test for proportions, or Fisher's exact test for small numbers as appropriate. The primary outcome for analysis will be maximum pain score. We will compare the median pain score reported at various intervals in the ibuprofen alone arm, compared to the oxycodone+ibuprofen arm using the Wilcoxon rank-sum test. NRS pain scores will be used. Analysis of changes in pain scores from baseline at the time of dilator placement, 2hr and 6hr post-dilator pain scores will be analyzed by group as well using the Wilcoxon rank-sum test.
Data and Safety Monitoring Plan	The Principal Investigator will be responsible for the data monitoring and safety of subjects.

Background and Study Rationale

This study will be conducted in full accordance with all applicable University of Pennsylvania Research Policies and Procedures and all applicable Federal and state laws and regulations including Introduction

Introduction
The United States is in the throes of an opioid epidemic[1]. The rise in prescription opioid-associated morbidity and mortality[2] contributes to this public health crisis[3]. Unused prescribed opioids are problematic, as the surplus of pills facilitates misuse, diversion and long-term dependence. Identifying patients who are unlikely to use most of their prescribed opioid medications could enable clinicians to safely prescribe fewer pills after surgery[4].

Dilation and evacuation is the most common technique used for second-trimester abortion. Pre-operative dilation of the cervix with the use of osmotic dilators decreases the risk of complications, and evidence-based research supports their use. Dilators remain in place for hours, often overnight, and expand; hence many women require overnight analgesia. Prescribing patterns are variable: women may or may not receive opioids for pain control, and this variability is provider dependent. Clinical data to inform best practices in this area are lacking.

We propose a pilot randomized trial to compare prescription for ibuprofen alone with ibuprofen + oxycodone for overnight analgesia, among women receiving osmotic dilators for second trimester abortion care. We will use a text messaging platform to record real-time pain scores, and collect information regarding the timing and type of therapies used between dilator insertion and evacuation procedure. The primary outcome will be to compare maximum pain scores between groups.

1.1 Background and Relevant Literature

After pain was coined "the fifth vital sign" in the 1990s, the sale of prescription opioids in the United States has quadrupled[5]. The pendulum has now swung to the other direction with the realization that opioid exposure places individuals at risk for long-term opioid use and abuse. Even opioid-naïve surgical patients, who are appropriately prescribed opioids for short-term use to treat post-procedural pain, are at risk of opioid dependency[6]. However, in the postoperative period, notably after minor surgical procedures, many patients do not take the prescribed opioids[7].

Women appear to be particularly susceptible to opioid abuse. In 2015, 1.2 million women were diagnosed with opioid misuse compared 0.9 million men[8]. Among women, opioid overdose deaths have risen five-fold from 1999-2010[1]. A recent study, evaluating post-cesarean section pain control, showed that there are opportunities to modify opioid exposure[9]. Like Cesarean section, dilation and evacuation (D&E) is a common procedure during which women may be exposed to opioids[10,11]. Overnight cervical preparation with osmotic dilators such as *Laminaria* or *Dilapan-S* is standard practice because of the associated decrease in surgical complications[12,13,14]. Women typically rate the pain of osmotic dilator insertion as moderate to severe[15], and pain can persist beyond the time of placement. Osmotic dilators exert radial pressure against the cervical stoma and cause the release of prostaglandins. This endogenous prostaglandin release can cause myometrial contractility, ultimately leading to uterine ischemia and pain[16].

Most providers prescribe medications for overnight analgesia, but evidence-based practices have not been established. An informal survey conducted among Society of Family Planning members showed that prescribing patterns vary from ibuprofen alone to opioids such as acetaminophen/codeine (T#3), oxycodone or hydrocodone +/− acetaminophen, or tramadol for outpatient analgesia after osmotic dilator placement (unpublished data).

Evidence from randomized trials has demonstrated that non-steroidal anti-inflammatory agents (NSAIDs), such as ibuprofen, are effective in treatment of pain resulting from prostaglandin release in the setting of dysmenorrhea[17]. NSAIDs may be sufficient (non-inferior to narcotics) for post-dilator pain, but this question has not been tested.

To our knowledge, no published studies have been conducted to specifically evaluate use of oxycodone for post-osmotic dilator pain control in patients receiving osmotic dilators for cervical preparation. Recently, Soon et al demonstrated the reduction in pain scores, and improved patient satisfaction, in those who received paracervical block for analgesia during laminaria insertion[2]. Because our thorough literature search did not uncover published data on the expected difference of mean pain scores or standard deviation in the post-osmotic dilator population, we chose our standard deviation from studies assessing similar outcomes in similar populations. The study by Renner et al[18], which evaluated pain scores in first trimester abortion, along with the study by Akers et al[19], which assessed pain scores at the time of and following intrauterine device placement, established a standard deviation of 30mm for pain scores in gynecologic care. Other studies have demonstrated a strong correlation of the Numerical Rating Scale (NRS) and VAS, and that it may be a more appropriate instrument for acute pain[20]. In the literature, a difference of 1.3 in the NRS has been considered clinically meaningful, within specific subsets. There have been recent studies that compare various analgesics for acute pain. A study by Chang et al, assessed patients who presented to the ED with acute extremity pain[21]. Patients were randomized to single dose treatment with ibuprofen and acetaminophen or with 3 different opioid and acetaminophen combination analgesics. NRS pain scores were used in this study. There was no statistically significant or clinically important reduction in pain scores with the use of opioids

2 Study Objectives

Our primary aim is to compare maximum pain scores between women randomized to receive ibuprofen alone to those randomized to receive ibuprofen + oxycodone in the setting of osmotic dilator placement for dilation and evacuation. Given the prevalence of abortion and the susceptibility of young women to opioid addiction, the ultimate goal is to reduce unnecessary exposure to opioids while ensuring effective pain management. This study will allow us to obtain preliminary estimates of maximum overnight pain scores among women receiving osmotic dilators who are randomized to one of two different analgesic options, ibuprofen or ibuprofen + oxycodone. Our overarching goal is to improve the care and safety of women requiring abortion procedures.

2.1 Primary Objective

To compare maximum pain scores between patients seeking induced abortion and requiring cervical preparation with osmotic dilators, randomized to receive prescription for 4 tablets 600 mg ibuprofen alone and those randomized to receive prescription for 4 tablets 600 mg ibuprofen + 8 tablets 5 mg oxycodone for overnight pain management after cervical preparation with osmotic dilators.

We hypothesize that such a trial is feasible, that 50% of our eligible patients will be willing to enroll. We will compute point estimates of the mean, median, and standard deviation for maximum pain scores among women randomized to use ibuprofen alone, and of women randomized to ibuprofen + oxycodone, to provide pilot data for future clinical trials.

3 Investigational Plan

3.1 General Design

We propose a pilot randomized trial, in which 70 eligible women who are receiving cervical preparation with osmotic dilators will be randomized to one of two arms: 1) prescription for ibuprofen alone or 2) prescription for ibuprofen + prescription for oxycodone. All patients are offered oral ibuprofen 600 mg to take prior to their procedure as standard of care, and will receive a paracervical block at the time of dilator placement. Additionally, all study participants will receive standardized counseling regarding pain management. Randomization will occur after dilator placement. Women randomized to arm 1 will receive a prescription for 4 tablets of 600 mg of ibuprofen. They will be instructed to take 600 mg ibuprofen, 1 tablet, every 6 hours, as needed for pain. Those randomized to arm 2 will receive a prescription for 4 tablets of 600 mg ibuprofen and a prescription for 8 tablets of oxycodone. Patients will be instructed to use oxycodone as an adjunctive medication, when ibuprofen was not sufficient in controlling pain. They will be told to take 1-2 tablets every 6 hours as needed for moderate to severe pain. As we expect participants to have dilators in for approximately 24 hours +/- 6 hours, we will prescribe 8 tablets, as this is commensurate with clinical practice.

3.2 Allocation to Interventional Group

The randomization scheme will be generated using www.randomization.com, and assignment will be performed using the randomization module in REDCap. A research assistant who will not be involved in opening the envelopes will ensure allocation concealment by placing study assignments in sequentially numbered, opaque, sealed envelopes. We will use block randomization with unequal block sizes of 4 and 6 to balance the number of participants in each group, given our small planned sample size.

3.3 Study Measures

We will use a Numerical Rating Scale (NRS 0-10) to measure pain scores in both arms at baseline (before osmotic dilator placement, at the time of the baseline questionnaire), immediately after osmotic dilator placement, and at arrival at preoperative holding area.

NRS scores will additionally be collected via text message at 2 hours and 6 hours after osmotic dilator placement. This study will allow us to document the feasibility of obtaining pain score data remotely using a text-messaging platform. A survey assessing pain, acceptability, and adequacy of pain control will be administered in the pre-operative holding area (Appendix F). The primary outcome will be maximum pain score during the study period.

3.4 Study Endpoints

3.4.1 Primary Study Endpoint

The primary outcome measure is maximum NRS as measured by subtracting baseline pain score, from maximum pain score. The pain scores are collected at baseline, immediately after dilator placement, 2

and 6 hours post-dilator placement and in the pre-operatively holding area. Maximum scores at any of these collection points will be the primary outcome in both arms.

Given onset of action of ibuprofen to be 30-60 minutes, with a maximum effect at 120 to 240 hours, and the onset of action of oxycodone to be 15-30 minutes, with peak effect at 30-60 min there was not a discrete time point that we felt to be concordant. Rather, a short interval pain score (2 hours), and score at potential maximum dilation (6 hours) will be used. We will use a text-messaging platform with automated prompts to collect real-time overnight pain scores.

Additional measures including medications taken, or interventions used, timing and dose of medications, number of tablets used will also be collected through a final questionnaire in the preoperative holding.

Procedural variables such as length of time dilators were in place and the number of dilators placed will also be collected.

4 Study Population and Duration of Participation

4.1 Duration of Study Participation

Enrollment for the study will occur between June 2018 and November 2018. The Pennsylvania Abortion Laws (Pennsylvania Abortion Control Act) require patients receive specific information, and sign consents regarding termination of pregnancy at least 24 hours prior to the start of an abortion procedure. Patients traditionally have consultation appointments that include procedural consents, and an ultrasound to establish gestational age, prior to the placement of osmotic dilators. Eligible patients will be identified research staff, who will then approach the patient at their consultation visit prior to osmotic dilator placement and offer participation in the study. Following this, those patients who have consented would return for follow-up the day prior to the procedure for osmotic dilator placement. Pain scores (NRS; 0-10) will be collected at the dilator visit. The patients will be followed overnight via the text-messaging platform, and ultimately followed up until the procedure in the operating room. The final questionnaire will be administered in the pre-operative holding. Once this is complete their study participation has ended. Total duration of participation is approximately 24 hours.

4.2 Total Number of Subjects and Sites

All women aged 18 or older, presenting for second-trimester abortion care, and desiring surgical management with uterine evacuation who require cervical preparation at the PEACE clinic will be approached for the study. Informed consent will be obtained for participation in the study. All 70 patients will be enrolled at Penn.

The Hospital of the University of Pennsylvania is the primary referral center for medically complex patients needing abortion care in the greater Philadelphia area. We see an increase in our volume annually, and we performed 300 second trimester D&Es in FY17. Ninety-five percent of these patients receive osmotic dilators the day before surgery. We anticipate being able to screen at least 140 women within a 6-month period, and enroll 70. We have a second practice at Penn Medicine Washington Square (Pennsylvania Hospital) with the same practice patterns that we will also utilize for recruitment.

4.3 Inclusion Criteria

English-speaking women
18 years or older
Access to cell phone with text-messaging capability/data
Receiving cervical preparation for induced abortion
Able to complete baseline survey on smartphone/tablet at screening visit

4.4 Exclusion Criteria

History of opioid or alcohol abuse
Contraindications or allergy to ibuprofen
Contraindications or allergy opioid medications
Seeking uterine evacuation for premature preterm rupture of membranes or advanced cervical dilation or intrauterine fetal demise

4.5 Subject Recruitment

All women aged 18 or older, presenting for second-trimester abortion care, and desiring surgical management with uterine evacuation who require cervical preparation at the PEACE clinic will be approached for the study. PEACE: Family Planning and Pregnancy Loss services clinic at Penn Medicine. We are a referral center for medically complex patients needing abortion care in the greater Philadelphia area. No advertising for this study will take place. Eligible patients will be identified research staff, who will then approach the patient at their consultation visit prior to osmotic dilator placement and offer participation in the study. Informed consent will be obtained for participation in the study by research staff

4.6 Vulnerable Populations:

This study involves pregnant women and fetuses.
The patient will be approached for study consents after clinical procedural consents have been signed. While individuals delegated on this study may be responsible for obtaining clinical consent for the patient's pregnancy termination, the person approaching and obtaining consent for study participation will be a different individual than the person who obtains the clinical consent.

If any Penn affiliates are approached for study participation, they will be informed that their decision of whether to participate in this study will in no way impact their standing with the institution.

5 Study Procedures

5.1

Study Phase	Screening/Visit1	Visit 2/Dilator	Text-messaging	Visit 3/ Procedure Day
Informed Consent/Assent	X			
Review Inclusion/Exclusion Criteria	X			
Vital Signs: BP, HR, RR	X	X		X
Height and Weight	X			
Data Collection Form	X			
Baseline Questionnaire	X			
Prior/Concomitant Medications	X		X	X
Clinical Laboratory Evaluation	X			

Ultrasound	X			
Text-messaging Questionnaire			X	
Final Questionnaire				X
NRS	X	X	X	X
VAS	X	X		X
Adverse Event / Unanticipated Problems Assessment				X

Does your study use MRI? (CAMRIS is the appropriate contact for all studies involving MRIs)

☐ Yes ☒ No (If No, no CAMRIS review needed)

Check of all that apply:

☐ 1.5T MRI
☐ 3T MRI
☐ 7TMRI

Does the MRI use investigational sequences and/ or coils?
(See Experimental Device Clause)

☐ Yes ☒ No ☐ Unsure (if unsure be sure to contact CAMRIS)

Does your study include pregnant women?
(See Pregnancy Clause and Justification)

☒ Yes ☐ No

Does the MRI require the use of Contrast Agents?
(See Contrast Risks)

☐ Yes ☒ No

Does your study involve the exposure to radiation, radiotracers and/or radiological imaging modalities?

☐ Yes ☒ No (If No, no RRSC review is needed)

Will any of the radiation exposure result from procedures that are or could be performed solely as a result of a subject's participation in the research protocol?

☐ Yes ☒ No

The following are examples of procedures involving ionizing radiation:
(Review appendix 15.3 and appendix 15.5)

- X-rays (examples: CT scan, chest x-ray, hand/wrist x-ray, abdomen x-ray, DEXA, pQCT, Fluoroscopy/Angiography)
- Nuclear Medicine scans (examples: FDG-PET, PET/CT, Tc-99m, SPECT, MUGA, bone scan)
- If you are unsure please contact Will Davidson in EHRS (wed@ehrs.upenn.edu).

Ultrasound

☐ Yes ☒ No

If yes, there is no protocol specific language to include but please contact Susan Schultz at: susan.schultz@uphs.upenn.edu

Will your study be using CT Scans? (CACTIS is the appropriate contact for studies involving CT scans)

☐ Yes ☒ No

Studies involving Nuclear Medicine: Will subjects be undergoing any of the following procedures specific to research:

☐ MUGA
(See Nuclear Medicine-Muga Scan)
☐ PET/CT Scan
(See PET/CT Scan)
☐ Bone /DXA
(See Bone Scan)

Check off all of the following procedures that will be performed in your research- each option you select will link to the template language document:

☐ Apheresis/plasma exchange
☐ Leukapheresis
☐ Bone Marrow Biopsy or Aspirate
☐ Use of AP clinical specimens
☐ Biopsies- check those which apply
☐ Blood draw

5.2 Screening

Screening/Visit 1

Informed Consent
Eligibility/Admission form
Medical Record Review- Data Collection Form (Age, Insurance status, gestational age, BMI)
Baseline Questionnaire (Race, Education, Marital status, Income, parity, prior surgical abortion)
Vital Signs (Blood pressure, heart rate)
Lab tests (Urine Protein/creatinine, urine glucose, type and screen, complete blood count)
Physical Exam (Height, Weight)
Ultrasound confirmation of gestational age
NRS pain score –collected in Baseline questionnaire

5.3 Study Intervention

Visit 2/ Dilators

Dilator placement
Randomization
Data collection form (No. dilators placed, type and size of dilators, length of dilators in place)
NRS pain score –Recorded in Data Collection Form

Text-messaging
Text Messaging Questionnaire (NRS to be collected)

Visit 3/Procedure Day
Final Questionnaire (NRS to be recorded)

5.3.1 Visit 2

5.4 Subject Withdrawal

Subjects may withdraw from the study at any time without impact to their care. Patients will be discontinued if there is a failure to place osmotic dilators for any reason. Reasons for failure may include change of decision to terminate pregnancy, decision by provider to not place osmotic dilators, or technical inability to place dilators secondary to anatomy (fibroids, etc.). It will be documented whether or not each subject completes the study.

5.4.1 Data Collection and Follow-up for Withdrawn Subjects

If a patient withdraws or is discontinued, data that has been collected prior to withdrawal or discontinuation will still be included in applicable statistical analyses. They will not be included in any analyses that require collection of pain scores.

6 Statistical Plan

6.1 Sample Size and Power Determination

As this is a pilot study, our sample size is a convenience sample. We will recruit 70 participants as part of this convenience sample. There has been literature to support a pilot trial sample size of 70 participants in order to reduce the imprecision around the estimate of the standard deviation[22]. Based upon our clinical volume we anticipate that it will be feasible to recruit 70 participants within a 6-month time period. Below are the possible effect size calculations, based on varying standard deviations, that we will demonstrate with n=70. The effect size quantifies the magnitude of the difference between the two study groups.

SD	N	Beta	Effect size
1.0	35 (per arm)	0.2	0.68
1.5	35 (per arm)	0.2	1.02
2.0	35 (per arm)	0.2	1.36
2.5	35 (per arm)	0.2	1.70

Given our high show-rate for abortion after dilator placement, we anticipate high retention rate, and ability to obtain maximum pain scores in all of the randomized participants.

Our primary analysis will be intention-to-treat analyses, although a per-protocol analysis will also be performed. Given that there are no published data on pain scores in the post-dilator time period, our study will be a crucial first step for optimizing the pain management and safety of these women.

6.2 Statistical Methods

Data analysis will be performed in Stata by the primary investigator in consultation with professional statisticians. Demographic and perioperative characteristics between groups will be compared using a Chi-square test for proportions, or Fisher's exact test for small numbers as appropriate. The primary outcome for analysis will be maximum pain scores. We will compare the maximum median pain score reported in the ibuprofen alone arm, compared to the oxycodone+ibuprofen arm using the Wilcoxon rank-

sum test. Analysis of changes in pain scores from baseline at the time of dilator placement, 2hr and 6hr post-dilator pain scores will be analyzed by group as well using the Wilcoxon rank-sum test. Additionally, analysis based on pain medication actually used, ibuprofen versus oxycodone will be performed. Sub-group analyses will be conducted similarly. We plan to perform subgroup analyses by gestational age (completed weeks), parity, number of dilators placed, BMI and by certain maternal demographic characteristics.

Control of Bias and Confounding
Given the side-effect profile of oxycodone, true participant blinding is not possible. Although we had considered the use of a placebo, and the strength of a placebo-controlled design, we have chosen to utilize a more "real-world" study design. However, in this study the research staff conducting the questionnaires and obtaining pain scores will be blinded to the intervention. By blinding the outcome assessor, we limit the potential for treatment effect estimates to be exaggerated. It also reduces bias in the way the questionnaires are asked, and primary outcome data collection is obtained.

6.2.1 Baseline Data
Baseline and demographic characteristics will be summarized by standard descriptive statistics.

6.2.2 Analysis of Primary Outcome of Interest
The primary outcome for analysis will be maximum pain scores, computed as the difference between baseline pain score and the participates maximum reported pain score. We will compare the median pain score reported at pre-operative holding in the ibuprofen alone arm, compared to the oxycodone+ibuprofen arm using the Wilcoxon rank-sum test.

6.2.3 Interim Analysis (only if applicable)
Not applicable.

7 Safety and Adverse Events
The safety of the medications used within this study is well established. The side effects that are known are listed below. We will be asking participants in the final questionnaire detailing which, if any, side effects they experienced.

7.1.1 Adverse Events
An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Not all events that would traditionally be defined as AEs will be collected by the sponsor for this trial.

There are a number of expected side effects related to the medications being used in this study:

<u>Ibuprofen</u>
Mechanism of action: reversibly inhibits cyclooxygenase-1 and 2 (Cox 1 and 2), which results in decreased formation of prostaglandin precursors

Onset of action: 30-60 minutes
Peak effect: 120 to 240 hours
Duration of effect: 6 to 8 hours
Half-life: 2 hours

Adverse reactions: edema (1-3%), dizziness (3-9%), headache (1-3%), nervousness (1-3%), skin rash (3-9%), pruritis (1-3%), fluid retention (1-3%), epigastric pain (3-9%), heartburn (3-9%), nausea (3-9%), abdominal pain (1-3%), constipation (1-3%), decreased appetite (1-3%), diarrhea (1-3%), dyspepsia (1-3%), flatulence (1-3%), vomiting (1-3%)

Oxycodone
Mechanism of action: binds to opiate receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression

Onset of action: 15-30 minutes
Peak effect: 30-60 minutes
Duration of effect: 3 to 6 hours
Half-life: 3.2 to 4 hours

Adverse reactions: drowsiness (23%), dizziness (9-13%), nausea (15-23%), constipation (23%), vomiting (12-13%), fever (1-11%), edema (1%), orthostatic hypotension (1-5%), anxiety (1-5%), confusion (1-5%), dysphoria (1-5%), nervousness (1-5%), twitching (1-5%), agitation (<1%), depression (<1%), diaphoresis (5%), diarrhea (1-6%), anorexia (1-5%), dyspepsia (1-5%), gastritis (1-5%), hiccups (1-5%), weakness (1-6%), dyspnea (1-5%)

All adverse events will be collected, recorded, and assessed locally by the investigator or her designee. Only events that are determined to be both unexpected and related to the study will be entered into the electronic CRF and report to the local IRB (as described below).

Serious Adverse Event
Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above.

Adverse Event Reporting Instructions
The Principal Investigator will evaluate women who experience a SAE as necessary until the event is resolved. Adverse events that are both serious and unexpected will be reported to the IRB per their local reporting requirements.

Adverse Event Reporting Period
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, initiation will be at the time of randomization, and the study treatment follow-up is completed at the time of the surgical procedure, once the osmotic dilators are removed.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study.

Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

Recording of Adverse Events
At each contact with the subject, the investigator or designee must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the study documents.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

7.1.2 Data and Safety Monitoring Plan

The Principal Investigator will be responsible for the data monitoring and safety of subjects.

8 Study Administration, Data Handling and Record Keeping

8.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

The program being used for the study text messages is Twilio. Twilio is a third-party application with the capability to integrate and directly feed data into REDCap. All study data will be maintained behind the UPHS firewall and in a password-protected encrypted REDCap database. Any paper research records will be collected by research staff and stored in study-specific files kept in a locked area in one of the research locations during the active phase of the study. Any electronic data will be kept on controlled access Departmental shared drives, or in a secured database on REDCap. Only the PI and study staff will have access to data with patient identifiers. There should not be a need to transmit data files containing PHI for this study. At the conclusion of the study data will be retained on site in the same secured manner for a minimum of two years, and may be transferred to a long-term storage facility (Iron Mountain) thereafter. There is no current plan to destroy the identifiable information.

8.2 Data Collection and Management

Data will be entered into a password protected REDCap database accessible only by study staff. Trained research staff will enter the data. Cleaning will occur throughout the data collection period and again after completion by the study staff.

8.3 Records Retention

Research data will be collected by research staff and stored in study-specific files kept in a locked area in one of the research locations during the active phase of the study. Any electronic data will be kept on controlled access Departmental shared drives, or in a secured database on REDCap. Only the PI and study staff listed will have access to data with patient identifiers. There should not be a need to transmit data files containing PHI for this study. At the conclusion of the study data will be retained on site in the same secured manner for a minimum of two years, and may be transferred to a long-term storage facility (Iron Mountain) thereafter. There is no current plan to destroy the identifiable information.

9 Study Monitoring, Auditing, and Inspecting

9.1 Study Monitoring Plan

The primary investigator will be responsible for ensuring the ongoing quality and integrity of the research study. The PI will annually complete PICA for monitoring at the time of continuing review.

9.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related. The investigator will ensure the capability for inspections of applicable study-related facilities

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10 Ethical Considerations

We will obtain IRB approval prior to beginning recruitment for the study. Any protocol amendments will be submitted to the IRB prior to implementation. We will additionally comply with all HHS regulations as outlined in 45CFR46 Subparts.

10.1 Risks

The risks included known side effects of the study medications, which are established and noted in the above section on safety. There is a potential risk of inadequate pain control in those randomized to ibuprofen alone. However, participants, will have access to on-call physician line with the capability of additional "rescue" prescription availability on an as needed basis. There are no reproductive risks to participating in the study.

10.2 Benefits

Participants are not expected to get direct benefits from being in the study. Anticipated benefits to future women include a better understanding of pain control while osmotic dilators are in place. Furthermore, the study may change pain management options for patients, that rather than being practice-based would be evidence-based.

10.3 Risk Benefit Assessment

This study is of minimal risk.

Informed Consent Process / HIPAA Authorization

All subjects for this study will be provided a consent form describing this study providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The subject, or legally acceptable surrogate, must sign the consent form, and the investigator-designated research professional obtaining the consent. Subjects will be consented by the study Principal Investigator, or appropriate designee. Potential subjects will review the consent form in detail with the person designated to consent (either PI or CRC) and have the ability to take the consent home for further review.

11 Study Finances

11.1 Funding Source

This study is financed through a grant from the Society for Family Planning.

11.2 Conflict of Interest

All University of Pennsylvania Investigators will follow the University of Pennsylvania Policy on Conflicts of Interest Related to Research.

11.3 Subject Stipends or Payments

For time and the inconvenience related to participation in this study, the participants will be paid for each study procedure completed using a Greenphire ClinCard. The payment will be approved and loaded onto the debit card following each completed study visit. If a patient is screened for the study and is not eligible to enroll, she will be paid for the screening visit if it is completed. No additional financial compensation will be provided.

Visit Type	Compensation
Screening/Visit 1	$25
Text Questionnaire at Hour 2	$25

Text Questionnaire at Hour 6	$25
Procedure Day/Visit 3	$25

A total of $100 will be distributed for completing all desired questionnaires.

12 Publication Plan

This is a single institution study and we do not anticipate any barriers to publication. Results will be disseminated via a publication(s) in a peer-reviewed journal

13 References

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14 Attachments

Information will be entered directly into a REDCap database. Please see attachments for study questionnaires, ICFs, etc.