Study Protocol and Statistical Analysis Plan for Clinical Trials

Official Title: Addition of Buprenorphine to Paracervical Block for Pain Control During Osmotic Dilator Insertion

NCT# NCT04254081

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UCSD Human Research Protections Program
New Biomedical Application
RESEARCH PLAN INSTRUCTIONS

These are instructions are for completing the Research Plan that is available in MS Word format from the HRPP website.
The headings on this set of instructions correspond to the headings of the Research Plan.
General Instructions: Enter a response in for all topic headings.
Enter "Not Applicable" rather than leaving an item blank if the item does not apply to this project.

Version date: 12/10/19

1. PROJECT TITLE

Addition of Buprenorphine to Paracervical Block Prior to Osmotic Dilator Insertion for Dilation and Evacuation: A Randomized Controlled Trial

2. PRINCIPAL INVESTIGATOR

Sheila Mody, MD MPH
Associate Professor
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Diego

3. FACILITIES

University of California, San Diego – Villa La Jolla Women's Health Clinic, Medical Offices South Women's Health Clinic
Planned Parenthood of the Pacific Southwest

4. ESTIMATED DURATION OF THE STUDY

18 months

5. LAY LANGUAGE SUMMARY OR SYNOPSIS (no more than one paragraph)

Cervical dilators are commonly used for preparation prior to second trimester abortion. Women have described the pain of osmotic dilator insertion as moderate to severe yet there have been few studies aimed at addressing pain during and after osmotic dilator insertion. One strategy to decrease pain with other gynecologic procedures is a paracervical block, or injection of anesthetic medication into the tissue surrounding the cervix. A randomized trial found that use of a paracervical block with 1% buffered lidocaine decreased pain with osmotic dilator insertion compared to a sham block. In addition, there are adjunct treatments to optimize analgesia with local anesthetics at a variety of other anatomic locations. Buprenorphine, a partial mu-opioid receptor agonist, has been found to increase the quality of the anesthetic at the time of administration and increase the duration of nerve block analgesia at several anatomic sites, though has never been studied as an adjunct in a paracervical block. This has been used extensively in orthopedic surgery with significant prolongation of the local anesthetic effect by almost threefold in some studies.

6. SPECIFIC AIMS

Primary aim:
To compare the mean pain score at the time of osmotic dilator insertion among women randomized to a 1% lidocaine and buprenorphine paracervical block compared to a 1% lidocaine paracervical block alone.

We hypothesize that in patients undergoing osmotic dilator insertion in preparation for dilation and evacuation, the addition of buprenorphine 0.15mg to a 1% lidocaine paracervical block will be associated with lower mean pain scores at time of osmotic dilator insertion compared to women who receive a 1% lidocaine paracervical block alone.

Secondary aims:

1. To compare the mean pain score 2 hours after osmotic dilator insertion among women randomized to a lidocaine and buprenorphine paracervical block compared to a lidocaine paracervical block alone.
2. To assess overall narcotic and ibuprofen use after osmotic dilator placement and before dilation and evacuation procedure.
3. To assess opioid related side effects.
4. To determine patient satisfaction with pain control during and after osmotic dilator insertion.

7. BACKGROUND AND SIGNIFICANCE

Dilation and evacuation (D&E) is the most common method of second trimester abortion in the United States[1]. Cervical preparation prior to the procedure is essential in order to allow passage of operative instruments and pregnancy tissue safely through the cervix and to decrease the risk of complications.[1–4] In the second trimester, cervical preparation is typically achieved with placement of osmotic dilators prior to the procedure. Women have described the pain of osmotic dilator insertion as moderate to severe yet there have been few studies aimed at addressing pain during and after osmotic dilator insertion.[5–8] A lidocaine paracervical block is commonly used for pain control during other gynecologic procedures including procedures involving cervical dilation like dilation and curettage.[6,7] One randomized controlled trial found that use of a paracervical block with 1% lidocaine decreased pain with osmotic dilator insertion compared to a sham block.[9] Because the dilators slowly expand after insertion, there is continued discomfort for several hours after placement. Research has shown that pain after osmotic dilator insertion peaks at 2 hours post-insertion with use of a lidocaine paracervical block and a local anesthetic is not sufficient to provide lasting pain relief.[10] Systemic medications, such as gabapentin and narcotic analgesics have been studied to treat post-insertional dilator pain, however these treatments have not been shown to be effective.[10,11]

There are many adjunct treatments to optimize the duration of local analgesia from a peripheral nerve block. Opioid receptors are expressed in the central as well as peripheral nervous system on peripheral sensory neurons.[12–17] Opioids can produce potent analgesic effects on peripheral receptors outside the central nervous system.[15] Various studies have provided evidence that opioid receptors, specifically mu-receptors, are found in the peripheral nervous system.[18–20] Essentially, opioid receptors are not restricted to the central nervous system, but are present in the peripheral nervous system, where their activation has been shown to exert analgesic effects without centrally mediated side effects.[15,21] The administration of local opioid agonists can result in a significant analgesic effect through the activation of peripheral opioid receptors while bypassing the central nervous system, and thus the centrally mediated side effects such as respiratory depression, alterations in mental status, and activation of reward pathways in the brain can be bypassed.[15] With the identification of opioid receptors in the peripheral nervous system, there has been interest in opioid adjuvants to peripheral nerve block to enhance analgesic effects and prolong duration of local anesthetic effect.

Buprenorphine, a partial mu-opioid receptor agonist, is a high potency, lipophilic opioid and has a high binding capacity for the mu-opioid receptor.[22,23] Because of the high binding capacity, buprenorphine has the longest duration of action of all opioids. When administered perineurally in combination with a local anesthetic, buprenorphine has been found to drastically increase the duration of analgesia at several anatomic sites, including axillary and subclavian brachial plexus blocks and infragluteal sciatic nerve blocks.[22–30] With the addition of buprenorphine at doses of 0.15 – 0.3mg, there is significant prolongation of the anesthetic sensory blockade up to three times the duration of the local anesthetic alone.[28] The use of perineural buprenorphine is well established for postoperative analgesia.[22,23]

Buprenorphine itself also has local anesthetic properties. Buprenorphine blocks voltage gated sodium channels and inhibits C-fiber action potentials, thereby contributing to an analgesic effect.[30,31] One study using

buprenorphine in conjunction with bupivacaine for a subclavian perivascular brachial plexus block found that the addition of buprenorphine improved the quality of the local anesthetic in terms of a denser sensory blockade at the time of administration.[27] Therefore, buprenorphine not only prolongs the duration of local anesthetic effect but also improve the analgesic properties when administered in a perineural block.
The addition of buprenorphine to a perineural local anesthetic has not been studied in with a paracervical block. This study will be the first trial to assess the efficacy of buprenorphine to provide analgesia for a gynecologic procedure. This medication has the additional benefit of providing long lasting pain relief for procedures that cause continued discomfort after the end of the procedure. We hypothesize that the addition of 0.15mg of buprenorphine to a lidocaine paracervical block will improve pain during osmotic dilator insertion and provide continued pain relief several hours after osmotic dilator insertion. If this intervention proves to provide better pain control than a lidocaine paracervical block alone, it would be an intervention for women during a painful clinic procedure.

Much of the information about buprenorphine as an adjunct for local pain control is found in the anesthesia literature. With the addition of buprenorphine at doses of 0.15 – 0.3mg, there is significant prolongation of the anesthetic sensory blockade up to three times the duration of the local anesthetic alone.[22,23] The use of perineural buprenorphine is well established for postoperative analgesia at several different anatomic sites though the use of buprenorphine as an adjunct to a paracervical block has never been studied.[22–32] Most peripheral nerve blocks are performed using ultrasound guidance to avoid large vessels, especially with brachial plexus and sciatic nerve blocks. Although visualization is used to avoid large vessels, there is still likely a small amount that is absorbed systemically. Because a paracervical block is performed blindly (though clinicians draw back before injection to ensure no entrance into a vessel) and there is a higher concentration of vessels around the cervix, we will be studying the lower 0.15mg dose of buprenorphine. This dose has still been shown to significantly prolong post-procedure analgesia, thus we anticipate that it will be effective in prolonging analgesia in our study.[22,33,34] In the orthopedic literature, there were no cases of respiratory depression from systemic absorption with either dose of adjunct buprenorphine.[35]

This study will be the first RCT to assess the efficacy of adding buprenorphine to a paracervical block for pain during osmotic dilator insertion.

In terms of potential risks to the fetus, a study by Mark et al. (2019) reported that less than 1% of women who present for second-trimester abortions and received osmotic dilators for cervical preparation had their dilators removed with the intent to continue the pregnancy.[36] Only case reports have been published with this clinical situation.[37] Women are counseled that the placement of osmotic dilators is the start of her two-day procedure. If a participant chooses to continue her pregnancy after osmotic dilators are placed and after study medication is administered (which as indicated, is extremely rare), a single dose of non-systemically administered buprenorphine in the second trimester is unlikely to affect the developing fetus. Studies in rats and rabbits have not found buprenorphine exposure to increase congenital malformations.[38] Studies in vitro studies have demonstrated that about 10 % of buprenorphine crosses the placenta and about 5% is metabolized to the active metabolite.[39] In this study, we are administering a single local dose of buprenorphine in a nerve block formulation. Very little of this medication (if any) would be systemically absorbed, and as such, almost none would cross the placenta and enter the fetal circulation.

There are no well controlled studies investigating the effects of buprenorphine in pregnant women. Overall, there is limited data about the rate of major congenital malformations with the use of buprenorphine, but the available data do not show an increased risk when compared to other opioids like methadone.[40–42] Additionally, women who use buprenorphine during pregnancy use it for a prolonged period of time as a daily medication and the amount of exposure is much higher than a single dose as used in this research study. There are no studies investigating a single dose of buprenorphine and the impact on a fetus.

From the available literature, there is no clear evidence of risk of major congenital malformations with use of buprenorphine in pregnancy.[35,36,37] If a woman changes her mind after insertion of osmotic dilators and desires to continue the pregnancy, she will be referred to perinatology (high risk pregnancy specialists) for follow up and monitoring of her pregnancy. The risks are described further in section 15.

8. PROGRESS REPORT

Not applicable

9. RESEARCH DESIGN AND METHODS

This is a randomized, 2-arm (1:1), double blinded clinical trial comparing pain scores at the time of osmotic dilator insertion and at specific points after insertion with a buprenorphine plus 1% lidocaine paracervical block compared to a paracervical block alone in women who have osmotic cervical dilators placed.

Primary Hypothesis:

In patients undergoing osmotic dilator insertion in preparation for dilation and evacuation, the addition of buprenorphine 0.15mg to a 1% lidocaine paracervical block will be associated with lower mean pain scores at time of osmotic dilator insertion compared to women who receive a 1% lidocaine paracervical block alone.

Secondary hypotheses:

In patients undergoing osmotic dilator insertion in preparation for dilation and evacuation, the addition of buprenorphine 0.15mg to a 1% lidocaine paracervical block will be associated with lower mean pain scores 2 hours after osmotic dilator insertion compared to women who receive a 1% lidocaine paracervical block alone.

In order to investigate this hypothesis, the following study design is proposed:

We plan to recruit at two study sites – the University of California, San Diego (UCSD) and Planned Parenthood of the Pacific Southwest (PPPSW). The UCSD study team will be responsible for all study procedures conducted at Planned Parenthood. Members of the UCSD study team will be determining eligibility, consenting patients, administering patient questionnaires, collecting data, and performing data analysis. Planned Parenthood clinicians will be administering the study medication during the procedure and will not be involved in any other research procedures.

Included in the study are women who present to the UCSD or PPPSW clinics seeking dilation and evacuation for any indication and who will require cervical preparation with osmotic dilators as determined by the evaluating clinician. Patients between 14 weeks 0 days gestation to 23 weeks 6 days gestation at the time of osmotic dilator insertion will be candidates for study inclusion. Participants will be excluded based on a brief questionnaire if they have a known allergy to the study medication or ibuprofen, any chronic pain conditions, have taken any narcotic medications in the last 24 hours, have chronic opiate use or any other drug abuse, request sedation during laminaria insertion, or have a history of chronic liver disease. Stratified randomization with be performed among participants based on vaginal parity (nulliparous and multiparous). Participants will be randomized to one of two study groups allocated one to one: (1) paracervical block with 20mL of 1% buffered lidocaine or (2) paracervical block with 20mL of 1% buffered lidocaine plus 0.15mg of buprenorphine.

During the procedure, the study team member will present the numeric rating scale (NRS) to the participant and ask her to mark her level of pain at each time point during the procedure (paracervical block placement, osmotic dilator insertion, 5 minutes post procedure) and will remain blinded to the study arm. These NRS scores will be recorded into REDCap utilizing an electronic tablet. The participant will be asked

about side effects such as dizziness and nausea during the procedure. The clinician will perform the osmotic dilator insertion in the usual fashion, and the study team member will record the time from speculum insertion to speculum removal.

After the procedure, the clinician will answer a brief questionnaire detailing if there were any adverse events or difficulty related to either the paracervical block or the osmotic dilator insertion. The clinician will also note whether or not cervical dilation was performed prior to osmotic dilator insertion and to what size dilator. They will also indicate their level of training. At 5 minutes after osmotic dilator insertion, the participant will indicate her level of pain and answer questions regarding side effects and satisfaction with pain control during the procedure.

The primary outcome of the study is pain as measured on the NRS at the time of osmotic dilator insertion. Studies have varied in the time point at which pain is measured during the procedure, as some assessed pain with dilator insertion and others have recorded it 5 minutes after dilator insertion[8-11]. Research studies addressing pain *during* osmotic dilator insertion have used the VAS, while studies looking at pain *after* dilator insertion have used the numeric rating scale (NRS)[8-11]. We plan to capture pain using the NRS (an 11-point scale from 0-10) as we are evaluating pain at multiple different timepoints, both during and after dilator insertion.

Our secondary outcome is pain at 2 hours post dilator insertion. Given that buprenorphine can extend the length of analgesic effect by 2-3 times, we anticipate that the prolonged anesthetic effect should last anywhere from 2-6 hours using 1% lidocaine and provide pain relief as the dilators are expanding. Patients will be receiving text messages with links to questionnaires at three different time points (1 hour, 2 hours, and 6 hours post-insertion) in order to assess their level of pain, analgesic use, as well as any other symptoms. These text messages will be time stamped depending on time of dilator insertion and will be sent out at the intervals we specify in the text messaging software.

	Before procedure	Paracervical block	Osmotic dilator placement (0 minutes)	5 minutes post dilator placement	1 hour post dilator placement	2 hours post dilator placement	6 hours post dilator placement	Prior to D&E
Baseline survey	x							
Pain scale	x	x	x	x	x	x	x	x
Side effect assessment			x	x	x	x	x	x
Clinician survey				x			x	
Assessment of oral analgesic medications needed					x	x	x	x
Participant satisfaction with pain control				x	x	x	x	x

Schedule of Assessments

The table below indicates the time point at which the various assessments will be performed. Assessments will be performed over one to two days: on the day of osmotic dilator insertion and on the day of D&E. If same day dilators are used, the final assessment will be performed immediately prior to D&E. Overall, the process of clinician evaluation, procedural consent, study recruitment, study consent, performance of procedure, and immediate post-procedure questionnaire should take about 30 minutes. The follow up questionnaires and questionnaire prior to D&E will take about 10 minutes. Participants will receive a questionnaire sent via text message link at 1 hour, 2 hours, and 6 hours post-procedure. This questionnaire

assesses the need for oral analgesics for pain as well as participant satisfaction with their pain control at that study point. Participants will take a questionnaire on the morning of D&E asking them to rate their current pain and to recall their maximum pain score over the preceding day and their overall satisfaction with their pain control. The need for follow up will be determined per usual clinician practice and preference.

Randomization:
Block randomization will be performed in alternating blocks of 4 and 6 stratified by vaginal parity (vaginally nulliparous versus vaginally multiparous). The study team member will open the designated sealed sequentially numbered opaque randomization envelope containing computer generated randomization code of the type of paracervical block and hand it to the clinician performing the procedure. A clinician who will not be administering the paracervical block will then open the envelope and prepare the designated paracervical block into two 10 mL syringes. A different clinician blinded to the treatment group will perform the standardized procedure for osmotic dilator insertion using a speculum, 25-gauge spinal needle to inject the paracervical block, Dennison dilators to dilate the cervix if that is the clinician's practice, and insertion of laminaria and/or Dilapan-S. The amount of time it takes to inject the paracervical block will be recorded.

Intervention: A paracervical block with 20mL of 1% buffered lidocaine plus 0.15mg of buprenorphine will be injected prior to osmotic dilator insertion. A paracervical block with 20mL of 1% buffered lidocaine will be used in the control group. The patient will not be charged for the study drug. All drug costs will be covered by the study (this is also stated in the consent form).

Outcomes:

1) **Sociodemographic and clinical data**: age, race, ethnicity, level of education, marital status, height, weight, obstetric history, history of cervical procedures (e.g. LEEP procedure or Conization), chronic baseline pain
2) **Primary outcome**: Level of pain as rated on an 11-point (0-10) numeric rating scale during osmotic dilator insertion.
3) **Secondary outcomes:**
    a. Pain (Numeric Rating Scale):
        i. Baseline (before procedure)
        ii. Paracervical block placement
        iii. 5 minutes post procedure
        iv. 1 hour post procedure
        v. 2 hours post procedure
        vi. 6 hours post-procedure
    b. Satisfaction
        i. Likert scale questions
            1. How satisfied are you with the amount of pain control that you had during the procedure?
            2. If you had to have these dilators placed for a procedure in the future, would you choose to have the same pain medication that you received today?
    c. Adverse events – side effects at time of paracervical block placement and after procedure
    d. Survey of provider (resident, fellow, attending, advance practice clinician) performing procedure
        i. Number of dilators placed

ii. Ease of osmotic dilator placement
iii. If patient will return for second set of dilators
iv. Major complications
v. Type of clinician (resident, attending, advance practice clinician)

No specimens will be collected for research purposes. All research data will be collected on electronic tablets and de-identified via REDCap.

Power Calculation:

It is suggested that a 2-point reduction in pain on the numeric rating scale (NRS) is clinically meaningful.[24-27] No existing study parallels the outcomes of our proposed research (pain at time of osmotic dilator insertion using the numeric rating scale). One previous study used the Visual Analog Scale (a 0-100mm linear scale) to compare pain at the time of osmotic dilator insertion between a 1% lidocaine paracervical block and vaginal lidocaine gel.[8] The visual analog scale and the numeric rating scale have modest correlation.[42] The median pain score during osmotic dilator insertion in the 1% lidocaine paracervical block group was 61 (which correlates to 6 on the numeric rating scale) with a range from 0-100.

In order to detect a 2-point difference on the NRS at the time of osmotic dilator insertion with 80% power and a two-sided alpha of 0.05, we will need a total of 52 patients in each study arm (26 per arm). We plan to stratify the groups by vaginal parity (nulliparous versus multiparous) as vaginal parity may affect pain at the time of osmotic dilator insertion. In order to stratify by vaginal parity, we will need a total of 104 women (52 in each strata) to see a difference between strata per group. We plan to enroll an additional 10% to account for protocol deviation and participant dropout for a total of 114 participants. With a one to one randomization allocation, approximately half will be randomized to receive a paracervical block with buprenorphine and 1% lidocaine and half will receive a paracervical block with 1% lidocaine alone. Additionally, randomization will be stratified by vaginal parity (vaginally nulliparous versus vaginally multiparous).

Data Analysis

The baseline participant survey, NRS scores, side effects, and post-procedure participant and provider surveys will be performed by the study coordinator using REDCap loaded on to an electronic tablet. This data will be transferred to a spreadsheet in SPSS. Bivariate comparisons will be analyzed using chi squared test or Fisher's Exact test for categorical variables and t-test or Mann-Whitney for continuous variables depending on the distribution of the data as appropriate. The primary outcomes will be evaluated per intent-to-treat analysis.

10. HUMAN SUBJECTS

Inclusion criteria:

1) Women over the age of 18 presenting to UC San Diego or Planned Parenthood of the Pacific Southwest for Dilation and Evacuation for any indication
2) Require cervical preparation with osmotic dilators based on clinician judgement
3) Speak English or Spanish

Exclusion criteria:

1) Women who desire sedation for osmotic dilator insertion
2) Dilation and evacuation planned on same day as osmotic dilator insertion
3) Pre-viable preterm rupture of membranes (PPROM) as indication for procedure

4) Known allergy/sensitivity to or refusal of any study medication (buprenorphine, ibuprofen, lidocaine)
5) If they have taken any narcotic medication (including prescription opiates, buprenorphine, methadone) or recreational drug in the preceding 24 hours
6) Current liver disease
7) Severe uncontrolled asthma, COPD, or other respiratory disorders
8) Severe respiratory depression as assessed by vital signs
9) Current or history of gastrointestinal obstruction
10) Incarceration

11. RECRUITMENT

The study will take place at UCSD and Planned Parenthood of the Pacific Southwest. Patients either self-refer to these clinics or are referred by another clinician. At UCSD, appointments are coordinated by a Family Planning Manager. During the time of the study, when a participant presents to clinical care for a D&E for any indication, she will be counseled on options including induction termination and D&E. If the patient desires a D&E and is at PPPSW, she will be assessed for ability to perform this procedure in the outpatient surgical center. If the patient has medical co-morbidities that increase the risk of the procedure, she may be referred to UCSD or another tertiary care center.

If the patient is a good candidate for D&E and the procedure is scheduled to occur the next day, the clinician will assess the need for osmotic dilator placement for cervical preparation; this is usually known based on gestational age, however patients between 14 weeks to 16 weeks may receive either dilators or misoprostol alone. This will be determined per clinician judgement. If the patient is eligible for osmotic dilator placement, informed consent will be obtained for the procedure, per standard clinic practice, and the clinician will notify the study team member. The study team member will then assess if the patient is interested in participating in the study, ensure that the patient is willing to be randomized to the study medication, and assess whether or not she has already taken ibuprofen that day in preparation for osmotic dilator placement. Eligibility criteria will be verified by the study team member using the script below. The study team member will obtain written informed consent to participate and perform the baseline survey. The participant will receive 800mg of oral ibuprofen if she has not already taken this medication prior to the appointment.

We will use the below recruitment script:

“We are conducting a study on pain control during osmotic dilator insertion. You are eligible to participate because your clinician has determined that is necessary to place dilators before your procedure. We are studying the addition of a medication called buprenorphine to cervical anesthesia. We would like to know if this medication helps to decrease pain during and after the procedure. We are looking for volunteers to participate in this study. This study will require that you participate in a pre-screening interview in which you will be asked questions about your basic health history.”

We are requesting a Waiver of Documented Consent before beginning the recruitment process. We are requesting approval to obtain a verbal consent before administering the pre-participation questionnaire. This questionnaire is a pre-screening tool asking only inclusion/exclusion questions. It is necessary to carry out the research as we need to determine if they qualify for the study. It is justified because the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. It is minimal risk

and the waiver will not adversely affect the rights and welfare of the subjects. Subjects will be provided with all additional pertinent information after they are enrolled as participants in the study.

12. INFORMED CONSENT

The patient will be consented by the research coordinator, a research assistant, or any of the co-investigators. The consent process will occur prior to randomization or completion of any study questionnaire. The consent process will occur in the patient room. We will only enroll patients who speak English or Spanish. Consent and all other study instruments will be translated into Spanish. Only study staff who are authorized interpreters at the respective study sites will deliver the pre-screening eligibility form and the consent to participate for Spanish-speaking participants. Medical Center Interpretation Services will be used as needed. The availability of medical interpreter services differs across sites and our study instruments are only available in English and Spanish. Therefore, to maintain consistency across sites and to ensure a consistent interpretation of the study instruments, we have limited enrollment to English and Spanish speakers. The consent form and HIPAA authorization will be signed and scanned into the participant's electronic medical record. Copies will be provided to the participant.

13. ALTERNATIVES TO STUDY PARTICIPATION

If the patient chooses not to participate in the study, they would receive the standard of care which is a 1% lidocaine paracervical block.

14. POTENTIAL RISKS

1) Loss of confidentiality
2) Pain with paracervical block injection or insertion of osmotic dilators
3) Side effects of the study medication include feeling sleepy, vertigo, dizziness, headache, fatigue, itching, sweating, nausea, constipation, vomiting, temporary elevation of liver enzymes
4) Rare side effects of the study medication include swelling, bruising or redness at the injection site; low blood pressure; constricted pupils; fainting; or slow breathing.
5) Unknown risks
6) Risk of randomization: one assigned study group might prove to be less effective or have more side effects than the other study group

We will be purchasing intramuscular naloxone in the rare event of respiratory depression from systemic absorption of the buprenorphine. This is an extremely rare anticipated side effect as the partial mu-agonist properties of this drug typically causes a ceiling effect and prevents respiratory depression. However, we will have this medication on hand in clinic in case of this extremely rare event.

Each clinic site is equipped with basic emergency equipment in the rare event that a medical emergency should happen during the study procedures. In the rare event of serious side effects (such as slowed breathing), naloxone would rapidly reverse all side effects. Given the low dose of buprenorphine being administered, only one dose of naloxone would be necessary to reverse the effects of the medication.

15. RISK MANAGEMENT PROCEDURES AND ADEQUACY OF RESOURCES

1) Ensuring confidentiality by assigning a patient study number and avoiding the use of patient identifiers.

2) The clinic is equipped with medical supplies if a participant has dizziness or vasovagal symptoms. These symptoms are usually transient.
3) If a woman decides to continue her pregnancy after administration of the study medication, there is unlikely to be any additional increased risk to the developing fetus from buprenorphine itself. There are far greater risks to pregnancy continuation due to osmotic dilator placement and resulting cervical dilation, and the buprenorphine does not mitigate or increase this risk. If a woman does decide to continue her pregnancy after she receives the study medication, she will be referred to perinatology for evaluation and for prenatal care.
4) Data will not be shared between UCSD and Planned Parenthood. All study instruments and data collection forms will be on a UCSD tablet and administered by UCSD study personnel. There will be no exchange of data between the two study sites.
5) All adverse events will be reported to the UCSD IRB in a timely fashion. The management of information that is relevant to the protection of participants including adverse events, UPRs, protocol violations/deviations, interim results and protocol modifications will be the responsibility of the PI (Dr. Mody).

16. PRIVACY AND CONFIDENTIALITY CONSIDERATIONS INCLUDING DATA ACCESS AND MANAGEMENT

Consent will be obtained in the patient's private exam room, in the private clinical space where participant can ask questions without feelings of embarrassment or discomfort. The physical exam will be conducted in the private examination room. Data will be reviewed by the principal investigator and research coordinators to ensure accuracy and completeness. Data will be monitored quarterly to ensure that data collection, coding, and management procedures are being conducted according to protocol and ethical guidelines.

There is a need for medical record access to assess patient demographics, history, and clinical outcomes. The baseline patient survey, NRS scores, side effects, and post-procedure participant and clinician surveys will be performed by the study team member using REDCap loaded on to an electronic tablet. REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Study data will be stored in the HIPPA-secure de-identified online REDCap data base housed at UCSD. Any printed study data will be secured in a locked cabinet/filebox, and only those directly involved in the study will have access to this including the investigators who will process it. Only de-identified data will be stored. Data entry and analysis will be performed on password-protected, institutionally secured computers. The research database will be banked indefinitely for the purpose of future research questions and will contain only de-identified information as above.

Participants will be contacted via text message to complete questionnaires at three different time points. The questionnaires will be sent over text via a hyperlink that connects to a secure platform that will input the data directly into a REDCap database. The application's template function will be used to ensure all outgoing text messages are uniform. Any incoming text messages are returned to the secure application platform. A key linking the participant's contact information to her participant ID will be stored in a locked cabinet in the study office separate from any data or patient information.

There will also be a need to collect participant email addresses to send compensation via Amazon e-gift cards. The research coordinator at UCSD, Marisa Hildebrand, is the only member of the study team who will have access to the email addresses from both sites; she will need email addresses in order to send e-gift cards.

17. POTENTIAL BENEFITS

Participants may not experience direct benefit from participation in this study. However, we hope that this study will help us determine if the addition of buprenorphine to a lidocaine paracervical block is effective in reducing pain with and after osmotic dilator placement. We hope that this study may change the practice of pain relief with osmotic dilator placement for women in the future.

18. RISK/BENEFIT RATIO

The benefit of possibly decreased pain during and after osmotic dilator placement outweighs the small chance of any unknown risk in the buprenorphine group.

19. EXPENSE TO PARTICIPANT

None

20. COMPENSATION FOR PARTICIPATION

Study participants will be compensated with up to $40 in Amazon e-gift cards for their time.

21. PRIVILEGES/CERTIFICATIONS/LICENSES AND RESEARCH TEAM RESPONSIBILITIES

Co-investigators:
Sheila Mody MD, MPH, Sarah Averbach MD, MAS, Nicole Economou MD, Marisa Hildebrand MPH, and Gennifer Kully MSc will organize and process the study data. They will also be involved in recruitment and consenting for participants in the study. Marisa Hildebrand MPH is the research coordinator/manager at UCSD, and Gennifer Kully MSc is the research assistant at UCSD.

Salary support is provided to Gennifer Kully, a research assistant on the study. No other salary support is provided to any of the co-investigators. All of the research team members have completed CITI training.

22. BIBLIOGRAPHY

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24. BIOLOGICAL MATERIALS TRANSFER AGREEMENT
Not applicable.
25. INVESTIGATIONAL DRUG FACT SHEET AND IND/IDE HOLDER
Not applicable. The IND Exemption Supplement is included with the submission.
26. IMPACT ON STAFF
May increase time spent per patient. There will be a strong effort for the research assistant to consent patients in a timely fashion in order minimize the effect on clinic flow the day of osmotic dilator insertion and prior to the D&E procedure. The clinic manager will be notified of possible changes to clinic work flow.
27. CONFLICT OF INTEREST
None
28. SUPPLEMENTAL INSTRUCTIONS FOR CANCER-RELATED STUDIES
Not applicable.
29. OTHER APPROVALS/REGULATED MATERIALS
Not applicable.
30. PROCEDURES FOR SURROGATE CONSENT AND/OR DECISIONAL CAPACITY ASSESSMENT
Not applicable.

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